United States Environmental Protection Agency

March 2008
EPA/600/R-07/093aB

Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

(Second External Review Draft)

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Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

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

DISCLAIMER

This document is a first external review draft being released for review purposes only and does not constitute U.S. Environmental Protection Agency (EPA) policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

National Ambient Air Quality Standards (NAAQS) are promulgated by the United States Environmental Protection Agency (EPA) to meet requirements set forth in Sections 108 and 109 of the U.S. Clean Air Act (CAA). Sections 108 and 109 require the EPA Administrator (1) to list widespread air pollutants that reasonably may be expected to endanger public health or welfare; (2) to issue air quality criteria for them that assess the latest available scientific information on nature and effects of ambient exposure to them; (3) to set "primary" NAAQS to protect human health with adequate margin of safety and to set "secondary" NAAQS to protect against welfare effects (e.g., effects on vegetation, ecosystems, visibility, climate, manmade materials, etc); and (5) to periodically review and revise, as appropriate, the criteria and NAAQS for a given listed pollutant or class of pollutants.

The purpose of this *revised Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria* is to critically evaluate and assess the latest scientific information published since that assessed in the above 1993 Nitrogen Oxides AQCD, with the main focus being on pertinent new information useful in evaluating health effects data associated with ambient air nitrogen oxides exposures. A First External Review Draft of this ISA (dated August 2007) was released for public comment and was reviewed by the Clean Air Scientific Advisory Committee (CASAC) in October 2007. Public comments and CASAC recommendations have been taken into account in making revisions to the document for incorporation into this Second External Review Draft ISA, which is now being released for public comment and CASAC review. Subsequently, a final ISA will be prepared that addresses comments received. This final ISA will be drawn on to provide inputs to risk and exposure analyses prepared by EPA's Office of Air Quality Planning and Standards (OAQPS) to pose options for consideration by the EPA

Administrator with regard to proposal and, ultimately, promulgation of decisions on potential retention or revision, as appropriate, of the current NO_2 NAAQS.

Preparation of this document was coordinated by staff of EPA's National Center for Environmental Assessment in Research Triangle Park (NCEA-RTP). NCEA-RTP scientific staff, together with experts from other EPA/ORD laboratories and academia, contributed to writing of document chapters. Earlier drafts of document materials were reviewed by non-EPA experts in peer consultation workshops held by EPA. The document describes the nature, sources, distribution, measurement, and concentrations of nitrogen oxides in outdoor (ambient) and indoor environments. It also evaluates the latest data on human exposures to ambient nitrogen oxides and consequent health effects in exposed human populations, to support decision making regarding the primary (health-based) NO_2 NAAQS.

NCEA acknowledges the valuable contributions provided by authors, contributors, and reviewers and the diligence of its staff and contractors in the preparation of this document.

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Abbreviations and Acronyms

[ ]	brackets signifying concentration(s)
α	alpha; the ratio of a person's exposure to a pollutant of ambient origin to the pollutant's ambient concentration
ACS	American Cancer Society
ADP	adenosine dinucleotide phosphate
a_i	air exchange rate for microenvironment *i*
AIRE	Asma Infantile Ricerca (Italian study)
AM	alveolar macrophage
APEX	Air Pollution Exposure (model)
APHEA	Air Pollution on Health: a European Approach (study)
AQCD	Air Quality Criteria Document
AQS	Air Quality System (database)
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
BHPN	*N*-bis(2-hydroxyl-propyl)nitrosamine
BHR	bronchial hyperresponsiveness
Br	bromine
C × T	concentration × time; concentration times duration of exposure
Ca^{++}	calcium ion
CAA	Clean Air Act
CALINE4	California line source dispersion (model)
CAMP	Childhood Asthma Management Program
CAPS	cavity attenuated phase shift (monitor)
CAPs	concentrated ambient particles
CARB	California Air Resources Board
CASAC	Clean Air Scientific Advisory Committee
CC16	Clara cell 16-kDa protein
CDC	Centers for Disease Control and Prevention
CHAD	Consolidated Human Activity Database
CHF	congestive heart failure
CHS	Children's Health Study
CI	confidence interval
CMAQ	Community Multiscale Air Quality (model)
CO	carbon monoxide
CO_2	carbon dioxide
COD	coefficient of divergence

CoH	coefficient of haze
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CTM	Chemistry-transport model
CVD	cardiovascular disease
DEPcCBP	diesel exhaust particulates extract-coated carbon black particles
DHHS	U.S. Department of Health and Human Services
DMA	dimethylamine
DMN	dimethylnitrosamine
DNA	deoxyribonucleic acid
DOAS	differential optical absorption spectroscopy
E_a	a person's exposure to pollutants of ambient origin
EC	elemental carbon
ECP	eosinophil cationic protein
ED	emergency department
ELF	epithelial lining fluid
E_{na}	a person's exposure to pollutants that are not of ambient origin
EPA	U.S. Environmental Protection Agency
EPO	eosinophil peroxidase
ER	emergency room
ETS	environmental tobacco smoke
FEF_{25}	forced expiratory flow at 25% of vital capacity
FEF_{25-75}	forced expiratory flow at 25 to 75% of vital capacity
FEF_{75}	forced expiratory flow at 75% of vital capacity
FE_{NO}	fractional exhaled nitric oxide
$FEV_{0.5}$	forced expiratory volume in 0.5 second
FEV_1	forced expiratory volume in 1 second
F_{infi}	the infiltration factor for microenvironment *i*
FRM	Federal Reference Method
FVC	forced vital capacity
GAM	Generalized Additive Model(s)
GEE	generalized estimating equation(s)
GEOS-CHEM	three-dimensional, global model of atmospheric chemistry driven by assimilated Goddard Earth Orbiting System observations
GIS	Geographic Information System
GM-CSF	granulocyte-macrophage colony stimulating factor
GSH	glutathione
GST	glutathione *S*-transferase (e.g., GSTM1, GSTP1, GSTT1)
H^+	hydrogen ion
HCHO	formaldehyde
HDL	high-density lipoprotein cholesterol

HNO_3	nitric acid
HNO_4	pernitric acid
HONO	nitrous acid
HR	heart rate
HRV	heart rate variability
HS	hemorrhagic stroke
H_2SO_4	sulfuric acid
hν	solar ultraviolet proton
ICAM-1	intercellular adhesion molecule-1
ICD, ICD9	International Classification of Diseases, Ninth Revision
id	identification
Ig	immunoglobulin (e.g., IgA, IgE, IgG)
IHD	ischemic heart disease
IIASA	International Institute for Applied Systems Analysis
IL	interleukin (e.g., IL-6, IL-8)
Ile	isoleucine
IN	inorganic particulate species
IOM	Institute of Medicine
IQR	interquartile range
IS	ischemic stroke
ISA	Integrated Science Assessment
ISAAC	International Study of Asthma and Allergies in Children
k_i	pollutant specific decay rate in microenvironment *i*
LDH	lactate dehydrogenase
LIF	laser-induced fluorescence
LOESS	locally estimated smoothing splines
LRD	lower respiratory disease
LT	leukotriene (e.g., LTB_4, LTC_4, LTD_4, LTE_4)
MEF_{25}	maximal expiratory flow at 25%
MEF_{50}	maximal expiratory flow at 50%
MEF_{75}	maximal expiratory flow at 75%
MENTOR	Modeling Environment for Total Risk
MI	myocardial infarction
MMEF	maximal midexpiratory flow
MoO_x	molybdenum oxide
MOZART	Model for Ozone and Related Chemical Tracers
MPO	myeloperoxidase
MPP	multiphase processes
MSA	metropolitan statistical area
N	nitrogen
n	number of observations

Na^+	sodium ion
NAAQS	National Ambient Air Quality Standards
$NaAsO_2$	sodium arsenite
NAL	nasal lavage
NAMS	National Air Monitoring Stations
NAS	National Academy of Sciences
$NC_{0.01-0.10}$	particle number concentration for particle aerodynamic diameter between 10 and 100 nm
NCHS	National Center for Health Statistics
NCICAS	National Cooperative Inner-City Asthma Study
NDMA	*N*-nitrosodimethylamine
NEI	National Emissions Inventory
NERL	National Exposure Research Laboratory
2NF	2-nitrofluoranthene
NHAPS	National Human Activity Pattern Survey
NHIS	National Health Interview Survey
NH_X	reduced nitrogen compounds (NH_3, NH_4^+)
NK	natural killer (lymphocytes)
NLCS	the Netherlands Cohort Study on Diet and Cancer
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NMOR	*N*-nitrosomorpholine
NN	nitronapthalene
NO	nitric oxide
NO_2	nitrogen dioxide
NO_2^-	nitrite ion
NO_3	nitrate radical
NO_3^-	nitrate ion
NO_X	sum of NO and NO_2
NO_Y	sum of NO_x and NO_z, total oxidized nitrogen
NO_Z	sum of all inorganic and organic reaction products of NO_x (HONO, HNO_3, HNO_4, organic nitrates, particulate nitrate, nitro-PAHS, etc.)
NOAA NCEP	U.S. National Oceanic and Atmospheric Administration's National Center for Environmental Prediction
1NP	1-nitropyrene
2NP	2-nitropyrene
NR, N/R	not reported
NRC	National Research Council
NSA	nitrosating agent
O_3	ozone
OC	organic carbon
OH	hydroxyl radical

OR	odds ratio
OVA	ovalbumin
P, p	probability value
P90	90th percentile
PAARC	French air pollution and chronic respiratory diseases study
PAF	paroxysmal atrial fibrillation
PAHs	polycyclic aromatic hydrocarbons
PAMS	Photochemical Aerometric Monitoring System
PAN	peroxyacetyl nitrate
PANs	peroxyacyl nitrates
PaO_2	pressure of arterial oxygen
Pb	lead
PD_{20}-FEV_1	provocative dose that produces a 20% decrease in FEV_1
PD100	provocative dose that produces a 100% increase in SRaw
PEACE	Pollution Effects on Asthmatic Children in Europe (study)
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
P_i	pollutant specific penetration coefficient for microenvironment *i*
PIH	primary intracerebral hemorrhage
PM	particulate matter
PM_{10}	particulate matter with an aerodynamic diameter of $\leq$10μm
$PM_{10-2.5}$	coarse particulate matter
$PM_{2.5}$	fine particulate matter
PMN	polymorphonuclear leukocytes
pNO_3^-	particulate nitrate
POM	particulate organic matter
ppb	parts per billion (by volume)
ppm	parts per million (by volume)
ppt	parts per trillion (by volume)
PRB	Policy Relevant Background
PT	prothombin time
PUFA	polyunsaturated fatty acids
R	intraclass correlation coefficient; organic radical
r	correlation coefficient
R^2	coefficient of determination
r_p	Pearson's correlation coefficient
r_s	Spearman's rank correlation coefficient
RAPS	Regional Air Pollution Study
RCS	random component superposition
$RONO_2$	organic nitrates

ROS	reactive oxygen species
RR	relative risk
RSV	respiratory syncytial virus
S	microenvironmental source strength
SAPALDIA	Study of Air Pollution and Lung Diseases in Adults
SAR	Site Audit Report
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SEP	social-economic position
SES	social-economic status
SGA	small for gestational age
SHEDS	Simulation of Human Exposure and Dose System
SIDS	sudden infant death syndrome
SLAMS	State and Local Air Monitoring Stations
SO_2	sulfur dioxide
SO_4^{2-}	sulfate ion
SRaw	specific airways resistance
STN	Speciation Trends Network
τ	tau; atmospheric lifetime
TEA	triethanolamine
Th2	T-derived helper 2 lymphocyte
TNF	tumor necrosis factor (e.g., TNF-α)
TSP	total suspended particulates
TVOCs	total volatile organic compounds
TX	thromboxane (e.g., TXA_2, TXB_2)
UFP	ultrafine particles; <0.1 μm diameter
URI	upper respiratory infections
V	volume of the microenvironment
Val	valine
VOCs	volatile organic compounds
VWF	von Willibrand Factor
WBC	white blood cell
y_i	the fraction of time people spend in microenvironment *i*
y_o	the fraction of time people spend outdoors
Z	Fisher's transform of the correlation coefficient

1. INTRODUCTION

The draft Integrated Science Assessment (ISA) presents a concise review, synthesis, and evaluation of the most policy-relevant science and communicates critical science judgments relevant to the review of national ambient air quality standards (NAAQS). In doing so, the evaluation focuses on the studies published since the most recent review, and builds upon key conclusions presented in previous U.S. Environmental Protection Agency (EPA) reports. This strategy of building on past findings is more efficient than starting with a new review of the pertinent literature and more effectively addresses the large body of work since the previous reviews. This draft ISA forms the scientific foundation for the review of the primary (health-based) NAAQS for nitrogen dioxide (NO_2).[1] The ISAs are accompanied by a series of Annexes that provide more detailed summaries of the most pertinent scientific literature.

The draft ISA is intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health which may be expected from the presence of [a] pollutant in ambient air" (Clean Air Act, Section 108 [U.S. Code, 2003a]). Scientific research is incorporated from atmospheric sciences, air quality analyses, exposure assessment, dosimetry, toxicology, clinical studies, and epidemiology. Annexes to the draft ISA also provide more details of the most pertinent scientific literature. The draft ISA and the Annexes serve to update and revise the information included in the 1993 Air Quality Criteria Document (AQCD) for Nitrogen Oxides (U.S. Environmental Protection Agency, 1993).

In this document, the terms "oxides of nitrogen" or "nitrogen oxides" refer to all forms of oxidized nitrogen compounds, including nitric oxide (NO), NO_2, and all other oxidized nitrogen-containing compounds transformed from NO and NO_2 (defined further in Chapter 2, Section 2.1).

1.1 LEGISLATIVE REQUIREMENTS

Two sections of the Clean Air Act (CAA) govern the establishment and revision of the NAAQS. Section 108 (U.S. Code, 2003a) directs the Administrator to identify and list "air

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

pollutants" that "in his judgment, may reasonably be anticipated to endanger public health and welfare" and whose "presence in the ambient air results from numerous or diverse mobile or stationary sources" and to issue air quality criteria for those that are listed. Air quality criteria are intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in ambient air."

Section 109 (U.S. Code, 2003b) directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants listed under Section 108. Section 109(b)(1) defines a primary standard as one "the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health."[2] A secondary standard, as defined in Section 109(b)(2), must "specify a level of air quality the attainment and maintenance of which, in the judgment of the Administrator, based on such criteria, is required to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air."[3]

The requirement that primary standards include an adequate margin of safety was intended to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting. It was also intended to provide a reasonable degree of protection against hazards that research has not yet identified. See Lead Industries Association v. EPA, 647 F.2d 1130, 1154 (D.C. Cir 1980), cert. denied, 449 U.S. 1042 (1980); American Petroleum Institute v. Costle, 665 F.2d 1176, 1186 (D.C. Cir. 1981), cert. denied, 455 U.S. 1034 (1982). Both kinds of uncertainties are components of the risk associated with pollution at levels below those at which human health effects can be said to occur with reasonable scientific certainty. Thus, in selecting primary standards that include an adequate margin of safety, the Administrator seeks to limit pollution levels demonstrated to be harmful as

[2] The legislative history of Section 109 indicates that a primary standard is to be set at "the maximum permissible ambient air level…which will protect the health of any [sensitive] group of the population" and that, for this purpose, "reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group" [U.S. Senate, 1970].

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

well as lower pollutant levels that may pose an unacceptable risk of harm, even if the nature or degree of risk is not precisely identified.

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

In setting standards that are "requisite" to protect public health and welfare, as provided in Section 109(b), EPA's task is to establish standards that are neither more nor less stringent than necessary for these purposes. In so doing, EPA may not consider the costs of implementing the standards. See generally Whitman v. American Trucking Associations, 531 U.S. 457, 465-472, and 475-76 (U.S. Supreme Court, 2001).

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

1.2 HISTORY OF PRIMARY NO_2 NAAQS REVIEWS

On April 30, 1971, EPA promulgated identical primary and secondary NAAQS for NO_2, under Section 109 of the Act, set at 0.053 parts per million (ppm), annual average (Federal Register, 1971). In 1982, EPA published *Air Quality Criteria for Oxides of Nitrogen* (U.S. Environmental Protection Agency, 1982), which updated the scientific criteria upon which the initial NO_2 standards were based. On February 23, 1984, EPA proposed to retain these standards (Federal Register, 1984). After taking into account public comments, EPA published the final decision to retain these standards on June 19, 1985 (Federal Register, 1985).

On July 22, 1987, EPA announced it was undertaking plans to revise the 1982 air quality criteria for oxides of nitrogen (Federal Register, 1987). In November 1991, EPA released an updated draft AQCD for CASAC and public review and comment (Federal Register, 1991). The draft document provided a comprehensive assessment of the available scientific and technical information on health and welfare effects associated with NO_2 and other oxides of nitrogen. The CASAC reviewed the document and concluded in a closure letter to the Administrator that the document "provides a scientifically balanced and defensible summary of current knowledge of the effects of this pollutant and provides an adequate basis for EPA to make a decision as to the appropriate NAAQS for NO_2" (Wolff, 1993).

The EPA also prepared a draft Staff Paper that summarized and integrated the key studies and scientific evidence contained in the revised AQCD and identified the critical elements to be considered in the review of the NO_2 NAAQS. The draft Staff Paper was reviewed by CASAC and revised by EPA staff in response to CASAC comments and recommendations. CASAC reviewed the final draft of the Staff Paper in June 1995 and responded by written closure letter (Wolff, 1996). In September 1995, EPA finalized the document entitled, *Review of the National Ambient Air Quality Standards for Nitrogen Dioxide Assessment of Scientific and Technical Information* (U.S. Environmental Protection Agency, 1995).

Based on that review, the Administrator announced her proposed decision not to revise either the primary or the secondary NAAQS for NO_2 (Federal Register, 1995). The decision not to revise the NO_2 NAAQS was finalized after careful evaluation of the comments received on the proposal (October 11, 1995). The level for both the existing primary and secondary NAAQS for NO_2 is 0.053 ppm annual arithmetic average, calculated as the arithmetic mean of the 1-h NO_2 concentrations.

1.3 POLICY-RELEVANT QUESTIONS

The *Integrated Plan for the Review of the Primary National Ambient Air Quality Standard for Nitrogen Dioxide* (U.S. Environmental Protection Agency, 2007) identifies a set of key policy-relevant questions. These questions frame this review of the scientific evidence that provides the scientific basis for a decision on whether the current primary NAAQS for NO_2 (0.053 ppm, annual average) should be retained or revised. The questions are:

- Has new information altered the scientific support for the occurrence of health effects following short- and/or long-term exposure to levels of nitrogen oxides found in the ambient air?
- What do recent studies focused on the near-roadway environment tell us about health effects of nitrogen oxides?
- At what levels of nitrogen oxides exposure do health effects of concern occur?
- Has new information altered conclusions from previous reviews regarding the plausibility of adverse health effects caused by exposure to nitrogen oxides?
- To what extent have important uncertainties identified in the last review been reduced and/or have new uncertainties emerged?
- What are the air quality relationships between short- and long-term exposures to nitrogen oxides?

1.4 DOCUMENT DEVELOPMENT

The EPA formally initiated the current review of the NO_2 NAAQS by announcing the commencement of the review in the Federal Register with a call for information (Federal Register, 2005). In addition to the call for information, publications are identified through an ongoing literature search process. Literature search strategies include extensive computer database mining on specific topics; reviewing previous EPA reports; reviewing peer reviewed publications reporting results from observational studies, clinical studies, and animal studies with information related to exposure-response relationships, mechanism(s) of action, or susceptible subpopulations; and review of reference lists from important publications. Additional evidence related to exposure is taken from published studies or EPA's analyses of air quality data and emissions data and the atmospheric chemistry, transport, and fate of these emissions. Information is also acquired from consultation with content and area experts and the public. The search strategies used in the draft ISA development are detailed in Annex AX1. The focus of this draft ISA is on literature published since the 1993 AQCD for nitrogen oxides. Key findings and conclusions from the 1993 review are discussed in conjunction with recent findings. Generally, only information that has undergone scientific peer review and that has been

published (or accepted for publication) in the open literature is considered. Details of the criteria for study selection for this draft ISA are found in Annex AX1.

1.5 DOCUMENT ORGANIZATION

This draft ISA includes five chapters. This introductory chapter (Chapter 1) presents an overview, including the framework for the evaluation of causality used in this review. Chapter 2 highlights key concepts or issues relevant to understanding the sources, atmospheric chemistry, exposure, and dosimetry of nitrogen oxides, following a "source-to-dose" paradigm. Chapter 3 evaluates and integrates health information relevant to the review of the primary NAAQS for NO_2. Chapter 4 provides information relevant to the public health impact of exposure to ambient nitrogen oxides, including identification of potentially susceptible population groups. Finally, Chapter 5 articulates findings and conclusions regarding the health evidence and makes recommendations pertinent to exposure and risk assessments.

In addition, a series of Annexes provides additional details of information in the ISA. Annex 1 is an introduction to the Annex series, and detailed discussions of the study selection process for the ISA and Annexes. Annex 2 contains 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 3 presents information on environmental concentrations, patterns, and human exposure to ambient nitrogen oxides. Annex 4 presents results from toxicological studies as well as information on dosimetry of nitrogen oxides. Annex 5 presents results from controlled human exposure studies, and Annex 6 presents evidence from epidemiologic studies. Annex tables for health studies are generally organized to include information about (1) concentrations of nitrogen oxides levels or doses and exposure times, (2) description of study methods employed, (3) results and comments, and (4) quantitative outcomes for nitrogen oxides measures.

1.6 EPA FRAMEWORK FOR CAUSAL DETERMINATIONS

It is important to have a consistent and transparent basis for the critical decisions on the causal nature of air pollution induced health effects. The framework described below establishes uniform language concerning causality and brings more specificity to the findings. It draws

normalizing language from across the Federal government and wider scientific community, especially from the recent National Academy of Sciences (NAS) Institute of Medicine (IOM) document, *Improving the Presumptive Disability Decision-Making Process for Veterans* (IOM, 2007), the most recent comprehensive work on evaluating the causality of health effects. This section:

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

Approaches to assessing the separate and combined lines of evidence from epidemiology, controlled human exposure studies, animal toxicology, and in vitro studies have been formulated by a number of regulatory and science agencies, including the Institute of Medicine of the National Academies of Science (IOM, 2007), the International Agency for Research on Cancer (IARC, 2006), the National Toxicology Programs (NTP, 2005), the EPA (U.S. Environmental Protection Agency, 2005), the Centers for Disease Control and Prevention (CDC, 2004), and the National Acid Precipitation Assessment Program (NAPAP, 1991). Highlights or excerpts from the various decision framework documents are included in Annex AX1. These formalized approaches offer guidance for assessing the relative weights of those lines of evidence. The frameworks are similar in nature, although adapted to different purposes, and have proven to be effective in providing a uniform structure and language for causal determinations. Moreover, these frameworks must support decision-making under conditions of great uncertainty.

Scientific Evidence Used in Establishing Causality

The most compelling evidence of a causal relationship between pollutant exposures and human health effects comes from controlled human exposure (i.e., clinical) studies. This type of

study experimentally evaluates the effects of administered exposures under highly controlled laboratory conditions.

In observational, or epidemiologic studies of humans, the investigator does not control exposures or intervene with the study population. Broadly speaking, observational studies can describe associations between exposures and effects and fall into several categories: cross-sectional, prospective cohort, time-series, and panel studies. "Natural experiments" occur occasionally in epidemiology; these include comparisons of epidemiologic results before and after a change in population exposures (e.g., closure of a pollution source).

The clinical and observational data are complemented by experimental animal data, which can support the biological plausibility of causation. In the absence of clinical or observational data, animal data alone may be sufficient to support a likely causal determination, assuming that humans respond similarly to the experimental species.

Association and Causation

Association and causation are not the same. The word *cause* conveys the notion of a significant, effectual relationship between an agent and an associated disorder or disease in the population. In contrast, *association* is the statistical dependence between two or more events, characteristics, or other variables. An association is prima facie evidence for causation, but not sufficient by itself for proving a causal relationship between exposure and disease. Unlike associations, causal claims support making counterfactual claims; that is, claims about what the world would have been like under different or changed circumstances (IOM, 2007). Currently, much of the newly available health information evaluated in the draft ISA comes from epidemiologic studies that report a statistical association between exposure and health outcome.

It would be naive to insist upon mono-etiology in pathological processes or in vital phenomena. Epidemiologists have long recognized that most chronic diseases (e.g., cancer or coronary heart disease) result from a complex web of causation, whereby one or more external agents (exposures) taken into the body initiate a disease process, the outcome of which could depend upon many factors including age, genetic susceptibility, nutritional status, immune competence, social factors, and others (IOM, 2007; Gee and Payne Sturges, 2004). Figure 1.6-1 shows a diagram of a variety of etiologic factors that contribute to disease.

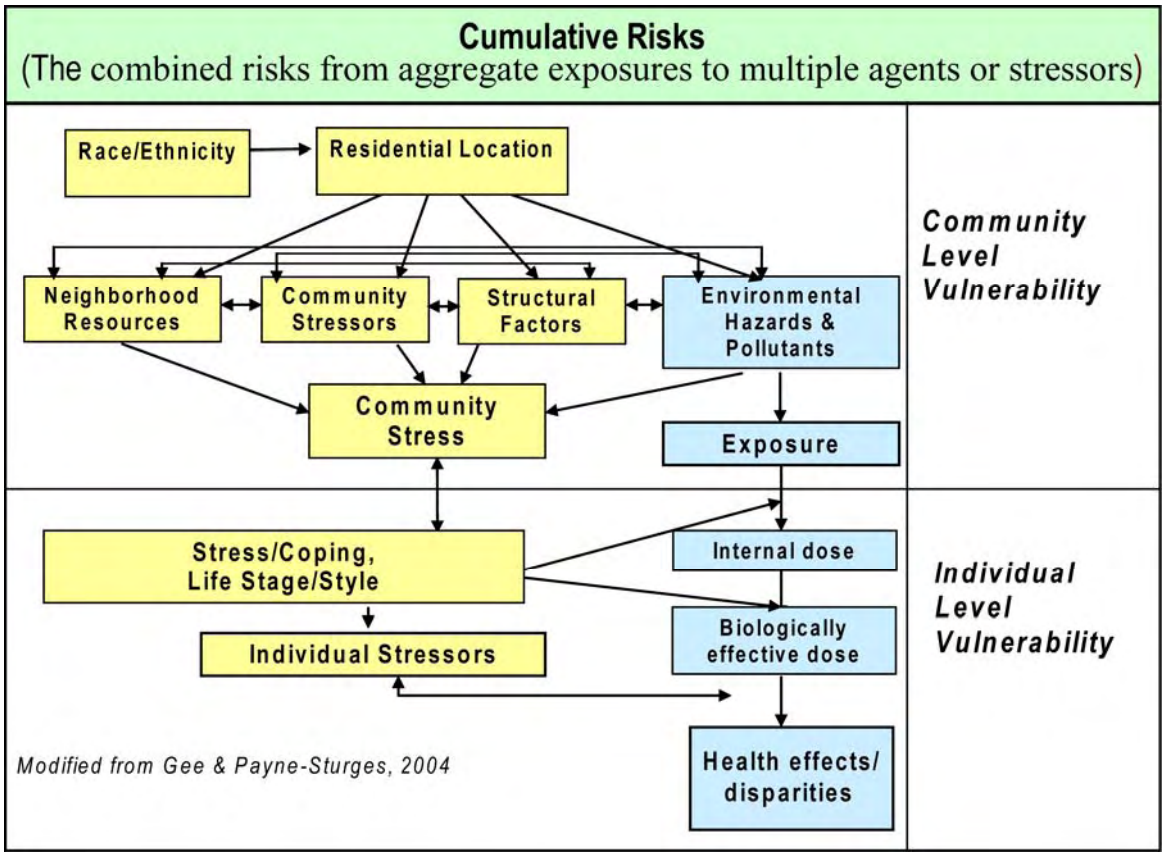

Figure 1.6-1. Exposure–disease–stress model for environmental health disparities.

Source: Modified from Gee and Payne-Sturges (2004).

Additionally, various exposure profiles can be important. Exposures may occur over an extended period of time with some cumulative effect; repetitive acute exposures may produce both episodic and chronic illness; exposure to multiple agents together could result in synergistic or antagonistic effects different from what might result from exposure to each separately.[4] The end results are the net effect of many actions and counteractions. Epidemiologists use the term *interaction* (or effect modification) to denote the departure of the observed joint risk from what might be expected based on the separate effects of the factors.

[4] For example, one could define a multiplicative interaction relative risk (RR) as: $RR_{Int(mult)} = RR_{joint}/RR_E \times RR_S$, or an additive interaction RR as $RR_{Int(add)} = RR_{joint} - RR_E - RR_S + 1$.

Evidence for Going Beyond Association to Causation

Developing evidence for going beyond association to causation involves experimental control, statistical control, and models. Controlled human exposure studies are experiments in which subjects in a population are randomly allocated into groups, usually called study and control groups, and exposed to a pollutant or a sham. The results are assessed by rigorous comparison of rates of appropriate outcome between the study and control groups. Randomized controlled human exposure studies are generally regarded as the most scientifically rigorous method of hypothesis testing available. By assigning exposure randomly, the study design attempts to remove the effect of any factor that might influence exposure, and any possible effect of the outcome on exposure. Done properly, and setting aside randomness, only a causal relationship from exposure to health outcome should produce observed associations in randomized clinical trials. In another type of controlled human exposure study, the same subject is exposed to a pollutant and a sham at different time points and the responses to the two types of exposures are compared. This study design is also effective at controlling for any potential confounders since the subject is serving as his/her own control. A lack of observation of effects from controlled human exposure studies does not mean that a causal relationship does not occur. Controlled human exposure studies are often limited because the study population is generally small. This restricts the power to discern statistically significant findings. In addition, the most susceptible individuals may be explicitly excluded (for ethical reasons), and more susceptible individuals or groups (e.g., those with nutritional deficits) may not be included.

Inferring causation from observational (epidemiologic) studies requires consideration of potential confounders. When associations are found in observational studies, the first approach for removing spurious associations from possible confounders is statistical control of the difference between characteristics of exposed and unexposed persons, frequently termed *adjustment*. Multivariable regression models constitute one tool for estimating the association between exposure and outcome after adjusting for characteristics of participants that might confound the results. Another way to adjust for potential confounding is through stratified analysis, i.e., examining the association within homogeneous groups with the confounding variable. Stratified analyses have the secondary benefit of allowing examination of effect modification through comparison of the effect estimates across different groups. If investigators have successfully measured characteristics that distort the results, then adjustment of these

factors will help separate a spurious from a true causal association. Appropriate statistical adjustment for confounders requires identifying and measuring all reasonably expected confounders. Deciding which variables to control for in a statistical analysis of the association between exposure and disease depends upon knowledge about the possible mechanisms connecting them. Identifying mechanisms allows us to identify and control for potential sources of spurious association.

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

It is important to recognize the difficulties of identifying and measuring all potential confounders. However, if observational studies are repeated in different settings with different subjects having different eligibility criteria and/or different exposure opportunities, each of which might eliminate another source of confounding from consideration, then confidence that unmeasured confounders are not producing the findings is increased. The number and degree of diversity of such studies as well as their interpretation for relevance to the potential confounders remain matters of scientific judgment. Multicity studies use a consistent method to analyze data from across locations with different levels of covariates and, thus, can provide insights on potential confounding in associations.

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

experimental data in causal deteminations. Principles for evaluating mechanisms or modes of action as part of causal determinations should be developed.

Multifactorial Causation

Scientific judgments are needed regarding the likely sources and magnitude of confounding, together with judgments about how well the existing constellation of study designs, results, and analyses address this potential threat to inferential validity. One key consideration in this review is evaluation of the potential contribution to health effects of NO_2 when it is a component of a complex air pollutant mixture. There are multiple ways by which NO_2 might cause or be associated with adverse health effects: (1) as a direct causal effect, (2) as an indirect causal effect mediated by other pollutants formed in the atmosphere including particulate matter (PM) and ozone (O_3), and (3) by acting as a surrogate for emissions from the same sources that emit NO_2 that are actually responsible for the adverse health effects observed; these relationships are illustrated in Figure 1.6-2. Moreover, these possibilities are not necessarily exclusive. Confounding, as usually defined, would refer to the production of an association between NO_2 and adverse health effects, by the actions of one or more other exposures, themselves associated with NO_2 in a particular study. Multivariate models are the most widely used strategy to address confounding in epidemiologic studies, but such models are not readily interpreted when the potential confounders such as PM may be mediating effects possibly attributable to NO_2.

Uncertainty

The science of estimating the causal influence of an exposure on disease is uncertain. Formal statistical descriptions provide one means for dealing with uncertainty; however, they do this in two distinct ways:

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

The uncertainty concerning the correct causal model involves uncertainty about (1) whether exposure causes the health outcome, (2) the set of confounders associated with exposure and disease, (3) which parametric forms for describing the relations of exposure and confounders with outcome are correct, and (4) whether other forms of bias could be affecting the evidence.

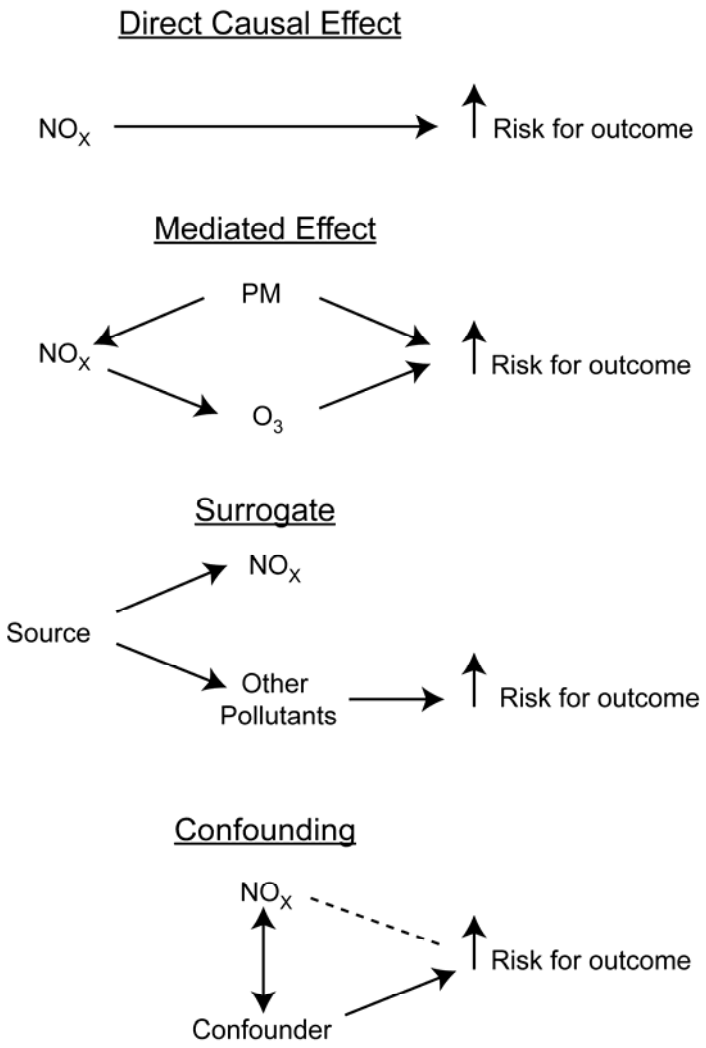

Figure 1.6-2. Potential relationships of NO_X with adverse health effects.

Uncertainty about the model is not limited to the qualitative causal structure: it also involves uncertainty about the parametric form of the model specified, the variables included, whether or not measurement error is modeled, and so on. When mechanistic knowledge exists, this sort of uncertainty can be reduced. Nevertheless, model uncertainty is perhaps the more important source of uncertainty. In contrast, uncertainty about the parameter estimates (regression coefficients) for a given model is a well-studied problem. The important point is that these reports of uncertainty are conditional on the model providing a sufficiently adequate approximation of reality so that inferences are valid. The overall scientific inference involves

evaluating uncertainty about the model and uncertainty about the parameter estimates given each model.

There are systematic, quantitative approaches for including uncertainty about the model in an assessment of overall uncertainty about a causal inference. These approaches include sensitivity analysis and model averaging. Sensitivity analysis attempts to quantify the sensitivity of the parameter estimate to assumptions about the model. Uncertainty ranges can be estimated using classical analysis (Robinson, 1989) or the Monte Carlo technique (Eggleston, 1993). Model averaging attempts to provide an overall uncertainty to the estimate by calculating the estimate of a common parameter or target and its uncertainty for each model considered to be plausible, and weighting the estimates and the uncertainties by the likelihood of each model.

Application of Framework

In EPA's framework for evaluation, a two-step approach is used to judge the scientific evidence about exposure to criteria pollutants and risks to public health. The first step is to determine the weight of evidence in support of causation and characterize the strength of any resulting causal classification. The second step includes further evaluation of the quantitative evidence regarding the shape of concentration-response or dose-response relationships and the levels at which effects are observed.

To aid judgment, decisive factors for the determination of a cause have been proposed by many philosophers and scientists. The most widely cited decisive factors in epidemiology and public health more generally were set forth by Sir Austin Bradford Hill in 1965. The nine "Hill criteria" were also incorporated in the EPA *Guidelines for Carcinogen Risk Assessment* (U.S. Environmental Protection Agency, 2005). These nine decisive factors for determination of causality are described in Table 1.6-1[5] (adapted from Hill, 1965, and U.S. Environmental Protection Agency, 2005). A number of these decisive factors are judged to be particularly salient in evaluating the body of evidence available in this review, including the factors described by Hill as strength, experiment, consistency, plausibility, and coherence. Other factors identified by Hill, including temporality and biological gradient, are also relevant and considered here (e.g., in characterizing lag structures and concentration-response relationships).

[5] We have chosen to use the words "decisive factors" in this document, as opposed to the commonly used term "criteria," in order to avoid confusion with criteria as characterized by the Clean Air Act.

TABLE 1.6-1. DECISIVE FACTORS TO AID IN JUDGING CAUSALITY

1. ***Consistency of the observed association.*** An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.
2. ***Strength of the observed association.*** The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. A modest risk, however, does not preclude a causal association and may reflect a lower level of exposure, an agent of lower potency, or a common disease with a high background level.
3. ***Specificity of the observed association.*** As originally intended, this refers to increased inference of causality if one cause is associated with a single effect or disease (Hill, 1965). Based on our current understanding this is now considered one of the weaker guidelines for causality; for example, many agents cause cancer at multiple sites and that many cancers have multiple causes. Thus, although the presence of specificity may support causality, its absence does not exclude it.
4. ***Temporal relationship of the observed association.*** A causal interpretation is strengthened when exposure is known to precede development of the disease.
5. ***Biological gradient (exposure-response relationship).*** A clear exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times). There are many possible reasons that an epidemiologic study may fail to detect an exposure-response relationship. Thus, the absence of an exposure-response relationship does not exclude a causal relationship.
6. ***Biological plausibility.*** An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A lack of mechanistic data, however, is not a reason to reject causality.
7. ***Coherence.*** An inference of causality may be strengthened by other lines of evidence that support a cause-and-effect interpretation of the association. Information is considered from animal bioassays, toxicokinetic studies, and short-term studies. The absence of other lines of evidence, however, is not a reason to reject causality.
8. ***Experimental evidence (from human populations).*** Experimental evidence is generally available from human populations for the criteria pollutants. The strongest evidence for causality can be provided when a change in exposure brings about a change in adverse health effect or disease frequency in either clinical or observational studies.
9. ***Analogy.*** Structure activity relationships (SARs) and information on the agent's structural analogs can provide insight into whether an association is causal. Similarly, information on mode of action for a chemical, as one of many structural analogs, can inform decisions regarding likely causality.

While these decisive factors frame considerations weighed in assessing the evidence, they do not lend themselves to being considered in terms of simple formulas or hard-and-fast rules of evidence leading to conclusions about causality (Hill, 1965). For example, one cannot simply count the number of studies reporting statistically significant results or statistically nonsignificant results for health effects and reach credible conclusions about the relative weight of the evidence and the likelihood of causality. Rather, these important considerations are taken

into account throughout the assessment with the goal of producing an objective appraisal of the evidence (informed by peer and public comment and advice), which includes the weighing of alternative views on controversial issues. Additionally, it is important to note that principles listed in Table 1.6-1 cannot be used as a strictly quantitative checklist. Rather, these principles should be used to determine the weight of the evidence for inferring causality. In particular, the absence of one or more of the principles does not automatically exclude a study from consideration (e.g., see discussion in CDC, 2004).

First Step—Determination of Causality

This draft ISA uses a five-level hierarchy that classifies the weight of evidence for causation, not just association; that is, whether the weight of scientific evidence makes causation at least as likely as not in the judgment of the reviewing group.[6] In developing this hierarchy, EPA has drawn upon the work of previous evaluations, most prominently the IOM's *Improving the Presumptive Disability Decision-Making Process for Veterans* (2007), EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. Environmental Protection Agency, 2005), and the U.S. Surgeon General's smoking reports (CDC, 2004). These efforts are presented in more detail in Annex AX1. In the draft ISA, causality of association was placed into one of five categories with regard to the weight of the evidence. These conclusions are based on EPA's evaluation of the weight of evidence from epidemiologic studies, animal studies, or other mechanistic, toxicological, or biological sources. These separate judgments are integrated into a qualitative statement about the overall weight of the evidence and causality. The five descriptors are:

- Sufficient to infer a causal relationship,
- Sufficient to infer a likely causal relationship (i.e., more likely than not),
- Suggestive but not sufficient to infer a causal relationship,
- Inadequate to infer the presence or absence of a causal relationship, and
- Suggestive of no causal relationship.

[6] It should be noted that the CDC and IOM frameworks use a four-category hierarchy for the strength of the evidence. A five-level hierarchy is used here to be consistent with the EPA *Guidelines for Carcinogen Risk Assessment* (U.S. Environmental Protection Agency, 2005).

Second Step—Evaluation of Population Response

Beyond judgments regarding causality are questions relevant to characterizing exposure and risk to populations. Such questions include:

- At what doses or concentrations are effects observed?
- What is the shape of the concentration-response or dose-response relationship?
- What population groups appear to be affected or more susceptible to effects?
- With what exposure time periods (e.g., peak, long-term average) are effects seen?

On the population level, causal and likely causal claims typically proceed to characterize how risk (the probability of health effects) changes in response to exposure. Initially, the response is evaluated within the range of observation. Approaches to analysis of the range of observation of epidemiologic and clinical studies are determined by the type of study and how dose and response are measured in the study. Extensive human data for concentration-response analyses exists for all criteria pollutants, unlike most other environmental pollutants. Animal data also can inform concentration-response, particularly relative to dosimetry, mechanisms of action, and characteristics of sensitive subpopulations.

An important consideration in characterizing the public health impacts associated with pollutant exposure is whether the concentration-response relationship is linear across the full concentration range encountered or if nonlinear departures exist along any part of this range. Of particular interest is the shape of the concentration-response curve at and below the level of the current standards. The complex molecular and cellular events that underlie cancer and noncancer toxicity are likely to be both linear and dose-transitional. At the human population level, however, various sources of both variability and uncertainty tend to smooth and "linearize" the concentration-response function, obscuring any thresholds that may exist. (This does not presume that the dose-response relationship will be linear for individuals.) There are limitations to identifying possible "thresholds" in epidemiologic studies, including difficulties related to the low data density in the lower concentration range, possible influence of measurement error, and individual differences in susceptibility to air pollution health effects. These attributes of population dose-response may explain why the available human data at ambient concentrations for some environmental pollutants (e.g., PM, secondhand tobacco smoke, lead, radiation) do not exhibit evident thresholds for cancer or noncancer health effects even though likely mechanisms of action include nonlinear processes for some key events. These attributes of human population

dose-response relationships have been extensively discussed in the broader epidemiologic literature (e.g., Rothman and Greenland, 1998).

1.7 CONCLUSIONS

The scientific assessment of air pollution-related health effects involves reviewing evidence from clinical, epidemiologic, and animal studies, including mechanistic evidence from basic biological science. Clinical studies can provide the strongest evidence for causation. Epidemiologic studies that are reasonably free of bias and confounding provide evidence that can support determination of causation, but may not provide proof of causation. Mechanistic knowledge of how particular agents might produce adverse health effects provides further evidence. For example, animal mechanism-of-action studies may provide further evidence by showing that an agent may induce the same effect as observed in human studies, using a mechanism that is conserved across species with key features of the mechanism observed. Uncertainty surrounding a causal claim can arise because of uncertainty about which among a set of plausible models is correct, uncertainty about study design and execution, uncertainty caused by simple sampling variability, or uncertainty in the basic science required to analyze other evidence. The overall uncertainty is some combination of all of these uncertainties.

The draft Integrated Science Assessment (ISA) presents a concise review, synthesis, and evaluation of the most policy-relevant science, and communicates critical science judgments relevant to the NAAQS review. Those judgments include determinations of causality. The draft ISA relies on widely accepted principles for determinations of causality based on decisive factors such as those put forth by Hill in 1965 and, subsequently, generally adopted by numerous agencies. Inferences, whether about causality or statistical associations, always carry some degree of uncertainty.

The draft ISA uses standardized language to express the evaluation of the evidence bearing on causality. This approach helps clarify the assessment and makes it possible for subsequent groups to measure progress by comparing their judgments with those expressed here. This structure also encourages the description of the sources of uncertainty in the evidence, which hopefully will stimulate necessary research. The framework used in this report should assist EPA and others, now and in the future, to accurately represent what is presently known and

what remains unknown concerning the effects of these environmental air pollutants on human health.

2. SOURCE TO TISSUE DOSE

This chapter provides concepts and findings relating to emissions sources, atmospheric science, human exposure assessment, and human dosimetry. The order of these topics essentially follows that given in the National Research Council paradigm for integrating air pollutant research (National Research Council, 2004) as shown in Figure 2-1. This chapter is meant to serve as a prologue for detailed discussions on the evidence on health effects that follow in Chapters 3 and 4.

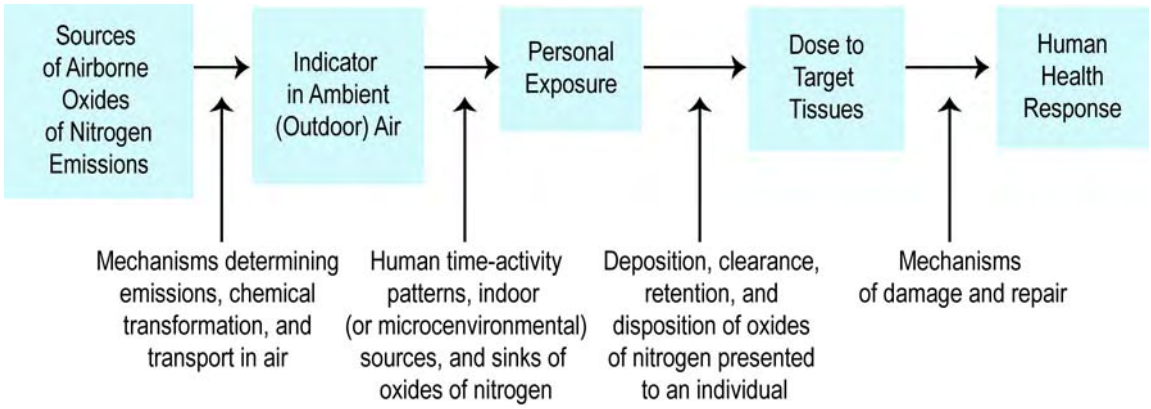

Figure 2-1. A generalized conceptual model for integrating research on oxides of nitrogen pollution and human health effects.

Source: Adapted from National Research Council (2004).

2.1 INTRODUCTION

As noted in Chapter 1, the definition of "nitrogen oxides" as it appears in the enabling legislation related to the national ambient air quality standard (NAAQS) differs from the one commonly used in the air pollution research and control communities. In this document, the terms "oxides of nitrogen" and "nitrogen oxides" (NO_X) refer to all forms of oxidized nitrogen (N) compounds, including nitric oxide (NO), nitrogen dioxide (NO_2), and all other oxidized

N-containing compounds formed from NO and NO_2.[1] In the Federal Register Notice for the previous Air Quality Criteria Document (AQCD) for Oxides of Nitrogen (Federal Register, 1995), the term "nitrogen oxides" was used to "describe the sum of NO, NO_2, and other oxides of nitrogen."

NO and NO_2, along with volatile organic compounds (VOCs; anthropogenic and biogenic hydrocarbons, aldehydes, etc.) and carbon monoxide (CO), are precursors in the formation of ozone (O_3) and photochemical smog. NO_2 is an oxidant and can react to form other photochemical oxidants, including organic nitrates ($RONO_2$) like the peroxyacyl nitrates (PANs). NO_2 can also react with toxic compounds such as polycyclic aromatic hydrocarbons (PAHs) to form nitro-PAHs, some of which are more toxic than either reactant alone. NO_2 and sulfur dioxide (SO_2), another U.S. Environmental Protection Agency (EPA) criteria air pollutant, can also be oxidized to form the strong mineral acids nitric acid (HNO_3) and sulfuric acid (H_2SO_4), respectively, thereby contributing to the acidity of cloud-, fog-, and rainwater and of ambient particles.

2.2 SOURCES AND ATMOSPHERIC CHEMISTRY

The role of NO_X in O_3 formation was reviewed in Chapter 2 (Section 2.2) of the latest *Air Quality Criteria for Ozone and Related Photochemical Oxidants* (2006 AQCD for O_3; U.S. Environmental Protection Agency, 2006) and has been presented in numerous texts (see, e.g., Seinfeld and Pandis, 1998; Jacob, 1999; Jacobson, 2002). Mechanisms for transporting O_3 precursors including NO_X, the factors controlling the efficiency of O_3 production from NO_X, methods for calculating O_3 from its precursors, and methods for measuring total oxidized nitrogen (NO_Y) were all reviewed in Section 2.6 of 2006 AQCD for O_3. The main points from that 2006 AQCD for O_3 will be presented here along with updates based on new material. The overall chemistry of reactive, oxidized N compounds in the atmosphere is summarized in Figure AX2.2-1 and described in greater detail in Annex AX2.

[1] This follows usage in the Clean Air Act Section 108(c): "Such criteria [for oxides of nitrogen] shall include a discussion of nitric and nitrous acids, nitrites, nitrates, nitrosamines, and other carcinogenic and potentially carcinogenic derivatives of oxides of nitrogen." By contrast, within the air pollution research and control communities, the terms "oxides of nitrogen" and "nitrogen oxides" are restricted to refer only to the sum of NO and NO_2, and this sum is commonly abbreviated as NO_X. The category label used by this community for the sum of all forms of oxidized nitrogen compounds including those listed in Section 108(c) is NO_Y.

2.2.1 Sources of NO_X

Both anthropogenic and natural (biogenic) processes emit NO_X. NO_X is emitted by combustion sources mainly as NO with smaller quantities of NO_2. The major combustion sources of NO_X in the United States are listed in Annex Table AX 2-3. Figure 2.2-1 shows schematically the on-road motor vehicles and electric utilities sources, the two largest NO_X sources in the United States, along with NO_X species and some reaction pathways. Stationary engines, off-road vehicles, and industrial facilities also emit NO_X, but because they are fewer in number or burn less fuel, their mass contribution is relatively smaller. The ratios of NO_2 to NO_X in emissions are variable with typical values being less than 0.1. However, ratios in emissions from retrofitted diesel engines range from 0.3 to 0.6 as shown in a study of public transit buses in New York City (Shorter et al., 2005). Sources of NO_X are distributed across various heights, some are at or near ground level (e.g., motor vehicles) and others aloft (e.g., electric utilities stacks), as indicated in Figure 2.2-1. Because the prevailing winds aloft are generally stronger than those at the surface, emissions from elevated sources can be distributed over a wider area than those emitted at the surface.

Biomass burning also produces NO_X. Apart from these anthropogenic sources, there are also smaller natural sources which include microbial activity in soils (particularly fertilized soils) and lightning. Wildfires can be large but epidosic and highly variable sources of NO_X. NO_X sources and emissions are described in greater detail in Annex Section AX2.6.

2.2.2 Chemical Transformations of NO_X

NO and NO_2 are often grouped together and given the category label "NO_X" because they are emitted together and can rapidly interconvert as shown in the inner box in Figure 2.2-1. NO_2 reacts with O_3 and various free radicals in the gas phase and on surfaces in multiphase processes to form the oxidation products shown in Figure 2.2-1. These products include inorganic species (shown on the left side of the outer box in Figure 2.2-1) and organic species (shown on the right side of the outer box in Figure 2.2-1). The oxidized N species in the outer box are often collectively termed NO_Z; thus, $NO_X + NO_Z = NO_Y$.

The concentrations and atmospheric lifetimes (τ) of inorganic and organic products from reactions of NO_X vary widely in space and time. Inorganic reaction products include nitrous acid (HONO), HNO_3, pernitric acid (HNO_4), and particulate nitrate (pNO_3^-). While a broad range of

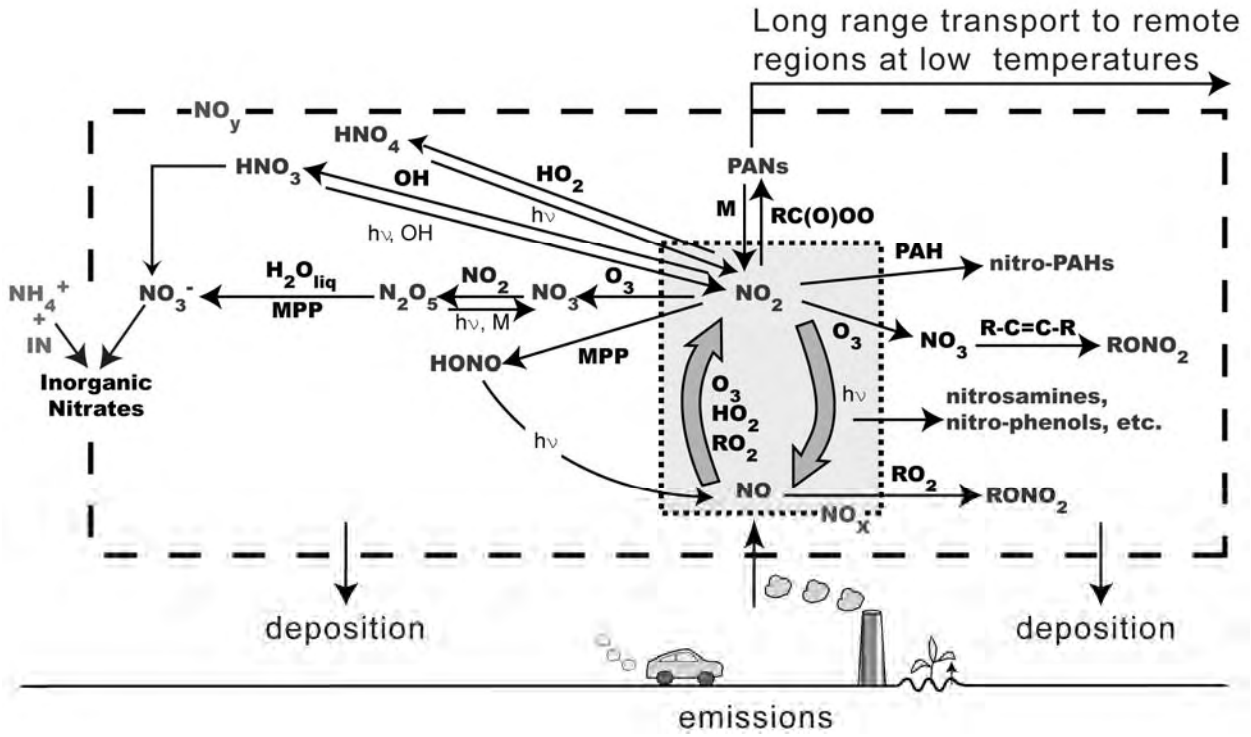

Figure 2.2-1. Schematic diagram of the cycle of reactive, oxidized N species in the atmosphere. IN refers to inorganic particulate species (e.g., sodium [Na^+], calcium [Ca^{++}]), MPP to multiphase processes, hν to a solar photon and R to an organic radical. Particle-phase $RONO_2$ are formed from the species shown on the right side.

organic N compounds are emitted by combustion sources (e.g., nitrosamines and nitro-PAHs), they are also formed in the atmosphere from reactions of NO and NO_2. These include PANs and isoprene nitrates, other nitro-PAHs, and the more recently identified nitrated organic compounds in the quinone family. Most of the mass of products shown in the outer box of Figure 2.2-1 is in the form of peroxyacetyl nitrate (PAN) and HNO_3, although other organic nitrates, e.g., isoprene nitrates and specific biogenic PANs can be important at locations closer to biogenic sources (Horowitz et al., 2007; Singh et al., 2007).

In addition to gas-phase reactions, reactions occurring on surfaces or occurring in multiple phases (MPP) are important for the formation of HONO and pNO_3^-. These reactions can occur on the surfaces of suspended particles, soil, and buildings, and within aqueous media. The τ of PAN is strongly temperature dependent and is long enough at low temperatures so that

PAN can be transported tens or hundreds of kilometers (depending on meteorological conditions) before decomposing to release NO_2, which can then participate in O_3 formation in these regions which are remote from the original NO_X source. HNO_3 can act similarly to some extent, but its high solubility and high deposition rate imply that it is removed from the gas phase faster than PAN, and thus would not be as important as a source of NO_X in remote regions. Characteristic concentrations of many of the NO_X species are given in Annex AX3.2.

The timescale for reactions of NO_X to form NO_Z products like PAN and HNO_3 typically ranges from a few hours during summer to about a day during winter. As a result, morning rush hour emissions of NO_X from motor vehicles can be converted almost completely to NO_Z products by late afternoon during warm, sunny conditions. Because the time required for mixing emissions down to the surface is similar to or longer than the time for oxidation of NO_X, emissions of NO_X from elevated sources like the stacks of electric utilities tend to be transformed to NO_Z before they reach the surface. However, people live closer to emissions from on-road and off-road motor vehicles fixed-site combustion engines (e.g., generators), and indoor sources, and so are more likely to be exposed to NO and NO_2 from these sources. Hence, because atmospheric dispersion and chemical reactions in this way determine the partitioning of a person's exposure to NO_2 and its reaction products from multiple different sources, a person's total exposure to NO_X cannot be judged solely by the NO and NO_2 source strengths given in the national emissions inventories (NEI).

Ultimately, oxidized N compounds are lost from the atmosphere by deposition to the earth's surface. Soluble species are taken up by aqueous aerosols and cloud droplets that can then be removed by either wet or dry deposition. Insoluble species are lost by dry deposition and washout. Discussions of the reactions in particles are beyond the scope of this review, but once in particles, a variety of organic and inorganic nitrates can be formed, which are then removed either by dry deposition to the surface or by rainout or washout.

2.2.2.1 Formation of Nitro-PAHs

Nitro-PAHs are produced either by direct emissions or by atmospheric reactions. 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 vary with fuel type, vehicle maintenance, and ambient conditions (Zielinska et al., 2004). In addition to direct emission, nitro-PAHs are formed from both gaseous

and heterogeneous reactions of PAHs with gaseous N-containing pollutants in the atmosphere; reactions of hydroxyl (OH) and nitrate (NO_3) radicals with PAHs are the major sources of nitro PAHs, (Arey et al., 1986, 1989, 1998; Perrini, 2005; Pitts, 1987; Sasaki et al., 1997; Zielinska et al., 1989; Bamford and Baker, 2003; Reisen and Arey, 2005, and references therein). Reactions involving OH radicals occur mainly during the day, while reactions with NO_3 radicals occur mainly during the night. 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, followed by reactions with OH and NO_3 radicals. The reaction mechanisms for forming and destroying nitro-PAHs in the atmosphere are described in Annex AX2.2.3.

In ambient particulate organic matter (POM), 2-nitrofluoranthene (2NF) is the dominant compound, followed by 1-nitropyrene (1NP) and 2-nitropyrene (2NP) (Arey et al., 1989; Bamford et al., 2003; Reisen and Arey, 2005; Zielinska et al., 1989). 2NF and 2NP are not directly emitted from primary combustion emissions, but are formed in the atmosphere. 1NP is generally regarded as a tracer of primary combustion sources, in particular, diesel exhaust. 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). More volatile nitro-PAHs, such as nitronapthalene (NN), remain mainly in the gas phase.

The concentrations for most nitro-PAHs found in ambient air are typically lower than 1 pg/m^3, except NNs, 1NP, and 2NF, which can be present at levels up to several tens or hundreds of pg/m^3. These levels are from ~2 to ~1000 times lower than those of 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 of <0.1 μm.

2.2.3 O_3 Formation

As mentioned earlier, NO and NO_2 are important precursors of O_3 formation. However, because O_3 changes in a nonlinear way with the concentrations of its precursor NO_X and VOCs, it is unlike many other secondarily formed atmospheric species whose rates of formation vary directly with emissions of their 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, and especially near busy streets and roadways and in power plant plumes, net destruction of O_3 is initiated with the excess NO found there. In the high NO_X regime, NO_2 scavenges OH radicals that would otherwise oxidize VOCs to produce peroxy radicals, which would in turn oxidize NO to NO_2. In the low NO_X regime, oxidation of VOCs generates excess free radicals; hence O_3 production is more nearly linear with NO_X. Between these two regimes, there is a transition zone in which O_3 shows only a weak dependence on [NO_X].

2.3 MEASUREMENT METHODS AND ASSOCIATED ISSUES

NO is routinely measured using the principle of gas-phase chemiluminescence induced by the reaction of NO with O_3 at low pressure. The Federal Reference Method (FRM) for NO_2 makes use of this technique of NO detection with a prerequisite step to reduce NO_2 to NO on the surface of a molybdenum oxide (MoO_X) substrate, heated to between 300 and 400 °C. Because the FRM monitor cannot detect NO_2 specifically, the concentration of NO_2 is determined as the difference between the air sample passed over the heated MoO_X substrate (the nitrogen oxides total) and the air sample that has not passed over the substrate (the NO).

Reduction of NO_2 to NO on the MoO_X substrate is not specific to NO_2; hence, the chemiluminescence analyzers are subject to unknown and varying interferences produced by the presence in the sample of the other oxidized N compounds, the NO_Z species shown in the outer box of Figure 2.2-1. This interference by NO_Z compounds has long been known (Fehsenfeld et al., 1987; Rodgers and Davis, 1989; U.S. Environmental Protection Agency, 1993, 2006; Crosley, 1996; Nunnermacker et al., 1998; Parrish and Fehsenfeld, 2000; McClenny et al., 2002; Dunlea et al., 2007; Steinbacher et al., 2007). These studies have relied on intercomparisons of measurements using the FRM and other techniques for measuring NO_2. The sensitivity of the FRM to potential interference by individual NO_Z compounds is variable and also depends in part on characteristics of individual monitors, such as the design of the instrument inlet, the temperature and composition of the reducing substrate, and on the interactions of atmospheric species with the reducing substrate.

Only recently have attempts been made to systematically quantify the magnitude and variability of the interference by NO_Z species in ambient measurements of NO_2. Dunlea et al. (2007) found an average of ~22% of ambient NO_2 (~9 to 50 parts per billion [ppb]) measured in

Mexico City was due to interference from NO_Z compounds. Comparable levels of NO_2 are found in many locations in the United States. Dunlea et al. (2007) compared NO_2 measured using the conventional chemiluminescent instrument with other (optical) techniques. The main sources of interference were HNO_3 and various $RONO_2$. Efficiency of conversion was estimated to be ~38% for HNO_3; for PAN, ~95% and ~ 95% for other $RONO_2$. Peak interference of up to 50% was found during afternoon hours and was associated with O_3 and NO_Z compounds such as HNO_3 and the alkyl and multifunctional alkyl nitrates.

In a study in rural Switzerland, Steinbacher et al. (2007) compared measurements of NO_2 continuously measured using a conventional NO_X monitor and measurements in which NO_2 was photolyzed to NO. They found the conventional technique using catalytic reduction (as in the FRM) overestimated the NO_2 measured using the photolytic technique on average by 10% during winter and 50% during summer.

Another approach to estimating the measurement interference is to use model calculations in conjunction with data for the efficiency of reduction of NO_Z species on the catalytic converters. Lamsal et al. (2007) used satellite data along with output from the GEOS-CHEM global chemical transport model (CTM) to derive seasonal correction factors across the United States. These factors range from <10% in winter in the East to >80%, with the highest values found during summer in relatively unpopulated areas. These correction factors are based on data collected during satellite overpass in early afternoon and, thus, are applicable only for that time of overpass. Calculations using EPA's Community Multiscale Air Quality (CMAQ) modeling system for the Mid-Atlantic region in a domain extending from Virginia to southern New Jersey were made at much higher spatial resolution than the GEOS-CHEM simulations (see http://www.mde.state.md.us/Programs/AirPrograms/air_planning/index.asp). The daily average interference for an episode during the summer of 2002 ranged from ~20% in Baltimore to ~80% in Madison, VA. Highest values were found during the afternoon, when photochemical activity is highest, and lowest values during the middle of the night. The model calculations showed episode averages of the NO_Z/NO_2 ratio ranging from 0.26 to 3.6 in rural Virginia; the highest ratios were in rural areas, and lowest were in urban centers closer to sources of fresh NO_X emissions. (The capabilities of three-dimensional CTMs such as GEOS-CHEM and CMAQ and issues associated with their use are presented in Annex AX2.7.) It appears that interference is likely to be on the order of 10% or less during most or all of the day during winter, but much

larger interference is likely to be found during summer in the afternoon. In general, the interference in the measurement of NO_2 is greater downwind of urban source areas and in relatively remote areas away from concentrated sources as compared to the level of interference at measurements in urban cores with fresh NO_X emissions.

2.3.1 Measurement Methods Specific to NO_2

There are approaches to measuring NO_2 not affected by the artifacts mentioned above. For example, NO_2 can be photolytically reduced to NO with an efficiency of ~70%, as used in the Steinbacher et al. (2007) study. This method requires additional development to ensure its cost effectiveness and reliability for extensive field deployment. The relatively low and variable conversion efficiency of this technique would necessitate more frequent calibration. Optical methods such as those using differential optical absorption spectroscopy (DOAS) or laser induced fluorescence (LIF) are also available, as described in Annex AX2.8. However, these particular methods are more expensive than either the FRM monitors or photolytic reduction technique and require specialized expertise to operate. Moreover, the DOAS obtains an area-integrated measurment rather than a point measurement. Cavity attenuated phase shift (CAPS) monitors are an alternative optical approach that is potentially less costly than DOAS or LIF (Kebabian et al., 2007). However, this technique is not highly specific to NO_2 and is subject to interference by other species absorbing at 440 nm, such as the 1,2-dicarbonyls. The extent of this interference and the potential of the CAPS technique for extensive field deployment have not been evaluated.

2.3.2 Measurement of Total Oxidized Nitrogen Species in the Atmosphere

Commercially available NO_X monitors have been converted to NO_Y monitors by moving the MoO_X convertor to interface directly with the sample inlet. Because of losses on inlet surfaces and differences in the efficiency of reduction of NO_Z compounds on the heated MoOx substrate, NO_X cannot be considered as a universal surrogate for NO_Y. However, in settings close to relatively high-concentration fresh emissions like those during urban rush hour, most of the NO_Y is present as NO_X. To the extent that all the major oxidized N species can be reduced quantitatively to NO, measurements of NO_Y should be more reliable than those of NO_X, particularly at typical ambient levels of NO_2. It is worth reiterating that with the current FRM monitors, the direct measurements of NO are the most specific. Measurements of total NO_Y

characterize the entire suite of oxidized N compounds to which humans are exposed. Reliable measurements of NO_Y and NO_2, especially at the low concentrations observed in many areas remote from sources are also crucial for evaluating the performance of three-dimensional, chemical transport models of oxidant and acid production in the atmosphere (described in Annex AX2.7).

2.4 AMBIENT CONCENTRATIONS OF NO_2 AND ASSOCIATED OXIDIZED NITROGEN SPECIES AND POLICY-RELEVANT BACKGROUND CONCENTRATIONS

This brief overview of ambient concentrations of NO_2 and associated oxidized N compounds in the United States provides estimates of Policy-Relevant Background (PRB) concentrations, i.e., background concentrations used to inform risk and policy assessments for the review of the NAAQS.

2.4.1 Ambient Concentrations

Figure 2.4-1 shows the distribution of monitoring sites for NO_2 across the United States. As can be seen from Figure 2.4-1, there are large areas of the United States for which data for ambient NO_2 are either not collected or are collected at very few sites. NO_2 is monitored mainly in several large urban areas. Few cities have more than two monitors and several large cities, including Seattle, WA, have none. Note that the number of NO_2 monitors has been decreasing in the United States as ambient average concentrations have fallen to a few tenths of the level of the NAAQS. There were, for example, 375 NO_2 monitors identified in mid 2006, but only 280 in November 2007.

Criteria for siting ambient monitors for NAAQS pollutants are given in the SLAMS / NAMS / PAMS Network Review Guidance (U.S. Environmental Protection Agency, 1998). As might be expected, criteria for siting monitors differ by pollutant. NO_2 monitors are meant to be representative of several scales: middle (several city blocks, 300 to 500 m), neighborhood (0.5 to 4 km), and urban (4 to 50 km). Middle- and neighborhood-scale monitors are used to determine highest concentrations and source impacts, while neighborhood- and urban-scale monitors are used for monitoring population exposures. As can be seen, there is considerable

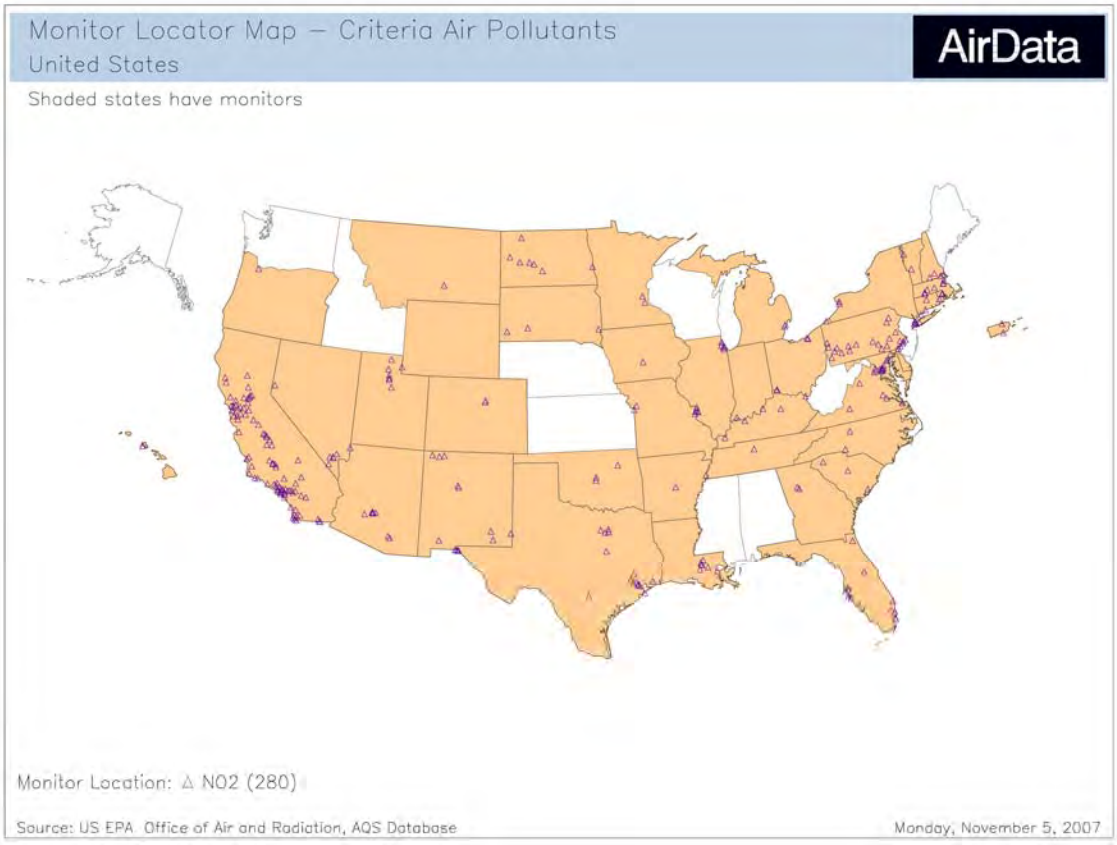

Figure 2.4-1. Location of ambient NO_2 monitors in the United States as of November 5, 2007. Shaded states have NO_2 monitors; unshaded states have none.

overlap between monitoring objectives and scales of representativeness. The distance of neighborhood- and urban-scale monitor inlets from roadways increases with traffic volume and can vary from 10 to 250 m away from roadways as traffic volume increases. Where the distance of an inlet to a road is shorter than the value in this range for the indicated traffic volume on that road, that monitor is classified as middle scale. Vertically, the inlets to NO_2 monitors can be set at a height from 2 to 15 m.

Figure 2.4-2 shows box plots of ambient concentrations of NO_2 measured at all monitoring sites located within Metropolitan Statistical Areas (MSAs) or urbanized areas in the United States from 2003 through 2005. As can be seen from Figure 2.4-2, mean [NO_2] are

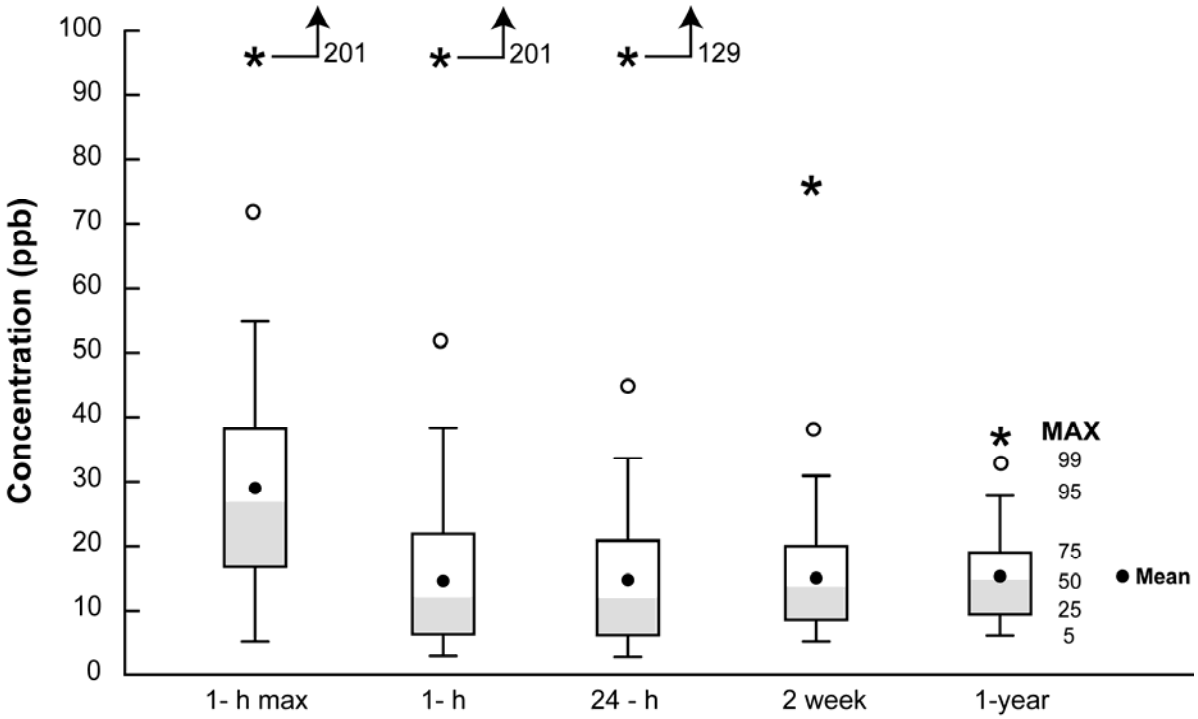

Figure 2.4-2. Ambient concentrations of NO_2 measured at all monitoring sites located within Metropolitan Statistical Areas in the United States from 2003 through 2005.

~15 ppb for averaging periods ranging from a day to a year, with an interquartile range (IQR) of 10 to 25 ppb. However, the average of the daily 1 h maximum [NO_2] over this 3-year period is ~30 ppb. These values are about twice as high as the 24-h average. The highest maximum hourly concentration (~200 ppb) found during the period of 2003 to 2005 was more than a factor of ten greater than the overall mean 24-h concentrations. The ratio of the 99th percentile concentration to the mean ranges from 2.1 for the 1-year averages to 3.5 for the 1-h averages.

Because ambient NO_2 monitoring data are so sparse across the United States (see Figure 2.4-1) and particularly so in rural areas, it would not be appropriate to use these data in constructing a map of NO_2 concentrations across the continental United States. The short τ of NO_2 with respect to conversion to NO_Z species and the concentrated nature of NO_2 emissions result in steep gradients and low concentrations away from major sources that are not adequately captured by the existing monitoring networks. Model predictions might be more useful for showing large-scale features in the distribution of NO_2 and could be used in conjunction with the

values shown in Figure 2.4-2 to provide a more complete picture of the variability of NO_2 across the United States. Monthly average NO_2 concentrations for July and December 2002 calculated using EPA's CMAQ model are shown in Figures 2.4-3a,b. (A description of the capabilities of CMAQ and other three-dimensional CTMs is given in Annex AX2.7) The high variation in NO_2 concentrations of at least a factor of 10 is apparent in these model estimates. As expected, the highest NO_2 concentrations are seen in large urban regions, such as the Northeast Corridor, and lowest values are found in sparsely populated regions located mainly in the West. NO_2 concentrations tend to be higher in December than in July.

2.4.2 Historical [NO_2]

Trends in NO_2 concentrations across the United States from 1980 to 2006 are shown in Figure 2.4-4. The white line shows the mean values and the upper and lower borders of the blue (shaded) areas represent the 10th and 90th percentile values. Information on trends at individual, local air monitoring sites can be found at www.epa.gov/airtrends/nitrogen.html.

Concentrations were substantially higher during earlier years in selected locations and contributed in those years to the "brown clouds" observed in many cities. Residents in Chattanooga, TN, for example, were exposed more than 30 years ago to high levels of NO_2 from a munitions plant (Shy and Love, 1980). Annual mean NO_2 concentrations there declined from ~102 ppb in 1968 to ~51 ppb in 1972. There was a strike at the munitions plant in 1973 and levels declined to ~32 ppb. With the implementation of control strategies, values dropped further. In 1988, the annual mean NO_2 concentration varied from ~20 ppb in Dallas, TX and Minneapolis, MN to 61 ppb in Los Angeles, CA. However, in New York City, the city with the second-highest annual mean concentration in the United States in 1988, the mean NO_2 concentration was 41 ppb.

In contrast to most urban areas in the United States, in other countires, NO_2 concentrations have increased. For example, annual mean NO_2 concentrations in central London increased during the 1980s from ~25 ppb in 1978 to ~40 ppb in 1989 at the background measurement site and from ~35 to ~45 ppb at the roadside site. Corresponding NO concentrations increased from ~20 ppb to ~40 ppb at the background site and from ~125 to ~185 ppb at the roadside site (Elsom, 1992).

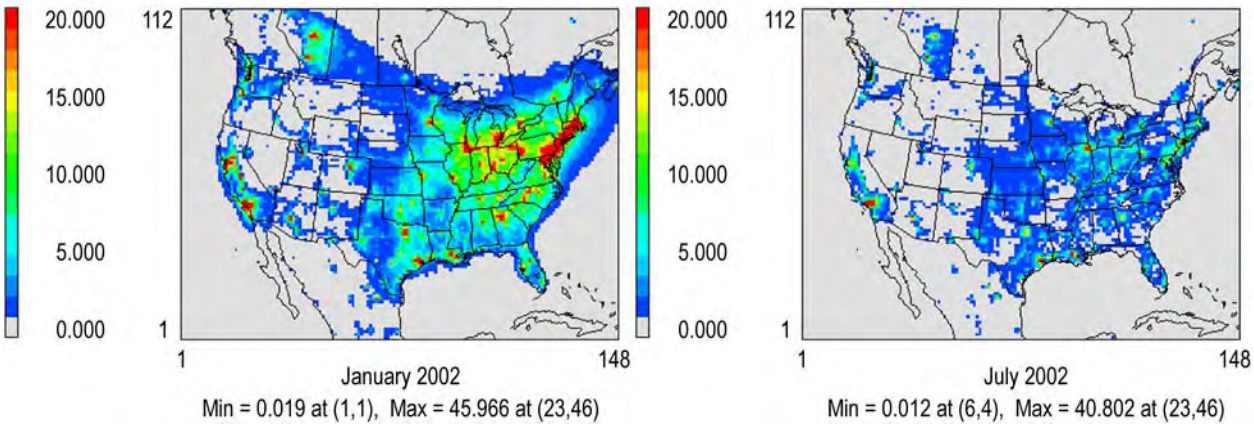

Figure 2.4-3a,b. Monthly average NO_2 concentrations for January 2002 (a) and July 2002 (b) calculated by CMAQ (36 × 36 km horizontal resolution).

2.4.3 Seasonal Variability in NO_2 at Urban Sites

The month-to-month variability in 24-h average NO_2 concentrations at two sites in Atlanta, GA is shown in Figure 2.4-5; variability at other individual sites in selected urban areas is shown in Annex 3, Figures AX3.4 to AX3.10. 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_2 concentrations in the data shown in Figures 2.4-5a-b. Higher concentrations are found during winter, consistent with the lowest mixing layer heights found during the year. Lower concentrations are found during summer, consistent with higher mixing layer heights and increased rates of photochemical oxidation of NO_2 to NO_Z. Note also the day-to-day variability in NO_2 concentration, which also tends to be larger during the winter. There appears to be a somewhat regular pattern for the other southern cities examined with their winter maxima and summer minima. Monthly maxima tend to be found from late winter to early spring in Chicago, IL, and New York, NY, with minima occurring from summer through the fall. However, in Los Angeles and Riverside, CA, monthly maxima tend to occur from autumn through early winter, with minima occurring from spring through early summer.

