

# **Integrated Science Assessment for Oxides of Nitrogen – Health Criteria**

**(First External Review Draft)**

# **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

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## PREFACE

### **Legislative Requirements**

Two sections of the Clean Air Act (CAA) govern the establishment and revision of the national ambient air quality standards (NAAQS). Section 108 (U.S. Code, 2003a) directs the Administrator to identify and list “air pollutants” that “in his judgment, may reasonably be anticipated to endanger public health and welfare” and whose “presence in the ambient air results from numerous or diverse mobile or stationary sources” and to issue air quality criteria for those that are listed. Air quality criteria are intended to “accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in ambient air.”

Section 109 (U.S. Code, 2003b) directs the Administrator to propose and promulgate “primary” and “secondary” NAAQS for pollutants listed under Section 108. Section 109(b)(1) defines a primary standard as one “the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health.”<sup>1</sup> 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.”<sup>2</sup>

The requirement that primary standards include an adequate margin of safety was intended to address uncertainties associated with inconclusive scientific and technical

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<sup>1</sup> The legislative history of Section 109 indicates that a primary standard is to be set at “the maximum permissible ambient air level ... which will protect the health of any [sensitive] group of the population” and that, for this purpose, “reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group” [U.S. Senate (1970)].

<sup>2</sup> 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.”

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 is seeking not only to prevent pollution levels that have been demonstrated to be harmful but also to prevent lower pollutant levels that may pose an unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree.

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

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

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

## **History of Reviews of the Primary NAAQS for NO<sub>2</sub>**

On April 30, 1971, EPA promulgated identical primary and secondary NAAQS for nitrogen dioxide (NO<sub>2</sub>), under Section 109 of the Act, set at 0.053 parts per million (ppm), annual average (Federal Register, 1971). In 1982, EPA published an Air Quality Criteria Document (AQCD) for Oxides of Nitrogen (Environmental Protection Agency, 1982), which updated the scientific criteria upon which the initial NO<sub>2</sub> 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 that it was undertaking plans to revise the 1982 AQCD 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<sub>2</sub> and other oxides of nitrogen. CASAC reviewed the document at a meeting held on July 1, 1993, 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<sub>2</sub>” (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<sub>2</sub> NAAQS. The Staff Paper received external review at a December 12, 1994, CASAC meeting. CASAC comments and recommendations were reviewed by EPA staff and incorporated into the final draft of the Staff Paper as appropriate. CASAC reviewed the final draft of the Staff Paper in June 1995 and responded by written closure letter (Wolff, 1995). In September of 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<sub>2</sub> (Federal Register, 1995). The decision not to revise the NO<sub>2</sub> NAAQS was finalized after careful evaluation of the comments received on the

proposal. The level for both the existing primary and secondary NAAQS for NO<sub>2</sub> is 0.053 ppm annual arithmetic average, calculated as the arithmetic mean of the 1-h NO<sub>2</sub> concentrations.

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## Abbreviations and Acronyms

$\alpha$	alpha
ACP	accumulation mode particle
ACS	American Cancer Society
ADP	adenosine dinucleotide phosphate
AgNOR	argyrophilic nucleolar organizer region
AIRC	Atherosclerosis Risk in Communities (study)
AIRE	Acute Infarction Ramipril Efficacy (study)
AM	alveolar macrophage
AMT	average medial thickness
APHEA	Air Pollution on Health: a European Approach (study)
AQCD	Air Quality Criteria Document
AsNaO <sub>2</sub>	sodium dioxoarsenate
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
BC	black carbon
BHPN	<i>N</i> -bis(2-hydroxyl-propyl)nitrosamine
BHR	bronchial hyperresponsivity
BMI	body mass index
BP	blood pressure
Br	bromine
BrdU	bromodeoxyuridine
BRFSS	Behavioral Risk Factor Surveillance System
C × T	concentration × time; concentration times duration of exposure
CAA	Clean Air Act
CAMP	Childhood Asthma Management Program
CAPs	concentrated ambient particles
CASAC	Clean Air Scientific Advisory Committee
CC10	Clara cell 10-kDa protein
CC16	Clara cell 16-kDa protein
CD4	helper T lymphocyte
CD8	suppressor T lymphocyte
CDC	Centers for Disease Control and Prevention
cGMP	cyclic guanosine-3',5'-monophosphate
CH <sub>4</sub>	methane
CHD	coronary heart disease
CHF	congestive heart failure
CHS	Children's Health Study
CI	confidence interval