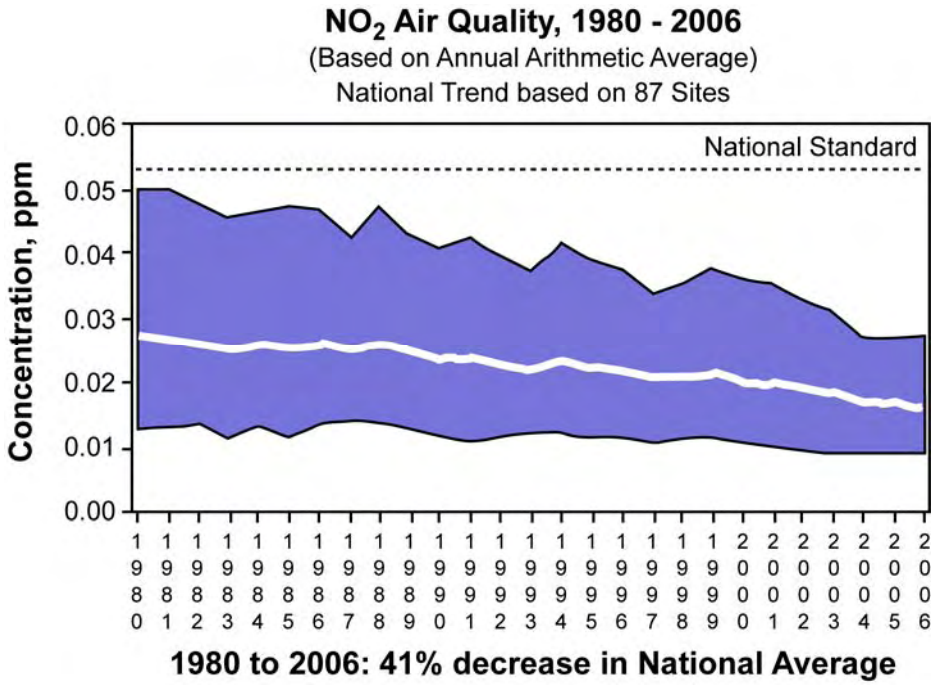

Figure 2.4-4. Nationwide trend in NO_2 concentrations. The white line shows the mean values, and the upper and lower borders of the blue (shaded) areas represent the 10th and 90th percentile values. Information on trends at individual, local air monitoring sites can be found at www.epa.gov/airtrends/nitrogen.html

Mean and peak NO_2 concentrations during winter can be up to a factor of two greater than those during the summer at sites in Los Angeles.

2.4.4 Diurnal Variability in NO_2 Concentrations

The diurnal variability in NO_2 concentrations at the same two sites in the Atlanta metropolitan area shown in Figures 2.4-5a,b is illustrated in Figures 2.4-6a-d. As can be seen from these figures, NO_2 typically exhibits daily maxima during the morning rush hours, although they can occur at other times of day. In addition, there are differences between weekdays and weekends. At both sites, NO_2 concentrations are generally lower and the diurnal cycles more compressed on weekends than on weekdays. The diurnal variability of NO_2 at these sites is typical of that observed at other urban sites. Monitor siting plays a role in determining diurnal

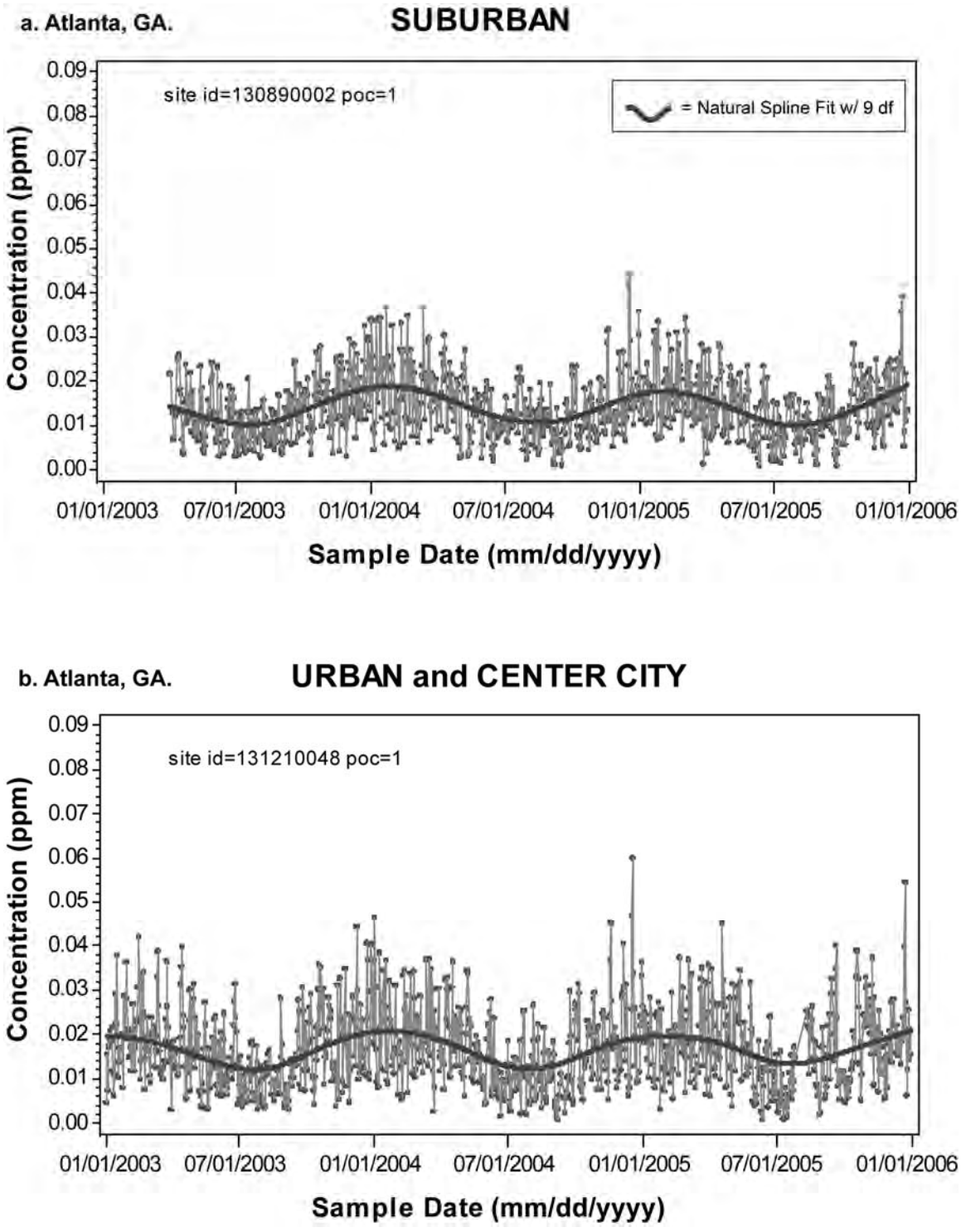

Figure 2.4-5a,b. Time series of 24-h average NO_2 concentrations at individual sites in Atlanta, GA from 2003 through 2005. A natural spline function (with 9 degrees of freedom) was fit and overlaid to the data (dark solid line).

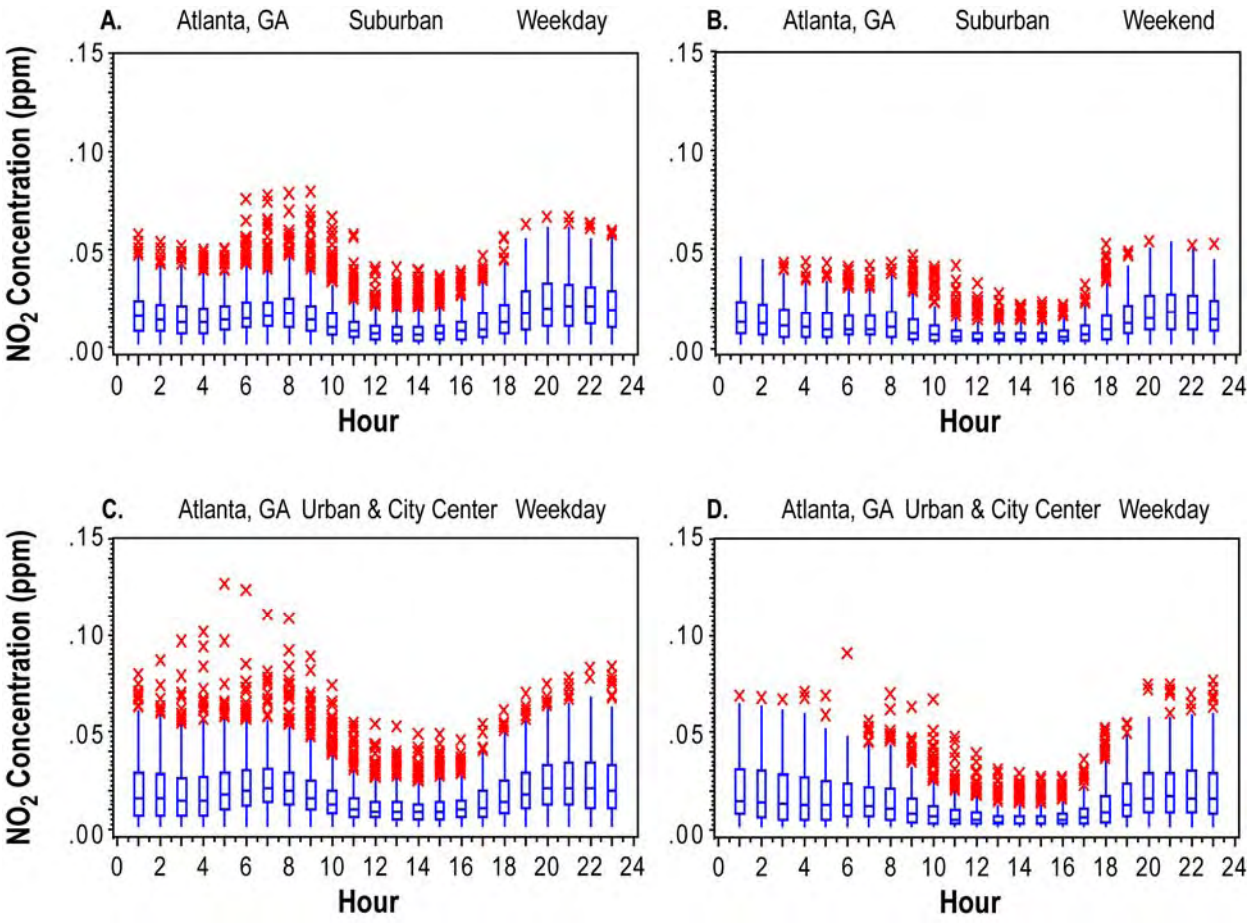

Figure 2.4-6a-d. Mean hourly NO_2 concentrations on weekdays and weekends measured at two sites in Atlanta, GA. A and B refer to a suburban site, and C and D refer to a site classified as urban and city center.

variability in the sense that monitors located farther from traffic will measure lower concentrations and show a flatter overall distribution of data compared to monitors located closer to traffic.

2.4.5 Concentrations of NO_Z Species

Data for concentrations of NO_Z species in urban areas in the United States are sparse. The most comprehensive set of data for any NO_Z species was obtained for HNO_3 as part of the Children's Health Study for which gas-phase HNO_3 was measured at 12 sites in southern California from 1994 through 2001 (Alcorn et al., 2004). Levels ranged from <1 ppb to >10 ppb in general, with the highest HNO_3 concentrations and the highest ratio of HNO_3/NO_2 found

downwind from central Los Angeles in the San Bernadino Valley during summer, as one would expect for this more oxidized N product.

Measurements of HONO in urban areas are very limited; however, data from Stutz et al. (2004) and Wang and Lu (2006) indicate that levels of HONO are <1 ppb even under heavily polluted conditions, with the highest levels found during the night and just after dawn and the lowest values found in the afternoon. Several field studies conducted at ground level (Hayden et al., 2003, in rural Quebec; Williams et al.,1987, near Boulder, CO) and aircraft flights (Singh et al., 2007, over eastern North America) have also found much higher [NO_Z] than [NO_X] in relatively unpolluted rural air.

2.4.6 Policy Relevant Background Concentrations of NO_2

Background NO_2 concentrations used for purposes of informing decisions about NAAQS are referred to as PRB concentrations. PRB concentrations are those that would occur in the United States in the absence of anthropogenic emissions in continental North America (defined here as the United States, Canada, and Mexico). PRB concentrations include contributions from natural sources everywhere in the world and from anthropogenic sources outside these three countries. Background levels defined in this way 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. These levels may also be used in quantitative risk assessments of human health and environmental effects.

Contributors to PRB concentrations include natural emissions of NO, NO_2, and 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. Biogenic emissions from agricultural activities, such as emissions of NO from fertilized soils, are not considered to be contributing to the formation of PRB concentrations. Discussions of the sources and estimates of emissions are given in Annex AX2.6.2.

2.4.6.1 Analysis of Policy Relevant Background Contribution to NO_2 Concentrations over the United States

The MOZART-2 global model of tropospheric chemistry (Horowitz et al., 2003) is used to estimate the PRB contribution to [NO_2]. 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 the U.S. National Oceanic and Atmospheric Administration's National Center for Environmental Prediction (NOAA NCEP) meteorological fields using 2001 data and using 2000 emissions from the International Institute for Applied Systems Analysis (IIASA). The model was run at a resolution of 1.9° × 1.9° with 28 sigma levels in the vertical dimension with both gas-phase and aerosol chemistry.

Figure 2.4-7 shows the annual mean [NO_2] 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 total surface [NO_2] are often >5 ppb, PRB is <300 parts per trillion (ppt) over most of the continental United States and <100 ppt in the eastern United States. The distribution of PRB (middle panel of Figure 2.4-7) largely reflects the distribution of soil NO emissions, with some local increases like those in western Montana due to biomass burning. In the northeastern United States, where present-day [NO_2] are highest, PRB contributes <1% to the total. Thus, it appears that PRB levels of NO_2 are much smaller than observed levels.

2.5 EXPOSURE ISSUES

2.5.1 Introduction

Human exposure to an airborne pollutant consists of contact between the human and the pollutant at a specific concentration for a specified period of time. People spend various amounts of time in different microenvironments characterized by different pollutant concentrations. The integrated exposure of a person to a given pollutant is the sum of the exposures over all time intervals for all microenvironments in which the individual spends time. Figure 2.5-1 represents a composite average of activity patterns across all age groups in the United States based on data collected in the National Human Activity Pattern Survey (NHAPS). The demographic distribution of the respondents was designed to be similar to that of overall

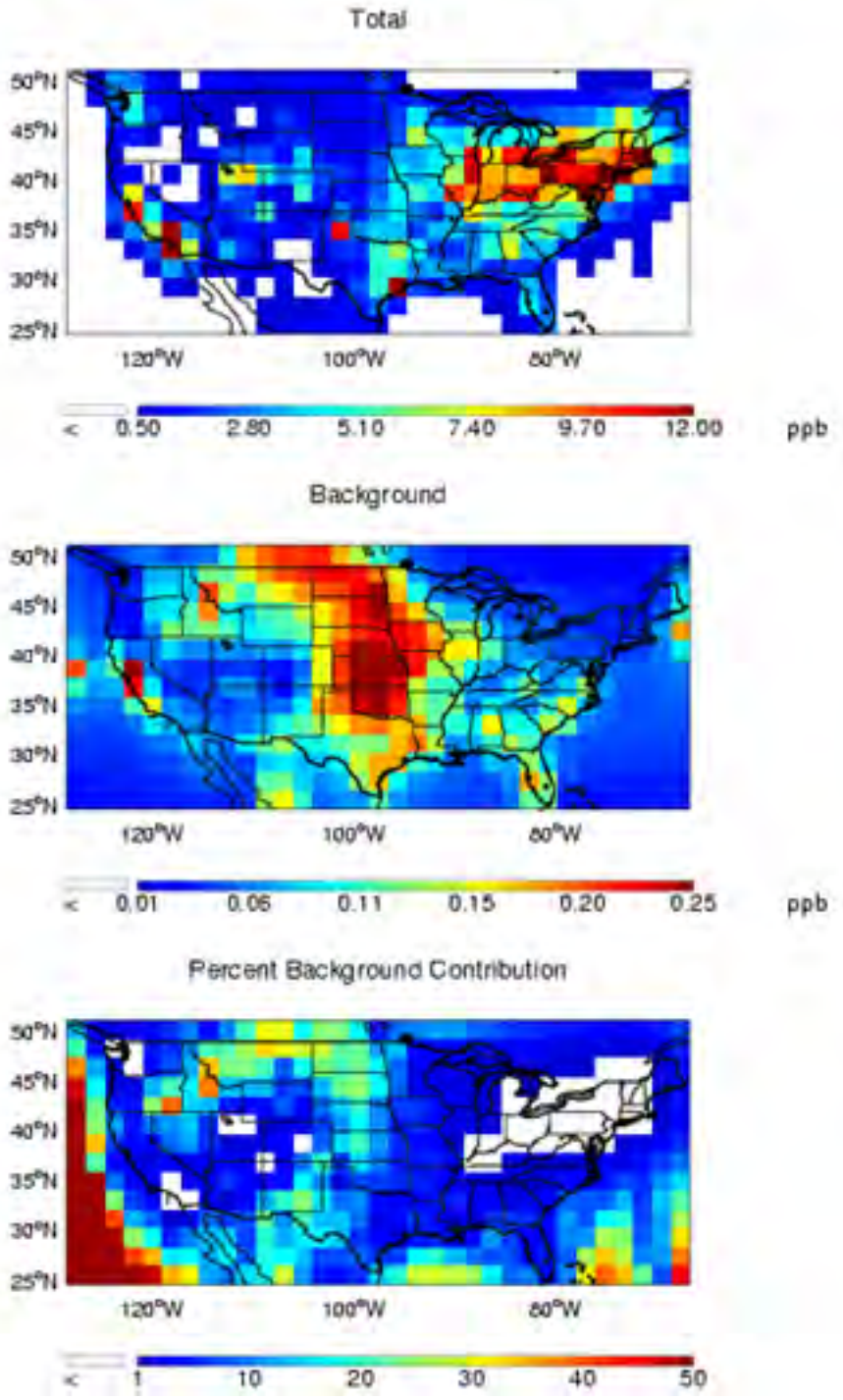

Figure 2.4-7. Upper panel: Annual mean NO_2 concentrations (in ppb) in the United States. Middle panel: Annual mean PRB concentrations (in ppb) for NO_2 in the United States. These simulations were made using the MOZART-2 global, chemical transport model. The lower panel shows PRB concentrations expressed as a percentage of total NO_2 concentrations shown in the upper panel. See text in Annex AX2.9 for details.

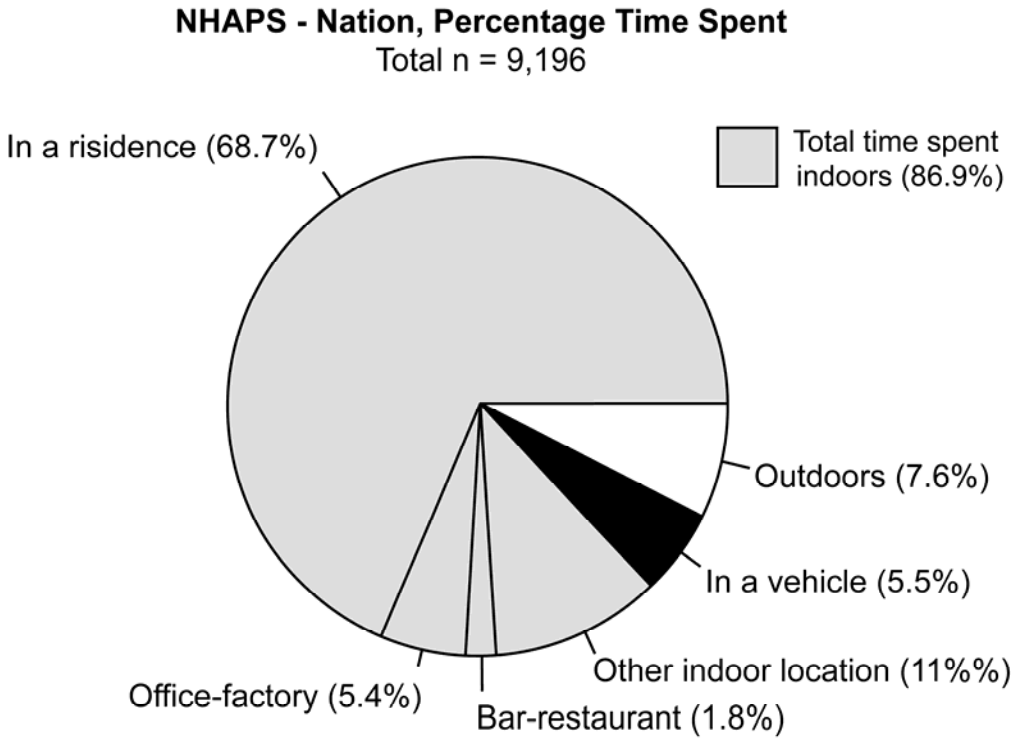

Figure 2.5-1. Percentage of time persons spend in different environments in the United States.

Source: Klepeis et al. (2001).

U.S. Census data. Different cohorts, e.g., the elderly, young and middle-aged working adults, and children exhibit different activity patterns.[2]

The personal exposure concentration to a pollutant, such as NO_2, can be represented by the following equation:

$$E_t = \sum_{i=1}^{n} C_i f_i \qquad (2.5\text{-}1)$$

where E_t is the time-weighted average personal exposure concentration over a certain period of time, n is the total number of microenvironments that a person encounters, f_i is the (fractional)

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

time spent in the i^{th} microenvironment, and C_i is the average concentration in the i^{th} microenvironment during the time fraction, f_i. The exposure a person experiences can be characterized as an instantaneous exposure, a peak exposure such as might occur during cooking, an average exposure, or an integrated exposure over all environments a person encounters. These distinctions are important because health effects caused by long-term, low-level exposures may differ from those caused by short-term, peak exposures.

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

$$E_T = E_a + E_{na} = \{y_o + \sum_i y_i \, [P_i a_i/(a_i + k_i)] \, \} C_a + E_{na} = \{y_o + \sum_i y_i F_{inf_i}\} C_a + E_{na} \quad (2.5\text{-}2)$$

subject to the constraint,

$$y_o + \sum_i y_i = 1 \quad (2.5\text{-}3)$$

where E_a is the person's exposure to pollutants of ambient origin; E_{na} is the person's exposure to pollutants that are not of ambient origin; y_o is the fraction of time people spend outdoors and y_i is the fraction of time they spend in microenvironment i; F_{inf_i}, P_i, a_i, and k_i are the infiltration factor, penetration coefficient, air exchange rate, and decay rate for microenvironment i. In the case where microenvironmental exposures occur mainly in one microenvironment, Equation 2.5-2 may be approximated by Equation 2.5-4:

$$E_T = E_a + E_{na} = \{y + (1-y)[Pa/(a + k)]\} C_a + E_{na} = \alpha C_a + E_{na} \quad (2.5\text{-}4)$$

where y is the fraction of time persons spend outdoors, and α is the ratio of a person's exposure to a pollutant of ambient origin to the pollutant's ambient concentration. Other symbols have the same definitions in Equation 2.5-2 and 2.5-3. If microenvironmental concentrations are considered, then Equation 2.5-4 can be recast as:

$$C_{me} = C_a + C_{nona} = [Pa/(a+k)] C_a + S/[V(a+k)] \quad (2.5\text{-}5)$$

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

Equation 2.5-4. In this equation, it is assumed that microenvironments do not exchange air with each other, but only with the ambient environment.

Microenvironments in which people are exposed to air pollutants such as NO_2 typically include residential indoor environments, other indoor locations, near-traffic outdoor environments, other outdoor locations, and in vehicles, as shown in Figure 2.5-1. Indoor combustion sources such as gas stoves and space heaters need to be considered when evaluating exposures to NO_2. Exposure misclassification may result when total human exposure is not disaggregated between various microenvironments, and this may obscure the true relationship between ambient air pollutant exposure and health outcome.

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

- The ambient concentration, C_a
- The air exchange rate, a_i
- The pollutant specific penetration coefficient, P_i
- The pollutant specific decay rate, k_i
- The fraction of time an individual spends in the microenvironment, y_i

These factors are in turn affected by the following exposure factors (see Annex AX3.5):

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

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

Time-activity diaries, completed by study participants, are often used in exposure models and assessments. The EPA's National Exposure Research Laboratory (NERL) has consolidated the majority of the most significant human activity databases into one comprehensive database

the Consolidated Human Activity Database (CHAD). Eleven different human activity pattern studies were evaluated to obtain over 22,000 person-days of 24-h human activities in CHAD (McCurdy et al., 2000). These data can be useful in assembling population cohorts to be used in exposure modeling and analysis.

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

In practice, it is extremely difficult to characterize community exposure by individual personal exposure. Instead, the distribution of personal exposure in a community, or the population exposure, is characterized by extrapolating measurements of personal exposure using various techniques or by stochastic, deterministic, or hybrid exposure modeling approaches such as APEX, SHEDS, and MENTOR (see AX3.7 for a description of modeling methods). Variations in community-level personal exposures are determined by cross-community variations in ambient pollutant concentrations and the physical and exposure factors mentioned above. These factors also determine the strength of the association between population exposure to NO_2 of ambient origin and ambient NO_2 concentrations.

Of major concern is the ability of NO_2 as measured by ambient monitors to serve as a reliable indicator of personal exposure to NO_2 of ambient origin. The key question is what errors are associated with using NO_2 measured by ambient monitors as a surrogate for personal exposure to ambient NO_2 and/or its oxidation products in epidemiologic studies. There are three aspects of this issue: (1) ambient and personal sampling issues; (2) the spatial variability of ambient NO_2 concentrations; (3) the associations between ambient concentrations and personal exposures as influenced by exposure factors, e.g., proximity to traffic, indoor sources and sinks, and the time people spend indoors and outdoors. These issues are treated individually in the following subsections.

2.5.2 Personal Sampling of NO_2

Personal exposures in human exposure and panel studies of NO_2 health effects are monitored by passive samplers. Their performance is evaluated by comparison to the chemiluminescence monitoring method. Some form of evaluation is crucial for determining measurement errors associated with exposure estimates. However, measurements of NO_2 are subject to artifacts both at the ambient level and at the personal level. As discussed in Section 2.3, measurements of ambient NO_2 are subject to an unknown and variable level of interference caused by other NO_Y compounds, in particular HNO_3, PANs, HONO, and $RONO_2$.

The most widely used passive samplers are Palmes tubes (Palmes et al., 1976), Yanagisawa badges (Yanagisawa and Nishimura, 1982), Ogawa samplers (Ogawa and Company, http://www.ogawausa.com), and radial diffusive samplers (Cocheo et al., 1996). The methodology and application of Palmes tubes and Yanagisawa badges were described in the last AQCD for Oxides of Nitrogen (U.S. Environmental Protection Agency, 1993). Descriptions of other commercialized samplers is in Annex AX3.3. These samplers do not use a pump to bring air into contact with the sampling substrate; rather, they rely on diffusion or small scale turbulence to transport NO_2 to a sorbent (Krupa and Legge, 2000). The sorbent can be either physically sorptive (e.g., active carbon) or chemisorptive (e.g., triethanolamine [TEA], KI, sodium arsenite [$NaAsO_2$]); passive samplers for NO_2 are chemisorptive, i.e., a reagent coated on a support (e.g., metal mesh, filter) chemically reacts with and captures 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.

The effect of environmental conditions (e.g., temperature, wind speed, humidity) on the performance of passive samplers is a concern when used for residential indoor, outdoor, and personal exposure studies because of sampling rates that deviate from the ideal and can vary throughout the sampling period. Overall, field test results of passive sampler performance are not consistent, and they have not been extensively studied over a wide range of concentrations, wind velocities, temperatures, and relative humidities (Varshney and Singh, 2003).

Another concern with the passive sampling method is interference from other pollutants. Interference from other NO_Y species can contribute to NO_2 exposure monitoring errors, but the kinetics and stoichiometry of interferent compound reactions have not been well established, especially for passive samplers; an NO_2 monitoring plan to use tube-type TEA passive samplers

has been proposed and implemented throughout Great Britain, for example. However, in a comparison of NO_2 concentrations measured outdoors by the passive samplers with those measured by the chemiluminescence method, NO_2 concentrations measured by the passive samplers were ~30% higher than those measured by the chemiluminescence method (Campbell et al., 1994).

Although most studies indicate that passive samplers have very good precision, generally within 5% (Gair et al., 1991; Gair and Penkett, 1995; Plaisance et al., 2004; Kirby et al., 2001), field evaluation studies showed that the overall average NO_2 concentrations calculated from diffusion tube measurements were likely to be within 10% of chemiluminescent measurement data (Bush et al., 2001; Mukerjee et al., 2004). As mentioned before, TEA-based diffusive sampling methods tend to overestimate NO_2 concentrations in field comparisons with chemiluminescence analyzers (Campbell et al., 1994). This could be due in part to chemical reactions between O_3 and NO occurring in the diffusion tube or to differential sensitivity to other forms of NO_Y, such as HONO, PAN, and HNO_3, between the passive samplers and the chemiluminescence analyzers (Gair et al., 1991). Due to spatial and temporal variability of NO and NO_2 concentrations, especially at roadsides where NO concentrations are relatively high and when sufficient O_3 is present for interconversion between the species, the lack of agreement between the passive samplers and ambient monitors can represent differences in sampler response (Heal et al., 1999; Cox, 2003).

A third aspect of passive sampler performance is that, compared with ambient chemiluminescence monitors, passive samplers give relatively longer time-averaged concentrations (from days to weeks). Consequently, diffusive samplers including those used for NO_2 monitoring provide integrated but not high time-resolution concentration measurements. Hourly fluctuations in NO_2 concentrations may be important to the evaluation of exposure-health effects relationships, and continuous monitors, such as the chemiluminescent monitors, remain the only approach for estimating short-term, peak exposures.

2.5.3 Spatial Variability in NO_2 Concentrations

2.5.3.1 Variability of NO_2 Concentrations Across Ambient Monitoring Sites

Summary statistics for the spatial variability in several urban areas across the United States are shown in Table 2.5-1. Data were obtained from EPA's Air Quality System (AQS).

TABLE 2.5-1. SPATIAL VARIABILITY OF NO_2 IN SELECTED UNITED STATES URBAN AREAS

	Mean Concentration (ppb)	r	P90 (ppb)	COD
New York, NY (5)	29 (25–37)	0.77–0.90	7–19	0.08–0.23
Atlanta, GA (5)	11 (5–16)	0.22–0.89	7–24	0.15–0.59
Chicago, IL (7)	22 (6–30)	−0.05–0.83	10–39	0.13–0.66
Houston, TX (7)	13 (7–18)	0.31–0.80	6–20	0.13–0.47
Los Angeles, CA (14)	25 (14–33)	0.01–0.90	8–32	0.08–0.51
Riverside, CA (9)	21 (5–32)	0.03–0.84	10–40	0.14–0.70

These areas were chosen because they are the major urban areas with at least five monitors operating from 2003 to 2005. Values in parentheses below the city name indicate the number of monitoring sites in that particular city. The second column shows the 3-year mean concentration across all sites and the range in these means at individual sites. Metrics for characterizing spatial variability include the use of Pearson correlation coefficients (r; column 3), the 90th percentile (P90) of the absolute difference in concentrations (column 4), and coefficient of divergence (COD; column 5).

These three metrics are calculated based on measurements of daily average concentrations at individual site pairs. The COD provides an indication of the variability across the monitoring sites in each city and is defined in Equation 2.5-6, as follows

$$COD_{jk} = \sqrt{\frac{1}{p}\sum_{i=1}^{p}\left(\frac{X_{ij} - X_{ik}}{X_{ij} + X_{ik}}\right)^2} \qquad (2.5\text{-}6)$$

where X_{ij} and X_{ik} represent observed concentrations averaged over some measurement averaging period (hourly, daily, etc.), for measurement period i at site j and site k, and p is the number of

observations. A COD of 0 indicates there are no differences between concentrations at paired sites (spatial homogeneity), while a COD approaching 1 indicates extreme spatial heterogeneity. The same statistics shown in Table 2.5-1 have been used to describe the spatial variability of $PM_{2.5}$ (U.S. Environmental Protection Agency, 2004; Pinto et al., 2004) and O_3 (U.S. Environmental Protection Agency, 2006).

As can be seen from Table 2.5-1, mean concentrations at individual sites vary by factors of 1.5 to 6 in the MSAs examined. The sites in New York City tend to be the most highly correlated and show the highest mean levels, reflecting their proximity to traffic, as evidenced by the highest mean concentration of all the entries. They are also located closer to each other than sites in western cities. Correlations between individual site pairs range from slightly negative to highly positive in all of the urban areas except for New York City. However, correlation coefficients are not sufficient for describing spatial variability, as daily average concentrations at two sites may be highly correlated but show differences in levels. Thus, the range in mean concentrations is given. Even in New York City, the spread in mean concentrations is ~40% of the citywide mean (12 ppb / 29 ppb). The relative spread in 3-year mean concentrations is larger in the other urban areas shown in Table 2.5-1. As might be expected, the 90th percentile concentration ranges are even larger than the ranges in the means.

Because of relative sparseness in data coverage for NO_2, spatial variability in all cities considered for $PM_{2.5}$ and O_3 could not be considered here. Thus, the number of cities included here is much smaller than for either O_3 (24 urban areas) or $PM_{2.5}$ (27 urban areas). Even in those cities where there were monitors for all three pollutants, data may not have been collected at the same locations, and even if they were, there will be different responses to local sources. For example, concentrations of NO_2 collected near traffic will be highest in an urban area, but concentrations of O_3 will tend to be lowest there because of titration by NO forming NO_2. However, some general observations can still be made. Mean concentrations of NO_2 at individual monitoring sites are not as highly variable as for O_3 but are more highly variable than $PM_{2.5}$. Lower bounds on intersite correlation coefficients for $PM_{2.5}$ and for O_3 tend to be much higher than for NO_2 in the same areas shown in Table 2.5-1. CODs for $PM_{2.5}$ are much lower than for O_3, whereas CODs for NO_2 tend to be the largest among these three pollutants.

2.5.3.2 Small-Scale Horizontal Variability

NO_2 monitors are sited for compliance with air quality standards rather than for capturing small-scale variability in NO_2 concentrations near sources such as roadway traffic. Significant gradients in NO_2 concentrations near roadways have been observed in several studies, and NO_2 concentrations have been found to be correlated (or inversely correlated) with distance from roadway, traffic volume, season, road length, open space, and population density (Gilbert et al., 2007; Bignal et al., 2007; Singer et al., 2004; Cape et al., 2004; Pleijel et al., 2004; Maruo et al., 2003; Roorda-Knape et al., 1998, 1999; Monn et al., 1997; Gauderman et al., 2005). A sample gradient is shown in Figure 2.5-2.

Singer et al. (2004) found a strong gradient for concentrations downwind of freeways within the first 230 m. Gilbert et al (2007) found that associations remained robust when sites within 200 m of roadways were removed from the analysis, indicating that traffic influences concentrations as far as 2000 to 3000 m from roadways. Small-scale spatial variations in NO_2 concentrations are more pronounced during spring and summer seasons due to meteorology and increased photochemical activity (Monn, 2001).

Localized effects of roadway sources lead to variability in NO_2 concentrations that is not captured by the regulatory monitoring network. This variation affects population-level exposure estimates and adds exposure error to time-series epidemiologic studies relying on ambient concentrations as indicators of exposure. Elevated concentrations near roadways also increase exposure of vulnerable populations residing, working, or attending school in the vicinity.

2.5.3.3 Small-Scale Vertical Variability

Inlets to instruments for monitoring gas-phase criteria pollutants can be located from 3 to 15 m above ground level (Code of Federal Regulations, 2002). Depending on the pollutant, there can be a positive, negative, or no vertical gradient from the surface to the monitor inlet. Positive gradients (i.e., concentrations increase with height) result when pollutants are formed over large areas by atmospheric photochemical reactions (i.e., secondary pollutants such as O_3) and destroyed by deposition to the surface or by reaction with pollutants emitted near the surface. Pollutants that are emitted by sources at or just above ground level show negative vertical gradients. Pollutants with area sources (widely dispersed surface sources) and that have minimal deposition velocities show little or no vertical gradient. Restrepo et al. (2004) compared data for

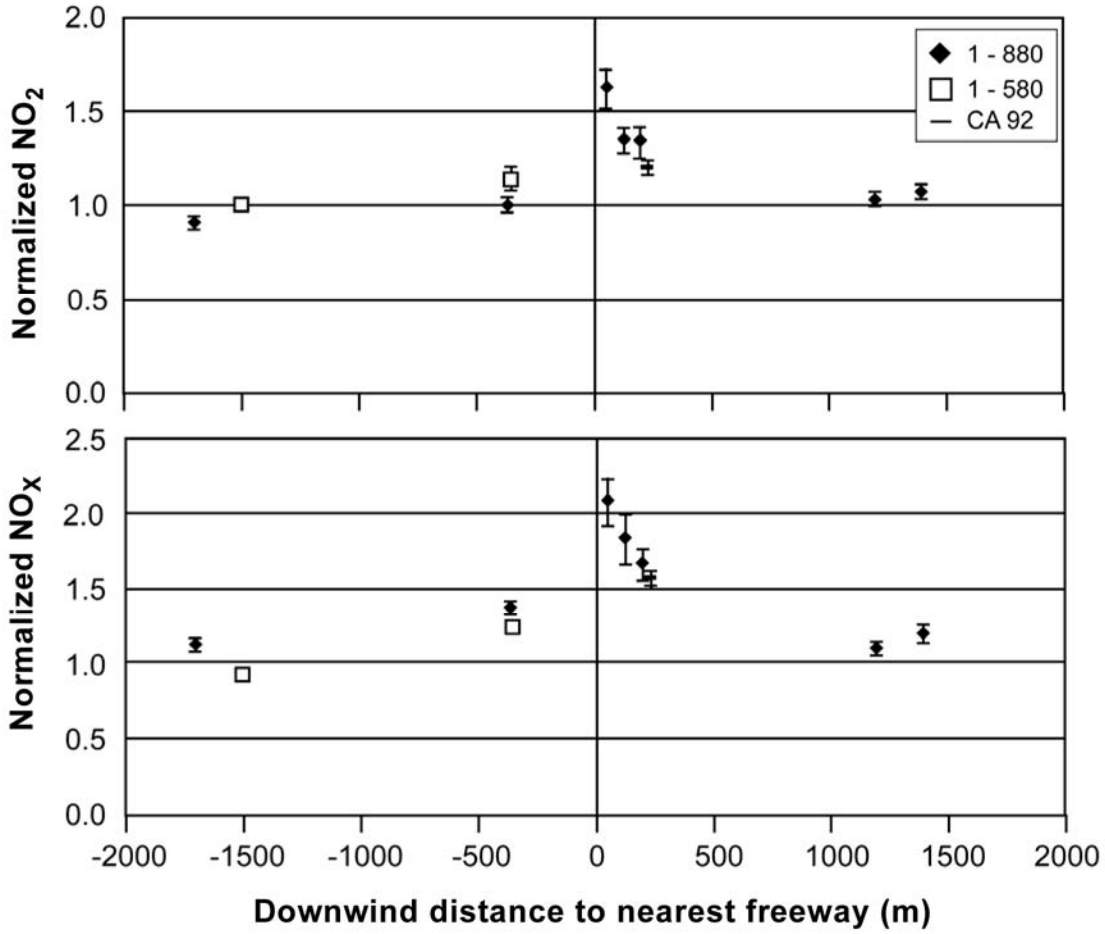

Figure 2.5-2. NO_2 and NO_X concentrations normalized to ambient values, plotted as a function of downwind distance from the freeway. Symbols indicate freeway closest to each monitor.

Source: Singer et al. (2004).

criteria pollutants collected at fixed monitoring sites at 15 m above the surface on a school rooftop to those measured by a van whose inlet was 4 m above the surface at monitoring sites in the South Bronx during two sampling periods in November and December 2001. They found that CO, SO_2, and NO_2 showed negative vertical gradients, whereas O_3 showed a positive vertical gradient and $PM_{2.5}$ showed no significant vertical gradient. As shown in Figure 2.5-3, NO_2 mixing ratios obtained at 4 m (mean ~74 ppb) were about a factor of 2.5 higher than at 15 m (mean ~30 ppb). Because tail pipe emissions occur at lower heights, NO_2 values could have

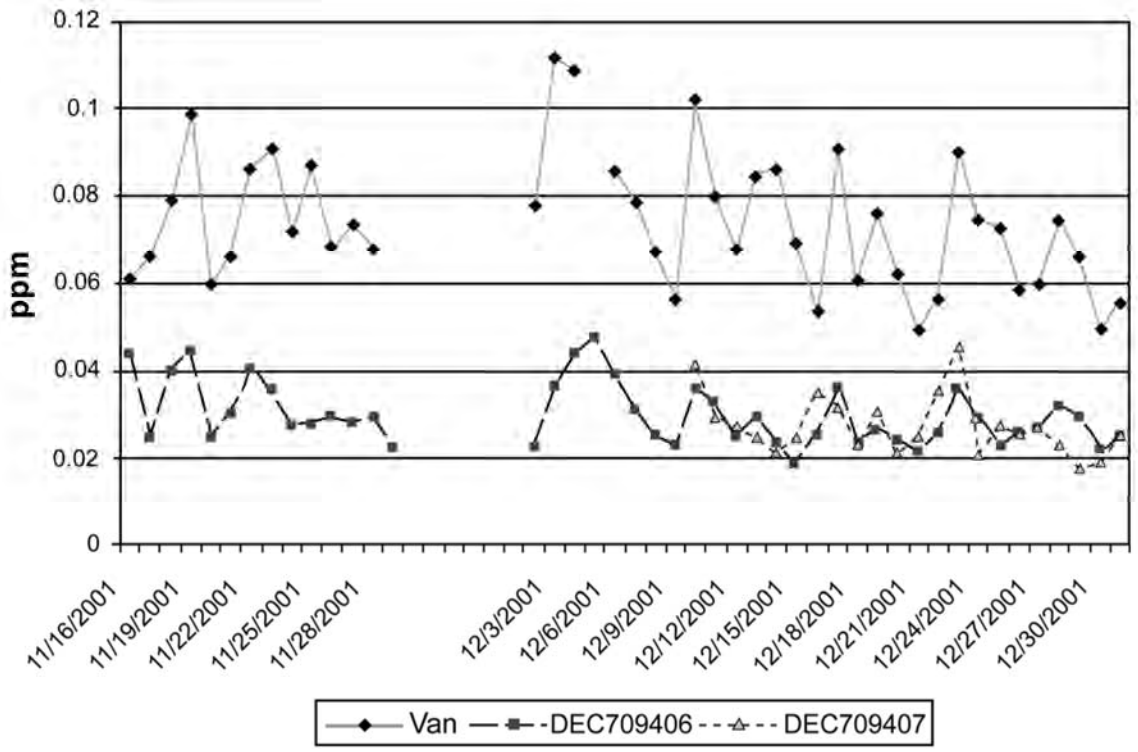

Figure 2.5-3. NO_2 concentrations measured at 4 m (Van) and at 15 m at NY Department of Environmental Conservation ambient monitoring sites (DEC709406 and DEC709407).

Source: Restrepo et al. (2004).

been much higher nearer to the surface and the underestimation of NO_2 values by monitoring at 15 m even larger. Restrepo et al. (2004) noted that the use of the NO_2 data obtained by the stationary monitors underestimates human exposures to NO_2 in the South Bronx. This situation is not unique to the South Bronx and could arise in other large urban areas in the United States with similar settings.

The magnitude of the vertical gradient of NO_2 in "street canyons" depends strongly on the configuration of the buildings forming the canyons and the meteorological conditions; in particular, static stability in the lower planetary boundary layer, local wind direction and speed, and differential solar heating all affect turbulence in street canyons. These meteorological factors also help determine the relative importance of turbulence induced by traffic, in addition to traffic volume and speed. Descriptions of the effects for many of these factors are available only from complex numerical models such as large eddy simulations and very fine grid

resolution computational fluid dynamics models. Thus the quantitative extrapolation of these results to other situations even at the same location at different times is highly problematic.

Weak associations might be found between concentrations at ambient monitors and other outdoor locations and between concentrations in indoor microenvironments and personal exposures in part because of the spatial (horizontal and vertical) variability in NO_2. This variability is itself location- and time-dependent, and can lead to either over- or underestimates of exposure, depending on the siting of monitors and location of the exposed population. NO_2 ambient monitors may be less representative of community or personal exposures than are ambient monitors for O_3 or $PM_{2.5}$ for their respective exposures. This conclusion is based on a comparison of metrics of spatial variability for O_3 or $PM_{2.5}$ used in the last AQCD for Particulate Matter (U.S. Environmental Protection Agency, 2004) and AQCD for O_3 (U.S. Environmental Protection Agency, 2006), indicating generally lower correlations and larger relative spreads in concentrations than for O_3 or $PM_{2.5}$. As mentioned earlier, there are far fewer monitors for NO_2 than for O_3 or $PM_{2.5}$, making estimation of the spatial variability in NO_2 levels more difficult than for O_3 or $PM_{2.5}$.

2.5.4 Traffic as a Source of NO_2

Lee et al. (2000) reported that NO_2 concentration in heavy traffic (~60 ppb) can be more than double that of the residential outdoor level (~26 ppb) in North America. Westerdahl et al. (2005) reported on-road NO_2 concentrations in Los Angeles ranging from 40 to 70 ppb on freeways, compared to 20 to 40 ppb on residential or arterial roads. NO_X concentrations measured at the Caldecott Tunnel in San Francisco in 1999 (Kean et al., 2001) were approximately 7-fold higher at the tunnel exit than at the entrance (1500 ppb versus 200 ppb). People in traffic can potentially experience high concentrations of NO_2 as a result of the high air exchange rates in vehicles. Park et al. (1998) observed that the air exchange in cars varied from 1 to 3 times per hour, with windows closed and no mechanical ventilation, to 36 to 47 times per h, with windows closed and the fan set on fresh air. These results imply that the NO_2 concentration inside a vehicle could rapidly approach the level outside the vehicle during commuting.

While driving, concentrations for personal exposure in a vehicle cabin could be substantially higher than ambient concentrations measured nearby. Sabin et al. (2005) reported

that NO_2 concentrations in the cabins of school buses in Los Angeles ranged from 24 to 120 ppb, which were typically factors of 2 to 3 (max, 5) higher than at ambient monitors in the area. Lewné et al. (2006) reported work hour exposures to NO_2 for taxi drivers (25.1 ppb), bus drivers (31.4 ppb), and truck drivers (35.6 ppb). These levels were 1.8, 2.7, and 2.8 times the ambient concentrations. Riediker et al. (2003) studied the exposure to NO_2 inside patrol cars. The authors found that the mean and maximum NO_2 concentrations in a patrol car were 41.7 ppb and 548.5 ppb compared to 30.4 ppb and 69.5 ppb for the ambient sites. These studies suggest that people in traffic can be exposed to much higher levels of NO_2 than are measured at ambient monitoring sites. Due to high peak exposures while driving, total personal exposure could be underestimated if exposures while commuting are not considered, and sometimes exposure in traffic can dominate personal exposure to NO_2 (Lee et al., 2000; Son et al., 2004). Variations in traffic-related exposure could be attributed to time spent in traffic, type of vehicle, ventilation in the vehicle, and distance from major roads (Sabin et al., 2005; Son et al., 2004; Chan et al., 1999). Sabin et al. (2005) reported that the intrusion of the vehicle's own exhaust into the passenger cabin is another NO_2 source contributing to personal exposure while commuting, but that the fraction of air inside the cabin from a vehicle's own exhaust was small, ranging from 0.02 to 0.28% and increasing with the age of the vehicle (CARB, 2007a,b).

Distance to major roadways could be another factor affecting indoor and outdoor NO_2 concentration and personal NO_2 exposure. Many studies show that outdoor NO_2 levels are strongly associated with distance from major roads (i.e., the closer to a major road, the higher the NO_2 concentration) (Gilbert et al., 2005; Roorda-Knape et al., 1998; Lal and Patil, 2001; Kodama et al., 2002; Gonzales et al., 2005; Cotterill and Kingham, 1997; Nakai et al., 1995). Meteorological factors (wind direction and wind speed) and traffic density are also important in interpreting measured NO_2 concentrations (Gilbert et al., 2005; Roorda-Knape et al., 1998; Rotko et al., 2001; Alm et al., 1998; Singer et al., 2004; Nakai et al., 1995). For example, Roorda-Knape et al. (1998) reported that NO_2 concentrations in classrooms were significantly correlated with car and total traffic density ($r = 0.68$), percentage of time downwind ($r = 0.88$), and distance of the school from the roadway ($r = -0.83$). Singer et al. (2004) reported results of the East Bay Children's Respiratory Health Study. The authors found that NO_2 concentrations increased with decreasing downwind distance for school and neighborhood sites within 350 m

downwind of a freeway, and schools located upwind or far downwind of freeways were generally indistinguishable from one another or by regional pollution levels.

Personal exposure is associated with traffic density and proximity to traffic, although personal exposure is also influenced by indoor sources. Alm et al. (1998) reported that weekly average NO_2 exposures (geometric mean) were higher ($p = 0.0001$) for children living in the downtown area of Helsinki (13.8 ppb) than in the suburban area (9.1 ppb). Within the urban area of Helsinki, Rotko et al. (2001) observed that the NO_2 exposure was significantly associated with traffic volume near homes. The average exposure level of 138 subjects having low or moderate traffic near their homes was 12.3 ppb, while the level was 15.8 ppb for the 38 subjects having high traffic volume near home. Gauvin et al. (2001) reported that the ratio of traffic density to distance from a roadway was one of the significant predictors of personal exposure in Grenoble, Toulouse, and Paris. After controlling for indoor source impacts on personal exposure, Kodama et al. (2002) and Nakai et al. (1995) observed that personal exposure decreased with increasing distance from residence to major road.

Although traffic is a major source of ambient NO_2, industrial point sources are also contributors to ambient NO_2. Nerriere et al. (2005) measured personal exposures to $PM_{2.5}$, PM with an aerodynamic diamter of $\leq$10 μm (PM_{10}), and NO_2 in traffic-dominated, urban background, and industrial settings in four French cities (Paris, Grenoble, Rouen, and Strasbourg). Ambient concentrations and personal exposures for NO_2 were generally highest in the traffic-dominated sector. It should be remembered that there can be high traffic emissions (including shipping traffic) in industrial zones, such as in the Ship Channel in Houston, TX, and in the Port of Los Angeles, CA. In rural areas where traffic is sparse, other sources could dominate. Martin et al. (2003) found that pulses of NO_2 released from agricultural areas occur after rainfall. Other rural contributors to NO_2 include wildfires and residential wood burning.

2.5.5 Indoor Sources and Sinks of NO_2 and Associated Pollutants

Indoor sources and indoor air chemistry of NO_2 are important, because they influence the indoor NO_2 concentrations to which humans are exposed and contribute to total personal exposures. These indoor source and sink terms must be characterized in an exposure assessment if the fraction of a person's exposure to NO_2 of ambient origin is to be determined.

Penetration of outdoor NO_2 and indoor combustion in various forms are the major sources of NO_2 to indoor environments, e.g., homes, schools, restaurants, theaters. 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). Contributions to indoor NO_2 from the reaction of NO in exhaled breath with O_3 could potentially be important in certain circumstances (see AX3.4.2 for sample calculations). 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, 2007a). Mechanisms by which NO_X is produced in the combustion zones of indoor sources were reviewed in the last AQCD for Oxides of Nitrogen (U.S. Environmental Protection Agency, 1993). It should be noted that indoor sources can affect ambient NO_2 levels, particularly in areas in which atmospheric mixing is limited, such as in valleys.

Combustion of fossil and biomass fuels is the major indoor source of nitrogen oxides. Combustion of fossil fuels occurs in appliances used for cooking, heating, and drying clothes, e.g., coal stoves, oil furnaces, kerosene space heaters. Motor vehicles and various types of generators in structures attached to living areas also contribute NO_2 to indoor environments. Indoor sources of NO_2 from combustion of biomass include wood-burning fireplaces and wood stoves and tobacco.

Many studies have noted the importance of gas cooking appliances as sources of NO_2 emissions. Depending on geographical location, season, other sources of NO_2, 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; Garcia-Algar et al., 2003; Raw et al., 2004; Leaderer et al., 1986). Gas cooking appliances remain significantly associated with indoor NO_2 concentrations after adjusting for several factors that influence exposures, including season, type of community, socioeconomic status, use of extractor fans, household smoking, and type of heating (Garcia-Algar et al., 2004; Garrett, 1999). Homes with gas appliances with pilot lights emit more NO_2, resulting in NO_2 concentrations ~10 ppb higher than in homes with gas appliances with electronic ignition (Spengler et al., 1994; Lee et al., 1998).

Secondary heating appliances are additional sources of NO_2 in indoor environments, particularly if the appliances are unvented or inadequately vented. As heating costs increase, the use of these secondary heating appliances tends to increase. Gas heaters, particularly when unvented or inadequately vented, produce high levels of indoor NO_2 (Kodoma et al., 2002). Results summarized by Brauer et al. (2007) 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. On the other hand, mean concentrations of NO_2 were all <10 ppb in a study of Canadian homes with vented gas and oil furnaces and electric baseboard heaters (Weichenthal et al., 2007), suggesting that these are not likely to be significant sources of NO_2 to indoor environments.

Table 2.5-2 shows average concentrations of NO_2 in homes while combustion sources (mainly gas fired) were in operation. Averaging periods ranged from minutes to hours in the studies shown. Table 2.5-3 shows 24-h to 2-week-long average concentrations of NO_2 in homes with primarily gas combustion sources.

As can be seen from Tables 2.5-2 and 2.5-3, average concentrations while appliances are in operation tend to be much higher than longer-term averages. As Triche et al. (2005) indicated, the 90th percentile concentrations can be substantially greater than the medians, even for 2-week samples. This finding illustrates the high variability of indoor NO_2 found among homes, reflecting differences in ventilation of emissions from sources, air exchange rates, the size of rooms, etc. The concentrations for short averaging periods listed in Table 2.5-2 correspond to ~10 to 30 ppb on a 24-h average basis. As can be seen from inspection of Table 2.5-3, these sources would contribute significantly to the longer-term averages reported if operated daily on a similar schedule. This implies measurements made with long averaging periods may not capture the nature of the diurnal pattern of indoor concentrations of NO_2 in homes with strong indoor sources, a problem that becomes more evident as ambient NO_2 levels decrease with more efficient controls on outdoor sources.

The emissions of NO_2 from burning biomass fuels indoors have not been characterized as extensively as those from burning gas. A main conclusion from the 1993 AQCD for Oxides of Nitrogen was that properly vented wood stoves and fireplaces would make only minor contributions to indoor NO_2 levels, and several studies have concluded that using wood-burning

TABLE 2.5-2. NO_2 CONCENTRATION NEAR INDOOR SOURCES: SHORT-TERM AVERAGES

Avg 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 gas range for 2 h, 20 min; 7 h TWA.	Fortmann et al. (2001)
400 kitchen living room bedroom	673 bedroom	Self-cleaning gas range. Avg's are over the entire cycle.	Fortmann et al. (2001)
90 (low setting) 350 (med setting) 360 (high setting)	N/R	Natural gas unvented fireplace, 0.5 h TWA in main living area of house (177 m^3).	Dutton et al. (2001)
N/R	1000	Room concentration with kerosene heater operating for 46 min.	Girman et al. (1982)
N/R	1500	Room concentration with gas heater operating for 10 min.	Girman et al. (1982)
180 to 650	N/R	Calculated steady-state concentration from specific unvented gas space heaters[1] operating in a 1400 ft^2 house, 1.0 h^{-1} for air exchange rate.	Girman et al. (1982)

N/R = not reported
TWA = time-weighted avg
[1] Unvented appliances are not permitted in many areas including California.

appliances does not increase indoor NO_2 concentrations (Levesque et al., 2001; Triche et al., 2005).

Other indoor combustion sources of NO_2 are candle burning and smoking. 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 (data not reported). 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, 1998b; Monn et al., 1998; Cyrys et al., 2000; Lee et al., 2000; García Algar, 2004), whereas others have not (e.g., Hackney et al., 1992; Kawamoto et al., 1993).

TABLE 2.5-3. NO_2 CONCENTRATION NEAR INDOOR SOURCES: LONG-TERM AVERAGES

Avg Concentration (ppb)	Comment	Reference
30 to 33	Gas stoves with pilot lights	Lee et al. (1998)
22	Gas stoves without pilot lights	
6 to 11	Electric ranges	
	Study conducted in 517 homes in Boston	
	Values represent 2-wk avgs	
55 (Median)	Gas space heaters	Triche et al. (2005)
41 (90th percentile)	No indoor combustion sources	
80 (90th percentile)	Fireplaces	
84 (90th percentile)	Kerosene heaters	
147 (90th percentile)	Gas space heaters	
52 (90th percentile)	Wood stoves	
	All values represent 2-wk avgs in living rooms	
18	Bedrooms	Zipprich et al. (2002)
19	Living rooms	
15	Outdoors	
	Almost all homes had gas stoves	
	Values represent 2-wk avgs	

2.5.5.1 Indoor Air Chemistry

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 O_3 or peroxy radicals, while NO_2 is removed by gas-phase reactions with O_3 and assorted free radicals and by surface-promoted hydrolysis and reduction reactions. The concentration of indoor NO_2 also affects the decomposition of PAN.

Indoors, NO can be oxidized to NO_2 by reacting with O_3 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 (Sawar et al., 2002a,b; Nazaroff and Weschler, 2004; Carslaw, 2007).

At an indoor O_3 concentration of 10 ppb and an indoor NO concentration that is significantly smaller than that of O_3, the half-life of NO is 2.5 min (using kinetic data contained in Jet Propulsion Laboratory, 2006). 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 (Weschler et al., 1994).

NO_2 reacts with O_3 to produce nitrate radicals (NO_3). To date, there have been no indoor measurements of the concentration of NO_3 radicals in indoor settings. Modeling studies by Nazaroff and Cass (1986), Weschler et al. (1992), Sarwar et al. (2002b), and Carslaw (2007) estimate indoor NO_3 radical concentrations in the range of 0.01 to 5 ppt, depending on the indoor levels of O_3 and NO_2. Once formed, NO_3 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 NO_3 radical may be a more important indoor oxidant than either O_3 or the OH radical (Nazaroff and Weschler, 2004; Wayne et al., 1991). Thus, NO_3 radicals and the products of NO_3 radical chemistry could contribute to uncertainty in NO_2 exposure-health outcome 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 onto indoor surfaces to produce mono- and dinitro-PAHs. 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 various indoor surfaces was reemitted as NO. Weschler and Shields (1996) found that the amount of NO_2 removed by charcoal filters used in buildings were almost equally matched by the amount of NO subsequently emitted by the same filters.

NO_2 can also be converted to HONO by reactions in indoor air. As noted above, HONO occurs in the atmosphere mainly through multiphase processes involving NO_2. HONO has been observed to form on surfaces containing partially oxidized aromatic structures (Stemmler et al., 2006) and on soot particles (Ammann et al., 1998). Indoors, surface-to-volume ratios are much larger than they are outdoors, and the surface-mediated hydrolysis of NO_2 is a major indoor source of HONO (Brauer et al., 1990, 1993; Febo and Perrino, 1991; Spicer et al., 1993; Spengler et al., 1993; Wainman et al., 2001; Lee et al., 2002). Lee et al. (2002) reported average indoor HONO levels were ~6 times higher than outdoor levels (4.6 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 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 increases with relative humidity. Spicer et al. (1993) reported that an equilibrium between adsorption of HONO from the gas range (or other indoor combustion sources) and HONO produced by surface reactions determines the relative importance of these processes in producing HONO in indoor air.

A person's total exposure to NO_2 cannot be estimated based on consideration of the estimates of emissions given in emissions inventories. Indoor and other microenvironmental sources and a person's activity pattern must be considered in determining the sources that exert the largest influence on a person's total exposure to NO_2. As examples, exposures in vehicle cabins while commuting to/from school or work, or exposures associated with operation of off-road engines (e.g., lawn and garden or construction equipment), could be larger than integrated 24-h exposures due to infiltration of outdoor air into a home.

2.5.6 Relationships of Personal Exposures to Ambient Concentrations

2.5.6.1 Associations among Ambient and Outdoor Concentrations and Personal Exposures

Results of studies reporting associations between ambient concentrations and personal exposures are shown in Table 2.5-4A and results of studies reporting associations between outdoor concentrations and personal exposures are shown in Table 2.5-4B. Study designs (longitudinal, daily-averaged, and pooled) used in of each of these studies are also briefly summarized in Tables 2.5-4A and B.

Figures 2.5-4a and b explicitly summarize the correlation coefficients between personal exposures and ambient concentrations for different populations with a forest plot for U.S. studies and European studies, respectively. Correlation coefficients shown in Figures 2.5-4a and b were transformed from the coefficients in Table 2.5-4A. Fisher's Z transform was used, ($Z = 0.5\ln((1 + r)/(1 - r))$), where r is the originally reported and Z is the transformed correlation coefficient (Fisher, 1925). The variance of Z is expressed as $1/(n-3)$, where n is the number of observations defined by the one of the following three presentations. (1) When the correlation coefficient was based on the average across subjects of personal exposures, n was the number of sampling days. (2) When the partial correlation coefficient was used in the original study, n was the total number of sampling by individual observations minus the sum of three and the number of covariates.

Study	Location	Season	Sampling Time	N	Fisher's Z-Transform	%<LOD**
Linn et al. (1996)	Southern California	All	1 day	107	Day's avg of children	NR*
Sarnat et al. (2001)	Baltimore	Summer	1 day	217	Individual	NR
Sarnat et al. (2001)	Baltimore	Winter	1 day	484	Individual	NR
Sarnat et al. (2005)	Boston	Summer	1 day	298	Individual	10.2
Sarnat et al. (2005)	Boston	Winter	1 day	341	Individual	2.2
Sarnat et al. (2006)	Steubenville	Summer	1 day	183	Individual	64.0
Sarnat et al. (2006)	Steubenville	Fall	1 day	228	Individual	15.0
Kim et al. (2006)	Toronto	All	1 day	15	Avg of individual correlations	NR

* Note: NR = Not reported
** Percent of data below detection limit
N = Number of observations

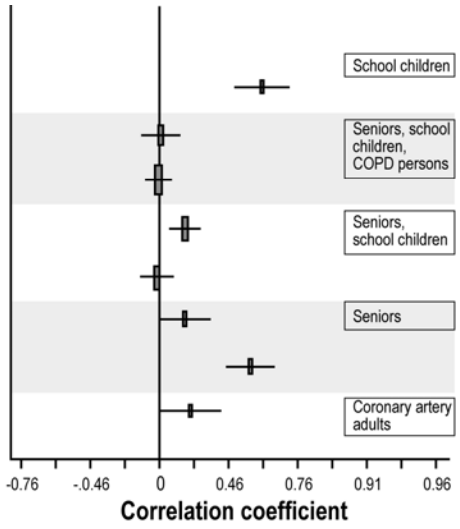

Figure 2.5-4a. Distribution of correlation coefficients (U.S. studies) between personal NO_2 exposure and ambient NO_2 concentrations based on Fisher's Z transform.

Study	Location	Season	Other	Sampling Time	N	Fisher's Z-Transform	%<LOD**
Alm et al. (1998)	Helsinki	Spring	Downtown	1 week	379	Avg of each of 4 daycares	NR*
Alm et al. (1998)	Helsinki	Spring	Suburban	1 week	469	Avg of each of 4 daycares	NR
Alm et al. (1998)	Helsinki	Winter	Downtown	1 week	279	Avg of each of 4 daycares	NR
Alm et al. (1998)	Helsinki	Winter	Suburban	1 week	195	Avg of each of 4 daycares	NR
Alm et al. (1998)	Helsinki	All	Downtown, Electric stove	1 week	NR	Avg of each of 4 daycares	NR
Alm et al. (1998)	Helsinki	All	Suburban, Gas stove	1 week	NR	Avg of each of 4 daycares	NR
Alm et al. (1998)	Helsinki	All	Downtown, Electric stove	1 week	NR	Avg of each of 4 daycares	NR
Alm et al. (1998)	Helsinki	All	Suburban, Nonsmoking	1 week	NR	Avg of each of 4 daycares	NR
Alm et al. (1998)	Helsinki	All	Downtown, Smoking	1 week	NR	Avg of each of 4 daycares	NR
Alm et al. (1998)	Helsinki	All	Suburban, Nonsmoking	1 week	NR	Avg of each of 4 daycares	NR
Alm et al. (1998)	Helsinki	All	Downtown, Smoking	1 week	NR	Avg of each of 4 daycares	NR
Alm et al. (1998)	Helsinki	All		1 week	NR	Avg of each of 4 daycares	NR
Gauvin et al. (2001)	Grenoble	All		2 days	24	Avg of children	NR
Gauvin et al. (2001)	Toulouse	All		2 days	32	Avg of children	NR
Gauvin et al. (2001)	Paris	All		2 days	23	Avg of children	NR
Liard et al. (1999)	Paris	Summer		4 days	NR	Partial corr adj for gas cook	~0%
Linaker et al. (2000)	Southampton	All		1 week	50	Individual	16.7
Liard et al. (1999)	Paris	Summer		4 days	NR	Partial corr adj for 5 covariat	~0%
Piechocki-Minguy et al.	Lille	All		2 days	44	Avg of adults	NR
Piechocki-Minguy et al.	Lille	Summer	No major indoor sources	2 days	31	Avg of adults	NR

* Note: NR = Not reported
** Percent of data below detection limit
N = Number of observations

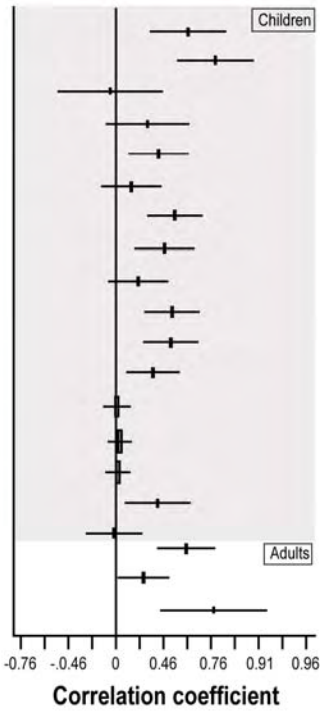

Figure 2.5-4b. Distribution of correlation coefficients (European studies) between personal NO_2 exposure and ambient NO_2 concentrations based on Fisher's Z transform.

(3) When the mean of individual correlations was used, the standard error was the standard deviation of the correlations divided by the square root of the number of subjects minus one.

As shown in Table 2.5-4A and Figures 2.5-4a and b longitudinal and pooled correlations between personal exposure and ambient NO_2 concentrations varied considerably among studies and study subjects. Most studies report longitudinal correlation coefficients ranging from weak to moderate but statistically significant, indicating that an individual's activities may have a significant effect on personal exposure. Meanwhile, pooled studies usually report poor correlation coefficients between personal exposures and ambient concentrations.

Two main aspects of these analyses are discussed below: (1) factors affecting the strength of the association between personal NO_2 exposure and ambient NO_2 concentrations, and (2) the meanings of the correlation coefficients in the context of exposure assessments in epidemiologic studies.

The strength of the association between personal exposures and ambient and/or outdoor concentrations for a population is determined by variations in indoor or other local sources, air exchange rate, penetration, and decay rate of NO_2 in different microenvironments and the time people spend in different microenvironments with different NO_2 concentrations.

Home ventilation is an important factor modifying the personal-ambient relationships; one would expect to observe the strongest associations for subjects spending time indoors with open windows. Alm et al. (1998) and Kodama et al. (2002) observed the association between personal exposure and ambient concentration became stronger during the summer than the winter. However, Sarnat et al. (2006) reported that R^2 values decreased from 0.34 for a low-ventilation population to 0.16 for a high-ventilation population in the summer, and from 0.47 for a low-ventilation population to 0.34 for a high-ventilation population in the fall. The mixed results remind us that the association between personal exposures and ambient concentrations is complex and determined by many factors.

Local and indoor sources also affect the strength of the association between personal exposures and ambient concentrations. Alm et al. (1998) found that the association between personal exposure and outdoor concentration was stronger than the correlation between personal exposure and central site concentration. However, Kim et al. (2006) found that the association was not improved using the ambient sampler closest to a home. The lack of improvement in the strength of the association by choosing the closest ambient monitor could be in part due to the

differences in the small-scale spatial heterogeneity of NO_2 in different urban areas, as shown in Table 2.5-1. Higher personal to ambient correlations have been found for subjects living in rural areas and lower correlations for subjects living in urban areas (Rojas-Bracho et al., 2002; Alm et al., 1998). Spengler et al. (1994) also observed that the relationship between personal exposure and outdoor concentration was highest in areas with lower ambient NO_2 levels ($R^2 = 0.47$) and lowest in areas with higher ambient NO_2 levels ($R^2 = 0.33$). This might reflect the highly heterogeneous distribution or the effect of local sources of NO_2 in an urban area.

Associations between ambient concentrations and personal exposures for the studies examined for NO_2 were not stratified by the presence of indoor sources except in Alm et al. (1998), Sarnat et al. (2006), Linaker et al. (2000) and Piechocki-Minguy et al. (2006). When there is little or no contribution from indoor sources, ambient concentrations primarily determine exposure; however, if there are indoor sources, the importance of outdoor levels in determining personal exposures decreases. The association between ambient concentrations and personal exposures strengthens after controlling for indoor sources. Raaschou-Nielsen et al. (1997), Spengler et al. (1994), and Gauvin et al. (2001) reported that R^2 values increased by 10 to 40% after controlling for indoor sources, such as gas appliances and ETS (see Table 2.5-4A).

The strength of the associations between personal exposures and ambient concentrations could also be affected by the quality of the data collected during the exposure studies. There are at least five aspects associated with the quality of the data: method precision, method accuracy (compared with FRM), percent of data above method detection limits (based on field blanks), completeness of the data collection and sample size, and soundness of the quality assurance/quality control procedures. Unfortunately, not all studies reported the five aspects of the data quality issue. Although data imprecisions and inaccuracies are less than 10% in most studies (Section 2.5.2), the fraction of data below the detection limit might be a concern for some studies (see e.g., Sarnat et al., 2000, 2001, 2006). Correlation coefficients would be biased low if data used in their calculation are below detection limits. Sampling interferences (caused by some NO_Y compounds and other gas species) associated with both ambient (see Section 2.3) and personal sampling (see Section 2.5.2) could also affect data quality. Therefore, caution must be exercised when interpreting the results in Table 2.5-4A.

Another factor that can have a substantial effect on the value of the resultant correlation coefficient is the exposure study design as presented in Table 2.5-4A. Not only does the

exposure study design affect the strength of the association between personal exposures and ambient concentrations, but it also determines the meaning of the correlation coefficients in the context of exposure assessment in epidemiologic studies. The correlation coefficient between personal exposures and ambient concentrations has different meanings for different study designs.

There are three types of correlations generated from different study designs as listed in Table 2.5-4A: longitudinal, "pooled," and daily-average correlations (U.S. Environmental Protection Agency, 2004). Longitudinal correlations are calculated when data from a study includes measurements over multiple days for each subject (longitudinal study design). Longitudinal correlations describe the temporal relationship between daily personal NO_2 exposure or microenvironment concentration and daily ambient NO_2 concentration for the same subject. The longitudinal correlation coefficient can differ between subjects. The distribution of correlations across a population could be obtained with this type of data (e.g. Linn et al., 1996; Alm et al., 1998; Linaker et al., 2000; Kim et al., 2006; Sarnat et al., 2000, 2001, 2005, 2006).

Pooled correlations are calculated when a study involves one or only a few measurements per subject and when different subjects are studied on subsequent days. Pooled correlations combine individual-subject/individual-day data for the calculation of correlations. Pooled correlations describe the relationship between daily personal NO_2 exposure and daily ambient NO_2 concentration across all subjects in the study (e.g., Piechocki-Minguy et al., 2006).

Daily-average correlations are calculated by averaging exposure across subjects for each day. Daily-average correlations then describe the relationship between the daily average exposure and daily ambient NO_2 concentration (e.g., Liard et al., 1999; Gauvin et al., 2001; U.S. Environmental Protection Agency, 2004).

In the context of determining the effects of ambient pollutants on human health, the association between the ambient component of personal exposures and ambient concentrations is more relevant than the association between personal total exposures (ambient component + nonambient component) and ambient concentrations. As described in Equations 2.5-2 and 2.5-4, personal total exposure can be decomposed into two parts; an ambient and a nonambient component. Usually, the ambient component of personal exposure is not directly measureable, but it can be estimated by exposure models, or the personal total exposure can be regarded as the personal exposure of ambient origin if there are no indoor or nonambient sources. Personal

exposures were clearly stratified by indoor sources in only four studies among the studies examined for NO_2 (Alm et al., 1998; Sarnat et al., 2006; Piechocki-Minguy et al., 2006; Linaker et al., 2000) and only two studies (Alm et al., 1998; Piechocki-Minguy et al., 2006) compared the association between personal total exposures and ambient concentrations and the association between the ambient component of personal exposures and ambient concentrations. A stronger association was observed between the ambient component of personal exposures and the ambient concentrations (Alm et al., 1998; Piechocki-Minguy et al., 2006). It is expected that the association between ambient concentrations and the ambient component of personal exposures would be stronger than the association between ambient concentrations and personal total exposures as long as the ambient and nonambient component of personal total exposure are independent. The correlation coefficients between personal ambient NO_2 exposures and ambient NO_2 concentrations in different types of exposure studies are relevant to different types of epidemiologic studies.

A longitudinal correlation coefficient between the ambient component of personal exposures and ambient concentrations is relevant to the panel epidemiologic study design. In Table 2.5-4A, most longitudinal studies reported the association between personal total exposures and ambient concentrations for each subject; for some subjects the associations were strong and for some subjects the associations were weak. The weak personal and ambient associations do not necessarily mean that ambient concentrations are not a good surrogate for personal exposures, because the weak associations could have resulted from the day-to-day variation in the nonambient component of total personal exposure. The type of correlation analysis can have a substantial effect on the value of the resultant correlation coefficient. Mage et al. (1999) showed that very low correlations between personal exposure and ambient concentrations could be obtained when people with very different nonambient exposures are pooled, even though their individual longitudinal correlations are high. Most studies (employing either cross-sectional or longitudinal study designs) examined in the current review showed that ambient NO_2 is associated with personal NO_2 exposure; however, the strength of the association varied considerably.

The association between community average exposures (ambient component) and ambient concentrations is more directly relevant to community time-series and long-term cohort epidemiologic studies, in which ambient concentrations are used as a surrogate for community

average exposure to NO_2 of ambient origin. However, exposure of the population to NO_2 of ambient origin has not been reported in all the studies examined. The following two European studies reported the associations between population total exposures and ambient or outdoor concentrations of NO_2. Liard et al. (1999) conducted an exposure study of 55 office workers and 39 children in Paris. Measurements were made during three 4-day-long measurement periods for each group. Apart from occasional lapses, data from the same participants were collected during each period. Liard et al. (1999) correlated the five-panel average personal exposures with ambient monitoring data and derived a longitudinal Spearman correlation coefficient of 1 ($p < 0.001$). R^2 between ambient monitors and individual personal exposures for adults was 0.41, and for children, R^2 was 0.17. Four-day averaging periods were chosen in this study to overcome limitations imposed by the levels of detection of the personal samplers. The results show that passive samplers could be used to measure personal exposures in panel studies over multiday periods and lend some credence to the use of stationary monitors as proxies for personal exposures to ambient NO_2.

Monn et al. (1998) and Monn (2001) reported personal NO_2 exposures obtained in the SAPALDIA study (eight study centers in Switzerland). In each study location, personal exposures for NO_2 were measured simultaneously for all participants; in addition, residential outdoor concentrations were measured for 1 year (Table 2.5-4B). Monn (2001) observed a strong association between the average personal exposures in each study location and corresponding average outdoor concentrations with an R^2 of 0.965. As pointed out by the author, in an analysis of individual single exposure and outdoor concentration data, personal versus outdoor R^2 was less than 0.3 (Monn et al., 1998). Because spatial heterogeneity in NO_2 concentrations likely produces stronger associations between average personal exposures and residential monitors than with central site ambient monitors in urban areas, caution should be exercised in using these data to infer that long-term averaged ambient concentrations are a good surrogate for population exposures in long-term cohort epidemiologic studies.

2.5.6.2 Ambient Contribution to Personal NO_2 Exposure

Another aspect of the relationship of personal NO_2 exposure and ambient NO_2 is the contribution of ambient NO_2 to personal exposures. The infiltration factor (F_{inf}) and alpha (α) are the keys to evaluate personal NO_2 exposure of ambient origin. As defined in Equations 2.5-2 through 2.5-5, the infiltration factor (F_{inf}) of NO_2, the physical meaning of which is the fraction

of ambient NO_2 found in the indoor environment, is determined by the NO_2 penetration coefficient (P), air exchange rate (a), and the NO_2 decay rate (k). Alpha (α) is a function of F_{inf} and the fraction of time people spend outdoors (y), and the physical meaning of α is the ratio of personal ambient exposure concentration to ambient concentration, (i.e., in the absence of exposures to nonambient sources (i.e., when $E_{na} = 0$).

The values for α and F_{inf} can be calculated physically using Equations 2.5-2 through 2.5-5, if P, k, a, and y are known. However, the values of P and k for NO_2 are rarely reported, and in most mass balance modeling work, P is assumed to equal 1 and k is assumed to equal 0.99 h^{-1} (Yamanaka, 1984; Yang et al., 2004a; Dimitroulopoulou et al., 2001; Kulkarni et al., 2002). Loupa et al. (2006) reported that k was 0.08 to 0.12 h^{-1} for NO and 0.04 to 0.11 h^{-1} for NO_2 based on real-time measurements in two medieval churches in Cyprus. It is well known that P and k are dependent on a large number of indoor parameters, such as temperature, relative humidity, surface properties, surface-to-volume ratio, the turbulence of airflow, building type, and coexisting pollutants (Lee et al., 1996; Cotterill et al., 1997; Monn et al., 1998; García-Algar et al., 2003; Sorensen et al., 2005; Zota et al., 2005). As a result, using a fixed value, as mentioned above, would either over- or underestimate the true α or F_{inf}.

Although specific P, k, and a were not reported by most studies, a number of studies investigated factors affecting P, k, and a (or indicators of P, k, and a), and their effects on indoor and personal exposures (Lee et al., 1996; Cotterill et al., 1997; Monn et al., 1998; García-Algar et al., 2003; Sørensen et al., 2005; Zota et al., 2005). García-Algar et al. (2003) observed that double-glazed windows had a significant effect on indoor NO_2 concentrations. Homes with double-glazed windows had lower indoor concentrations (6 ppb lower) than homes with single-glazed windows. Cotterill et al. (1997) reported that having single- or double-glazed windows was a significant factor affecting NO_2 concentrations in kitchens in homes with gas-cookers (31.4 ppb and 39.8 ppb for homes with single- and double-glazed windows, respectively). The reduction of ventilation resulting from the presence of double-glazed windows can block outdoor NO_2 from coming into the indoor environment, and at the same time can also increase the accumulation of indoor generated NO_2.

A similar effect was found for homes using air conditioners. Lee et al. (2002) observed that NO_2 was 9 ppb higher in homes with an air conditioner than in homes without. The authors also observed that the use of a humidifier would reduce indoor NO_2 by 6 ppb.

House type was another factor reported affecting ventilation (Lee et al., 1996; García-Algar et al., 2003). Lee et al. (1996) reported that the building type was significantly associated with air exchange rate: the air exchange rate ranged from 1.04 h^{-1} for single dwelling unit to 2.26 h^{-1} for large multiple dwelling unit. Zota et al. (2005) reported that the air exchange rates were significantly lower in the heating season than the nonheating season (0.49 h^{-1} for the heating season and 0.85 h^{-1} for the nonheating season.

Although models based on dynamic flow and mass transfer equations might help better simulate indoor and outdoor concentration and personal exposure, in practice, people still rely heavily on Equations 2.5-2 through 2.5-5 because of the lack of real-time measurement data. The assumed equilibrium condition 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) (Ekberg, 1996). As a result, the relationship between *P*, *k*, and *a* has not been thoroughly investigated, but factors mentioned above can significantly affect *P*, *k*, and *a*, and thus affect the relationships between indoor and outdoor NO_2 concentration and between personal exposure and outdoor NO_2 concentration. It should also be pointed out that both *P* and *k* are functions of the complicated mass transfer processes that occur on indoor surfaces and therefore are associated with air exchange rate, which has an effect on the turbulence of indoor airflows. However, the relationship between *P*, *k*, and *a* has not been thoroughly investigated.

Alternatively, the ratio of personal exposure to ambient concentration can be regarded as α in the absence of indoor or nonambient sources. Only a few studies have reported the value and distribution of the ratio of personal NO_2 exposure to ambient NO_2 concentration, and even fewer studies have reported the value and distribution of α based on sophisticated study designs. Rojas-Bracho et al. (2002) reported the median personal-outdoor ratio was 0.64 (with an IQR of 0.45), but the authors reported that α was overestimated by this ratio because of indoor sources.

The random component superposition (RCS) model is an alternative way to calculate F_{inf} or α using observed ambient and personal exposure concentrations (Ott et al., 2000). The RCS

statistical model (shown in Equations 2.5-2 through 2.5-5) uses the slope of the regression line of personal concentration on the ambient NO_2 concentration to estimate the population averaged attenuation factor and means and distributions of ambient and nonambient contributions to personal NO_2 concentrations (the intercept of the regression is the averaged nonambient contribution to personal exposure) (U.S. Environmental Protection Agency, 2004). As shown in Table 2.5-5, α calculated by the RCS model ranges from 0.3 to 0.6. Similarly, as shown in Table 2.5-6 (see end of chapter), F_{inf} ranges from 0.4 to 0.7.

The RCS model calculates ambient contributions to indoor concentrations and personal exposures based on the statistical inferences of regression analysis. However, personal-outdoor regressions could be affected by extreme values (outliers on either the x or the y axis). Another limitation of the RCS model is that this model is not designed to estimate ambient and nonambient contributions for individuals, in part because the use of a single value for α does not account for the large home-to-home variations in actual air exchange rates and penetration and decay rates of NO_2. In the RCS model, α is also determined by the selection of the predictor. Using residential outdoor NO_2 concentrations as the model predictor might give a different estimate of α than using ambient NO_2 because of the spatial variability of NO_2 mentioned early in this section. As mentioned earlier, personal NO_2 exposure is affected not only by air infiltrating from outdoors but also by indoor sources (see Section 2.5.5).

Nerriere et al. (2005) used data from the Genotox ER study in France (Grenoble, Paris, Rouen, and Strasbourg) and reported that factors affecting the differences between personal exposure to ambient NO_2 and corresponding ambient monitoring site concentrations were season, city, and land use dependence. During the winter, city and land use categorization account for 31% of the variation, and during the summer, 54% of the variation can be explained by these factors. When data from the ambient monitoring site were used to represent personal exposures, the largest difference between ambient and personal exposure was found at the "proximity to traffic" site, while the smallest difference was found at the "background" site. When using data from the urban background site, the largest difference was observed at the "industry" site, and the smallest difference was observed at the background site, which reflected the heterogeneous distribution of NO_2 in an urban area. During winter, differences between ambient site and personal exposure concentrations were larger than those in the summer.

In summary, NO_2 is monitored at far fewer sites than either O_3 or PM. Significant spatial variations in ambient NO_2 concentrations were observed in urban areas. Measurements of NO_2 are subject to artifacts both at the ambient level and at the personal level. Personal exposure to ambient and outdoor NO_2 is determined by many factors as listed in Sections 2.5.1 and 2.5.2. These factors all influence the contribution of ambient NO_2 to personal exposures. Personal activities determine when, where, and how people are exposed to NO_2. The variations of these physical and exposure factors determine the strength of the association between personal exposure and ambient concentrations in both longitudinal and cross-sectional studies. In Section 2.5.6.1, three types of correlation coefficients were presented. The observed strength of the association between personal exposures and ambient concentrations are not only affected by the variation in physical parameters (e.g., *P*, *k*, *a* and indoor sources) but also affected by data quality and study design. The association between the ambient component of personal exposures and ambient concentrations is more relevant to the interpretation of epidemiologic evidence but this type of correlation coefficient is not reported. Therefore, the weak association between personal total exposures and ambient concentrations in some longitudinal studies might not reflect the true association between the ambient component of personal exposures and ambient concentrations. In the absence of indoor and local sources, personal exposures to NO_2 are between the ambient level and the indoor level. However, personal exposures could be much higher than either indoor or outdoor concentrations in the presence of these sources. A number of studies found that personal NO_2 was associated with ambient NO_2, but the strength of the association ranged from poor to good.

Some researchers concluded that ambient NO_2 may be a reasonable proxy for personal exposures, while others noted that caution must be exercised if ambient NO_2 is used as a surrogate for personal exposure. Reasons for the differences in study results are not clear, but are related in large measure to differences in study design, to the spatial heterogeneity of NO_2 in study areas, to control of indoor sources, to the seasonal and geographic variability in the infiltration of ambient NO_2, and to differences in the time spent in different microenvironments. Measurement artifacts at the ambient and personal levels and differences in analytical measurement capabilities among different groups could also have contributed to the mixed results. The collective variability in all of the above parameters, in general, contributes to exposure misclassification errors in air pollution-health outcome studies.

2.5.8 NO_2 as a Component of Mixtures

2.5.8.1 Correlations between Ambient NO_2 and Ambient Copollutants

Relationships between ambient concentrations of NO_2 and other pollutants that are emitted by the same sources, such as motor vehicles, should be evaluated in designing and interpreting air pollution-health outcome studies, as ambient concentrations are generally used to reflect exposures in epidemiologic studies. Thus, the majority of studies examining pollutant associations in the ambient environment have focused on ambient NO_2, $PM_{2.5}$ (and its components), and CO, with fewer studies reporting the relationship between ambient NO_2 and ambient O_3 or SO_2.

Data were compiled from EPA's AQS and a number of exposure studies. Correlations between ambient concentrations of NO_2 and other pollutants, $PM_{2.5}$ (and its components, where available), CO, O_3, and SO_2 are summarized in Table 2.5-7.

Mean values of correlations between monitoring sites are shown. As can be seen from the table, NO_2 is moderately correlated with $PM_{2.5}$ (range: 0.37 to 0.78) and with CO (0.41 to 0.76) in suburban and urban areas. At locations such as Riverside, CA, associations between ambient NO_2 and ambient CO concentrations (both largely traffic-related pollutants) are much lower, likely as the result of other sources of both CO and NO_2 increasing in importance in going from urban environments to more rural and sparsely populated areas. These sources include oxidation of methane (CH_4) and other biogenic compounds; residential wood burning and prescribed and wild land fires for CO; and soil emissions, lightning, and residential wood burning and wild land fires for NO_2. In urban areas, the ambient NO_2-CO correlations vary widely. The strongest correlations are seen between NO_2 and elemental carbon (EC). Note that the results of Hochadel et al. (2006) for $PM_{2.5}$ optical absorbance have been interpreted in terms of EC. Correlations between ambient NO_2 and ambient O_3 are mainly negative, owing to the chemical interaction between the two, with again considerable variability in the observed correlations. Only one study (Sarnat et al., 2001) examined associations between ambient NO_2 and ambient SO_2 concentrations, and it showed a negative correlation during winter.

Figures 2.5-5a-d show seasonal plots of correlations between NO_2 and O_3 versus correlations between NO_2 and CO. As can be seen from the figures, NO_2 is positively correlated with CO during all seasons at all sites. However, the sign of the correlation of NO_2 with O_3

TABLE 2.5-7. PEARSON CORRELATION COEFFICIENT BETWEEN AMBIENT NO_2 AND AMBIENT COPOLLUTANTS

Study (Ambient)	Location	$PM_{2.5}$	CO	O_3	SO_2
This Assessment	Los Angeles, CA	0.49 (u[2]) 0.56 (s)	0.59 (u) 0.64 (s)	–0.29 (u) –0.11 (s)	
This Assessment	Riverside, CA		0.43 (u) 0.41 (s) 0.15 (r)	0.045 (u) 0.10 (s) –0.31 (r)	
This Assessment	Chicago, IL	0.49 (s)	0.53 (u) 0.46 (s)	–0.20 (u)	
This Assessment	New York, NY	0.58 (u)	0.46 (u)	–0.06 (u)	
Kim et al. (2006)	Toronto, Canada	0.44	0.72		
Sarnat et al. (2006)	Steubenville, OH (autumn)	0.78 (0.70 for sulfate 0.82 for EC)			
Sarnat et al. (2006)	Steubenville, OH (summer)	0.00 (0.1 for sulfate 0.24 for EC)			
Connell et al. (2005)	Steubenville, OH	0.50			
Kim et al. (2005)	St. Louis, MO (RAPS)		0.64[4]		
Sarnat et al. (2001)[1]	Baltimore, MD (summer)	0.37	0.75	0.02 not significant	
Sarnat et al. (2001)	Baltimore, MD (winter)	0.75	0.76	–0.71	–0.17
Hochadel et al. (2006)	Ruhr area, Germany	0.41 (0.93 for EC[3])			
Hazenkamp-von Arx et al. (2004)	21 European cities	0.75			
Cyrys et al. (2003)	Ehrfurt, Germany	0.50	0.74		
Mosqueron et al. (2002)	Paris, France	0.69			
Rojas-Bracho et al. (2002)	Santiago, Chile	0.77			

[1] Spearman correlation coefficient was reported.
[2] u: urban; s: suburban; and r: rural
[3] Inferred based on EC as dominant contributor to $PM_{2.5}$ absorbance.
[4] Value with respect to NO_X.

varies with season, ranging from negative during winter to slightly positive during summer. There are at least two main factors contributing to the observed seasonal behavior. Ozone and radicals correlated with it tend to be higher during the summer, thereby tending to increase the ratio of NO_2 to NO. Nitrogen oxide compounds formed by further oxidation of NO_X are also

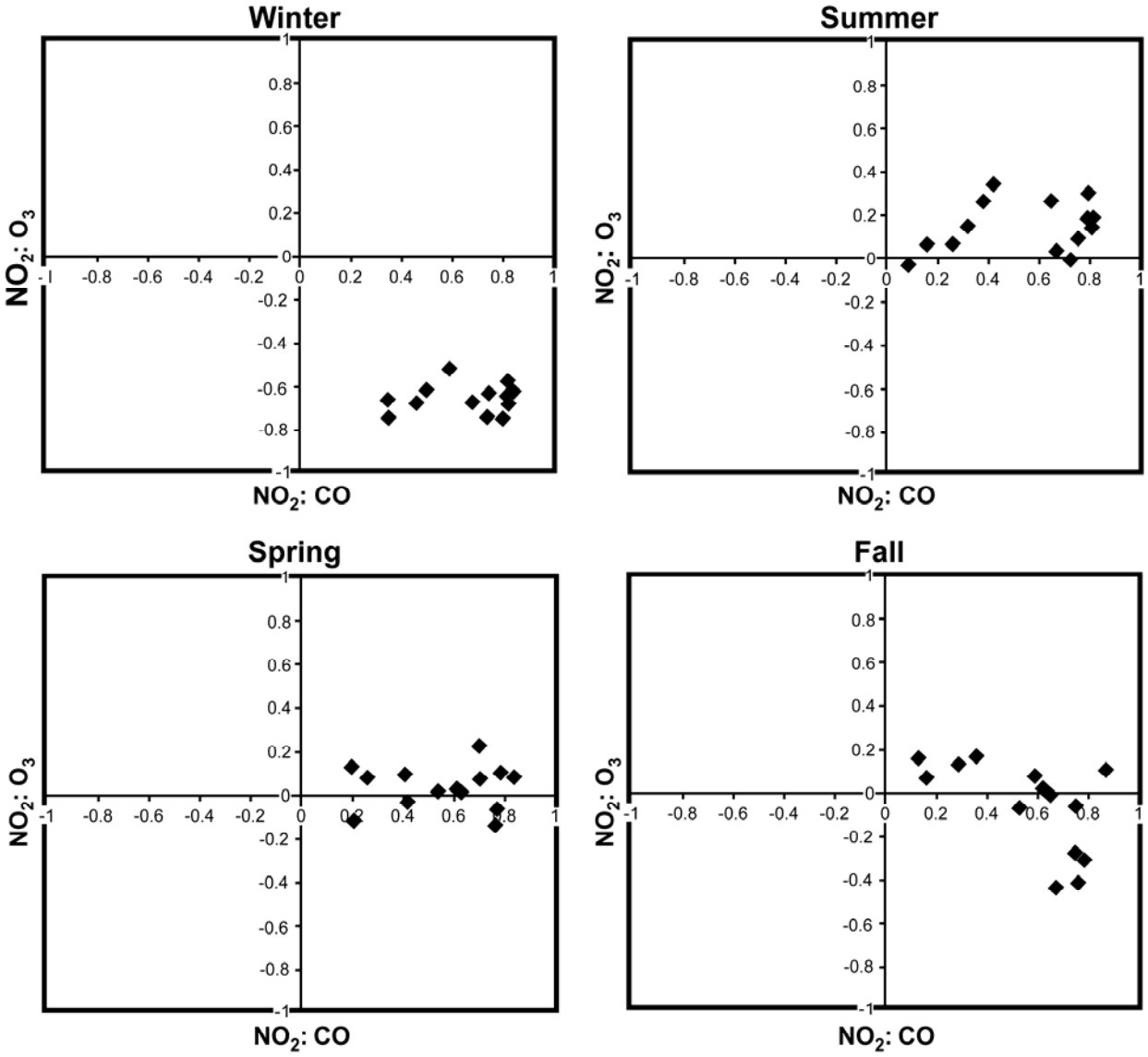

Figure 2.5-5a-d. Correlations of NO_2 to O_3 versus correlations of NO_2 to CO for Los Angeles, CA (2001-2005).

expected to be correlated with O_3 and increased summertime photochemical activity. Because some of these additionally oxidized N compounds create a positive artifact in the FRM for NO_2, they may also tend to increase the correlation of NO_2 with O_3 during the warmer months.

A number of case studies show similar correlations between ambient NO_2 and other pollutants presented above. Particulate and gaseous copollutant data were analyzed at 10 sites in the St. Louis Regional Air Pollution Study (RAPS) dataset (1975, 1977) by Kim et al. (2005).

This study examined the spatial variability in source contributions to $PM_{2.5}$. Table 2.5-8 shows correlations between NO_X and traffic pollutants measured in ambient air.

TABLE 2.5-8. PEARSON CORRELATION COEFFICIENT BETWEEN NO_X AND TRAFFIC-GENERATED POLLUTANTS

NO_X: $PM_{2.5}$ (MV component)	$0.48 < r < 0.75$[1]	$0.48 < r < 0.75$[2]
NO_X: CO	$0.30 < r < 0.77$[1]	$0.54 < r < 0.77$[2]
NO_X: Pb	$0.42 < r < 0.76$[1]	$0.48 < r < 0.76$[2]
NO_X: Br	$0.55 < r < 0.73$[1]	$0.58 < r < 0.73$[2]
NO_2: EC[3] 0.93		
NO_2: EC[4] 0.82 autumn, 0.24 summer		

[1]St. Louis RAPS (Kim et al., 2006), all sites
[2]St. Louis RAPS (Kim et al., 2006), all sites with upwind background site removed
[3]Ruhr Valley (Hochadel et al., 2006)
[4]Steubenville, OH (Sarnat et al., 2006)

Leaded gasoline was in use at the time of RAPS, making lead (Pb) and bromine (Br) good markers for motor vehicle exhaust. Motor vehicle emissions are the main anthropogenic source of CO in urban areas. However, outside of urban areas and away from sources burning fossil fuels, biomass burning and the oxidation of biogenic hydrocarbons, in particular isoprene and methane, can represent the major source of CO. In general, biogenic emissions of precursors to CO formation or CO from biomass burning can cause the relationship between CO and motor vehicles to break down.

In the Restrepo et al. (2004) study, NO_2 behaved as if traffic were its main source, since NO_2 behaved similarly to CO and $PM_{2.5}$; i.e., their concentrations decreased with height. O_3 showed the opposite vertical gradient; i.e., its concentration increased with height. Seaton and Dennekamp (2003) suggested that NO_2 may be a surrogate for ultrafine particles (UFPs), in particular for particle number concentrations. The results from the measurements made at a background site in Aberdeen, Scotland, over the course of 6 months showed very high correlation between the number concentration of particles <100 nm in diameter and NO_2. The correlation between NO_2 and the particle number concentration ($r = 0.89$) was much higher than

that between NO_2 and $PM_{2.5}$ (r = 0.55) and that between NO_2 and PM_{10} (r = 0.45). A time-series mortality study (Wichmann et al., 2000; re-analysis by Stölzel et al., 2003) conducted in Erfurt, Germany, measured, and analyzed UFP number and mass concentrations as well as NO_2. Unlike Seaton and Dennekamp's data, in this data set, the correlation between NO_2 and various number concentration indices were not much stronger than those between $PM_{2.5}$ and number concentration indices or those between PM_{10} and number concentration indices. For example, the correlation between $NC_{0.01\text{-}0.10}$ (particle number concentration for particle diameter between 10 and 100 nm) and NO_2, $PM_{2.5}$, and PM_{10} were 0.66, 0.61, and 0.61, respectively.

2.5.8.2 Correlations of Personal and Ambient NO_2 and Personal and Ambient Copollutants

Correlations between ambient concentrations of NO_2 and personal copollutants, $PM_{2.5}$ (and its components where available), CO, O_3, and SO_2 are summarized in Table 2.5-9.

TABLE 2.5-9. PEARSON CORRELATION COEFFICIENT BETWEEN AMBIENT NO_2 AND PERSONAL COPOLLUTANTS

Study	Location	$PM_{2.5}$	Sulfate	EC	Ultrafine Particle
Sarnat et al. (2006)	Steubenville, OH Fall	0.71	0.52	0.70	—
Sarnat et al. (2006)	Steubenville, OH Summer	0.00	0.1 not significant	0.26	—
Vinzents et al. (2005)	Copenhagen, Denmark	—	—	—	0.49 (R^2) explained by ambient NO_2 and ambient temperature

Correlations between personal concentrations of NO_2 and ambient copollutants, $PM_{2.5}$ (and its components where available), CO, O_3, and SO_2 are summarized in Table 2.5-10, and correlations between personal NO_2 concentrations and personal copollutant concentrations are shown in Table 2.5-11.

Most studies examined above show that personal NO_2 concentrations are significantly correlated with either ambient or personal level $PM_{2.5}$ or other combustion-generated pollutants, e.g., CO, EC.

TABLE 2.5-10. PEARSON CORRELATION COEFFICIENT BETWEEN PERSONAL NO_2 AND AMBIENT COPOLLUTANTS

Study	Location	$PM_{2.5}$	Sulfate	EC	PM_{10}	CO
Sarnat et al. (2006)	Steubenville, OH Fall	0.46	0.35	0.57	—	—
Sarnat et al. (2006)	Steubenville, OH Summer	0.00	0.1 not significant	0.17	—	—
Kim et al. (2006)	Toronto, Canada	0.30	—	—	—	0.20
Rojas-Bracho et al. (2002)	Santiago, Chile	0.65	—	—	0.39	—

TABLE 2.5-11. PEARSON CORRELATION COEFFICIENT BETWEEN PERSONAL NO_2 AND PERSONAL COPOLLUTANTS

Study	Location	$PM_{2.5}$	CO	VOCs	HONO
Kim et al. (2006)	Toronto, Canada	0.41	0.12		—
Modig et al. (2004)	Umea, Sweden	—	—	0.06 for 1,3-butadiene; 0.10 for benzene	—
Mosqueron et al. (2002)	Paris, France	0.12 but not significant	—	—	—
Jarvis et al. (2005)	21 European cities	—	—	—	0.77 for indoor NO_2 and indoor HONO
Lee et al. (2002)	—	—	—	—	0.51 for indoor NO_2 and indoor HONO
Lai et al. (2004)	Oxford, England	–0.1	0.3	–0.11 for TVOCs	—

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 ~10% of primary emissions in the form of NO_2. The diurnal pattern of NO and NO_2 concentrations are 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, and NO and NO_2 are converted to NO_Z. During the afternoon rush hour, mixing layer heights are often still at or 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 subsequent photolysis of NO_2 recreating 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) is shown in Figure 2.5-6. Figure 2.5-6 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 ~13 ppb to ~25 ppb. However, individual hourly concentrations can be considerably higher than these typical median values, and hourly NO_2 concentrations of >0.10 parts per million (ppm) can be found at any time of day. The diurnal pattern in median concentrations shown in Figure 2.5-6 is consistent with that shown in Figures 2.4-5 and 2.4-6 for Atlanta, indicating some commonality in sources across these cities. The pattern in the median concentrations is consistent with traffic as the major source of variability. However, the patterns in the upper end of the concentration distribution differ between cities and the composite, indicating that other sources and meteorological processes affect NO_2 levels, causing them to differ from city to city.

Information concerning the seasonal variability of ambient NO_2 concentrations is given in the Annex in Section AX3.3. NO_2 levels are highest during the cooler months of the year and still show positive correlations with CO. Mean NO_2 levels are lowest during the summer months, though of course, there can be large positive excursions associated with the development of high-pressure systems. In this regard, NO_2 behaves as a primary pollutant, although there is no good reason to suspect strong seasonal variations in its emissions.

2.5.8.3 Associations among NO_2 and Other Pollutants in Indoor Environments

In addition to NO_2, indoor combustion sources such as gas ranges and unvented gas heaters emit other pollutants that are present in the fuel or are formed during combustion. The

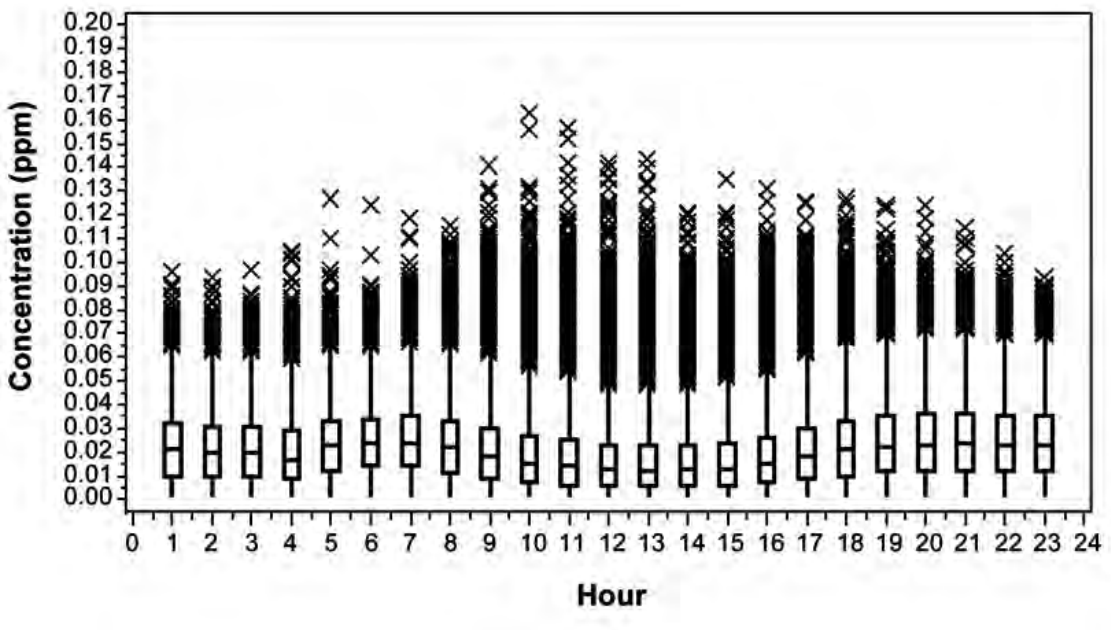

Figure 2.5-6. Composite, diurnal variability in 1-h average NO_2 in urban areas. Values shown are averages from 2003 through 2005. Boxes define the interquartile range, and the whiskers the 5th and 95th percentile values. X's denote individual values above the 95th percentile.

major products from the combustion of natural gas are carbon dioxide (CO_2) and CO followed by formaldehyde (HCHO) with smaller amounts of other oxidized organic compounds in the gas phase. PM, especially in the ultrafine-size range and HONO are also emitted. The production of pollutants by reactions of NO_2 in indoor air was covered in Section 2.5.5.

2.5.8.3.1 NO and HONO

Dennekamp et al. (2001) measured levels of NO, NO_2, and UFPs generated by gas and electric cooking ranges in a test laboratory room. They found average levels of NO ranging from ~500 to ~3,000 ppb, with peak (15-min average) levels ranging from ~1,000 to ~6,000 ppb depending on how many burners (1 to 4) were turned on and for how long (15 min to 2 h). Corresponding levels of NO_2 tracked those of NO but were typically factors of 2 to 5 lower. 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 ~84% of the measured increase

in HONO. In a study of homes in southern California, Lee et al. (2002) found that indoor levels of NO_2 and HONO were positively associated with the presence of gas ranges.

2.5.8.3.2 Carbon-Containing Gaseous Pollutants

In a study of pollutants emitted by unvented gas heaters, Brown et al. (2004) found that CO in a room test chamber ranged from 1 to 18 ppm and NO_2, from 100 to 300 ppb. Corresponding levels of HCHO were highly variable, ranging from <10 ppb to a few hundred ppb (with an outlier at >2 ppm).

2.5.8.3.3 PM

PM in the sub-micrometer size range is also produced during natural gas combustion. Dennenkamp et al. (2001) in the study mentioned above found enhancements in UFP concentrations when gas burners were turned on. Peak (15-min average) concentrations for different experiments ranged from ~140,000 to ~ 400,000/cm^3 corresponding to average levels of ~80,000 to 160,000/cm^3. Concentrations before the experiments were begun were in the range of a few thousand per cm^3. However, Ristovski et al. (2000) measured emission rates for individual particles, which are expected to be present mainly in the UFP size range but concluded that these rates are low, and they could not detect an increase in particle number from one of the two heater models tested.

Rogge et al. (1993) found that at least 22% of the fine particle mass emitted by natural gas heaters consists of PAHs, oxy-PAHs, and aza-and thia-arenes. They also identified emissions of speciated alkanes, *n*-alkanoic acids, polycyclic aromatic ketones, and quinones. However, these accounted for only another ~4% of the emitted fine PM. Although the PM emissions rates were low and not likely to affect PM levels, the PAH content of natural gas combustion emissions in this study indicates that natural gas combustion could be a significant source of PAHs in indoor environments

2.6 DOSIMETRY OF INHALED NITROGEN OXIDES

This section provides a brief overview of NO_2 dosimetry and updates information provided in the 1993 AQCD for Oxides of Nitrogen. A more extensive discussion of NO_2 dosimetry appears in Annex 4. NO_2, classified as a reactive gas, interacts with surfactants,

antioxidants, and other compounds in the epithelial lining fluid (ELF). The compounds thought to be responsible for adverse pulmonary effects of inhaled NO_2 are the reaction products themselves or the metabolites of these products in the ELF.

Acute NO_2 uptake in the lower respiratory tract is thought to be rate-limited by chemical reactions of NO_2 with ELF constituents rather than by gas solubility in the ELF (Postlethwait and Bidani, 1990). Postlethwait and Bidani (1994) concluded that the reaction between NO_2 and water does not significantly contribute to the absorption of inhaled NO_2. Rather, uptake is a first-order process for NO_2 concentrations of <10 ppm, is aqueous substrate-dependent, and is saturable. Postlethwait et al. (1991) reported that inhaled NO_2 (<10 ppm) does not penetrate the ELF to reach underlying sites and suggested that cytotoxicity may be due to NO_2 reactants formed in 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.

Glutathione (GSH) and ascorbate are the primary NO_2 absorption substrates in rat ELF (Postlethwait et al., 1995). Velsor and Postlethwait (1997) investigated the mechanisms of acute epithelial injury from NO_2 exposure. 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. GSH- and ascorbic acid-related membrane oxidation were superoxide- and hydrogen peroxide-dependent, respectively. The authors suggested that increased absorption of NO_2 occurred at the higher antioxidant concentrations, but little secondary oxidation of the membrane occurred because the reactive species (e.g., superoxide and hydrogen peroxide) generated during absorption were quenched. A lower rate of NO_2 absorption occurred at the low antioxidant concentrations, but oxidants were not quenched and so were available to interact with the cell membrane. Illustrating the complex interaction of antioxidants, some studies suggest that NO_2-oxidized GSH may be again reduced by uric acid and/or ascorbic acid (Kelly et al., 1996; Kelly and Tetley, 1997).

Very limited work related to the quantification of NO_2 uptake has been reported since the 1993 AQCD for Oxides of Nitrogen. In both humans and animals, the uptake of NO_2 uptake by the upper respiratory tract decreases with increasing ventilator rates. This causes a greater proportion of inhaled NO_2 to be delivered to the lower respiratory tract. In humans, the breathing pattern shifts from nasal to oronasal during exercise relative to rest. Since the nasal

passages absorb more inhaled NO_2 than the mouth, exercise (with respect to the resting state) delivers a disproportionately greater quantity of the inhaled mass to the pulmonary region of the lung, where the NO_2 is readily absorbed. Bauer et al. (1986) reported a statistically significant increase in uptake from 72% during rest to 87% during exercise in a group of 15 asthmatic adults. The minute ventilation also increased from 8.1 L/min during rest to 30.4 L/min during exercise. Hence, exercise increased the dose rate of NO_2 by 5-fold in these subjects. Similar results have been reported for beagle dogs where the dose rate of NO_2 was 3-fold greater for the dogs during exercise than rest (Kleinman and Mautz, 1991).

Modeling studies also 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 these reactants to the tissues have not been modeled.

TABLE 2.5-4A. ASSOCIATION BETWEEN PERSONAL EXPOSURE AND AMBIENT CONCENTRATION

Study	Study Design	Mean Concentration (ppb)	Association Variable	Location	Season	r_p, r_s, or R^2
Linn et al. (1996)	Type: Longitudinal; Location: Southern California Subjects: 269 school children Time period: fall, winter, spring, 1992-1994 Method: 24-h avg, 1-wk consecutive measurement for each season for each child.	Ambient: 37 Personal: 22	Personal vs. central	Pooled	Pooled	0.63 (r_p) (n = 107)
Alm et al. (1998)	Type: Longitudinal; Location: Helsinki, Finland Subjects: 246 children aged 3-6 yrs old Time period: winter and spring, 1991 Method: 1-wk averaged sample for each person, 6 consecutive wks in the winter and 7 consecutive wks in the spring.	Ambient: 16.8–26.3 Personal: 9–16.6	Personal vs. central	Downtown	Spring	0.64 (r_p) $p < 0.001$ (n=NR**)
			Personal vs. central	Suburban	Spring	0.78 (r_p) $p < 0.001$ (n = NR)
			Personal vs. central	Downtown	Winter	−0.06 (r_p) $p > 0.05$ (n = NR)
			Personal vs. central	Suburban	Winter	0.32 (r_p) $p > 0.05$ (n = NR)
			Personal vs. central	Downtown (electric stove home)	Pooled	0.42 (r_p) $p < 0.01$ (n = NR)
			Personal vs. central	Downtown (gas stove home)	Pooled	0.16 (r_p) $p > 0.01$ (n = NR)
			Personal vs. central	Suburban (electric stove home)	Pooled	0.55 (r_p) $p < 0.001$ (n = NR)
			Personal vs. central	Downtown (non-smoking home)	Pooled	0.47 (r_p) $p < 0.001$ (n = NR)
			Personal vs. central	Downtown (smoking home)	Pooled	0.23 (r_p) $p > 0.01$ (n = NR)
			Personal vs. central	Suburban (non-smoking home)	Pooled	0.53 (r_p) $p < 0.001$ (n = NR)
			Personal vs. central	Suburban (smoking home)	Pooled	0.52 (r_p) $p < 0.001$ (n = NR)
			Personal vs. central	Pooled	Pooled	0.37 (R^2) (n = 24)

TABLE 2.5-4A (cont'd). ASSOCIATION BETWEEN PERSONAL EXPOSURE AND AMBIENT CONCENTRATION

Study	Study Design	Mean Concentration (ppb)	Association Variable	Location	Season	r_p, r_s, or R^2
Liard et al. (1999)	Type: Daily avg/cross-sectional; Location: Paris, France Subjects: 55 adults and 39 children Time period: May-June 1996 Method: three 4-day avg measurements for each person, during each measurement session, all subjects were measured at the same time.	Ambient: 26.3–36.8 Personal: 15.8–26.3	Adults vs. central	Urban	Summer	0.41 (R^2) $p < 0.0001$ (n = NR)
			Children vs. central	Urban	Summer	0.17 (R^2) $p = 0.0004$ (n = NR)
Linaker et al. (2000)	Type: Longitudinal; Location: Southampton, Hampshire, UK Subjects: 114 asthmatic children, aged 7-12 Time period: Oct 1994 to Dec 1995 Method: at least 16 consecutive samples (1-wk avgs) for each child (mean duration of follow-up: 32 wks).	Ambient: 6.5 Personal: 8.9	Personal vs. central (overall measurements across children and time)	Pooled, urban, no major indoor sources	Pooled	Not significant (n = NR)
			Personal vs. central (subject-wise)	By person	Pooled	−0.77 to 0.68 and median −0.02 (r_p) (n = NR)
Gauvin et al. (2001)	Type: Daily avg/cross-sectional; Location: three French metropolitan areas Subjects: 73 children Time period: Apr-June 1998 in Grenoble May-June 1998 in Toulouse; June-Oct 1998 in Paris Method: one 48-h avg measurement for each child; all children in the same city were measured on the same day.	Ambient: 10.2–25.7 Personal: 13.2–17	Personal vs. central (Grenoble)	Urban	Pooled	0.01 (R^2) (n = NR)
			Personal vs. central (Toulouse)	Urban	Pooled	0.04 (R^2) (n = NR)
			Personal vs. central (Paris)	Urban	Pooled	0.02 (R^2) (n = NR)
Piechocki-Minguy et al. (2006)	Type: Pooled; Location: Lille (northern France) Subjects: 13 participants in the first campaign, and 31 participants in the second campaign Time period: winter 2001 (first campaign); summer 2002 (second campaign) Method: two 24-h sampling periods (one on workdays; one on 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).	Ambient: 15.8–57.9 Personal: 8.9–20.0	Personal (exposure at home) vs. central	Urban	Pooled	0.09 (R^2) $p = 0.0101$ (n = NR)
			Personal (exposure at home) vs. central	Urban (electric stove and electric heater home)	Summer	0.61 (R^2) $p = 0.0001$ (n = NR)

TABLE 2.5-4A (cont'd). ASSOCIATION BETWEEN PERSONAL EXPOSURE AND AMBIENT CONCENTRATION

Study	Study Design	Mean Concentration (ppb)	Association Variable	Location	Season	r_p, r_s, or R^2
Kim et al. (2006)	Type: Longitudinal; Location: Toronto, Canada Subjects: 28 adults with coronary artery disease Time period: Aug 1999 to Nov 2001 Method: 1 day/wk, 24-h avg, for a max of 10 wks for each person.	Ambient: 24 Personal: 14	Personal vs. central (subject wise)	Urban	Pooled	−0.36 to 0.94 (r_s) with a median of 0.57 (15 subjects)
Sarnat et al. (2000)	Type: Longitudinal; Location: Baltimore, MD Subjects: 20 senior, healthy, non-smoking people (average age 75) Time period: summer of 1998; winter of 1999 Method: 1 day averaged sample, for 12 consecutive days for each subject; four to six subjects were measured concurrently during each 12-day monitoring period.	Ambient: 21.4–39.2 Personal: 7.9–42.7	Personal vs. central (subject wise)	Urban	Summer	−0.63 to 0.75 (r_s) with a median of −0.01 (14 subjects)
					Winter	−0.64 to 0.74 (r_s) with a median of −0.01 (14 subjects)
Sarnat et al. (2001); Koutrakis et al. (2005)	Type: Longitudinal; 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 samples) in each of the one or two seasons, except children, who were measured for 8 consecutive days during the summer.	Ambient: 20–25 Personal: 10–15	Personal vs. central (subject wise)	Urban	Summer	−0.45 to 0.85 (r_s) with a median of 0.05* (24 subjects)
					Winter	−0.6 to 0.75 (r_s) with a median of 0.05* (45 subjects)
Sarnat et al. (2005); Koutrakis et al. (2005)	Type: Longitudinal; Location: Boston, MA Subjects: 43 seniors and schoolchildren Time period: summer of 1999; winter of 2000 Method: Similar study design as Sarnat et al. (2001).	Ambient: 21.1– 32.6 Personal: 10.6–29.6	Personal vs. central (subject wise)	Urban	Summer	−0.25 to 0.5 (r_s) with a median of 0.3* (n = NR) Slope = 0.19 0.08-0.30
					Winter	−0.5 to 0.9 (r_s) with a median of 0.4* (n = NR) Slope = −0.03 −0.21-0.15
Sarnat et al. (2006)	Type: Longitudinal; Location: Steubenville, OH 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	Ambient: 9.5–11.3 Personal: 9.9–12.1	Personal vs. central	Urban	Summer	0.14 (R^2) (n = 122) $p < 0.05$
					Fall	0.43 (R^2) $p < 0.05$ (n = 138)

* Values were estimated from figures in the original paper.

** NR: Not Reported.

TABLE 2.5-4B. ASSOCIATION BETWEEN PERSONAL EXPOSURE AND OUTDOOR CONCENTRATION

Study	Study Design	Association Variable	Location	Season	r_p, r_s, or R^2
Krämer et al. (2000)	Location: Germany; Subjects: 191 children Time period: Mar and Sep 1996 Method: two 1-wk averaged measurements for each child in each mo.	Personal vs. outdoor	Pooled	Pooled	0.37 (r_p) (n = 281)
		Personal vs. outdoor	Urban	Pooled	0.06 (r_p) (n = 182)
Rojas-Bracho et al. (2002)	Location: Santiago, Chile; Subjects: 20 children Time period: winters of 1998 and 1999 Method: five 24-h avg samples for 5 consecutive days for each child.	Personal vs. outdoor	Urban	Winter	0.27 (R^2) (n = 87)
Raaschou-Nielsen et al. (1997)	Location: Copenhagen, Denmark and rural areas; Subjects: 204 children Time period: Oct 1994, Apr, May, and June 1995 Method: two 1-wk avg measurements for each child in each mo.	Personal vs. outdoor	Urban	Pooled	0.15 (R^2) (n = 97)
		Personal vs. outdoor	Rural	Pooled	0.35 (R^2) (n = 99)
Alm et al. (1998)	Location: Helsinki, Finland; Subjects: 246 children aged 3-6 yrs old Time period: winter and spring of 1991 Method: 1-wk averaged sample for each person for 6 consecutive wks in the winter and 7 consecutive wks in the spring.	Personal vs. outdoor	Downtown	Winter	0.46 (r_p) (n = NR)
		Personal vs. outdoor	Suburban	Winter	0.49 (r_p) (n = NR)
		Personal vs. outdoor	Downtown	Spring	0.80 (r_p) (n = NR)
		Personal vs. outdoor	Suburban	Spring	0.82 (r_p) (n = NR)
		Personal vs. outdoor	Downtown (electric stove home)	Pooled	0.55 (r_p) (n = NR)
		Personal vs. outdoor	Downtown (gas stove home)	Pooled	0.59 (r_p) (n = NR)
		Personal vs. outdoor	Suburban (electric stove home)	Pooled	0.63 (r_p) (n = NR)
		Personal vs. outdoor	Downtown (non-smoking home)	Pooled	0.73 (r_p) (n = NR)
		Personal vs. outdoor	Downtown (smoking home)	Pooled	0.51 (r_p) (n = NR)
		Personal vs. outdoor	Suburban (non-smoking home)	Pooled	0.59 (r_p) (n = NR)
		Personal vs. outdoor	Suburban (smoking home)	Pooled	0.46 (r_p) (n = NR)
		Personal vs. outdoor	Pooled	Pooled	0.86 (R^2) (n = 23)

TABLE 2.5-4B (cont'd). ASSOCIATION BETWEEN PERSONAL EXPOSURE AND OUTDOOR CONCENTRATION

Study	Study Design	Association Variable	Location	Season	r_p, r_s, or R^2
Monn et al. (1998)	Location: Geneva, Basel, 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).	Personal vs. outdoor	Pooled	Pooled	0.33 (R^2) (n = 1,494)
Levy et al. (1998b)	Location: 18 cities across 15 countries Subjects: 568 adults Time period: Feb or Mar 1996 Method: one 2-day avg measurement for each person, all people were measured on the same winter day.	Personal vs. outdoor	Urban	Winter	0.57 (r_s) (n = 546)
Kodama et al. (2002)	Location: Tokyo, Japan Subjects: 150 junior-high school students and their family members Time period: Feb 24-26, June 2-4, July 13-15, and Oct 14-16 in 1998 and Jan 26-28 in 1999 Method: 3-day avg, personal exposures were monitored on the same day.	Personal vs. outdoor	Urban	Summer	0.24 (r_p) (n = NR)
		Personal vs. outdoor	Urban	Winter	0.08 (r_p) (n = NR)
Spengler et al. (1994)	Location: Los Angeles Basin, CA Subjects: probability-based sample, 70 subjects Time period: May 1987 to May 1988 Method: each participant was monitored during each of 8 cycles (48-h avg sampling period) throughout the yr in the microenvironmental component of the study.	Personal vs. outdoor	Pooled	Pooled	0.48 (R^2) (n = NR)
Lai et al. (2004)	Location: Oxford, England Subjects: 50 adults Time period: Dec 1998 to Feb 2000 Method: one 48-h avg measurement per person.	Personal vs. outdoor	Urban	Pooled	0.41 (r_p) (n = NR)

* Values were estimated from figures in the original paper.

** NR: Not Reported.

TABLE 2.5-5. 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)	—	—

TABLE 2.5-5 (cont'd). SUMMARY OF REGRESSION MODELS OF PERSONAL EXPOSURE TO AMBIENT/OUTDOOR NO_2

Study	Location	Season	Model Type	Slope (SE)	Intercept / ppb	R^2
Piechocki-Minguy et al. (2006)	Location: Pooled, Lille (northern France) 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).	All	Personal vs. central (Assuming people stayed indoors all the time)	0.13	6.0	0.09
		Summer (homes with no major indoor NO_2 sources)		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*	—	—

TABLE 2.5-5 (cont'd). SUMMARY OF REGRESSION MODELS OF PERSONAL EXPOSURE TO AMBIENT/OUTDOOR NO_2

Study	Location	Season	Model Type	Slope (SE)	Intercept / ppb	R^2
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
		Fall	Personal vs. central (n = 138)	0.49 (0.05)	—	0.43

*Not significant at the 5% level.

TABLE 2.5-6. INDOOR/OUTDOOR RATIO AND THE INDOOR VS. OUTDOOR REGRESSION SLOPE

Study	Description	Season	Regression Format or Ratio	Indoor Characteristics	F_{inf}	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 NO_2 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 during 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.

TABLE 2.5-6 (cont'd). INDOOR/OUTDOOR RATIO AND THE INDOOR VS. OUTDOOR REGRESSION SLOPE

Study	Description	Season	Regression Format or Ratio	Indoor Characteristics	F_{inf}	Comments
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)	—
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 NOR2R 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 Homes without smokers and gas-cooking	0.47 (n = 1544) 0.40 (n = 968)	R^2 was 0.37. 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 Gas range without pilot light Electric stove	0.49 (n = 314) 0.4 (n = 148) 0.4 (n = 170)	R^2 was 0.44. R^2 was 0.39. R^2 was 0.41.

3. INTEGRATED HEALTH EFFECTS OF NO_2 EXPOSURE

In this chapter, we assess the health effects associated with human exposure to ambient nitrogen dioxide (NO_2) in the United States. The main goal of this chapter is to (1) integrate newly available epidemiologic, human clinical, and animal toxicological evidence with consideration of key findings from the 1993 Air Quality Criteria Document (AQCD) for Oxides of Nitrogen (U.S. Environmental Protection Agency, 1993) and (2) draw conclusions about the causal nature of NO_2 relative to a variety of health effects. These causal determinations utilize the framework outlined in Chapter 1.

This chapter is organized to present morbidity and mortality associated with short-term exposures to NO_2, followed by morbidity and mortality associated with long-term exposures. Within these divisions, the chapter is organized by health outcome, such as respiratory symptoms in asthmatics, emergency department (ED) visits and hospital admissions for respiratory and cardiovascular diseases (CVDs), and premature mortality. The sections describe the findings of epidemiologic studies that have characterized the association between ambient NO_2 exposure and heath outcomes and includes relevant human clinical and animal toxicologic data, when available. This integrated discussion underlies judgments in causal inference.

The epidemiologic studies contain important information on potential associations between health effects and exposures of human populations to ambient levels of NO_2, and they help to identify susceptible subgroups and associated risk factors. However, the associations derived for specific air pollutants and health outcomes in epidemiologic studies may be confounded or obscured by copollutants and/or meteorological conditions and can be influenced by model specifications in the analytical methods. Extensive discussion of issues related to confounding effects among air pollutants in epidemiologic studies is provided in the 2004 AQCD for Particulate Matter (PM) and so is not repeated in detail here. Briefly, though, the use of multipollutant regression models has been the approach most commonly used to control for these potential copollutant confounders. One specific concern has been that a given pollutant may act as a surrogate for other unmeasured or poorly measured pollutants or pollutant mixtures. Specifically, traffic is a nearly ubiquitous source of combustion pollutant mixtures that include NO_2 and can be an important contributor to NO_2 levels in near-road locations. Although this

complicates efforts to disentangle specific NO_2-related health effects as distinct from those effects of the whole traffic-generated combustion mix, multipollutant models with terms for measured variables remain important tools for partitioning the variance structures in multisource epidemiologic studies.

Model specification and model selection also are factors to consider in the interpretation of the epidemiologic evidence. Epidemiologic studies investigated the association between various measures of NO_2 (e.g., multiple lags, different exposure metrics) and various health outcomes using different model specifications (for further discussion, see 2006 AQCD for Ozone [O_3] AQCD [U.S. Environmental Protection Agency, 2006]). The summary of health effects evidence in this chapter is vulnerable to the errors of publication bias and multiple testing, and efforts have been made to reduce the impact of multiple testing errors on the conclusions in this evaluation. 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 multipollutant models that include NO_2 were considered and examined for robustness of results.

Human clinical studies conducted in controlled exposure chambers use fixed concentrations of air pollutants under carefully regulated environmental conditions and subject activity levels to minimize possible confounding of the health associations by other factors. Additionally, sensitive experimental techniques can be used to measure health effects that are not evaluated in epidemiologic studies, e.g. airways hyperresponsiveness. These studies provide important information on the biological plausibility of associations observed between NO_2 exposure and health outcomes in epidemiologic studies. While human clinical studies provide a direct quantitative assessment of the NO_2 exposure-health response relationship, such studies have a number of limitations. First, it is requisite that subjects be either healthy individuals or individuals whose level of illness does not preclude them from participating in the study. Therefore, the results of human clinical studies may underestimate the health effects of exposure to certain sensitive subpopulations. Second, studies of controlled exposure to NO_2 typically have used concentrations that are higher than those normally present in ambient air. Third, human clinical studies normally are conducted on a relatively small number of subjects, which reduces the power of the study to detect significant differences in the health outcomes of interest between exposure to varying concentrations of NO_2 and clean air.

Similar to human clinical studies, animal toxicological studies have the advantage of being conducted under controlled conditions, using fixed concentrations of air pollutants in carefully regulated environmental conditions. These studies allow for evaluation of biological responses with exposures to substances in doses that could be hazardous to human health and for extended durations that are not possible in human clinical studies. However, limitations on study population size require the use of higher doses to allow the identification of rare events. An important caveat in interpretation of the toxicological data is that the high doses used in many of the studies may produce different effects on the lung than inhalation exposures at lower ambient concentrations. That is, "realistic" doses associated with ambient nitrogen oxides exposures may activate cells and pathways entirely disparate from those activated at high experimental doses. In addition, significant differences in biology can exist, depending on species and strain selected, that can affect the response.

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

3.1 RESPIRATORY MORBIDITY RELATED TO NO_2 SHORT-TERM EXPOSURE

In the 1993 AQCD for Oxides of Nitrogen, human clinical evidence indicated that NO_2 caused decrements in lung function, particularly increased airways resistance in healthy subjects, with exposures of >2.0 parts per million (ppm) for 2 h. Other studies showed increased airways responsiveness in healthy subjects at concentrations of >1 ppm for 1 h. Asthmatics and chronic obstructive pulmonary disease (COPD) patients demonstrated increased decrements in lung function that were dependent on exposure conditions. However, concentration-response relationships were not observed for changes in lung function, airways responsiveness, or symptoms, and no association was apparent between lung function responses and respiratory symptoms.

At the time of the 1993 AQCD for Oxides of Nitrogen, many of the available epidemiologic studies consisted predominately of indoor NO_2 exposure studies. Although indoor sources in these studies include both gas-fueled cooking and heating appliances, in most of the

earlier studies the focus was primarily on cooking stoves. Although there was some evidence suggesting that increased NO_2 exposure was associated with increased respiratory symptoms in children aged 5 to 12 years, the main conclusion was that there was insufficient epidemiologic evidence for an association between short-term exposure and health effects. The 1993 AQCD also presented an intervention study conducted in 1972 and 1973 in Chattanooga, TN (Shy and Love, 1980; Love et al., 1982) that reported a reduction of the respiratory illness rate in 1973 associated with a strike at a primary source that resulted in lowered NO_2 pollution. The study suggested that short-term (peak) exposure may be more important than long-term exposure to NO_2. A limitation of this study was that it offered only qualitative information evaluating the question of removing exposures leading to reduced risk.

Animal toxicology studies evaluated in the 1993 AQCD identified biochemical and cellular mechanisms whereby NO_2 induces effects at concentrations of as low as 0.04 ppm. The biochemical effects observed in the respiratory tract after NO_2 exposure include chemical alteration of lipids, amino acids, proteins, and enzymes and changes in oxidant/antioxidant homeostasis. Membrane polyunsaturated fatty acids and thiol groups are the main biochemical targets for NO_2 exposure. Data available in the 1993 AQCD indicated that NO_2 induces lipid peroxidation and changes in lipid content of cell membranes. The biochemical pertubations mentioned above could result in cellular damage either directly through the generation of reactive oxygen species, or by rendering the cells more susceptible to injury by altering the protective mechanisms (i.e. membrane integrity, antioxidant levels).

A large body of epidemiologic evidence has been published since the 1993 AQCD for Oxides of Nitrogen on respiratory health outcomes associated with short-term exposure to NO_2. The health outcomes studied included occurrence of respiratory symptoms, changes in lung function, and ED visits and hospitalizations for respiratory diseases. Relatively few new clinical and animal toxicologic studies have been published since 1993.

3.1.1 Lung Host Defenses and Immunity

Lung host defenses are sensitive to NO_2 exposure, with numerous measures of such effects observed at concentrations of <1 ppm. Potential mechanisms, according to Chauhan et al. (2003), include “direct effects on the upper and lower airways by ciliary dyskinesis (Carson et al., 1993), epithelial damage (Devalia et al., 1993a), increases in pro-inflammatory mediators

and cytokines (Devalia et al., 1993b), rises in IgE concentration (Siegel et al., 1997), and interaction with allergens (Tunnicliffe et al., 1994), or indirectly through impairment of bronchial immunity (Sandstrom et al., 1992a)." Table 3.1-1 summarizes a range of proposed mechanisms by which exposure to NO_2 in conjunction with viral infections may exacerbate upper and lower airways symptoms (Chauhan et al., 1998). Another major concern has been the potential for NO_2 exposure to enhance susceptibility to or the severity of illness resulting from respiratory infections and asthma, especially in children. The following discussion focuses on studies published since the 1993 AQCD and conducted at near-ambient exposure concentrations but, as needed, refers to studies in the 1993 AQCD for Oxides of Nitrogen.

Several epidemiologic studies investigated the host defenses interplay with prior NO_2 exposure and viral infection. Personal exposure to NO_2 and the severity of virus-induced asthma (Chauhan et al., 2003), including risk of airflow obstruction (Linaker et al., 2000) was studied in a group of 114 asthmatic children in England. Children were supplied with Palmes diffusion tubes, which they attached to their clothing during the day and placed in their bedroom at night. Tubes were changed every week for the duration of the 13-month study period. Nasal aspirates were obtained and analyzed for a variety of respiratory illness-causing viruses. The authors observed that exposure to NO_2 levels of greater than 14 $\mu g/m^3$ (7.4 parts per billion [ppb]) in the week preceding any viral infection was associated with increases in the four-point symptom severity score (score increase of 0.6 [95% CI: 0.01, 1.18]) in the week immediately after the infection. Associations also were observed for the respiratory syncytial virus (RSV) alone (score increase of 2.1 [95% CI: 0.52, 3.81]). A significant reduction in peak expiratory flow (PEF) was associated with exposure greater than 14 $\mu g/m^3$ (7.3 ppb) (by 12 L/min [95% CI: −23.6, −0.80]) (Chauhan et al., 2003). Exploration of the relationship between PEF and NO_2 showed that the risk of a PEF episode (as diagnosed by a clinician's review of each child's PEF data) beginning within a week of an upper respiratory infection was significantly associated with exposure to NO_2 greater than 28 $\mu g/m^3$ (14.9 ppb) (relative risk [RR] = 1.9 [95% CI: 1.1, 3.4]) (Linaker et al., 2000). Thus, high personal NO_2 exposure in the week before an upper respiratory infection was associated with either increased severity of lower respiratory tract symptoms or reduction of PEF for all virus types together and for two of the common respiratory viruses, C picornavirus and RSV, individually.

TABLE 3.1-1. PROPOSED MECHANISMS WHEREBY NO_2 AND RESPIRATORY VIRUS INFECTIONS MAY EXACERBATE UPPER AND LOWER AIRWAY SYMPTOMS

	Proposed Mechanisms
Upper Airways	
Epithelium	↓ Ciliary beat frequency
	↑ Epithelial permeability
Lower Airways	
Epithelium	(as in upper airways)
Cytokines	↓ Epithelial-derived IL-8, GM-CSF, TNF-α
	↑ Macrophage-derived IL-1b, IL-6, IL-8, TNF-α
Inflammatory cells	↑ Mast cell tryptase
	↑ Neutrophils
	↑ Total lymphocytes
	↑ NK lymphocytes
	↓ T-helper/T-cytotoxic cell ratio
Inflammatory mediators	↑ Free radicals, proteases, TXA_2, TXB_2, LTB_4
Allergens	↑ Penetrance due to ciliostasis
	↓ PD_{20}-FEV_1
	↑ Antigen-specific IgE
	↑ Epithelial permeability
Peripheral Blood	
	↓ Total macrophages
	↓ B and NK lymphocytes
	↓ Total lymphocytes

Source: Adapted from Chauhan et al. (1998).

Several clinical studies have attempted to address the question of whether NO_2 exposures impair host defenses and/or increase susceptibility to infection (Rehn et al., 1982; Goings et al., 1989; Rubenstein et al., 1991; Sandström et al. 1990, 1991, 1992a,b; Devlin 1992, 1999; Frampton et al., 2002) (see the 1993 AQCD for details of older studies and Annex Table AX5.2-1 for additional details on newer studies). These studies have reported inconsistent results. One approach has been to examine the effects of in vivo NO_2 exposure on the function

of alveolar macrophages (AMs) obtained by bronchoalveolar lavage (BAL), including the susceptibility of these cells to viral infection in vitro. Two studies since 1993 involved 2.0-ppm NO_2 exposures for 4 or 6 h with intermittent exercise and found no effect on AM inactivation of influenza virus either immediately or 18 h after exposure (Azadniv et al., 1998; Devlin et al., 1999). However, Devlin et al. (1999) found reduced AM phagocytic capacity after NO_2 exposure, suggesting a reduced ability to clear inhaled bacteria or other infectious agents. Frampton et al. (2002) examined NO_2 effects on viral infectivity of airways epithelial cells. Subjects were exposed to air, or 0.6- or 1.5-ppm NO_2, for 3 h, and bronchoscopy was performed 3.5 h after exposure. Epithelial cells were harvested from the airways by brushing and then challenged in vitro with influenza virus and RSV. NO_2 exposure did not alter viral infectivity, but appeared to enhance epithelial cell injury in response to infection with RSV ($p = 0.024$). Similar results were reported with influenza virus. These findings suggest that prior exposure to NO_2 may increase the susceptibility of the respiratory epithelium to injury by subsequent viral challenge.

There is evidence from both animal and human studies indicating that exposure to NO_2 may alter lymphocyte subsets in the lung and possibly in the blood. Lymphocytes, particularly T lymphocytes and NK cells, play a key role in the innate immune system and host defense against respiratory viruses. Rubenstein et al. (1991) found that a series of four daily, 2-h exposures to 0.60-ppm NO_2 resulted in a small increase in NK cells recovered by BAL. Sandström et al. (1990, 1991) observed a significant, dose-related increase in lymphocytes and mast cells recovered by BAL 24-h after a 20-min exposure to NO_2 at 2.25 to 5.50 ppm. In contrast, repeated exposures to 1.5- or 4-ppm NO_2 for 20 min every second day on six occasions resulted in decreased $CD16^+56^+$ (NK cells) and $CD19^+$ cells (B lymphocytes) in BAL fluid 24-h after the final exposure (Sandström et al., 1992a,b). No effects were reported on polymorphonuclear leukocytes (PMNs) or total lymphocyte numbers. Solomon et al. (2000) found a decrease in $CD4^+$ T lymphocytes in BAL fluid 18-h after three daily, 4-h exposures to 2.0-ppm NO_2. Azadniv et al. (1998) observed a small but significant reduction in $CD8^+$ T lymphocytes in peripheral blood, but not BAL fluid, 18 h following single 6-h exposures to 2.0-ppm NO_2. Frampton et al. (2002) found small increases in BAL lymphocytes and decreases in blood lymphocytes with exposures to 0.6 and 1.5 ppm NO_2 for 3 h.

The observed effects on lymphocyte responses, as described above, have not been consistent among studies. Differing exposure protocols and small numbers of subjects among these studies may explain the varying and conflicting findings. Furthermore, the clinical significance of transient, small changes in lymphocyte subsets is unclear. It is possible that the inflammatory response to NO_2 exposure involves both lymphocytes and PMNs, with lymphocyte responses occurring transiently and at lower concentrations, and PMN responses predominating at higher concentrations or more prolonged exposures. The airways lymphocyte responses do not provide convincing evidence of impairment in host defense.

One clinical study used fiber-optic bronchoscopy and found that 20-min exposures to NO_2 at 1.5 to 3.5 ppm transiently reduced airways mucociliary activity (Helleday et al., 1995). Reduced mucus clearance is expected to increase susceptibility to infection by reducing the removal rate of microorganisms from airways. However, the study was weakened by the lack of a true air control exposure as well as by the absence of randomization and blinding. As a clarification, Helleday et al. (1995) did not measure mucus clearance rates directly using radiolabeled particles; rather they utilized an optical technique to characterize ciliary activity. Rehn et al. (1982) examined the effect of NO_2 exposure on mucociliary clearance of a radiolabeled Teflon aerosol. After a 1-h exposure to either 0.27- or 1.06-ppm (500 or 2000 $\mu g/m^3$) NO_2, there were no changes in airways clearance rates.

Animal studies provide clearer evidence that host defense system components such as mucociliary transport and AMs (see Annex Table AX4.3) are targets for inhaled NO_2. Animal studies further show that NO_2 can impair the respiratory host defense system sufficiently to render the host more susceptible to respiratory infections (See Annex Table AX4.6). Exposure of guinea pigs to 3- or 9-ppm NO_2 6 h/day, 6 days/week for 2 weeks resulted in concentration-dependent decreases in ciliary activity of 12 and 30% of control values, respectively (Ohashi et al., 1994). These concentration-dependent decreases were accompanied by a concentration-dependent increase in eosinophil accumulation on the epithelium and submucosal connective tissue layer of the nasal mucosa. For foreign agents such as some bacteria and viruses that deposit below the mucociliary region in the gas-exchange region of the lung, AMs primarily provide host defenses by acting to remove or kill viable particles, remove nonviable particles, and process and present antigens to lymphocytes for antibody production. AMs are one of the sensitive targets for NO_2, as evidenced by in vivo animal exposures and in vitro studies (see

Annex Table AX4.3 for details of studies related to each of these morphological or functional parameters in exposed animals).

Suppression of host defense mechanisms by NO_2 as described in the studies above are expected to result in an increased incidence and severity of pulmonary infections (Miller et al., 1987, Gardner et al., 1979; Coffin and Gardner, 1972). Various experimental approaches have been employed using animals in an effort to determine the overall functional efficiency of the host's pulmonary defenses following NO_2 exposure. In the most commonly used infectivity model, animals are exposed to either NO_2 or filtered air and the treatment groups are combined and exposed briefly to an aerosol of a viable agent, such as *Streptococcus* spp., *Klebsiella pneumoniae*, *Diplococcus pneumoniae*, or influenza virus and mortality rates are determined (Ehrlich, 1966; Henry et al., 1970; Coffin and Gardner, 1972; Ehrlich et al., 1979; Gardner, 1982). Although the endpoint is mortality, this experimental test is considered a sensitive indicator of the depression of the defense mechanisms and is a commonly used assay for assessing immunotoxicity. The susceptibility to bacterial and viral pulmonary infections in animals also increases with NO_2 exposures of as low as 0.5 ppm. No new studies published since 1993 were identified that evaluated this endpoint. Annex Table AX4.6 summarizes the effects of NO_2 exposure and infectious agents in animal studies as compiled in the 1993 AQCD for Oxides of Nitrogen, and provides evidence that the host's response to inhaled NO_2 can be influenced significantly by the duration and temporal patterns of exposure. This is important in considering continuous versus intermittent exposures and attempting to understand observed differences in reported results.

Summary of Evidence on the Effect of Short-Term Exposure to NO_2 on Lung Host Defenses and Immunity

Impaired host-defense systems and increased risk of susceptibility to both viral and bacterial infections have been observed in epidemiologic, human clinical, and animal toxicological studies. A recent epidemiologic study provided evidence that increased personal exposures to NO_2 worsened virus-associated lower respiratory tract symptoms in children with asthma (Chauhan et al., 2003). The limited evidence from human clinical studies indicates that NO_2 may increase susceptibility to injury by subsequent viral challenge at exposures of as low as 0.6 ppm for 3 h (Frampton et al., 2002). Toxicological studies have shown that lung host defenses are sensitive to NO_2 exposure, with several measures of such effects observed at

concentrations of less than 1 ppm. The epidemiologic and experimental evidence together show coherence for effects of NO_2 exposure on host defense or immune system effects. This group of outcomes also provides plausibility and potential mechanistic support for other respiratory effects described subsequently, such as respiratory symptoms or ED visits for respiratory diseases.

3.1.2 Airways Inflammation

Epidemiologic studies have examined biological markers for inflammation (exhaled nitric oxide [NO] and inflammatory nasal lavage [NAL] markers) and lung damage (urinary Clara cell protein CC16). Several studies have been conducted in cohorts of children. Steerenberg et al. (2001) studied 126 schoolchildren from urban and suburban communities in the Netherlands. Sampling of exhaled air and NAL fluid was performed seven times, once per week over the course of 2 months. On average, the ambient NO_2 concentrations were 1.5 times higher, and ambient NO concentrations were 7.8 times higher, in the urban compared to the suburban community. Compared to children in the suburban community, urban children had significantly greater levels of inflammatory NAL markers (interleukin [IL]-8, urea, uric acid, albumin) but not greater levels of exhaled NO. However, within the urban group, a statistically significant concentration-response relationship for exhaled NO was observed. Exhaled NO increased by 6.4 to 8.8 ppb per 20-ppb increase in NO_2 lagged by 1 or 3 days. Another study by Steerenberg et al. (2003) of 119 schoolchildren in the Netherlands found associations between ambient NO_2 and level of exhaled NO, but quantitative regression results were not given. The authors concluded from their data that an established, ongoing inflammatory response to pollen was not exacerbated by subsequent exposure to high levels of air pollution or pollen.

In one recent U.S. study, Delfino et al. (2006) evaluated the relationship between personal and ambient levels of fine PM ($PM_{2.5}$), elemental carbon (EC), organic carbon (OC), and NO_2 and fractional exhaled NO (FE_{NO}), a biomarker of airway inflammation, in a panel of 45 schoolchildren with persistent asthma living in two southern California communities (Riverside and Whittier). FE_{NO} is higher in subjects with poorly controlled asthma. Positive associations were found for FE_{NO} with several air pollutants, including NO_2, with evidence from multipollutant approaches suggesting that traffic-related sources of air pollutants underlie the findings. The authors concluded that the "association of FE_{NO} with personal and ambient NO_2

was largely independent of personal and ambient EC and OC fractions of $PM_{2.5}$ in two-pollutant models, suggesting that both ambient and personal NO_2 represent other causal pollutant components not sufficiently captured by ambient EC or OC in the study regions." While the effect was small ($\leq$2.5 ppb FE_{NO}), making it difficult to determine if it is clinically relevant, the findings suggest that air pollutant exposure increases inflammation in children.

Several studies have evaluated effects in adult cohorts. Adamkiewicz et al. (2004) studied 29 elderly adults in Steubenville, OH and found significant associations between increased exhaled NO and increased daily levels of $PM_{2.5}$, but no association was found with ambient NO_2. Timonen et al. (2004) collected biweekly urine samples for 6 months from 131 adults with coronary heart disease living in Amsterdam, Helsinki, and Erfurt, Germany. Estimates using data from all three communities showed significant associations between urinary levels of Clara cell protein CC16 (a marker for lung damage) with elevations in daily $PM_{2.5}$ concentration, but not ambient NO_2. In Helsinki, however, a statistically significant positive association was observed between NO_2 lagged by 3 days and CC16 levels. Interestingly, the correlation between NO_2 and $PM_{2.5}$ was lower in Helsinki ($r = 0.35$) compared to this correlation in Amsterdam ($r = 0.49$) or Erfurt ($r = 0.82$). Bernard et al. (1998) examined personal exposure to NO_2 and its effect on plasma antioxidants in a group of 107 healthy adults in Montpellier, France. Subjects wore passive monitors for 14 days. When subjects were divided into two exposure groups (above and below 40 $\mu g/m^3$ [21.3 ppb]), those in the high-exposure group had significantly lower plasma β-carotene levels. This difference was even greater when the analysis was stratified by dietary β-carotene intake: exposure to >40-$\mu g/m^3$ (21.3 ppb) NO_2 had the largest effect on plasma β-carotene level among subjects whose diet contained <4 mg/day β-carotene ($p < 0.005$). No other pollutants were included in this study.

The 1993 AQCD for Oxides of Nitrogen cited preliminary findings from two clinical studies showing modest airways inflammation, as indicated by increased PMN numbers in BAL fluid after exposure to 2.0-ppm NO_2 for 4 to 6 h with intermittent exercise. Both of those studies now have been published in complete form (Azadniv et al, 1998; Devlin et al, 1999), and additional studies summarized below provide a clearer picture of the airways inflammatory response to NO_2 exposure.

Annex Table AX5.1 summarizes the key clinical studies of NO_2 exposure in healthy subjects published since 1993, with a few key studies included prior to that date. Figure 3.1-1

illustrates the dose-response relationship between NO_2 exposure and inflammatory responses in healthy subjects.

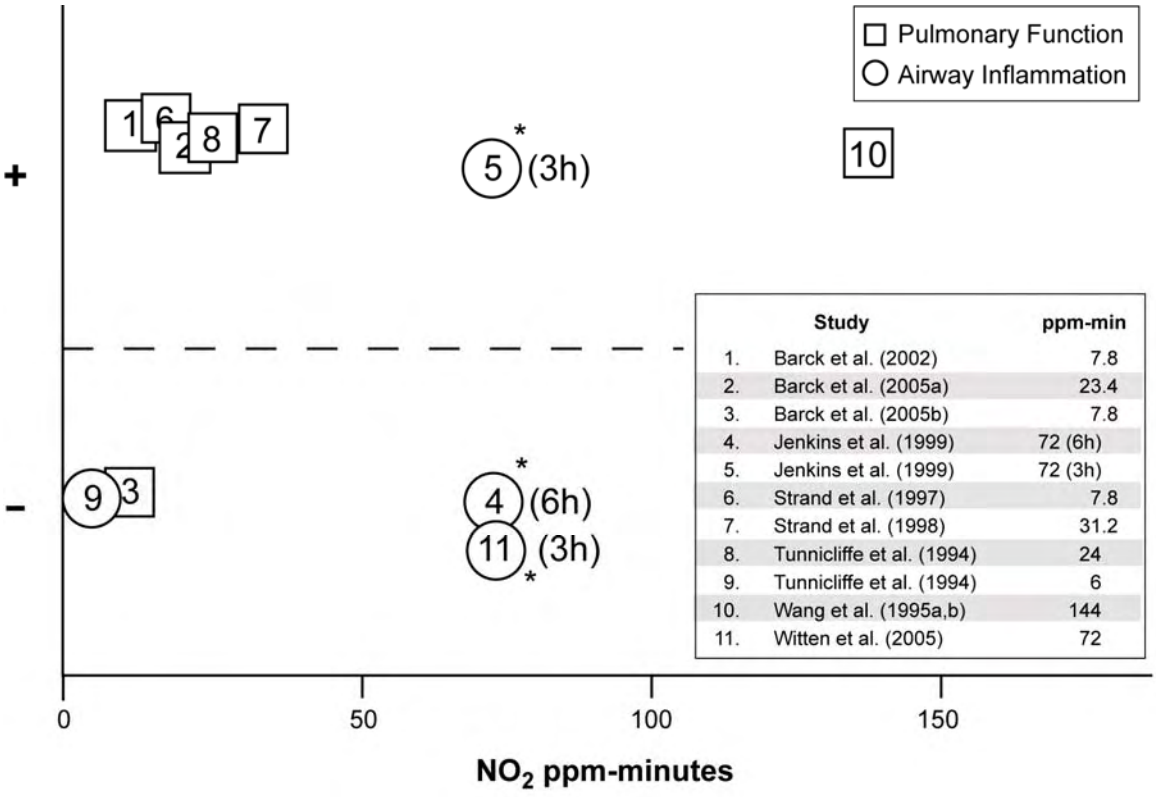

Figure 3.1-1. Studies of airways inflammatory responses in relation to the total exposure to NO_2, expressed as ppm-minutes. All of the studies involved intermittent exercise, and no attempt was made to adjust the exposure metric for varying intensity and duration of exercise. Studies that did not include a proper control air exposure and those that used multiple daily exposures were not included in this figure.

Healthy volunteers exposed to 2.0-ppm NO_2 for 6 h with intermittent exercise showed a slight increase in the percentage of PMNs obtained in BAL fluid 18 h after exposure (air, 2.2 ± 0.3%; NO_2, 3.1 ± 0.4%) (Azadniv et al., 1998). Gavras et al. (1994) studied a separate group of subjects exposed using the same protocol but assessed immediately after exposure. In this case, no effects were found in AM phenotype or expression of the cell adhesion molecule CD11b or receptors for IgG. Blomberg et al. (1997) reported that 4-h exposures to 2.0-ppm NO_2 resulted in an increase in IL-8 and PMNs in the proximal airways of healthy subjects, although no changes were seen in bronchial biopsies. This group also studied the effects of repeated 4-h

exposures to 2-ppm NO_2 on 4 consecutive days, with BAL, bronchial biopsies, and BAL fluid antioxidant levels assessed 1.5-h after the last exposure (Blomberg et al., 1999). The bronchial wash fraction of BAL fluid showed a 2-fold increase in PMNs and a 1.5-fold increase in myeloperoxidase, indicating persistent mild airways inflammation with repeated NO_2 exposure. Devlin et al. (1999) exposed 8 healthy nonsmokers to 2.0-ppm NO_2 for 4-h with intermittent exercise. BAL performed the following morning showed a 3.1-fold increase in PMNs recovered in the bronchial fraction, indicating small airways inflammation. These investigators also observed a reduction in AM phagocytosis and superoxide production, indicating possible adverse effects on host defense.

Pathmanathan et al. (2003) conducted four repeated daily exposures of healthy subjects to 4-ppm NO_2 or air for 4 h, with intermittent exercise. Exposures were randomized and separated by 3 weeks. Bronchoscopy and bronchial biopsies were performed 1-h after the last exposure. Immunohistochemistry of the respiratory epithelium showed increased expression of IL-5, IL-10, and IL-13, as well as intercellular adhesion molecule-1 (ICAM-1). These interleukins are upregulated in Th2 inflammatory responses, which are characteristic of allergic inflammation. The findings suggest repeated NO_2 exposures may drive the airways inflammatory response toward a Th2 or allergic-type response. Unfortunately, the report provided no data on inflammatory cell responses in the epithelium or on the cells or cytokines in BAL fluid. Thus, the findings cannot be considered conclusive regarding allergic inflammation. Furthermore, the exposure concentrations of 4 ppm are considerably higher than ambient outdoor concentrations.

Recent studies provide evidence for airways inflammatory effects at concentrations of <2.0 ppm. Frampton et al. (2002) examined NO_2 concentration responses in 21 healthy nonsmokers. Subjects were exposed to air or 0.6- or 1.5-ppm NO_2 for 3 h, with intermittent exercise, with exposures separated by at least 3 weeks. BAL was performed 3.5-h after exposure. PMN numbers in the bronchial lavage fraction increased slightly (<3-fold) but significantly ($p = 0.0003$) after exposure to 1.5-ppm NO_2; no increase was evident at 0.6-ppm NO_2. Lymphocyte numbers increased in the bronchial lavage fraction after 0.6-ppm NO_2, but not 1.5 ppm. $CD4^+$ T lymphocyte numbers increased in the alveolar lavage fraction, and lymphocytes decreased in blood. These findings suggest a lymphocytic airways inflammatory response to 0.6-ppm NO_2, which changes to a mild neutrophilic response at 1.5-ppm NO_2. Solomon et al. (2000) also showed increased PMNs in the bronchial fraction of BAL 18 h after

the third consecutive day of exposure to 2.0 ppm NO_2 for 4 h with intermittent exercise. Jörres et al. (1995) found that 3-h exposures to 1-ppm NO_2 with intermittent exercise altered levels of eicosanoids, but not inflammatory cells, in BAL fluid collected 1-h after exposure. Eicosanoids are chemical mediators of the inflammatory response; their increase in BAL fluid reported in this study suggests inflammation. The absence of an increase in PMN numbers may reflect the timing of bronchoscopy (1 h after exposure). The peak influx of PMNs may occur several hours after exposure, as it does following NO_2 exposure.

The clinical studies summarized above provide evidence for airways inflammation at NO_2 concentrations of <2.0 ppm in healthy adults. Analyzing the bronchial fraction of BAL separately appears to increase the sensitivity for detecting airways inflammatory effects of NO_2 exposure. The onset of inflammatory responses in healthy subjects appears to be between 100 and 200 ppm-min, i.e., 1 ppm for 2 to 3 h (see Figure 3.1-1).

Animal toxicological studies demonstrating changes in protein and enzyme levels in the lung following inhalation of NO_2 are presented in Annex Table AX4.2. These studies are reported in the 1993 AQCD and summarized below. Changes in protein and enzyme levels reflect the ability of NO_2 to cause lung inflammation associated with concomitant infiltration of serum protein, enzymes, and inflammatory cells. However, interpretation of the array of changes observed may also reflect other factors. For example, NO_2 exposure may induce differentiation of some cell populations in response to damage-induced tissue remodeling. Thus, some changes in lung enzyme activity and protein content may reflect changes in cell types, rather than the direct effects of NO_2 on protein infiltration. Furthermore, some direct effects of NO_2 on enzymes are possible because NO_2 can oxidize certain reducible amino acids or side chains of proteins in aqueous solution (Freeman and Mudd, 1981).

It has been reported that protein content changes in BAL fluid can be dependent on dietary antioxidant status. NO_2 exposure increases the protein content of BAL fluid in vitamin C-deficient guinea pigs at NO_2 levels of as low as 1880 $\mu g/m^3$ (1.0 ppm) after a 72-h exposure, but a 1-week exposure to 752 $\mu g/m^3$ (0.4 ppm) did not increase protein levels (Selgrade et al., 1981). However, Sherwin and Carlson (1973) found increased protein content of BAL fluid from vitamin C-deficient guinea pigs exposed to 752-$\mu g/m^3$ (0.4 ppm) NO_2 for 1 week. Differences in exposure techniques, protein measurement methods, and/or degree of vitamin C deficiencies may explain the difference between the two studies. Hatch et al. (1986) found that

the NO_2-induced increase in BAL protein in vitamin C-deficient guinea pigs was accompanied by an increase in lung content of nonprotein sulfhydryls and ascorbic acid and a decrease in vitamin E content. The increased susceptibility to NO_2 was observed when lung vitamin C was reduced (by diet) to levels <50% of normal.

Studies in rats and mice published since the 1993 AQCD for Oxides of Nitrogen have investigated the ability of NO_2 to induce protein level changes consistent with inflammation. Overall, these newer studies, such as Muller et al. (1994) and Pagani et al. (1994), suggest that markers of inflammation measured in BAL fluid such as total protein content and content of markers of cell membrane permeability (e.g., lactate dehydrogenase [LDH]) increase only at or above 5-ppm exposure.

Summary of Evidence on the Effect of Short-Term Exposure to NO_2 on Airways Inflammation

Overall, short-term exposure to NO_2 has been found to increase airways inflammation in human clinical and animal toxicological studies with exposure concentrations that are higher than ambient levels. Human clinical studies provide evidence for increased airways inflammation at NO_2 concentrations of <2.0 ppm; the onset of inflammatory responses in healthy subjects appears to be between 100 and 200 ppm-min, i.e., 1 ppm for 2 to 3 h. Increases in biological markers of inflammation were not observed consistently in healthy animals at levels of less than 5 ppm; however, increased susceptibility to NO_2 concentrations of as low as 0.4ppm was observed when lung vitamin C was reduced (by diet) to levels <50% of normal. The few available epidemiologic studies are suggestive of an association between ambient NO_2 concentrations and inflammatory response in the airways in children, though the associations were inconsistent in the adult populations examined.

3.1.3 Airways Hyperresponsiveness

Inhaled pollutants such as NO_2 may have direct effects on lung function, or they may enhance the inherent responsiveness of the airways to challenge with a bronchoconstricting agent. Asthmatics are generally more sensitive to nonspecific bronchoconstricting agents than nonasthmatics, and airways challenge testing is used as a diagnostic test in asthma. There is a wide range of airways responsiveness in healthy people, and responsiveness is influenced by many factors, including medications, cigarette smoke, pollutants, respiratory infections, occupational exposures, and respiratory irritants. Several drugs and other stimuli that cause

bronchoconstriction have been used in challenge testing, including the cholinergic drugs methacholine and carbachol, as well as histamine, hypertonic saline, cold air, and sulfur dioxide (SO_2). Challenge with "specific" allergens is considered in asthmatics. Standards for airways challenge testing have been developed for the clinical laboratory (American Thoracic Society, 2000a). However, variations in methods for administering the bronchoconstricting agents may substantially affect the results (Cockcroft et al., 2005).

3.1.3.1 Allergen Responsiveness

Clinical Studies of Allergen Responsiveness in Asthmatic Persons

In asthmatics, inhalation of an allergen to which a person is sensitized can cause bronchoconstriction and increased airways inflammation, and this is an important cause of asthma exacerbations. Aerosolized allergens can be used in controlled airways challenge testing in the laboratory, either clinically to identify specific allergens to which the individual is responsive or in research to investigate the pathogenesis of the airways allergic response or the effectiveness of treatments. The degree of responsiveness is a function of the concentration of inhaled allergen, the degree of sensitization as measured by the level of allergen-specific IgE, and the degree of nonspecific airways responsiveness (Cockcroft and Davis, 2006).

It is difficult to predict the level of responsiveness to an allergen, and although rare, severe bronchoconstriction can occur with inhalation of very low concentrations of allergen. Allergen challenge testing, therefore, involves greater risk than nonspecific airways challenge with drugs such as methacholine. Asthmatics may experience both an "early" response, with declines in lung function within minutes after the challenge, and a "late" response, with a decline in lung function hours after the exposure. The early response primarily reflects release of histamine and other mediators by airways mast cells; the late response reflects enhanced airways inflammation and mucous production. Responses to allergen challenge are typically measured as changes in pulmonary function, such as declines in the forced expiratory volume in 1 s (FEV_1). However, the airways inflammatory response can also be assessed using BAL, induced sputum, or exhaled breath condensate.

The potential for NO_2 exposure to enhance responsiveness to allergen challenge in asthmatics deserves special mention. Several recent studies, summarized in Annex Table AX5.3-2, have addressed the question of whether 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 airways inflammatory response. Figure 3.1-2 categorizes the allergen challenge studies as "positive," i.e., showing evidence for increased responses to allergen in association with NO_2 exposure, or "negative," with the exposure metric expressed as ppm-min. In comparing Figure 3.1-2 with Figure 3.1-1, the enhancement of allergic responses in asthmatics occurs at exposure levels more than an order of magnitude lower than those associated with airway inflammation in healthy subjects. The dosimetry difference is even greater when considering that the allergen challenge studies generally were performed at rest, while the airway inflammation studies in healthy subjects were performed with intermittent exercise.

Tunnicliffe et al. (1994) exposed 8 subjects with mild asthma to 0.1- or 0.4-ppm NO_2 for 1 h at rest and reported that 0.4-ppm NO_2 exposure slightly increased responsiveness to a fixed dose of allergen during both the early and late phases of the response. In two U.K. studies (Devalia et al., 1994; Rusznak et al., 1996), exposure to the combination of 0.4-ppm NO_2 and 0.2-ppm SO_2 increased responsiveness to subsequent allergen challenge in mild atopic asthmatics, whereas neither pollutant alone altered allergen responsiveness.

A series of studies from the Karolinska Institute in Sweden have explored airways responses to allergen challenge in asthmatics. Strand et al. (1997) demonstrated that single 30-min exposures to 0.26-ppm NO_2 increased the late phase response to allergen challenge 4 h after exposure. In a separate study (Strand et al., 1998), four daily repeated exposures to 0.26-ppm NO_2 for 30 min increased both the early and late phase responses to allergen. Barck et al. (2002) used the same exposure and challenge protocol as used in the earlier Strand et al. (1997) studies (0.26 ppm for 30 min, with allergen challenge 4-h after exposure) and performed BAL 19-h after the allergen challenge to determine NO_2 effects on the allergen-induced inflammatory response. NO_2 followed by allergen caused increases in the BAL recovery of PMN and eosinophil cationic protein (ECP), with reduced volume of BAL fluid and reduced cell viability, compared with air followed by allergen. ECP is released by degranulating eosinophils, is toxic to respiratory epithelial cells, and is thought to play a role in the pathogenesis of airways injury in asthma. These findings indicate that NO_2 exposure enhanced the airways inflammatory response to allergen. Subsequently, Barck et al. (2005a) exposed 18 mild asthmatics to air or

NO_2 for 15 min on day 1, followed by two 15-min exposures separated by 1-h on day 2, with allergen challenge after exposures on both days 1 and 2. Sputum was induced before exposure

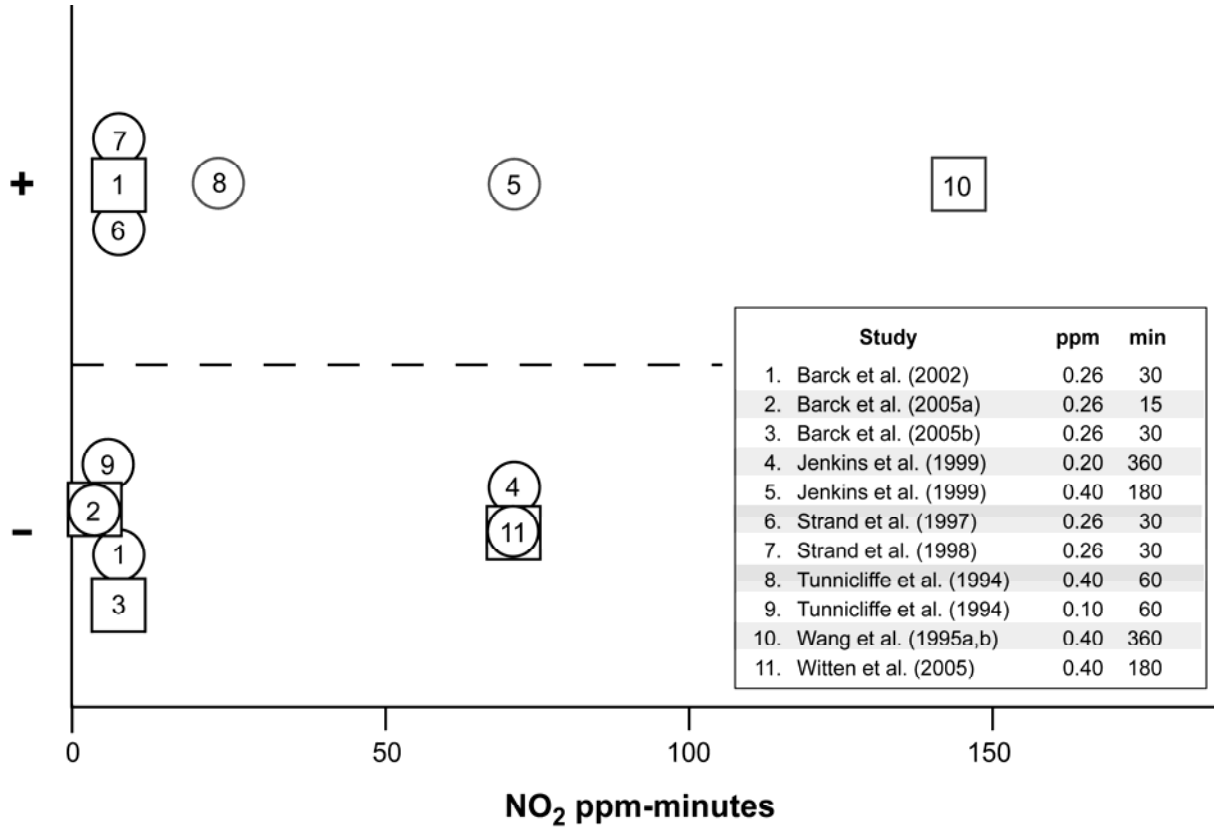

Figure 3.1-2. Airways responsiveness to allergen challenge in asthmatic subjects following a single exposure to NO_2. Responsiveness was assessed using spirometric (circles) and inflammatory (squares) endpoints. On the vertical axis, positive and negative indicate studies finding statistically significant and non-significant effects of NO_2 on group mean responsiveness to allergen, respectively.

on day 1 and after exposures (morning of day 3). NO_2 + allergen, compared to air + allergen, treatment resulted in increased levels of ECP in both sputum and blood and increased myeloperoxidase levels in blood. A separate study examined NO_2 effects on nasal responses to nasal allergen challenge (Barck et al., 2005b). Single 30-min exposures to 0.26 ppm NO_2 did not enhance nasal allergen responses. All exposures in the Karolinska Institute studies (Barck et al., 2002, 2005a; Strand et al., 1997, 1998) used subjects at rest. These studies utilized an adequate number of subjects, included air control exposures, randomized exposure order, and separated

exposures by at least 2 weeks. Together, they indicate that quite brief exposures to 0.26-ppm NO_2 can cause effects in allergen responsiveness in asthmatics.