CMAQ	Community Multiscale Air Quality (model)
CO	carbon monoxide
CoH	coefficient of haze
CO <sub>2</sub>	carbon dioxide
COD	coefficient of divergence
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
Δ	delta; change in a variable
DEP	diesel exhaust particulates
DEP <sub>c</sub> CBP	diesel exhaust particulates extract-coated carbon black particles
DLCO	diffusing capacity of the lung for carbon monoxide
DMA	dimethylamine
DMN	dimethylnitrosamine
DNA	deoxyribonucleic acid
EC	elemental carbon
ED	emergency department
ECG	electrocardiography; electrocardiogram
ECP	eosinophil cationic protein
ELF	epithelial lining fluid
EMECAM	Spanish Multicentre Study on Air Pollution and Mortality
EPA	U.S. Environmental Protection Agency
ER	emergency room
ETS	environmental tobacco smoke
EXPOLIS	Air Pollution Exposure Distributions of Adult Urban Populations in Europe
FEF <sub>25-75</sub>	forced expiratory flow at 25 to 75% of vital capacity
FEF <sub>75</sub>	forced expiratory flow at 75% of vital capacity
FEV <sub>1</sub>	forced expiratory volume in 1 second
FRM	Federal Reference Method
FVC	forced vital capacity
GAM	Generalized Additive Model(s)
GEE	Generalized Estimating Equation(s)
GIS	Geographic Information System
GLMM	Generalized Linear Mixed Model(s)
GM-CSF	granulocyte-macrophage colony stimulating factor
GSH	glutathione; reduced glutathione
GSSG	oxidized glutathione
GST	glutathione <i>S</i> -transferase (e.g., GST M1, GST P1, GST T1)
H <sup>+</sup>	hydrogen ion
HCHO	formaldehyde
HF	high frequency

HNO <sub>3</sub>	nitric acid
HNO <sub>4</sub>	pernitric acid
HONO	nitrous acid
H <sub>2</sub> O <sub>2</sub>	hydrogen peroxide
HR	heart rate
HRV	heart rate variability
HS	hemorrhagic stroke
H <sub>2</sub> SO <sub>4</sub>	sulfuric acid
hν	solar ultraviolet proton
ICAM-1	intercellular adhesion molecule-1
ICD, ICD9	International Classification of Diseases, Ninth Revision
ICDs	implanted cardioverter defibrillators
Ig	immunoglobulin (e.g., IgA, IgE, IgG)
IHD	ischemic heart disease
IL	interleukin (e.g., IL-6, IL-8)
iNOS	inducible nitric oxide synthase
IQR	interquartile range
IS	ischemic stroke
ISA	Integrated Science Assessment
ISAAC	International Study of Asthma and Allergies in Children
KI	potassium iodide
LDH	lactate dehydrogenase
LF	low frequency
LOESS, LOWESS	locally weighted least squares
LT	leukotriene (e.g., LTB <sub>4</sub> , LTC <sub>4</sub> , LTD <sub>4</sub> , LTE <sub>4</sub> )
MI	myocardial infarction
MMEF	maximal midexpiratory flow
MoO <sub>x</sub>	molybdenum oxide
mRNA	messenger ribonucleic acid
MSA	metropolitan statistical area
MV	motor vehicle emissions
N, n	number of observations
NAAQS	National Ambient Air Quality Standards
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NAL	nasal lavage
NAS	Normative Aging Study
NCEA-RTP	National Center for Environmental Assessment in Research Triangle Park, NC
NC <sub>0.01-0.10</sub>	particle number concentration for particle diameter between 10 and 100 nm
NCICAS	National Cooperative Inner-City Asthma Study

NDMA	<i>N</i> -nitrosodimethylamine
NK	natural killer (lymphocytes)
NLCS	the Netherlands Cohort Study on Diet and Cancer
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NMOR	<i>N</i> -nitrosomorpholine
NO	nitric oxide
NO <sub>2</sub>	nitrogen dioxide
NO <sub>3</sub>	nitrate radical
NO <sub>3</sub> <sup>-</sup>	nitrate
NO <sub>x</sub>	oxides of nitrogen
NO <sub>y</sub>	sum of NO <sub>x</sub> and NO <sub>z</sub>
NO <sub>z</sub>	oxides of nitrogen and nitrates (difference between NO <sub>x</sub> and NO <sub>y</sub> )
N <sub>2</sub> O <sub>5</sub>	dinitrogen pentoxide
N/R	not reported
NRC	National Research Council
NSA	nitrosating agent
O <sub>3</sub>	ozone
OC	organic carbon
OH	hydroxyl radical
OR	odds ratio
P, p	probability value
PAARC	French air pollution and chronic respiratory diseases study
PAF	paroxysmal atrial fibrillation
PAH	polycyclic aromatic hydrocarbon
PAN	peroxyacyl nitrate; peroxyacetyl nitrate
Pb	lead
PC	principal components
PCR	polymerase chain reaction
PD20	provocative dose that produces a 20% decrease in FEV <sub>1</sub>
PD100	provocative dose that produces a 100% increase in sRAW
PEACE	Pollution Effects on Asthmatic Children in Europe (study)
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PM	particulate matter
PM <sub>10</sub>	combination of coarse and fine particulate matter
PM <sub>10-2.5</sub>	coarse particulate matter
PM <sub>2.5</sub>	fine particulate matter
PMA	phorbol myristate acetate
PMN	polymorphonuclear leukocytes
ppb	parts per billion

ppm	parts per million
PS	penalized splines
R	intraclass correlation coefficient; proprietary statistical package
r	correlation coefficient
$r_p$	Pearson's correlation coefficient
$r_s$	Spearman's rank correlation coefficient
$R^2$	multiple correlation coefficient
RCS	Robust Component Selection (regression model)
r-MSSD	square root of the mean of the squared difference between adjacent normal R-R intervals
ROS	reactive oxygen species
RR	rate ratio; relative risk
RSV	respiratory syncytial virus
SAPALDIA	Study of Air Pollution and Lung Diseases in Adults
SCE	sister chromatid exchange
SD	standard deviation
SDNN	standard deviation of normal R-R intervals
SE	standard error
SGA	small for gestational age
SNPs	single nucleotide polymorphisms
SO <sub>2</sub>	sulfur dioxide
SO <sub>4</sub> <sup>2-</sup>	sulfate
S-PLUS	general purpose statistics package
sRAW	specific airway resistance
STN	Speciation Trends Network
TEA	triethanolamine
Th2	T-derived helper 2 lymphocyte
TNF	tumor necrosis factor (e.g., TNF- $\alpha$ )
TSP	total suspended particulates
TWA	time-weighted average
TX	thromboxane (e.g., TXA <sub>2</sub> , TXB <sub>2</sub> )
UFP	ultrafine particles; <0.1 $\mu$ m diameter
VESTA	Five (V) Epidemiological Studies on Transport and Asthma
VOCs	volatile organic compounds
WHI	Women's Health Initiative
WHO	World Health Organization

# 1. INTRODUCTION

This draft Integrated Science Assessment (ISA) presents a concise synthesis and evaluation of the most policy-relevant science. It forms the scientific foundation for the review of the primary (health-based) National Ambient Air Quality Standards (NAAQS) for nitrogen dioxide (NO<sub>2</sub>).<sup>1</sup> The draft ISA is intended to “accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health which may be expected from the presence of [a] pollutant in ambient air” (Clean Air Act, Section 108 (42 U.S.C. 7408)).<sup>2</sup> Scientific research is incorporated from: atmospheric sciences, air quality analyses, exposure assessment, dosimetry, controlled human exposure studies, toxicology, and epidemiology. This document focuses on the gaseous oxides of nitrogen. The draft ISA contains the key information and judgments formerly found in the Air Quality Criteria Document (AQCD) for Oxides of Nitrogen. Also, a series of Annexes to the draft ISA provide more details of the most pertinent scientific literature. The draft ISA and the Annexes, thus serves to update and revise the information included in the 1993 AQCD document (U.S. Environmental Protection Agency, 1993).

It will be useful at the outset to distinguish between the definition of “nitrogen oxides” as it appears in the enabling legislation related to the NAAQS and the definition commonly used in the air pollution research and management community. In this document, the terms “oxides of nitrogen” and “nitrogen oxides” refer to all forms of oxidized nitrogen compounds, including nitric oxide (NO), nitrogen dioxide (NO<sub>2</sub>), and all other oxidized nitrogen-containing compounds transformed from NO and NO<sub>2</sub>. 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 community, the terms “oxides of nitrogen” and “nitrogen oxides” are restricted to refer only to the sum of NO and NO<sub>2</sub>, and this sum is commonly abbreviated as NO<sub>x</sub>. The category label used by this community for

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<sup>1</sup> Information on legislative requirements and history of NO<sub>2</sub> NAAQS reviews are presented in the Preface.

<sup>2</sup> The secondary NAAQS for NO<sub>2</sub> is being reviewed independently, in conjunction with the review of the secondary NAAQS for sulfur dioxide (SO<sub>2</sub>). A review of the primary NAAQS for SO<sub>2</sub> is also underway.



1 the sum of all forms of oxidized nitrogen compounds including those listed in Section 108(c) is  
2 NO<sub>y</sub>.

3 For the current review, multiple species of many nitrogen oxides are considered, as  
4 appropriate and as allowed by the available data. For example, descriptions of the atmospheric  
5 chemistry of nitrogen oxides include both gaseous and particulate species, because a meaningful  
6 analysis would not be possible otherwise. In addition, the health effects of gaseous nitrogen  
7 oxides other than NO<sub>2</sub> are evaluated when information on these other species is available.  
8 Finally, the possible influence of other atmospheric pollutants on the interpretation of the role of  
9 NO<sub>2</sub> in health effects studies is considered, including interactions of NO<sub>2</sub> with other pollutants  
10 that co-occur in the environment (e.g., sulfur dioxide [SO<sub>2</sub>], carbon monoxide [CO], ozone [O<sub>3</sub>],  
11 particulate matter [PM]). The available database for this draft ISA largely provides information  
12 on the health effects of NO<sub>2</sub>, with limited information examining other forms of oxides of  
13 nitrogen (e.g., nitrous acid [HONO]).

14 As discussed in the Draft Integrated Plan for the Review of the Primary NAAQS for  
15 Nitrogen Dioxide (U.S. Environmental Protection Agency, 2007), a series of policy-relevant  
16 questions frames this review of the scientific evidence to provide a scientific basis for a decision  
17 on whether the current primary NAAQS for NO<sub>2</sub> (0.053 parts per million (ppm), annual average)  
18 should be retained or revised. The draft ISA focuses on evaluation of the newly available  
19 scientific evidence to best inform consideration of these framing questions, including the  
20 following:

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

- 1 • What are the air quality relationships between short-term and long-term exposures  
2 to oxides of nitrogen?