The findings in these studies of allergen responsiveness may shed some light on the variable results in earlier studies of NO_2 effects on nonspecific airways responsiveness. It is possible that some prior studies may have been variably confounded by environmental allergen exposure, increasing the variability in subject responses to NO_2 and perhaps explaining some of the inconsistent findings.

Several studies have been conducted using longer NO_2 exposures. Wang et al. (1995a,b, 1999) found that more intense (0.4 ppm) and prolonged (6 h) NO_2 exposures enhanced allergen responsiveness in the nasal mucosa in subjects with allergic rhinitis. Jenkins et al. (1999) examined FEV_1 decrements and airways responsiveness to allergen in a group of mild, atopic asthmatics. The subjects were exposed for 3-h to 0.4-ppm NO_2, 0.2-ppm O_3, and 0.4-ppm NO_2 + 0.2-ppm O_3. The subjects were also exposed for 6-h to produce exposure concentrations that would provide identical doses to the 3-h protocols (i.e., equivalent in concentration times duration of exposure [C $\times$ T]). Significant increases in airways responsiveness to allergen occurred following all the 3-h exposures, but not following the 6-h exposures. However, Witten et al. (2005) did not find enhanced airways inflammation or a reduction in allergen provocative dose that produces a 20% decrease in FEV_1 (PD_{20}-FEV_1) with allergen challenge in 15 asthmatic subjects allergic to house dust mite allergen who were exposed to air and 0.4 ppm NO_2 for 3-h with intermittent exercise. Allergen challenge was performed immediately after exposure, and sputum induction was performed 6 and 26 h after the allergen challenge. There was no overall effect of NO_2 on allergen responsiveness, although 3 subjects required a much smaller concentration of allergen after NO_2 than after air exposure and were deemed to be NO_2 "responders." NO_2 exposure was surprisingly associated with a reduction in sputum eosinophils, with no increase in allergen-induced neutrophilic inflammation.

The differing findings in these studies may relate in part to differences in timing of the allergen challenge, the use of multiple- versus single-dose allergen challenge, the use of BAL versus sputum induction, exercise versus rest during exposure, and differences in subject susceptibility. Taken together, these studies suggest that NO_2 short-term exposures of less than 1 ppm enhance allergen responsiveness in some allergic asthmatics.

Lastly, one study examined the effects on allergen responsiveness of exposure to traffic exhaust in a tunnel (Svartengren et al., 2000). Twenty mild asthmatics sat in a stationary vehicle within a busy tunnel for 30 min. Allergen challenge was performed 4 h later. The control exposure was in a hotel room in a suburban area with low air pollution levels. Exposures were separated by 4 weeks and the order was randomized. Median NO_2 levels in the vehicle were 313 $\mu g/m^3$ (range, 203 to 462), or 0.166 ppm, (range, 0.106 to 0.242). PM_{10} levels were 170 $\mu g/m^3$ (range, 103 to 613), and $PM_{2.5}$ levels were 95 $\mu g/m^3$ (range, 61 to 128). Median NO_2 levels outside the hotel were 11 $\mu g/m^3$ or 0.006 ppm. Subjects in the tunnel experienced increased cough, and also reported awareness of noise and odors. More importantly, there was a greater allergen-induced increase in specific airways resistance after the tunnel exposure than after the control exposure (44% versus 31% respectively). Thoracic gas volume also was increased to a greater degree after the tunnel exposure, suggesting increased gas trapping within the lung. These findings were most pronounced in the subjects exposed to the highest levels of NO_2. This study suggests that exposure to traffic exhaust, and particularly the NO_2 component, increases allergen responsiveness in asthmatics, and the results fit well with the findings in studies of clinical exposures of NO_2 (Barck et al., 2002, 2005a). However, it was not possible to blind the exposures, and the control exposure (hotel room, presumably quiet and relaxed) was not well matched to the experimental exposure (vehicle, noisy, odorous). It remains possible that factors other than NO_2 contributed to, or were responsible for, the observed differences in allergen responsiveness.

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 airways inflammatory response. Enhancement of allergic responses in asthmatics occurs at exposure levels of more than an order of magnitude lower than those associated with airways inflammation in healthy subjects. The dosimetry difference is even greater when considering that the allergen challenge studies generally were performed at rest, while the airways inflammation studies in healthy subjects were performed with intermittent exercise. Enhancement of allergen responses has been found at exposures of as low as 8 ppm-min, i.e., 0.26 ppm for 30 min. Additional work is needed to understand more completely the exposure-response characteristics of NO_2 effects on allergen responses, as well as the effects of exercise,

relationship to the severity of asthma, the role of asthma medications, and other clinical factors. Additional animal and in vitro studies are needed to establish the precise mechanisms involved.

Toxicologic Studies of Allergen Responsiveness

Acute exposures of Brown Norway rats to NO_2 at a concentration of 5 ppm for 3 h resulted in increased specific immune response to house dust mite allergen and increased immune-mediated pulmonary inflammation (Gilmour et al., 1996). Higher levels of antigen-specific serum IgE, local IgA, IgG, and IgE were observed when rats were exposed to NO_2 after both the immunization and challenge phase but not after either the immunization or challenge phase alone. Increases in the number of inflammatory cells in the lungs and lymphocyte responsiveness to house dust mite allergen in the spleen and mediastinal lymph node were observed. The authors concluded that this increased immune responsiveness to house dust mite allergen may be the result of the increased lung permeability caused by NO_2 exposure, enhancing translocation of the antigen to local lymph nodes and circulation to other sites in the body.

A delayed bronchial response, seen as increased respiration rate, occurred in NO_2-exposed, *Candida albicans*-sensitized guinea pigs 15 to 42 h after a challenge dose of *C. albicans* (Kitabatake et al., 1995). Guinea pigs were given an intraperitoneal injection of *C. albicans*, followed by a second injection 4 weeks later. Two weeks after the second injection, the animals were given an inhalation exposure of killed *C. albicans*. Animals were also exposed 4 h/day to 4.76-ppm NO_2 from the same day as the first injection of *C. albicans*, for a total of 30 exposures (5 days/week).

In a study with NO_2-exposed rabbits, pulmonary function (lung resistance, dynamic compliance) was not affected when immunized intraperitoneally within 24-h of birth until 3 months of age to either *Alternaria tenuis* or house dust mite antigen. The rabbits were given intraperitoneal injections once weekly for 1 month, and then every 2 weeks thereafter, and exposed to 4-ppm NO_2 for 2 h daily (Douglas et al., 1994).

To determine the effect of NO_2 on allergenic airways responses in sensitized animals, Hubbard et al. (2002) exposed ovalbumin (OVA)-sensitized mice to NO_2 (0.7 or 5 ppm, 2 h/day for 3 days) or air. While the air-exposed mice developed lower airways inflammation (increased total BAL cellularity and increased eosinophil levels), the NO_2-exposed mice had significantly lower levels of eosinophils for both NO_2 concentrations, with the greatest effect seen at the lower NO_2 concentration. These results were confirmed in a subsequent study (0.7-ppm NO_2 for 3 or

10 days) showing significant reductions in BAL cellularity and eosinophil levels for both time points. In a similar study (Proust et al., 2002), mice were sensitized and challenged with OVA and then exposed to NO_2 (5 or 20 ppm, 3 h). The 20-ppm NO_2 exposure resulted in a significant increase in bronchopulmonary hyperreactivity 24 h after exposure, as compared to the OVA-air and 5-ppm NO_2 group. However, exposure to 5-ppm NO_2 resulted in a marked reduction in bronchopulmonary hyperreactivity as compared to both the 20-ppm NO_2 and OVA-air groups. By 72 h, bronchopulmonary hyperreactivity in all groups were comparable. The measurement of fibronectin in the BAL fluid was used as a marker of epithelial permeability. At 24 h after exposure, fibronectin levels were significantly higher in the 20-ppm NO_2 group as compared to both the 5-ppm NO_2 and air groups. However, fibronectin levels in the 5-ppm NO_2 group were significantly lower than the OVA-air group. After 72 h, there was no difference in fibronectin levels between the OVA-air and 5-ppm NO_2 groups, while fibronectin levels of the 20-ppm NO_2 group remained significantly higher than the 5-ppm NO_2 group. The recruitment of PMNs as measured in the BAL fluid at 24 h postexposure, revealed a dose-dependent increase reaching significance only with the 20-ppm NO_2 exposure. By 72 h, all groups were comparable. In contrast, the recruitment of eosinophils, as measured in the BAL fluid, showed no significant differences between groups at the 24 h time point, yet at the 72-h point, eosinophils were significantly decreased in the 5 ppm NO_2 group as compared to OVA-air group. Eosinophil peroxidase (EPO) in the lung tissue showed a similar trend with NO_2 exposure reducing the EPO levels as compared to OVA-air controls. At 24 h, EPO was significantly lower in the 5- and 20-ppm NO_2 groups as compared to the OVA-air group, while at 72 h, only the 5-ppm NO_2 group was significantly lower. IL-5 was measured in the BAL fluid, and the 5-ppm NO_2 group was significantly lower in IL-5 than all other groups, and the 20-ppm NO_2 was significantly higher.

3.1.3.2 Nonspecific Responsiveness

Nonspecific Responsiveness in Healthy Individuals

Several observations indicate that NO_2 exposures in the range of 1.5 to 2.0 ppm cause small but significant increases in airways responsiveness in healthy subjects. Mohsenin (1988) found that a 1-h exposure to 2-ppm NO_2 increased responsiveness to methacholine, as measured by changes in specific airways conductance, without directly affecting lung function.

Furthermore, pretreatment with ascorbic acid prevented the NO_2-induced increase in airways responsiveness (Mohsenin, 1987a). A mild increase in responsiveness to carbachol was observed following a 3-h exposure to 1.5-ppm NO_2, but not to intermittent peaks of 2.0 ppm (Frampton et al., 1991). Thus, the lower threshold concentration of NO_2 for causing increases in nonspecific airways responsiveness in healthy subjects appears to be in the 1- to 2-ppm range.

Nonspecific Responsiveness in Asthmatic Individuals

The 1993 AQCD for Oxides of Nitrogen reported results from some early studies that suggested that NO_2 might enhance subsequent responsiveness to challenge was observed in some, but not all studies, at relatively low NO_2 concentrations within the range of 0.2 to 0.3 ppm. Appearing in Tables 15-9 and 15-10 of the 1993 AQCD, the meta-analysis by Folinsbee (1992) also provided suggestive evidence of increased airways responsiveness in 63% of asthmatics exposed to a NO_2 concentration of only 0.1 ppm for 1 h during rest. However, numerous studies had not reported independent effects of NO_2 on lung function in asthmatic individuals.

Roger et al. (1990), in a comprehensive, concentration-response experiment, were unable to confirm the results of a pilot study suggesting airways responses occur in asthmatic subjects. Twenty-one male asthmatics exposed to NO_2 at 0.15, 0.30, or 0.60 ppm for 75 min did not experience significant effects on lung function or airways responsiveness compared with air exposure. Bylin et al. (1985) found significantly increased bronchial responsiveness to histamine challenge compared with sham exposure in 8 atopic asthmatics exposed to 0.30-ppm NO_2 for 20 min. Five of 8 asthmatics demonstrated increased reactivity, while 3 subjects showed no change, as assessed by specific airways resistance. Mohsenin (1987b) reported enhanced responsiveness to methacholine in 8 asthmatic subjects exposed to 0.50-ppm NO_2 at rest for 1 h; airways responsiveness was measured by partial expiratory flow rates at 40% vital capacity, which may have increased the sensitivity for detecting small changes in airways responsiveness. Jörres and Magnussen (1991) found no effects on lung function or methacholine responsiveness in 11 patients with mild asthma after exposure to 0.25-ppm NO_2 for 30 min with 10 min of exercise. Strand et al. (1996) performed a series of studies in mild asthmatics exposed to 0.26 ppm for 30 min and found increased responsiveness to histamine as well as to allergen challenge.

The effects of NO_2 exposure on SO_2-induced bronchoconstriction have been examined, but with inconsistent results. Jörres and Magnussen (1990) found an increase in airways

responsiveness to SO_2 in asthmatic subjects following exposure to 0.25-ppm NO_2 for 30 min at rest; yet Rubenstein et al. (1990) found no change in responsiveness to SO_2 inhalation following exposure of asthmatics to 0.30-ppm NO_2 for 30 min with 20 min of exercise.

The varied results of these studies have not been satisfactorily explained. It is evident that a wide range of responses occurs among asthmatics exposed to NO_2. This variation may in part reflect differences in subjects and exposure protocols: mouthpiece versus chamber, obstructed versus non-obstructed asthmatics, rest versus exercise, and varying use of medication(s) among subjects. Indeed, via meta-analysis, Folinsbee (1992) found that airways responsiveness was greater in asthmatics exposed to NO_2 at rest than during exercise. Following NO_2 exposures of between 0.2- and 0.3-ppm NO_2, only 52% of subjects exposed with exercise had increased responsiveness, whereas 76% of subjects had increased responsiveness in protocols using resting exposures. Identification of factors that predispose to NO_2 responsiveness also is needed. These studies have typically involved volunteers with mild asthma; data are lacking from more severely affected asthmatics, who may be more susceptible. Overall, there is suggestive evidence that short-term exposures to NO_2 at outdoor ambient concentrations (<0.3 ppm) alters lung function or nonspecific airways responsiveness in people with mild asthma. However, it remains possible that more severe asthmatics, or individuals with particular sensitivity to NO_2 airways effects, would experience reductions in lung function or increased airways responsiveness when exercising outdoors at NO_2 concentrations of <0.3 ppm.

Toxicological Studies of Airways Responsiveness

In the previous review, toxicological evidence supported a conclusion that airways responsiveness was one of the key health responses to NO_2 exposure. A number of recent animal studies have also reported airways responsiveness with NO_2 exposure. Overall, many studies have demonstrated the ability of NO_2 exposure to increase bronchial sensitivity to various challenge agents, although the mechanisms for this response are not fully known.

Kobayashi and Miura (1995) studied the concentration- and time-dependency of airways hyperresponsiveness to inhaled histamine aerosol in guinea pigs exposed subchronically to NO_2. In one experiment, guinea pigs were exposed by inhalation to 0-, 0.06-, 0.5-, or 4.0-ppm NO_2, 24 h/day for 6 or 12 weeks. Immediately following the last exposure, airways responsiveness was assessed by measurement of specific airways resistance as a function of increasing concentrations of histamine aerosol. Animals exposed to 4-ppm NO_2 for 6 weeks exhibited

increased airways response to inhaled histamine aerosol; airways response at 12 weeks was not determined. No effects were observed at the lower exposure levels. In another experiment conducted in this study (Kobayashi and Miura, 1995), guinea pigs were exposed by inhalation to 0-, 1.0-, 2.0-, or 4.0-ppm NO_2, 24 h/day for 6 or 12 weeks, and the airways hyperresponsiveness was determined. Increased hyperresponsiveness to inhaled histamine was observed in animals exposed to 4 ppm for 6 weeks, 2 ppm for 6 and 12 weeks, and 1 ppm for 12 weeks only. The results also showed that at 1- or 2-ppm NO_2, airways hyperresponsiveness developed to a higher degree with the passage of time. Higher concentrations of NO_2 were found to induce airways hyperresponsiveness faster compared to lower concentrations. When the specific airways resistance was compared to values determined 1 week prior to initiation of the NO_2 exposure, values were increased in the 2.0- and 4.0-ppm animals at 12 weeks only. Specific airways resistance was also increased to a higher degree with the passage of time.

3.1.3.3 Summary of Evidence on the Effect of Short-Term Exposure to NO_2 on Airways Responsiveness

The evidence from human and animal experimental studies provides suggestive evidence for increased airways responsiveness to specific allergen challenges following NO_2 exposure. Recent human clinical studies involving allergen challenge suggest that NO_2 exposure may enhance the sensitivity to allergen-induced decrements in lung function and increase the allergen-induced airway inflammatory response at exposures of as low as 0.26-ppm NO_2 for 30 min (Figure 3.1-2). The inflammatory responses to the allergen challenge were not accompanied by any changes in pulmonary function or subjective symptoms. Increased immune-mediated pulmonary inflammation was also observed in rats exposed to house dust mite allergen following exposure to 5-ppm NO_2 for 3 h.

Exposure to NO_2 also has been found to enhance the inherent responsiveness of the airways to subsequent nonspecific challenges in human clinical studies; however, the results are less consistent than those of animal toxicologic studies. In general, small but significant increases in nonspecific airways responsiveness were observed in the range of 1.5 to 2.0 ppm for 3 h in healthy adults and between 0.2- and 0.3-ppm NO_2 for 30 min for asthmatics, but a wide range of responses were observed, particularly among the asthmatics. Subchronic exposures (6 to 12 weeks) of animals to NO_2 also increase responsiveness to nonspecific challenges at 1- to 4-ppm NO_2.

There is inconsistency in the results of the human studies; with some, but not all studies, finding increased responsiveness following exposure to NO_2. However, a variety of factors are recognized that may lead to this apparent inconsistency. For instance, responsiveness has been observed to be greater following resting than exercising exposures to NO_2, despite the greater dose of NO_2 to the respiratory tract during exercise. In addition, the methods for administering the bronchoconstricting challenge agents and degree of sensitization to specific allergen also are recognized to affect responsiveness (Cockcroft et al., 2005; Cockcroft and Davis, 2006).

3.1.4 Effects of Short-Term NO_2 Exposure on Respiratory Symptoms

Since the 1993 AQCD, additional studies have reported health effects associated with NO_2 from indoor exposure, personal exposure, and ambient concentration studies. The following section characterizes the results of these studies.

3.1.4.1 Indoor and Personal NO_2 Exposure and Respiratory Outcomes

Indoor NO_2 exposure studies may differ from ambient exposure in relation to pattern, levels, and associated copollutants (see Annex Table AX6.3-1 for details). Samet and Bell (2004) state that while "evidence from studies of outdoor air pollution cannot readily isolate an effect of NO_2 because of its contribution to the formation of secondary particles and O_3, observational studies of exposure indoors can test hypotheses related to NO_2 specifically although confounding by combustion sources in the home is a concern."

Most of the studies conducted since 1993 have taken place in Australia and attempted to capture indoor exposures (with passive diffusion badges) from both cooking and heating sources in homes and schools (Pilotto et al., 1997a, 2004; Rodriguez et al., 2007; Garrett et al., 1998; Smith et al., 2000). Several indoor exposure studies have also been conducted in the United States (Kattan et al., 2007; Belanger et al., 2006; van Strien et al., 2004), Europe (Farrow et al., 1997; Simoni et al., 2002, 2004), and Singapore (Ng et al., 2001). The results from these studies are summarized in Annex Table AX6.3-1.

One intervention study provides strong evidence of a detrimental effect of exposure to indoor levels of NO_2. Pilotto et al. (2004) conducted a randomized intervention study of respiratory symptoms of asthmatic children in Australia before and after selective replacement of unflued gas heaters in schools. In the study, 18 schools using unflued gas heaters were randomly allocated to have an electric heater (n = 4) or a flued gas heater (n = 4) installed or to retain their

original heaters (n = 10). Changes to the heating systems were disguised as routine maintenance to prevent bias in reporting of symptoms. Children were eligible for the study if they had physician-diagnosed asthma and no unflued heater in their home. For the 114 children enrolled, symptoms were recorded daily and reported in biweekly telephone interviews during 12 weeks in the winter. Passive diffusion badges were used to measure NO_2 exposure in classrooms (6 h/day) and in the children's homes. Schools in the intervention group (with new heaters) averaged overall means (SD) of 15.5 (6.6) ppb NO_2, while control schools (with unflued heaters) averaged 47.0 (26.8) ppb. Exposure to NO_2 in the children's homes was quite variable but with similar mean levels. Levels at homes for the intervention group were 13.7 (19.3) ppb and 14.6 (21.5) ppb for the control group. Children attending intervention schools had significant reductions in several symptoms (see Table 3.1-2): difficulty breathing during the day (RR = 0.41 [95% CI: 0.07, 0.98]) and at night (RR = 0.32 [95% CI: 0.14, 0.69]); chest tightness during the day (RR = 0.45 [95% CI: 0.25, 0.81]) and at night (RR = 0.59 [95% CI: 0.28, 1.29]); and asthma attacks during the day (RR = 0.39 [95% CI: 0.17, 0.93]).

Samet and Bell (2004) state that Pilotto et al. (2004) provide persuasive evidence of an association between exposure to NO_2 from classroom heaters and the respiratory health of children with asthma and further that the intervention study design alleviates some potential limitations of observational studies. The two groups of children studied had similar baseline characteristics. In addition, the concentrations in the home environment were similar for the two groups, implying that exposure at school was likely to be the primary determinant of a difference in indoor NO_2 exposure between the two groups. It is, however, possible that confounding by particle emissions, particularly ultrafine particles, may be present.

In an earlier study of the health effects of unflued gas heaters on wintertime respiratory symptoms of 388 Australian schoolchildren, Pilotto et al. (1997a) measured NO_2 in 41 classrooms in 8 schools, with half using unflued gas heaters and half using electric heat. Although similar methods were used to measure NO_2 levels (passive diffusion badge monitors exposed for 6 h at a time), there were three major differences between this study and the Pilotto et al. (2004) study: (1) the 1997 study was not a randomized trial, (2) enrollment was not restricted to asthmatic children, and (3) enrollment was not restricted to children from homes

TABLE 3.1-2. MEAN RATES (SD) PER 100 DAYS AT RISK AND UNADJUSTED RATE RATIO (RR)* FOR SYMPTOMS/ACTIVITIES OVER 12 WEEKS DURING THE WINTER HEATING PERIOD

Symptom/Activity	Mean Rate Intervention (n = 45)	Mean Rate Control (n = 69)	RR	(95% CI)
Wheeze during the day	4.9 (15.2)	5.1 (10.5)	0.95	(0.45, 2.01)
Wheeze during the night	2.2 (5.6)	2.3 (5.5)	0.94	(0.36, 2.50)
Difficulty breathing during the day	2.2 (3.7)	5.4 (12.1)	0.41	(0.07, 0.98)
Difficulty breathing during the night	0.8 (2.2)	2.6 (6.9)	0.32	(0.14, 0.69)
Chest tightness during the day	2.3 (4.3)	5.1 (9.9)	0.45	(0.25, 0.81)
Chest tightness during the night	1.5 (3.3)	2.5 (6.2)	0.59	(0.28, 1.29)
Cough during the day	17.5 (21.5)	13.7 (13.7)	1.27	(0.81, 2.00)
Cough during the night	10.7 (16.6)	11.6 (12.4)	0.92	(0.49, 1.73)
Difficulty breathing after exercise	3.8 (7.4)	6.4 (13.9)	0.59	(0.31, 1.13)
Asthma attacks during the day	1.1 (2.3)	2.7 (5.3)	0.39	(0.17, 0.93)
Asthma attacks during the night	0.7 (2.1)	1.8 (3.8)	0.38	(0.13, 1.07)
Missed school due to asthma	1.6 (2.0)	1.2 (2.8)	1.34	(0.68, 2.60)
Visit to health care facilities due to asthma	0.5 (0.8)	0.8 (1.2)	0.60	(0.35, 1.03)
Taking any asthma medication	26.9 (36.7)	34.6 (37.1)	0.77	(0.49, 1.21)
Taking any reliever	13.8 (23.2)	22.4 (28.8)	0.62	(0.31, 1.25)
Taking any preventer	26.2 (40.1)	29.9 (42.2)	0.87	(0.53, 1.44)

*Following adjustment for hay fever and parental education at baseline, results remained substantially unchanged except that difficulty breathing during the day assumed borderline significance (RR = 0.46: 95% CI: 0.19, 1.08) while the reduction in asthma attacks during the night reached statistical significance (RR = 0.33; 95% CI: 0.13, 0.84).

Source: Adapted from Pilotto et al. (2004).

without unflued gas heaters. In Pilotto et al. (1997a), only children from nonsmoking homes were enrolled and a subset of children (n = 121) living in homes with unflued gas heaters were given badges to be used at home. Each child's parents recorded symptoms daily. Children were classified into low- and high-exposure groups based on their measured exposure at school, their measured exposure at home (if they lived in homes with unflued gas heaters), or their reported use of electric heat at home. Maximum hourly concentrations in these classrooms each day over 2 weeks of hourly monitoring were highly correlated with their corresponding 6-h concentrations measured over the same 2 weeks (r = 0.85). Hourly peaks of NO_2 on the order of $\geq$80 ppb were associated with 6-h average levels of approximately $\geq$40 ppb. They inferred that children in classrooms with unflued gas heaters that had 6-h average levels of $\geq$40 ppb were experiencing approximately 4-fold or higher 1-h peaks of exposure than the NO_2 levels experienced by children who had no gas exposure (6-h average levels of 20 ppb). The importance of this study

is that it examines the effect of repeated peaks over time as have been used in the toxicological infectivity studies (e.g., Miller et al., 1987) that were noted earlier in Section 3.1.2.

Pilotto et al. (1997a) reported that during the winter heating season, children in the high-exposure category (NO_2 > 40 ppb) had higher rates of sore throat, colds, and absenteeism than all other children. In models adjusted for personal risk factors including asthma, allergies, and geographic area, classroom NO_2 level and school absence were significantly associated (odds ratio [OR] = 1.92 [95% CI: 1.13, 3.25]). Increased likelihood of individual respiratory symptoms was not significantly associated with classroom NO_2 level (e.g., cough with phlegm adjusted OR = 1.28 [95% CI: 0.76, 2.15]). Exposure-response relationships are illustrated in Figure 3.1-3 for symptom rates for cough with phlegm and proportion of children absent from school. Statistically significant positive exposure-response trends were found for mean rates for cough with phlegm ($p = 0.04$, adjusted for confounders) and proportion of children absent from school ($p = 0.002$) using mixed models allowing for correlation between children within classrooms. Pilotto et al. (1997b) noted that this study "provides evidence that short-term exposure to the peak levels of NO_2 produced by unflued gas appliances affects respiratory health and that the significant dose-response relationship seen with increasing NO_2 exposure strengthens the evidence for a cause-effect relationship."

In a cross-sectional survey of 344 children in Australia, Ponsonby et al. (2001) used passive gas samplers to measure personal exposure to NO_2. Personal badges were pinned to a child's clothing at the end of each school day and removed when the child arrived at school the next day. School exposures were measured with passive samplers placed in each child's classroom. Sampling took place over two consecutive days. Mean (SD) personal exposure was 10.4 (11.1) ppb and mean total NO_2 exposure (personal plus schoolroom) was 10.1 (8.6) ppb. Of the health outcomes measured (recent wheeze, asthma ever, lung function measured when NO_2 sampling stopped), only the forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio following cold air challenge was significantly associated with NO_2 levels measured with the personal badges (−0.12 [95% CI: −0.23, −0.01]) per 1-ppb increase in personal exposure). In Finland, Mukula et al. (1999, 2000) studied 162 preschool-age children. Mukula et al. (2000) used passive monitors exposed for 1-week periods over the course of 13 weeks both indoors

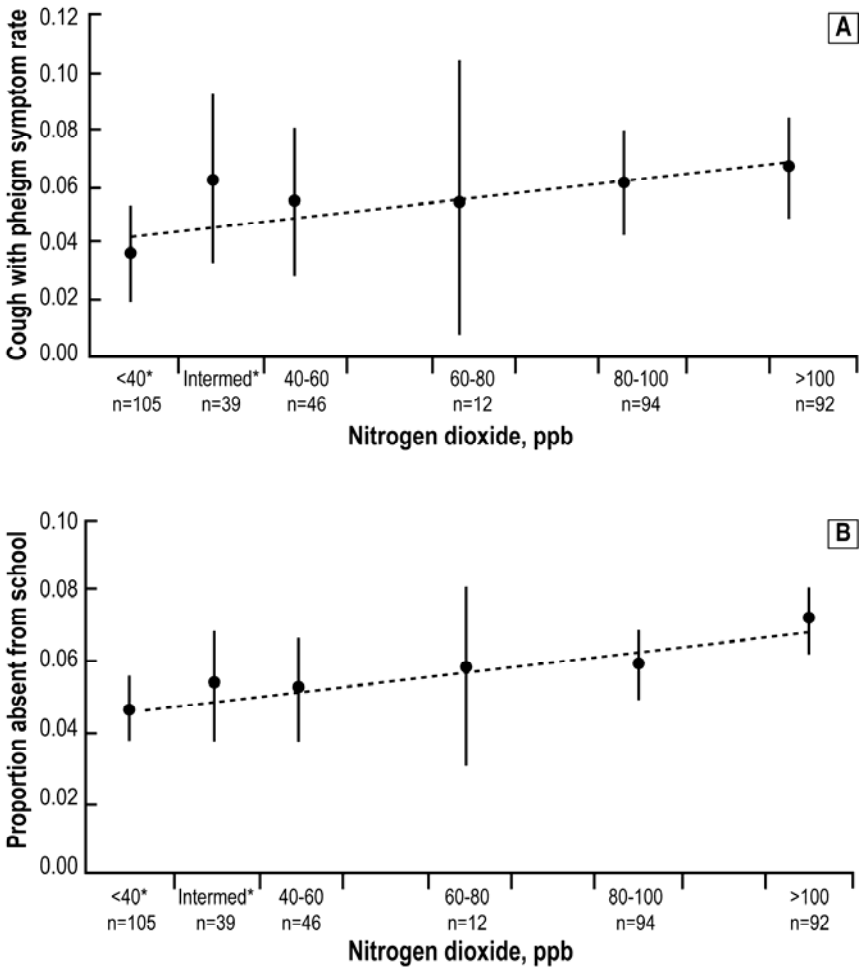

Figure 3.1-3. Geometric mean symptom rates (95% confidence intervals) for cough with phlegm (panel A) and proportions (95% confidence intervals) of children absent from school for at least 1 day (panel B) during the winter heating period grouped by estimated NO_2 exposure at home and at school (n = number of children at that NO_2 level). Group means estimated using mixed models. * "<40 ppb" group (n = 105) includes children from electrically heated schools while the "Intermed" group (n = 39) includes children from unflued gas heater heaters where the exposures were consistently below 40 ppb. Both groups of children did not have exposure to gas combustion at home.

Source: Adapted from Pilotto et al. (1997a).

and outdoors and on the clothing of preschool children attending eight day care centers in Helsinki. The only significant association between personal NO_2 measurements and symptoms was for cough during the winter (RR = 1.86 [95% CI: 1.15, 3.02] for NO_2 at level above

27.5 µg/m^3 [14.5 ppb]). Similar results were obtained when data were analyzed unstratified by season, but including a factor for season (RR = 1.52 [95% CI: 1.00, 2.31] for NO_2 at levels above 27.5 µg/m^3 [14.5 ppb], Mukala et al., 1999).

One recent birth cohort study in the United States measured indoor exposure to NO_2 (Belanger et al., 2006; van Strien et al., 2004). Families were eligible for this study if they had a child with physician-diagnosed asthma (asthmatic sibling) and a newborn infant (birth cohort subject). NO_2 levels were measured using Palmes tubes left in the homes for 2 weeks. Higher levels of NO_2 were measured in homes with gas stoves (mean [SD], 26 [18] ppb) than in homes with electric ranges (9 [9] ppb). Children living in multifamily homes were exposed to higher NO_2 (23 [17] ppb) than children in single-family homes (10 [12] ppb). The authors examined associations between NO_2 concentrations and respiratory symptoms experienced by the asthmatic sibling in the month prior to sampling (Belanger et al., 2006). For children living in multifamily homes, each 20-ppb increase in NO_2 concentration increased the likelihood of any wheeze or chest tightness (OR for wheeze = 1.52 [95% CI: 1.04, 2.21]; OR for chest tightness = 1.61 [95% CI: 1.04, 2.49]) as well as increasing the risk of suffering additional days of symptoms. No significant associations were found between level of NO_2 and symptoms for children living in single-family homes. The authors suggested that the low levels of exposure may have been responsible for the lack of association observed in single-family homes. In these same families, van Strien et al. (2004) compared the measured NO_2 concentrations with respiratory symptoms experienced by the birth cohort infants during the first year of life. Although wheeze was not associated with NO_2 concentration, persistent cough was associated with increasing NO_2 concentration in an exposure-response relationship (Figure 3.1-4) (van Strien et al., 2004).

Results from a recent analysis of a subset of 469 asthmatic children enrolled in the National Cooperative Inner City Asthma Study (NCICAS) (Kattan et al., 2007) where household measurements of NO_2 levels were also available are consistent with those described above for Belanger et al. (2006). The median level of indoor NO_2, measured with Palmes tubes left for 7 days, was 29.8 ppb, with median level in homes with gas stoves (31.4 ppb) significantly higher than levels in homes with electric stoves (15.9 ppb). Associations between exposure to high levels of NO_2 and symptoms in the previous 2 weeks or peak flow of <80% predicted were

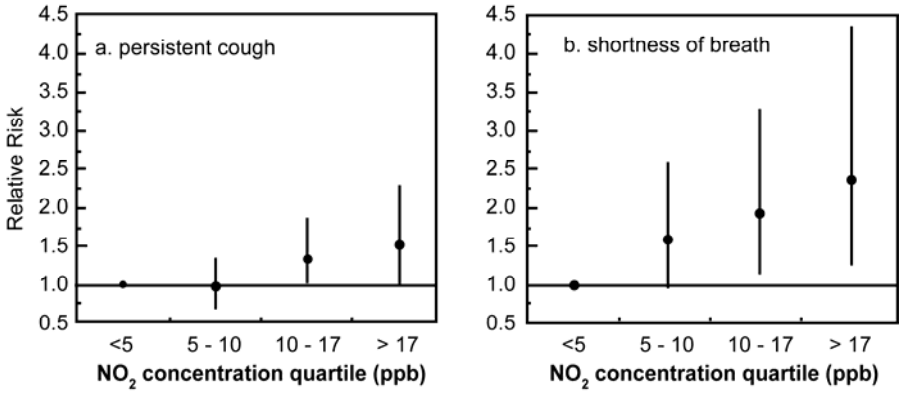

Figure 3.1-4. Adjusted association of increasing indoor NO_2 concentrations with number of days with persistent cough (panel a) or shortness of breath (panel b) for 762 infants during the first year of life. Relative risks from Poisson regression analyses adjusted for confounders.

Source: Adapted from van Strien et al. (2004).

examined with models that adjusted for study site, gender, medication use, household smoking, and SES variables and were stratified by season or by atopic status. Among the subset of 76 children without positive skin tests, the adjusted risk ratio (95% CI) for asthma symptoms was 1.75 (95% CI: 1.10, 2.78) for those with higher NO_2 exposure. Among the 317 children with NO_2 measured in the cold season, the risk ratio for a peak flow measurement of <80% predicted was 1.46 (95% CI: 1.07, 1.97). One limitation of the study is that the "high" NO_2 level was defined vaguely as approaching the U.S. Environmental Protection Agency (EPA) National Ambient Air Quality Standards (NAAQS) level of 53 ppb.

Other studies have also collected personal exposure data for NO_2. Nitschke et al. (2006) used passive diffusion badges for measuring NO_2 exposures in 6-h increments at home and school for 174 asthmatic children in Australia. School and home measurements were based on three consecutive days of sampling. The maximum of 9 days of sampling (for 6 h each day) NO_2 value was selected as the representative daily exposure for exposure-response analyses. Children kept a daily record of respiratory symptoms for the 12-week study period. Significant associations were found between the maximum NO_2 level at school or home and respiratory symptom rates, though the exposure-response curve indicated that the major difference in respiratory symptoms rates were between NO_2 exposures of >80 ppb (see Annex Table AX 6.3-1).

An important consideration in the evaluation of the indoor exposure studies is that NO_X is part of a complex mixture of chemicals emitted from unvented gas heaters. In addition to NO and NO_2, indoor combustion sources such as unvented gas heaters emit other pollutants that are present in the fuel or are formed during combustion. These pollutants include carbon dioxide (CO_2), carbon monoxide (CO), formaldehyde (HCHO) and other volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), and PM, particularly ultrafine particles, as described in Section 2.5.8.3. The studies of unvented heaters or gas stoves did not measure indoor concentrations of other combustion-related emissions. Unvented combustion is a potential source of ultrafine particles. High numbers of ultrafine particles, along with NO_2, are generated during the operation of gas heaters, gas stoves, and during cooking (Dennekamp et al., 2001; Wallace et al., 2004). It is possible that the improved respiratory symptoms observed in the Pilotto et al. (2004) intervention study were related to reductions in ultrafine particle exposure, other gaseous emissions, or the pollutant mix. The findings of these recent indoor and personal exposure studies, combined with studies available in the previous AQCD, provide evidence that NO_2 exposure is associated with respiratory effects. These studies provide a potential bridge between epidemiologic studies using ambient concentrations from centrally located monitors and controlled human exposure studies, as discussed in the previous sections, and provide some evidence of coherence for respiratory effects.

3.1.4.2 Ambient NO_2 Exposure and Respiratory Symptoms

Since the 1993 AQCD, results have been published from several single- and multicity studies investigating ambient NO_2 levels, including three large longitudinal studies in urban areas covering the continental United States and southern Ontario: the Harvard Six Cities study (Six Cities; Schwartz et al., 1994), the National Cooperative Inner-City Asthma Study (NCICAS; Mortimer et al., 2002), and the Childhood Asthma Management Program (CAMP; Schildcrout et al., 2006). Because of similar analytic techniques (i.e., multistaged modeling and generalized estimating equations [GEE]), one strength of all three of these studies is that, as Schildcrout et al. (2006) stated, they could each be considered as a meta-analysis of "large, within-city panel studies" without some of the limitations associated with meta-analyses, e.g., "between-study heterogeneity and obvious publication bias."

The report from the Six Cities study includes 1,844 schoolchildren, followed for 1 year (Schwartz et al., 1994). Symptoms (in 13 categories, analyzed as cough, lower or upper

respiratory symptoms), were recorded daily. Cities included Watertown, MA, Baltimore, MD, Kingston-Harriman, TN, Steubenville, OH, Topeka, KS, and Portage, WI. In Mortimer et al. (2002), 864 asthmatic children from the eight NCICAS cities (New York City, NY, Baltimore, MD, Washington, DC, Cleveland, OH, Detroit, MI, St Louis, MO, and Chicago, IL) were followed daily for four 2-week periods over the course of 9 months. Morning and evening asthma symptoms (analyzed as none versus any) and peak flow were recorded. Schildcrout et al. (2006) reported on 990 asthmatic children living within 50 miles of one of 31 NO_2 monitors located in eight North American cities, seven of which included data for NO_2 (Boston, MA, Baltimore, MD, Toronto, ON, St. Louis, MO, Denver, CO, Albuquerque, NM, and San Diego, CA). Symptoms (analyzed as none versus any per day) and rescue medication use (analyzed as number of uses per day) were recorded daily such that each subject had an approximate average of 2 months of data. All three studies found significant associations between ambient NO_2 concentrations and risk of respiratory symptoms in children (Schwartz et al., 1994), and in particular, asthmatic children (Mortimer et al., 2002; Schildcrout et al., 2006).

In Schwartz et al. (1994), a significant association was found between a 4-day mean of NO_2 exposure and incidence of cough among all children in single-pollutant models: the odds ratio (OR) standardized to a 20-ppb increase in NO_2 was OR = 1.61 (95% CI: 1.08, 2.43). Cough incidence was not significantly associated with NO_2 on the previous day. The local nonparametric smooth of the 4-day mean concentration showed increased cough incidence up to approximately the mean concentration (~13 ppb) ($p = 0.01$), after which no further increase was observed. The significant association between cough and 4-day mean NO_2 remained unchanged in models that included O_3, but was attenuated in two-pollutant models including PM_{10} (OR for 20-ppb increase in NO_2 = 1.37 [95% CI: 0.88, 2.13]) or SO_2 (OR = 1.42 [95% CI: 0.90, 2.28]).

In Mortimer et al. (2002), the greatest effect of the pollutants studied for morning symptoms was for a 6-day moving average. For increased NO_2, the risk of any asthma symptoms (cough, wheeze, shortness of breath) among the asthmatic children in the NCICAS was somewhat higher than for the healthy children in the Six Cities study: OR = 1.48 (95% CI: 1.02, 2.16). Effects were generally robust in multipollutant models that included O_3 (OR for 20-ppb increase in NO_2 = 1.40 [95% CI: 0.93, 2.09]), O_3 and SO_2 (OR for NO_2 = 1.31 [95% CI: 0.87, 2.09]), or O_3, SO_2, and PM with an aerodynamic diameter of $\leq$10 μm (PM_{10}) (OR for NO_2 = 1.45 [95% CI: 0.63, 3.34]).

In the CAMP study (Schildcrout et al., 2006), the strongest association between NO_2 and increased risk of cough was found for a 2-day lag: each 20-ppb increase in NO_2 occurring 2 days before measurement increased risk of cough (OR = 1.09 [95% CI: 1.03, 1.15]). Joint-pollutant models including CO, PM_{10}, or SO_2 produced similar results (see Figure 3.1-5, panel A). Further, increased NO_2 exposure was associated with increased use of rescue medication in the CAMP study, with the strongest association for a 2-day lag, both for single- and joint-pollutant models (e.g., for an increase of 20-ppb NO_2 in the single-pollutant model, the RR for increased inhaler usage was 1.05 (95% CI: 1.01, 1.09) (See Figure 3.1-5, panel B).

Single-city studies also provide updated information to the 1993 AQCD, particularly with regard to children. Two 3-month-long panel studies recruited asthmatic children from one outpatient clinic in Paris: one study followed 84 children in the fall of 1992 (Segala et al., 1998), and the other followed 82 children during the winter of 1996 (Just et al., 2002). Significant associations were observed between respiratory symptoms and level of NO_2 (See Annex Table AX6.3-2). No multipollutant analyses were conducted. In metropolitan Sydney, 148 children with a history of wheeze were followed for 11 months (Jalaludin et al., 2004). Daily symptoms, medication use, and doctor visits were examined. Associations were found between increased likelihood of wet cough and each 20-ppb increase in NO_2 (OR = 1.13 [95% CI: 1.00, 1.26]). The authors reported that estimates did not change in multipollutant models including O_3 or PM_{10}. Ward et al. (2002) examined respiratory symptoms in a panel of 162 children in the United Kingdom. No significant associations were reported for the winter period, but a significant association was reported for the summer period for cough and NO_2 (lag 0; OR = 1.09 [95% CI: 1.17, 1.01]).

Another Australian study includes a large number of children (n = 263) at risk for developing allergy who were followed for 5 years (Rodriguez et al., 2007). Daily air pollutant concentrations, including those for NO_2, were averaged over 10 monitoring sites in the Perth metropolitan region. Mean level of 24-h NO_2 for the 8-year study period was 7 ppb (range 0-24 ppb). Significant associations were found between same-day level of NO_2 (both 1- and 24-h avg) and cough (OR 1.0005 [95% CI: 1.0000, 1.0011]) per 20 ppb increase in 24-h avg NO_2). No multipollutant models were presented.

Boezen et al. (1999) reported associations between ambient NO_2 exposure and lower respiratory symptoms among children (n = 121) with bronchial hyperreactivity and elevated total

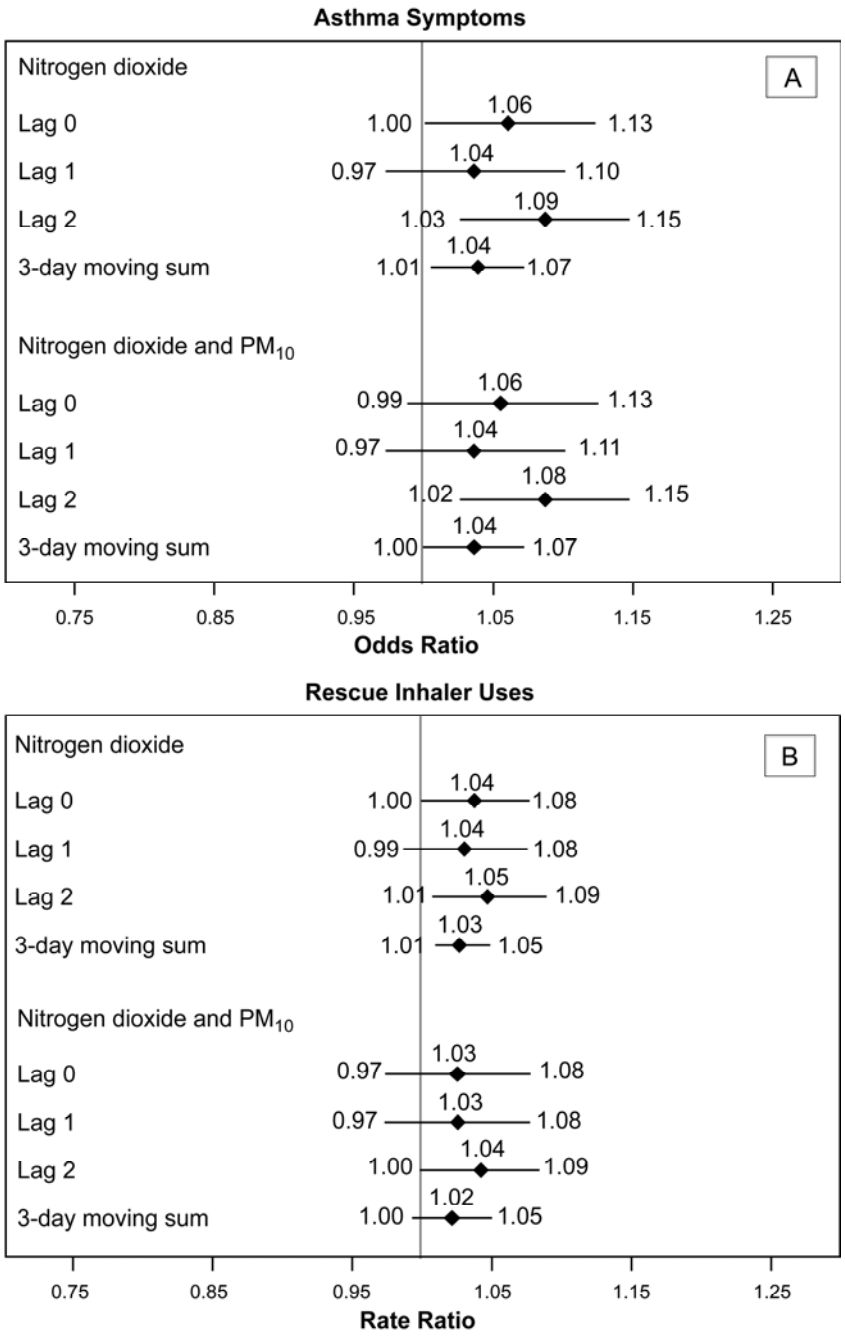

Figure 3.1-5. Odds ratios (95% confidence interval [CI]) for daily asthma symptoms (panel A) and rate ratios (95% CI) for daily rescue inhaler use (panel B) associated with shifts in within-subject concentrations of NO_2 for single- and joint (with PM_{10})-pollutant models from the Childhood Asthma Management Program (November 1993-September 1995). The city-specific estimates from Boston, Baltimore, Toronto, St. Louis, Denver, Albuquerque, and San Diego were included in the calculations of study-wide effects.

Source: Schildcrout et al. (2006).

IgE in urban and rural areas of the Netherlands. These effects were seen for all lags examined (lag 0-, 1-, 2-, and 5-day mean), with the strongest association for the 5-day mean (OR = 1.75 [95% CI: 1.37, 2.22]) for each 20 ppb increase). Significant associations between lower respiratory symptoms and ambient exposures were seen in single-pollutant models with PM_{10}, black smoke, and SO_2. No multipollutant models were reported.

For adults, most studies examining associations between ambient NO_2 pollution and respiratory symptoms have been conducted in Europe. Various studies have enrolled older adults, (van der Zee et al., 2000; Harre et al., 1997; Silkoff et al., 2005), nonsmoking adults (Segala et al., 2004), patients with COPD (Higgins et al., 1995; Desqueyroux et al., 2002), and individuals with bronchial hyperresponsiveness (Boezen et al., 1998) or asthma (Hiltermann et al., 1998; Forsberg et al., 1998; Von Klot et al., 2002). Associations were found between NO_2 and either respiratory symptoms or inhaler use in a number of studies (van der Zee et al., 2000; Harre et al., 1997; Silkoff et al., 2005; Segala et al., 2004; Hiltermann et al., 1998), but not in all studies (Desqueyroux et al., 2002; Von Klot et al., 2002).

Among the studies discussed above, odds ratios and 95% CI for associations with asthma symptoms in children are presented in Figure 3.1-6. The figure shows the several lag periods presented in each study. In the figure, the area of the square denoting the odds ratio represents the relative weight of that estimate based on the width of the 95% CI. When combined in a random effect meta-analysis[1], the combined OR for asthma symptoms from a meta-analysis was 1.14 (95% CI: 1.05, 1.24) and the test for heterogeneity had a p value of 0.055. The results of multipollutant analyses for the three U.S. multicity studies are presented in Figure 3.1-7. Associations with NO_2 were generally robust to adjustment for copollutants, as stated previously. Odds ratios were often unchanged with the addition of copollutants, though reductions in magnitude are apparent in certain models, such as with adjustment for SO_2 in the Six Cities study results (Schwartz et al., 1994).

[1] The effects used in the meta-analysis were selected using the following methodology. One lag period per study was selected, with studies having 0 lag preferred to 1-day lags and moving averages; longer single-day lags were not included in the meta-analysis. If a study had both incidence and prevalence, then the incidence effect was to be used.

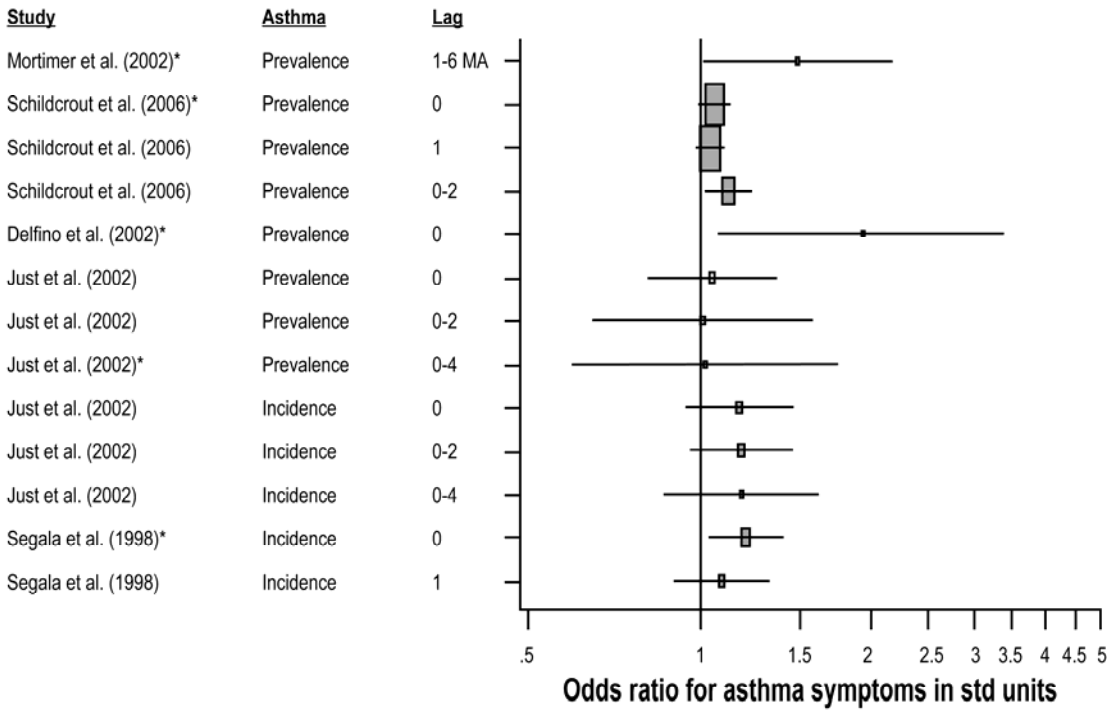

Figure 3.1-6. Odds ratios (95% CI) for associations between asthma symptoms and 24-h average NO_2 concentrations (per 20 ppb). The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.

3.1.4.3 Summary of Evidence on the Effects of Short-Term NO_2 Exposure on Respiratory Symptoms

Consistent evidence has been observed for an association of respiratory effects with indoor and personal NO_2 exposures in children at levels similar to ambient concentrations. In particular, the Pilotto et al. (2004) intervention study provided evidence of improvement in respiratory symptoms with reduced NO_2 exposure in asthmatic children.

The epidemiologic studies using community ambient monitors also find associations between ambient NO_2 concentration and respiratory symptoms. The results of new U.S. multicity studies (Schildcrout et al., 2006; Mortimer et al., 2002) provide further support for

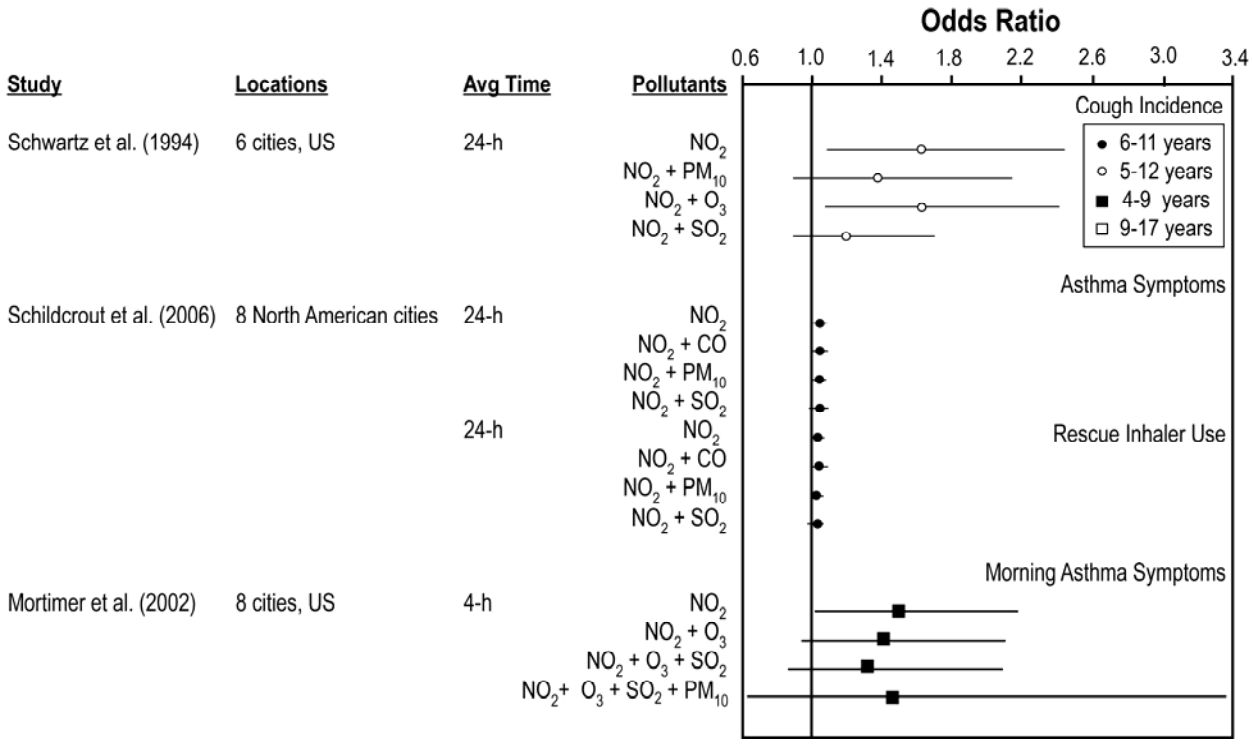

Figure 3.1-7. Odds ratios and 95% confidence intervals for associations between asthma symptoms and 24-h average NO_2 concentrations (per 20 ppb) from multipollutant models.

associations with respiratory symptoms and medication use in asthmatic children. Associations were observed in cities where the median range was 18 to 26 ppb for a 24-h avg (Schildcrout et al., 2006) and the mean NO_2 level was 32 ppb for a 4-h avg (Mortimer et al., 2002). Multipollutant models in these multicity studies were generally robust to adjustment for copollutants including O_3, CO, and PM_{10}. Most human clinical studies did not report or observe respiratory symptoms with NO_2 exposure, and animal toxicologic studies do not measure effects that would be considered symptoms. The experimental evidence on airways inflammation and immune system effects discussed previously, however, provides some plausibility and coherence for the observed respiratory symptoms in epidemiologic studies.

3.1.5 Effects of Short-Term NO_2 Exposure on Lung Function

3.1.5.1 Epidemiologic Studies of Lung Function

Spirometry in Children

Reliable measurement of lung function in children presents special challenges. The method that produces the most accurate results is spirometry, which requires special equipment and trained examiners. Of the short-term exposure studies reviewed here that did use spirometry (Hoek and Brunekreef, 1994; Linn et al., 1996; Timonen et al., 2002; Moshammer et al., 2006), all conducted repeated lung function measurements in schoolchildren. All found significant associations between small decrements in lung function and increases in ambient NO_2 levels. Hoek and Brunekreef (1994) enrolled 1,079 children in the Netherlands to examine the effects of low-level winter air pollution on FVC, FEV_1, maximal midexpiratory flow (MMEF), and PEF. A significant effect was found only for the PEF measure: the mean (over all subjects) slope (SE) was a reduction of 52 mL/s (95% CI: 21, 83) for a 20-ppb increase in the previous day's NO_2. The authors do not present mean values for lung function measurements, so it is not possible to calculate what percentage of PEF this decrement represents. Linn et al. (1996) examined 269 Los Angeles-area schoolchildren and short-term air pollution exposures. The authors found statistically significant associations between previous-day 24-h avg NO_2 concentrations and FVC the next morning (mean decline of 8 mL [95% CI: 2, 14] per 20-ppb increase in NO_2) and current-day 24-h avg NO_2 concentrations and morning to evening changes in FEV_1 (mean decline of 8 mL [95% CI: 2, 14] per 20-ppb increase in NO_2). Timonen et al. (2002) enrolled 33 Finnish children with chronic respiratory symptoms to study the effects of exercise-induced lung function changes and ambient air pollution. No significant effects were observed for lung function changes due to exercise, but significant associations were observed for level of NO_2 lagged by 2 days and baseline FVC (mean decline of 21 mL [95% CI: −29, −12] for 20-ppb NO_2) and FEV_1 (mean decline of 20 mL [95% CI: −26, −13] for 20-ppb NO_2). An Austrian study enrolled 163 healthy children for repeated lung function testing (11 to 12 tests during the school year) (Moshammer et al., 2006). A central site monitor adjacent to the school were used to calculate 8-h avg (midnight. to 8 a.m.) PM and NO_2 concentrations. The median 8-h avg NO_2 concentration was 17.5 $\mu g/m^3$ (9.2 ppb). In both single pollutant and multipollutant models including $PM_{2.5}$, the authors found each 20-ppb increase in NO_2 level produced reductions in lung function of around 4% for FEV_1, FVC, forced expiratory volume in 0.5 s ($FEV_{0.5}$), maximal

expiratory flow at 50% (MEF_{50}), and maximal expiratory flow at 25% (MEF_{25}). $PM_{2.5}$ was not significantly associated with lung function decrements in the multipollutant model.

Peak Flow Meter Measurements in Children

Studies involving supervised lung function measurements in schoolchildren using peak flow devices do not show a consistent relationship between NO_2 exposure and measurements of peak flow (Scarlett et al., 1996; Peacock et al., 2003; Steerenberg et al., 2001) (Annex Table AX6.3-2). Other studies using home-use peak flow meters with children did not report any significant associations with ambient NO_2 (Roemer et al., 1998 [2,010 children in the Pollution Effects on Asthmatic Children in Europe (PEACE) study]; Roemer et al., 1999 [a subset of 1,621 children from the PEACE study with chronic respiratory symptoms]; Mortimer et al., 2002 [846 asthmatic children from the NCICAS]; Van der Zee et al., 1999 [633 children in the Netherlands]; Timonen and Pekkanen, 1997 [169 children including asthmatics in Finland]; Ranzi et al., 2004 [118 children, some with asthma, in the Italian Asma Infantile Ricerca (AIRE) study]; Segala et al., 1998 and Just et al., 2002 [over 80 asthmatic children in Paris]; Delfino et al., 2003a [22 asthmatic children in southern California]).

Ward et al. (2000) examined the effect of correcting peak flow for nonlinear errors on NO_2 effect estimates in a panel study of 147 children (9-year olds, 47% female). The correction resulted in a small increase in the group mean PEF (1.1 $L\text{-}min^{-1}$). For the entire panel, NO_2 effect estimates were all corrected in the positive direction with a narrowing of the 95% CI, and all but the result for 0-day lag were decreased in absolute size by up to 73% (e.g., effect estimate for NO_2 lagged 3 days corrected from −0.56 to −0.15% per 10 ppb). When only the symptomatic/atopic children (i.e., reported wheezing and positive skin test) were considered, the estimates for associations with 5-d avg NO_2 decreased in size from −5.0 to −1.8% per 20 ppb. In the case of lag 0, the effect estimate became significant with an increase in magnitude from −1.1 to −2.3% per 20 ppb. The authors concluded that correction for PEF meter measurements resulted in small but important shifts in the direction and size of effect estimates and probable interpretation of results. The effects of correction were, however, not consistent across pollutants or lags and could not be easily predicted.

Lung Function in Adults

Spirometry was used in a large cross-sectional study in Switzerland (Schindler et al., 2001). A subset of 3,912 lifetime nonsmoking adults participated in the spirometric lung function measurements in the SAPALDIA study (Study of Air Pollution and Lung Diseases in Adults). Significant inverse relationships were found between increases in NO_2 and decreases in FVC (by 2.74% [95% CI: 0.83, 4.62]) and FEV_1 (by 2.52% [95% CI: 0.49, 4.55]) for a 20-ppb increase in NO_2 on the same day as the examination. Forced expiratory flow at 25 to 75% of FVC (FEF_{25-75}) was found to decrease by 6.73% (95% CI: 0.038, 13.31) for each 20-ppb increase in average NO_2 concentration over the previous 4 days. One study (Lagorio et al., 2006) of COPD patients found significant inverse relationships for FEV_1 in both COPD and asthmatic patients. Another study of COPD subjects (Silkoff et al., 2005) observed no adverse effects of ambient air pollution on lung function for the first winter; however, in the second winter, a significant decrease in morning PEF associated with same day and previous day NO_2 level was seen (quantitative results not provided). In a study of 60 asthmatic adults in London, decreases in two lung function measures, FEV_1 and FEF_{25-75}, and increased FE_{NO} were reported with increased NO_2 exposure while walking along a roadway with heavy traffic; associations were also reported with $PM_{2.5}$, ultrafine particles, and EC (McCreanor et al., 2007).

Of the adult studies reviewed that employed portable peak flow meters for subject-measured lung function, none reported significant associations with NO_2 levels (van der Zee et al., 2000 [489 adults in the Netherlands]; Higgins et al., 1995 [153 adults in the United Kingdom, including COPD and asthma patients]; Park et al., 2005a [64 asthmatic adults in Korea]; Hiltermann et al., 1998 [60 asthmatic adults in the Netherlands]; Harre et al., 1997 [40 adults with COPD in New Zealand]; Forsberg et al., 1998 [38 adult asthmatics in Sweden]; Higgins et al., 2000 [35 adults with COPD or asthma in the United Kingdom]).

3.1.5.2 Clinical Studies of Lung Function

Healthy Adults

Studies examining responses of healthy volunteers to acute exposure to NO_2 have generally failed to show alterations in lung mechanics such as airways resistance (Hackney et al., 1978; Kerr et al., 1979; Linn et al., 1985a; Mohsenin, 1987a, 1988; Frampton et al., 1991; Kim et al., 1991; Morrow et al., 1992; Rasmussen et al., 1992; Vagaggini et al., 1996; Azadniv et al.,

1998; Devlin et al., 1999). Exposures ranging from 75 min to 5 h at concentrations of up to 4.0-ppm NO_2 did not alter pulmonary function. Bylin et al. (1985) found increased airways resistance after a 20-min exposure to 0.25-ppm NO_2 and decreased airways resistance after a 20-min exposure to 0.5-ppm NO_2, but no change in airways responsiveness to aerosolized histamine challenge in the same subjects. These effects have not been confirmed in other laboratories.

Few human clinical studies of NO_2 have included elderly subjects. Morrow et al. (1992) studied the responses of 20 healthy volunteers (13 smokers, 7 nonsmokers) of mean age 61 years, following exposure to 0.3-ppm NO_2 for 4 h with light exercise. There was no significant change in lung function related to NO_2 exposure for the group as a whole. However, the 13 smokers experienced a slight decrease in FEV_1 during exposure, and their responses were significantly different from the 7 nonsmokers (percent change in FEV_1 at end of exposure: −2.25 versus + 1.25%, $p = 0.01$). The post-hoc analysis and small numbers of subjects, especially in the nonsmoking group, limits the interpretation of these findings.

The controlled human exposure studies reviewed in the O_3 AQCD (U.S. Environmental Protection Agency, 2006) generally reported only small pulmonary function changes after combined exposures of NO_2 or nitric acid (HNO_3) with O_3, regardless of whether the interactive effects were potentiating or additive. Hazucha et al. (1994) found that preexposure of healthy women to 0.6-ppm NO_2 for 2 h enhanced spirometric responses and methacholine airways responsiveness induced by a subsequent 2-h exposure to 0.3-ppm O_3, with intermittent exercise. Following a 1-h exposure with heavy exercise, Adams et al. (1987) found no differences between spirometric responses to 0.3-ppm O_3 and the combination of 0.6-ppm NO_2 + 0.3-ppm O_3. However, the increase in airways resistance was significantly less for adults exposed to 0.6-ppm NO_2 + 0.3-ppm O_3 compared to 0.3-ppm O_3 alone.

Gong et al. (2005) studied 6 healthy elderly subjects (mean age 68 years) and 18 patients with COPD (mean age 71 years), all exposed to: (a) air, (b) 0.4-ppm NO_2, (c) ~200 $\mu g/m^3$ concentrated ambient fine particles (CAPs), and (d) CAPs + NO_2. Exposures were for 2-h with exercise for 15 min of each half hour. CAPs exposure was associated with small reductions in midexpiratory flow rates on spirometry, and reductions in oxygen saturation, but there were no effects of NO_2 on lung function, oxygen saturation, or sputum inflammatory cells. However, the exposures were not fully randomized or blinded, and most of the NO_2 exposures took place

months after completion of the CAPs and air exposures. In addition, the small number of healthy subjects severely limits the statistical power for this group.

Patients with COPD

Few studies have examined responses to NO_2 in subjects with COPD. Hackney et al. (1978) found no lung function effects of exposure to 0.3-ppm NO_2 for 4-h with intermittent exercise in smokers with symptoms and reduced FEV_1. In a group of 22 subjects with moderate COPD, Linn et al. (1985b) found no pulmonary effects of 1-h exposures to 0.5-, 1.0-, or 2.0-ppm NO_2 with 30 min of exercise.

In a study by Morrow et al. (1992), 20 subjects with COPD were exposed for 4-h to 0.3-ppm NO_2 in an environmental chamber, with intermittent exercise. Progressive decrements in FVC occurred during the exposure, becoming statistically significant only at the end of the exposure. The decrements in FVC occurred without changes in flow rates. These changes in lung function were typical of the "restrictive" pattern seen with NO_2 rather than the obstructive changes described by some studies of NO_2 exposure in asthmatics.

Gong et al. (2005) exposed 6 elderly healthy adults and 10 COPD patients to four separate atmospheres: (a) air, (b) 0.4-ppm NO_2, (c) ~200-$\mu g/m^3$ CAPs, or (d) CAPs + NO_2. As noted above, there were no significant effects of NO_2 in either the healthy or the COPD subjects.

Patients with Asthma

Kleinman et al. (1983) evaluated the response of lightly exercising asthmatic subjects to inhalation of 0.2-ppm NO_2 for 2 h, during which resting minute ventilation doubled. Forced expiratory flows and airways resistance were not altered by the NO_2 exposure. Bauer et al. (1986) studied the effects of mouthpiece exposure to 0.3-ppm NO_2 for 30 min (20 min at rest followed by 10 min of exercise at ~40 L/min) in 15 asthmatics. At this level, NO_2 inhalation produced significant decrements in forced expiratory flow rates after exercise, but not at rest. Jörres and Magnussen (1991) found no effects on lung function in 11 patients with mild asthma exposed to 0.25-ppm NO_2 for 30-min, including 10-min of exercise. However, small reductions in FEV_1 were observed following 1-ppm NO_2 exposure for 3-h with intermittent exercise in 12 mild asthmatics. Koenig et al. (1994) found no pulmonary function effects of exposure to 0.3-ppm NO_2 in combination with 0.12-ppm O_3, with or without sulfuric acid (H_2SO_4)

(70 μg/m^3) or HNO_3 (0.05 ppm), in 22 adolescents with mild asthma. However, 6 additional subjects dropped out of the study citing uncomfortable respiratory symptoms.

Jenkins et al. (1999) examined FEV_1 decrements and airways responsiveness to allergen in a group of mild, atopic asthmatics. The subjects were exposed during rest for 6 h to filtered air, 200-ppb NO_2, 100-ppb O_3, or 200-ppb NO_2 + 100-ppb O_3. The subjects were also exposed for 3 h to 400-ppb NO_2, 200-ppb O_3, or 400-ppb NO_2 + 200-ppb O_3 to provide doses identical to those in the 6-h protocols (i.e., equal C × T). Immediately following the 3-h exposure, but not after the 6-h exposure, there were significant decrements in FEV_1 following O_3 and NO_2 + O_3 exposures.

3.1.5.3 Summary of Evidence of the Effect of Short-Term NO_2 Exposure on Lung Function

In summary, epidemiologic studies using data from supervised lung function measurements (spirometry or peak flow meters) report small decrements in lung function (Hoek and Brunekreef, 1994; Linn et al., 1996; Moshammer et al., 2006; Schindler et al., 2001; Peacock et al., 2003). No significant associations were reported in any studies using unsupervised, self-administered peak flow measurements with portable devices. Correcting peak flow measurements for nonlinear errors resulted in small but important shifts in the direction and size of effect estimates; however, these effects were not consistent across pollutants or lags.

Overall, clinical studies have not provided compelling evidence of NO_2 effects on pulmonary function. Acute exposures of young, healthy volunteers to NO_2 at levels of as high as 4.0 ppm do not alter lung function as measured by spirometry or airways resistance. The small number of studies of COPD patients prevents any conclusions about effects on pulmonary function. The Morrow et al. (1992) study, performed in Rochester, NY, suggested restrictive type effects of 0.3-ppm NO_2 exposure for 4 h. However, three other studies, performed in southern California at similar exposure concentrations, found no effects. The contrasting findings in these studies may, in part, reflect the difference in duration of exposure or the differing levels of background ambient air pollution to which the subjects were exposed chronically, as there were much lower background levels in Rochester, NY than in southern California. For asthmatics, the effects of NO_2 on pulmonary function have also been inconsistent at exposure concentrations of less than 1-ppm NO_2. Overall, clinical studies have failed to show effects of NO_2 on pulmonary function at exposure concentrations relevant to ambient exposures.

However, the range of findings in COPD and asthmatic patients may reflect that some individuals within such groups may be particularly more susceptible to NO_2 effects than others.

3.1.6 Hospital Admissions and ED Visits for Respiratory Outcomes

Total respiratory causes for ED visits and hospitalizations typically include asthma, bronchitis and emphysema (collectively referred to as COPD), pneumonia, upper and lower respiratory infections, and other minor categories. Temporal associations between ED visits or hospital admissions for respiratory diseases and the ambient concentrations of NO_2 have been the subject of more than 50 well-conducted research publications since 1993. These studies form a new body of literature that was unavailable in 1993, when the previous criteria document was published. In addition to considerable statistical and analytical refinements, the more recent studies have examined responses of morbidity in different age groups and multipollutant models to evaluate potential confounding effects of copollutants.

3.1.6.1 All Respiratory Outcomes (ICD9 460–519)

Overall, the majority of studies that have examined all respiratory outcomes as a single group have focused on hospital admission data. The results from the hospitalization and ED visit studies, for all ages and stratified by age group are presented in Figures 3.1-8 and 3.1-9. More details are provided in Annex Tables AX6.3-1, AX6.3-2, and AX6.3-3. Collectively, studies of hospitalizations and ED visits provide suggestive evidence of an association between ambient NO_2 levels and ED visits and hospitalizations for all respiratory causes when participants of all ages are considered in the analyses. Stronger and more consistent associations were observed among children and older adults (65+ years) compared to adults (<65 years), with an interquartile range (IQR) of 1 to 13% excess risk estimated per 20 ppb incremental change in 24-h avg NO_2 or 30 ppb incremental change in 1-h max NO_2.

Peel et al. (2005) examined ED visits for all respiratory causes among all ages in relation to ambient NO_2 concentrations in Atlanta, GA during the period of 1993 to 2000. They found a 2.4% (95% CI: 0.9, 4.1) increase in respiratory ED visits associated with a 30-ppb increase in 1-h max NO_2 concentrations. Tolbert et al. (2007) recently reanalyzed these data with 4 additional years of data and found similar results (2.0% increase, 95% CI: 0.5, 3.3).

Two multicity studies combined the effects of ambient air pollution (including NO_2) in several cities and describe similar response rates and respiratory health outcomes as measured by

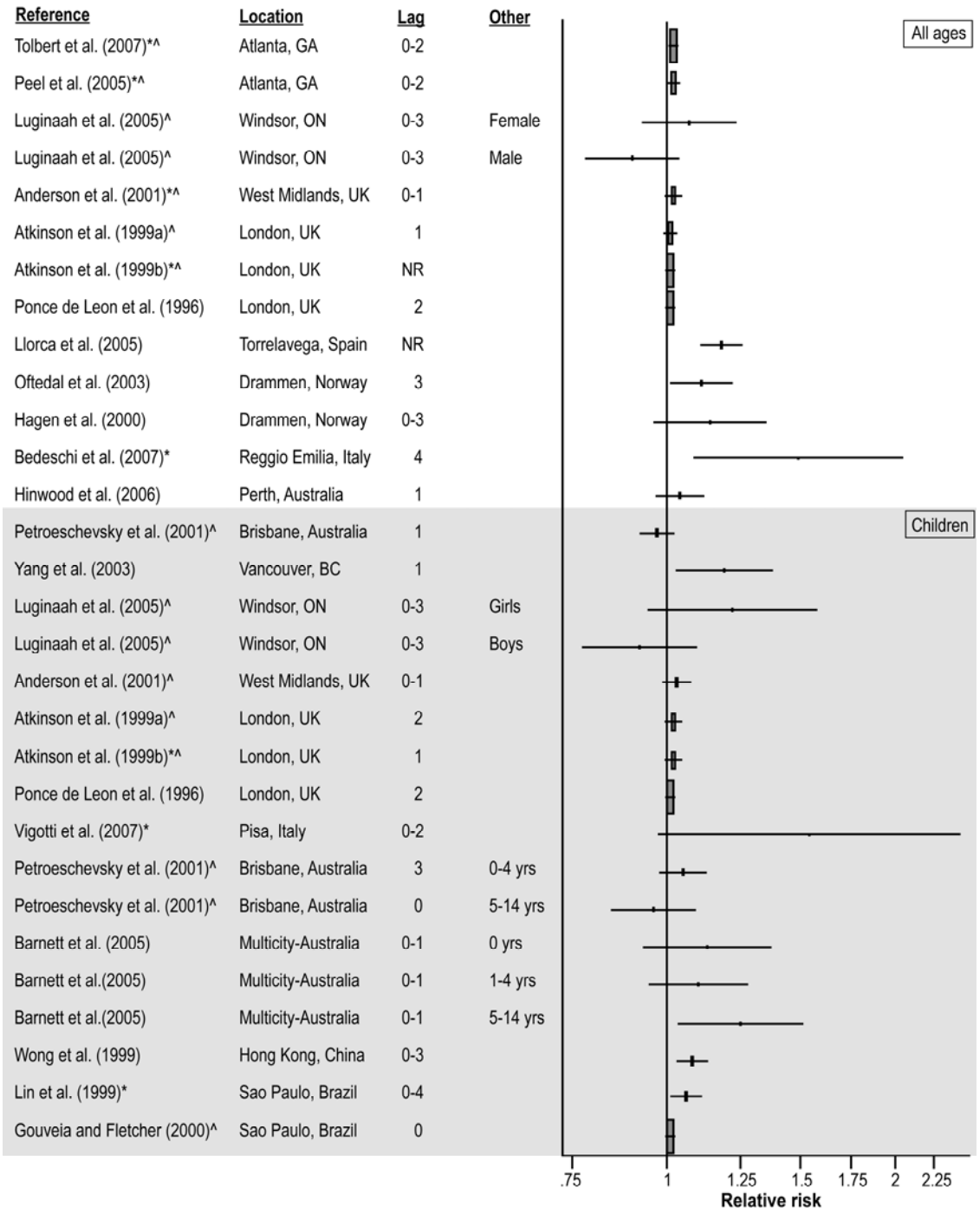

Figure 3.1-8. Relative Risks (95% CI) for hospital admissions or ED visits for all respiratory disease stratified by all ages or children. Results from studies using 24-h average standardized to a 20-ppb increase, results from studies using 1-h max standardized to a 30-ppb increase (* indicates ED visits, all others are hospital admissions; ^ indicates 1-h max averaging times, all others are 24-h mean averaging times).

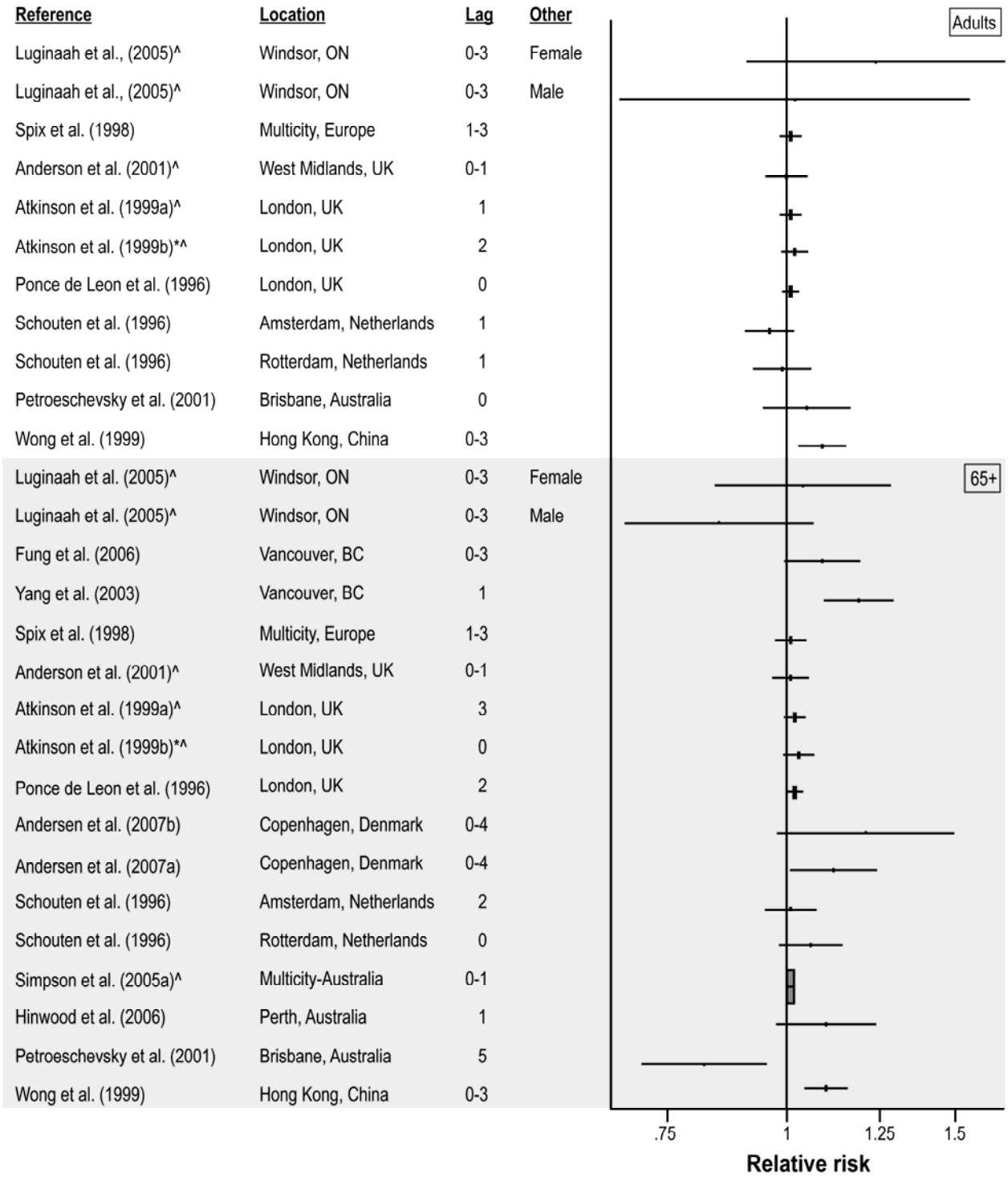

Figure 3.1-9. Relative Risks (95% CI) for hospital admissions or ED visits for all respiratory disease stratified by adults and older adults (≥65 years). Results from studies using 24-h average standardized to a 20-ppb increase, results from studies using 1-h max standardized to a 30-ppb increase (* indicates ED visits, all others are hospital admissions; ^ indicates 1-h max averaging times, all others are 24-h mean averaging times).

increased hospital admissions (Barnett et al., 2005; Simpson et al., 2005a). Barnett et al. (2005) used a case-crossover method to study ambient air pollution effects on respiratory hospital admissions of children (age groups 0, 1 to 4, and 5 to 14 years) in multiple cities in both Australia and New Zealand during the study period 1998 to 2001. No significant associations were observed between NO_2 and increased hospital admissions for infants. For all respiratory admissions among children 1 to 4 years, a 9.6% (95% CI: 2.3, 17.3) increase was found for a 30-ppb increase in the daily 1-h max concentration of NO_2, and for children aged 5 to14 years the same increase in NO_2 resulted in a 16.5% increase in admission for all respiratory disease (95% CI: 5.4, 28.8) both lagged 0 to 1 day (Barnett et al., 2005).

In a multicity study of all hospitalizations for respiratory disease for adults ages $\geq$65 years, Simpson et al. (2005a) examined the response to a change in the daily 1-h max level of NO_2. The standardized percent increase was 8.4% (95% CI: 4.6%, 12.4%; lag 0 to 1 day per 30-ppb increase). The authors presented results from three statistical models that produced similar results overall for the four cities.