### 3 4 5 **1.1 DOCUMENT DEVELOPMENT**

6 The U.S. Environmental Protection Agency formally initiated the current review of the  
7 NO<sub>2</sub> NAAQS by announcing the commencement of the review in the Federal Register with a call  
8 for information (Federal Register, 2005). In addition to the call for information, publications are  
9 identified through an ongoing literature search process that includes searching MEDLINE and  
10 other databases using as key words the terms: nitrogen oxides, nitrogen dioxide, NO, NO<sub>x</sub>, NO<sub>y</sub>,  
11 nitric acid, HNO<sub>3</sub>, pernitric acid, HNO<sub>4</sub>, nitrate radical, NO<sub>3</sub><sup>-</sup>, dinitrogen pentoxide, N<sub>2</sub>O<sub>5</sub>,  
12 organic nitrates, nitrous acid, HONO or HNO<sub>2</sub>, peroxyacetyl nitrate, PAN, and total reactive  
13 nitrogen. The search strategy is periodically reexamined and modified to enhance identification  
14 of pertinent published papers. Additional papers are identified for inclusion in the publication  
15 base in several ways. First, EPA staff reviews pre-publication tables of contents for journals in  
16 which relevant papers may be published. Second, expert chapter authors are charged with  
17 independently identifying relevant literature. Finally, additional publications that may be  
18 pertinent are identified by both the public and CASAC during the external review process. The  
19 focus of this ISA is on literature published since the 1993 AQCD for Oxides of Nitrogen. Key  
20 findings and conclusions from the 1993 review are discussed in conjunction with recent findings.  
21 Generally, only information that has undergone scientific peer review and that has been  
22 published (or accepted for publication) in the open literature is considered. The following  
23 sections briefly summarize criteria for selection of studies for this draft ISA.

#### 24 25 ***General Criteria for Study Selection***

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

- 28 • To what extent are the aerometric data, exposure, or dose metrics of adequate quality and  
29 sufficiently representative to serve as credible exposure indicators?
- 30 • Were the study populations adequately selected and are they sufficiently well defined to  
31 allow for meaningful comparisons between study groups?
- 32 • Are the health endpoint measurements meaningful and reliable?

- 1 • Does the study contain unique data such as the documentation of a previously unreported  
2 effect, documentation of the mechanism for an observed effect, or information on  
3 exposure-response relationships?
- 4 • Are the statistical analyses appropriate, properly performed, and properly interpreted?
- 5 • Are likely covariates (i.e., potential confounders or effect modifiers) adequately  
6 controlled or taken into account in the study design and statistical analysis?
- 7 • Are the reported findings internally consistent, biologically plausible, and coherent in  
8 terms of consistency with other known facts?

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

11  
12 ***Criteria for Selecting Epidemiological Studies***

13 In selecting epidemiological studies for this assessment, EPA considered whether a given  
14 study contains information on (1) associations with measured oxides of nitrogen concentrations  
15 using short- or long-term exposures at or near ambient levels of oxides of nitrogen, (2) health  
16 effects of specific oxides of nitrogen species or indicators related to oxides of nitrogen sources  
17 (e.g., motor vehicle emissions, combustion-related particles), (3) health endpoints and  
18 populations not previously extensively researched, (4) multiple pollutant analyses and other  
19 approaches to address issues related to potential confounding and modification of effects, and/or  
20 (5) important methodological issues (e.g., lag of effects, model specifications, thresholds,  
21 mortality displacement) related to interpretation of the health evidence. Among the  
22 epidemiological studies, particular emphasis has been focused on those most relevant to standard  
23 settings in the United States. Specifically, studies conducted in the United States or Canada are  
24 discussed in more detail than those from other geographic regions. Particular emphasis has been  
25 placed on: (A) new multicity studies that employ standardized methodological analyses for  
26 evaluating effects of oxides of nitrogen and that provide overall estimates for effects based on  
27 combined analyses of information pooled across multiple cities, (B) new studies that provide  
28 quantitative effect estimates for populations of interest, and (C) studies that consider oxides of  
29 nitrogen as a component of a complex mixture of air pollutants.

30

1 ***Criteria for Selecting Animal and Human Toxicological Studies***

2 Criteria for the selection of research evaluating animal toxicological or controlled human  
3 exposure studies include a focus on those studies conducted at levels within about an order of a  
4 magnitude of ambient NO<sub>2</sub> concentrations and those studies that approximate expected human  
5 exposure conditions in terms of concentration and duration. Studies that elucidate mechanisms  
6 of action and/or susceptibility, particularly if the studies were conducted under atmospherically  
7 relevant conditions, are emphasized whenever possible.

8 The selection of research evaluating controlled human exposures to oxides of nitrogen is  
9 mainly limited to studies in which subjects were exposed to <1 ppm NO<sub>2</sub>. For these controlled  
10 human exposures, emphasis is placed on studies that (1) investigate potentially susceptible  
11 populations such as asthmatics, particularly studies that compare responses in susceptible  
12 individuals with those in age-matched healthy controls; (2) address issues such as concentration-  
13 response or time-course of responses; (3) investigate exposure to NO<sub>2</sub> separately and in  
14 combination with other pollutants such as O<sub>3</sub> and SO<sub>2</sub>; (4) include control exposures to filtered  
15 air; and (5) have sufficient statistical power to assess findings.

16  
17

18 **1.2 ORGANIZATION OF THE DOCUMENT**

19 This draft ISA includes five chapters. This introductory chapter (Chapter 1) presents  
20 background information on the purpose of the document and characterizes how policy-relevant  
21 scientific studies are identified and selected for inclusion in the ISA. Chapter 2 highlights key  
22 concepts or issues relevant to understanding the atmospheric chemistry, sources, exposure and  
23 dosimetry of oxides of nitrogen, following a “source to dose” paradigm. Chapter 3 evaluates and  
24 integrates health information relevant to the review of the primary NAAQS for NO<sub>2</sub>. In this  
25 chapter, findings from epidemiological controlled human exposure and toxicological studies are  
26 integrated into an assessment of the relationships between exposure to ambient oxides of  
27 nitrogen and health outcomes. This chapter focuses on the strength of epidemiological or  
28 toxicological evidence and the consistency, coherence, and plausibility of the body of evidence  
29 for effects on the respiratory, cardiovascular, or other system. Chapter 4 provides information  
30 relevant to the public health impact of exposure to ambient oxides of nitrogen, including  
31 potential susceptible population groups. Finally, Chapter 5 articulates findings, conclusions

1 regarding the health evidence and makes recommendations pertinent to exposure and risk  
2 assessments.

3           In addition, a series of Annexes provide additional details of information in the ISA.  
4 Annex 1 is an introduction and background for the Annex series. In Annex 2, we present  
5 evidence related to the physical and chemical processes controlling the production, destruction,  
6 and levels of reactive nitrogen compounds in the atmosphere, including both oxidized and  
7 reduced species. Annex 3 presents information on environmental concentrations, patterns, and  
8 human exposure to ambient oxides of nitrogen. Annex 4 presents results from toxicological  
9 studies as well as information on dosimetry of oxides of nitrogen. Annex 5 presents results from  
10 controlled human exposure studies, and Annex 6 presents evidence from epidemiological  
11 studies. Annex tables for health studies are generally organized to include information about  
12 (1) concentrations of oxides of nitrogen levels or doses and exposure times, (2) description of  
13 study methods employed, (3) results and comments, and (4) quantitative outcomes for oxides of  
14 nitrogen measures. Annexes 2 and 3 contain additional discussion of information because these  
15 Annexes will be used for other ISAs, such as Oxides of Sulfur (SO<sub>x</sub>).

## 2. SOURCE TO TISSUE DOSE

This chapter provides basic information about concepts and findings relating to considerations in atmospheric science, human exposure assessment, and human dosimetry. It is meant to serve as a prologue for detailed discussions on the evidence on health effects to follow in Chapters 3 and 4. The order of topics essentially follows that given in the National Research Council paradigm for integrating air pollutant research (National Research Council, 1998).

### 2.1 INTRODUCTION

As noted in Chapter 1, the definition of “nitrogen oxides” as it appears in the enabling legislation related to the NAAQS and the definition commonly used in the air pollution research and control community differ. In this document, the terms “oxides of nitrogen” and “nitrogen oxides” refer to all forms of oxidized nitrogen compounds, including nitric oxide (NO), NO<sub>2</sub>, and all other oxidized nitrogen-containing compounds transformed from NO and NO<sub>2</sub>.<sup>1</sup> In the Federal Register Notice for the last AQCD for Oxides of Nitrogen (1996), the term “nitrogen oxides” was used to “*describe the sum of NO, NO<sub>2</sub> and other oxides of nitrogen.*”

Nitric oxide and NO<sub>2</sub>, along with volatile organic compounds (VOCs); anthropogenic and biogenic hydrocarbons, aldehydes, etc.) and carbon monoxide (CO), are precursors in the formation of ozone (O<sub>3</sub>) and photochemical smog. Nitrogen dioxide is an oxidant and can react to form other photochemical oxidants, including organic nitrates like the peroxyacyl nitrates (PANs). Nitrogen dioxide 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. Nitrogen dioxide and sulfur dioxide (SO<sub>2</sub>), another EPA criteria air pollutant, can also be oxidized to the strong mineral acids nitric acid (HNO<sub>3</sub>) and sulfuric acid (H<sub>2</sub>SO<sub>4</sub>), respectively, thereby contributing to the acidity of cloud, fog, and rainwater and ambient particles.