Two Canadian studies compared multiple statistical methods for data analysis in studies of hospitalizations for all respiratory outcomes. In Vancouver, Fung et al. (2006) used time-series analysis, the method of Dewanji and Moolgavkar (2000), and case-crossover analyses to examine the association of ambient NO_2 concentrations with all respiratory hospitalizations for adults aged 65 years and older. All three methods showed similar results, with positive associations between incremental changes in NO_2 of 5.43 ppb (IQR) from a mean concentration of 16.83 ppb. Using a time-series analysis, Fung et al. (2006) reported a percent increase (standardized to 20 ppb) of 6.8% ([95% CI: 1.1%, 13.1%] lag 0), while the case-crossover analysis showed a significant change in the percent increase of 10.7% ([95% CI: 3.7%, 15.5%] lag 0). The Dewanji and Moolgavkar (2000) model did not produce a statistically significant association between NO_2 and hospitalization for an increase of 20 ppb, though the central estimate remained positive (percent increase = 4.5% [95% CI: $-$1.1%, 10.3%] lag 0)]. In the second of these two studies, Luginaah et al. (2005) used two approaches that included both time-series and case-crossover analyses segregated by sex. They noted a positive trend between an incremental change in 24-h avg NO_2 of 20 ppb and respiratory admissions. Though associations for females in each of the age groups examined were positive, the authors found only one statistically significant association in females aged 0 to 14 years that identified an increased

percent of hospitalization of 24.1% using the case-crossover analysis (24.1% [95% CI: 0.3%, 53.8%] lag 2). The results of the time-series analyses from the Fung et al. (2006) and Luginaah et al. (2005) studies are presented in Figures 3.1-8 and 3.1-9, respectively.

European studies on associations with respiratory hospitalizations were conducted in London, Paris, and in Drammen, Norway (Ponce de Leon et al., 1996; Dab et al., 1996; Oftedal et al., 2003). Ponce de Leon et al. (1996) found significant positive relative risks for all ages and for children (0 to 14 year olds), but not for adults (15 to 64 years). Dab et al. (1996) determined that there was no statistically significant association between admissions for all respiratory causes combined based on an incremental change of 52.35 ppb, though the estimates were positive. Oftedal et al. (2003) reported that the relative rate of hospitalizations for all respiratory disease increased based on an increment of 20 ppb NO_2 (RR = 1.111 [95% CI: 1.031, 1.19.9] lag 3 days). Other studies also found positive outcomes (Andersen et al., 2007a,b; Atkinson et al., 1999a,b; Bedeschi et al., 2007; Burnett et al., 2001; Farchi et al., 2006; Hinwood et al., 2006; Lin et al., 1999; Llorca et al., 2005; Pantazopoulou et al., 1995; Vigotti et al., 2007; Wong et al., 1999; Yang et al., 2003). Several studies presented null results (Anderson et al., 2001; Gouveia and Fletcher, 2000; Hagen et al., 2001; Schouten et al., 1996). Finally, a number of studies were considered that could not inform the association of NO_2 concentration on all respiratory disease hospital admissions or ED visits. These studies are included in Annex Tables AX6.3-1, AX6.3-2, and AX6.3-3 (Atkinson et al., 2001; Buchdahl et al., 1996; Burnett et al., 1997a; Chen et al., 2005; Fung et al., 2007; Linares et al., 2006; Pantazopoulou et al., 1995; Prescott et al., 1998; Villeneuve et al., 2006).

To assess potential confounding by copollutants, results from multipollutant models were evaluated. As noted in Annex 3B, multipollutant models may have limited utility to distinguish the independent effects of specific pollutants if model assumptions are not met. Despite this limitation, these models are widely used in air pollution research. Figures 3.1-10 and 3.1-11 present NO_2 risk estimates for all respiratory causes with and without adjustment for various particulate and gaseous copollutants, respectively, in two-pollutant models. Collectively, copollutant regression analyses indicated that NO_2 risk estimates for respiratory ED visits and hospitalizations, in general, were not sensitive to the inclusion of additional gaseous or particulate pollutants.

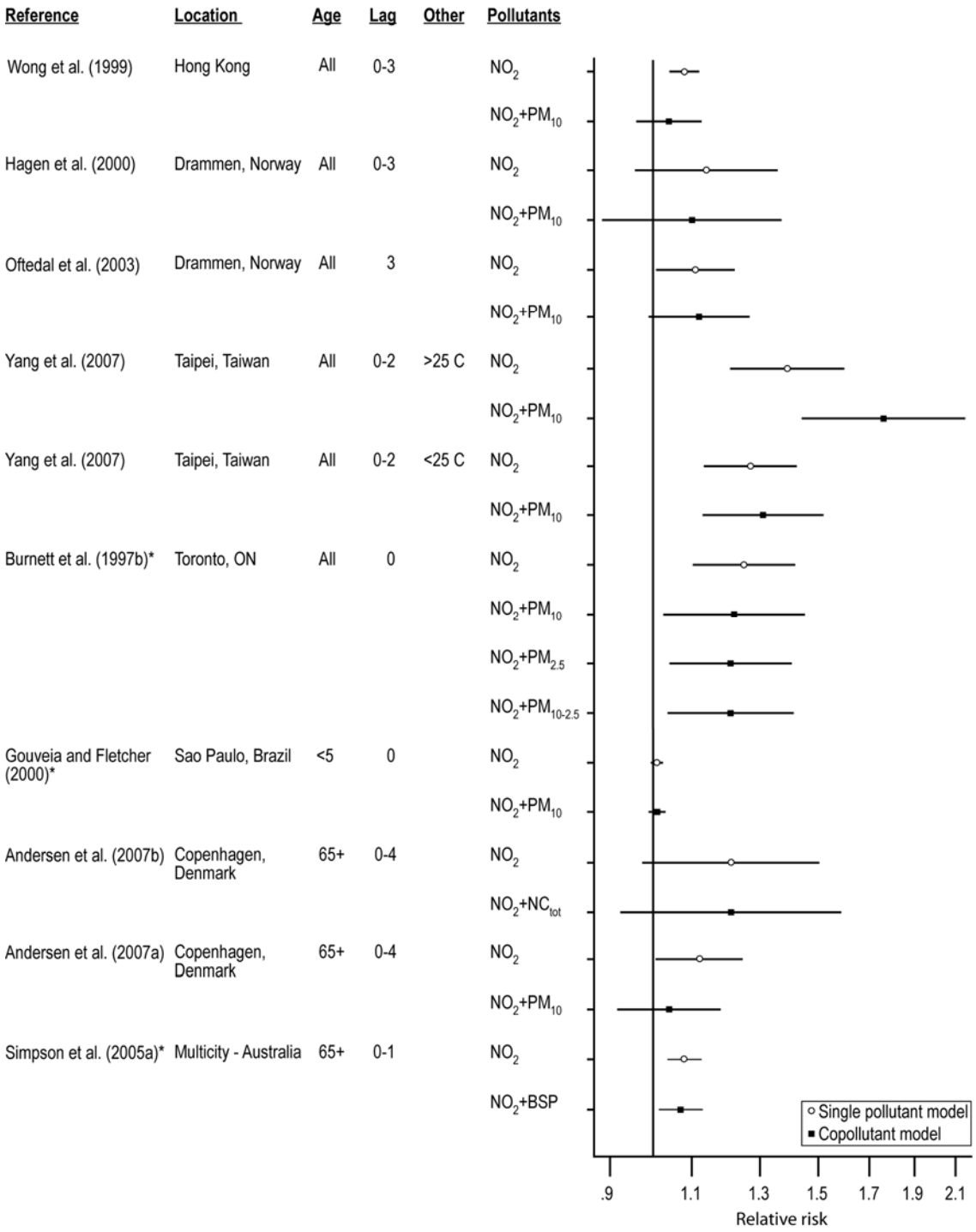

Figure 3.1-10. Relative Risks (95% CI) for hospital admissions or emergency department visits for all respiratory causes, standardized from two-pollutant models adjusted for particle concentration. (* indicates 1-h peak avg times, all others are 24-h avg; effect estimates from studies using 1-h peak measurements are standardized to a 30-ppb increase; effect estimates from studies using 24-h average measurements are standardized to a 20-ppb increase).

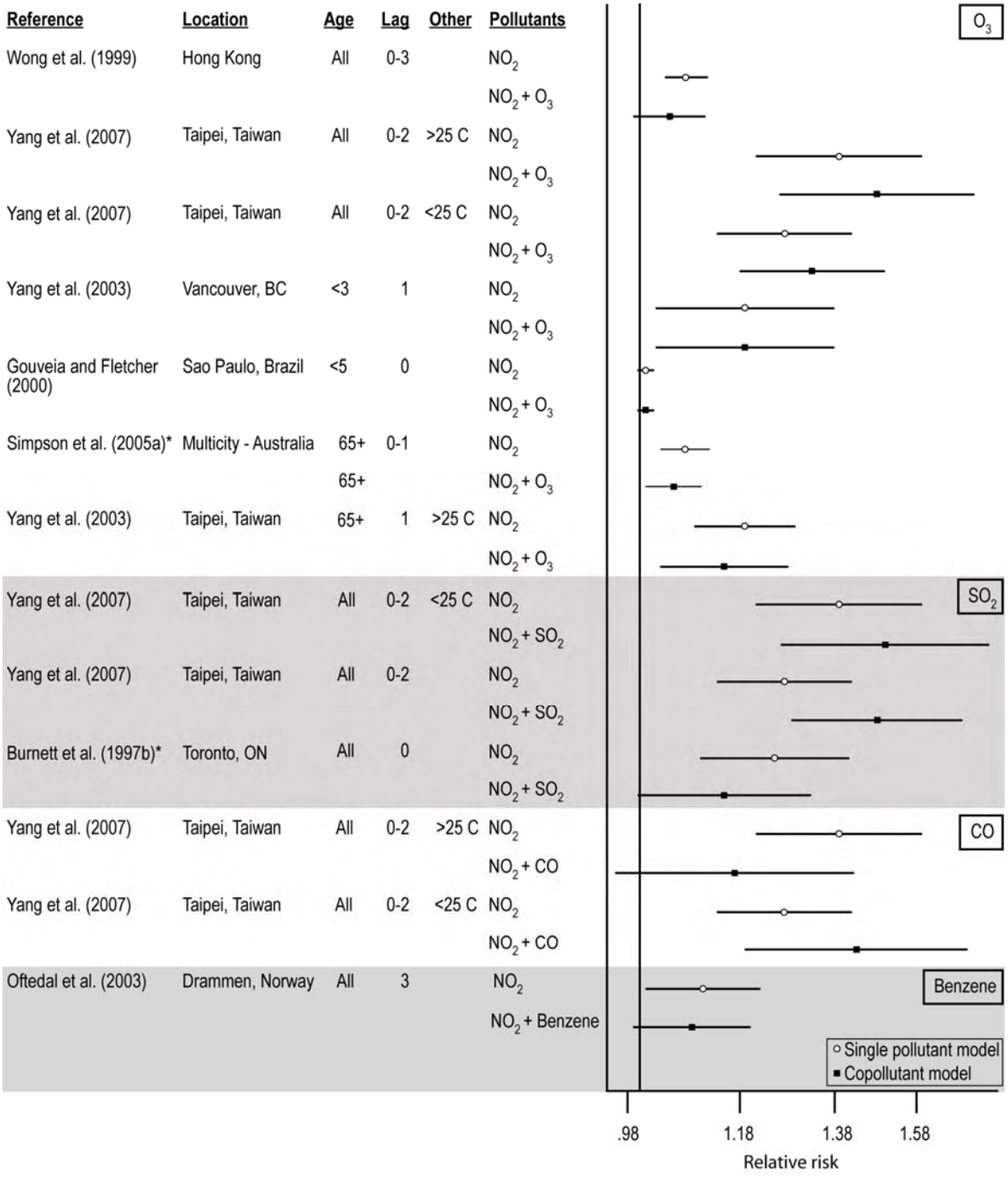

Figure 3.1-11. Relative Risks (95% CI) for hospital admissions or emergency department visits for all respiratory causes, standardized from two-pollutant models adjusted for gaseous pollutant concentration. (* indicates 1-h peak averaging times, all others are 24-h average; effect estimates from studies using 1-h peak measurements are standardized to a 30-ppb increase; effect estimates from studies using 24-h average measurements are standardized to a 20-ppb increase).

3.1.6.2 Asthma (ICD9 493)

Studies of ED visits and hospitalizations provide suggestive evidence of an association between ambient NO_2 levels and ED visits and hospitalizations for asthma among children and adults. Figures 3.1-12 and 3.1-13 show the relative risks (and 95% confidence limits) of hospitalizations and visits to the ED for asthma associated with daily NO_2 concentrations, for allages and stratified by age. Larger effect estimates were generally observed for children compared to adults and older adults (65+ years), with an IQR of 1 to 25% excess risk estimated per 20 ppb incremental change in 24-h avg NO_2 or 30 ppb incremental change in 1-h max NO_2. The few studies that examined the association of asthma and NO_2 levels among older adults (65+ years) generally reported positive central estimates, though none of these was statistically significant. When subjects of all ages were examined, the results of ED visits and hospitalizations were overwhelmingly positive, especially when the 24-h averaging time was used. The epidemiologic studies of ED visits and hospital admissions for asthma are summarized in Annex Tables AX6.3-1, AX6.3-2, and AX6.3-3.

In Atlanta, GA, Peel et al. (2005) examined various respiratory ED visits in relation to pollutant levels from 1993 to 2000. Results for the a priori single-pollutant models examining a 3-day moving average (lag 0, 1, and 2) of NO_2 showed a small positive, but not statistically significant, association with asthma visits (percent increase = 2.1% [95% CI: −0.4%, 4.5%) for all age groups. In a secondary analysis of patients ages 2 to 18 years, a 30-ppb increase in the day 5 lag of the NO_2 concentration yielded a percent increase of 4.1% (95% CI: 0.8%, 7.6%).

In New York City, NY, Ito et al. (2007) examined numbers of ED visits for asthma in relation to pollution levels from 1999 to 2002. NO_2 was generally the most significant (and largest in effect size per the same distributional increment) predictor of asthma ED visits among $PM_{2.5}$, O_3, SO_2, and CO (percent increase = 12% (95% CI: 7%, 15%) per 20 ppb increase). Further, NO_2's risk estimates were most robust to the addition of other pollutants in the model, and the addition of NO_2 reduced other pollutant's risk estimates most consistently.

Jaffe et al. (2003) examined the effects of ambient pollutants during the summer months (June through August) on the daily number of ED visits for asthma among Medicaid recipients aged 5 to 34 years from 1991 to 1996 in Cincinnati and Cleveland. The percent change in ED visits for asthma as the primary diagnosis per 20-ppb increase in 24-h avg NO_2 concentration

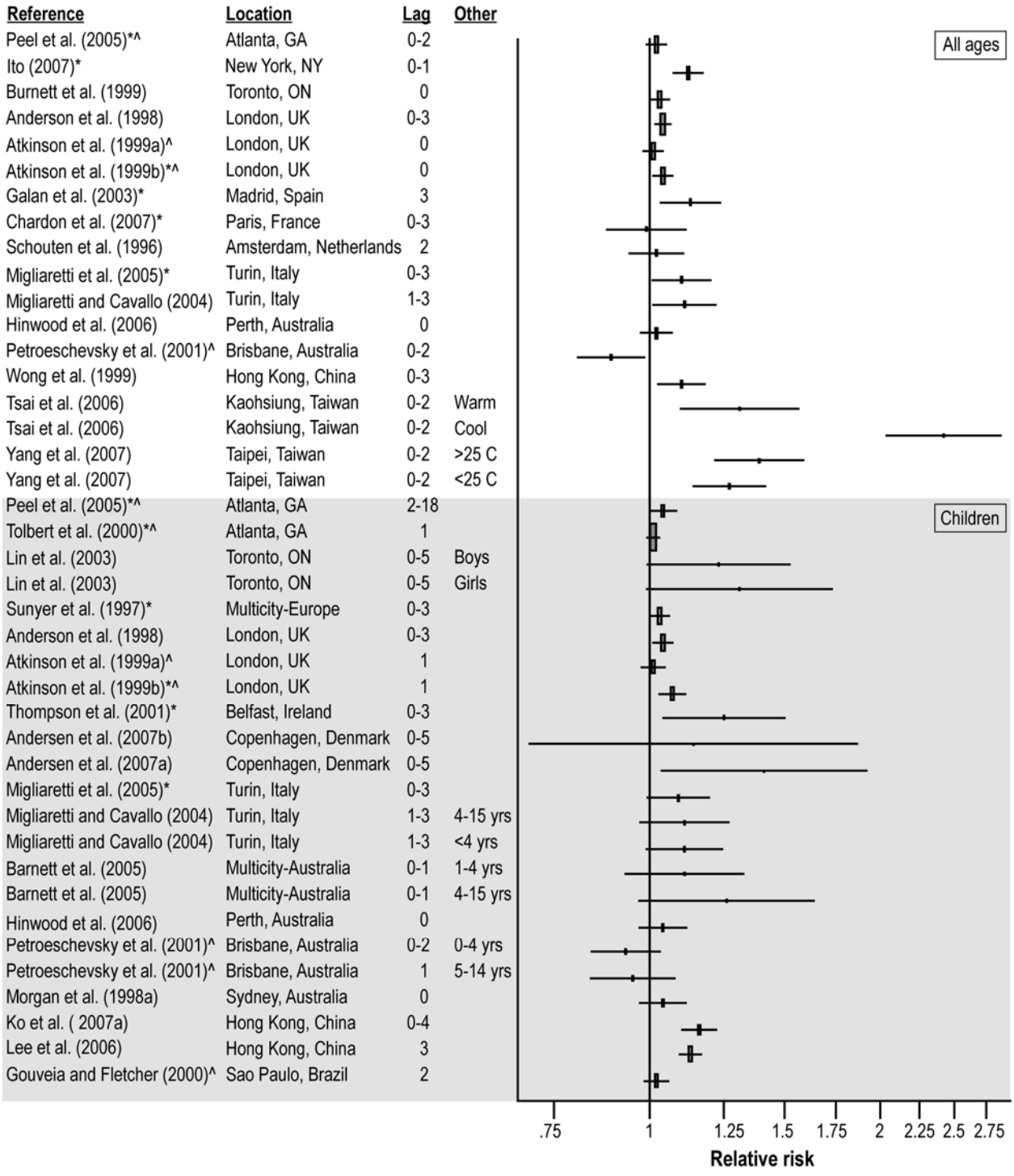

Figure 3.1-12. Relative Risks (95% CI) for hospital admissions or emergency department visits for asthma stratified by all ages or children. Results from studies using 24-h average standardized to a 20-ppb increase, results from studies using 1-h max standardized to a 30-ppb increase (* indicates ED visits, all others are hospital admissions; ^ indicates 1-h max averaging times, all others are 24-h mean averaging times).

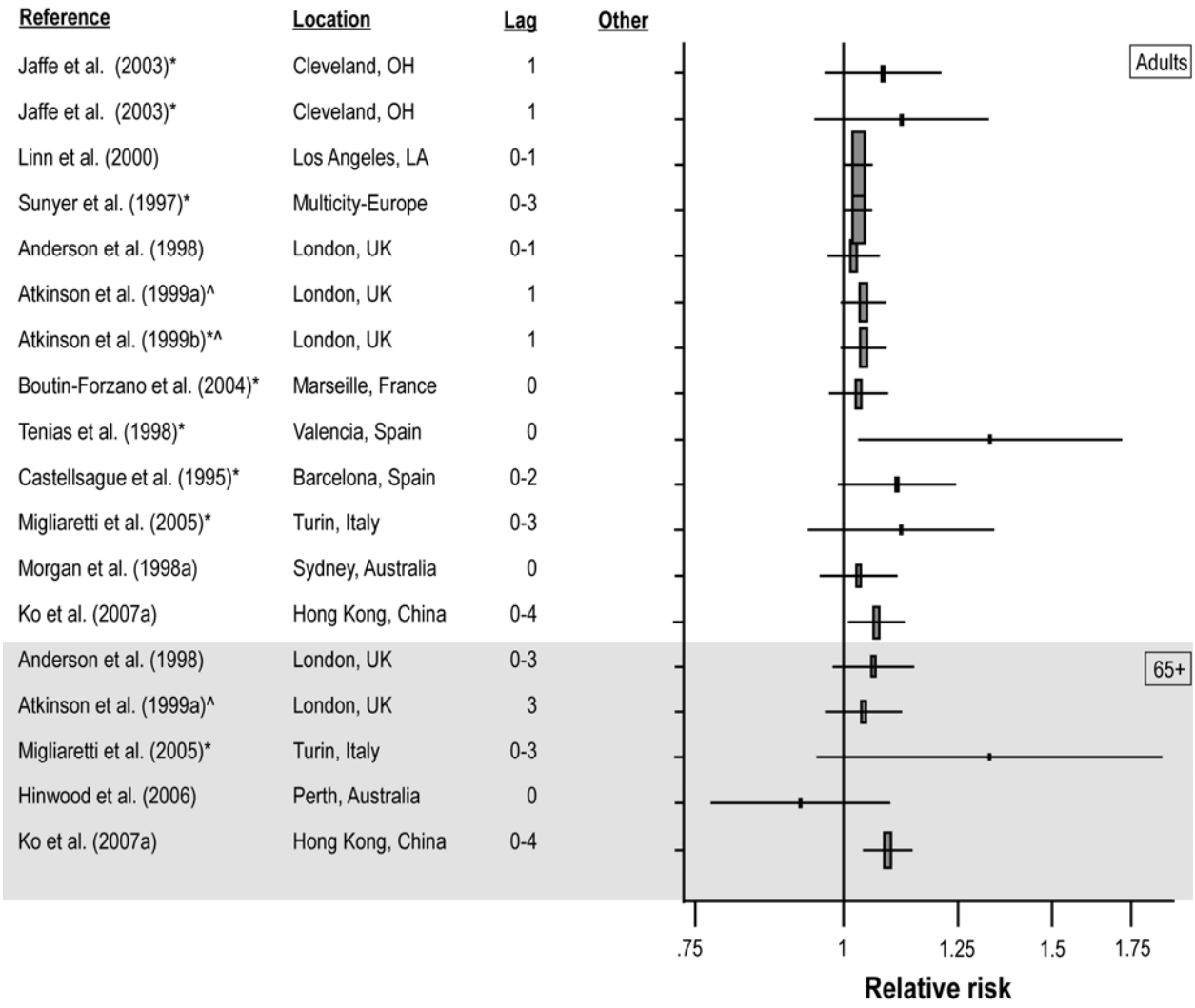

Figure 3.1-13. Relative Risks (95% CI) for hospital admissions or emergency department (ED) visits for asthma stratified by adults and older adults (≥65 years). Results from studies using 24-h average standardized to a 20-ppb increase, results from studies using 1-h max standardized to a 30-ppb increase (* indicates ED visits, all others are hospital admissions; ^ indicates 1-h max averaging times, all others are 24-h mean averaging times).

was 12% (95% CI: −2, 28) in Cincinnati and 8% (95% CI: −2, 16.6) in Cleveland, with an overall percent increase in ED visits of 6% (95% CI: −2, 14).

Barnett et al. (2005) examined specific respiratory disease outcomes and did not find associations between incremental changes in NO_2 concentration and respiratory admissions for asthma among children 1 to 4 years old. The largest association found in this study was a 25.7%

increase in asthma admissions in the 5- to 14-year age group related to a 20-ppb increase in 24-h NO_2, with evidence of a seasonal impact that resulted in larger increases in admissions during the warm season. When the same groups were examined for the effect of a 30-ppb change in the 1-h max concentration of NO_2, there were no significant associations between NO_2 and hospitalizations for asthma.

Lin et al. (2004) studied gaseous air pollutants and 3,822 asthma hospitalizations (2,368 boys, and 1,454 girls) among children 6 to 12 years of age with low household income in Vancouver, Canada, between 1987 and 1998. NO_2 levels were derived from 30 monitoring stations, and daily levels were found to be significantly and positively associated with asthma hospitalizations for males in the low socioeconomic group but not in the high socioeconomic group. This effect did not persist among females. Lin et al. (2003) conducted a case-crossover analysis of the effect of short-term exposure to gaseous pollution on 7,319 asthma hospitalizations (4,629 boys, 2,690 girls), in children in Toronto between 1980 and 1994. NO_2 concentrations measured from four monitoring stations were positively associated with asthma admissions in both sexes. Differences in the results of these two studies might be attributed to differences in the study designs or differences in subject population sizes.

A time-series analysis in Sydney examined respiratory outcomes in children and adults, but reported no association between changes in NO_2 (24-h avg) for asthma admissions (Morgan et al., 1998a). For children aged 1 to 14, a 10.9% increase in hospital admissions for asthma ([95% CI: 2.2, 20.3] lag 0) was associated with the daily 1-h maximum value based on 30-ppb incremental change. The association with adults was positive, but not statistically significant.

Studies of ED visits and hospitalizations for asthma have been reported in London, U.K. (Atkinson et al., 1999a,b; Hajat et al., 1999); Belfast, Ireland (Thompson et al., 2001); Valencia, Barcelona, and Madrid, Spain (Tenías et al., 1998; Galán et al., 2003; Castellsague et al., 1995); Turin, Italy (Migliaretti and Cavallo, 2004; Migliaretti et al., 2005); Marseille and Paris, France (Boutin-Forzano et al., 2004; Dab et al., 1996); Amsterdam and Rotterdam, the Netherlands (Schouten et al., 1996), and Melbourne, Brisbane and Perth, Australia (Erbas et al., 2005; Hinwood et al., 2006). Sunyer et al. (1997) have described a meta-analysis of several cities under the umbrella of the Air Pollution on Health: a European Approach (APHEA) protocol (Katsouyanni et al., 1996). Additional studies report a positive association between NO_2 concentration and hospital admissions or ED visits (Andersen et al., 2007a; Anderson et al.,

1998; Arbex et al., 2007; Burnett et al., 1999; Kim et al., 2007; Ko et al., 2007; Lee et al., 2006; Linn et al., 2000; Tsai et al 2006; Wong et al., 2001; Yang et al., 2007). Several studies have reported null or negative associations (Andersen et al., 2007b; Anderson et al., 1998; Chardon et al., 2007; Gouveia and Fletcher 2000; Petroeschevsky et al., 2001; Spix et al., 1998; Tanaka et al., 1998; Tolbert et al., 2000).

Copollutant and multipollutant regression analyses were performed in several of these studies. Results generally indicated that NO_2 risk estimates for respiratory ED visits and hospitalizations were not sensitive to the inclusion of additional gaseous or particulate pollutants.

Finally, there were a number of studies that were considered but did not inform the association of NO_2 concentration on all respiratory disease hospital admissions or ED visits. These studies are included in Annex Tables AX6.3-1, AX6.3-2, and AX6.3-3 (Atkinson et al., 2001; Bates et al., 1990; Chew et al., 1999; Garty et al., 1998; Kesten et al., 1995; Lipsett et al., 1997; Magas et al., 2007; Neidell, 2004; Pönkä, 1991; Pönkä and Vitanen 1996; Rossi et al., 1993; Stieb et al., 1996; Sun et al., 2006; Tobias et al., 1999).

3.1.6.3 COPD (ICD9 490–496)

Relatively few studies have examined the association of ED visits and hospitalizations for COPD and ambient NO_2 levels. The epidemiologic studies of ED visits and hospital admissions for COPD are summarized in Annex Tables AX6.3-1, AX6.3-2, and AX6.3-3. Studies examining COPD outcomes have focused on hospital admission data, including multicity studies in the United States (Moolgavkar, 2000, 2003), Europe (Anderson et al., 1997) and Australia (Simpson et al., 2005a), and single-city studies in the United States (Peel et al., 2005), Canada (Yang et al., 2005), Europe (Anderson et al., 2001; Atkinson et al., 1999a; Dab et al., 1996; Tenias et al., 2002), Australia (Morgan et al., 1998a; Hinwood et al., 2006), and Asia (Lee et al., 2007; Yang and Chen, 2007).

In a time-series study in Vancouver, an area with low pollution concentrations (24-h mean NO_2 of 17.03 ppb), Yang et al. (2005) reported associations between NO_2 and hospital admissions for COPD in patients $\geq$65 years for both the lag 1 day (RR = 1.19; 95% CI: 1.04, 1.37) and 7-day extended lag period (RR = 1.46 [95% CI: 1.15, 1.94]). Additional studies found weaker, though statistically significant positive associations with ambient levels of NO_2 and COPD (Moolgavkar, 2003; Anderson et al., 1997; Simpson et al., 2005a). A time-series analysis

in Sydney, Australia, examined respiratory outcomes in children and adults but did not show an association between changes in NO_2 (24-h average) for increased hospital admissions among COPD patients ≥65 years (Morgan et al., 1998a). Similarly, a study in Paris, France, of COPD and related obstructive respiratory disease found that NO_2 was not statistically significantly associated with increased hospital admissions (Dab et al., 1996).

3.1.6.4 Respiratory Diseases Other than Asthma or COPD

ED visits or hospital admissions for respiratory diseases include upper respiratory infections (URIs), pneumonia, bronchitis, allergic rhinitis, and lower respiratory disease (LRD). The reviewed epidemiologic studies of ED visits and hospital admissions for these respiratory diseases are summarized in Annex Tables AX6.3-1, AX6.3-2, and AX6.3-3. Though some of these studies reported positive and statistically significant results (Atkinson et al., 1999a; Burnett et al., 1997b, 1999; Farchi et al., 2006; Gouveia and Fletcher, 2000; Hwang and Chan, 2002; Ilabaca et al., 1999; Lin et al., 2005; Peel et al., 2005; Simpson et al., 2005a), others reported null or negative associations (Barnett et al., 2005; Chardon et al., 2007; Hinwood et al., 2006; Karr et al., 2006; Lin et al., 1999; Pönkä and Virtanen, 1994; Zanobetti and Schwartz, 2006). Finally, there are two studies that were considered but could not inform the association of NO_2 concentration on all respiratory disease hospital admissions or ED visits (Bates et al., 1990; Linares et al., 2006). These studies are included in Annex Tables AX6.3-1, AX6.3-2, and AX6.3-3.

3.1.6.5 Summary of the Evidence on the Effect of Short-Term Exposure to NO_2 on Respiratory ED Visits and Hospitalizations

In summary, many studies have observed positive associations between ambient NO_2 concentrations and ED visits and hospitalizations for all respiratory diseases and asthma. These associations are particularly consistent among children and older adults (65+ years) for hospital admissions for all respiratory diseases. For asthma hospitalization, the effect estimates were largest when children and subjects of all ages were included in the analysis. Results from copollutant models suggested that the effect of NO_2 on ED visits and hospitalizations for all respiratory causes and asthma were generally robust and independent of the effects of ambient particles or gaseous copollutants. In preceding sections, exposure to NO_2 has been found to result in host defense and immune system changes, airways inflammation, and airways

responsiveness. While not providing specific mechanistic data linking exposure to ambient NO_2 and respiratory hospitalization or ED visits, these findings provide plausibility and coherence for such a relationship.

However, the limited evidence does not support a relationship between ED visits and hospitalizations for COPD and ambient NO_2 levels, and there were limited studies providing inconsistent results for many of the health outcomes other than asthma, making it difficult to draw conclusions about the effects of NO_2 on these diseases.

3.1.7 Summary and Integration—Respiratory Health Effects with Short-Term NO_2 Exposure

Taken together, the findings of epidemiologic, human clinical, and animal toxicological studies provide evidence that is sufficient to infer a *likely causal* relationship for respiratory effects with short-term NO_2 exposure. The body of evidence from epidemiologic studies has grown substantially since the 1993 AQCD and provides scientific evidence that short-term exposure to NO_2 is associated with a broad range of respiratory morbidity effects, including altered lung host defense, inflammation, airways hyperresponsiveness, respiratory symptoms, lung function decrements, and ED visits and hospital admissions for respiratory diseases. New evidence comes from large longitudinal studies, panel studies, and time-series studies. NO_2 exposure is associated with aggravation of asthma effects that include symptoms, medication use, and lung function. Effects of NO_2 on asthma were most evident with cumulative lag of 2 to 6 days, rather than same-day levels of NO_2. Time-series studies also demonstrated a relationship in children between hospital admissions or ED visits for asthma and NO_2 exposure. In many of these studies, there were high correlations between ambient measures of NO_2 and CO and PM; however, the effect estimates for NO_2 were robust after the inclusion of CO and PM in multipollutant models. Recent epidemiologic studies provide somewhat inconsistent evidence on short-term exposure to NO_2 and inflammatory responses in the airways, as well as for associations with lung function decrements. The epidemiologic evidence for these effects can be characterized as consistent, in that associations are reported in studies conducted in numerous locations with a variety of methodological approaches. While the individual risk estimates are small in magnitude, and thus not considered strong individually, the body of epidemiologic evidence has strength in that fairly precise and robust risk estimates have been reported from multicity studies.

Important evidence also is available from epidemiologic studies of indoor NO_2 exposures. A number of recent studies show associations with wheeze, chest tightness, and length of symptoms (Belanger et al., 2006); respiratory symptom rates (Nitschke et al., 2006); school absences (Pilotto et al., 1997a); respiratory symptoms, likelihood of chest tightness, and asthma attacks (Smith et al., 2000); and severity of virus-induced asthma (Chauhan et al., 2003). A particular intervention study (Pilotto et al., 2004) provides strong evidence of a detrimental effect of exposure to NO_2. Considering this large body of epidemiologic studies alone, the findings are coherent in the sense that the studies report associations with respiratory health outcomes that are logically linked together.

Experimental evidence offers some coherence and plausibility for the observed epidemiologic associations. Toxicologic studies have also shown that lung host defenses, including mucociliary clearance and AM and other immune cell functions, are sensitive to NO_2 exposure, with effects observed at concentrations of less than 1 ppm (see Annex Table AX4.3 and AX4.5). The limited evidence from human studies indicates that NO_2 may increase susceptibility to injury by subsequent viral challenge. Devlin et al. (1999) found reduced AM phagocytic capacity after NO_2 exposure, which suggest a reduced ability to clear inhaled bacteria or other infectious agents. Frampton et al. (2002) found enhanced epithelial cell injury in response to RSV infection after NO_2 exposure. Taken together with the epidemiologic evidence described above linking NO_2 exposure with viral illnesses, there is coherent and consistent evidence that NO_2 exposure can result in lung host defense or immune system effects. This group of outcomes provides some plausibility for other respiratory system effects as well. For example, effects on ciliary action (clearance) or on macrophage function (i.e. phagocytosis, cytokine production) can lead to the type of outcomes assessed in epidemiologic studies, such as respiratory illness or symptoms.

Controlled human exposure studies provide evidence for airways hyperresponsiveness i.e., a heightened bronchoconstrictive response to a challenge agent, following short-term exposure to NO_2. In acute exacerbations of asthma, bronchial smooth muscle contraction (bronchoconstriction) occurs quickly to narrow the airways in response to exposure to various stimuli including allergens or irritants. Bronchoconstriction is the dominant physiological event leading to clinical symptoms and interference with airflow (National Heart, Lung, and Blood Institute, 2007). Recent studies involving allergen challenge in asthmatics suggest that NO_2 may

enhance the sensitivity to allergen-induced decrements in lung function and affect allergen-induced inflammatory responses following exposures as low as 0.26 ppm NO_2 for 30 min during rest. Nonspecific responsiveness is also increased following 30-min exposures of resting asthmatic subjects to 0.2- to 0.3-ppm NO_2 and following 1-h exposures to 0.1-ppm NO_2.

The few recent epidemiologic studies have reported associations between ambient NO_2 exposure and airways inflammation. These studies are suggestive of effects in children, but offer more limited evidence for effects in adults. Controlled human exposure studies provide consistent evidence for airways inflammation at NO_2 concentrations of <2.0 ppm; the onset of inflammatory responses in healthy subjects appears to be between 100 and 200 ppm-min, i.e., 1 ppm for 2 to 3 h. Biological markers of inflammation are reported in antioxidant-deficient laboratory animals with exposures to 0.4-ppm NO_2, though healthy animals do not respond until exposed to much higher levels, i.e., 5-ppm NO_2. The biochemical effects observed in the respiratory tract following exposure to NO_2 include chemical alteration of lipids, amino acids, proteins, enzymes, and changes in oxidant/antioxidant homeostasis, with membrane polyunsaturated fatty acids and thiol groups as the main biochemical targets for NO_2 exposure. However, the biological implications of such alterations are unclear. Potential mechanisms for effects on the respiratory system include membrane damage from increases in reactive oxygen species, lipid and protein pertubations, and recruitment of inflammatory cells from epithelial cell injury by reactive oxygen species.

In evaluating the potential relationships between short-term exposure to NO_2 and respiratory effects, it is important to note the interrelationships between NO_2 and other pollutants, and the potential for NO_2 to serve as a marker for a pollutant mixture, particularly traffic-related pollution. As outlined in the preface to this draft Integrated Science Assessment (ISA), this includes consideration of potential pathways, such as the direct causal pathway for effects, mediation of effects, the pollutant acting as a surrogate for a pollutant mixture, or confounding between pollutants. As observed above, associations with NO_2 were often robust to adjustment for traffic-related pollutants (e.g., PM and CO), even in locations where the correlations between pollutants were substantial. The epidemiologic evidence has thus been found to be consistent and coherent for respiratory symptoms and respiratory hospitalization and ED visits. In addition, toxicologic and clinical studies report effects of exposure to gaseous NO_2, as discussed previously, for outcomes related to lung host defense and immune system changes.

The experimental studies indicate that NO_2 is solely responsible for the effects reported. The findings of direct effects of NO_2 in toxicologic or human clinical studies, in combination with robust associations reported in epidemiologic studies, support a conclusion that NO_2 is independently responsible for some respiratory effects. There is little available evidence to evaluate the potential for NO_2 effects to be mediated by other pollutants or exposures; further, clinical and epidemiologic study findings do not appear to suggest that coexposure with another pollutant is required to observe NO_2-related effects.

The evidence summarized here supports the conclusion that there is a likely causal relationship between short-term exposure to NO_2 and effects on the respiratory system. However, the challenge remains in considering the potential for NO_2 to serve as a surrogate for a mixture of combustion-related pollutants. Most studies examined show that personal NO_2 exposures are significantly correlated either with ambient or personal level $PM_{2.5}$, or other combustion-generated products (e.g., CO and EC). As discussed in Chapter 2, ambient NO_2 measurements can provide a valid estimate of personal exposure to ambient NO_2 as used in most epidemiology studies. Although the evidence indicates that NO_2 exposure is independently associated with some respiratory health effects, there remains the possibility that NO_2 also serves as a marker for combustion-related emissions, particularly from traffic, for some health outcomes.

3.2 CARDIOVASCULAR EFFECTS ASSOCIATED WITH SHORT-TERM NO_2 EXPOSURE

The current review includes approximately 40 studies published since 1993 characterizing the effect of short-term NO_X exposure on hospitalizations or ED visits for CVD. These studies form a new body of literature that was unavailable in 1993, when the previous AQCD was published.

3.2.1 Heart Rate Variability, Repolarization Changes, Arrhythmia, and Markers of Cardiovascular Function in Humans and Animals

3.2.1.1 Heart Rate Variability

Heart rate variability (HRV), a measure of the beat-to-beat change in heart rate, is a reflection of the overall autonomic control of the heart. It is hypothesized that increased air

pollution levels may stimulate the autonomic nervous system and lead to an imbalance of cardiac autonomic control characterized by sympathetic activation unopposed by parasympathetic control (Liao et al., 2004; Brook et al., 2004). Such an imbalance of cardiac autonomic control may predispose susceptible people to greater risk of ventricular arrhythmias and consequent cardiac deaths (Liao et al., 2004; Brook et al., 2004). HRV has been studied most frequently in coronary artery disease populations, particularly in the post-myocardial infarction (MI) population. Lower time domain as well as frequency domain variables (i.e., measures of reduced HRV) are associated with an increase in cardiac and all-cause mortality among this susceptible population. Those variables most closely correlated with parasympathetic tone appear to have the strongest predictive value in heart disease populations. Specifically, acute changes in RR-variability may temporally precede and are predictive of increased long-term risk for the occurrence of ischemic sudden death and/or precipitating ventricular arrhythmias in individuals with established heart disease (for example, see La Rovere et al., 2003). Findings from studies of ambient NO_2 and HRV were mixed with some studies reporting an adverse effect (reduction in variability) (Liao et al., 2004; Chan et al., 2005; Wheeler et al., 2006), while other studies reported no significant change (Luttman-Gibson et al., 2006; Holguin et al., 2003; Schwartz et al. 2005). In some studies reporting reductions in HRV, reductions for PM were similar to those observed for NO_2 (Liao et al., 2004; Wheeler et al. 2006). See Annex AX6.3-10 for a detailed discussion of HRV studies.

3.2.1.2 Arrhythmias Recorded on Implanted Defibrillators

Results from studies directly measuring ventricular arrhythmias were inconsistent and potentially confounded by PM (Peters et al., 2000; Dockery et al., 2005; Rich et al., 2005, 2006a; Metzger et al,. 2007). Among the ambient air pollutants, the strongest association with arrhythmias was observed for PM, which was highly correlated to NO_2 concentrations in these studies (Dockery et al., 2005; Rich et al., 2005; Metzger et al., 2007). Rich et al. (2006b) did not observe an association between NO_2 level and paroxysmal atrial fibrillation (PAF). See Annex AX6.3-11 for detailed discussion of defibrillator studies.

3.2.1.3 Repolarization Changes

In addition to the role played by the autonomic nervous system in arrhythmogenic conditions, myocardial vulnerability and repolarization abnormalities are believed to be key

factors contributing to the mechanism of such diseases. Measures of repolarization include QT duration, T-wave complexity, variability of T-wave complexity, and T-wave amplitude. Henneberger et al. (2005) reported that NO_2 and NO were not associated with repolarization abnormalities.

3.2.1.4 Markers of Cardiovascular Disease Risk

Several investigators have explored potential mechanisms by which air pollution could cause CVD. In particular, markers of inflammation, cell adhesion, coagulation, and thrombosis have been evaluated in epidemiologic studies. Pekkanen et al. (2000) reported a significant increase in fibrinogen associated with short-term NO_2 exposure while Steinvil et al. (2007) reported significant decreases in fibrinogen associated with NO_2. Schwartz (2001) reported increases in fibrinogen and platelet count associated with NO_2 level in single-pollutant models, which changed direction in multipollutant models also containing PM_{10}. Liao et al. (2005) did not observe differences in white blood cell (WBC) count, Factor VIII-C, fibrinogen, von Willibrand Factor (VWF), or albumin associated with 24-h avg NO_2 levels. However, PM_{10} was associated with factor VIII-C in the cohort examined. Ruckerl et al. (2006) observed a significant association of NO_2 (lagged 2-6 days) with C-reactive protein (CRP) greater than the 90th percentile but the strongest effect on CRP was observed for ultrafine particles. Baccarelli et al. (2007) reported a shorter prothrombin time (PT) with increasing NO_2 levels but, a similar decrease in PT was observed for PM_{10}.

Collectively, associations reported for NO_2 and markers of cardiovascular risk in epidemiologic studies appear to be potentially confounded by PM and other traffic-related pollutants. Several authors suggest that these biomarker studies provide evidence for biologic plausibility of the effect of PM on cardiovascular health rather than NO_2 (Schwartz 2001; Seaton and Dennekamp, 2003).

A limited number of controlled human exposure studies suggest effects of NO_2 exposure on cardiac output, blood pressure, and circulating red blood cells at concentrations of less than 2.0 ppm (Drechsler-Parks, 1995; Linn et al., 1985a; Posin et al., 1978; Frampton et al., 2002) require confirmation. Drechsler-Parks (1995) observed a lower mean stroke volume for NO_2 + O_3 than for air and speculated that chemical interactions between O_3 and NO_2 at the level of the epithelial lining fluid led to the production of nitrite, leading to vasodilatation, with reduced cardiac preload and cardiac output. Linn et al. (1985a) reported small but statistically significant

reductions in blood pressure after exposure to 4-ppm NO_2 for 75 min, a finding consistent with systemic vasodilatation in response to the exposure; this finding has not been repeated. Frampton et al. (2002) reported a concentration-related reduction in hematocrit and hemoglobin in both males and females, among health subjects exposed to NO_2, confirming the findings of an earlier study conducted by Posin et al. (1978). See Annex AX6 for a detailed discussion of these studies.

The results on the effect of NO_2 on various hematological parameters in animals are inconsistent and, thus, provide little biological plausibility for the epidemiology findings. There have also been reported changes in the red blood cell membranes of experimental animals following NO_2 exposure. Red blood cell D-2,3-diphosphoglycerate was reportedly increased in guinea pigs following exposure to 0.36-ppm NO_2 for 1 week (Mersch et al., 1973). An increase in red blood cell sialic acid, indicative of a younger population of red blood cells, was reported in rats exposed to 4.0-ppm NO_2 continuously for 1 to 10 days (Kunimoto et al., 1984). However, in another study, exposure to the same concentration of NO_2 resulted in a decrease in red blood cell number (Mochitate and Miura, 1984). A more recent study (Takano et al., 2004) using an obese rat strain found changes in blood triglycerides, high-density lipoprotein cholesterol (HDL), and HDL/total cholesterol ratios with a 24-week exposure to 0.16-ppm NO_2. In the only study conducted with an exposure of less than 5-ppm NO_2 that evaluated methemoglobin formation, Nakajima and Kusumoto (1968) reported that, in mice exposed to 0.8-ppm NO_2 for 5 days, the amount of methemoglobin was not increased. This is in contrast to some (but not all) in vitro and high-concentration NO_2 in vivo studies, which have found methemoglobin effects (U.S. Environmental Protection Agency, 1993).

3.2.1.5 Toxicology of Inhaled Nitric Oxide

Nitric oxide is used in humans therapeutically as a pulmonary vasodilator, and has shown little evidence for adverse respiratory effects. The literature on therapeutic uses of nitric oxide provides the strongest evidence for its lack of toxicity. Infants and adults with acute respiratory failure and refractory hypoxemia, as well as pulmonary hypertension, are sometimes considered candidates for inhaled NO. Inhaled NO acts as a selective pulmonary vasodilator, causing vascular smooth muscle relaxation and increased perfusion in ventilated lung regions. Beneficial effects in patients with respiratory failure include reduced pulmonary artery pressures and

improved ventilation-perfusion matching. Nitric oxide is used clinically at concentrations ranging from five ppm to as high as 80 ppm. There has been little or no toxicity reported, even when used in premature infants with respiratory failure. In a recently published multicenter study (Kinsella et al., 2006), 793 premature infants with respiratory failure were randomized to therapy with inhaled NO or air. NO therapy was associated with a reduced risk of brain injury, and in a reduced risk of bronchopulmonary dysplasia, a chronic lung condition resulting from lung injury in infancy, in infants weighing at least 1000 gm. NO can cause methemoglobinemia, and this was seen transiently in only 2 infants. NO can inhibit activation of blood leukocytes and platelets (Gianetti et al. 2002); however there was no evidence for increased susceptibility to infection or bleeding. One of the concerns about NO therapy is the potential for NO to be oxidized to NO_2, so administration systems are designed to avoid this.

3.2.2 Studies of Hospital Admissions and ED Visits for CVD

Cases of CVD are typically identified using ICD codes, which are recorded on hospital discharge records in these studies. However, counts of hospital or ED admissions are used in some studies. Studies of ED visits may include cases that are less severe than those included in hospital admission studies. Hospital admission studies are distinguished from ED visit studies in the annex tables (Annex AX6.3-6 through AX6.3-9). Many studies group all CVD diagnoses (ICD9 codes 390–459), evaluating cardiac diseases (ICD9 codes 390–429), and cerebrovascular disease (ICD9 430–448) together. Other studies evaluate cardiac and cerebralvascular diseases separately or further distinguish ischemic heart disease (IHD: ICD9 410–414), myocardial infarction (MI: ICD9 410), congestive heart failure (CHF: ICD9 428), cardiac arrhythmia (ICD9 427), angina pectoris (ICD9 413), or stroke (ICD9 430-438).

Numerous studies have shown a positive association between both 24-h avg and 1-h max NO_2 levels and hospital admissions or ED visits for all CVD, in single-pollutant models (Linn et al., 2000; Metzger et al., 2004; Tolbert et al., 2007; Ballester et al., 2001, 2006; Anderson et al., 2007a; Atkinson et al., 1999a,b; Poloniecki et al., 1997; Barnett et al., 2006; Hinwood et al., 2006; Jalaludin et al., 2006; Chang et al., 2005; Wong et al., 1999; Yang et al., 2004b). A discussion of results from studies reporting associations between NO_2 and all CVD are found in Annex AX6.2.1.

3.2.2.1 Cardiac Disease (ICD9 390–429)

Findings from studies examining the association of NO_2 with cardiac disease are found in Figure 3.2-1. Most investigators who distinguished cardiac disease from all CVD report significant positive associations in single-pollutant models. Increased risks were observed in Canadian populations (Burnett et al., 1997b; Fung et al., 2005). The average daily 1-h max NO_2 level was approximately 39 ppb in metropolitan Toronto, ON, where these studies were conducted. Estimates from two Australian multicity studies (Barnett et al., 2006; Simpson et al., 2005a) were also significantly increased. The 24-h NO_2 level in the Australian cities studied by Barnett et al. (2006) was 7 to 11.5 ppb. The range of 1-h max NO_2 level in cities studied by Simpson et al. (2005a) was 16 to 24 ppb. Von Klot et al. (2005) observed a statistically significant association between readmission for cardiac disease among MI survivors, a potentially susceptible subpopulation and NO_2 concentrations in five European cities. The range in 24-h NO_2 level was 15.8 to 26 ppb in the five cities studied. Two single-city Australian studies and one single-city Taiwanese study also reported positive single-pollutant model results (Jalaludin et al., 2006; Morgan et al., 1998a; Chang et al., 2005). Studies of the association of 24-h avg and 1-h max NO_2 level with IHD, MI, CHF and arrhythmia are less consistently positive and significant. Results from these studies are described in Annex AX6.2-1.

Most investigators reporting results from multipollutant models observed diminished effect estimates for NO_2 and hospital admissions or ED visits for CVDs. In two U.S. studies conducted in Los Angeles, investigators 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 an Atlanta study, Metzger et al. (2004) and Tolbert et al. (2007) also observed a diminished effect of NO_2 on visits for CVD when CO was modeled with NO_2, while the effect of CO remained robust. Tolbert et al. (2007) discussed the limitations of multipollutant models and concluded that these models might help researchers identify the strongest predictor of disease, but might not isolate the independent effect of each pollutant. NO_2 was not robust to adjustment for other pollutants in several non-U.S. studies (Jalaludin et al., 2006; Ballester et al., 2006; Simpson et al., 2005a; Poloniecki et al., 1997; Barnett et al., 2006; Llorca et al., 2005). However, in other studies, investigators reported that the effect of NO_2 was robust in multipollutant models (Von Klot et al.,

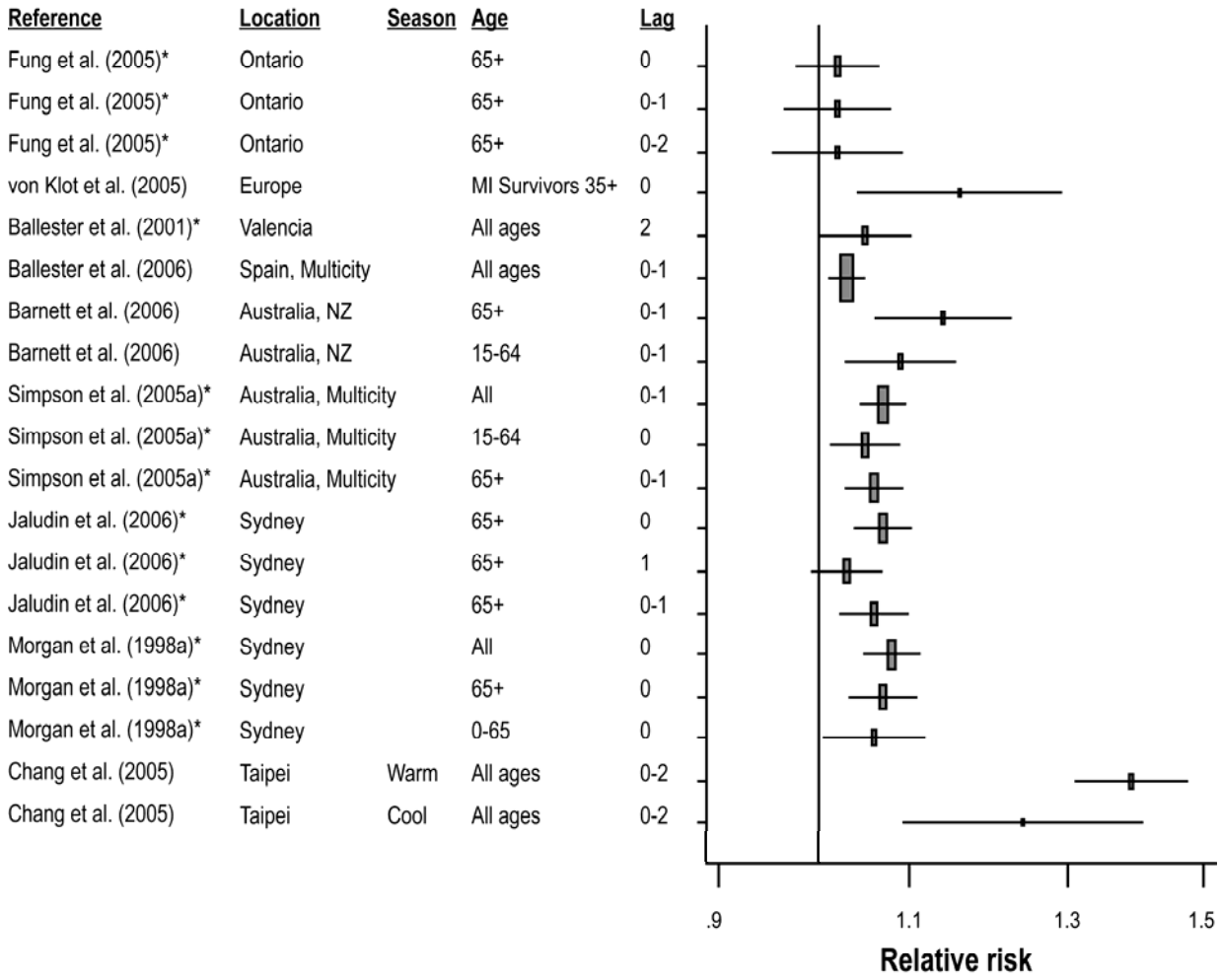

Figure 3.2-1. Relative risks (95% CI) for associations of 24-h NO_2 (per 20 ppb) and daily 1 hour maximum* NO_2 (per 30 ppb) with hospitalizations or emergency department visits for cardiac diseases. Primary author and year of publication, city, stratification variable(s), and lag are listed. Results for lags 0 or 1 are presented as available.

2005; Yang et al., 2004b; Chang et al., 2005; Morgan et al., 1998a; Burnett et al., 1997a, 1999). See Annex AX6.2.1.6 for a detailed description of results from multipollutant models.

3.2.2.2 Hospital Admissions for Stroke and Cerebrovascular Disease (ICD9 430–448)

Studies of the association between all cerebrovascular disease and ambient NO_2 concentration are summarized in Figure 3.2-2. Results from these studies are generally inconsistent. Metzger et al. (2004) reported a significant increase in cerebrovascular disease

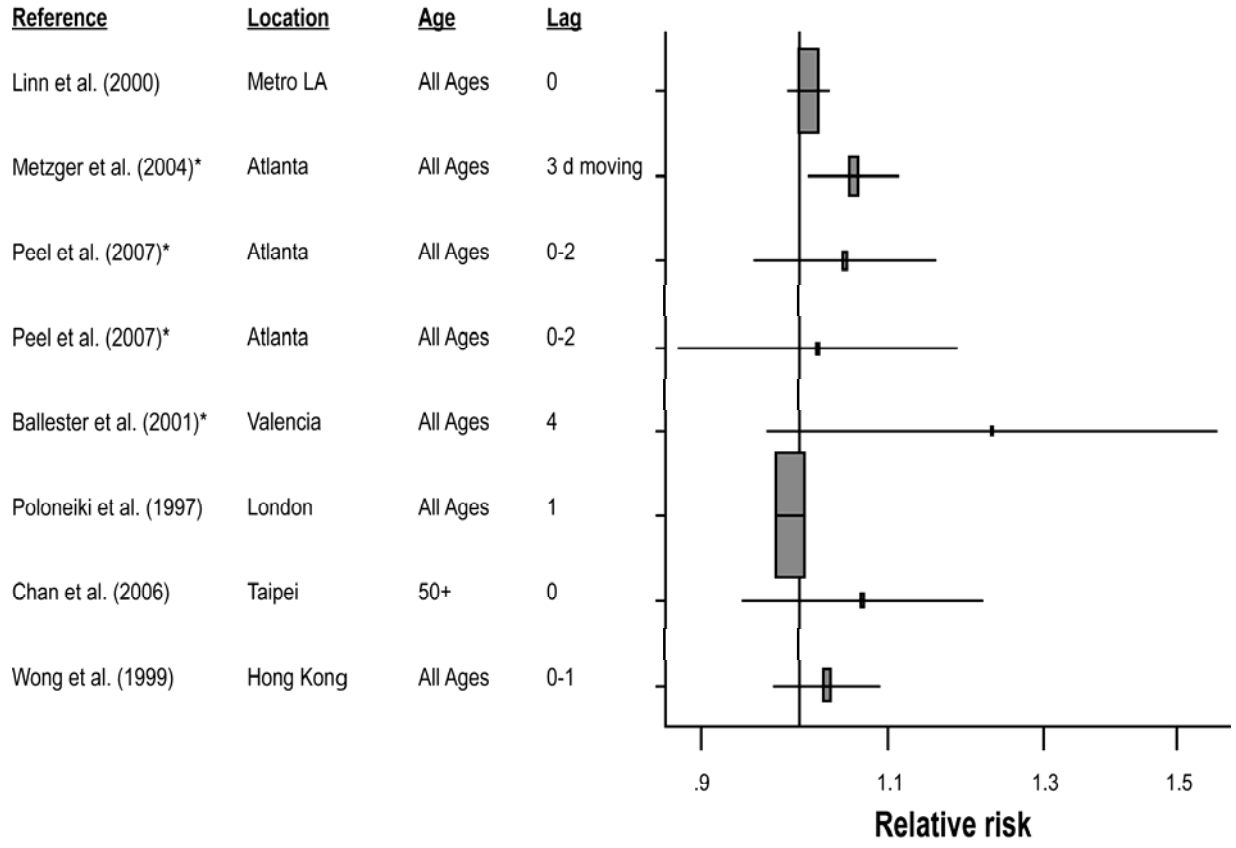

Figure 3.2-2. Relative risks (95% CI) for associations of 24-h NO_2 exposure (per 20 ppb) and daily 1 h maximum NO_2* (per 30 ppb) with hospitalizations for all cerebrovascular disease. Primary author and year of publication, city, stratification variable(s), and lag are listed. Results for lags 0 or 1 are presented as available.

emergency visits in Atlanta. However, Peel et al. (2007) did not find associations between cerebrovascular disease visits and NO_2 concentrations among those with hypertension and diabetes in the same city. The daily 1-h max NO_2 level in Atlanta during the study period ranged from 26 to 45.9 ppb (Metzger et al., 2004; Peel et al., 2007). Ballester et al. (2001) reported a relatively large increased risk in cerebrovascular admissions in the Spanish city of Valencia at lag 4, while Poloniecki et al. (1997) and Pönkä and Virtanen (1996) did not observe associations in London and Helsinki. Two Asian studies report positive but nonsignificant associations of cerebrovascular disease with 24-h avg NO_2 (Chan et al., 2006; Wong et al., 1999). The 24-h avg

NO_2 levels reported for Taipei and Hong Kong were approximately 30 ppb and 27 ppb, respectively (Chan et al., 2006; Wong et al., 1999).

Studies of hospital admissions or ED visits for specific cerebrovascular diseases provide little evidence for a NO_2 effect. In a large study, conducted in metropolitan Los Angeles where the mean 24-h NO_2 level ranges from 28 to 41 ppb depending on the season, no association was observed for all cerebrovascular disease (Linn et al., 2000). However, authors reported an increase in hospitalizations of 4.0% (95% CI: 2.0, 6.0) for occlusive stroke per 20 ppb increase in NO_2.

Wellenius et al. (2005) found a 5% increase in ischemic stroke (IS) admissions per 20-ppb increase in 24-h avg NO_2 level. A study of all-stroke in Ontario reported null findings for 24-h avg NO_2 at lags 0 and 1 (Ito et al. 2004). Villeneuve et al. (2006) reported an association between NO_2 exposure and IS during the winter months among the elderly (OR = 1.41 [95% CI: 1.13, 1.75], per 20 ppb, lag 3 day average). Villeneuve et al. (2006) also reported positive but nonsignificant associations for hemorrhagic stroke (HS) (OR = 1.25 95% CI: 0.91, 1.71 per 20-ppb increase in NO_2). No associations between air pollutants and stroke were reported in a multicity study conducted in Australia and New Zealand (Barnett et al., 2006). An increase in 24-h avg NO_2 resulted in increased risk of hospitalization for primary intracerebral hemorrhage (PIH) (OR: 1.68 [95% CI: 1.39, 2.04] lag 0 to 2 per 20 ppb increase), and ischemic stroke (IS) (OR: 1.67 95% CI: 1.49 1.88, lag 0-2) during the warm season in Taiwan (Tsai et al., 2003).

Several investigators presented estimates for the association of NO_2 with cerebrovascular outcomes from multipollutant models. The association of NO_2 with stroke was not robust to adjustment for CO in a Canadian study (Villeneuve et al., 2006). Although results from a Taiwanese study indicated the effect of NO_2 on stroke admissions was robust in two-pollutant models, the authors noted that the association of NO_2 with stroke might not be causal if NO_2 is a surrogate for other components of the air pollution mixture (Tsai et al., 2003).

3.2.3 Summary of Evidence of the Effect of Short-Term NO_2 Exposure on Cardiovascular Morbidity

The available evidence on the effect of short-term exposure to NO_2 on cardiovascular health effects is inadequate to infer the presence or absence of a causal relationship at this time. Evidence from epidemiologic studies of HRV, repolarization changes, and cardiac rhythm

disorders among heart patients with ICDs are inconsistent. In most studies, observed associations with PM were similar or stronger than associations with NO_2. Generally positive associations between ambient NO_2 concentrations and hospital admissions or ED visits for CVD have been reported in single-pollutant models; however, most of the effect estimates were diminished in multipollutant models also containing CO and PM indices. Mechanistic evidence of a role for NO_2 in the development of CVDs from studies of biomarkers of inflammation, cell adhesion, coagulation, and thrombosis is lacking. Furthermore, the effects of NO_2 on various hematological parameters in animals are inconsistent and, thus, provide little biological plausibility for effects of NO_2 on the cardiovascular system. However, there is limited evidence from controlled human exposure studies suggesting a reduction in hemoglobin with NO_2 exposure at concentrations of 1.0 to 2.0 ppm (with 3-h exposures) that requires confirmation.

3.3 MORTALITY ASSOCIATED WITH SHORT-TERM NO_2 EXPOSURE

There was no epidemiologic study reviewed in the 1993 AQCD that examined the mortality effects of ambient NO_2. Since the 1993 AQCD, a number of studies, mostly using time-series analyses, reported short-term mortality risk estimates for NO_2 (see Annex Table AX6.3-19). However, since most of these studies' original focus or hypothesis was on PM, a quantitative interpretation of the NO_2 mortality risk estimates requires caution. Risk estimates are summarized across studies after reviewing individual multicity studies.

3.3.1 Multicity Studies and Meta-Analyses

In reviewing the range of mortality risk estimates, multicity studies provide the most useful information because they analyze multiple cities data in a consistent method, avoiding potential publication bias. Risk estimates from multicity studies usually are reported for consistent lag days, further reducing potential bias caused by choosing the "best" lag in individual studies. There have been several multicity studies from the United States, Canada, and Europe. Meta-analysis studies also provide useful information on describing heterogeneity of risk estimates across studies, but unlike multicity studies, the heterogeneity of risk estimates seen in meta-analysis may also reflect the variation in analytical approaches across studies. Thus, we focus our review mainly on the results from multicity studies, and effect estimates from

these studies are summarized. Discussion will focus on the studies that were not affected by GAMs with convergence issues (Dominici et al., 2002; Ramsay et al., 2003) unless otherwise noted when the studies raise relevant issues.

3.3.1.1 National Morbidity, Mortality, and Air Pollution Study (NMMAPS)

The time-series analysis of the largest 90 U.S. cities (Samet et al., 2000; reanalysis Dominici et al., 2003) in the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) is by far the largest multicity study conducted to date to investigate the mortality effects of air pollution, but its primary interest was PM (i.e., PM_{10}), and NO_2 was not measured in 32 of the 90 cities. This study's model adjustment for weather effects employs more terms than other time-series studies in the literature, suggesting that the model adjusts for potential confounders more aggressively than the models in other studies. PM_{10} and O_3 (in summer) appeared to be more strongly associated with mortality than the other gaseous pollutants. Regarding NO_2, SO_2, and CO, the authors stated, "The results did not indicate associations of these pollutants with total mortality." PM_{10}, NO_2, SO_2, and CO showed the strongest association at lag 1 day (for O_3, it was lag 0 day), and the addition of other copollutants in the model at lag 1 day hardly affected the mortality risk estimates for PM_{10} or the gaseous pollutants. Figure 3.3-1 shows the total mortality risk estimates for NO_2 from Dominici et al. (2003). The NO_2 risk estimates in the multipollutant models were about the same or larger. Thus, these results do not indicate that the NO_2-mortality association was confounded by PM_{10} or other pollutants (and vice versa).

3.3.1.2 Canadian Multicity Studies

There have been four Canadian multicity studies conducted by the same group of investigators (Burnett et al., 1998, 2000, 2004; Brook et al., 2007). This section focuses on Burnett et al. (2004) and Brook et al. (2007), as these studies are most extensive both in terms of the length and coverage of cities.

Total (nonaccidental), cardiovascular, and respiratory mortality were analyzed in the Burnett et al. (2004) study of 12 Canadian cities from 1981 to 1999. Daily 24-h avg as well as 1-h max values were analyzed for all the gaseous pollutants and coefficient of haze (CoH). For $PM_{2.5}$, coarse PM ($PM_{10-2.5}$), PM_{10}, CoH, SO_2, and CO, the strongest mortality association was found at lag 1, whereas for NO_2, it was the 3-day moving average (i.e., average of 0-, 1-, and 2-day lags), and for O_3, it was the 2-day moving average. Of the single-day lag estimates for NO_2,

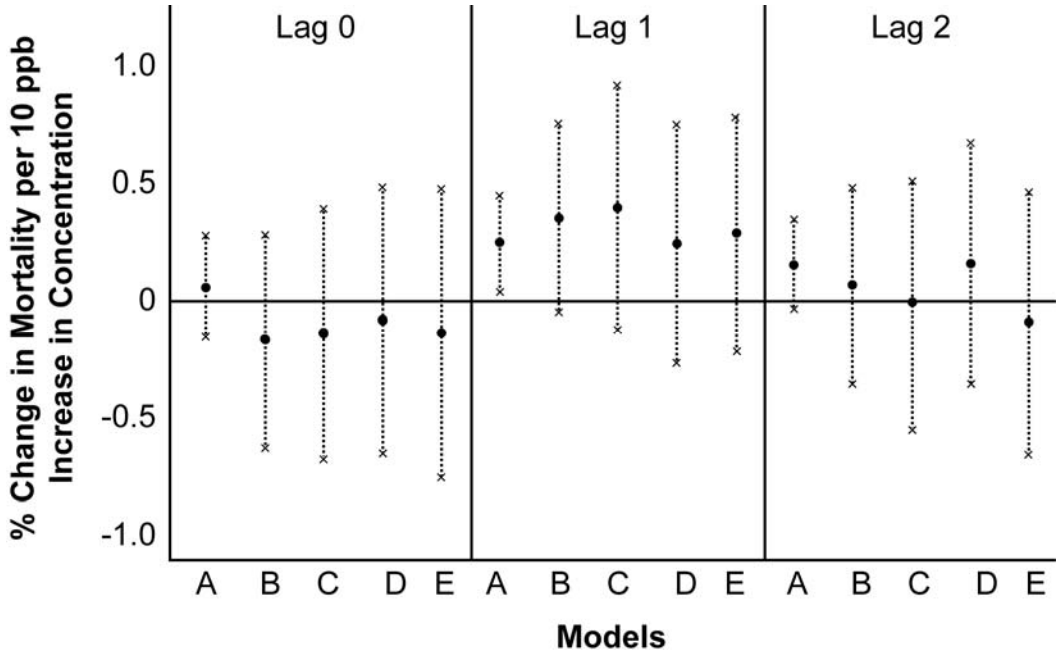

Figure 3.3-1. Posterior means and 95% posterior intervals of national average estimates for NO_2 effects on total mortality from nonexternal causes at lags 0, 1, and 2 within sets of the 90 cities with pollutant data available. Models A = NO_2 alone; B = NO_2 + PM_{10}; C = NO_2 + PM_{10} + O_3; D = NO_2 + PM_{10} + SO_2; E = SO_2 + PM_{10} + CO.

Source: Dominici et al. (2003).

lag 1 day showed the strongest associations, which is consistent with the NMMAPS result, but its risk estimate was more than 4 times larger than that for the NMMAPS study. The 24-h avg values showed stronger associations than the 1-h max values for all the gaseous pollutants and CoH except for O_3. The pooled NO_2 mortality risk estimate in a single-pollutant model (for all available days) was 2.0% (95% CI: 1.1, 2.9) per 20-ppb increase in the 3-day moving average of NO_2. The magnitudes of the effect estimates were similar for total, cardiovascular, and respiratory mortality. Larger risk estimates were observed for warmer months. NO_2 was most strongly correlated with CoH (r = 0.60), followed by $PM_{2.5}$ (r = 0.48). The NO_2-mortality association was not sensitive to adjustment for these or any of other pollutants in the two-pollutant models. However, Burnett et al. (2004) noted that simultaneous inclusion of daily $PM_{2.5}$ data (available for 1998 and 2000; sample size comparable to the main analysis [every 6th day from 1981 to 1999] but more recent years) and NO_2 in the model resulted in a considerable

reduction of the NO_2 risk estimates. Authors discussed that reducing combustion would result in public health benefits because NO_2 or its products originate from combustion sources, but cautioned that they could not implicate NO_2 as a specific causal pollutant.

Brook et al. (2007) further examined data from 10 Canadian cities with a special focus on NO_2 and the role of other traffic-related air pollutants. Again, NO_2 showed the strongest associations with mortality among the pollutants examined including NO, and none of the other pollutants substantially reduced NO_2 risk estimates in multipollutant models. The analysis also confirmed the Burnett et al. (2004) study results that NO_2 risk estimate was larger in the warm season. Generally, NO showed stronger correlation with the primary VOCs (e.g., benzene, toluene, xylenes) than NO_2 or $PM_{2.5}$. NO_2 was more strongly correlated with the organic compounds than it was with the PM mass indices or trace metals in $PM_{2.5}$. Brook et al. (2007) concluded that the strong NO_2 effects seen in Canadian cities could be a result of it being the best indicator, among the pollutants monitored, of fresh combustion as well as photochemically processed urban air.

In summarizing the Canadian multicity studies, NO_2 was most consistently associated with mortality among the air pollutants examined, especially in the warm season. Adjustments for PM indices and its components generally did not reduce NO_2 risk estimates. NO_2 also was shown to be associated with organic compounds that are indicative of combustion products (traffic-related air pollution) and photochemical reactions.

3.3.1.3 Air Pollution and Health: A European Approach (APHEA) Studies

The APHEA project is a European multicity effort, analyzing data from multiple studies using a standardized methodology. This section focuses on the more recent APHEA2 studies which included 29 European cities.

Samoli et al. (2006) analyzed 29 APHEA2 cities to estimate NO_2 associations for total, cardiovascular, and respiratory deaths. The average of lags 0-1 days were chosen a priori to avoid potential bias with the "best" lag approach. In addition, the association of total mortality with NO_2 over 6 days (lags 0-5) were summarized over all cities using a cubic polynomial distributed lag model. Results from this model suggested multiday effects, with the strongest association shown at lag 1 day, which is consistent with the results from NMMAPS and Canadian multicity studies. The risk estimates for total, cardiovascular, and respiratory causes were comparable. In the two-pollutant models with black smoke, PM_{10}, SO_2, and O_3, the risk

estimates for total and cardiovascular mortality were not affected. The second-stage analysis examined possible effect modifiers. For total and cardiovascular mortality, the geographical area (defined as western, southern, and central eastern European cities) was the most important effect modifier (estimates were lower in eastern cities), followed by smoking prevalence (NO_2 risk estimates were higher in cities with a lower prevalence of smoking). The authors concluded that the results showed effects of NO_2 on mortality, but that the role of NO_2 as a surrogate of other unmeasured pollutants could not be completely ruled out.

In an earlier study, Katsouyanni et al. (2001; reanalysis, 2003) analyzed data from 29 European cities and reported risk estimates for PM_{10} and not for NO_2, but found that the cities with higher NO_2 levels tended to have larger PM_{10} risk estimates. Furthermore, simultaneous inclusion of PM_{10} and NO_2 reduced the PM_{10} risk estimate by half. An analysis of the elderly mortality in the same 28 cities (Aga et al., 2003) also found a similar effect modification of PM by NO_2. Thus, PM and NO_2 risk estimates in these European cities may be reflecting the health effects of the same air pollution source and/or act as effect modifiers of each other.

3.3.1.4 The Netherlands Study

While the Netherlands studies for the 1986 to 1994 data (Hoek et al., 2000, 2001; reanalysis in Hoek, 2003) are not multicity studies and the Netherlands data were also analyzed as part of APHEA2 (Samoli et al., 2006), the results from the reanalysis (Hoek, 2003) are discussed here, because the database comes from a large population (14.8 million for the entire country) and a more extensive analysis was conducted than in the multicity studies. PM_{10}, black smoke, O_3, NO_2, SO_2, CO, sulfate (SO_4^{2-}), and nitrate (NO_3^-) were analyzed at lags 0, 1, and 2 days and the average of lags 0-6 days. All the pollutants were associated with total mortality, and for single-day models, lag 1 day showed strongest associations for all the pollutants. NO_2 was most highly correlated with black smoke ($r = 0.87$), and the simultaneous inclusion of NO_2 and black smoke reduced both pollutants' risk estimates (the NO_2 estimate was reduced by more than 50%). PM_{10} was less correlated with NO_2 ($r = 0.62$), and the simultaneous inclusion of these pollutants resulted in an increase in the NO_2 risk estimate.

3.3.1.5 Other Multicity Studies

Other European multicity studies, conducted in eight Italian cities (Biggeri et al., 2005), nine French cities (Le Tertre et al., 2002) and seven Spanish cities (Saez et al., 2002) provide

evidence for a short-term NO_2 effect on mortality. An additional multicity study was conducted in Australian cities (Simpson et al., 2005b). The studies by Biggeri et al. (2005) and Simpson et al. (2005b) are summarized in this section. The studies by Le Tertre et al. (2002) and Saez et al. (2002), conducted using Generalized Additive Model (GAM) methods with the default convergence setting, are presented in Annex Table AX6.3-19.

Biggeri et al. (2005) analyzed eight Italian cities (Turin, Milan, Verona, Ravenna, Bologna, Florence, Rome, and Palermo) from 1990 to 1999. Only single-pollutant models were examined in this study. Statistically significant positive associations were observed between NO_2 and total, cardiovascular, and respiratory mortality, with the largest effect estimate observed for respiratory mortality. Since all the pollutants showed positive association and the correlations among the pollutants were not presented, it is not clear how much of the observed associations are shared or confounded. The mortality risk estimates were not heterogeneous across cities for all the gaseous pollutants.

Simpson et al. (2005b) analyzed data from four Australian cities (Brisbane, Melbourne, Perth, and Sydney) using methods similar to the APHEA2 approach. They also examined sensitivity of results to alternative regression models. Associations between mortality and NO_2, O_3, and nephelometer readings (a measure of PM) were examined at single-day lag 0, 1, 2, and 3 days and using the average of 0- and 1-day lags. Among the three pollutants, correlation was strongest between NO_2 and nephelometer readings, ranging from ($r \sim 0.62$ among the four cities). Of the three pollutants, NO_2 showed the largest mortality risk estimates per interquartile range. Similar to the study by Biggeri et al. (2005), the strongest association was observed between NO_2 and respiratory mortality, compared to total or cardiovascular mortality. The three alternative regression models yielded similar results. The NO_2 risk estimates were not sensitive to the addition of nephelometer readings in the two-pollutant models for total mortality, but the nephelometer risk estimate was greatly reduced in the model with NO_2.

3.3.1.6 Meta-Analyses of NO_2 Mortality Studies

Stieb et al. (2002) reviewed time-series mortality studies published between 1985 and 2000, and conducted a meta-analysis to estimate combined effects for each of PM_{10}, CO, NO_2, O_3, and SO_2. Since many of the studies reviewed in that analysis were affected by the GAM convergence issue, Stieb et al. (2003) updated the estimates by separating the GAM versus non-GAM studies and by single- versus multipollutant models. There were more GAM estimates

than non-GAM estimates for all the pollutants except SO_2. For NO_2, there were 11 estimates from single-pollutant models and only 3 estimates from multipollutant models. The lags and multiday averaging used in these estimates varied. The combined estimate for total mortality was 0.8% (95% CI: 0.2, 1.5) per 20-ppb increase in the daily average NO_2 from the single-pollutant models and 0.4% (95% CI: −0.2, 1.1) per 20-ppb increase in the 24-h average from the multipollutant models. Note that, although the estimate from the multipollutant models was smaller than that from the single-pollutant models, the number of the studies for the multipollutant models was small (3), also, the data extraction procedure of this meta-analysis for the multipollutant models was to extract from each study the multipollutant model that resulted in the greatest reduction in risk estimate compared with that observed in single-pollutant models. It should be noted that all the multicity studies whose combined estimates have been discussed above were published after this meta-analysis.

3.3.2 Summary of Evidence of the Effect of Short-Term NO_2 Exposure on Mortality

The epidemiologic evidence on the effect of short-term exposure to NO_2 on total nonaccidental and cardiopulmonary mortality is suggestive but not sufficient to infer a causal relationship. The epidemiologic studies are generally consistent in reporting positive associations. However, there is little evidence available to evaluate coherence and plausibility for the observed associations, particularly for cardiovascular and total mortality.

In the short-term exposure studies, the range of NO_2 total mortality risk estimates is 0.5 to 3.6% per 20-ppb increase in the 24-h average NO_2 or 30-ppb increase in daily 1-h max (Figure 3.3-2). The use of various lag periods, averaging days, and distributed lags does not appear to alter the estimates substantially. The heterogeneity of estimates in these studies may be due to several factors, including the differences in (1) model specification, (2) NO_2 levels, and (3) effect modifying factors. Interestingly, the Canadian 12-city study showed combined risk estimates (average of 0-1 day or single 1-day lag) about 4 times larger than that for the U.S. estimate, despite the fact that the range of Canadian NO_2 concentrations (10 to 26 ppb) was somewhat lower than that for the U.S. data (9 to 39 ppb for the 10%-trimmed data). In fact, the NMMAPS estimate is the smallest among the multicity studies. Since a similar pattern (i.e., the NMMAPS estimate being the smallest among multicity studies) was seen for PM_{10} mortality risk estimates

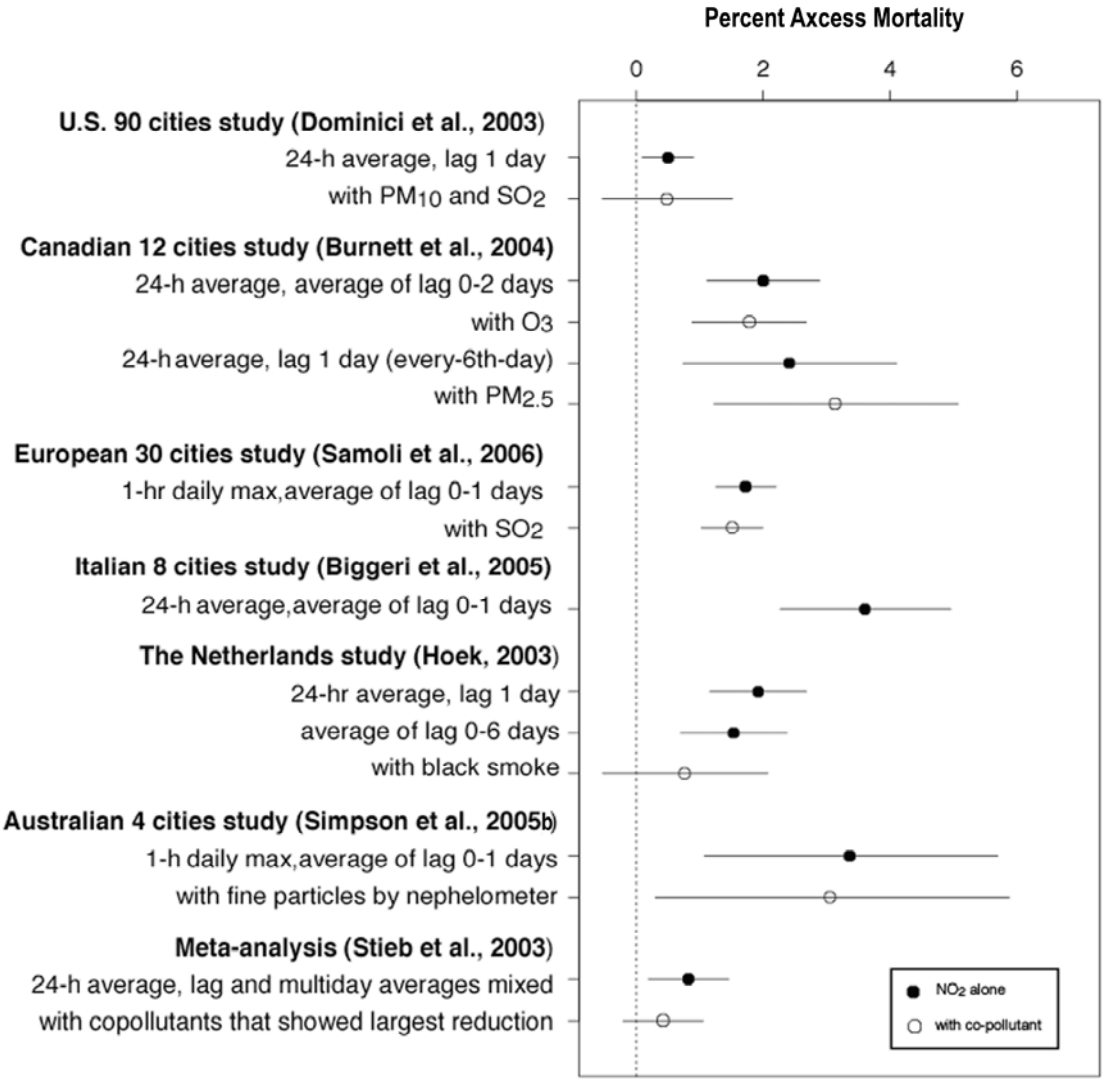

Figure 3.3-2. Combined NO_2 mortality risk estimates from multicity and meta-analysis studies. Risk estimates are computed per 20-ppb increase for 24-h average or 30-ppb increase for 1-h daily maximum NO_2 concentrations. For multipollutant models, results from the models that resulted in the greatest reduction in NO_2 risk estimates are shown.