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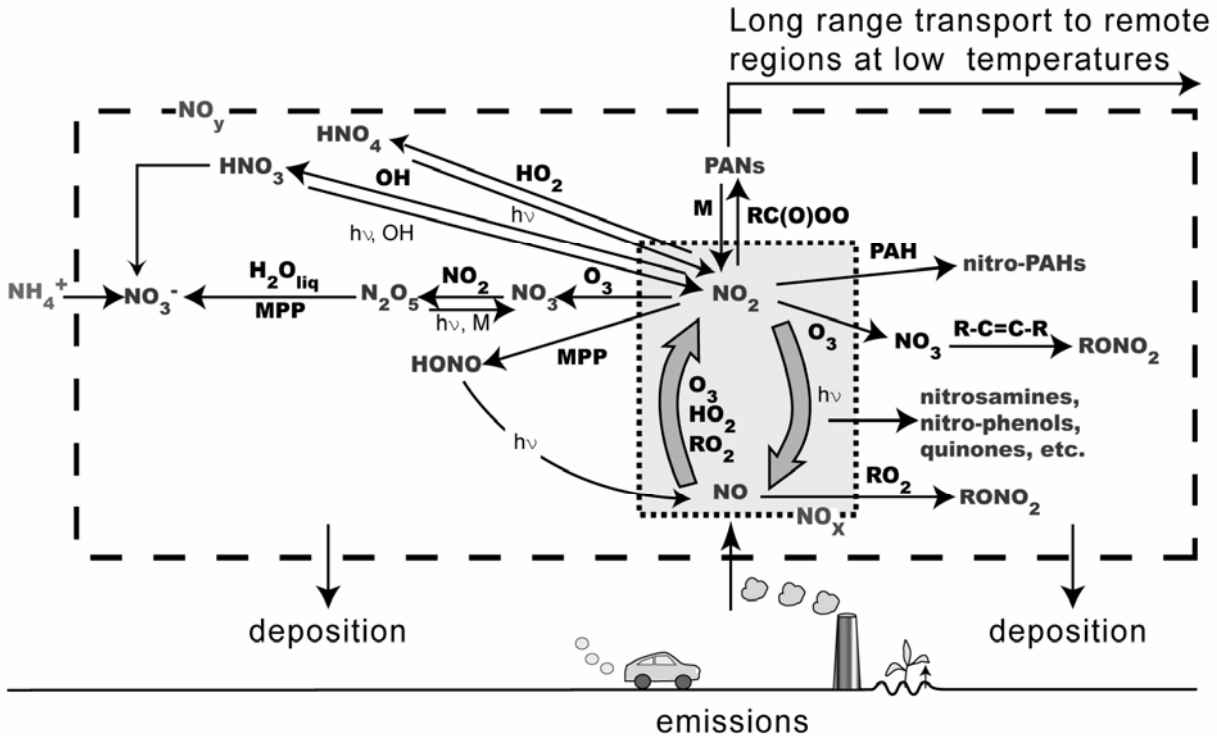
<sup>1</sup> This follows usage in the Clean Air Act Section 108(c): “Such criteria [for oxides of nitrogen] shall include a discussion of nitric and nitrous acids, nitrites, nitrates, nitrosamines, and other carcinogenic and potentially carcinogenic derivatives of oxides of nitrogen.” By contrast, within the air pollution research and control community, the terms “oxides of nitrogen” and “nitrogen oxides” are restricted to refer only to the sum of NO and NO<sub>2</sub>, and this sum is commonly abbreviated as NO<sub>x</sub>. 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<sub>y</sub>.

## 2.2 ATMOSPHERIC CHEMISTRY

The role of  $\text{NO}_x$  in  $\text{O}_3$  formation was reviewed in Chapter 2 (Section 2.2) of the latest Air Quality Criteria for Ozone and Related Photochemical Oxidants (2006 AQCD for  $\text{O}_3$ ) (U.S. Environmental Protection Agency, 2006), and has been presented in numerous texts (e.g., Seinfeld and Pandis, 1998; Jacob, 1999; Jacobson, 2002). Mechanisms for transporting  $\text{O}_3$  precursors including  $\text{NO}_x$ , the factors controlling the efficiency of  $\text{O}_3$  production from  $\text{NO}_x$ , methods for calculating  $\text{O}_3$  from its precursors, and methods for measuring  $\text{NO}_y$  were all reviewed in Section 2.6 of 2006 AQCD for  $\text{O}_3$ . The main points from 2006 AQCD for  $\text{O}_3$  will be presented here along with updates based on new material.

The overall chemistry of reactive nitrogen compounds in the atmosphere is summarized in Figure 2.2-1 and described in greater detail in this document's Annex AX2.2. Nitrogen oxides are emitted by combustion sources mainly as  $\text{NO}$  with quantities of  $\text{NO}_2$  typically in the range of 5 to 10% of  $\text{NO}$ . The major combustion sources of  $\text{NO}_x$ , shown schematically in Figure 2.2-1, are motor vehicles and electrical utilities, although stationary engines, off-road vehicles, and industrial facilities also emit  $\text{NO}_x$ . In addition to emissions from fossil fuel combustion, biomass burning also produces  $\text{NO}_x$ . And apart from these anthropogenic sources, there are also smaller natural sources which include microbial activity in soils, lightning, and wildfires.

$\text{NO}$  and  $\text{NO}_2$  are often grouped together and given the category label " $\text{NO}_x$ " because they are emitted together and can rapidly interconvert as shown in the inner box in Figure 2.2-1. Nitrogen dioxide reacts with 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 nitrogen species in the outer box are often collectively termed  $\text{NO}_z$ : thus,  $\text{NO}_x + \text{NO}_z = \text{NO}_y$ . The time scale for reactions of  $\text{NO}_x$  to form products shown in the outer box of Figure 2.2-1 typically ranges from a few hours during summer to about a day during winter. As a result, morning rush hour emissions of  $\text{NO}_x$  can be converted almost completely to products by late afternoon during



**Figure 2.2-1. Schematic diagram of the cycle of reactive nitrogen species in the atmosphere. MPP refers to multiphase processes, R to an organic radical, and  $h\nu$  to a solar photon.**

1 warm, sunny conditions. As shown in Figure 2.2-1, different sources emit  $\text{NO}_x$  at different  
 2 altitudes. Because the prevailing winds aloft are generally stronger than those at the surface,  
 3 emissions from elevated sources can be distributed over a wider area than those emitted at the  
 4 surface, and because of the time required for mixing of emissions to the surface, emissions of  
 5  $\text{NO}_x$  from elevated sources will tend to be transformed to the more oxidized  $\text{NO}_z$  products before  
 6 they reach the surface.

7 The concentrations and atmospheric lifetimes of inorganic and organic products from  
 8 reactions of  $\text{NO}_x$  vary widely in space and time. Inorganic reaction products include HONO,  
 9  $\text{HNO}_3$ ,  $\text{HNO}_4$ , and particulate nitrate ( $\text{pNO}_3^-$ ). While a broad range of organic nitrogen  
 10 compounds are emitted by combustion sources (e.g. nitrosamines and nitro-PAHs), they are also  
 11 formed in the atmosphere from reactions of NO and  $\text{NO}_2$ . These include peroxyacyl and  
 12 isoprene nitrates, other nitro-PAHs, and the more recently identified nitrated organic compounds



1 in the quinone family. The largest fractions of the mass of products shown in the outer box of  
2 Figure 2.2-1 are in the form of PAN and HNO<sub>3</sub>, although other organic nitrates, e.g., isoprene  
3 nitrates and specific biogenic PANs can be important at locations nearer to biogenic sources  
4 (Horowitz et al., 2007; Singh et al., 2007).

5 In addition to gas-phase reactions, reactions occurring on surfaces or occurring in  
6 multiple phases are important for the formation of HONO and pNO<sub>3</sub><sup>-</sup>. These reactions can  
7 occur on the surfaces of suspended particles, soil, and buildings and within aqueous media.  
8 The lifetime of PAN is strongly temperature dependent and is stable enough at low temperatures  
9 to be transported long distances before decomposing to release NO<sub>2</sub>, which can then participate  
10 in O<sub>3</sub> formation in these regions remote from the original NO<sub>x</sub> source. Nitric acid can act  
11 similarly to some extent, but its high solubility and fast deposition rate mean that it is removed  
12 from the atmosphere by uptake on aqueous aerosols and cloud droplets or to the surface faster  
13 than PAN. Characteristic concentrations of many of the oxides of nitrogen species are given in  
14 Annex AX3.2.

15 As mentioned earlier, NO and NO<sub>2</sub> are important precursors of O<sub>3</sub> formation. However,  
16 because O<sub>3</sub> changes in a nonlinear way with the concentrations of its precursors, it is unlike  
17 many other secondarily-formed atmospheric species whose rates of formation vary directly with  
18 emissions of their precursors. At the low NO<sub>x</sub> concentrations found in most environments  
19 (ranging from remote continental areas to rural and suburban areas downwind of urban centers)  
20 the net production of O<sub>3</sub> increases with increasing NO<sub>x</sub>. At the high NO<sub>x</sub> concentrations found in  
21 downtown metropolitan areas and especially near busy streets and roadways and in power plant  
22 plumes, net destruction of O<sub>3</sub> is initiated with the excess NO found there. In the high NO<sub>x</sub>  
23 regime, NO<sub>2</sub> scavenges OH radicals that would otherwise oxidize VOCs to produce peroxy  
24 radicals, which would in turn oxidize NO to NO<sub>2</sub>. In the low NO<sub>x</sub> regime, oxidation of VOCs  
25 generates excess free radicals, and hence O<sub>3</sub> production varies more nearly directly with NO<sub>x</sub>.  
26 Between these two regimes, there is a transition zone in which O<sub>3</sub> shows only a weak  
27 dependence on NO<sub>x</sub> concentrations.