(U.S. Environmental Protection Agency, 2004), it is possible that this may be due to the difference in model specifications.

Several multicity studies provided risk estimates for broad cause-specific categories (typically all-cause, cardiovascular, and respiratory) using consistent lags/averaging for broad

causes (cardiovascular and respiratory), but the patterns were not always consistent. This inconsistency was likely due to smaller sample size, or the lags reported not being consistent across the specific causes examined (Figure 3.3-3). While the smaller multicity studies (the Italian and Australian studies) reported larger risk estimates for respiratory mortality, the larger Canadian and APHEA2 studies reported comparable risk estimates among the broad specific causes of deaths. In addition, since other pollutants also showed similar associations with these causes or categories, it is difficult to discuss consistency with causal inference that is specific to NO_2. The multipollutant models in these studies generally did not alter NO_2 risk estimates, except for the Netherlands study in which NO_2 was highly correlated with the copollutant black smoke. While the multipollutant results generally suggest a lack of confounding, it is difficult to attribute the observed excess mortality risk estimates to NO_2 alone.

While the multicity studies examining the relationship between short-term NO_2 exposure and mortality observed statistically significant associations for total, cardiovascular, and respiratory causes, the issue of surrogacy of the role of NO_2 and possible interactions with PM and other pollutants remain unresolved. As reviewed in earlier sections, controlled human exposure studies, by necessity, are limited to acute, fully reversible functional and/or symptomatic responses in healthy or mildly asthmatic subjects. Animal studies have not used mortality as an endpoint in acute exposure studies. However, a number of animal studies (described in Section 3.1.3) have shown biochemical, lung host defense, permeability, and inflammation effects with acute exposures and may provide limited biological plausibility for mortality in susceptible individuals. A 5-ppm NO_2 exposure for 24 h in rats caused increases in blood and lung total glutathione (GSH) and a similar exposure resulted in impairment of alveolar surface tension of surfactant phospholipids due to altered fatty acid content. A fairly large body of literature describes the effects of NO_2 on lung host defenses at low exposures. However, most of these effects are seen only with subchronic or chronic exposure and, therefore, do not correlate well with the short lag times evidenced in the epidemiologic studies. The corresponding evidence of interaction between NO_2 and other pollutants in controlled human and toxicologic studies are also very limited. Thus, there is a gap between the observed associations between short-term exposure to NO_2 mortality reported in observational epidemiologic studies and available evidence from controlled human and toxicologic studies in establishing a causal link.

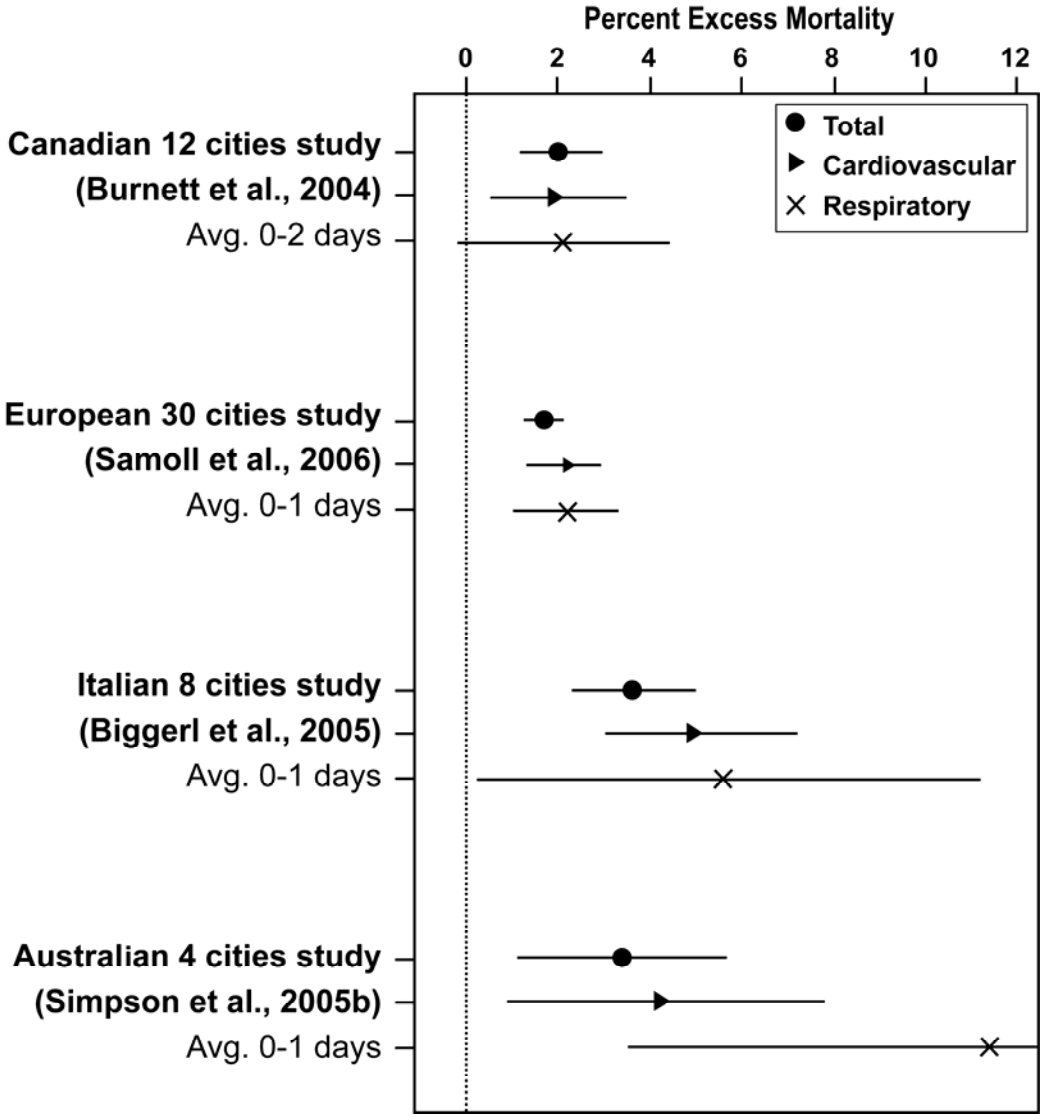

Figure 3.3-3. Combined NO_2 mortality risk estimates for broad cause-specific categories from multicity studies. Risk estimates are computed per 20-ppb increase for 24-h average or 30-ppb increase for 1-h daily maximum NO_2 concentrations.

Results from several large U.S. and European multicity studies and a meta-analysis study observed positive associations between ambient NO_2 concentrations and risk of all-cause (nonaccidental) mortality, with effect estimates ranging from 0.5 to 3.6% excess risk in mortality per standardized increment[1] (Section 3.3.1, Figure 3.3-2). In general, the NO_2 effect estimates were robust to adjustment for copollutants. Both cardiovascular and respiratory mortality have

been associated with increased NO_2 concentrations in epidemiologic studies (Figure 3.3-3); however, similar associations were observed for other pollutants, including PM and SO_2. The range of mortality excess risk estimates was generally smaller than that for other pollutants such as PM.

While NO_2 exposure, alone or in conjunction with other pollutants, may contribute to increased mortality, evaluation of the specificity of this effect is difficult. Clinical studies showing hematologic effects and animal toxicologic studies showing biochemical, lung host defense, permeability, and inflammation changes with short-term exposures to NO_2 provide limited evidence of plausible pathways by which risks of morbidity and, potentially, mortality may be increased, but no coherent picture is evident at this time.

3.4 RESPIRATORY EFFECTS ASSOCIATED WITH LONG-TERM NO_2 EXPOSURE

There was no epidemiologic evidence available in the 1993 AQCD on the respiratory effects of long-term exposure (>2 weeks) to ambient NO_2. The 1993 AQCD reported that chronic exposure to high NO_2 levels (>8 ppm) caused emphysema in several animal species. Since the 1993 AQCD, a number of studies reported associations between long-term NO_2 exposure and respiratory effects (see Annex Tables AX6.3-15, AX6.3-16, and AX6.3-17).

3.4.1 Lung Function Growth

Epidemiologic Studies

Studies of lung function demonstrate some of the strongest effects of long-term exposure to NO_2. Recent cohort studies have examined the effect of long-term exposure to NO_2 in both children and adults (see Annex Table AX6.3-15). Forest plots of the results for FEV_1 and FVC from the three major children's cohort studies (Gauderman et al., 2004; Rojas-Martinez et al., 2007a,b; Oftedal et al., 2008) are presented in Figures 3.4-1 and 3.4-2.

The Children's Health Study (CHS) in southern California is a longitudinal cohort study designed to investigate the effect of chronic exposure to several air contaminates (including NO_2) on respiratory health in children. Twelve California communities were selected based on historical data indicating different levels of specific pollutants. In each community, monitoring

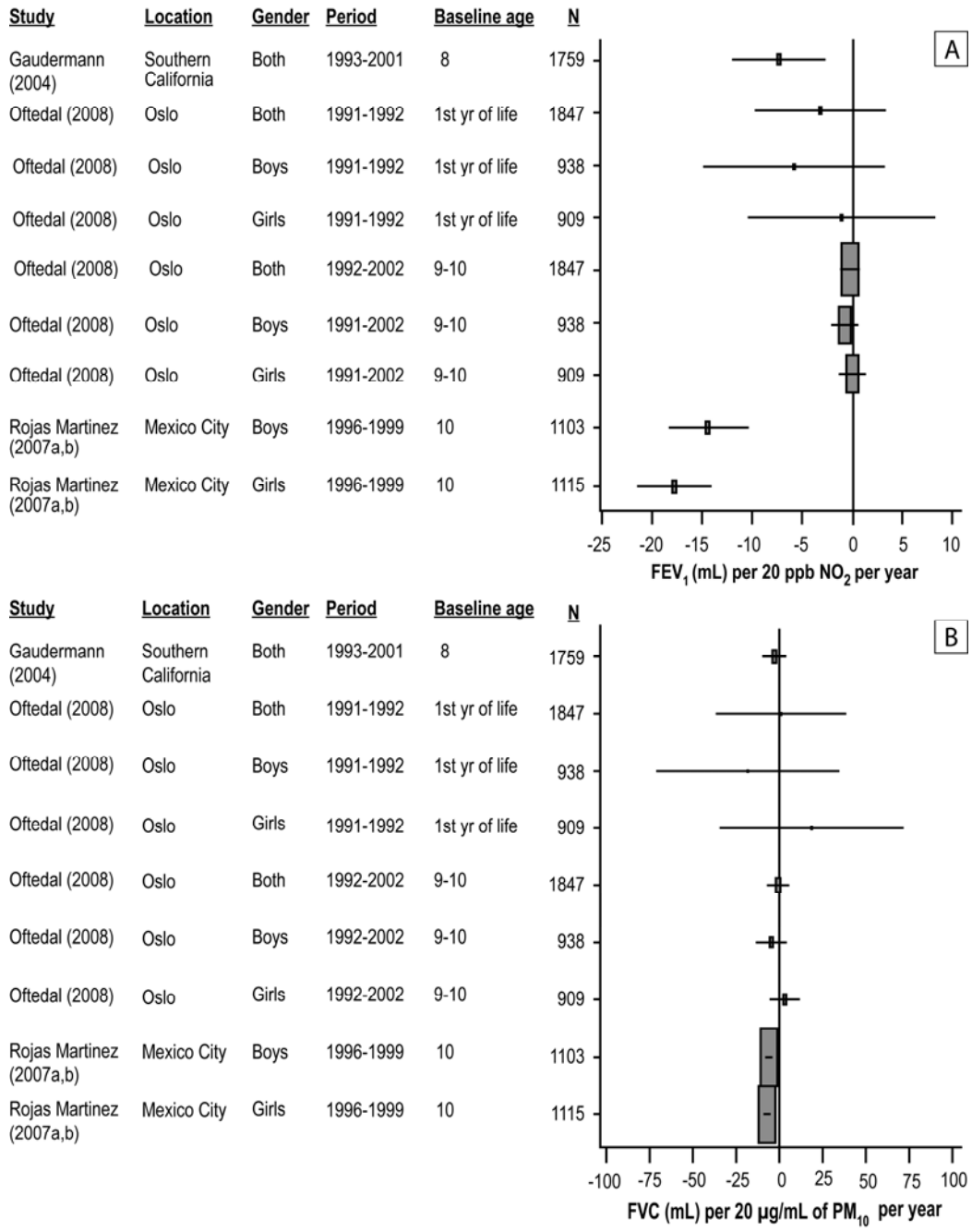

Figure 3.4-1. Decrements in forced expiratory volume in 1 s (FEV_1) associated with a 20-ppb increase in NO_2 (A) and a 20-µg/m^3 increase in PM_{10} (B) in children, standardized per year of follow-up. Results from three major children's long-term cohort studies are presented.

Source: Gauderman et al. (2004); Oftedal et al. (2008), Rojas-Martinez et al. (2007a,b).

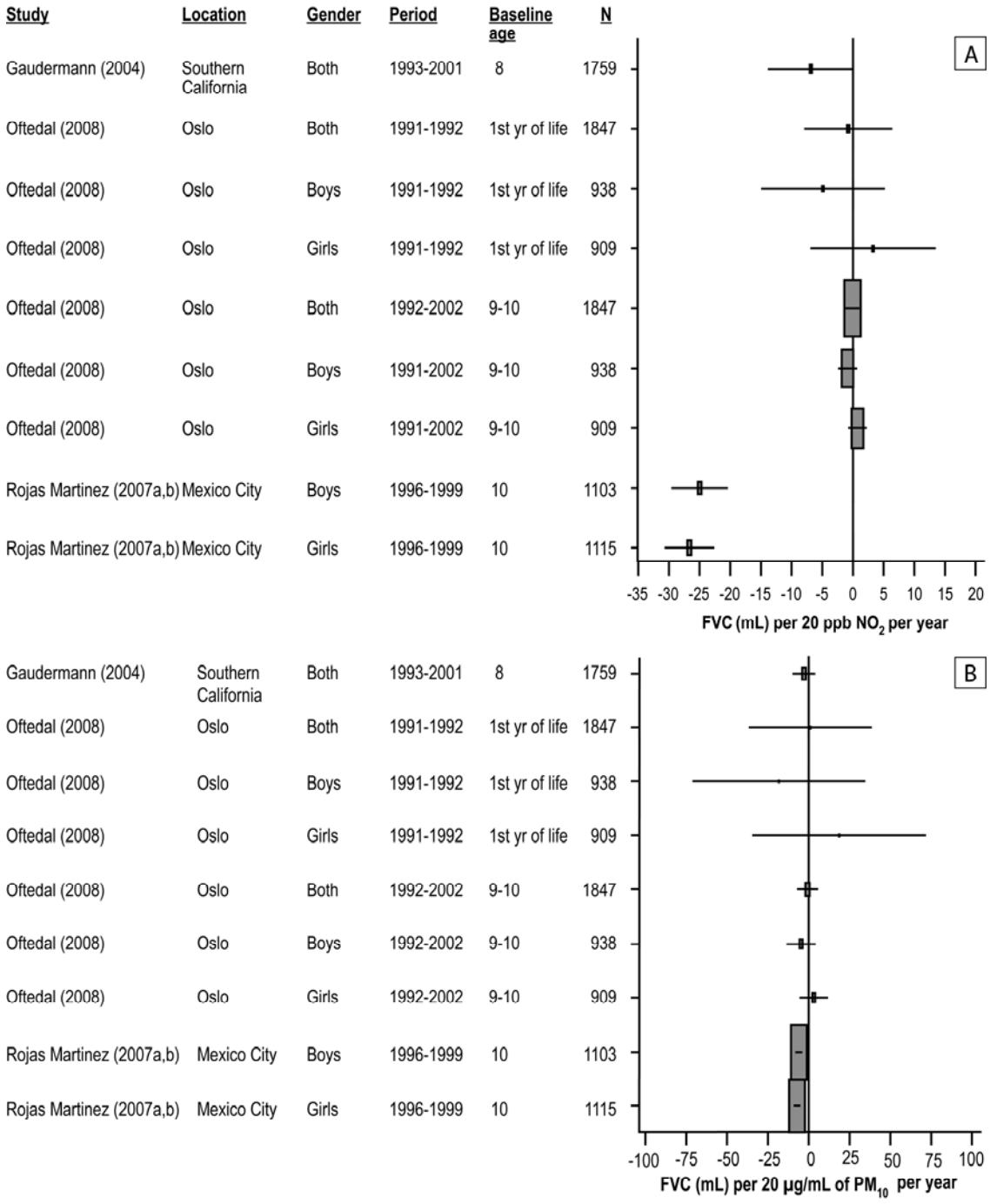

Figure 3.4-2. Decrements in forced vital capacity (FVC) associated with a 20-ppb increase in NO_2 (A) and a 20-µg/m^3 increase in PM_{10} (B) in children, standardized per year of follow-up. Results from three major children's long-term cohort studies are presented.

Source: Gauderman et al. (2004); Oftedal et al. (2008), Rojas-Martinez et al. (2007a,b).

sites were set up to measure hourly O_3, NO_2, and PM_{10} and 2-week averages of $PM_{2.5}$, and acid vapor. Children in grades 4, 7, and 10 were recruited though local schools. The study followed children for 10 years, with annual questionnaires and lung function measurement. The study had several important characteristics: it was prospective and exposure and outcome data were collected in a consistent manner over the duration of the study, and confounding by SES was controlled in the models by selecting communities similar in demographic characteristics at the outset.

Peters et al. (1999) reported the initial results from the CHS: a cross-sectional analysis of lung function tests conducted on 3,293 children in the first year of the study. Both NO_2 and PM_{10} were associated with decreases in FVC, FEV_1, and MMEF. Avol et al. (2001) then studied the effect of relocating to areas of differing air pollution levels in 110 children 10 years of age who were participating in the CHS. As a group, subjects who had moved to areas of lower NO_2 showed increased growth in lung function, but the effects did not reach statistical significance. In general, the authors focused on associations with PM, where larger and statistically significant effects were observed.

In 2004, Gauderman et al. reported results for an 8-year follow up of the children enrolled in grade 4 (n = 1,759). Exposure to NO_2 was significantly associated with deficits in lung growth over the 8-year period. The difference in FVC for children exposed to the lowest versus the highest levels of NO_2 (34.6 ppb) was −95.0 mL (95% CI: −189.4 to −0.6). For FEV_1, the difference was −101.4 mL (95% CI: −165.5 to −38.4), and for MMEF, −221.0 mL/s (95% CI: −377.6, −44.4). Results were similar for boys and girls and among children without a history of asthma. These deficits in growth of lung function resulted in clinically significant differences in FEV_1 at age 18. In addition, the NO_2 concentration associated with deficits in lung growth was 34.6 ppb (range of means across communities: 4.4−39.0 ppb), a level below the current standard. Similar results were reported for acid vapor (resulting primarily from photochemical conversions of NO_X to HNO_3). These results are depicted in Figure 3.4-3. The authors concluded that the effects of NO_2 could not be distinguished from the effects of particles ($PM_{2.5}$ and PM_{10}) as NO_2 was strongly correlated with these contaminants (0.79, and 0.67, respectively).

More recently, Gauderman et al. (2007) has reported results of an 8-year follow-up on 3,677 children who participated in the CHS. Children living <500 m from a freeway (n = 440)

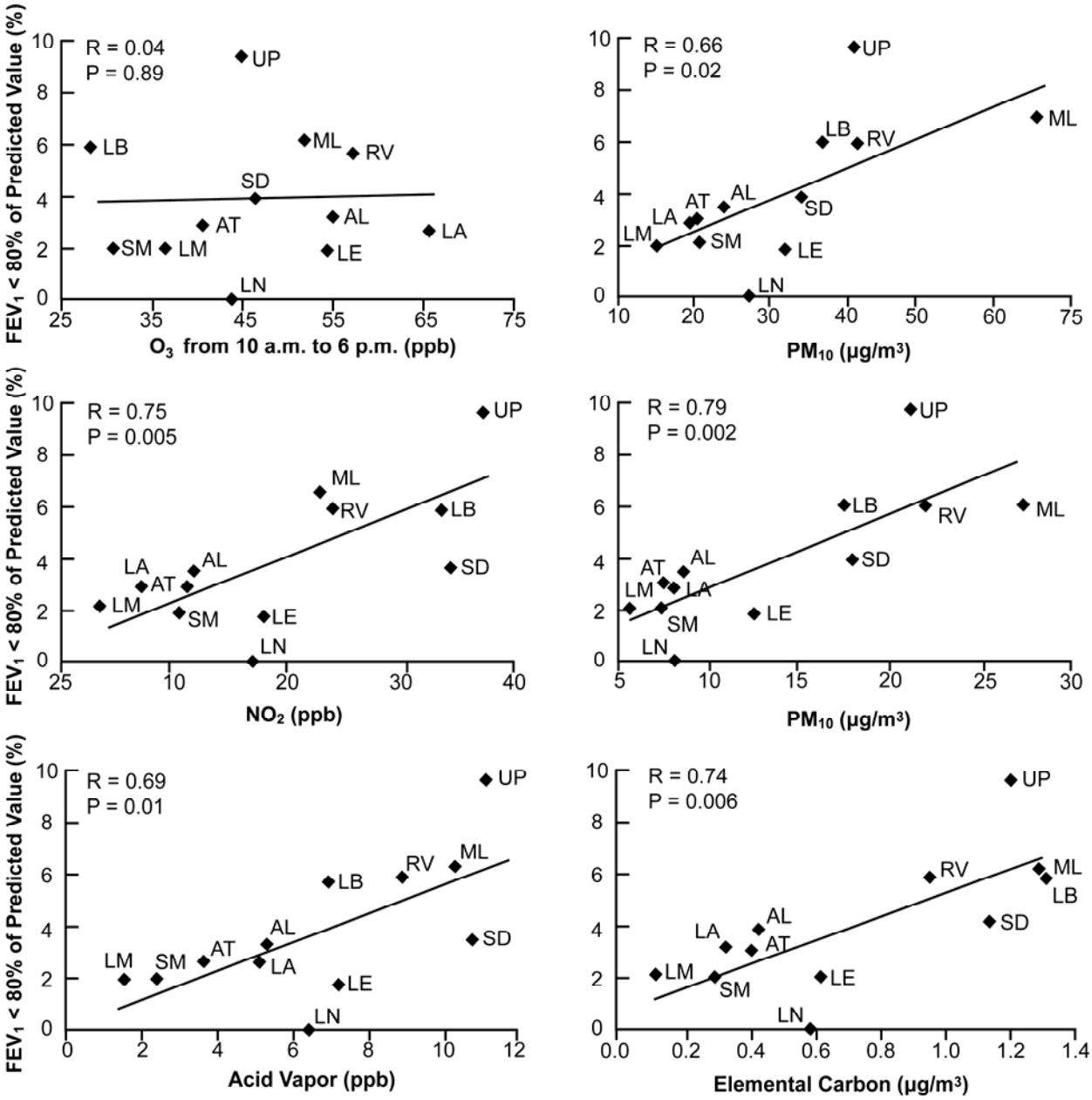

Figure 3.4-3. Proportion of 18-year olds with a FEV_1 below 80% of the predicted value plotted against the average levels of pollutants from 1994 through 2000 in the 12 southern California communities of the Children's Health Study.

AL = Alpine; AT = Atascadero; LA = Lake Arrowhead; LB = Long Beach; LE = Lake Elsinore; LM = Lompoc; LN = Lancaster; ML = Mira Loma; RV = Riverside; SD = San Dimas; SM = Santa Maria; UP = Upland

Source: Derived from Gauderman et al. (2004).

had significant deficits in lung growth over the 8-year follow-up compared to children who lived at least 1500 m from a freeway. The difference in FVC was −63 mL (−131 to 5); the difference in FEV_1 −81 mL (−143 to −18); and the difference in MMEF −127 mL/s (−243 to −11). This study did not attempt to measure specific pollutants near freeways or to estimate exposure to specific pollutants for study subjects. Thus, while the study presents important findings with respect to traffic pollution and respiratory health in children, it does not provide evidence that NO_2 is responsible for these deficits in lung growth.

Further evaluation of exposure estimation was done in this cohort of schoolchildren (Molitor et al., 2007). Several models of interurban air pollution exposure were used to classify and predict FVC in an integrated Bayesian modeling framework using three interurban predictors: distance to a freeway, traffic density, and predicted average NO_2 exposure from the California line source dispersion (CALINE4) model. Results suggested that the inclusion of residual spatial terms can reduce uncertainty in the prediction of exposures and associated health effects.

In Mexico City, Rojas-Martinez et al. (2007a,b) evaluated the association between long-term exposure to PM_{10}, O_3, and NO_2 and lung function growth in a cohort of 3,170 children aged 8 years at baseline in 31 schools from April 1996 through May 1999. Ten air-quality monitoring stations within 2 km of the schools provided exposure data. Figure 3.4-4 shows the results for FEV_1, by gender and pollutant with adjustments noted for copollutants. The results of this 3-year study support the hypothesis that long-term exposure to ambient air pollutants is associated with deficit in lung growth in children. The results are, in part, consistent with previous results from the CHS. Similar to the CHS, the high correlation among the three pollutants studied did not allow independent effects to be accurately estimated in this long-term exposure study.

Another cohort study in Oslo, Norway, examined short- and long-term NO_2 and other pollutant exposure effects on lung function (PEF, forced expiratory flow at 25% of forced vital capacity [FEF_{25}], forced expiratory flow at 50% of forced vital capacity [FEF_{50}]) in 2,307 nine- and ten-year-old children (Oftedal et al., 2008). The EPISODE dispersion model (Slordal et al., 2003) was used for the exposure estimate and evaluation concluded that the modeled NO_2 and PM levels represent the long- and short-term exposure reasonably well. An incremental change equal to the IQR of lifetime exposure to NO_2, PM_{10}, and $PM_{2.5}$ was associated with changes in

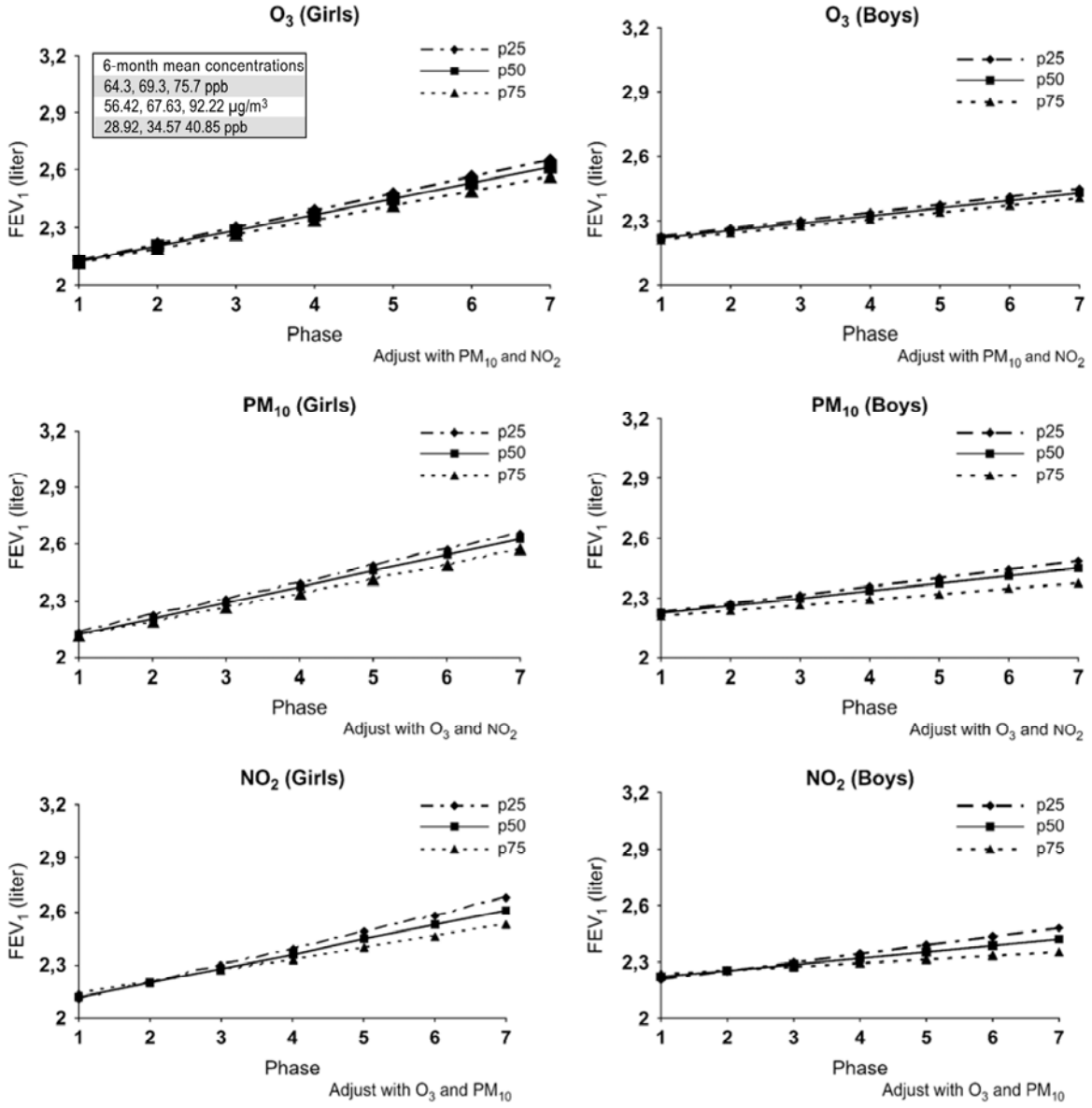

Figure 3.4-4. Estimated annual growth in FEV_1, of long-term ozone (O_3), particulate matter ≤10 µm in diameter (PM_{10}), and nitrogen dioxide (NO_2) in girls and boys. Mexico City, 1996 to 1999 (multipollutant models). Adjusted for age, body mass index, height, height by age, weekday time spent in outdoor activities, environmental tobacco smoke exposure, pervious-day mean air pollutant concentration, and study phase.

Source: Derived from Rojas-Martinez et al. (2007a,b).

adjusted peak flow of −79 mL/s (95% CI: −128,−31), −66 mL/s (95% CI: −110, −23), and −58 mL/s (95% CI: −94, −21), respectively. Examining short- and long-term NO_2 exposures simultaneously yielded only the long-term effects. Adjusting for a contextual socioeconomic factor diminished the association. Comparable PEF to the CHS were found but forced volumes were considerably weaker.

In another European study, Moseler et al. (1994) measured NO_2 outside the homes of 467 children, including 106 who had physician-diagnosed asthma, in Freiburg, Germany. Five of six lung function parameters were reduced among asthmatic children exposed to NO_2 at concentrations of >21 ppb. No significant reductions in lung function were detected among children without asthma.

To examine the effect of lifetime exposure to air pollutants in young adults, lung function in students attending the University of California (Berkeley) who had been lifelong residents of the Los Angeles or San Francisco areas was assessed (Tager et al, 2005). Using geocoded address histories, a lifetime exposure to air pollution was constructed for each student. Increasing lifetime exposure to NO_2 was associated with decreased FEF_{75} and FEF_{25-75}. In models including O_3 and PM_{10} as well as NO_2, the effect of NO_2 diminished significantly while the O_3 effect remained robust.

The SAPALDIA (Study of Air Pollution and Lung Diseases in Adults) study (Ackermann-Liebrich et al., 1997) compared 9,651 adults (age 18 to 60) in eight different regions in Switzerland. Significant associations of NO_2, SO_2, and PM_{10} with FEV_1 and FVC were found with a 10-$\mu g/m^3$ (5.2 ppb) increase in annual average exposure. Due to the high correlations between NO_2 and the other pollutants (SO_2: $r = 0.86$; PM_{10}: $r = 0.91$), it was difficult to assess the effect of a specific pollutant. A random subsample of 560 adults from SAPALDIA recorded personal measurements of NO_2 and measurements of NO_2 outside their homes (Schindler et al., 1998). Using the personal and home measurements of NO_2, similar associations were reported between NO_2 with FEV_1 and FVC. Downs et al. (2007) reported the relationship in this group of long-term reduced exposure to PM_{10} and age-related decline in lung function, but they did not examine NO_2 or other pollutants.

Goss et al. (2004) examined the relationship of ambient pollutants on individuals with cystic fibrosis using the Cystic Fibrosis Foundation National Patient Registry in 1999 and 2000. Exposure was assessed by linking air pollution values from the Aerometric Information Retrieval

System with the patient's home ZIP code. Associations were reported between PM and exacerbations or lung function changes, but no clear associations were found for O_3, SO_2, NO_2, or CO. The odds of patients with cystic fibrosis having two or more pulmonary exacerbations during 2000 per 10-ppb NO_2 is 0.98 (95% CI: 0.91, 1.01).

Toxicological Studies

A limited number of animal studies, especially those using spikes of NO_2, have shown decrements in vital capacity and lung distensibility, which may provide biological plausibility for these lung function findings. NO_2 concentrations in many urban areas of the United States and elsewhere consist of spikes superimposed on a relatively constant background level. As discussed in the 1993 AQCD, Miller et al. (1987) evaluated this urban pattern of NO_2 exposure in mice using continuous 7-days/week, 23-h/day exposures to 0.2 ppm NO_2 with twice daily (5 days/week) 1-h spike exposures to 0.8-ppm NO_2 for 32 and 52 weeks. Mice exposed to clean air and to the constant background concentration of 0.2-ppm NO_2 served as controls. Vital capacity tended to be lower ($p = 0.054$) in mice exposed to NO_2 with diurnal spikes than in mice exposed to air. Lung distensibility, measured as respiratory system compliance, also tended to be lower in mice exposed to diurnal spikes of NO_2 compared with constant NO_2 exposure or air exposure. These changes suggest that $\leq$52 weeks of low-level NO_2 exposure with diurnal spikes may produce a subtle decrease in lung distensibility, although part of this loss in compliance may be a reflection of the reduced vital capacity. Vital capacity appeared to remain suppressed for at least 30 days after exposure. Lung morphology in these mice was evaluated only by light microscopy (a relatively insensitive method) and showed no exposure-related lesions. The decrease in lung distensibility suggested by this study is consistent with the thickening of collagen fibrils in monkeys (Bils, 1976) and the increase in lung collagen synthesis rates of rats (Last et al., 1983) after exposure to higher levels of NO_2.

Tepper et al. (1993) exposed rats to 0.5-ppm NO_2, 22 h/day, 7 days/week, with a 2-h spike of 1.5-ppm NO_2, 5 days/week for up to 78 weeks. No effects on pulmonary function were observed between 1 and 52 weeks of exposure. However, after 78 weeks of exposure, flow at 25% FVC was decreased, perhaps indicating airways obstruction. A significant decrease in the frequency of breathing was also observed at 78 weeks that was paralleled by a trend toward

increased expiratory resistance and expiratory time. Taken together, these results suggest that few, if any, significant effects were seen that suggest incipient lung degeneration.

There were no effects on pulmonary function (lung resistance, dynamic compliance) in NO_2-exposed rabbits that were immunized intraperitoneally within 24-h of birth until 3 months of age to either *Alternaria tenuis* or house dust mite antigen. The rabbits were given intraperitoneal injections once weekly for 1 month, and then every 2 weeks thereafter, and exposed to 4-ppm NO_2 for 2 h daily (Douglas et al., 1994).

A number of epidemiologic studies examined the effects of long-term exposure to NO_2 and observed associations with decrements in lung function and partially irreversible decrements in lung function growth. Results from the Southern California Children's Health Study indicated that decrements were similar for boys compared to girls, and among children who did not have a history of asthma (Gauderman et al., 2004). As shown in Appendix Table 5B, the mean NO_2 concentrations in these studies range from 21.5 to 34.6 ppb; thus, all have been conducted in areas where NO_2 levels are below the level of the NAAQS. The epidemiologic studies of long-term exposure to NO_2, however, are likely confounded by other ambient copollutants. In particular, similar associations have also been found for PM and proximity to traffic (<500 m).

3.4.2 Asthma Prevalence and Incidence

Several publications from the CHS in southern California report results on the associations of NO_2 exposure with asthma prevalence and incidence. Gauderman et al. (2005) conducted a study of children randomly selected from the CHS with exposure measured at children's homes. Although only 208 were enrolled, exposure to NO_2 was strongly associated with both lifetime history of asthma and asthma medications use. Gauderman et al. (2005) measured ambient NO_2 with Palmes tubes attached to the subjects' homes at the roofline eaves, signposts, or rain gutters at an approximate height of 2 m above the ground. Samplers were deployed for 2-week periods in both summer and fall. Traffic-related pollutants were characterized by three metrics: (1) proximity of home to freeway, (2) average number of vehicles within 150 meters, and (3) model-based estimates. Yearly average NO_2 levels within the 10 communities ranged from 12.9 to 51.5 ppb. The average NO_2 concentration measured at home was associated with asthma prevalence (OR = 8.33 [95% CI: 1.15, 59.87] per 20 ppb) with similar results by season and when taking into account several potential confounders. In

each community studied, NO_2 was more strongly correlated with estimates of freeway-related pollution than with non-freeway-related pollution. In a related CHS study, McConnell et al. (2006) studied the relationship of proximity to major roads and asthma and also found a positive relationship.

Islam et al. (2007) studied whether lung function is associated with new onset asthma and whether this relationship varies by exposure to ambient air pollutants by examining a cohort of 2,057 fourth-grade children who were asthma- and wheeze-free at the start of the CHS and following them for 8 years. A hierarchal model was used to evaluate the effect of individual air pollutants (NO_2, PM_{10}, $PM_{2.5}$, and acid vapor, NO_2, EC, and OC) on the association of lung function with asthma. This study shows that better airflow, characterized by higher FEF_{25-75} and FEV_1 during childhood was associated with decreased risk of new-onset asthma during adolescence. However, exposure to high levels of ambient pollutants (NO_2 and others) attenuated this protective association of lung function on asthma occurrence.

Millstein et al. (2004) studied the effects of ambient air pollutants on asthma medication use and wheezing among 2,034 fourth-grade schoolchildren from the CHS. Included in the pollutants examined were NO_2 and HNO_3. They observed that monthly average pollutant levels produced primarily by photochemistry (i.e., HNO_3, acetic acid), but not NO_2, were suggestive of a positive association with asthma medication use among children with asthma—especially among children who spent more than the calculated median time outdoors. The March-August OR for HNO_3 (IQR 1.64 ppb) was 1.62 (95% CI: 0.94, 2.80) and for NO_2 (IQR 5.74 ppb), 0.96 (95% CI: 0.68, 1.37).

Kim et al. (2004a) reported associations with both NO_2 and NO_X for girls in the San Francisco bay area. They studied 1,109 students (grades 3 to 5) at 10 school sites for bronchitis symptoms and asthma in relation to ambient pollutant levels to include NO, NO_2, and NO_X measured at the school site. Mean levels ranged for schools from 33 to 69 ppb for NO_X; 19 to 31 for NO_2; and 11 to 38 ppb for NO. NO_X and NO_2 measurements at school sites away from traffic were similar to levels measured at the regional site. They found associations between traffic-related pollutants and asthma and bronchitis symptoms, which is consistent with previous reports of traffic and respiratory outcomes. The higher effect estimates with black carbon, NO_X, and NO compared with NO_2 and $PM_{2.5}$ suggest that primary or fresh traffic emissions may play

an etiologic role in these relationships and that, while NO_X and NO may serve as indicators of traffic exposures, they also may act as etiologic agents themselves.

Brauer et al. (2007) assessed the development of asthmatic/allergic symptoms and respiratory infections during the first 4 years of life in a birth cohort study in the Netherlands (n = 4,000, but the number of participants decreased over the study to ~3,500). Air pollution concentrations at the home address at birth were calculated by a validated model combining air pollution measurements with a Geographic Information System (GIS). Wheeze, physician-diagnosed asthma, and flu and serious colds were associated with air pollutants (considered traffic-related: NO_2, $PM_{2.5}$, soot) after adjusting for other potential confounding variables; for example, NO_2 was associated with physician-diagnosed asthma (OR = 1.28 [95% CI: 1.04, 1.56]) as a cumulative lifetime indicator. In comments to this study, Jerrett (2007) observed that the effects were larger and more consistent than in participants of the same study at age 2 and that these effects suggested that onset and persistence of respiratory disease formation begins at an early age and continues. He further noted that the more sophisticated method for exposure assessment based on spatially and temporally representative field measurements and land use regression was capable of capturing small area variations in traffic pollutants.

Other studies (see Annex Table AX6.3-16) also have investigated asthma prevalence and incidence in children associated with NO_2 exposure. Although several of these studies have reported positive associations, the large number of comparisons made and the limited number of positive results do not suggest a strong relationship between long-term NO_2 exposure and asthma. Several studies used the International Study of Asthma and Allergies in Children (ISAAC) protocol. Children were interviewed in school and results of the questionnaire were compared with air pollution measurements in their communities. These studies included thousands of children in several European countries and Taiwan, and the results in all but one study were nonsignificant. Exposure in these studies varied, but medians were often greater than 20 ppb. Most of the studies did not report correlations of NO_2 exposure with other air pollutants; therefore, it is not possible to determine whether some of these associations were related to other air contaminants.

Overall, results from the available epidemiologic evidence investigating the association between long-term exposure to NO_2 and increases in asthma prevalence and incidence are inconsistent. Two major cohort studies, the Children's Health Study in southern California

(Gauderman et al., 2005) and a birth cohort study in the Netherlands (Brauer et al., 2007) observed significant associations; however, several other studies did not find consistent associations between long-term NO_2 exposure and asthma outcomes.

3.4.3 Respiratory Symptoms

Annex Table AX6.3-17 lists studies examining the association between long-term exposure to NO_2 and respiratory symptoms. Most of the studies reported some positive associations with NO_2 exposure and symptoms, but all reported a large number of negative results. Only one of these studies (Peters et al., 1999) reported an association of NO_2 exposure with wheeze, and in boys. This was despite the fact that wheeze was investigated in a large number of studies, including several studies that included thousands of children.

McConnell et al. (2003) studied the relationship between bronchitis symptoms and air pollutants in the CHS. Symptoms assessed yearly by questionnaire from 1996 to 1999 were associated with the yearly variability for the pollutants for NO_2 (OR = 1.071 [95% CI: 1.02, 1.13). In two-pollutant models, the effects of yearly variation in NO_2 were only modestly reduced by adjusting for other pollutants except for OC and NO_2 (Figure 3.4-5). McConnell et al. (2006) further evaluated whether the association of exposure to air pollution with annual prevalence of chronic cough, phlegm production, or bronchitis was modified by dog or cat ownership indicators or allergen and endotoxin exposure. Subjects consisted of 475 children from the CHS. Among children owning a dog, there was a strong association between bronchitis symptoms and all pollutants studied. Odds ratio for NO_2 were 1.49 (95% CI: 1.14, 1.95), indicating that dog ownership may worsen the relationship between air pollution and respiratory symptoms in asthmatic children.

Two studies of infants were conducted in Germany and the Netherlands using the same exposure protocol (Gehring et al., 2002; Brauer et al., 2002). In Munich, 1,756 infants were enrolled and followed for 2 years. Outcomes of interest were asthma, bronchitis, and respiratory symptoms including wheeze, cough, and nasal symptoms. To determine exposure, 40 measuring sites were selected in Munich, including sites along main roads and side streets and background sites. At each site, NO_2 was measured four times (once in each season) for 14 days using Palmes tubes. Regression modeling was used to relate annual average pollutant concentrations to a set

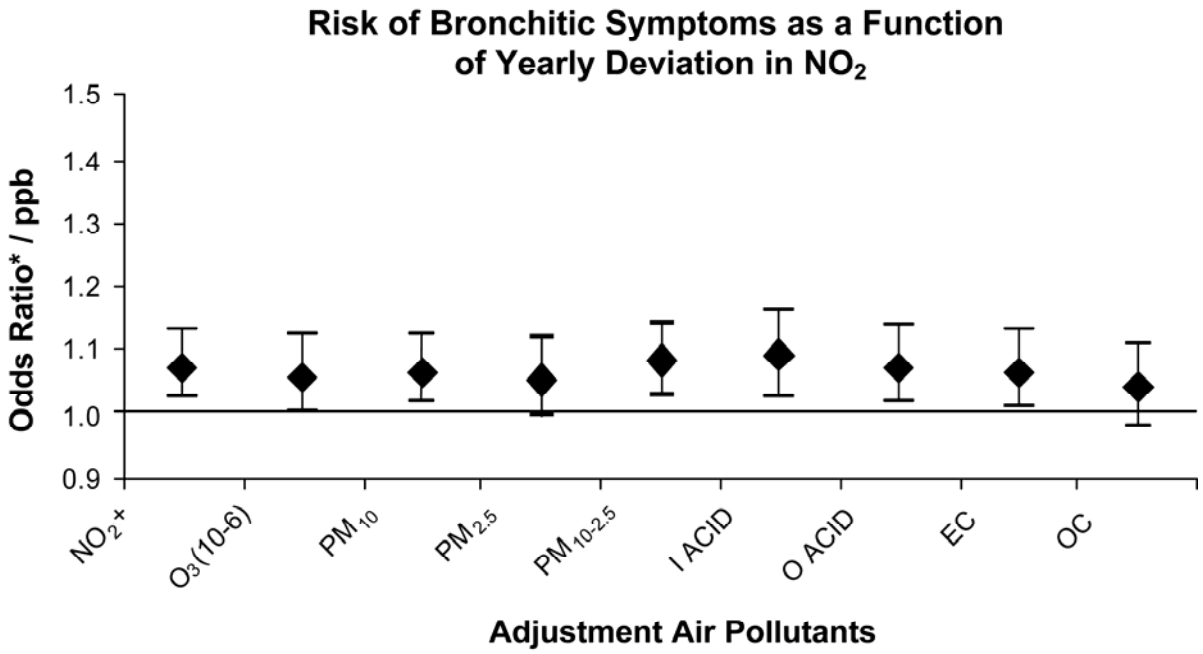

Figure 3.4-5. Odds ratios for within-community bronchitis symptoms associations with NO_2, adjusted for other pollutants in two-pollutant models for the 12 communities of the Children's Health Study.

Source: McConnell et al. (2003).

of predictor variables (i.e., traffic density, heavy vehicle density, household density, population density) obtained from GIS. The percentage of variability explained by the model (R^2) was 0.62 for NO_2. Using geocoded birth addresses, values for the predictor variables were obtained for each child, and the model was used to assign an estimate of NO_2 exposure. At 1 year of age, an increase of 8.5 $\mu g/m^3$ (4.5 ppb) of NO_2 was associated with cough (OR = 1.40 [95% CI: 1.12, 1.75]) and dry cough at night (OR = 1.36 [95% CI: 1.07, 1.74]). NO_2 exposure was not associated with wheeze, bronchitis, or respiratory infections. Estimated $PM_{2.5}$ exposure was also associated with cough and dry cough at night, with nearly identical odds ratios.

In the Netherlands (Brauer et al., 2002), the same protocol was used to estimate NO_2 exposure in a birth cohort of 3,730 infants. However, these study subjects lived in many different communities from rural areas to large cities in northern, central, and western parts of the Netherlands. Forty sites were selected to represent different exposures and measurements were taken as in the Gehring et al. (2002) study. In this study, ear, nose, and throat infections (OR = 1.16 [95% CI: 1.00, 1.34]) and physician-diagnosed flu (OR = 1.11 [95% CI: 1.00,

1.23]) were marginally significant. The association of NO_2 with dry cough at night could not be replicated, nor was NO_2 associated with asthma, wheeze, bronchitis, or eczema.

In both of these studies, the 40 monitoring sites set up to measure NO_2 also measured $PM_{2.5}$ with Harvard Impactors. Estimates of NO_2 and $PM_{2.5}$ were highly correlated in Brauer et al. ($r = 0.97$). The correlation was not reported in Gehring et al. (2002); however, the similarity of odds ratios for each pollutant suggests that the estimated exposures were also highly correlated. Thus, a major limitation of these studies is the inability to distinguish the effects of different pollutants.

In a study of 3,946 Munich schoolchildren, Nicolai et al. (2003) assessed traffic exposure using two different methods. First, all street segments within 50 m of each child's home were identified and the average daily traffic counts were totaled. Second, a model was constructed based on measurement of NO_2 at 34 sites throughout the city using traffic counts and street characteristics ($R^2 = 0.77$). The model was then used to estimate NO_2 exposure at each child's home address. When traffic counts of $\leq$50m were used as an exposure variable, a significant association was found with current asthma (OR = 1.79 [95% CI: 1.05, 3.05]), wheeze (OR = 1.66 [95% CI: 1.07, 2.57]), and cough (OR = 1.62 [95% CI: 1.16, 2.27]). Similar results were found when modeled NO_2 exposure was substituted as the exposure variable (current asthma OR = 1.65 [95% CI: 0.94, 2.90], wheeze OR = 1.58 [95% CI: 1.05, 2.48], cough OR = 1.60 [95% CI: 1.14, 2.23]). Asthma, wheeze, and cough were also associated with estimated exposures to soot and benzene derived from models, suggesting that some component of traffic pollution is increasing risk of respiratory conditions in children, but making it difficult to determine whether NO_2 is the cause of these conditions.

In summary, epidemiologic studies conducted in both the United States and Europe have observed inconsistent results regarding an association between long-term exposure to NO_2 and respiratory symptoms. While some positive associations were noted, a large number of symptom outcomes were examined and the results across specific outcomes were inconsistent.

3.4.4 Animal Studies of Long-Term Morphological Effects to the Respiratory System

Animal toxicology studies demonstrate morphological changes to the respiratory tract from exposure to NO_2 that may provide further biological plausibility for the decrements in lung function growth observed in epidemiologic studies discussed above. Several investigators have

studied the temporal progression of early events due to NO_2 exposure in the rat (e.g., Freeman et al., 1966, 1968, 1972; Stephens et al., 1971, 1972; Evans et al., 1972, 1973a,b, 1974, 1975, 1976, 1977; Cabral-Anderson et al., 1977; Rombout et al., 1986) and guinea-pig (Sherwin and Carlson, 1973). The results of these studies were summarized in the 1993 AQCD. Overall, animal toxicological studies demonstrated that NO_2 exposure resulted in permanent alterations resembling emphysema-like disease, morphological changes in the centriacinar region of the lung and in bronchiolar epithelial proliferation, which might provide biological plausibility for the observed epidemiologic associations between long-term exposure to NO_2 and respiratory morbidity.

3.4.5 Summary and Integration of Evidence on Long-Term NO_2 Exposure and Respiratory Illness and Lung Function Decrements

Overall, the epidemiologic and experimental evidence is suggestive but not sufficient to infer a causal relationship between long-term NO_2 exposure and respiratory morbidity. The available database evaluating the relationship between respiratory illness in children associated with long-term exposures to NO_2 has increased. Three recent studies in large cohorts in three countries have examined this relationship. The CHS, examining NO_2 exposure in children over an 8-year period, demonstrated deficits in lung function growth (Gauderman et al., 2004). This has been observed also in Mexico City, Mexico (Rojas-Martinez et al., 2007a,b), and in Oslo, Norway (Oftedal et al., 2008).

Deficit in lung function growth is a known risk factor for chronic respiratory disease and possibly for premature mortality in later life stages. Lung growth continues from early development through early adulthood, reaches a plateau, and then eventually declines with advancing age. Dockery and Brunekreef (1996) have hypothesized that the risk for chronic respiratory disease is associated with maximum lung size, the length of time the lung size has been at the plateau, and the rate of decline of lung function. Therefore, exposures to NO_2 and other air pollutants in childhood may reduce maximum lung size by limiting lung growth and subsequently increase the risk in adulthood for chronic respiratory disease.

Models and/or mechanisms of action for decrements in lung function growth and other respiratory effects from long-term exposure to air pollution are not clearly established. Figure 3.4-6 is adapted from an earlier model discussed by Gilliland et al. (1999), reflective of efforts of the CHS research. Gilliland et al. proposed that respiratory effects in children from exposure to

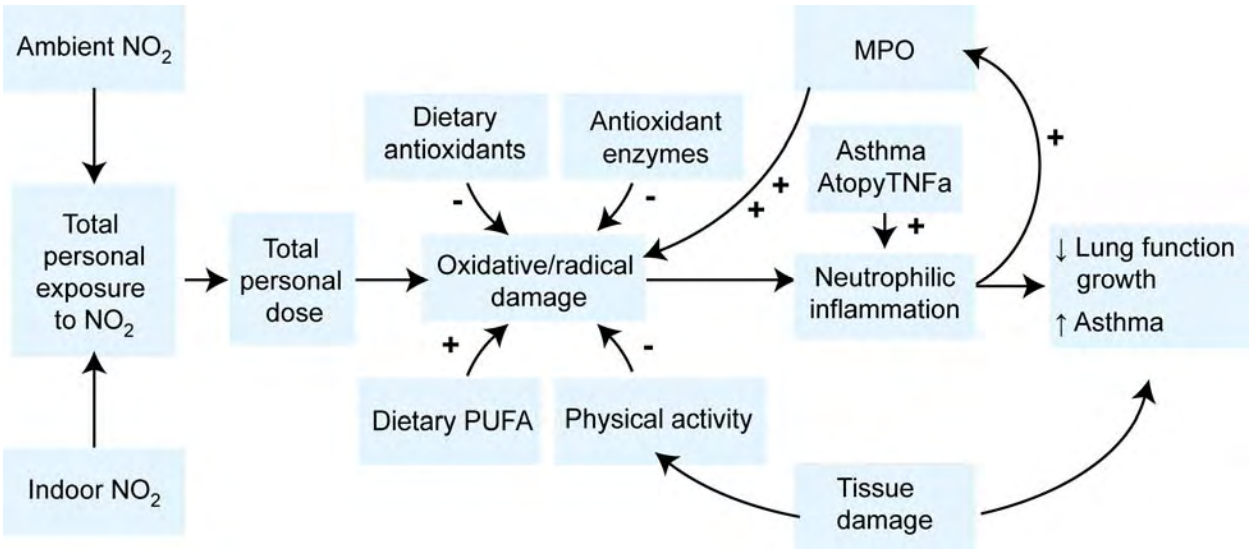

Figure 3.4-6. Biologic pathways of long-term NO_2 exposure on morbidity.

MPO = myeloperoxidase; PUFA = polyunsaturated fatty acids; TNF-α = tumor necrosis factor-alpha.

Source: Adapted from Gilliland et al. (1999).

gaseous and particulate air pollutants result from chronically increased oxidative stress, alterations in immune regulation, and repeated pathologic inflammatory responses that overcome lung defenses to disrupt the normal regulatory and repair processes. Rojas-Martinez et al. (2007a,b) noted that oxidative stress resulting from increased exposure to oxidized compounds (O_3, NO_2, and particle components) has been identified as a major feature underlying the toxic effects of air pollutants (Kelly et al., 2003; Saxon and Diaz-Sanchez, 2005; Cross et al., 2002). They further noted that the resulting increased expression of enhanced proinflammatory cytokines leads to enhanced inflammatory response (Saxon and Diaz-Sanchez, 2005) and potential chronic lung damage. If this results in permanent loss, it is not clear whether repeated versus average exposure is the major factor. Current data and the nonlinear pattern of childhood lung function growth (Pérez-Padilla et al., 2003) are noted by Rojas-Martinez et al. (2007a,b) as limitations on estimating the impact on lung function attained in early adulthood.

Other important biochemical mechanisms examined in animals may provide biological plausibility for the chronic effects of NO_2 observed in epidemiologic studies. The main biochemical targets of NO_2 exposure appear to be antioxidants, membrane polyunsaturated fatty acids, and thiol groups. Reactions of NO_2 with these species in the extracellular lining fluid of

the lung leads to the formation of nitrite (NO_2^-) and hydrogen (H^+) ions. NO_2 effects include changes in oxidant/antioxidant homeostasis and chemical alterations of lipids and proteins. Lipid peroxidation has been observed at NO_2 exposures as low as 0.04 ppm for 9 months and at exposures of 1.2 ppm for 1 week, suggesting lower effect thresholds with longer durations of exposure. Other studies show decreases in formation of key arachidonic acid metabolites in AMs following NO_2 exposures of 0.5 ppm. NO_2 has been shown to increase collagen synthesis rates at concentrations of as low as 0.5 ppm. This could indicate increased total lung collagen, which is associated with pulmonary fibrosis, or increased collagen turnover, which is associated with remodeling of lung connective tissue. Morphological effects following chronic NO_2 exposures have been identified in animal studies that link to these increases in collagen synthesis and may provide plausibility for the deficits in lung function growth described in epidemiologic studies.

An alternative explanation for the decrease in lung function growth observed in the CHS needs to be considered. Since this response was associated with both NO_2 and HNO_3 exposure, ambient levels of NO may also have been involved. Three groups have reported emphysematous changes in animal studies following prolonged exposure to NO. In the Mercer study (1995), a decreased number of interstitial cells and thinning of the alveolar septa was observed. Other studies in vitro and in animal models have demonstrated that NO inhibits protein synthesis and cellular proliferation. Whether NO plays a role in maintaining the alveolar interstitial compartment requires further investigation. Furthermore, the formation of NO or NO-related species may have occurred following complex reactions of NO_2 and HNO_3 with components of the extracellular lining fluid. The role of NO_2^-, H^+, NO and other metabolites in modulating responses to NO_2 and/or HNO_3 is unknown.

In regard to asthma prevalence incidence associated with NO_2 long-term exposure, two major cohorts, the CHS in southern California and birth cohort in the Netherlands, and several other studies provide the evidence for this outcome. Again, the studies are well designed and implemented. However, these results are not consistent with a number of other studies that have investigated this relationship.

Animal toxicologic studies provide biological plausibility for the observed increased incidence of respiratory illness among children. A number of defense system components such as AMs and humoral and cell-mediated immunity have been demonstrated to be targets for

inhaled NO_2. The animal studies described above show that NO_2 exposure impairs the host defense system, increasing susceptibility to respiratory infections. Morphological changes are elicited in ciliated epithelial cells at NO_2 concentrations of as low as 0.5 ppm for 7 months; however, early studies showed that mucocilary clearance, the first line of defense, is not affected by exposures of <5 ppm. A more recent study in guinea pigs showed a concentration-dependent decrease in ciliary activity at 3-ppm NO_2. The AMs, a second line of defense in the lung, are affected by NO_2 in a concentration- and species-dependent manner with both acute and chronic exposures. Mechanisms whereby NO_2 affects AM function include membrane lipid peroxidation, decreased ability to produce superoxide anion, inhibition of migration, and decreased phagocytic activity. Decreases in bactericidal and phagocytic activities are likely related to increased susceptibility to pulmonary infections. More recent studies have confirmed that AMs are a primary target for NO_2 at exposure levels of <1 ppm. Humoral and cell-mediated immunity form a third line of defense that has been shown to be suppressed by NO_2 exposure. The use of animal infectivity studies provides key evidence for the effects of NO_2 on respiratory morbidity and mortality. For these studies, the animals are exposed to NO_2, and subsequently to an aerosol containing the infectious agent. This body of work shows that NO_2 decreases intrapulmonary bactericidal activity in mice in a concentration-dependent manner, with no concurrent changes in mucociliary clearance.

Thus, evidence indicates that the reduced efficacy of lung defense systems may be an important mechanism for the observed increase in incidence and severity of respiratory infections. Overall, the NO_2 toxicologic literature suggests a linear concentration-response relationship that exists in an exposure range of 0.5 to >5ppm and mortality resulting from pulmonary infection. NO_2 exposure reduces the efficiency of defense against infections at concentrations of as low as 0.5 ppm. The exposure protocol is important, with concentration being more important than duration of exposure and with peak exposures being important in the overall response. The effect of concentration is stronger with intermittent exposure than with continuous exposure. Repeated exposures of low levels of NO_2 are necessary for many respiratory effects. The animal toxicologic studies also demonstrate differences in species sensitivity to NO_2 and differences in responses to the microbes used for the infectivity tests. Animal to human extrapolation is limited by a poor understanding of the quantitative relationship between NO_2 concentrations and effective doses between animals and humans. However,

animals and humans share many host defense components, making the infectivity model useful for understanding the mechanisms whereby NO_2 elicits adverse respiratory health effects.

3.5 OTHER MORBIDITY EFFECTS ASSOCIATED WITH LONG-TERM NO_2 EXPOSURE

The current review includes a number of studies published since 1993 characterizing the effect of long-term NO_X exposure on cancer, CVD, reproductive, and developmental morbidity. These studies form a new body of literature that was unavailable in 1993, when the previous AQCD was published.

3.5.1 Cancer Incidence Associated with Long-Term NO_2 Exposure

Two studies (see Annex Table AX6.3-18) have investigated the relationship between NO_2 exposure and lung cancer and reported positive associations. Although this literature review has concentrated on studies that measured exposure to NO_2, modeled exposures will be considered for cancer studies. This is necessary because the relevant exposure period for lung cancer may be 30 years or more.

Nyberg et al. (2000) reported results of a case control study of 1,043 men age 40 to 75 years with lung cancer and 2,364 controls in Stockholm County. They mapped residence addresses to a GIS database indicating 4,300 traffic-related line sources and 500 point sources of NO_2 exposure. Exposure was derived from a model validated by comparison to actual measurements of NO_2 at six sites. Exposure to NO_2 at 10 $\mu g/m^3$ (5.2 ppb) was associated with an OR of 1.10 (95% CI: 0.97, 1.23). Exposure to the 90th percentile ($\geq$29.26 $\mu g/m^3$ [15.32 ppb]) of NO_2 was associated with an OR of 1.44 (95% CI: 1.05, 1.99).

Very similar results were reported in a Norwegian study (Nafstad et al., 2003). The study population is a cohort of 16,209 men who enrolled in a study of CVD in 1972. The Norwegian cancer registry identified 422 incident cases of lung cancer. Exposure data was modeled based on residence, estimating exposure for each person in each year from 1974 to 1998. Each 10 $\mu g/m^3$ (5.2 ppb) of NO_2 was associated with an OR of 1.08 (95% CI: 1.02, 1.15). Cancer incidence with exposure of $\geq$30 $\mu g/m^3$ (15.7 ppb) was associated with an OR of 1.36 (95% CI: 1.01, 1.83); however, controlling for SO_2 exposure did appreciably change the effect estimates for NO_2.

What is particularly striking in these two studies is the similarity in the estimate of effect. Despite the fact that these two studies were conducted by different investigators, in different countries, using different study designs and different methods for modeling exposure, the odds ratios and confidence intervals for exposure per 10 $\mu g/m^3$ (5.2 ppb) and above 30 $\mu g/m^3$ (15.7 ppb) are virtually identical.

Animal and In Vitro Carcinogenicity and Genotoxicity Studies

There is no clear evidence that NO_2 or gaseous nitrogen oxides act as a complete carcinogen. No studies were found on NO_2 using classical carcinogenesis whole-animal bioassays. Of the existing studies that have evaluated the carcinogenic and cocarcinogenic potential of NO_2, results are often unclear or conflicting. Witschi (1988) critically reviewed some of the important theoretical issues in interpreting these types of studies. NO_2 does appear to act as a tumor promoter at the site of contact (i.e., in the respiratory tract from inhalation exposure), possibly due to its ability to produce cellular damage and, thus, promote regenerative cell proliferation. This hypothesis is supported by observed hyperplasia of the lung epithelium from NO_2 exposure (see Lung Morphology section, U.S. Environmental Protection Agency, 1993), which is a common response to lung injury, and enhancement of endogenous retrovirus expression (Roy-Burman et al., 1982). However, these findings were considered by EPA (1993) to be inconclusive.

When studied using in vivo assays, no inductions of recessive lethal mutations were observed in Drosophila exposed to NO_2 (Inoue et al., 1981; Victorin et al., 1990). NO_2 does not increase chromosomal aberrations in lymphocytes and spermatocytes or micronuclei in bone marrow cells (Gooch et al., 1977; Victorin et al., 1990). No increased stimulation of poly (ADP-ribose) synthetase activity (an indicator of DNA repair, suggesting possible DNA damage) was reported in AMs recovered from BAL of rats continuously exposed to 1.2-ppm NO_2 for 3 days (Bermudez, 2001).

NO_2 has been shown to be positive when tested for genotoxicity in vitro assays. NO_2 is mutagenic in bacteria and in plants. In cell cultures, three studies showed chromosomal aberrations, sister chromatid exchanges (SCEs), and DNA single-strand breaks. However, a fourth study (Isomura et al., 1984) concluded that NO, but not NO_2, was mutagenic in hamster cells (see Annex Tables AX4.11A, 4.11B, and 4.11C).

Toxicological Studies of Coexposure with NO_2 and Known Carcinogens

Rats were injected with *N*-bis (2-hydroxy-propyl) nitrosamine (BHPN) and continuously exposed to 0.04-, 0.4-, or 4-ppm NO_2 for 17 months. Although the data indicated 5 times as many lung adenomas or adenocarcinomas in the rats injected with BHPN and exposed to 4-ppm NO_2 (5/40 compared to 1/10), the results failed to achieve statistical significance (Ichinose et al., 1991). In a later study, Ichinose and Sagai (1992) reported increased lung tumors in rats injected with BHPN, followed the next day by either clean air (0%), 0.05-ppm NO_2 (8.3%), 0.05-ppm NO_2 + 0.4-ppm O_3 (13.9%), or 0.4-ppm O_3 + 1 mg/m^3 H_2SO_4-aerosol (8.3%) for 13 months, and then maintained for another 11 months until study termination. Exposure to NO_2 was continuous, while the exposures to O_3 and H_2SO_4-aerosol were intermittent (exposure for 10 h/day). The increased lung tumors from combined exposure of NO_2 and O_3 were statistically significant.

Ohyama et al. (1999) coexposed rats to diesel exhaust particle extract-coated carbon black particles (DEPcCBP) once a week for 4 weeks by intratracheal instillation and to either 6-ppm NO_2, 4-ppm SO_2, or 6-ppm NO_2 + 4-ppm SO_2 16 h/day for 8 months, and thereafter exposed to clean air for 8 months. Alveolar adenomas were increased in animals exposed to DEPcCBP and either NO_2 and/or SO_2 compared to animals in the DEPcCBP-only group and to controls. The incidences of lung tumors for the NO_2, SO_2, and NO_2 and/or SO_2 groups were 6/24 (25%), 4/30 (13%), and 3/28 (11%), respectively. No alveolar adenomas were observed in animals exposed to DEPcCBP alone or in the controls. Increased alveolar hyperplasia was elevated in all groups compared to controls. In addition, DNA adducts, as determined by ^{32}P postlabelling, were observed in the animals exposed to both DEPcCBP and either NO_2 and/or SO_2, but not in animals exposed to DEPcCBP alone or controls. The authors concluded that the cellular damage induced by NO_2 and/or SO_2 may have resulted in increased cellular permeability of the DEPcCBP particles into the cells.

Studies in Animals with Spontaneously High Tumor Rates

The frequency and incidence of spontaneously occurring pulmonary adenomas was increased in strain A/J mice (with spontaneously high tumor rates) after exposure to 10-ppm NO_2 for 6 h/day, 5 days/week for 6 months (Adkins et al., 1986). These small, but statistically significant, increases were only detectable when the control response from nine groups (n = 400) were pooled. Exposure to 1-and 5-ppm NO_2 had no effect. In contrast, Richters and Damji

(1990) found that an intermittent exposure to 0.25-ppm NO_2 for up to 26 weeks decreased the progression of a spontaneous T cell lymphoma in AKR/cum mice and increased survival rates. The investigators attributed this effect to an NO_2-induced decrease in the proliferation of T lymphocyte subpopulation in the spleen (especially T-helper/inducer CD^+ lymphocytes) that produces growth factors for the lymphoma. A study by Wagner et al. (1965) suggested that NO_2 may accelerate the production of tumors in CAF1/Jax mice (a strain that has spontaneously high pulmonary tumor rates) after continuous exposure to 5-ppm NO_2. After 12 months of exposure, 7/10 mice in the exposed group had tumors, compared to 4/10 in the controls. No differences in tumor production were observed after 14 and 16 months of exposure. A statistical evaluation of the data was not presented.

Facilitation of Metastases

Whether NO_2 facilitates metastases has been the subject of several experiments by Richters and Kuraitis (1981, 1983), Richters and Richters (1983), and Richters et al. (1985). Mice were exposed to several concentrations and durations of NO_2 and were injected intravenously with a cultured-derived melanoma cell line (B16) after exposure, and subsequent tumors in the lung were counted. Although some of the experiments showed an increased number of lung tumors, statistical methods were inappropriate. Furthermore, the experimental technique used in these studies probably did not evaluate metastases formation as the term is generally understood, but more correctly, colonization of the lung by tumor cells.

Production of* N-*Nitroso Compounds and other Nitro Derivatives

Because of evidence that NO_2 could produce NO_2^- and NO_3^- in the blood and the fact that NO_2^- is known to react with amines to produce animal carcinogens (nitrosamines), the possibility that NO_2 could produce cancer via nitrosamine formation has been investigated. Iqbal et al. (1980) were the first to demonstrate a linear time- and concentration-dependent relationship between the amount of *N*-nitrosomorpholine (NMOR, an animal carcinogen) found in whole-mouse homogenates after the mice were gavaged with 2 mg of morpholine (an exogenous amine that is rapidly nitrosated) and exposure to 15- to 50-ppm NO_2 for between 1 and 4 h. In a follow-up study at more environmentally relevant exposures, Iqbal et al. (1981) used dimethylamine (DMA), an amine that is slowly nitrosated to dimethylnitrosamine (DMN). They reported a concentration-related increase in biosynthesis of DMN at NO_2 concentrations of as

low as 0.1 ppm; however, the rate was significantly greater at concentrations above 10-ppm NO_2. Increased length of exposure also increased DMN formation between 0.5 and 2 h, but synthesis of DMN was less after 3 or 4 h of exposure than after 0.5 h.

Mirvish et al. (1981) concluded that the results of Iqbal et al. (1980) were technically flawed, but they found that in vivo exposure to NO_2 could produce a nitrosating agent (NSA) that would nitrosate morpholine only when morpholine was added in vitro. Further experiments showed that the NSA was localized in the skin (Mirvish et al., 1983) and that mouse skin cholesterol was a likely NSA (Mirvish et al., 1986). It has also been reported that only very lipid-soluble amines, which can penetrate the skin, would be available to the NSA. Compounds such as morpholine, which are not lipid-soluble, could only react with NO_2 when painted directly on the skin (Mirvish et al., 1988). Iqbal (1984), responding to the Mirvish et al. (1981) criticisms, verified their earlier (Iqbal et al., 1980) studies.

The relative significance of NO_2^- from NO_2 compared with other NO_2 sources such as food, tobacco, and nitrate-reducing oral bacteria is uncertain. Nitrosamines have not been detected in tissues of animals exposed by inhalation to NO_2 unless precursors to nitrosamines and/or inhibitors of nitrosamine metabolism are coadministered. Rubenchik et al. (1995) could not detect *N*-nitrosodimethylamine (NDMA) in tissues of mice exposed to 7.5- to 8.5-mg/m^3 NO_2 for 1 h. NDMA was found in tissues, however, 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 endogenously formed, and food is also a contributing source of nitrite (from nitrate conversion).

Summary of Evidence on the Effects of Long-Term NO_2 Exposure on Cancer Incidence

In summary, two epidemiologic studies conducted in Europe showed an association between long-term NO_2 exposure and incidence of cancer (Nyberg et al., 2000; Nafstad et al., 2003); however, the animal toxicologic studies have provided no clear evidence that NO_2 directly acts as a carcinogen, though it does appear to act as a tumor promoter at the site of contact (Section 3.5.1). There are no in vivo studies that suggest that NO_2 causes teratogenesis or malignant tumors. Only very high exposure studies, i.e., levels not relevant to ambient NO_2 levels, demonstrate increased chromosomal aberrations and mutations in vitro studies. A more likely pathway for NO_2 involvement in cancer induction is through secondary formation of nitro-

polycylic aromatic hydrocarbons (nitro-PAHs), as nitro-PAHs are known to be more mutagenic than their parent compounds. The evidence for a causal relationship between NO_2 and increased cancer risk is inadequate to infer the presence or absence of a causal relationship at this time.

The information presented in this section is relevant to potential mechanisms by which exposure to products formed by reaction of gaseous nitrogen oxides with organic compounds can be carcinogenic. As discussed previously in Section 2.2, nitro-PAHs and other nitrated organic compounds can be produced through reactions of NO_2 or NO with organic compounds in the atmosphere. Nitro-PAHs are largely found on particles, and they can also be including in direct emissions of particles, such as diesel exhaust particles. Effects of particulate nitrogen compounds have been considered in previous reviews of the PM NAAQS.

In addition, it is possible that the products of NO_2 (NO_2^- and NO_3^-) could produce carcinogens (e.g., N-nitrosomorpholine) from exposure from an environmentally occurring precursor compound (e.g., morpholine) within the body. The studies do demonstrate that this is a possible mechanism; however, it should be pointed out that (1) that these studies are limited to a single precursor compound whereas humans would be exposed to multiple precursor compounds thus producing an array of nitrosamines and other nitrated compounds. (2) The level of nitrosamines *per se* produced in this fashion would be small compared to the nitrosamines that come from cigarette smoke, smoked meats, and other food sources and from the atmospheric transformation of products in the ambient air, (3) a wide array of nitrated products are produced in the ambient air with a number of these products known to be carcinogens and/or mutagens.

3.5.2 Cardiovascular Effects Associated with Long-Term NO_2 Exposure

One epidemiologic study examined the association of cardiovascular effects with long-term exposure to NO_2. Miller et al. (2007) studied 65,893 postmenopausal women between the ages of 50 and 79 years without previous CVD in 36 U.S. metropolitan areas from 1994 to 1998. They examined the association between one or more fatal or nonfatal cardiovascular events and the women's exposure to air pollutants. Subject's exposures to air pollution were estimated by assigning the annual mean levels of air pollutants in 2000 measured at the monitor nearest the residence based on its five-digit ZIP Code centroid, which resulted in a more spatially resolved exposure estimate. A total of 1,816 women had one or more fatal or nonfatal cardiovascular events, including 261 deaths from cardiovascular causes. The main focus of the study was

$PM_{2.5}$, but the overall CVD events (but not results for death events only) using all the copollutants (PM_{10}, $PM_{10-2.5}$, SO_2, NO_2, CO, and O_3) in both single- and multipollutant models were presented. The results for the models only including subjects with non-missing exposure data (n = 28,402 subjects resulting in 879 CVD events) are described here. In the single-pollutant model results, $PM_{2.5}$ showed the strongest associations with the CVD events by far among the pollutants, followed by SO_2. NO_2 did not show any association with the overall CVD events (heart rate [HR] = 0.98 [95% CI: 0.89, 1.08] per 10-ppb increase in the annual average). In the multipollutant model, which included all the pollutants, the association of $PM_{2.5}$ and SO_2 with overall CVD events became even stronger. NO_2 became negatively associated with the overall CVD events (HR = 0.82 [95% CI: 0.70, 0.95]). Correlations among these pollutants were not described; therefore, it is not possible to estimate the extent of confounding among these pollutants in these associations, but it is clear that $PM_{2.5}$ was the best predictor of the CVD events.

Limited toxicology data exist on the effect of NO_2 on the heart. Alterations in vagal responses have been shown to occur in rats exposed to 10-ppm NO_2 for 24 h; however, exposure to 0.4-ppm NO_2 for 4 weeks revealed no change (Tsubone and Suzuki, 1984). NO_2-induced effects on cardiac performance are suggested by a significant reduction in the pressure of oxygen in arterial blood (PaO_2) in rats exposed to 4.0-ppm NO_2 for 3 months. When exposure was decreased to 0.4-ppm NO_2 over the same exposure period, PaO_2 was not affected (Suzuki et al., 1981). In addition, a reduction in HR has been shown in mice exposed to both 1.2- and 4.0-ppm NO_2 for 1 month (Suzuki et al., 1984). Whether these effects are the direct result of NO_2 exposure or secondary responses to lung edema and changes in blood hemoglobin content is not known (U.S. Environmental Protection Agency, 1993). A more recent study (Takano et al., 2004) using an obese rat strain found changes in blood triglycerides, HDL, and HDL/total cholesterol ratios with a 24-week exposure to 0.16-ppm NO_2.

No effects on hematocrit and hemoglobin have been reported in squirrel monkeys exposed to 1.0-ppm NO_2 for 16 months (Fenters et al., 1973) or in dogs exposed to $\leq$5.0-ppm NO_2 for 18 months (Wagner et al., 1965). There were, however, polycythemia and an increased ratio of PMNs to lymphocytes in rats exposed to 2.0 + 1.0 ppm NO_2 for 14 months (Furiosi et al., 1973).

The few available epidemiologic and toxicological evidence do not suggest that long-term exposure to NO_2 has cardiovascular effects. The U.S. Women's Health Initiative study (Miller et al., 2007) did not find any associations between long-term NO_2 exposure and cardiovascular events. The toxicological studies observed some effects of NO_2 on cardiac performance and heart rate, but only at exposure levels of as high as 4 ppm. Overall, these data are inadequate to infer the presence or absence of a causal relationship.

3.5.3 Reproductive and Developmental Effects Associated with Long-Term NO_2 Exposure

Epidemiologic Studies

The effects of maternal exposure during pregnancy to air pollution have been examined by several investigators in recent years (2000 through 2006). These outcomes were not evaluated in the 1993 AQCD. The most common endpoints studied are low birth weight, preterm delivery, and measures of intrauterine growth (e.g., small for gestational age [SGA]). Generally, these studies have used routinely collected air pollution data and birth certificates from a given area for their analysis.

While most studies analyzed average NO_2 exposure for the whole pregnancy, many also considered exposure during specific trimesters or other time periods. Fetal growth, for example, is much more variable during the third trimester. Thus, studies of fetal growth might anticipate that exposure during the third trimester would have the greatest likelihood of an association, as is true for the effect of maternal smoking during pregnancy. However, growth can also be affected through placentation, which occurs in the first trimester. Similarly, preterm delivery might be expected to be related to exposure early in pregnancy affecting placentation, or through acute effects occurring just before delivery.

Of the three studies conducted in the United States, one (Bell et al., 2007) reported a significant decrease in birthweight associated with exposure to NO_2 among mothers in Connecticut and Massachusetts. The two studies conducted in California did not find associations between NO_2 exposure with any adverse birth outcome (Ritz et al., 2000; Salam et al., 2005). Differences in these studies that may have contributed to the differences in results include the following: sample size, exposure assessment methods, average NO_2 concentration, and different pollution mixtures. The results reported by Bell et al. (2007) had the largest sample

size and, therefore, greater power to assess small increases in risk. The two California studies reported higher mean concentrations of NO, but also strong correlations of NO_2 exposure with PM mass and CO.

Annex Table AX6.3-12 lists seven studies that investigated the relationship of ambient NO_2 exposure with birth weight. Since low birth weight may result from either inadequate growth in utero or delivery before the usual 40 weeks of gestation, three of the authors only considered low birth weight (<2500 g) in full-term deliveries (>37 weeks); the other four controlled for gestational age in the analysis. When correlations with other pollutants were reported in these studies, they ranged from 0.5 to 0.8. All of these studies reported strong effects for other pollutants.

Lee et al. (2003) reported a significant association between NO_2 and low birth weight, and the association was only for exposure in the second trimester. It is difficult to hypothesize any biological mechanism relating NO_2 exposure and fetal growth specifically in the second trimester. Bell et al. (2007) reported an increased risk of low birth weight with NO_2 exposure averaged over pregnancy (OR = 1.027 [95% CI: 1.002, 1.051]) and a deficit in birthweight specific to the first trimester. In addition, the deficit in birthweight appeared to be greater among black mothers (−12.7 g per IQR increase in NO_2 [95% CI: −18.0, −7.5]) than for white mothers (−8.3 g per IQR increase in NO_2 [95% CI: −10.4, −6.3]).

Six studies investigated NO_2 exposure related to preterm delivery (Annex Table AX6.3-13). Three reported positive associations (Bobak, 2000; Maroziene and Grazuleviciene, 2002; Leem et al., 2006) and three reported no association (Liu et al., 2003; Ritz et al., 2000; Hansen et al., 2006). Among the studies reporting an association, two (Bobak, 2000; Leem et al., 2006) reported significant associations for both the first trimester and the third trimester of pregnancy. The third (Maroziene and Grazuleviciene, 2002) reported significant increases in risk for exposure in the first trimester and averaged over all of pregnancy. In two (Bobak, 2000; Leem et al., 2006) of the positive studies, NO_2 exposure was correlated with SO_2 exposure (r = 0.54, 0.61 for the two studies); the third study did not report correlations.

Three studies (see details in Annex Table AX6.3-14) specifically investigated fetal growth by comparing birth weight for gestational age with national standards. Two of these studies reported associations of small for gestational age with NO_2 exposure. Mannes et al. (2005) determined increased risk for exposure in trimesters 2 and 3, while Liu et al. (2003)

reported risks associated only with NO_2 exposure in the first month of pregnancy. In all three studies, NO_2 exposure was correlated with CO exposure (r = 0.69, 0.57, 0.72 in the three studies) (Mannes et al., 2004; Liu et al., 2003).

Two additional studies found that NO_2 concentrations were associated with hospitalization for respiratory disease in the neonatal period (Dales et al., 2006) and sudden infant death syndrome (SIDS) (Dales et al, 2004).

Toxicological Studies

Only a few studies have investigated the effects of NO_2 on reproduction and development of NO_2. Exposure to 1-ppm NO_2 for 7 h/day, 5 days/week for 21 days resulted in no alterations in spermatogenesis, germinal cells, or interstitial cells of the testes of 6 rats (Kripke and Sherwin, 1984). Similarly, breeding studies by Shalamberidze and Tsereteli (1971) found that long-term NO_2 exposure had no effect on fertility. However, there was a statistically significant decrease in litter size and neonatal weight when male and female rats exposed to 1.3-ppm NO_2, 12 h/day for 3 months were bred. In utero death due to NO_2 exposure resulted in smaller litter sizes, but no direct teratogenic effects were observed in the offspring. In fact, after several weeks, NO_2-exposed litters approached weights similar to those of controls.

Following inhalation exposure of pregnant Wistar rats to 0.5- and 5.3-ppm NO_2 for 6 h/day throughout gestation (21 days), maternal toxic effects and developmental disturbances in the progeny were reported (Tabacova et al., 1985; Balabaeva and Tabacova, 1985; Tabacova and Balabaeva, 1988). Maternal weight gain during gestation was significantly reduced at 5.3 ppm, with findings of pathological changes, e.g., desquamative bronchitis and bronchiolitis in the lung, mild parenchymal dystrophy and reduction of glycogen in the liver, and blood stasis and inflammatory reaction in the placenta. At gross examination, the placentas of the high-dose dams were smaller in size than those of control rats. A marked increase of lipid peroxides was found in maternal lungs and particularly in the placenta at both exposure levels by the end of gestation (Balabaeva and Tabacova, 1985). Disturbances in the prenatal development of the progeny were registered, such as 2- to 4-fold increase in late post-implantation lethality at 0.5 and 5.3 ppm, respectively, as well as reduced fetal weight at term and stunted growth at 5.3 ppm. These effects were significantly related to the content of lipid peroxides in the placenta, which was suggestive of a pathogenetic role of placental damage. Teratogenic effects were not observed, but dose-dependent morphological signs of embryotoxicity and retarded intrauterine

development, such as generalized edema, subcutaneous hematoma, retarded ossification, and skeletal aberrations, were found at both exposure levels.

In a developmental neurotoxicity study, Wistar rats were exposed by inhalation to 0, 0.025-, 0.05-, 0.5-, or 5.3-ppm NO_2 during gestational days 0 through 21. Maternal toxicity was not reported. Viability and physical development (i.e., incisor eruption and eye opening) were significantly affected in the group exposed only to 5.3 ppm. There was a concentration-dependent change in neurobehavioral endpoints such as disturbances in early neuromotor development, including coordination deficits, retarded locomotor development, and decreased activity and reactivity. Statistical significance was observed in some or all of the endpoints at the time point(s) measured in the 0.05-, 0.5-, and 5.3-ppm exposure groups.

Di Giovanni et al. (1994) investigated whether in utero exposure of rats to NO_2 changed ultrasonic vocalization, a behavioral response indicator of the development of emotionality. Pregnant Wistar female rats were exposed by inhalation to 0-, 1.5-, and 3-ppm NO_2 from day 0 to 20 of gestation. Dam weight gain, pregnancy length, litter size at birth, number of dams giving birth, and postnatal mortality were unaffected by NO_2. There was a significant decrease in the duration of ultrasonic signals elicited by the removal of the pups from the nest in the 10-day and 15-day-old male pups in the 3-ppm NO_2-exposed group. No other parameters of ultrasonic emission, or of motor activity, were significantly affected in these prenatally exposed pups. Since prenatal exposure to NO_2 did not significantly influence the rate of calling, the authors concluded that this decrease in the duration of ultrasounds in the 3-ppm NO_2 exposed group does not necessarily indicate altered emotionality, and the biological significance of these findings remains to be determined.

Summary of Evidence on the Effects of Long-Term NO_2 Exposure on Reproductive and Developmental Effects

In summary, the epidemiologic evidence does not consistently report associations between NO_2 exposure and growth retardation; however, some evidence is accumulating for effects on preterm delivery. Similarly, scant animal evidence supports a weak association between NO_2 exposure and adverse birth outcomes and provides little mechanistic information or biological plausibility for the epidemiology findings.

3.5.4 Summary of Other Morbidity Effects Associated with Long-Term NO_2 Exposure

This section has presented epidemiologic and toxicological studies evaluating limited evidence of cancer incidence, cardiovascular effects, and reproductive and developmental effects linked to long-term NO_2 exposure. The epidemiologic evidence is limited but suggestive for effects of long-term NO_2 exposure on adverse birth outcomes and cancer incidence. Animal studies do not provide mechanistic information to support these observational findings. Some toxicological studies have demonstrated an effect of NO_2 exposure on cardiovascular endpoints. However, whether these effects are the direct result of NO_2 exposure or secondary responses to lung edema and changes in blood hemoglobin content are not known. Similar findings have been reported in the epidemiologic literature for short-term exposures only. Overall, these data are inadequate to infer the presence or absence of a causal relationship.

3.6 MORTALITY ASSOCIATED WITH LONG-TERM EXPOSURE

No studies of mortality associated with long-term NO_2 exposure were evaluated in the 1993 AQCD. More recently, there have been several studies that examined mortality associations with long-term exposure to air pollution, including NO_2, using Cox proportional hazards regression models with adjustment for potential confounders. The U.S. studies tended to focus on effects of PM, while the European studies tended to investigate the influence of traffic-related air pollution.

3.6.1 U.S. Studies on the Long-Term NO_2 Exposure Effects on Mortality

Dockery et al. (1993) conducted a prospective cohort study to examine the effects of air pollution, focusing on PM components, in six U.S. cities, which were chosen based on the levels of air pollution (with Portage, WI being the least polluted and Steubenville, OH, the most polluted). In this study, a 14-to-16-year mortality follow-up of 8,111 adults in the six cities was conducted. Fine particles were the strongest predictor of mortality; NO_2 was not analyzed in this study. Krewski et al. (2000) conducted sensitivity analysis of the Harvard Six Cities study and examined associations between gaseous pollutants (i.e., O_3, NO_2, SO_2, CO) and mortality. NO_2 showed risk estimates similar to those for $PM_{2.5}$ per "low to high" range increment with total (1.15 [95% CI: 1.04, 1.27] per 10-ppb increase), cardiopulmonary (1.17 [95% CI: 1.02, 1.34]),

and lung cancer (1.09 [95% CI: 0.76, 1.57]) deaths; however, in this dataset NO_2 was highly correlated with $PM_{2.5}$ (r = 0.78), SO_4^{2-} (r = 0.78), and SO_2 (r = 0.84).

Pope et al. (1995) examined PM effects on mortality using the American Cancer Society (ACS) cohort. Air pollution data from 151 U.S. metropolitan areas in 1980 were linked with individual risk factors in 552,138 adults who resided in these areas when enrolled in the study in 1982. Mortality was followed up until 1989. As with the Harvard Six Cities Study, the main hypothesis of this study was focused on fine particles and SO_4^{2-}, and gaseous pollutants were not analyzed. Krewski et al. (2000) examined association between gaseous pollutants (means by season) and mortality in the Pope et al. (1995) study data set. NO_2 showed weak but negative associations with total and cardiopulmonary deaths using either seasonal means. An extended study of the ACS cohort doubled the follow-up time (to 1998) and tripled the number of deaths compared to the original study (Pope et al., 2002). In addition to $PM_{2.5}$, all the gaseous pollutants were examined. SO_2 was associated with all the mortality outcomes (including all other cause of deaths), but NO_2 showed no associations with the mortality outcomes (RR = 1.00 [95% CI: 0.98, 1.02] per 10-ppb increase in multiyear average NO_2).

Lipfert et al. (2000a) conducted an analysis of a national cohort of ~70,000 male U.S. military veterans who were diagnosed as hypertensive in the mid 1970s and were followed up for about 21 years (up to 1996). This cohort was 35% black and 81% had been smokers at one time. Thus, unlike other cohort studies described in this section, this hypertensive cohort with a very high smoking rate is not representative of the U.S. population. Total suspended particulates (TSP), PM_{10}, CO, O_3, NO_2, SO_2, SO_4^{2-}, $PM_{2.5}$, and $PM_{10-2.5}$ were considered. The county of residence at the time of entry to the study was used to estimate exposures. Four exposure periods (1960-1974, 1975-1981, 1982-1988, and 1989-1996) were defined, and deaths during each of the three most recent exposure periods were considered. Lipfert et al. (2000a) noted that the pollution risk estimates were sensitive to the regression model specification, exposure periods, and the inclusion of ecological and individual variables. The authors reported that indications of concurrent mortality risks were found for NO_2 (the estimate was not given with confidence bands) and peak O_3. Their subsequent analysis (Lipfert et al., 2003) reported that the air pollution-mortality associations were not sensitive to the adjustment for blood pressure. Lipfert et al. (2006a) also examined associations between traffic density and mortality in the same cohort, whose follow-up period was extended to 2001. They reported that traffic density was a

better predictor of mortality than the ambient air pollution variables, with the possible exception of O_3. The log-transformed traffic density variable was moderately correlated with NO_2 ($r = 0.48$) and $PM_{2.5}$ ($r = 0.50$) in this data set. For the 1989 to 1996 data period (the period that showed generally the strongest associations with exposure variables among the four periods), the estimated mortality relative risk for NO_2 was 1.025 (95% CI: 0.983, 1.068) per 10-ppb increase in a single-pollutant model. The two-pollutant model with the traffic density variable reduced NO_2 risk estimates to 0.996 (95% CI: 0.954, 1.040). Interestingly, as the investigators pointed out, the risk estimates due to traffic density did not vary appreciably across these four periods. They speculated that other environmental factors such as particles from tire, traffic noise, spatial gradients in socioeconomic status might have been involved. Lipfert et al. (2006b) further extended analysis of the veteran's cohort data to include one year of the EPA's Speciation Trends Network (STN) data, which collected chemical components of $PM_{2.5}$. As in the previous Lipfert et al. (2006a) study, traffic density was the most important predictor of mortality, but associations were also seen for EC, vanadium, NO_3^-, and nickel. NO_2, O_3, and PM_{10} also showed positive but weaker associations. The risk estimate for NO_2 was 1.043 (95% CI: 0.967, 1.125) per 10-ppb increase in a single-pollutant model. Multipollutant model results were not presented for NO_2 in this updated analysis. The results from the series of studies by Lipfert et al. are suggestive of traffic-related air pollution, but the study population (hypertensive with very high smoking rate) was not representative of the general U.S. population.

Abbey et al. (1999) investigated associations between long-term ambient concentrations of PM_{10}, O_3, NO_2, SO_2, and CO (1973 to 1992) and mortality (1977 to 1992) in a cohort of 6,338 nonsmoking California Seventh-day Adventists. Monthly indices of ambient air pollutant concentrations at 348 monitoring stations throughout California were interpolated to ZIP code centroids according to home or work location histories of study participants, cumulated, and then averaged over time. They reported associations between PM_{10} and total mortality for males and nonmalignant respiratory mortality for both sexes. NO_2 was not associated with all-cause, cardiopulmonary, or respiratory mortality for either sex. Lung cancer mortality showed large risk estimates for most of the pollutants in either or both sexes, but the number of lung cancer deaths in this cohort was very small (12 for female and 18 for male); therefore, it is difficult to interpret these estimates.

When comparing the results of the U.S. studies mentioned above, differences in study population characteristics and geographic unit of averaging for pollution exposure estimates need to be considered. Most of the U.S. studies used a "semi-individual" study design, in which information on health outcomes and potential confounders are collected and adjusted for on an individual basis, but community-level air pollution exposure estimates are used. It is not clear to what extent exposure error affects these types of studies. Unlike regional air pollutants (e.g., SO_4^{2-}, $PM_{2.5}$) in the eastern United States whose levels are generally uniform within the scale of the metropolitan area, the within-city variation for more locally-impacted pollutants such as NO_2, SO_2, and CO are likely to be larger and, therefore, are more likely to have larger exposure errors in the semi-individual studies. The smaller number of monitors available for NO_2 in the United States may make the relative error worse for NO_2 compared to other pollutants. Exposure error in these long-term studies likely contributes to the inconsistencies observed across studies. For example, the ACS study found no associations with NO_2; however, NO_2 was among the pollutants that showed associations with mortality in the veterans' study, with traffic density showing the strongest association. The geographic resolution of air pollution exposure estimation varied in these studies: the Metropolitan Statistical Area (MSA)-level averaging in the ACS study and county-level averaging in the veterans' study. Traffic density and other pollutants that showed mortality associations in the veterans study, including EC and NO_2, are more localized pollutants; therefore, using county-level aggregation, rather than MSA-level, may have resulted in smaller exposure misclassification.

3.6.2 European Studies on the Long-Term NO_2 Exposure Effects on Mortality

In contrast to the U.S. studies described above, the European studies described below, have more spatially-resolved exposure estimates, because their hypotheses or study aims involved mortality effects of traffic-related air pollution. Only one study from France (Filleul et al., 2005) used a design similar to the Harvard Six Cities study or ACS in that it did not study traffic-related air pollution and the exposure estimate was not done on an individual basis.

Hoek et al. (2002) investigated a random sample of 5,000 subjects from the Netherlands Cohort Study on Diet and Cancer (NLCS) ages 55 to 69 from 1986 to 1994. Long-term exposure to traffic-related air pollutants (black smoke and NO_2) was estimated using 1986 home addresses. Exposure was estimated with the measured regional and urban background

concentration and an indicator variable for living near major roads. Cardiopulmonary mortality was associated with living near a major road (RR = 1.95 [95% CI: 1.09, 3.52]) and less strongly with the estimated air pollution levels (e.g., for NO_2, RR = 1.32 [95% CI: 0.88, 1.98] per 10-ppb increase). The risk estimate for living near a major road was 1.41 (95% CI: 0.94, 2.12) for total mortality. For estimated NO_2 (incorporating both background and local impact), the RR was 1.15 (95% CI: 0.60, 2.23) per 10 ppb). Because the NO_2 exposure estimates were modeled, interpretation of their risk estimates is not straightforward. However, these results do suggest that NO_2, as a marker of traffic-related air pollution, was associated with these mortality outcomes.

Filleul et al. (2005) investigated long-term effects of air pollution on mortality in 14,284 adults who resided in 24 areas from seven French cities when enrolled in the PAARC survey (for air pollution and chronic respiratory diseases) in 1974. Models were run before and after exclusion of six area monitors influenced by local traffic as determined by the NO/NO_2 ratio of >3. Before exclusion of the six areas, none of the air pollutants were associated with mortality outcomes. After exclusion of these areas, analyses showed associations between total mortality and TSP, black smoke, NO_2, and NO. The estimated NO_2 risks were 1.28 (95% CI: 1.07, 1.55), 1.58 (95% CI: 1.07, 2.33), and 2.12 (95% CI: 1.11, 4.03) per 10-ppb increase in NO_2 mean over the study period for total, cardiopulmonary, and lung cancer mortality, respectively. From these results, the authors noted that inclusion of air monitoring data from stations directly influenced by local traffic could overestimate the mean population exposure and bias the results. This point raises a concern for NO_2 exposure estimates used in other studies (e.g., ACS) in which the average of available monitors was used to represent the exposure of each city's entire population.

Nafstad et al. (2004) investigated the association between mortality and long-term air pollution exposure in a cohort of Norwegian 16,209 men followed from 1972/1973 through 1998. PM was not considered in this study because measurement methods changed during the study period. NO_X, rather than NO_2, was used. Exposure estimates for NO_X and SO_2 were constructed using models based on subjects' addresses and emission data for industry, heating, and traffic and measured concentrations. Addresses linked to 50 of the busiest streets were given an additional exposure based on estimates of annual average daily traffic. The adjusted risk estimate for total mortality was 1.16 [95% CI: 1.12, 1.22] for a 10 ppb) increase in the estimated exposure to NO_X. Corresponding mortality risk estimates for respiratory causes other than lung

cancer was 1.16 (95% CI: 1.06, 1.26); for lung cancer, 1.11 (95% CI: 1.03, 1.19); and for ischemic heart diseases, 1.08 (95% CI: 1.03, 1.12). SO_2 did not show similar associations. The risk estimates presented for categorical levels of these pollutants showed mostly monotonic exposure-response relationships for NO_X. These results are suggestive of the effects of traffic-related air pollution on long-term mortality, but NO_X likely represented the combined effects of that source, possibly including PM, which could not be analyzed in this study. A case-control study of 1,043 men aged 40 to 75 with lung cancer and 2,364 controls in Stockholm County (Nyberg et al., 2000) reported similar results to this study. They mapped residence addresses to a GIS database indicating 4,300 traffic-related line sources and 500 point sources of NO_2 exposure. Exposure was derived from a model validated by comparison to actual measurements of NO_2 at six sites. Exposure to NO_2 at 10 ppb was associated with an OR of 1.20 (95% CI: 0.94 1.49). Exposure to the 90th percentile ($\geq$29.26 $\mu g/m^3$) of NO_2 was associated with an OR of 1.44 (95% CI: 1.05, 1.99).

Næss et al. (2007) investigated the concentration-response relationships between air pollution (i.e., NO_2, PM_{10}, $PM_{2.5}$) and cause-specific mortality using all the inhabitants of Oslo, Norway, aged 51 to 90 years on January 1, 1992 (n = 143,842), with follow-up of deaths from 1992 to 1998. An air dispersion model was used to estimate the air pollution levels for 1992 through 1995 in all 470 administrative neighborhoods. Correlations among these pollutants were high (ranged 0.88 to 0.95). All causes of deaths, cardiovascular causes, lung cancer, and COPD were associated with all indicators of air pollution for both sexes and both age groups. The investigators reported that the effects appeared to increase at NO_2 levels higher than 40 $\mu g/m^3$ (21 ppb) in the younger age (51 to 70 years) group and with a linear effect in the interval of 20 to 60 $\mu g/m^3$ (10 to 31 ppb) for the older age group (see Figure 3.6-1). However, they also noted that a similar pattern was found for both $PM_{2.5}$ and PM_{10}. Thus, the apparent threshold effect was not unique to NO_2. NO_2 risk estimates for all-cause mortality were presented only in a figure. The findings are generally consistent with those from Nafstad et al. (2003, 2004) studies, in which a smaller number of male-only subjects were analyzed. While NO_2 effects were suggested, the high correlation among the PM indices and NO_2 or NO_X makes it difficult to ascribe these associations to NO_2/NO_X alone.

Gehring et al. (2006) investigated the relationship between long-term exposure to air pollution originating from traffic and industrial sources and total and cause-specific mortality in

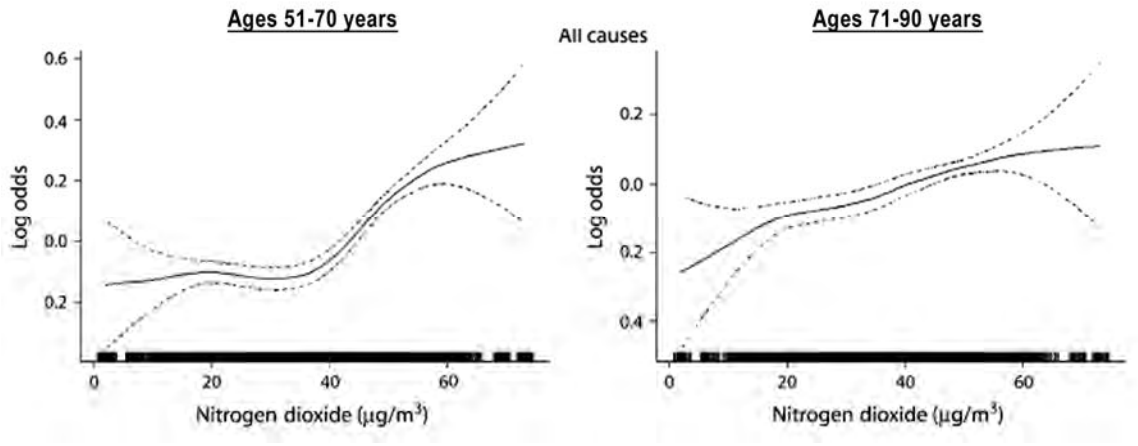

Figure 3.6-1. Age-adjusted, nonparametric smoothed relationship between NO_2 and mortality from all causes in Oslo, Norway, 1992 through 1995.

Source: Næss et al. (2007).

a cohort of women living in North Rhine-Westphalia, Germany. The area includes the Ruhr region, one of Europe's largest industrial areas. Approximately 4,800 women (age 50 to 59 years) were followed for vital status and migration. Exposure to air pollution was estimated by GIS models using the distance to major roads, NO_2, and PM_{10} (estimated from 0.71 $\times$ TSP, based on available PM_{10} and TSP data in the area) concentrations from air monitoring station data. Cardiopulmonary mortality was associated with living within a 50-m radius of a major road (RR = 1.70 [95% CI: 1.02, 2.81]) and NO_2 (RR = 1.72 [95% CI: 1.28, 2.29] per 10-ppb increase in annual average). Exposure to NO_2 was also associated with all-cause mortality (1.21 [95% CI: 1.03, 1.42] per 10 ppb). NO_2 was generally more strongly associated with mortality than the indicator for living near a major road (within versus beyond a 50-m radius) or PM_{10}.

Most of the European cohort studies estimated an individual subject's exposure based on spatial modeling using emission and concentration data. These studies may provide more accurate exposure estimates than the community-level air pollution estimates typically used in the U.S. studies. However, because they generally involve modeling with such information as traffic volume and other emission estimates in addition to monitored concentrations, additional uncertainties may be introduced. Thus, validity and comparability of various methods may need to be examined. In addition, because the relationship between the concentration measured at the community monitors and the health effects is ultimately of interest in this review, interpreting the

risk estimates based on individual-level exposures will require an additional step to translate the difference. Finally, a more accurate exposure estimate does not solve the problem of the surrogate role that NO_2 may play. Most of these studies do acknowledge this issue and generally treat NO_2 as a surrogate marker, but the extent of such surrogacy and confounding with other traffic- or combustion-related pollutant is not clear at this point. In the Hoek et al. study (2002), the indicator of living near a major road was a better predictor of mortality than the estimated NO_2 exposures. In the Gehring et al. (2006) study, the estimated NO_2 exposure was a better predictor of total and cardiopulmonary mortality than the indicator of living near a major road. Comparing the results for the indicators of living near a major road and the estimated NO_2 or NO_X exposures is not straightforward, but it is possible that, depending on the presence of other combustion sources (e.g., the North Rhine-Westphalia area included highly industrial areas), NO_2 may represent more than traffic-related pollution.

3.6.3 Summary of Evidence of the Effect of Long-Term NO_2 Exposure on Mortality

Figure 3.6-2 summarizes the NO_2 relative risk estimates for total mortality from the studies reviewed in the previous sections. The relative risk estimates are grouped by those that used community- or ecologic-level exposure estimates and those that used individual-level exposure estimates, but because of the small number of studies listed, no systematic pattern could be elucidated. The relative risk estimates for total mortality ranged from 0 to 1.28 per 10-ppb increase in annual or longer averages of NO_2.

Potential confounding by copollutants needs to be considered in the interpretation of the NO_2 risk estimates. Not all of the studies presented correlations between NO_2 and other pollutants, but those that did indicated generally moderate to high correlations. For example, in the Harvard Six Cities study (Krewski et al, 2000), the French study (Filleul et al., 2005), and the German study (Gehring et al., 2006), the correlation between NO_2 and PM indices ranged from 0.72 to 0.8. The high correlations between NO_2 and PM suggest possible confounding between these pollutants. Further, the results from the Netherlands study (Hoek et al., 2002), that living near major roads was more strongly associated with mortality than NO_2, supports a possible surrogate role of NO_2 as a marker of traffic-related pollution. However, this does not preclude the possibility of NO_2 playing a role in interactions among the traffic-related pollutants.

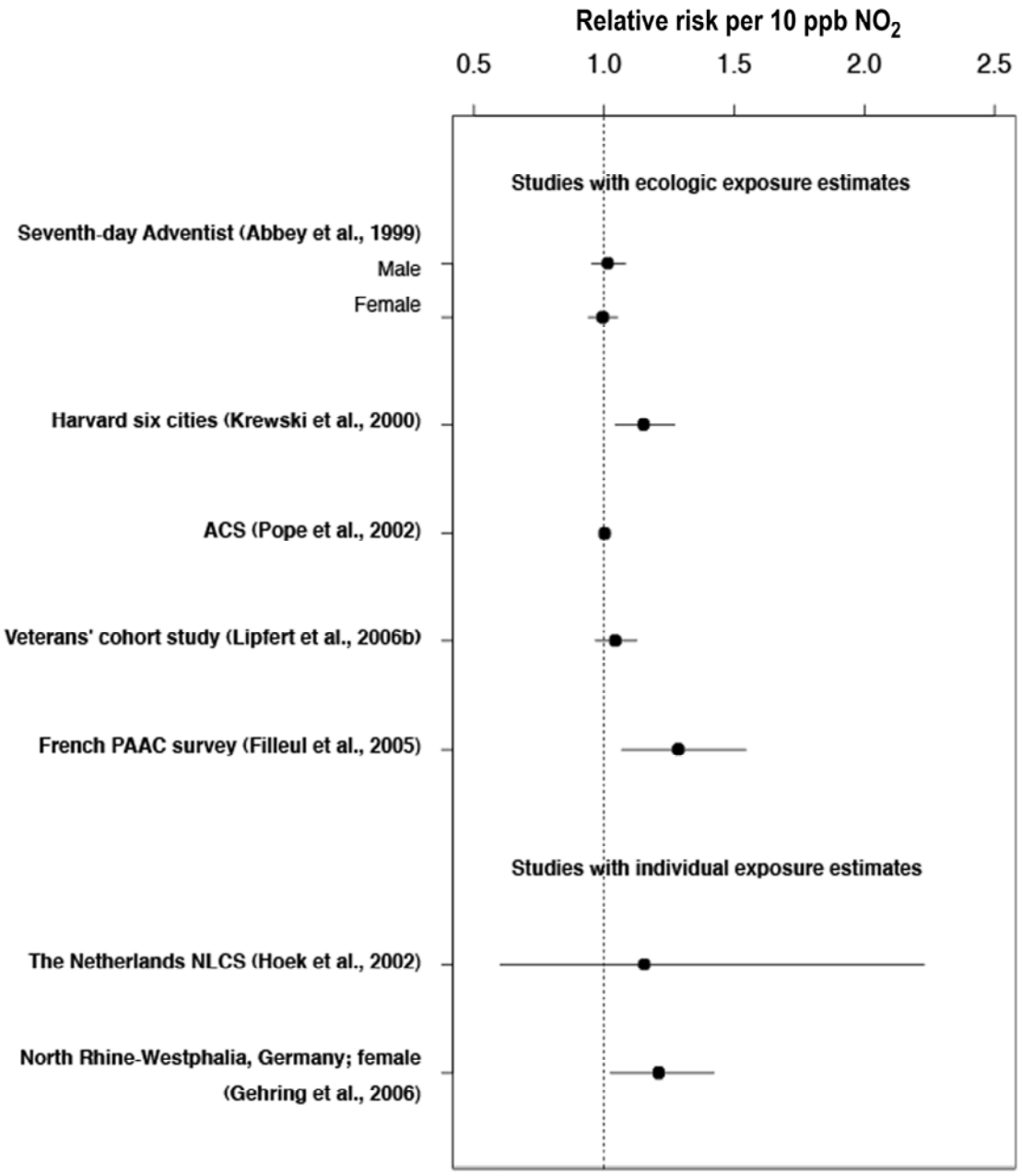

Figure 3.6-2. Total mortality relative risk estimates from long-term studies. The original estimate for the Norwegian study was estimated for NO_X. Conversion of $NO_2 = 0.35 \times NO_X$ was used.

Essentially no information is available on the possible effect modification of apparent NO_2-mortalty associations.

Available information on risk estimates for more specific causes of death with long-term exposure to NO_2 is limited. Among the studies with larger number of subjects, the ACS study (Pope et al., 2002) examined cardiopulmonary and lung cancer deaths, but as with the all-cause deaths, they were not associated with NO_2. In the Næss et al. (2007) analysis of all inhabitants of Oslo, Norway, NO_2 relative risk estimates for COPD were higher than those for other causes, but the same pattern was seen for $PM_{2.5}$ and PM_{10}. In the German study by Gehring et al. (2006), NO_2 relative risk estimates for cardiopulmonary mortality were larger than those for all-cause mortality, but, again, the same pattern was seen for PM_{10}. Thus, higher risk estimates seen for specific causes of deaths were not specific to NO_2 in these studies.

In long-term studies, different geographic scales were used to estimate air pollution exposure estimates across studies. Since the relative strength of association with health outcomes among various air pollutant indices may be affected by the spatial distribution of the pollutants (i.e., regional versus local), the numbers of monitors available, and the scale of aggregation in the study design, it is not clear how these factors affected the apparent difference in results.

In the U.S. and European cohort studies examining the relationship between long-term exposure to NO_2 and mortality, results were generally not consistent. Further, when associations were suggested, they were not specific to NO_2, also implicating PM and other traffic indicators. The relatively high correlations reported between NO_2 and PM indices ($r \sim 0.8$) and the unresolved issue of surrogacy and interactions make it difficult to interpret the observed associations; thus, these data are inadequate to infer the presence or absence of a causal relationship.

4. PUBLIC HEALTH SIGNIFICANCE

This chapter discusses several issues relating to the broader public health significance of exposure to nitrogen oxides (NO_X). Topics discussed are (1) defining adverse health effects, (2) the shape of the concentration-response relationship for nitrogen dioxide (NO_2) and evidence for thresholds, (3) potentially susceptible subpopulations and both intrinsic and extrinsic factors that influence susceptibility, and (4) the size of potentially susceptible population in the United States. Exposure to ambient NO_2 is associated with a variety of outcomes including increases in respiratory symptoms, particularly among asthmatic children, and emergency department (ED) visits and hospital admissions for respiratory diseases among children and older adults (65+ years).

4.1 DEFINING ADVERSE HEALTH EFFECTS

The American Thoracic Society (ATS) published an official statement titled "What Constitutes an Adverse Health Effect of Air Pollution?" (ATS, 2000b). This statement updated the guidance for defining adverse respiratory health effects published 15 years earlier (ATS, 1985), taking into account new investigative approaches used to identify the effects of air pollution and reflecting concern for impacts of air pollution on specific susceptible groups. In the 2000 update, there was an increased focus on quality-of-life measures as indicators of adversity and a more specific consideration of population risk. As shown in Figure 4.1-1, a shift in the population mean may or may not result in clinically significant health consequences for individuals within the population. However, an increased risk to the entire population is viewed as adverse, even though it may not increase the risk of any identifiable individual to an unacceptable level (ATS, 2000b). For example, a population of asthmatics could have a distribution of lung function such that no identifiable single individual has a level associated with significant impairment, and exposure to air pollution could shift the distribution to lower levels that still do not bring any identifiable individual to a level that is associated with clinically relevant effects. This shift to a lower level would be considered adverse because individuals within the population would have diminished reserve function and, therefore, would be at

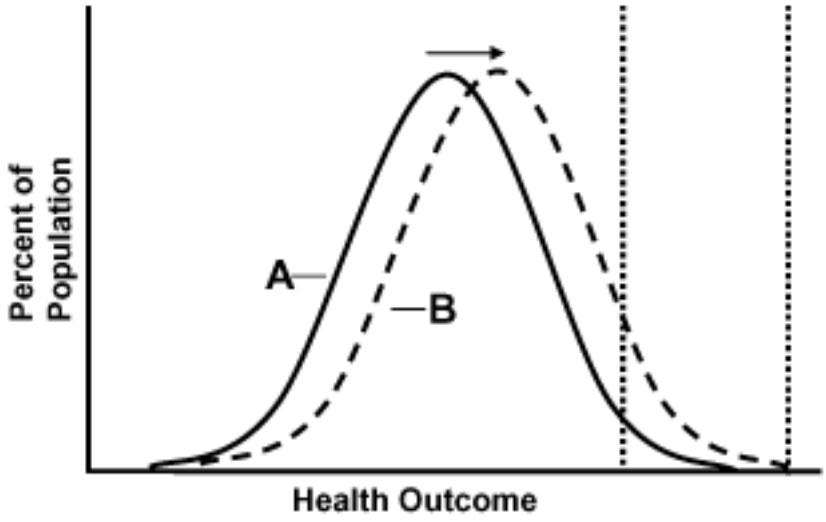

Figure 4.1-1. The frequency distribution of hypothetical health outcome (A) and the consequence of a shift in the population mean on the tails of the distribution (B). The dashed line in this figure denotes the boundary of unacceptable risk. Individuals within the population may or may not cross this boundary if there is a shift in the population mean.

Source: Figure adapted from the American Thoracic Society Statement (ATS, 2000b).

increased risk if affected by another agent or if experiencing diminished reserve function as a result of aging.

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

The 2006 Ozone Air Quality Criteria Document (AQCD) (U.S. Environmental Protection Agency, 2006) also provided information useful in helping to define adverse health effects associated with ambient O_3 exposure by describing the gradation of severity and adversity of respiratory-related O_3 effects. The definitions that relate to responses in impaired persons are reproduced and presented here in Table 4.1-1. The severity of effects described in the table and

TABLE 4.1-1. GRADATION OF INDIVIDUAL RESPONSES TO SHORT-TERM NO_2 EXPOSURE IN PERSONS WITH IMPAIRED RESPIRATORY SYSTEMS

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

An increase in bronchial responsiveness of 100% is equivalent to a 50% decrease in provocative dose that produces a 20% decrease in FEV_1 (PD20) or provocative dose that produces a 100% increase in SRaw (PD100).

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

the approaches taken to define their relative adversity are valid and reasonable in the context of the new ATS (2000b) statement.

As assessed in detail in earlier chapters of this document and briefly recapitulated in preceding sections of this chapter, exposures to a range of NO_2 concentrations have been reported to be associated with increased severity of health effects, such as respiratory symptoms, ED visits and hospital admission for respiratory causes. Respiratory effects associated with short-term NO_2 exposures have been extensively studied and are clearly causally related to NO_2 exposure.

4.2 CONCENTRATION-RESPONSE FUNCTIONS AND POTENTIAL THRESHOLDS

An important consideration in characterizing the public health impacts associated with NO_2 exposure is whether the concentration-response relationship is linear across the full concentration range encountered or if nonlinear departures exist along any part of this range. Of particular interest is the shape of the concentration-response curve at and below the level of the current annual average standard of 53 parts per billion (ppb) (0.053 parts per million [ppm]).

Identifying possible "thresholds" in air pollution epidemiologic studies is challenging. Various factors tend to linearize the concentration-response relationship, obscuring any threshold that may exist. Factors that complicate determining the shape of the concentration-response curve included: interindividual variation in susceptibility and response, additivity of pollutant-induced effects to naturally occurring background disease processes, the extent to which additional health effects are due to other environmental insults having a mode of action similar to NO_2, exposure error, response error, and low data density in the lower concentration range. Additionally, if the concentration-response relationship is shallow, identification of any existing threshold will be more difficult.

The slope of the NO_2 concentration-response relationship has been explored in several studies. To examine the shape of the concentration-response relationship between NO_2 and daily physician consultations for asthma and lower respiratory disease in children, Hajat et al. (1999) used bubble plots to examine residuals of significant models plotted against moving averages of NO_2 concentration. They noted a weak trend for asthma and 0-1 day moving average of NO_2 and suggested that effects are weaker at lower concentrations and stronger at higher concentrations than predicted by the linear model. These departures are in accord with the sigmoidal dose-response models. A number of epidemiologic studies have reported no evidence

for nonlinear relationships or a threshold response in relationships between NO_2 and mortality or morbidity. One multicity time-series study (Samoli et al., 2006) examined the relationship between mortality and NO_2 in 29 European cities. There was no indication of a response threshold, and the concentration-response curves were consistent with a linear relationship. Kim et al. (2004b) investigated the presence of a threshold in relationships between air pollutants and mortality in Seoul, Korea, by analyzing data using a log-linear Generalized Additive Model (GAM; linear model), a cubic natural spline model (nonlinear model), and a B-mode splined model (threshold model). There was no evidence NO_2 had a nonlinear association with mortality. Burnett et al. (1997a) used the locally estimated smoothing splines (LOESS) smoothing curves to describe the concentration-response for respiratory and cardiac hospitalizations. The curves appeared linear, and there was no significant nonlinearity detected by the inclusion of a quadratic in the models (Burnett et al., 1997b).

In general, positive associations were observed between ambient NO_2 concentrations and ED visits and hospitalizations for asthma in various epidemiologic studies conducted in different study locations and during varying time periods. The effect was strongest when subjects of all ages were included in the analyses. Several of these studies demonstrated a concentration-response function. Jaffe et al. (2003) found a positive association between ambient NO_2 and asthma ED visits among Medicaid-enrolled asthmatics in two urban cities in Ohio. When a concentration-response relationship was examined by quintile of NO_2 concentration, risk decreased in the second quintile in both cities and increased monotonically in the third and fourth quintiles in Cleveland, but decreased in the third quintile in Cincinnati. The lack of consistency in results may be due to the uncontrolled effects of copollutants, or other factors. Tenías et al. (1998) reported a positive and significant association between ambient NO_2 and ED visits in Valencia's Hospital Clìnic Universitari from 1994 to 1995. Castellsague et al. (1995) found a small but significant association of NO_2 and ED visits due to asthma in Barcelona. Specifically, the adjusted risk estimates of asthma visits for each quartile of NO_2 showed increased risks in each quartile for the summer months, but not the winter months. Together these four studies indicate some disagreement in the trend of the concentration-response curve from about 30 to 50 ppb 24-h NO_2 and indicate increased risk above 50 ppb.

4.3 POTENTIALLY SUSCEPTIBLE POPULATIONS TO HEALTH EFFECTS RELATED TO SHORT-TERM AND LONG-TERM EXPOSURE TO NO_2

Many factors such as genetic (Kleeberger et al., 2005) and social (Gee and Payne-Sturges, 2006) determinants of disease may contribute to interindividual variability and heightened susceptibility to NO_2 among persons within populations. The previous AQCD for Oxides of Nitrogen (U.S. Environmental Protection Agency, 1993) identified certain groups within the population that may be more susceptible to the effects of NO_2 exposure, including persons with preexisting respiratory disease, children, and older adults. Findings from new studies support the conclusions from the previous assessment with regard to susceptibility.

4.3.1 Preexisting Disease as a Potential Risk Factor

A recent report of the National Research Council (NRC) emphasized the need to evaluate the effect of air pollution on susceptible groups including those with respiratory illnesses and cardiovascular disease (CVD) (NRC, 2004). Generally, chronic obstructive pulmonary disease (COPD), conduction disorders, congestive heart failure (CHF), diabetes, and myocardial infarction (MI) are conditions believed to put persons at greater risk for adverse events associated with air pollution. In addition, epidemiologic evidence indicates persons with bronchial hyperresponsiveness (BHR) as determined by methacholine provocation may be at greater risk for symptoms such as phlegm and lower respiratory symptoms than subjects without BHR (Boezen et al., 1998). Several researchers have investigated the effect of air pollution among potentially sensitive groups with preexisting medical conditions.

Asthmatics

There is evidence from epidemiologic studies for an association between NO_2 exposure and children's hospital admissions, ED visits, and calls to doctors for asthma. This evidence comes from large longitudinal studies, panel studies, and time-series studies. NO_2 exposure is associated with aggravation of asthma effects that include symptoms, medication use, and lung function. Effects of NO_2 on asthma were most evident with a cumulative lag of 2 to 6 days, rather than same-day levels of NO_2. Time-series studies also demonstrated a relationship in children between hospital admissions or ED visits for asthma and NO_2 exposure, even after adjusting for copollutants such as particulate matter (PM) and carbon monoxide (CO). Important

evidence is also available from epidemiologic studies of indoor NO_2 exposures. A number of recent studies show associations with wheeze, chest tightness, and length of symptoms (Belanger et al., 2006); respiratory symptom rates (Nitschke et al., 2006); school absences (Pilotto et al., 1997a); respiratory symptoms, likelihood of chest tightness, and asthma attacks (Smith et al., 2000); and severity of virus-induced asthma (Chauhan et al., 2003). However, several studies (Mukala et al., 1999, 2000; Farrow et al., 1997) evaluating younger children found no association between indoor NO_2 and respiratory symptoms.

Airways hyperresponsiveness in asthmatics to both nonspecific chemical and physical stimuli and to specific allergens appears to be the most sensitive indicator of response to NO_2 (U.S. Environmental Protection Agency, 1993). Responsiveness is determined using a challenge agent, which causes an abnormal degree of constriction of the airways as a result of smooth muscle contraction. This response ranges from mild to severe (spanning orders of magnitude) and is often accompanied by production of sputum, cough, wheezing, shortness of breath, and chest tightness. Though some asthmatics do not have this bronchoconstrictor response (Pattemore et al., 1990), increased airways responsiveness is correlated with asthma symptoms and increased asthma medication usage. Clinical studies have reported increased airways responsiveness to allergen challenge in asthmatics following exposure to 0.26-ppm NO_2 for 30 min during rest (Barck et al., 2002; Strand et al., 1997, 1998).

Toxicological studies provide biological plausibility that asthmatics are likely susceptible to the effects of NO_2 exposure. Numerous animal studies provide evidence that NO_2 can produce inflammation and lung permeability changes. These studies provide evidence for several mechanisms by which NO_2 exposure can induce effects, including reduced mucociliary clearance, and alveolar macrophage function such as depressed phagocytic activity and altered humoral- and cell-mediated immunity. These are all mechanisms that can provide biological plausibility for the NO_2 effects in asthmatic children observed in epidemiologic studies. One limitation of this work is that effects on markers of inflammation, such as bronchoalveolar lavage fluid levels of total protein and lactate dehydrogenase and recruitment or proliferation of leukocytes, occur only at exposure levels of ≥ 5 ppm. Studies conducted at these higher exposure concentrations may elicit mechanisms of action and effects that do not occur at near-ambient levels of NO_2. Chauhan et al. (2003) reviewed potential mechanisms by which NO_2 exacerbates asthma in the presence of viral infections. These mechanisms include “direct effects on the

upper and lower airways by ciliary dyskinesis, epithelial damage, increases in pro-inflammatory mediators and cytokines, rises in IgE concentration, and interactions with allergens, or indirectly through impairment of bronchial immunity."

Cardiopulmonary Disease and Diabetes

While less evidence is available for these conditions, it is possible that preexisting cardiovascular-related conditions may lead to heightened susceptibility to the effects of NO_2 exposure. Some recent epidemiologic studies have reported that persons with preexisting conditions may be at increased risk for adverse cardiac health events associated with ambient NO_2 concentrations (Peel et al., 2006; Mann et al., 2002; D'Ippoliti et al., 2003; von Klot et al., 2005). Peel et al. (2006) reported evidence of effect modification by comorbid hypertension and diabetes on the association between ED visits for arrhythmia and NO_2 exposure. In another study, a statistically significant positive relationship was reported between NO_2 concentrations and hospitalizations for ischemic heart disease (IHD) among those with prior diagnoses of CHF and arrhythmia (Mann et al., 2002). However, Mann et al (2002) notes the vulnerability in the secondary CHF group could be due to increased prevalence of MI as the primary diagnosis in this group. In addition, these authors state they were unable to distinguish the effects of NO_2 from other traffic pollutants (Mann et al., 2002). Von Klot et al. (2005) reported cardiac readmission among MI survivors was associated with NO_2 and this association was robust to adjustment for PM_{10}. Modification of the association between NO_2 and MI by conduction disorders but not diabetes or hypertension was observed by D'Ippoliti et al. (2003). Park et al. (2005b) examined the relationship of NO_2 and heart rate variability (HRV) among those with IHD, hypertension and diabetes but did not find an association.

There is limited evidence from clinical or toxicological studies on potential susceptibility to NO_2 in persons with CVDs; however, the limited epidemiologic evidence suggests that these individuals may be more sensitive to effects of NO_2 exposure or air pollution in general. Reductions in blood hemoglobin (~10%) have been reported in healthy subjects following exposure to NO_2 (1 to 2 ppm) for a few hours during intermittent exercise (Frampton et al., 2002). The clinical significance of hemoglobin reduction in persons with significant underlying lung disease, heart disease, or anemia has not been evaluated, but the reductions could lead to adverse cardiovascular consequences. These consequences would be exacerbated by

concomitant exposure to CO, a combustion copollutant of NO_X that binds to hemoglobin and reduces oxygen availability to tissues and organs.

4.3.2 Age-Related Variations in Susceptibility

Children and older adults (65+ years) are often considered at increased risk from air pollution compared to the general population. The American Academy of Pediatrics (2004) concludes that children and infants are among the most susceptible to many air pollutants, including NO_2. Because 80% of alveoli are formed postnatally and changes in the lung continue through adolescence, the developing lung is highly susceptible to damage from exposure to environmental toxicants (Dietert et al., 2000). In addition to children, older adults frequently are classified as being particularly susceptible to air pollution. The basis of the increased sensitivity in the elderly is not known, but one hypothesis is that it may be related to changes in the respiratory tract lining fluid antioxidant defense network and/or to a decline in immune system surveillance or response (Kelly et al., 2003). The generally declining health status of many older adults may also increase their risks to air pollution-induced effects.

There is evidence that associations of NO_2 with both respiratory ED visits and hospitalizations are stronger among children (Peel et al., 2005; Atkinson et al., 1999b; Fusco et al., 2001; Hinwood et al., 2006; Anderson et al., 1998) and older adults (Migliaretti et al., 2005; Atkinson et al., 1999b; Schouten et al., 1996; Ponce de Leon et al., 1996; Prescott et al., 1998). However, two studies (Sunyer et al., 1997; Migliaretti et al., 2005) found no difference in the rates of ED visits associated with NO_2 concentrations for children (<15 years) and adults (15 to 64 years). Luginaah et al. (2005) and Wong et al. (1999) found no statistically significant difference in the elderly and adult age groups.

Many field studies focused on the effect of NO_2 on the respiratory health of children, while fewer field studies have compared the effect of NO_2 in adults and other age groups. In general, children and adults experienced decrements in lung function associated with short-term ambient NO_2 exposures (see Section 3.1.5). Importantly, a number of long-term exposure studies suggest effects in children that include impaired lung function growth, increased respiratory symptoms and infections, and onset of asthma (see Section 3.4).

In elderly populations, associations between NO_2 and hospitalizations or ED visits for CVD, including stroke, have been observed in several studies (Anderson et al., 2007a; Atkinson

et al., 1999b; Jalaludin et al., 2006; Hinwood et al., 2005; Wong et al., 1999; Barnett et al., 2006; Zanobetti and Schwartz, 2006; Simpson et al., 2005a; Wellenius et al., 2005b; Morgan et al., 1998; Morris et al., 1995). However, some results were inconsistent across cities (Morris et al., 1995), and investigators could not distinguish the effect of NO_2 from the effect of other traffic-related pollutants such as PM and CO (Simpson et al., 2005a; Barnett et al., 2006; Morgan et al., 1998b; Jalaludin et al., 2006; Zanobetti and Schwartz, 2006).

Several mortality studies investigated age-related differences in NO_2 effects. Among the studies that observed positive associations between NO_2 and mortality, a comparison of all-age– or ≤64-years-of-age–group NO_2-mortality risk estimates to that of the ≥65-years-of-age group indicates that, in general, the elderly population is more susceptible to NO_2 effects (Biggeri et al., 2005; Burnett et al., 2004). One study (Simpson et al., 2005a) found no difference in increases in CVD mortality associated with NO_2 concentrations between all ages and those participants of ≥65 years of age.

4.3.3 Gender

A limited number of studies stratified results by gender. Lugninaah et al. (2005) found increases in hospital admissions associated with NO_2 among females but not males. In a study of children in Toronto, Canada, NO_2 was positively associated with asthma admissions among both boys and girls (Lin et al., 2005). However, in a study of asthma admissions among children in Vancouver, NO_2 was significantly and positively associated with asthma hospitalization only for boys in the low socioeconomic group (Lin et al., 2004). An increased association with asthma with exposure to traffic pollutants was observed for girls (Kim et al., 2004a). Decrements in forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) growth associated with NO_2 were reported in male and female children in Mexico (Rojas-Martinez et al., 2007a,b).

4.3.4 Genetic Factors for Oxidant and Inflammatory Damage from Air Pollutants

A consensus now exists among epidemiologists that genetic factors related to health outcomes and ambient pollutant exposures merit serious consideration (Kauffmann et al., 2004; Gilliland et al., 1999). Interindividual variation in human responses to air pollutants suggests that some subpopulations are at increased risk of detrimental effects from pollutant exposure, and it has become clear that genetic background is an important susceptibility factor (Kleeberger,

2005). Several criteria must be satisfied in selecting and establishing useful links between polymorphisms in candidate genes and adverse respiratory effects. First, the product of the candidate gene must be significantly involved in the pathogenesis of the adverse effect of interest, often a complex trait with many determinants. Second, polymorphisms in the gene must produce a functional change in either the protein product or in the level of expression of the protein. Third, in epidemiologic studies, the issue of confounding by other environmental exposures must be carefully considered.

Several glutathione *S*-transferase (GST) families have common, functionally important polymorphic alleles that significantly affect host defense function in the lung (e.g., homozygosity for the null allele at the GSTM1 and GSTT1 loci, homozygosity for the A105G allele at the GSTP1 locus). GST genes are inducible by oxidative stress. Exposure to radicals and oxidants in air pollution induces decreased glutathione (GSH) that increases transcription of GSTs. Individuals with genotypes that result in enzymes with reduced or absent peroxide activity are likely to have reduced oxidant defenses and potentially increased susceptibility to inhaled oxidants and radicals.

Studies of genotype, respiratory health, and air pollution in general have been conducted (Lee et al., 2004; Gilliland et al., 2002; Gauderman et al., 2007). NO_2-related genetic effects have been presented primarily by Romieu et al. (2006) and indicate that asthmatic children with GSTM1 null and GSTP1 Val/Val genotypes appear to be more susceptible to developing respiratory symptoms related to O_3, but not NO_2, concentrations. It was suggested that ambient NO_2 concentrations may affect breathing in children regardless of their GSTM1 or GSTP1 genotypes. GSTM1-positive and GSTP1 Ile/Ile- and Ile/Val-genotype children were more likely to experience cough and bronchodilator use in response to NO_2 than GSTM1-null and GSTP1-Val/Val children. Contrary to expectations, a 20-ppb increase in ambient NO_2 concentrations was associated with a decrease in bronchodilator use among GSTP1 Val/Val-genotype children. It remains plausible that there are genetic factors that can influence health responses to NO_2, though the few available studies do not provide specific support for genetic susceptibility to NO_2 exposure.

4.3.5 Populations with Potentially High Exposure

Certain groups may experience relatively high exposure to NO_2, thus forming a potentially vulnerable or susceptible population. Many studies find that indoor, personal, and outdoor NO_2 levels are strongly associated with proximity to traffic or traffic density (see Section 2.5.4). NO_2 concentrations in heavy traffic or on freeways, which have been observed in the range of 40 to 70 ppb, can be more than twice the residential outdoor or residential/arterial road level (Lee et al., 2000; Westerdahl et al., 2005). Due to high air exchange rates, NO_2 concentrations inside a vehicle could rapidly approach levels outside the vehicle during commuting; the mean in-vehicle NO_2 concentration has been observed to be between 2 to 3 times ambient levels (see Section 2.5.4). Those with occupations that require them to be in or close to traffic or roadways (e.g., bus and taxi drivers, highway patrol officers, toll collectors) or those with long commutes could be exposed to relatively high levels of NO_2 compared to ambient levels.

4.3.6 Socioeconomic Position

Social-economic position (SEP) is a known determinant of health, and there is evidence that SEP modifies the effects of air pollution (O'Neill et al. 2003; Makri and Stilianakis, 2008). Higher exposures to air pollution and greater susceptibility to its effects may contribute to a complex pattern of risk among those with lower SEP. Conceptual frameworks have been proposed to explain the relationship between SEP, susceptibility, and exposure to air pollution. Common to these frameworks is the consideration of the broader social context in which persons live, and its effect on health in general (O'Neill et al., 2003; Gee and Payne-Sturges, 2004), as well as on maternal and child health (Morello-Frosch and Shenassa, 2006) and asthma (Wright and Subramanian, 2007) specifically. Multilevel modeling approaches that allow parameterization of community-level stressors such as increased life stress as well as individual risk factors are considered by these authors. In addition, statistical methods that allow for temporal and spatial variability in exposure and susceptibility have been discussed in the recent literature (Jerrett and Finkelstein, 2005; Künzli et al., 2005).

Most studies to date have examined modification by SEP indicators on the association between mortality and PM (O'Neill et al., 2003; Martins et al., 2004; Jerrett et al., 2004; Finkelstein et al., 2003; Romieu et al., 2004a) or other indices such as traffic density, distance to

roadway or a general air pollution index (Ponce et al., 2003; Woodruff et al., 2003; Finkelstein et al., 2004). However, modification of NO_2 associations has been examined in a few studies. For example, in a study conducted in Seoul, Korea, community-level SEP indicators modified the association of air pollution with ED visits for asthma: of the five criteria air pollutants evaluated, NO_2 showed the strongest association in lower SEP districts compared to high SEP districts (Kim et al., 2007.) In addition, Clougherty et al. (2007) evaluated exposure to violence (a chronic stressor) as a modifier of the effect of traffic-related air pollutants, including NO_2, on childhood asthma. The authors reported an elevated risk of asthma with a 4.3-ppb increase in NO_2 exposure solely among children with above-median exposure to violence in their neighborhoods.

4.4 ESTIMATION OF POTENTIAL NUMBERS OF PERSONS IN AT-RISK SUSCEPTIBLE POPULATION GROUPS IN THE UNITED STATES

Although NO_2-related health risk estimates may appear to be small, they may well be biologically significant from an overall public health perspective owing to the large numbers of persons in the potential risk groups. Several population groups have been identified as possibly having increased susceptibility or vulnerability to adverse health effects from NO_2, including children, older adults, and persons with preexisting pulmonary diseases. One consideration in the assessment of potential public health impacts is the size of various population groups that may be at increased risk for health effects associated with NO_2-related air pollution exposure. Table 4.4.1 summarizes information on the prevalence of chronic respiratory conditions in the U.S. population in 2004 and 2005 (National Center for Health Statistics, 2006a,b). Individuals with preexisting cardiopulmonary disease constitute a fairly large proportion of the population, with tens of millions of persons included in each disease category. Of most concern are those persons with preexisting respiratory conditions, with approximately 10% of adults and 13% of children having been diagnosed with asthma and 6% of adults with COPD (chronic bronchitis and/or emphysema).

There are approximately 2.5 million deaths from all causes per year in the U.S. population, with about 100,000 deaths from chronic lower respiratory diseases (Kochanek et al., 2004) and 4,000 from asthma (NCHS, 2006c). For respiratory health diseases, there are

TABLE 4.4-1. PREVALENCE OF SELECTED RESPIRATORY DISORDERS BY AGE GROUP AND BY GEOGRAPHIC REGION IN THE UNITED STATES (2004 [U.S. ADULTS] AND 2005 [U.S. CHILDREN] NATIONAL HEALTH INTERVIEW SURVEY)

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

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

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

nearly 4 million hospital discharges per year (DeFrances et al., 2005), 14 million ED visits (McCaig and Burt, 2005), 112 million ambulatory care visits (Woodwell and Cherry, 2004), and an estimated 700 million restricted-activity days per year due to respiratory conditions (Adams et al., 1999). Of the total number of visits for respiratory disease, 1.8 million annual ED visits are reported for asthma, including more than 750,000 visits by children. In addition, nearly 500,000 annual hospitalizations for asthma are reported (NCHS, 2006c).

Centers for Disease Control and Prevention (CDC) analyses have shown that the burden of asthma has increased over the past two decades (NCHS, 2006c). In 2005, approximately 22.2 million (7.7% of the population) currently had asthma. The incidence was higher among children (8.9% of children) compared to adults (7.2%) (Note: 2004 data is shown in Table 4.4-1, with a prevalence of 6.7%). In addition, prevalence and severity is higher among certain ethnic or racial groups such as Puerto Ricans, American Indians, Alaskan Natives, and African Americans. The asthma hospitalization rate for black persons was 240% higher than for white persons. Puerto Ricans were reported to have the highest asthma death rate (360% higher than non-Hispanic white persons) and non-Hispanic black persons had an asthma death rate that was 200% higher than non-Hispanic white persons. Furthermore, a higher prevalence of asthma among persons of lower SEP and an excess burden of asthma hospitalizations and mortality in minority and inner-city communities have been observed in several studies (Wright and Subramanian, 2007). Gender and age are also determinants of prevalence and severity: adult females had a 40% higher prevalence than adult males; and boys, a 30% higher prevalence than girls. Overall, females had a hospitalization rate about 35% higher than males.

In addition, population groups based on age group also comprise substantial segments of the population that may be potentially at risk for NO_2-related health impacts. Based on U.S. census data from 2000, about 72.3 million (26%) of the U.S. population are under 18 years of age, 18.3 million (7.4%) are under 5 years of age, and 35 million (12%) are 65 years of age or older. Hence, large proportions of the U.S. population are in age groups that are likely to have increased susceptibility and vulnerability for health effects from ambient NO_2 exposure.

Based on data from the American Housing Survey, approximately 36 million persons live within 300 feet (~90 meters) of a four-lane highway, railroad, or airport and 12.6% of U.S. housing units are located within this distance (U.S. Census Bureau, 2006). Furthermore, several exposure studies offer insight into differential exposures to NO_2 from traffic in childhood. In

California, 2.3% of schools, grades K–12, with a total enrollment of more than 150,000 students were located within ~500 feet (150 m) of high-traffic roads, and a higher proportion of nonwhite and economically disadvantaged students attended schools within close proximity to these high-traffic roadways (Green et al., 2004). Similar findings were reported for Detroit schoolchildren (Wu and Batterman, 2006). Figure 4.4-1 shows the proportion of the population living within a certain distance from major roadways as measured by field studies, the U.S. Census, and population exposure models. It also presents results of air quality measurements showing the decrease in concentration of black carbon, a traffic-related pollutant, with increasing distance from the roadway. The considerable size of the population groups at risk indicate that exposure to ambient NO_2 could have a significant impact on public health in the United States.

4.5 SUMMARY

Both general and specific definitions of adversity are discussed. These general and specific definitions of adversity are multifaceted, involving clinically observable effects, effects on quality of life, loss of reserve capacity, and population distributions of effects.

In the limited studies that have specifically examined concentration-response relationships between NO_2 and health outcomes, there is little evidence of an effect threshold. However, various factors, such as interindividual variation in response, additivity to background of effect and/or exposure, and measurement error, tend to linearize the dose-response relationship and obscure any population-level thresholds that might exist.

Persons with preexisting respiratory disease, children, and older adults may be more susceptible to the effects of NO_2 exposure. Individuals in sensitive groups may be affected by lower levels of NO_2 than the general population or experience a greater impact with the same level of exposure. A number of factors may increase susceptibility to the effects of NO_2. Studies generally report a positive excess risk for asthmatics, and there is emerging evidence that cardiovascular disease (CVD) may cause persons to be more susceptible, though it is difficult to distinguish the effect of NO_2 from other traffic pollutants. Children and older adults (65+ years) may be more susceptible than adults, possibly due to physiological changes occurring among these age groups. Evidence, albeit inconsistent, exists for a gender-age–based difference in susceptibility, with the incidence of asthma differing for boys and girls at different ages (higher for boys at younger ages, higher for girls at older ages).

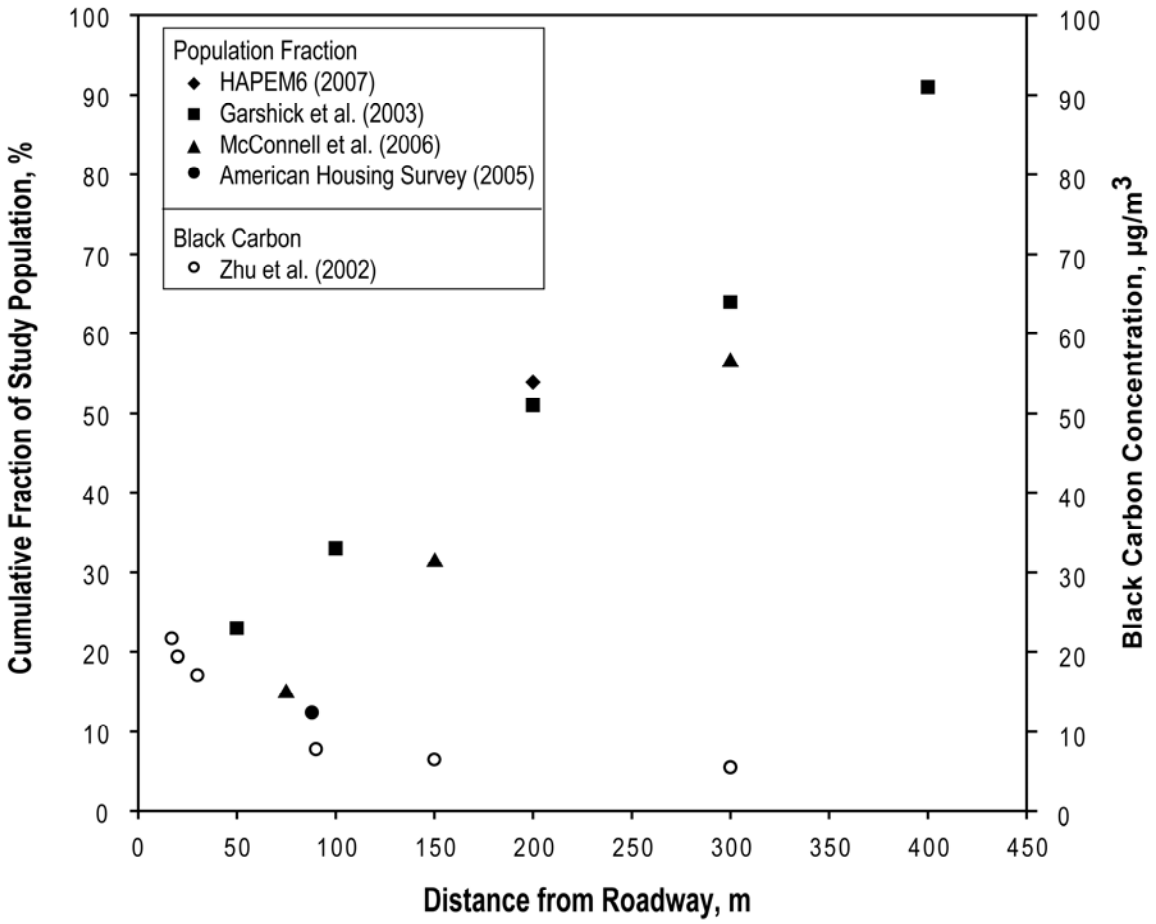

Figure 4.4-1. Fraction of the population living within a specified distance from roadways. For comparison, concentrations of the traffic copollutant black carbon are plotted as a function of distance from the roadway.

Although increases in risk associated with NO_2 exposure may be small in magnitude, the population potentially affected by NO_2 is large. A considerable fraction of the population resides, works, or attends school near major roadways, and these persons are likely to have increased exposure to NO_2. Of this population, those with physiological susceptibility will have even greater risks of health effects related to NO_2. New studies of genetic determinants of NO_2-related health effects as well as community-level stressors that influence susceptibility may inform future assessment of the health effects of NO_2, but current evidence is limited as few studies have been conducted. Furthermore, there may be interactions between factors that influence susceptibility.

5. INTEGRATIVE SUMMARY AND CONCLUSIONS

5.1 INTRODUCTION

The previous chapters present the most policy relevant science pertaining to this National Ambient Air Quality Standards (NAAQS) review. This chapter first summarizes and then draws conclusions about atmospheric sciences, exposure assessment, nitrogen dioxide (NO_2) exposure indices, and health effects associated with exposure to oxides of nitrogen (NO_X). These conclusions have been derived based on explicit guidelines (Section 1.3) derived from the Hill criteria (Hill, 1965) and modeled on other pertinent frameworks.

As discussed in the *Integrated Plan for the Primary National Ambient Air Quality Standard for Nitrogen Dioxide* (U.S. Environmental Protection Agency, 2007), a series of policy relevant questions was devised to frame this assessment of the scientific evidence, which will form the scientific basis for a decision on whether the current primary NAAQS for NO_2 (0.053 parts per million [ppm], annual average) should be retained or revised. This draft Integrated Science Assessment (ISA) focuses on evaluating the newly available scientific evidence to best inform consideration of these framing questions:

- Has new information altered the scientific support for the occurrence of health effects following short- and/or long-term exposure to levels of nitrogen oxides found in the ambient air?
- What do recent studies focused on the near-roadway environment tell us about health effects of nitrogen oxides?
- At what levels of nitrogen oxides exposure do health effects of concern occur?
- Has new information altered conclusions from previous reviews regarding the plausibility of adverse health effects caused by exposure to nitrogen oxides?
- To what extent have important uncertainties identified in the last review been reduced and/or have new uncertainties emerged?
- What are the air quality relationships between short- and long-term exposures to nitrogen oxides?

The evidence relative to causality is summarized and integrated across disciplines and conclusions about the health effects of NO_2 exposure are presented. The framework for the

evaluation of evidence regarding causality is described in Chapter 1. The framework and language draws from similar efforts across the Federal government and wider scientific community, especially from the recent National Academy of Sciences (NAS) Institute of Medicine (IOM) document *Improving the Presumptive Disability Decision-Making Process for Veterans* (IOM, 2007). A five-level hierarchy is used here to be consistent with the *Guidelines for Carcinogen Risk Assessment* (U.S. Environmental Protection Agency, 2005). Conclusions concerning causality of association will be placed into one of five categories with regard to weight of the evidence based on the Hill criteria (Hill, 1965). The five descriptors follow:

- Sufficient to infer a causal relationship,
- Sufficient to infer a likely causal relationship (i.e. more likely than not),
- Suggestive but not sufficient to infer a causal relationship,
- Inadequate to infer the presence or absence of a causal relationship, and
- Suggestive of no causal relationship.

This integrative discussion begins with some key conclusions from the atmospheric sciences that are relevant to the interpretation of the health evidence and important underpinnings for potential quantitative assessments, including information about ambient concentrations and monitoring, and estimation of policy relevant background. Consideration of exposure error and related issues is an essential component of this review, and Section 5.2.2 provides an overview of the findings that have informed our evaluation of the health evidence. Conclusions regarding causality for different categories of health outcomes, using the framework described previously, are presented along with highlights of the findings for more specific health outcomes.

5.2 KEY FINDINGS RELATED TO THE SOURCE-TO-DOSE RELATIONSHIP

5.2.1 Atmospheric Science and Ambient Concentrations

An understanding of atmospheric processes affecting a given pollutant is crucial for understanding the causal chain linking its sources to health effects. NO_2 plays a key role in the formation of ozone (O_3) and photochemical smog. NO_2 is an oxidant and can react to form other photochemical oxidants, including organic nitrates like the peroxyacyl nitrates (PANs) and

inorganic acids like nitric acid (HNO_3). NO_2 also reacts with toxic compounds such as polycyclic aromatic hydrocarbons (PAHs) to form nitro-PAHs, some of which are more toxic than either reactant alone.

As noted in Chapter 2, nitric oxide (NO) and NO_2 interconvert rapidly in the atmosphere, and so it is often convenient to refer to their sum (NO_X) instead of to them individually. The category definition of nitrogen oxides contains a number of nitrogen (N)-containing compounds formed by the oxidation of NO_2 as described in Chapter 2.

- Major anthropogenic sources of NO_X include motor vehicles, power plants, and fossil fuel combustion in general. NO_X is also emitted by burning biomass fuels.
- Natural NO_X sources include wildfires, microbial activity in soils, and lightning.
- NO_X is emitted by all of the above sources mainly as NO. Atmospheric reactions oxidize NO to NO_2. Thus, most NO_2 in the atmosphere is the result of the oxidation of primary NO.
- The current method of determining ambient NO_X and then reporting NO_2 concentrations by subtraction of NO is subject to interference by NO_X oxidation products, chiefly HNO_3, as well as peroxyacetyl nitrate (PAN) and other oxidized N-containing compounds. Limited available evidence suggests that these compounds and other reaction products result in an overestimation of NO_2 levels of as much as 25% at typical ambient levels (~15 ppb) during summer and in smaller overestimations during winter.
- Measurements of these oxidation products in urban areas are sparse. Relationships between these products and NO_2 are complex and difficult to predict. However, products are expected to peak in the afternoon because of the continued oxidation of NO_2 emitted during the morning rush hours.
- Within the urban core of metropolitan areas, where many of the ambient monitors are sited close to strong NO_X sources such as motor vehicles on busy streets and highways, the positive artifacts are much smaller on a relative basis. Conversely, the positive artifacts are larger in locations more distant from local NO_X sources. Therefore, variable, positive artifacts associated with measuring NO_2 using the Federal Reference Method (FRM) severely limit its ability to serve as a precise

indicator of NO_2 concentrations at the typical ambient levels generally encountered outside of urban cores.

- Because its dominant urban source is typically on-road vehicle emissions, ambient NO_2 generally behaves with the temporal and spatial variability of other traffic-generated pollutants in urban areas.
- Nitro-PAHs and other potentially toxic compounds are emitted directly from the exhaust of on- and off-road vehicles and engines. In addition, nitro-PAHs also are formed as products of atmospheric reactions of NO_2.
- The annual average concentrations of NO_2 of ~15 parts per billion (ppb) reported by the regulatory monitoring networks are well below the level of the current NAAQS (53 ppb). However, daily maximum 1-h average concentrations can be greater than 100 ppb in some locations, e.g., areas with heavy traffic.
- Policy Relevant Background concentrations of NO_2 are much lower than average ambient concentrations and are typically less than 0.1 ppb over most of the United States, with highest values found in agricultural areas.

5.2.2 Exposure Assessment

In addition to ambient NO_2, people are also exposed to NO_2 produced by indoor sources (such as gas stoves) and by other microenvironmental sources (such as vehicle exhaust while commuting) and to the oxidation products of NO_2 either indoors or outdoors. Indoor and outdoor microenvironmental sources of NO_X, are often of greater importance in determining a person's total exposure than the largest sources in the national emissions inventories. The amount of time a person spends in different microenvironments and the infiltration characteristics (as a function of the NO_2 penetration coefficient (P), air exchange rate (a), and the NO_2 decay rate (k) of these microenvironments are strong determinants of a person's total exposure to NO_2 and of the association between ambient NO_2 concentrations and personal exposures to ambient NO_2. Key findings related to assessing NO_2 exposures are listed below.

- NO_2 concentrations are highly spatially and temporally variable in urban areas. Intersite correlations for NO_2 concentrations range from slightly negative to highly positive in examined cities. The range of spatial variation in NO_2 concentrations is similar to that for O_3, but larger than that of fine particulate matter ($PM_{2.5}$). Twenty-

four-hour concentration differences between individual paired sites in a metropolitan statistical area (MSA) can be larger than the annual means at these sites.

- This variability can lead to exposure error in epidemiologic studies conducted in areas for which NO_2 concentrations are not well correlated between ambient monitoring sites and the community average, or in areas with differences in levels between ambient monitoring sites and the community average.
- Rooftop NO_2 measurements, particularly in inner cities, likely underestimate levels occurring at lower elevations, closer to motor vehicle emissions.
- Co-located samples show that passive NO_2 samplers generally correlate well with FRM ambient samplers, and the concentration differences are generally within 10%. However, personal passive samplers and the ambient samplers are both subject to measurement artifacts.
- In the absence of indoor sources, indoor NO_2 levels are about one-half those found outdoors. In the presence of indoor sources, particularly unvented combustion sources, NO_2 levels can be much higher than reported ambient concentrations.
- Alpha (α), the ratio of personal exposure to NO_2 of ambient origin to the ambient NO_2 concentration, ranged from ~0.3 to ~0.6 in studies where it was determined.
- Indoor exposures to NO_2 are accompanied by exposures to other products of indoor combustion and to products of indoor NO_2 chemistry, such as nitrous acid (HONO).
- The evidence relating ambient levels to personal exposures is inconsistent. Some of the longitudinal studies examined found that ambient levels of NO_2 were reliable proxies of personal exposures to NO_2. However, a number of studies did not find significant associations between ambient and personal levels of NO_2. The differences in results are related in large measure to differences in study design and in exposure determinants. Measurement artifacts and differences in analytical measurement capabilities could also have contributed to the inconsistent results. Indeed, in a number of the studies examined, the majority of measurements of personal NO_2 concentrations were beneath detection limits, and in all studies some personal measurements were beneath detection limits.
- The collective variability in all of the above parameters, in general, contributes to exposure measurement errors in air pollution-health outcome studies.

- In two European studies, community averages of personal total exposures were highly correlated with either ambient or outdoor concentrations. However, because of limitations in these studies, caution should be exercised in using these results to determine whether ambient concentrations of NO_2 can be used as surrogates for community average exposures in epidemiologic studies.

Two points about ambient and personal exposures are crucial for interpreting the epidemiologic findings reported in this ISA. First, ambient NO_2 contributes significantly to total personal NO_2 exposure, with the ratio of personal NO_2 exposure of ambient origin to ambient NO_2 concentrations, or α, ranging from 0.3 to 0.6. Second, the observational evidence relating ambient NO_2 concentrations to community-average exposures is very limited. For example, although two studies found strong associations between ambient or outdoor [NO_2] and community-average personal exposures, the utility and universality of these results is compromised by the designs of these studies. Moreover, treating ambient [NO_2] as a surrogate for personal NO_2 exposures is additionally complicated by factors such as ambient [NO_2] spatial variability, errors in ambient [NO_2] measurements, and variance in exposure factors within a population. The first two of these additional complications are described above in Chapter 2 and the third in Chapter 3.

5.3 KEY HEALTH EFFECTS FINDINGS

5.3.1 Findings from the Previous Review of the National Ambient Air Quality Standard for Nitrogen Oxides

The 1993 *Air Quality Criteria for Nitrogen Oxides* (AQCD for Nitrogen Oxides) concluded that there were two key health effects of greatest concern at ambient or near-ambient concentrations of NO_2:

- Increases in airways responsiveness of asthmatic individuals after short-term exposures.
- Increased occurrence of respiratory illness among children associated with longer-term exposures to NO_2.

Evidence also was found for increased risk of emphysema, but this appeared to be of major concern only with exposures to levels of NO_2 that were much higher than current ambient

levels of NO_2 (U.S. Environmental Protection Agency, 1993). Qualitative evidence regarding airways responsiveness and lung function changes was drawn from controlled human exposure and animal toxicological studies; studies did not elucidate a concentration-response relationship. Epidemiologic studies reported increased respiratory symptoms with increased indoor NO_2 exposures. Animal toxicological findings of lung host defense system changes with NO_2 exposure provided a biologically plausible basis for these results. Subpopulations considered potentially more susceptible to the effects of NO_2 exposure included persons with preexisting respiratory disease, children, and the elderly. In the 1993 AQCD, the epidemiologic evidence for respiratory health effects was limited, and no studies had considered effects such as hospital admissions, emergency department (ED) visits, or mortality.

5.3.2 New Findings on the Health Effects of Exposure to Nitrogen Oxides

New evidence developed since 1993 generally has confirmed and extended the conclusions articulated in the 1993 AQCD. Since the 1993 AQCD, the epidemiologic evidence has grown substantially, including new field or panel studies on respiratory health outcomes, numerous time-series epidemiologic studies of effects such as hospital admissions, and a substantial number of studies evaluating mortality risk with short-term NO_2 exposures. As noted above, no epidemiologic studies were available in 1993 that assessed relationships between nitrogen oxides and outcomes such as hospital admissions, ED visits, or mortality; in contrast, dozens of epidemiologic studies on such outcomes are now included in this evaluation. Several new studies have reported findings from prospective cohort studies on respiratory health effects with long-term NO_2 exposure. In addition, significant new evidence characterizing the responses of susceptible and vulnerable populations has developed since 1993, particularly concerning children, asthmatics, and those living or working near roadways. While not as marked as the growth in the epidemiologic literature, a number of new toxicological and controlled human exposure studies provide further insights into relationships between NO_2 exposure and health effects. The conclusions and findings of this evaluation are summarized in Table 5.3-1. Table 5.3-1 also summarizes the conclusions drawn in the previous NAAQS review along with those from this draft ISA, and the contrast in available evidence discussed above is clearly illustrated in this table. The marked increase in evidence from epidemiologic studies, along with additional new evidence from human and animal experimental studies, has greatly increased the support for

associations between short-term NO_2 exposures and respiratory effects compared with evidence available in the previous review and has provided some suggestive evidence for other effects, as highlighted below.

5.3.2.1 Short-Term Exposure to NO_2 and Respiratory Health Effects

Taken together, recent studies provide scientific evidence that NO_2 is associated with a range of respiratory effects and are *sufficient to infer a likely causal relationship* between short-term NO_2 exposure and adverse effects on the respiratory system. This finding is supported by the large body of new epidemiologic evidence, in combination with findings from human and animal experimental studies. The epidemiologic evidence for respiratory effects can be characterized as consistent, in that associations are reported in studies conducted in numerous locations with a variety of methodological approaches. Considering this large body of epidemiologic studies alone, the findings are coherent in the sense that the studies report associations with respiratory health outcomes that are logically linked together. The consistency and coherence of findings for respiratory effects is illustrated in Figure 5.3-1; this figure combines effect estimates for respiratory symptoms, hospitalizations or ED visits, and respiratory mortality, drawn from figures presented in Chapter 3. Here it can be seen that there are generally positive associations between NO_2 and respiratory symptoms and hospitalization or ED visits, with a number being statistically significant, particularly the more precise effect estimates. There is also a pattern of positive associations with respiratory mortality, though most are not statistically significant. A number of the epidemiologic studies have been conducted in locations where the ambient NO_2 levels are well below the level of the current NAAQS; some descriptive statistics for the NO_2 concentrations used in those studies are included in Appendix Tables 5A and 5B.

These health effects associations have been observed in epidemiologic studies reporting maximum ambient concentrations of as high as 100 to 300 ppb, concentrations within the range of the controlled animal and human exposures used in current toxicological and clinical studies reporting respiratory effects. Tables 5.3-2 and 5.3-3 summarize the health endpoints that have been linked with NO_2 exposure in human clinical and animal toxicological studies, respectively, along with the lower range of doses or concentrations with which these effects have been reported. To put the concentration and dose information in perspective, maximum ambient concentrations from earlier years in the United States and elsewhere were substantially greater

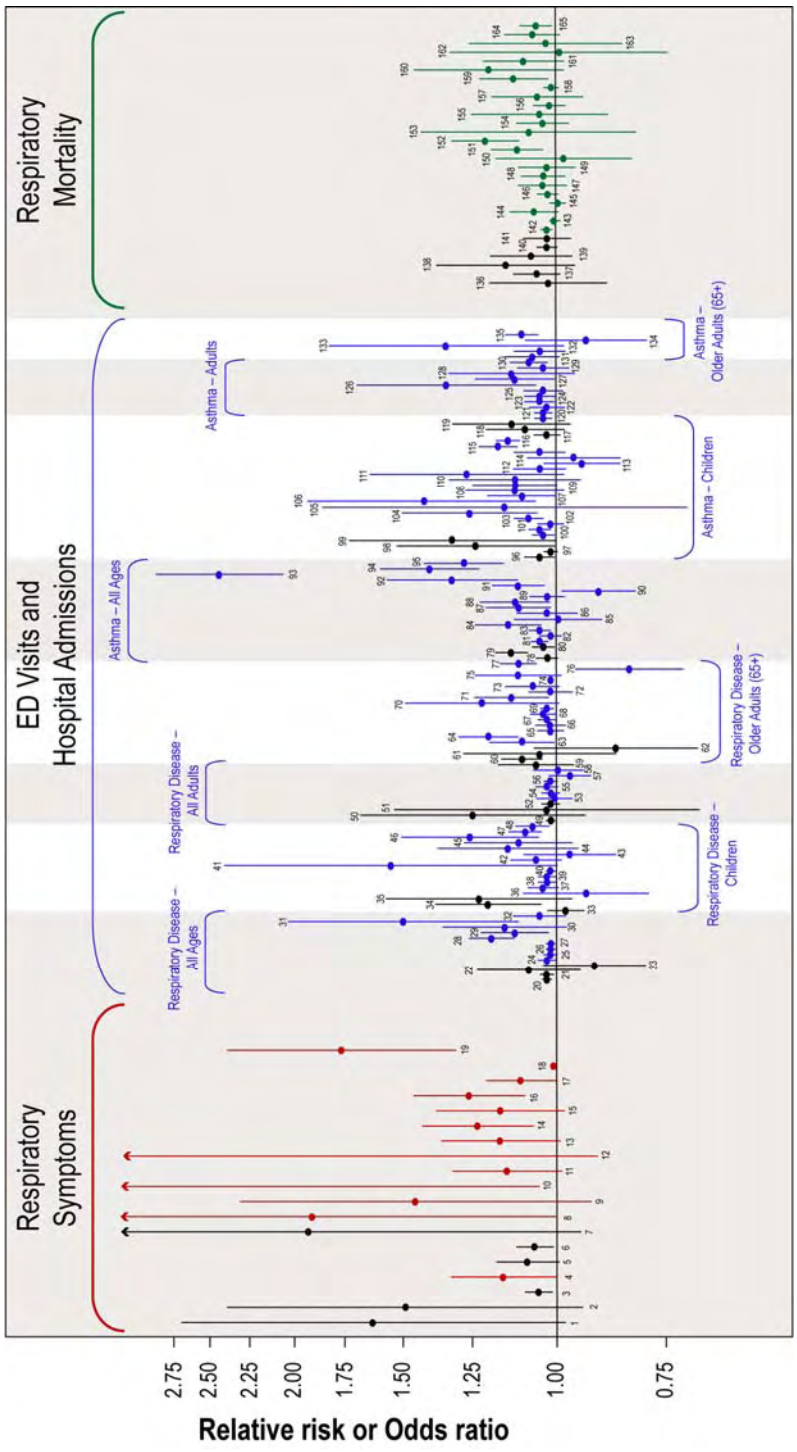

Figure 5.3-1. Summary of Epidemiologic Studies Examining Short-Term Exposures to Ambient NO_2 and Respiratory Outcomes. Circles represent effect estimates and lines indicate the 95% confidence intervals. Effect estimates for studies conducted in the United States or Canada are presented in black. ED=emergency department visit. References are listed by study number in Table 5.3-4.

TABLE 5.3-2. KEY HUMAN HEALTH EFFECTS OF EXPOSURE TO NITROGEN DIOXIDE—CLINICAL STUDIES[a]

NO_2 (ppm)	Exposure Duration	Observed Effects	References
0.26	0.5 h	Asthmatics exposed to NO_2 during rest experienced enhanced sensitivity to challenge-induced decrements in lung function and increased allergen-induced airways inflammatory response. Inflammatory response to allergen observed in the absence of allergen-induced lung function response. No NO_2-induced change in lung function.	Barck et al. (2002, 2005a) Strand et al. (1996,1997, 1998)
0.1-0.3	0.5-2.0 h	Meta-analysis showed increased airways responsiveness following NO_2 exposure in asthmatics. Large variability in protocols and responses. Most studies used nonspecific airways challenges. Airways responsiveness tended to be greater for resting (mean 45 min) than exercising (mean 102 min) exposure conditions.	Folinsbee (1992)
0.3-0.4	2-4 h	Inconsistent effects on FVC and FEV_1 in COPD patients with mild exercise.	Gong et al. (2005) Morrow et al. (1992) Vagaggini et al. (1996)
1.0-2.0	2-6 h	Increased inflammatory response and airways responsiveness to nonspecific challenge in healthy adults exposed during intermittent exercise. Effects on lung function and symptoms in healthy subjects not detected by most investigators. Small decrements in FEV_1 reported for asthmatics.	Azadniv et al. (1998) Blomberg et al. (1997, 1999) Devlin et al. (1999) Frampton et al. (2002) Jörres et al. (1995)
≥2.00	1-3 h	Lung function changes (e.g., increased airways resistance) in healthy subjects. Effects not found by others at 2-4 ppm.	Beil and Ulmer (1976) Nieding et al. (1979) Nieding and Wagner (1977) Nieding et al. (1980)

[a]NO_2 = Nitrogen dioxide.
FEV_1 = Functional expiratory volume in 1 s.
FVC = Forced vital capacity.
COPD = Chronic obstructive pulmonary disease.

TABLE 5.3-3. SUMMARY OF TOXICOLOGICAL EFFECTS FROM NO_2 EXPOSURE (LOWEST-OBSERVED-EFFECT LEVEL BASED ON CATEGORY)

Concentration (ppm)	Exposure Duration	Species	Effect	Category	Reference
0.2	From conception to 12 wks post delivery	Rats	Increase in BALF lymphocytes	Inflammation	Kumae and Arakawa (2006)
0.5	Weanling period (from 5 wks old to 12 wks)	Rats	Suppression of ROS	Lung host defense	Kumae and Arakawa (2006)
0.5	0.5-10 days	Rats	Depressed activation of arachidonic acid metabolism and superoxide production	Lung host defense	Robison et al. (1993)
0.5 with spikes of 1.5	9 wks	Rats	Increase in the number of fenestrae in the lungs	Morphological effects	Mercer et al. (1995)
0.8	1 or 3 days	Rats	Increase in bronchiolar epithelial proliferation	Morphological effects	Barth et al. (1994a)

BALF = Bronchoalveolar lavage fluid.
ROS = Reactive oxygen species.

than current levels; yet in the 3-year period 2003–2005, 1-h excursions in the United States have been observed in the range of 100 to 200 ppb (see Chapter 2). The human and animal findings underlying this causal judgment are summarized below.

Lung Host Defenses and Immunity

- Impaired host-defense systems and increased risk of susceptibility to both viral and bacterial infections after NO_2 exposures have been observed in epidemiologic, human clinical, and animal toxicological studies (Section 3.1.2). A recent epidemiologic study (Chauhan et al., 2003) provided evidence that increased personal exposure to NO_2 worsened virus-associated symptoms and decreased lung function in children with asthma. The limited evidence from human clinical studies indicates that NO_2 may increase susceptibility to injury by subsequent viral challenge at exposures of as low as 0.6 ppm for 3 h (Frampton et al., 2002). Toxicological studies have shown that lung host defenses are sensitive to NO_2 exposure, with several measures of such effects observed at concentrations of less than 1 ppm. The epidemiologic and experimental evidence indicates coherence for effects of NO_2 exposure on host defense (i.e., immune system effects). This group of outcomes also provides plausibility and potential mechanistic support for other respiratory effects described subsequently, such as respiratory symptoms or increased ED visits for respiratory diseases.

Airways Inflammation

- Effects of NO_2 on airways inflammation have been observed in human clinical and animal toxicological studies at higher than ambient levels The few available epidemiologic studies are suggestive of an association between ambient NO_2 concentrations and inflammatory response in the airways in children, though the associations were inconsistent in the adult populations examined (Section 3.1.3). Human clinical studies provide evidence for increased airways inflammation at NO_2 concentrations of <2.0 ppm; the onset of inflammatory responses in healthy subjects appears to be between 100 and 200 ppm-min, i.e., 1 ppm for 2 to 3 h (Figure 3.1-1). Increases in biological markers of inflammation were not observed consistently in healthy animals at levels of less than 5 ppm; however, increased susceptibility to NO_2

concentrations of as low as 0.4 ppm was observed when lung vitamin C was reduced (by diet) to levels that were <50% of normal. Together, the findings of human and animal studies provide suggestive evidence for airways inflammation with NO_2 exposure, particularly in the more sensitive groups such as children or asthmatics.

Airways Hyperresponsiveness

- The evidence from human and animal experimental studies provides suggestive evidence for increased airways responsiveness to specific allergen challenges following NO_2 exposure (Section 3.1.4.1). Recent human clinical studies involving allergen challenge in asthmatics suggest that NO_2 exposure may enhance the sensitivity to allergen-induced decrements in lung function and increase the allergen-induced airways inflammatory response at exposures of as low as 0.26-ppm NO_2 for 30 min (Figure 3.1-2). Increased immune-mediated pulmonary inflammation was also observed in rats exposed to house dust mite allergen following exposure to 5-ppm NO_2 for 3 h.
- Exposure to NO_2 also has been found to enhance the inherent responsiveness of the airways to subsequent nonspecific challenges in human clinical studies (Section 3.1.4.2). In general, small but significant increases in nonspecific airways responsiveness were observed in the range of 1.5 to 2.0 ppm for 3 h exposures in healthy adults and between 0.2- and 0.3-ppm NO_2 for 30-min exposures in asthmatics. Subchronic exposures (6 to 12 weeks) of animals to NO_2 also increase responsiveness to nonspecific challenges at exposures of 1 to 4 ppm.

Respiratory Symptoms

- Consistent evidence has been observed for an association of respiratory effects with indoor and personal NO_2 exposures in children at ambient concentration levels (Section 3.1.5.1). In particular, the Pilotto et al. (2004) intervention study provided evidence of improvement in respiratory symptoms with reduced NO_2 exposure in asthmatic children. This study linked respiratory effects with exposure to NO_2 from an indoor combustion source, i.e., unflued gas heaters, thus, increasing confidence that NO_2 is not solely a marker for an air pollution mixture in observed associations with NO_2 from outdoor sources (particularly traffic).

- The epidemiologic studies using community ambient monitors also found associations between ambient NO_2 concentration and respiratory symptoms (Section 3.1.4.2, see Figure 3.1-6). The results of new multicity studies (Schildcrout et al., 2006; Mortimer et al., 2002) provide further support for associations with respiratory symptoms and medication use in asthmatic children. Positive associations were observed in cities where the median (90th percentile) range was 18 to 26 (34 to 37) ppb for a 24-h average (24-h avg) (Schildcrout et al., 2006) and the mean NO_2 level (range) was 32 (7 to 96) ppb for a 4-h avg (Mortimer et al., 2002). These concentrations are within the range of 24-h avg concentrations observed in recent years. In the results of multipollutant models, NO_2 associations in these multicity studies were generally robust to adjustment for copollutants including O_3, carbon monoxide (CO), and particulate matter with an aerodynamic diameter of $\leq$10 μm (PM_{10}) (Figure 3.1-7).
- Most human clinical studies did not report or observe respiratory symptoms with NO_2 exposure, and animal toxicological studies do not measure effects that would be considered symptoms. The experimental evidence on airways inflammation and immune system effects discussed previously, however, provides some plausibility and coherence for the observed respiratory symptoms in epidemiologic studies.

Lung Function

- Recent epidemiologic studies that examined the association between ambient NO_2 concentrations and lung function in children and adults generally produced inconsistent results (Section 3.1.5.1). Human clinical studies did not generally find direct effects of NO_2 on lung function in healthy adults at levels of as high as 4.0 ppm (Section 3.1.5.2). For asthmatics, the direct effects of NO_2 on lung function have also been inconsistent at exposure concentrations of less than 1-ppm NO_2.

Respiratory ED Visits and Hospitalizations

- Epidemiologic evidence exists for positive associations of short-term ambient NO_2 concentrations below the current NAAQS with increased numbers of ED visits and hospital admissions for respiratory causes, especially asthma (Section 3.1.7). As shown in Appendix Table 5B, a number of studies were conducted in locations where

mean (maximum) 24-h concentrations were in the range of 15 to 20 (28 to 82) ppb. These associations are particularly consistent among children and older adults (65+ years) when all respiratory outcomes are analyzed together (Figures 3.1-8 and 3.1-9), and among children and subjects of all ages for asthma admissions (Figures 3.1-12 and 3.1-13). When examined with copollutant models, associations of NO_2 with respiratory ED visits and hospital admissions were generally robust and independent of the effects of copollutants (Figures 3.1-10 and 3.1-11). In preceding sections, mechanistic evidence has been described related to host defense and immune system changes, airways inflammation, and airways responsiveness that provide plausibility and coherence for these observed effects.

5.3.2.2 Short-Term Exposure to NO_2 and Cardiovascular Health Effects

The available evidence on the effects of short-term exposure to NO_2 or cardiovascular health effects is *inadequate to infer the presence or absence of a causal relationship* at this time.

- Evidence from epidemiologic studies of heart rate variability (HRV), repolarization changes, and cardiac rhythm disorders among heart patients with ischemic cardiac disease are inconsistent (Section 3.2.1). In most studies, associations with PM were found to be similar or stronger than associations with NO_2. The mean 24-h concentrations generally were in the range of 9 to 39 ppb (Annex Table AX6.3-6). Generally positive associations between ambient NO_2 concentrations and hospital admissions or ED visits for cardiovascular disease have been reported in single-pollutant models where mean 24-h concentrations generally were in the range of 20 to 40 ppb (Section 3.2.2); however, most of these effect estimate values were diminished in multipollutant models that also contained CO and PM indices.
- Mechanistic evidence of a role for NO_2 in the development of cardiovascular diseases from studies of biomarkers of inflammation, cell adhesion, coagulation, and thrombosis is lacking (Section 3.2.1.4; Seaton and Dennekamp, 2003). Furthermore, the effects of NO_2 on various hematological parameters in animals are inconsistent and, thus, provide little biological plausibility for effects of NO_2 on the cardiovascular system. However, limited evidence from controlled human exposure studies is

suggestive of a reduction in hemoglobin with NO_2 exposure at concentrations between 1.0 and 2.0 ppm (with 3 h exposures).

5.3.2.3 Effects of Short-Term Exposure to NO_2 on Mortality

The epidemiologic evidence is *suggestive but not sufficient to infer a casual relationship* of short-term exposure to NO_2 with nonaccidental and cardiopulmonary-related mortality.

- Results from several large U.S. and European multicity studies and a meta-analysis study indicated positive associations between ambient NO_2 concentrations and the risk of all-cause (nonaccidental) mortality, with effect estimates ranging from 0.5 to 3.6% excess risk in mortality per standardized increment[1] (Section 3.3.1, Figure 3.3-2). In general, the NO_2 effect estimates were robust to adjustment for copollutants. Both cardiovascular and respiratory mortality have been associated with increased NO_2 concentrations in epidemiologic studies (Figure 3.3-3); however, similar associations were observed for other pollutants, including PM and sulfur dioxide (SO_2). The range of risk estimates for mortality excess was generally smaller than that for other pollutants such as PM.
- While NO_2 exposure, alone or in conjunction with other pollutants, may contribute to increased mortality, evaluation of the specificity of this effect is difficult. Clinical studies showing hematologic effects and animal toxicological studies showing biochemical, lung host defense, permeability, and inflammation changes with short-term exposures to NO_2 provide limited evidence of plausible pathways by which risks of morbidity and, potentially, mortality may be increased, but no coherent picture is evident at this time.

5.3.2.4 Effects of Long-Term Exposure to NO_2 on Respiratory Morbidity

The epidemiologic and toxicological evidence examining the effect of long-term exposure to NO_2 on respiratory morbidity is suggestive but not *sufficient to infer a casual relationship* at this time.

- A number of epidemiologic studies examined the effects of long-term exposure to NO_2 and reported positive associations with decrements in lung function and partially

[1]Excess risk estimates are standardized to a 20-ppb incremental change in daily 24-h avg NO_2 or a 30-ppb incremental change in daily 1-h max NO_2.

irreversible decrements in lung function growth (Section 3.4.1, Figures 3.4-1 and 3.4-2). Results from the Southern California Children's Health Study indicated that decrements were similar for boys and girls and among children who had no history of asthma (Gauderman et al., 2004). The mean NO_2 concentrations in these studies range from 21.5 to 34.6 ppb; thus, all have been conducted in areas where NO_2 levels are below the level of the NAAQS. Similar associations have also been found for PM, O_3, and proximity to traffic (<500 m), though these studies did not report the results of copollutant models. The high correlation among traffic-related pollutants made it difficult to accurately estimate the independent effects in these long-term exposure studies.

- Results from the available epidemiologic evidence investigating the association between long-term exposure to NO_2 and increases in asthma prevalence and incidence are suggestive (Section 3.4.2). Two major cohort studies, the Children's Health Study in southern California (Gauderman et al., 2005) and a birth cohort study in the Netherlands (Brauer et al., 2007) observed significant associations; however, several other studies did not find consistent associations between long-term NO_2 exposure and asthma outcomes.
- Epidemiologic studies conducted in both the United States and Europe also have produced inconsistent results regarding an association between long-term exposure to NO_2 and respiratory symptoms (Section 3.4.3). While some positive associations were noted, a large number of symptom outcomes were examined and the results across specific outcomes were inconsistent.
- Animal toxicological studies demonstrated that NO_2 exposure resulted in morphological changes in the centriacinar region of the lung and in bronchiolar epithelial proliferation (Section 3.4.4), which may provide some biological plausibility for the observed epidemiologic associations between long-term exposure to NO_2 and respiratory morbidity. Susceptibility to these morphological effects was found to be influenced by many factors, such as age, compromised lung function, and acute infections.

5.3.2.5 Other Morbidity Effects Associated with Long-Term Exposure to NO_2

The available epidemiologic and toxicological evidence is *inadequate to infer the presence or absence of a causal relationship* for carcinogenic, cardiovascular, and reproductive and developmental effects related to long-term NO_2 exposure.

- Two epidemiologic studies conducted in Europe showed an association between long-term NO_2 exposure and increased incidence of cancer (Nyberg et al., 2000; Nafstad et al., 2003). However, the animal toxicological studies have provided no clear evidence that NO_2 acts as a carcinogen, though it does appear to act as a tumor promoter at the site of contact (Section 3.5.1). There are no in vivo studies suggesting that NO_2 causes teratogenesis or malignant tumors. A more likely pathway for NO_2 involvement in cancer induction is through secondary formation of nitro-polycylic aromatic hydrocarbons (nitro-PAHs), as nitro-PAHs are known to be more mutagenic than the parent compounds.
- The very limited epidemiologic and toxicological evidence does not suggest that long-term exposure to NO_2 has cardiovascular effects (Section 3.5.2). The U.S. Women's Health Initiative study (Miller et al., 2007) did not find any associations between long-term NO_2 exposure and cardiovascular events. The toxicological studies found some effects of NO_2 on cardiac performance and heart rate, but only at exposure levels of above 4 ppm.
- The epidemiologic evidence is not consistent for associations between NO_2 exposure and growth retardation; however, some evidence is accumulating for effects on preterm delivery (Section 3.5.3). Similarly, scant animal evidence supports a weak association between NO_2 exposure and adverse birth outcomes and provides little mechanistic information or biological plausibility for the epidemiologic findings.

5.3.2.6 Effects of Long-Term Exposure to NO_2 on Mortality

The epidemiologic evidence is *inadequate to infer the presence or absence of a causal relationship* between long-term exposure to NO_2 and mortality. In the U.S. and European cohort studies examining the relationship between long-term exposure to NO_2 and mortality, results were generally inconsistent (Section 3.6, Figure 3.6-2). Further, when associations were suggested, they were not specific to NO_2, but also implicated PM and other traffic indicators.

The relatively high correlations reported between NO_2 and PM indices ($r \sim 0.8$) make it difficult to interpret these observed associations at this time.

5.3.2.7 Concentration-Response Relationships and Thresholds

In studies that have examined concentration-response relationships between NO_2 and health outcomes specifically, there is little evidence of an effect threshold (Section 4.2). Factors that make it difficult to identify any threshold that may exist include exposure error, response measurement error, low data density in the lower concentration range, interindividual variation in susceptibility to health effects, additivity of pollutant-induced effects to the naturally occurring background disease processes, and the extent to which health effects are due to other environmental insults having a mode of action similar to that of NO_2. Additionally, if the concentration-response relationship is shallow, identification of any threshold that may exist will be more difficult.

5.3.2.8 NO_2 Exposure Indices

The available NO_2 indices used to indicate short-term ambient NO_2 exposure are daily maximum 1-h (1-h max); 24-h average (24-h avg); and 2-week average NO_2 concentrations. New data on short-term exposures have been published since the 1993 AQCD for Nitrogen Oxides. Some studies examined only one index, and these studies form an evidence base for that individual index. A few studies used both 1-h and 24-h data and, thus, allow a comparison of these averaging periods. These include studies of respiratory symptoms, ED visits for asthma, hospital admissions for asthma, and mortality.

- Meta-analysis regression results for asthma ED visits comparing effect estimates for the 1-h and 24-h time periods indicate that effect estimates are slightly, but not significantly, larger with a 24-h avg compared with a 1-h max NO_2.
- Experimental studies in both animals and humans provided evidence that short-term NO_2 exposure (i.e., <1 h to 2–3 h) can result in respiratory effects such as increased airways responsiveness or inflammation, thereby, increasing the potential for exacerbation of asthma. These findings generally support epidemiologic evidence on short-term exposures, but do not provide evidence that distinguishes effects for one short-term averaging period from another.

- Differences between daily 1-h max and 24-h avg exposures estimates are unlikely to be well characterized by this limited data.

5.3.2.9 Susceptible and Vulnerable Populations

- Based on both short- and long-term studies of an array of respiratory health effects data, persons with preexisting pulmonary conditions are at greater risk from ambient NO_2 exposures than the general public, with the most extensive evidence available for asthmatics as a potentially susceptible group. In addition, studies suggest that upper respiratory viral infections can trigger susceptibility to the effects of exposure to NO_2.
- There is supporting evidence of age-related differences in susceptibility to NO_2 health effects such that the elderly population (>65 years of age) appears to be at increased risk of mortality and hospitalizations and that children (<18 years of age) experience other potentially adverse respiratory health outcomes with increased NO_2 exposure.
- People with occupations that require them to be in or close to traffic or roadways (i.e., bus and taxi drivers, highway patrol officers) may have enhanced exposure to NO_2 compared to the general population, possibly increasing their vulnerability. A considerable portion of the population resides and/or attends school near major roadways, increasing their exposure to NO_2 and other traffic pollutants. Otherwise susceptible individuals (schoolchildren, older adults) in this subpopulation, therefore, may be at increased risk.
- Recent studies have evaluated the effect of socioeconomic position (SEP) on susceptibility to the effects of NO_2 exposure; however, to date, these studies are too few in number to draw conclusions.
- While data are emerging (Romieu et al., 2006; Islam et al., 2007) and it is believed that a genetic component could be important in characterizing the association between NO_2 exposure and adverse health effects, currently there are no studies that specifically evaluate this relationship.

5.4 CONCLUSIONS

New evidence confirms previous findings in the 1993 Air Quality Criteria Document that short-term nitrogen dioxide (NO_2) exposure is associated with increased airways responsiveness,

often accompanied by respiratory symptoms, particularly in children and asthmatics. Additionally, the new body of epidemiologic data provides abundant evidence of associations with increased emergency department (ED) visits and hospital admissions for respiratory causes, especially asthma, and short-term ambient exposure to NO_2. These new findings are based on numerous studies, including panel and field studies, multipollutant studies that control for the effects of other pollutants, and studies conducted in areas where the whole distribution of ambient 24-h average (24-h avg) NO_2 concentrations was below the current National Ambient Air Quality Standard (NAAQS) level of 53 ppb (see data in Appendix Tables 5A and 5B). These conclusions are supported by evidence from toxicological and controlled human exposure studies. These data sets form a plausible, consistent, and coherent description of a relationship between NO_2 exposures and an array of adverse health effects that range from the onset of respiratory symptoms to hospital admission. Though an array of studies that examined short-term (24-h avg and 1-h maximum [1-h max]) NO_2 exposures and respiratory morbidity consistently produced positive associations, it is not possible to discern whether these effects are attributable to average daily (or multiday) concentrations (24-h avg) or high, peak exposures (1-h max).

The available evidence on the effects of short-term exposure to NO_2 for cardiovascular health effects is inadequate to infer the presence or absence of a causal relationship at this time. Though there is no human clinical or animal toxicological evidence, the epidemiologic evidence is suggestive but not sufficient to infer a casual relationship of short-term exposure to NO_2 with nonaccidental and cardiopulmonary-related mortality.

While the evidence supports a direct effect of short-term NO_2 exposure on respiratory morbidity, the available evidence is inadequate to infer the presence or absence of a causal relationship for morbidity and mortality effects related to long-term NO_2 exposure. Further, the health evidence is found to be inadequate to infer the presence or absence of a causal relationship for carcinogenic, cardiovascular, and reproductive and developmental effects, or for premature mortality, related to long-term NO_2 exposure.

It is difficult to determine from these new studies the extent to which NO_2 is independently associated with respiratory effects or if NO_2 is a marker for the effects of another traffic-related pollutant or mix of pollutants (see Chapter 2, Section 5.2.2 for more details on exposure issues). On-road vehicle exhaust emissions are a nearly ubiquitous source of

combustion pollutant mixtures that include NO_2 and can be an important contributor to NO_2 levels in near-road locations. Although this complicates efforts to disentangle specific NO_2-related health effects, the evidence summarized in this assessment indicates that NO_2 associations generally remain robust in multipollutant models and supports a direct effect of short-term NO_2 exposure on respiratory morbidity at ambient concentrations below the current NAAQS. The robustness of epidemiologic findings to adjustment for copollutants, coupled with data from animal and human experimental studies, support a determination that the relationship between NO_2 and respiratory morbidity is likely causal, while still recognizing the relationship between NO_2 and other traffic-related pollutants. In addition, an intervention study by Pilotto et al. (2004) found that exposure to NO_2 from an indoor combustion source is associated with respiratory effects; in this study NO_2 effects would not be confounded by other motor vehicle emission pollutants, though potential confounding by other pollutants from gas stove emissions, such as ultrafine particles could occur.

Identification of a concentration-response relationship is an additional uncertainty that must be considered when describing the association of NO_2 and adverse health effects. In studies that have examined concentration-response relationships between NO_2 and health outcomes specifically, there is little evidence of an effect threshold. Because ambient levels of NO_2 are well below the current NAAQS in many of the epidemiologic study sites, the concentration-response relationship may be shallow, making it difficult to identify any threshold that may exist.

Integrating across the epidemiologic, human clinical, and animal toxicological evidence presented above, we find that it is plausible that current NO_2 exposures can result in adverse impacts to public health at ambient concentrations below the current NAAQS for NO_2. In particular, a set of coherent and consistent respiratory health outcomes are associated with short-term NO_2 exposures including exacerbated asthma and other respiratory symptoms, increased airways hyperresponsiveness, inflammation, impaired host defense, aggravated viral infections, and increased emergency department visits and hospital admissions.

TABLE 5.3-1. SUMMARY OF EVIDENCE FROM EPIDEMIOLOGICAL, HUMAN CLINICAL, AND ANIMAL TOXICOLOGICAL STUDIES ON THE HEALTH EFFECTS ASSOCIATED WITH SHORT- AND LONG-TERM EXPOSURE TO NO_2.

Health Outcome	Conclusion from Previous NAAQS Review for NO_X	Conclusion from 2008 NO_X ISA
SHORT-TERM EXPOSURE TO NO_2		
Respiratory Morbidity	**No Overall Conclusion**	***"sufficient to infer a likely causal relationship"***
Lung Host Defense	Human clinical studies of host defenses are rare and their results are equivocal, but suggestive of the potential for NO_2 effects; Animal toxicological studies provide important evidence indicating that several defense system components are targets for inhaled NO_2, including key elements of host defenses such as alveolar macrophages (AMs) and the humoral and cell-mediated immune systems and further show that NO_2 exposure can impair the respiratory host defense system sufficiently so as to result in the host being more susceptible to respiratory infection.	Impaired host-defense systems and increased risk of susceptibility to both viral and bacterial infections after NO_2 exposures have been observed in epidemiologic, human clinical, and animal toxicologic studies. Increased susceptibility to cell injury during ex-vivo viral challenge was observed following NO_2 exposures to 0.6 ppm for 3 h in one human clinical study.
Airways Inflammation	No Studies.	Human clinical studies have reported effects of NO_2 on airways inflammation at 1 ppm for 2 to 3 h exposures in healthy humans. The animal toxicologic studies and limited available epidemiologic studies on children support these findings.
Airways Responsiveness	The physiological end point that appears to be the most sensitive indicator of response to NO_2 is a change in airways responsiveness to bronchoconstrictors in asthmatics. In the range of 0.20 and 0.30 ppm, the increase in responsiveness was attributable to asthmatics exposed NO_2 at rest. Increased responsiveness observed in healthy individuals exposed to $\geq$1.5 ppm NO_2 for 60 min or more.	Human clinical studies of allergen and nonspecific bronchial challenges in asthmatics observed increased airways responsiveness following exposures of 0.2 to 0.3ppm NO_2 for 30 min at rest. Increased responsiveness to nonspecific challenges were also observed in animals at higher NO_2 levels (1-4 ppm).
Respiratory Symptoms	Results of a meta-analysis of 9 epidemiologic studies show that children (5-12 years old) living in homes with gas stoves are at increased risk for developing respiratory diseases and illnesses compared to children living in homes without gas stoves.	Epidemiologic studies provide consistent evidence of an association of respiratory effects with indoor and personal NO_2 exposures in children. Multicity studies provide further support for associations between ambient NO_2 concentrations and respiratory symptoms in asthmatic children at median 24-h avg levels of 18-26 ppb.

TABLE 5.3-1 (cont'd). SUMMARY OF EVIDENCE FROM EPIDEMIOLOGICAL, HUMAN CLINICAL, AND ANIMAL TOXICOLOGICAL STUDIES ON THE HEALTH EFFECTS ASSOCIATED WITH SHORT- AND LONG-TERM EXPOSURE TO NO_2.

Health Outcome	Conclusion from Previous NAAQS Review for NO_X	Conclusion from 2008 NO_X ISA
Lung Function	NO_2 induced lung function changes in asthmatics have been reported at low (0.2 to 0.5 ppm), but not higher (up to 4 ppm), NO_2 concentrations. No convincing evidence of lung function decrements in healthy individuals at concentrations below 1.0 ppm NO_2.	The association between ambient NO_2 concentrations and lung function in epidemiologic studies were generally inconsistent. Recent clinical evidence generally confirms prior findings.
ED Visits / Hospital Admissions	No Studies	Positive and generally robust associations were observed between ambient NO_2 concentrations and increased ED visits and hospital admissions for respiratory causes, especially asthma. These effects were observed in studies with mean 24-h avg concentrations in the range of 15-20 ppb.
Cardiovascular Morbidity	**No Studies**	***"inadequate to infer the presence or absence of a causal relationship"***
Cardiovascular Effects	No Studies	Evidence from epidemiologic studies of heart rate variability, repolarization changes, and cardiac rhythm disorders among heart patients with ischemic cardiac disease are inconsistent.
ED Visits / Hospital Admissions	No Studies	Generally positive associations between ambient NO_2 concentrations and hospital admissions or ED visits for cardiovascular disease have been reported; however, the effects were not robust to adjustment for copollutants.
Mortality	**No Studies**	***"suggestive but not sufficient to infer a casual relationship"***
Nonaccidental and Cardiopulmonary Mortality	No Studies	Large multicity studies and a meta-analysis study indicated positive and generally robust associations between ambient NO_2 concentrations and risk of nonaccidental and cardiopulmonary mortality.

TABLE 5.3-1 (cont'd). SUMMARY OF EVIDENCE FROM EPIDEMIOLOGICAL, HUMAN CLINICAL, AND ANIMAL TOXICOLOGICAL STUDIES ON THE HEALTH EFFECTS ASSOCIATED WITH SHORT- AND LONG-TERM EXPOSURE TO NO_2.

Health Outcome	Conclusion from Previous NAAQS Review for NO_X	Conclusion from 2008 NO_X ISA
LONG-TERM EXPOSURE TO NO_2		
Respiratory Morbidity	**No Overall Conclusion.**	***"suggestive but not sufficient to infer a casual relationship"***
Respiratory Effects	At sufficiently high concentrations of NO_2 (i.e., >8 ppm) for long periods of exposure, NO_2 can cause emphysema (meeting the human definition criteria) in animals.	A number of epidemiological studies observed decrements in lung function growth associated with long-term exposure to NO_2. These effects were observed in studies with mean NO_2 concentrations in the range of 21.5 to 34.6 ppb.
Other Morbidity	**No Studies.**	***"inadequate to infer the presence or absence of a causal relationship"***
Cancer	No Studies.	While limited epidemiological studies observed an association between long-term NO_2 exposure and incidence of cancer; animal toxicological studies have not provided clear evidence that NO_2 acts as a carcinogen.
Cardiovascular Effects	No Studies.	The very limited epidemiological and toxicological evidence does not suggest that long-term exposure to NO_2 has cardiovascular effects.
Birth Outcomes	No Studies.	The epidemiological evidence for an association between long-term exposure to NO_2 and birth outcomes is generally inconsistent, with limited support from animal toxicological studies.
Mortality	**No Studies.**	***"inadequate to infer the presence or absence of a causal relationship"***
Nonaccidental and Cardiopulmonary Mortality	No Studies.	The results of epidemiological studies examining the association between long-term exposure to NO_2 and mortality were generally inconsistent.

TABLE 5.3-4. LEGEND FOR FIGURE 5.3-1: SUMMARY OF EPIDEMIOLOGIC STUDIES EXAMINING SHORT-TERM EXPOSURES TO AMBIENT NO_2 AND RESPIRATORY OUTCOMES

RESPIRATORY SYMPTOMS

Ref #	Reference	Outcome	Location	Age	Avg Time	Lag	Other
1	Schwartz et al. (1994)	Cough	Multicity-U.S.	Children	24-h	1-4	
2	Mortimer et al. (2002)	Asthma symptoms	Multicity-U.S.	Children	4-h	1-6	
3	Schildcrout et al. (2006)	Asthma symptoms	Multicity-U.S.	Children	24-h	0-2	
4	Pino et al. (2004)	Wheezy bronchitis	Chile	Infants	24-h	3	
5	Ostro et al. (2001)	Wheeze	Southern CA	Children	1-h max	3	
6	Ostro et al. (2001)	Cough	Southern, CA	Children	1-h max	3	
7	Delfino et al. (2002)	Asthma symptoms	Southern CA	Children	8-h	0	
8	Segala et al. (1998)	Asthma symptoms	Paris, France	Children	24-h	0	
9	Segala et al. 1998	Cough	Paris, France	Children	24-h	3	
10	Just et al. (2002)	Cough	Paris, France	Children	24-h	0	
11	Jalaludin et al. (2004)	Cough	Australia	Children	15-h	0	
12	Segala et al. (2004)	Cough	Paris, France	Adults	24-h	0-4	
13	von Klot et al. (2002)	Wheeze	Germany	Adults	24-h	0-4	
14	von Klot et al. (2002)	Phlegm	Germany	Adults	24-h	0-4	
15	von Klot et al. (2002)	Cough	Germany	Adults	24-h	0-4	
16	von Klot et al. (2002)	Breathing problems	Germany	Adults	24-h	0-4	
17	Ward et al (2002)	Cough	U.K.	Children	24-h	0	
18	Rodriguez et al. (2007)	Cough	Perth, Australia	Children	24-h	0	
19	Boezen et al. (1999)	LRS	Netherlands	Children	24-h	0-4	

HOSPITAL ADMISSIONS/ED VISITS

Ref #	Reference	HA/ED	Location	Age	Avg Time	Lag	Other
Respiratory Disease – All Ages							
20	Tolbert et al. (2007)	ED	Atlanta	All	1-h max	0-2	
21	Peel et al. (2005)	ED	Atlanta	All	1-h max	0-2	
22	Luginaah et al. (2005)	HA	Windsor, ON	All	1-h max	0-3	Female
23	Luginaah et al. (2005)	HA	Windsor, ON	All	1-h max	0-3	Male
24	Anderson et al. (2001)	ED	West Midlands, U.K.	All	1-h max	0-1	
25	Atkinson et al., (1999a)	HA	London	All	1-h max	1	
26	Atkinson et al., (1999b)	ED	London	All	1-h max		
27	Ponce de Leon et al. (1996)	HA	London	All	24-h	2	
28	Llorca et al. (2005)	HA	Torrelavega, Spain	All	24-h	NR	
29	Oftedal et al. (2003)	HA	Drammen, Norway	All	24-h	3	
30	Hagen et al. (2000)	HA	Drammen, Norway	All	24-h	0-3	
31	Bedeschi et al. (2007)	HA	Reggio Emilia, Italy	All	24-h	3	
32	Hinwood et al., (2006)	HA	Perth, Australia	All	24-h	1	
33	Petroeschevsky et al. (2001)	HA	Brisbane, Australia	All	1-h max	1	
Respiratory Disease – Children							
34	Yang et al. (2003)	HA	Vancouver, BC	<3	24-h	1	
35	Luginaah et al. (2005)	HA	Windsor, ON	0-14	1-h max	0-3	Female
36	Luginaah et al. (2005)	HA	Windsor, ON	0-14	1-h max	0-3	Male
37	Anderson et al. (2001)	HA	West Midlands, U.K.	0-14	1-h max	0-1	
38	Atkinson et al. (1999a)	HA	London	0-14	1-h max	2	

TABLE 5.3-4 (cont'd). LEGEND FOR FIGURE 5.3-1: SUMMARY OF EPIDEMIOLOGIC STUDIES EXAMINING SHORT-TERM EXPOSURES TO AMBIENT NO_2 AND RESPIRATORY OUTCOMES

HOSPITAL ADMISSIONS/ED VISITS (cont'd)

Ref #	Reference	HA/ED	Location	Age	Avg Time	Lag	Other
Respiratory Disease – Children (cont'd)							
39	Atkinson et al. (1999b)	ED	London	0-14	1-h max	1	
40	Ponce de Leon et al. (1996)	HA	London	0-14	24-h	2	
41	Vigotti et al. (2007)	HA	Pisa, Italy	<10	24-h	0-2	
42	Petroeschevsky et al. (2001)	HA	Brisbane, Australia	0-4	1-h max	3	
43	Petroeschevsky et al. (2001)	HA	Brisbane, Australia	5-14	1-h max	0	
44	Barnett et al. (2005)	HA	Multicity-Australia	0	24-h	0-1	
45	Barnett et al. (2005)	HA	Multicity-Australia	1-4	24-h	0-1	
46	Barnett et al. (2005)	HA	Multicity-Australia	5-14	24-h	0-1	
47	Wong et al. (1999)	HA	Hong Kong	0-4	24-h	0-3	
48	Lin et al. (1999)	ED	Sao Paulo, Brazil	<13	24-h	0-4	
49	Gouveia and Fletcher (2000)	HA	Sao Paulo, Brazil	<5	1-h max	0	
Respiratory Disease – Adults							
50	Luginaah et al. (2005)	HA	Windsor, ON	15-64	1-h max	0-3	Female
51	Luginaah et al. (2005)	HA	Windsor, ON	15-64	1-h max	0-3	Male
52	Spix et al. (1998)	HA	Multicity-Europe	15-64	24-h	1-3	
53	Anderson et al. (2001)	HA	West Midlands, U.K.	15-64	1-h max	0-2	
54	Atkinson et al. (1999a)	HA	London	15-64	1-h max	1	
55	Atkinson et al. (1999b)	ED	London	15-64	1-h max	2	
56	Ponce de Leon et al. (1996)	HA	London	15-64	24-h	1	
57	Schouten et al. (1996)	HA	Amsterdam	15-64	24-h	1	
58	Schouten et al. (1996)	HA	Rotterdam	15-64	24-h	1	
59	Petroeschevsky et al. (2001)	HA	Brisbane, Australia	15-64	24-h	0	
60	Wong et al. (1999)	HA	Hong Kong	5-64	24-h	0-3	
Respiratory Disease – Older Adults (65+)							
61	Luginaah et al. (2005)	HA	Windsor, ON	65+	1-h max	0-3	Female
62	Luginaah et al. (2005)	HA	Windsor, ON	65+	1-h max	0-3	Male
63	Fung et al. (2006)	HA	Vancouver, BC	65+	24-h	0-3	
64	Yang et al. (2003)	HA	Vancouver, BC	65+	24-h	1	
65	Spix et al. (1998)	HA	Multicity-Europe	65+	24-h	1-3	
66	Anderson et al. (2001)	HA	West Midlands, U.K.	65+	1-h max	0-2	
67	Atkinson et al. (1999a)	HA	London	65+	1-h max	3	
68	Atkinson et al. (1999b)	ED	London	65+	1-h max	0	
69	Ponce de Leon et al. (1996)	HA	London	65+	24-h	2	
70	Andersen et al. (2007b)	HA	Copenhagen	65+	24-h	0-4	
71	Andersen et al. (2007a)	HA	Copenhagen	65+	24-h	0-4	
72	Schouten et al. (1996)	HA	Amsterdam	65+	24-h	2	
73	Schouten et al. (1996)	HA	Rotterdam	65+	24-h	0	
74	Simpson et al. (2005)	HA	Multicity-Australia	65+	1-h max	0-1	
75	Hinwood et al. (2006)	HA	Perth, Australia	65+	24-h	1	
76	Petroeschevsky et al. (2001)	HA	Brisbane, Australia	65+	24-h	5	
77	Wong et al. (1999)	HA	Hong Kong	65+	24-h	0-3	

TABLE 5.3-4 (cont'd). LEGEND FOR FIGURE 5.3-1: SUMMARY OF EPIDEMIOLOGIC STUDIES EXAMINING SHORT-TERM EXPOSURES TO AMBIENT NO_2 AND RESPIRATORY OUTCOMES

HOSPITAL ADMISSIONS/ED VISITS (cont'd)

Ref #	Reference	HA/ED	Location	Age	Avg Time	Lag	Other
Asthma – All Ages							
78	Peel et al. (2005)	ED	Atlanta	All	1-h max	0-2	
79	Ito et al. (2007)*	ED	New York, NY	All	24-h	0-1	
80	Burnett et al. (1999)	HA	Toronto	All	24-h	0	
81	Anderson et al. (1998)	HA	London	All	24-h	0-3	
82	Atkinson et al. (1999a)	HA	London	All	1-h max	0	
83	Atkinson et al. (1999b)	ED	London	All	1-h max	0	
84	Galan et al. (2003)	ED	Madrid, Spain	All	24-h	3	
85	Chardon et al. (2007)	HA	Paris, France	All	24-h	0-3	
86	Schouten et al. (1996)	HA	Amsterdam	All	24-h	2	
87	Migliaretti et al. (2005)	ED	Turin, Italy	All	24-h	0-3	
88	Migliaretti and Cavallo (2004)	HA	Turin, Italy	All	24-h	1-3	
89	Hinwood et al. (2006)	HA	Perth, Australia	All	24-h	0	
90	Petroeschevsky et al. (2001)	HA	Brisbane, Australia	All	1-h max	0-2	
91	Wong et al., (1999)	HA	Hong Kong	All	24-h	0-3	
92	Tsai et al. (2006)	HA	Kaohsiung, Taiwan	All	24-h	0-2	Warm
93	Tsai et al. (2006)	HA	Kaohsiung, Taiwan	All	24-h	0-2	Cool
94	Yang et al. (2007)	HA	Taipei, Taiwan	All	24-h	0-2	Warm
95	Yang et al. (2007)	HA	Taipei, Taiwan	All	24-h	0-2	Cool
Asthma – Children							
96	Peel et al. (2005)	ED	Atlanta	2-18	1-h max	0-2	
97	Tolbert et al. (2000)	ED	Atlanta	0-16	1-h max	1	
98	Lin et al. (2003)	HA	Toronto	6-12	24-h	0-5	Male
99	Lin et al. (2003)	HA	Toronto	6-12	24-h	0-5	Female
100	Sunyer et al. (1997)	ED	Multicity-Europe	0-14	24-h	0-3	
101	Anderson et al. (1998)	HA	London	0-14	24-h	0-3	
102	Atkinson et al. (1999a)	HA	London	0-14	1-h max	3	
103	Atkinson et al. (1999b)	ED	London	0-14	1-h max	1	
104	Thompson et al. (2001)	ED	Belfast, Ireland	<18	24-h	0-3	
105	Andersen et al. (2007b)	HA	Copenhagen	5-18	24-h	0-4	
106	Andersen et al. (2007a)	HA	Copenhagen	5-18	24-h	0-4	
107	Migliaretti et al. (2005)	ED	Turin, Italy	0-14	24-h	0-3	
108	Migliaretti and Cavallo (2004)	HA	Turin, Italy	4-15	24-h	1-3	
109	Migliaretti and Cavallo (2004)	HA	Turin, Italy	<4	24-h	1-3	
110	Barnett et al. (2005)	HA	Multicity-Australia	1-4	24-h	0-1	
111	Barnett et al. (2005)	HA	Multicity-Australia	5-14	24-h	0-1	
112	Hinwood et al. (2006)	HA	Perth, Australia	0-14	24-h	0	
113	Petroeschevsky et al. (2001)	HA	Brisbane, Australia	0-4	1-h max	0	
114	Petroeschevsky et al. (2001)	HA	Brisbane, Australia	5-14	1-h max	1	
115	Morgan et al. (1998)	HA	Sydney, Australia	1-14	24-h	0	
116	Ko et al. (2007)	HA	Hong Kong	0-14	24-h	0-4	
117	Lee et al. (2006)	HA	Hong Kong	<18	24-h	3	
118	Gouveia and Fletcher (2000)	HA	Sao Paulo, Brazil	<5	1-h max	2	

TABLE 5.3-4 (cont'd). LEGEND FOR FIGURE 5.3-1: SUMMARY OF EPIDEMIOLOGIC STUDIES EXAMINING SHORT-TERM EXPOSURES TO AMBIENT NO_2 AND RESPIRATORY OUTCOMES

HOSPITAL ADMISSIONS/ED VISITS (cont'd)

Ref #	Reference	HA/ED	Location	Age	Avg Time	Lag	Other
Asthma – Children (cont'd)							
119	Jaffe et al. (2003)	ED	Cleveland	5-34	24-h	1	
120	Jaffe et al. (2003)	ED	Cincinnati	5-34	24-h	1	
121	Linn et al. (2000)	HA	Los Angeles	>30	24-h	0-1	
Asthma – Adults							
122	Sunyer et al. (1997)	ED	Multicity, Europe	15-64	24-h	0-3	
123	Anderson et al. (1998)	HA	London	15-64	24-h	0-1	
124	Atkinson et al. (1999a)	HA	London	15-64	1-h max	1	
125	Atkinson et al. (1999b)	ED	London	15-64	1-h max	1	
126	Boutin-Forzano et al. (2004)	ED	Marseille, France	3-49	24-h	0	
127	Tenias et al. (1998)	ED	Valencia, Spain	>14	24-h	0	
128	Castellsague et al. (1995)	ED	Barcelona, Spain	15-64	24-h	0-2	
129	Migliaretti et al. (2005)	ED	Turin, Italy	15-64	24-h	0-3	
130	Morgan et al. (1998)	HA	Sydney, Australia	15-64	24-h	0	
131	Ko et al. (2007)	HA	Hong Kong	15-64	24-h	0-4	
Asthma – Older Adults (65+)							
132	Anderson et al. (1998)	HA	London	65+	24-h	0-3	
133	Atkinson et al. (1999a)	HA	London	65+	1-h max	3	
134	Migliaretti et al. (2005)	ED	Turin, Italy	65+	24-h	0-3	
135	Hinwood et al. (2006)	HA	Perth, Australia	65+	24-h	0	
136	Ko et al. (2007)	HA	Hong Kong	65+	24-h	0-4	

RESPIRATORY MORTALITY

Ref #	Reference	Location	Age	Avg Time	Lag
137	Ostro et al. (2000)	Coachella Valley, CA		24-h	0
138	Fairley (1999); (Reanalysis 2003)	Santa Clara County, CA		24-h	1
139	Gamble (1998)	Dallas, TX		24-h	4-5
140	Gwynn et al. (2000)	Buffalo, NY		24-h	1
141	Burnett et al. (2004)	Multicity-Canada		24-h	0-2
142	Villeneuve et al. (2003)	Vancouver, BC		24-h	0
143	Samoli et al. (2006)	Multicity-Europe		1-h max	0-1
144	Zmirou et al. (1998)	Multicity-Europe		24-h	0-3
145	Biggeri et al. (2005)	Multicity-Italy		24-h	0-1
146	Anderson et al. (1996)	London, U.K.		24-h	1
147	Bremner et al. (1999)	London, U.K.		24-h	3
148	Anderson et al. (2001)	West Midlands, U.K.		1-h max	0-1
149	Le Terte et al. (2002a)	Multicity-France		24-h	0-1
150	Dab et al. (1996)	Paris, France		24-h	0
151	Zmirou et al. (1996)	Lyon, France		24-h	2
152	Hoek et al. (2000); (Reanalysis, Hoek (2003)	The Netherlands		24-h	0-6
153	Hoek et al. (2000); (Reanalysis, Hoek (2003)	The Netherlands		24-h	0-6

TABLE 5.3-4 (cont'd). LEGEND FOR FIGURE 5.3-1: SUMMARY OF EPIDEMIOLOGIC STUDIES EXAMINING SHORT-TERM EXPOSURES TO AMBIENT NO_2 AND RESPIRATORY OUTCOMES

RESPIRATORY MORTALITY (cont'd)

Ref #	Reference	Location	Age	Avg Time	Lag
154	Saez et al. (2002)	Multicity-Spain		24-h	0-3
155	Garcia-Aymerich et al. (2000)	Barcelona, Spain		24-h	0-1
156	Saez et al. (1999)	Barcelona, Spain	2-45 yrs	24-h	0-2
157	Sunyer et al. (1996)	Barcelona, Spain		1-h max	0
158	Borja-Aburto et al. (1998)	Mexico City, Mexico	65+	24-h	1-5
159	Gouveia and Fletcher (2000b)	Sao Paulo, Brazil	65+	1-h max	2
160	Simpson et al. (2005a,b)	Multicity-Australia		1-h max	0-1
161	Simpson et al. (2000)	Brisbane, Australia		24-h	0-1
162	Tsai et al. (2003)	Kaohsiumg, Taiwan		24-h	0-2
163	Yang et al. (2004b)	Taipei, Taiwan		24-h	0-2
164	Wong et al. (2001)	Hong Kong, China		24-h	0
165	Wong et al. (2002)	Hong Kong, China		24-h	0-1

APPENDIX 5A

TABLE 5A. EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Schwartz et al. (1994) Six cities, United States 1984-1988	1,844 elementary school children in 6 U.S. cities	24-h avg: 13.3	NR	NR	Max: 44.2	Cough Incidence: 61.3% (8.2, 143.4)
Mortimer et al. (2002) Eight urban areas, United States 1993	Asthmatic children (4-9 yrs) from the National Cooperative Inner-City Asthma Study (NCICAS) cohort	4-h avg: 32	NR	NR	~7, 96	Morning Asthma Symptoms: 48% (2, 116)
Schildcrout et al. (2006) Eight North American Cities 1993-1995	990 asthmatic children (aged 5-13 yrs) enrolled in Childhood Asthma Management Program (CAMP) cohort	24-h avg: 17.8-26.0	NR	NR	NR	Asthma Symptoms: 4.0% (1.0, 7.0) Rescue Inhaler Use: 3.0% (1.0, 5.0)
Ostro et al. (2001) Los Angeles and Pasadena, CA, United States Aug-Oct 1993	138 African-American asthmatic children (8-13 yrs)	L.A.: 1-h max: 79.5 (43.6) Pasadena: 1-h max: 68.1 (31.3)	NR	NR	L.A.: 20.0, 220.0 Pasadena: 30.0, 170.0	Shortness of Breath: Day w/symptoms: 4.7% (−0.6, 10.4) Onset of symptoms: 8.2% (−0.6, 17.6) Wheeze: Day w/symptoms: 4.7% (1.2, 8.7) Onset of symptoms: 7.6% (2.4, 13.8) Cough: Day w/symptoms: 1.8% (−1.8, 5.3) Onset of symptoms: 7.0% (1.0, 13.8)

TABLE 5A (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Delfino et al. (2002) Alpine, CA, United States Mar-Apr 1996	22 children with asthma (9-19 yrs old) living in nonsmoking households	1-h max: 24 (10)	NR	NR	8, 53	Asthma Symptoms: NO_2 Alone: 34.6% (−17.9, 122.1) On Medication: −8.9% (−79.1, 297.6) Not on Medication: 80.3% (−10.7, 263.7) With (compared to without) Respiratory Infection: 299% (−50.6, 1,708)
Delfino et al. (2003a) East Los Angeles County, CA, United States Nov 1999 - Jan 2000	22 Hispanic school children (ages 10-15) with asthma	1-h max: 7.2 (2.1)	NR	NR	3, 14	Asthma Symptoms: Symptom Scores >1, lag 0: 119.7% (−45.8, 2,038.2) Symptom Scores >1, lag 1: 197.4% (−36.7, 5,793.5) Symptom Scores >2, lag 0: 360.6% (−95.8, 3,039,358) Symptom Scores >2, lag 1: −75.7% (−205.5, 138,807.3)
Adamkiewicz et al. (2004) Steubenville, OH, United States Sept-Dec 2000	29 nonsmoking adults (ages 53+)	24-h avg: 10.9	NR	NR	NR	Change in Fraction of Exhaled NO: 24-h moving average: 0.53 ppb (−0.35, 1.41)
Linn et al. (1996) Los Angeles, CA, United States 1992-1994	269 school children (during 4th and 5th grade school years)	24-h avg: 33 (22)	NR	NR	1, 96	Total Symptom Score: Previous 24-h, Morning Score: −18.2% (−47.3, 27.1) Current 24-h, Evening Score: −42.9% (−65.4, −5.9)

TABLE 5A (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Ségala et al. (1998) Paris, France 1992	84 children 7-15 yrs old that had at least one asthma attack in the past 12 months	24-h avg: 29.8 (8.1)	NR	NR	12.5, 63.8	Mild Asthmatics: Incident Episodes Asthma 91% (13, 223) lag 0 Cough 76% (21, 156) lag 4 Shortness of Breath 24% (−32, 125) lag 4 Respiratory Infections 88% (4, 243) lag 3 Moderate Asthmatics: Incident Episodes Asthma 31% (−16, 106) lag 3 Wheeze 26% (−7, 70) lag 0 Cough 39% (3, 87) lag 2 Shortness of Breath 18% (−6, 47) lag 4 Respiratory Infections 36% (−31, 168) lag 3
Just et al. (2002) Paris, France 1996	82 children 7-15 yrs old that had at least one asthma attack in the past 12 months	24-h avg: 28.2 (8.8)	NR	NR	12.0, 58.1	Incident Episodes Asthma 82% (−39, 271) lag 0-2 Cough 82% (−11, 292) lag 0-2 Respiratory Infections 675% (4, 5719) lag 0-2

TABLE 5A (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Ward et al. (2002) United Kingdom 1997	162 children 9 yrs old	24-h Median: Winter: 18.0 Summer: 13.3	NR	NR	Winter: 4, 35 Summer: 3, 29	Winter Cough 18% (−14, 64) lag 2 Illness 18% (−1, 40) lag 0 Shortness of Breath 7% (−13, 32) lag 0 Wheeze 12% (−13, 49) lag 3 Summer Cough 28% (3, 57) lag 0 Illness 3% (−24, 38) lag 0 Shortness of Breath 35% (−3, 85) lag 0 Wheeze −8% (−37, 31) lag 0
Jalaludin et al. (2004) Sydney, Australia 1994	148 children in 3rd to 5th grade with a history of wheezing in the previous 12 months	24-h avg: 15 (6)	NR	NR	Max = 47	Wheeze 7% (−5, 21) lag 2 Dry Cough 7% (−9, 26) lag 0 Wet Cough 13% (0, 26) lag 0

TABLE 5A (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Boezen et al. (1999) the Netherlands (Rural: Bodegraven, Meppel, Nunspeet; Urban: Rotterdam, Amsterdam) 1992-1995	632 children 7-11 yrs old	24-h avg: Rural: 15.3 Urban: 25.6	NR	NR	NR	With Bronchial Hyperresponsiveness (BHR) and High Serum Total IgE Lower Respiratory Symptoms: 19% (3, 37) lag 0 Upper Respiratory Symptoms: 4% (−5, 13) lag 2 With BHR and Low Serum Total IgE Lower Respiratory Symptoms: −27% (−46, −1) lag 0 Upper Respiratory Symptoms: 3% (−9, 16) lag 2 Without BHR or Low Serum Total IgE Lower Respiratory Symptoms: 12% (−8, 37) lag 0 Upper Respiratory Symptoms: 8% (−1, 17) lag 2 Without BHR or High Serum Total IgE Lower Respiratory Symptoms: 4% (−14, 26) lag 0 Upper Respiratory Symptoms: 9% (−3, 21) lag 0

TABLE 5A (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Van der Zee et al. (2000) the Netherlands (Rural: Bodegraven, Meppel, Nunspeet; Urban: Rotterdam, Amsterdam) 1992-1995	489 adults 50-70 yrs old	24-h Median: Urban: 25.7 Nonurban: 12.3	NR	NR	NR	Symptomatic Adults Urban Lower Respiratory Symptoms: −4% (−13, 7) lag 0 Upper Respiratory Symptoms: 11% (1, 22) lag 0 Nonsymptomatic Adults Urban >10% PEF: 0% (−30, 46) lag 1 Upper Respiratory Symptoms: 0% (−14, 16) lag 0
Harré et al. (1997) Christchurch, New Zealand 1994	40 people >55 with COPD	NR	NR	NR	NR	Morning Asthma Symptoms: −2% (−4, 0) lag 1 Evening Asthma Symptoms: 0% (−1, 2) lag 1 Chest Symptoms: 140% (−66, 1634) lag 1 Wheeze: 91% (−47, 613) lag 1
Ségala et al. (2004) Paris, France 1999-2000	46 adult nonsmokers 18-64 yrs old	24-h avg: 30 (8.6)	NR	NR	11.5, 70.1	Cough: 113% (0, 358) lag 0-4
Higgins et al. (1995)						

TABLE 5A (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Desqueyroux et al. (2002) Paris, France 1995-1996	60 severe asthmatic adults	24-h avg: 28.3 (8.1)	NR	NR	11.0, 67.0	Incident Asthma Attacks 16% (−21, 70) lag 1 29% (−30, 134) lag 0-5
Desqueyroux et al. (2002) Paris, France 1995-1996	39 adults with COPD	24-h avg: 28.3 (8.1)	NR	NR	11.0, 67.0	Exacerbation of COPD 24-h avg: 8% (−39, 94) lag 1 −24% (−73, 120) lag 0-5 1-h max: 12% (−70, 1378) lag 1 12% (−78, 2599) lag 0-5
Boezen et al. (1998) the Netherlands (Meppel, Amsterdam) 1993-1994	189 adults 48-73 yrs old	24-h avg: Urban: 24.1 Rural: 13.9	NR	NR	Urban: 11.6, 39.7 Rural: 3.4, 28.4	Without Bronchial Hyperresponsiveness Upper Respiratory Symptoms 5% (−5, 16) lag 0 Lower Respiratory Symptoms 1% (−11, 15) lag 0 Cough: -2% (−11, 9) lag 0 Phlegm: 1% (−8, 11) lag 0
Hiltermann et al. (1998) the Netherlands 1995	60 nonsmoking adults with intermittent to severe persistent asthma 18-55 yrs old	24-h avg: 11.1	NR	NR	3.6, 22.1	Shortness of Breath: 25% (0, 54 lag 0 Cough and/or Phlegm: 4% (−11, 25) lag 1 Nasal Symptoms: −14% (−33, 12) lag 0

TABLE 5A (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Forsberg et al. (1998) Landskrona, Sweden	38 people with asthma or asthma-like symptoms >15 yrs old	24-h avg: 16.0 (7.0)	NR	NR	3.0, 37.5	Day: Any Asthma: 17% Severe Asthma: 127% Evening: Any Asthma: 19% Severe Asthma: 134%
Von Klot et al. (2002) Erfurt, Germany 1996-1997	53 adult asthmatics	24-h avg: 24.1	NR	NR	4.2, 62.3	Wheeze: 1% (−5, 7) lag 0 8% (1, 15) lag 0-5 Shortness of Breath: 0% (−5, 5) lag 0 6% (−1, 14) lag 0-5 Phlegm: 5% (−1, 10) lag 0 11 (5, 19) lag 0-5 Cough: 3% (−3, 8) lag 0 8% (0, 15) lag 0-5
Pino et al. (2004) Santiago, Chile 1995-1996	504 infants	24-h avg: 41.1 (19.2)	NR	NR	NR	Wheezing Bronchitis: 14% (4, 30) lag 6

TABLE 5A (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
van der Zee et al. (1999)	633 children 7-11 yrs old with and without respiratory symptoms	24-h avg: Urban: 25.5	NR	NR	NR	With Symptoms: Lower Respiratory Symptoms: 11% (−7, 30) lag 2 Upper Respiratory Symptoms: −2% (−11, 8) lag 2 Cough: 3% (−6, 12) lag 2 Without Symptoms: Upper Respiratory Symptoms: 5% (−8, 19) lag 0 Cough: 1% (−11, 13) lag 2

*24-h avg NO_2 standardized to 20 ppb increment; 1-h max NO_2 standardized to 30 ppb increment

COPD = Chronic obstructive pulmonary disease.

NR = Not reported.

PEF = Peak expiratory flow.

TABLE 5B. EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Emergency Department Visits—All Respiratory						
Peel et al. (2005) Atlanta, GA, United States Jan 1993-Aug 2000	484,830 ED visits, all ages from 31 hospitals	1-h max: 45.9 (17.3)	52	59	Max: 256	1.024 (1.009, 1.041)
Stieb et al. (2000) Saint John, New Brunswick, Canada Jul 1992-Mar 1996	19,821 ED visits	24-h avg: 8.9	NR	NR	0, 82	−14.70%
Emergency Department Visits—Asthma						
Jaffe et al. (2003) 2 cities, OH, United States (Cleveland, Cincinnati) Jul 91-Jun 96	4,416 ED visits for asthma, age 5-34	24-h avg: Cincinnati: 50 (15) Cleveland: 48 (15)	NR	NR	NR	6.1% (−2.0, 14.0)
Norris[†] et al. (1999) Seattle, WA, United States, 1995-1996	900 ED visits for asthma, <18 yrs	24-h avg: 20.2 (7.1) 1-h max: 34.0 (11.3)	NR	NR	NR	24-h avg: −2.0% (−21, 19) 1-h avg: 5% (−2, 33)
Lipsett et al (1997) Santa Clara County, CA, United States, 1988-1992 (winter only)	ED visits for asthma	1-h max: 69 (28)	NR	NR	29, 150	48%

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Emergency Department Visits—Asthma						
Peel et al. (2005) Atlanta, GA, United States Jan 1993-Aug 2000	Asthma ED visits, all ages and 2-18 yrs from 31 hospitals	1-h max: 45.9 (17.3)	NR	NR	NR	All Ages: 2.1% (−0.4, 4.5) 2-18 yrs: 4.1% (0.8, 7.6)
Sunyer et al. (1997) Multi-city, Europe (Barcelona, Helsinki, Paris, London) 1986-1992	ED visits for asthma for ages <15 and 15-64	24-h avg: 24.1	NR	NR	2.6, 181.7	<15 yrs: 3% (0, 5) 15-64 yrs: 3% (1, 5)
Atkinson et al. (1999b) London, United Kingdom 1992-1994	98,685 all respiratory and asthma ED visits for all ages, 0-14, 15-64, and 65+ from 12 hospitals	1-h max: 50.3 (17.0)	NR	NR	NR	All ages: 4% (1, 6) 0-14 yrs: 7% (4, 11) lag 1 15-64 yrs: 4% (0, 7) lag 2
Thompson et al. (2001) Belfast, Northern Ireland 1993-1995	1,044 asthma ED visits for children	24-h avg: 21.3	NR	NR	NR	25% (6, 44) lag 0-3
Boutin-Forzano et al. (2004) Marseille, France 1997-1998	549 asthma ED visits for ages 3-49	24-h avg: 18.3	NR	NR	1.6, 44.5	3% (−2, 7) lag 0

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Emergency Department Visits—Asthma (cont'd)						
Castellsague et al. (1995) Barcelona, Spain 1986-1989	Asthma ED visits for ages 15-64	24-h avg: 26.8	NR	NR	NR	11% (2, 22) lag 0-2
Galán et al. (2003) Madrid, Spain 1995-1998	4,827 asthma ED visits for all ages	24-h avg: 35.1 (9.4)	NR	NR	Max: 77.2	13% (5, 22) lag 3
Tenías et al. (1998) Valencia, Spain 1993-1995	734 asthma ED visits for ages >14	24-h avg: 30.2 1-h max: 52.9	NR	NR	NR	24-h avg: 33% (8, 62) lag 0 1-h max: 23% (5, 45) lag 0
Migliaretti et al. (2005) Turin, Italy 1997-1999	1,401 asthma ED visits for ages <15, 15-64, and >64 and 201,071 controls	24-h avg: 59 (15.8)	NR	NR	NR	All ages; 10% (2, 18) lag 0-3 0-14 yrs: 9% (1, 18) lag 0-3 15-64 yrs: 12% (0, 33) lag 0-3 >65 yrs: 33% (1, 72) lag 0-3
Kim et al. (2007) Seoul, Korea 2002	92,535 asthma ED visits for all ages	24-h avg: 36.0 (14.7)	NR	NR	2.3, 108.0	
Tolbert et al. (2000) Atlanta, GA, United States, 1993-1995	5,934 ED visits for asthma, age 0-16	1-h max: 81.7 (53.8)	NR	NR	5.35, 306	0.7% (−0.8, 2.3)

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Emergency Department Visits—Asthma (cont'd)						
Cassino† et al. (1999) New York City, NY, United States 1989-1993	1,115 ED visits from 11 hospitals	24-h avg: 45.0	NR	NR	NR	lag 0: −4% (−19, 12) lag 1: 5% (−11, 25) lag 2: 9% (−8, 28)
Stieb et al. (1996) St. John, New Brunswick, Canada 1984-1992 (summers only)	1,163 ED visits for asthma, ages 0-15, 15+ from 2 hospitals	1-h max: 25.2	NR	NR	0, 120	$NO_2 + O_3$: −11%
Hospital Admissions—All Respiratory						
Gwynn† et al. (2000) Buffalo, NY, United States, 1988-1990, Days: 1,090	Respiratory hospital admissions	24-h avg: 20.5	NR	NR	4.0, 47.5	2.20%
Burnett et al. (1997a) 16 Canadian Cities, Canada, 4/1981-12/1991, Days: 3,927	All respiratory admission from 134 hospitals	1-h max: 35.5 (16.5)	NR	87	NR	Only report results or multipollutant model adjusted for CO, O_3, SO_2 and CoH: −0.3% (−2.4%, 1.8%)

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—All Respiratory (cont'd)						
Yang et al. (2003) Vancouver, BC, Canada 1986-1998, Days: 4,748	Respiratory hospital admissions among young children (<3 yrs) and elderly (≥65 yrs)	24-h avg: 18.74 (5.66)	NR	NR	NR	<3 yrs: 19.1% (7.4, 36.3) >65 yrs: 19.1% (11.2, 36.3)
Fung et al. (2006) Vancouver, BC, Canada 6/1/95-3/31/99	All respiratory admissions for elderly (65+ yrs)	24-h avg: 16.83 (4.34)	NR	NR	7.22, 33.89	9.1% (1.5, 17.2)
Burnett[†] et al. (2001) Toronto, ON, Canada 1980-1994	All respiratory admissions for young children (<2 yrs)	1-h max: 44.1	NR	86	Max = 146	18.20%
Luginaah et al. (2005) Windsor, ON, Canada 4/1/95-12/31/00	All respiratory admissions ages 0-14, 15-64, and 65+ from 4 hospitals	1-h max: 38.9 (12.3)	NR	NR	NR	All ages, female: 6.7% (−5.4, 20.4) All ages, male: −10.3% (−20.3, 1.1) 0-14, female: 22.4% (−1.2, 51.5) 0-14, male: −8.3% (−13.7, 0.8) 15-64, female: 23.9% (−4.1, 60.0) 15-64, male: 2.3% (−17.7, 44.3) 65+, female: 3.8% (−12.8, 23.5) 65+, male: −14.6 (−29.2, 3.0)

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—All Respiratory (cont'd)						
Simpson et al. (2005a) Multicity study, Australia (Sydney, Melbourne, Brisbane, Perth) 1996-1999	All respiratory, asthma, and pneumonia with bronchitis hospital admissions for ages 15-64 and 65+ years	1-h max: 22	NR	NR	NR	>65 yrs: 8% (5, 12) lag 0-1
Barnett et al. (2005) Multicity, Australia/New Zealand (Auckland, Brisbane, Canberra, Christchurch, Melbourne, Perth, Sydney) 1998-2001	All respiratory, asthma, and pneumonia with bronchitis hospital admissions for ages 0, 1-4, and 5-14	24-h avg: 10 1-h max: 19.1	NR	NR	NR	24-h avg: 0 yrs: 13% (−4, 32) lag 0-1 1-4 yrs: 10% (−3, 24) lag 0-1 5-14 yrs: 25% (7, 46) lag 0-1 1-h max: 0 yrs: 8% (−5, 22) lag 0-1 1-4 yrs: 10% (2, 17) lag 0-1 5-14 yrs: 17% (5, 29) lag 0-1
Hinwood et al. (2006) Perth, Australia 1992-1998	COPD, pneumonia, and asthma hospital admissions for all ages, <15, and 65+	24-h avg: 10.3 (5.0)	NR	NR	NR	All ages: 4% (−4, 8) lag 1 >65 yrs: 10% (2, 24) lag 1

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—All Respiratory (cont'd)						
Petroeschevsky et al. (2001) Brisbane, Australia 1987-1994	All respiratory (33,710) and asthma (13,246) hospital admissions for all ages, 0-4, 5-14, 15-64, and 65+	24-h avg: 139 1-h max: 282	NR	NR	24-h avg: 12, 497 1-h max: 35, 1558	24-h avg: 15-64 yrs: 5% (−3, 15) lag 0 >65 yrs: −18% (−28, −8) lag 5 1-h max: All ages: −3% (−7, 1) lag 1 0-4 yrs: 5% (−1, 11) lag 3 5-14 yrs: −4% (−14, 6) lag 0
Schouten et al. (1996) Multicity, the Netherlands (Amsterdam, Rotterdam) 1977-1989	All respiratory, asthma, and COPD hospital admissions for all ages, 15-64, and 65+	24-h avg: Amsterdam: 26.2 Rotterdam: 28.3 1-h max: Amsterdam: 39.3 Rotterdam: 42.9	NR	NR	NR	24-hr avg: Amsterdam: 15-64 yrs: −4% (−9, 0) lag 1 >65 yrs: 1% (−4, 6) lag 2 Rotterdam (1985-1989): 15-64 yrs: −1% (−7, 4) lag 1 >65 yrs: 6% (0, 13) lag 0 1-h max:: Amsterdam: 15-64 yrs: −6% (−11, −2) lag 1 >65 yrs: 1% (−5%, 5) lag 2 Rotterdam: 15-64 yrs: 2% (−3, 7) lag 1 >65 yrs: 4% (−2, 10) lag 0

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—All Respiratory (cont'd)						
Ponce de Leon et al. (1996) London, England 1987-1988; 1991-02/1992	19,901 all respiratory hospital admissions for all ages, 0-14, 15-64, and 65+	24-h avg: 37.3 (13.8)	NR	NR	NR	All ages: 1% (0, 2) lag 2 0-14 yrs: 1% (0, 2) lag2 15-64 yrs: 1% (−1, 2) lag 1 >65 yrs: 2% (0, 3) lag 2
Atkinson et al. (1999a) London, England 1992-1994	165,032 all respiratory, asthma, asthma + COPD, lower respiratory disease hospital admissions for all ages, 0-14, 15-64, and 65+	1-h max: 50.3 (17.0)			22.0, 224.3	All ages: 1% (0, 3) lag 1 0-14 yrs: 2% (0, 4) lag 2 15-64 yrs: 1% (−1, 3) lag 1 >65 yrs: 2% (0, 4) lag 3
Spix et al. (1998) Multicity (London, Amsterdam, Rotterdam, Paris), Europe 1977 + 1991	All respiratory and asthma hospital admissions for ages 15-64 and 65+	24-h avg: London: 18.3 Amsterdam: 26.2 Rotterdam: 27.7 Paris: 22.0	NR	NR	NR	15-64 yrs: 1% (−1, 3) >65 yrs: 1% (−1, 5)

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—All Respiratory (cont'd)						
Wong[†] et al. (2002) London England and Hong Kong London: 1992-1994 Hong Kong: 1995-1997	All respiratory and asthma hospital admissions for all ages, 15-64, and 65+	24-h avg: Hong Kong: 29.3 (10.2) London: 33.7 (10.7)	NR	NR	Hong Kong: 15.3, 151.5 London: 23.7, 255.8	>65 yrs Hong Kong: 7% (5, 9) lag 0-1 5% (3, 7) lag 0 London: 0% (−2, 2) lag 0-1 3% (2, 5) lag 3
Anderson et al. (2001) West Midlands conurbation, United Kingdom 1994-1996	All respiratory, asthma, and COPD hospital admissions for all ages, 0-14, 15-64, and 65+	1-h max: 37.2 (15.1)	NR	NR	10.7, 176.1	All ages: 2% (0, 4) lag 0-1 0-14 yrs: 3% (−1, 6) lag 0-1 15-64 yrs: 0% (−4, 4) lag 0-1 >65 yrs: 1% (−2, 5) lag 0-1
Prescott et al. (1998) Edinburgh, United Kingdom 1992-1995	All respiratory hospital admissions (i.e., Pneumonia and COPD + asthma) for ages <65 and 65+	24-h avg: 26.4 (7)	NR	NR	9, 58	>65 yrs: 6% (−9, 24) rolling 3-day avg <65 yrs: 0% (−14, 16) rolling 3-day avg
Hagen et al. (2000) Drammen, Norway 1994-1997	All respiratory admissions for all ages at 1 hospital	24-h avg: 18.9 (8.4)	NR	NR	NR	14% (−1, 31) lag 0-3

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—All Respiratory (cont'd)						
Oftedal et al. (2003) Drammen, Norway 1994-2000	All respiratory admissions for all ages	24-h avg: 17.7 (8.4)	NR	NR	NR	11% (3, 20) lag 3
Andersen et al. (2007a) Copenhagen, Germany 1999-2004	Chronic bronchitis, emphysema, COPD, and asthma hospital admissions for ages 5-18, and 65+	24-h avg: 12 (5)	NR	NR	NR	>65 yrs: 12% (3, 22) lag 5 day moving avg
Andersen et al. (2007b) Copenhagen, Germany 2001-2004	Chronic bronchitis, emphysema, COPD, and asthma hospital admissions for ages 5-18, and 65+	24-h avg: 11 (5)	NR	NR	NR	>65 yrs: 21% (3, 46) lag 0-4 moving avg
Dab[†] et al. (1996) Paris, France 1987-1992	All respiratory, asthma, and COPD hospital admissions for all ages at 27 hospitals	24-h avg: 23.6 1-h max: 38.6	NR	24-h avg: 56.7 1-h max: 106.1	NR	24-h avg: 2% (0, 3) lag 0 1-h max: 1% (0, 2) lag 0

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—All Respiratory (cont'd)						
Llorca et al. (2005) Torrelavega, Spain 1992-1995	All respiratory hospital admissions for all ages at 1 hospital	24-h avg: 11.2 (8.6)	NR	NR	NR	18% (12, 24)
Farchi et al. (2006) Rome, Italy 1994-1995	2,947 all respiratory hospital admissions for ages 6-7	24-h avg: 24.6 (5.3)	NR	NR	12.6, 34.6	157% (−7, 624)
Fusco[†] et al. (2001) Rome, Italy 1995-1997	All respiratory, asthma, COPD, and respiratory infection hospital admissions for all ages and 0-14	24-h avg: 45.4 (8.5)	NR	NR	NR	All ages: 4% (2, 7) lag 0 0-14 yrs: 7% (1, 13) lag 0
Pantazopoulou et al. (1995) Athens, Greece 1988	15,236 all respiratory hospital admissions for all ages at 14 hospitals	24-h avg: Winter: 49.2 (13.1) Summer: 58.1 (16.8)	NR	NR	NR	Winter: 11% (3, 20) Summer: 3% (−5, 8)
Gouveia and Fletcher, (2000) São Paulo, Brazil 1992-1994	All respiratory, pneumonia, and asthma or bronchitis hospital admissions for ages <1 and <5	1-h max: 91.3 (53.0)	NR	NR	13.6, 362.8	<5 yrs: 1% (0, 2) lag 0

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—All Respiratory (cont'd)						
Braga[†] et al. (2001) São Paulo, Brazil 1993-1997	All respiratory hospital admissions for ages 0-19, <2, 3-5, 6-13, and 14-19	24-h avg: 74.0 (37.3)	NR	NR	13.1, 341.4	<2 yrs: 7% (4, 9) lag 5 3-5 yrs: 1% (−5, 7) 6-13 yrs: 2% (−4, 7) 14-19 yrs: −2% (−11, 7) 0-19 yrs: 5% (2, 7)
Wong et al. (1999) Hong Kong, China 1994-1995	All respiratory, asthma, COPD, and pneumonia hospital admissions for all ages, 0-4, 5-64, and 65+ at 12 hospitals	24-h avg: 26.9	NR	NR	8.6, 64.1	0-4 yrs: 8% (4, 12) lag 0-3 5-64 yrs: 9% (4, 14) lag 0-3 >65 yrs: 10% (5, 14) lag 0-3
Hospital Admissions—Asthma						
Linn et al. (2000) Los Angeles, CA, United States 1992-1995	302,600 COPD and asthma hospital admissions	24-h avg: Winter: 3.4 (1.3); Spring: 2.8 (0.9); Summer: 3.4 (1.0); Autumn: 4.1 (1.4); all yr: 3.4 (1.3)	NR	NR	NR	2.8% ± 1.0%

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—Asthma (cont'd)						
Lin[†] et al. (2004) Vancouver, BC, Canada 1987-1991	Asthma hospital admissions among 6-12 yr olds	24-h avg: 18.65 (5.59)	NR	NR	4.28, 45.36	Boys, low SES: 45.3% (12.7, 88.3) Boys, high SES: 12.7% (−14.6, 49.3) Girls, low SES: 23.0% (−11.7, 70.2) Girls, high SES: 3.1% (−27.6, 45.3)
Lin et al. (2003) Toronto, ON, Canada 1981-1993	Asthma hospital admissions among 6-12 yr olds	24-h avg: 25.24 (9.04)	NR	NR	3.0, 82.0	Boys: 18.9% (1.8, 39.3) Girls: 17.0% (−5.4, 41.4)
Burnett et al. (1999) Toronto, ON, Canada 1980-1994	Asthma hospital admissions	24-h avg: 25.2 (9.1)	NR	NR	NR	2.60%
Barnett et al. (2005) Multicity, Australia/New Zealand; (Auckland, Brisbane, Canberra, Christchurch, Melbourne, Perth, Sydney) 1998-2001	All respiratory, asthma, and pneumonia with bronchitis hospital admissions for ages 0, 1-4, and 5-14	24-h avg: 8 1-h max: 19.1	NR	NR	NR	24-h avg: 1-4 yrs: 11% (−5, 28) lag 0-1 5-14 yrs: 26% (1, 57) lag 0-1 1-h max: 1-4 yrs: 9% (−1, 18) lag 0-1 5-14 yrs: 9% (−7, 28) lag 0-1

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—Asthma (cont'd)						
Erbas et al. (2005) Melbourne, Australia 2000-2001	8, 955 asthma hospital admissions among 1-15 yr olds for 6 hospitals	24-h avg: 16.80 (8.61)	NR	NR	2.43, 63.00	Inner Melbourne: −14% (−26, −2) lag 0 Western Melbourne: 10% (2, 18) lag 2 Eastern Melbourne: 8% (−8, 25) lag 0 South/Southeastern Melbourne: −2% (−23, 21) lag 1
Hinwood et al. (2006) Perth, Australia 1992-1998	COPD, pneumonia, and asthma hospital admissions for all ages, <15, and 65+	24-h avg: 10.3 (5.0)	NR	NR	NR	All ages: 2% (−2, 6) lag 0 0-14 yrs: 4% (−4, 8) lag 0 >65 yrs: −8% (−11, 4) lag 0
Petroeschevsky et al. (2001) Brisbane, Australia 1987-1994	All respiratory (33,710) and asthma (13,246) hospital admissions for all ages, 0-4, 5-14, 15-64, and 65+	1-h max: 282	NR	NR	1-h max: 35, 1558	All ages: −11% (−18, -3) lag 0-2 0-4 yrs: −7% (−15, 1) lag 0 5-64 yrs: −5% (−15, 5) lag 1

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—Asthma (cont'd)						
Morgan et al. (1998a) Sydney, Australia 1990-1994	COPD and asthma hospital admissions for ages 1-14, 15-64, 65+, all ages for 27 hospitals	24-h avg: 15 (6) 1-h max: 29 (3)	NR	NR	24-h avg: 0, 52 1-h max: 0, 139	24-h avg: 1-14 yrs: 4% (−2, 10) lag 0 15-64 yrs: 3% (−3, 9) lag 0 1-h max: 1-14 yrs: 5% (1, 10) lag 0 15-64 yrs: 3% (2, 8) lag 0
Sunyer et al. (1997) Multicity, Europe (Barcelona, Helsinki, Paris, London) 1986-1992	Asthma hospital admissions for ages <15 and 15-64	24-h avg: 24.1	NR	NR	NR	<15 yrs: 3% (0, 5) lag 0-3, cumulative 15-64 yrs: 3% (1, 5) lag 0-3, cumulative
Schouten et al. (1996) Multicity, the Netherlands (Amsterdam, Rotterdam) 1977-1989	All respiratory, asthma, and COPD hospital admissions for all ages, 15-64, and 65+	24-h avg: Amsterdam: 26.2 Rotterdam: 28.3 1-h max: Amsterdam: 39.3 Rotterdam: 42.9	NR	NR	NR	24-h avg: Amsterdam: All ages: 2% (−4, 10) lag 2

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—Asthma (cont'd)						
Atkinson et al. (1999a) London, England 1992-1994	165,032 all respiratory, asthma, asthma + COPD, lower respiratory disease hospital admissions for all ages, 0-14, 15-64, and 65+	1-h max: 50.3 (17.0)			22.0, 224.3	All ages: 1% (−1, 4) lag 0 0-14 yrs: 1% (−1, 5) lag 3 15-64 yrs: 4% (1, 8) lag 1 >65 yrs: 4% (−2, 10) lag 3
Wong[†] et al. (2002) London England and Hong Kong London: 1992-1994 Hong Kong: 1995-1997	All respiratory and asthma hospital admissions for all ages, 15-64, and 65+	24-h avg: Hong Kong: 29.3 (10.2) London: 33.7 (10.7)	NR	NR	Hong Kong: 15.3, 151.5 London: 23.7, 255.8	15-64 yrs: Hong Kong: −2% (−8, 4) lag 0-1 −5% (−10, 0) lag 1 London: 4% (0, 8) lag 0-1 4% (1, 8) lag 2
Anderson et al. (1998) London, England 1987-1992	Asthma hospital admissions for all ages, <15, 15-64, and 65+	24-h avg: 37.2 (12.3)	NR	NR	24-h avg: 14, 182	All ages: 4% (2, 6) lag 0-3 0-14 yrs: 4% (1, 6) lag 0-3 15-64 yrs: 2% (−1, 7) lag 0-1 >65 yrs: 6% (0, 13) lag 0-3
Thompson et al. (2001) Belfast, Northern Ireland 1993-1995	1,095 asthma hospital admissions for ages 0-14	24-h avg: 21.3	NR	NR	13, 28	25% (6, 44) lag 0-3

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—Asthma (cont'd)						
Pönkä (1991) Helsinki, Finland 1987-1989	Asthma hospital admissions for ages 0-14, 15-64, and 65+	24-h avg: 20.2 (8.5)	NR	NR	2.1, 88.8	
Andersen et al. (2007a) Copenhagen, Germany 1999-2004	Chronic bronchitis, emphysema, COPD, and asthma hospital admissions for ages 5-18, and 65+ at 9 hospitals	24-h avg: 12 (5)	NR	NR	NR	5-18 yrs: 41% (9, 83) lag 6 day moving avg
Andersen et al. (2007b) Copenhagen, Germany 2001-2004	Chronic bronchitis, emphysema, COPD, and asthma hospital admissions for ages 5-18, and 65+ at 9 hospitals	24-h avg: 11 (5)	NR	NR	NR	5-18 yrs: 14% (−24, 74) lag 0-5 moving avg
Dab[†] et al. (1996) Paris, France 1987-1992	All respiratory, asthma, and COPD hospital admissions for all ages at 27 hospitals	24-h avg: 23.6 1-h max: 38.6	NR	24-h avg: 56.7 1-h max: 106.1	NR	24-h avg: 6% (2, 11) lag 0-1 1-h max: 5% (1, 8) lag 0-1

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—Asthma (cont'd)						
Migliaretti and Cavallo (2004) Turin, Italy 1997-1999	734 asthmatics age matched (<4 or 4-15 yrs) with 25,523 other respiratory disease controls	24-h avg: 59.3	NR	NR	NR	All ages: 11% (0, 17) lag 1-3 cumulative <4 yrs: 11% (0, 21) lag 1-3 cumulative 4-15 yrs: 11% (0, 25) lag 1-3 cumulative
Fusco[†] et al. (2001) Rome, Italy 1995-1997	All respiratory, asthma, COPD, and respiratory infection hospital admissions for all ages and 0-14	24-h avg: 45.4 (8.5)	NR	NR	NR	All ages: 8% (−1, 18) lag 0 0-14 yrs: 19% (5, 35) lag 1
Gouveia and Fletcher, (2000) São Paulo, Brazil 1992-1994	All respiratory, pneumonia, and asthma or bronchitis hospital admissions for ages <1 and <5	1-h max: 91.3 (53.0)	NR	NR	13.6, 362.8	<5 yrs: 2% (−1, 5) lag 2
Lee et al. (2006) Hong Kong, China 1997-2002	26,663 asthma hospital admissions for ages <18	24-h avg: 33.9 (10.9)	NR	NR	NR	13% (10, 16) lag 3

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—Asthma (cont'd)						
Tsai et al. (2006) Kaohsiung, Taiwan 1996-2003	17,682 asthma hospital admissions for all ages	24-h avg: 27.2 (17)	NR	NR	4.83, 63.4	>25°C: 31% (13, 52) lag 0-2 <25°C: 142% (109, 179) lag 0-2
Lee[†] et al. (2002) Seoul, Korea 1997-1999	6,436 asthma hospital admissions for ages <15	24-h avg: 31.5 (10.3)	NR	NR	NR	21% (14, 28) lag 0-2
Yang et al. (2007) Taipei, Taiwan 1996-2003	25,602 asthma hospital admissions for all ages at 47 hospitals	24-h avg: 30.77	NR	NR	3.84, 77.97	>25°C: 39% (24, 55) lag 0-2 <25°C: 27% (16, 39) lag 0-2
Ko et al. (2007) Hong Kong, China 2000-2005	69,176 asthma hospital admissions for all ages at 15 hospitals	24-h avg: 27.9 (10.1)	NR	NR	6.96, 78.3	All ages: 11% (8, 14) lag 0-4 0-14 yrs: 16% (11, 21) lag 0-4 15-64 yrs: 7% (3, 12) lag 0-4 >65 yrs: 9% (5, 13) lag 0-4
Lee et al. (2006) Hong Kong, China 1997-2002	26,663 asthma hospital admissions for ages <18	24-h avg: 33.9 (10.9)	NR	NR	NR	13% (10, 16) lag 3

TABLE 5B (cont'd). EFFECTS OF SHORT-TERM NO_2 EXPOSURE ON EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS FOR RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO_2 Levels (ppb)	Statistics for NO_2 Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Hospital Admissions—Asthma (cont'd)						
Wong et al. (1999) Hong Kong, China 1994-1995	All respiratory, asthma, COPD, and pneumonia hospital admissions for all ages, 0-4, 5-64, and 65+ at 12 hospitals	24-h avg: 26.9	NR	NR	8.6, 64.1	All ages: 10% (4, 17) lag 0-3
Wong et al. (2001) Hong Kong, China 1993-1994	1,217 asthma hospital admissions for ages <15 at 1 hospital	24-h avg: 22.7 (8.7)	NR	NR	4.7, 55.5	34%

*24-h avg NO_2 standardized to 20 ppb increment; 1-h max NO_2 standardized to 30 ppb increment.

†GAM impacted study.

CoH = Coefficient of haze.

COPD = Chronic obstructive pulmonary disease.

NR = Not reported.

SES = Socioeconomic status.

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