### 28 29 *Formation of Nitro-PAHs*

30 Nitro-polycyclic aromatic hydrocarbons (nitro-PAHs) are produced either by either direct  
31 emissions or by atmospheric reactions. Among combustion sources, diesel emissions have been

1 identified as the major source of nitro-PAHs in ambient air (Bezabeh et al., 2003; Gibson, 1983;  
2 Schuetzle, 1983; Tokiwa and Ohnishi, 1986). Direct emissions of “nitro-patts” in PM vary with  
3 type of fuel, vehicle maintenance, and ambient conditions (Zielinska et al., 2004). In addition to  
4 being directly emitted, nitro-PAHs can also be formed from both gaseous and heterogeneous  
5 reactions of PAHs with gaseous nitrogen-containing pollutants in the atmosphere, with the  
6 reactions of OH and NO<sub>3</sub> radicals with PAHs being the major sources of nitro-PAHs. (Arey  
7 et al., 1986; Arey et al., 1989, 1998; Giancarlo Perrini, 2005; Pitts et al., 1987; Sasaki et al.,  
8 1997; Zielinska et al., 1989; Bamford and Baker, 2003; Reisen and Arey, 2005 and references  
9 therein). Reactions involving OH and NO<sub>3</sub> radicals imply that nitro-PAH formation occurs  
10 during both daytime and nighttime in the atmosphere. The major loss process of nitro-PAHs is  
11 photodecomposition (Fan et al., 1996; Feilberg et al., 1999; Feilberg and Nielsen, 2001) with  
12 lifetimes on the order of hours, followed by reactions with OH and NO<sub>3</sub> radicals. The reaction  
13 mechanisms for forming and destroying nitro-PAHs in the atmosphere have been described in  
14 Section AX2.2.3.

15 In ambient particulate organic matter (POM), 2-nitrofluoranthene (2NF) is the dominant  
16 compound, followed by 1-nitropyrene (1NP) and 2-nitropyrene (2NP) (Arey et al., 1989;  
17 Bamford et al., 2003; Reisen and Arey, 2005; Zielinska et al., 1989). 2NF and 2NP are not  
18 directly emitted from primary combustion emissions, but are formed in the atmosphere. 1NP is  
19 generally regarded as a tracer of primary combustion sources, in particular, diesel exhaust. After  
20 formation, nitro-PAHs with low vapor pressures (such as 2NF and 2NP) immediately migrate to  
21 particles under ambient conditions (Fan et al., 1995; Feilberg et al., 1999). More volatile nitro-  
22 PAHs, such as nitronaphthalene (NN) remain mainly in the gas phase.

23 The concentrations for most nitro-PAHs found in ambient air are typically lower than  
24 1 pg/m<sup>3</sup>, except NNs, 1NP, and 2NF, which can be present at levels up to several tens or  
25 hundreds of pg/m<sup>3</sup>. These levels are much lower (~2 to ~1000 times lower) than their parent  
26 PAHs. However, nitro-PAHs are much more toxic than PAHs (Durant et al., 1996; Grosovsky  
27 et al., 1999; Salmeen et al., 1982; Tokiwa et al., 1998; Tokiwa and Ohnishi, 1986). Moreover,  
28 most nitro-PAHs are present in particles with a mass median diameter of <0.1 μm.

29  
30

## 2.3 MEASUREMENT METHODS AND ASSOCIATED ISSUES

Nitric oxide is routinely measured using the principle of gas-phase chemiluminescence induced by the reaction of NO with O<sub>3</sub> at low pressure. The Federal Reference Method (FRM) for NO<sub>2</sub> makes use of this technique of NO detection with a prerequisite step to reduce the NO<sub>2</sub> to NO on the surface of a molybdenum oxide (MoO<sub>x</sub>) substrate heated to between 300 and 400 C. Because the FRM monitor cannot detect NO<sub>2</sub>, the concentration of NO<sub>2</sub> is determined as the difference between the sample passed over the heated MoO<sub>x</sub> substrate (the nitrogen oxides total) and the sample not reduced (the NO). However, the reduction of NO<sub>2</sub> to NO on the MoO<sub>x</sub> substrate is not specific to NO<sub>2</sub>; hence, the chemiluminescence analyzers are subject to unknown and varying interferences produced by the presence in the sample of the other oxidized nitrogen compounds (i.e., NO<sub>z</sub> compounds shown in the outer box of Figure 2.2-1).

Interference by NO<sub>z</sub> 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). These studies have relied on intercomparisons of measurements using the FRM and other techniques for measuring NO<sub>2</sub>. The sensitivity of the instrument to potential interference by individual NO<sub>z</sub> compounds is highly variable and is dependent in part on instrument inlet design and on the temperature of the reducing substrate, and on the interactions of species with the reducing substrate. Commercially available NO<sub>x</sub> monitors have been converted to NO<sub>y</sub> monitors by moving the MoO<sub>x</sub> convertor to interface directly with the sample inlet. Because of losses on inlet surfaces and differences in the efficiency of reduction of NO<sub>z</sub> compounds on the heated MoO<sub>x</sub> substrate, NO<sub>x</sub> can not be considered as a universal surrogate for NO<sub>y</sub>. However, in settings close to relatively high concentration fresh emissions like those in urban areas during rush hour, most of the NO<sub>y</sub> is present as NO<sub>x</sub>. To the extent that all the major oxidized nitrogen species can be reduced quantitatively to NO, measurements of NO<sub>y</sub> should be more reliable than those for NO<sub>x</sub>, particularly at typical ambient levels of NO<sub>2</sub>. Routine measurement reporting of total NO<sub>y</sub> rather than of NO and NO<sub>2</sub> by subtraction has the additional benefit of characterizing the entire suite of oxidized nitrogen compounds to which humans are exposed. Reliable measurements of NO<sub>y</sub> and NO<sub>2</sub>, especially at the low concentrations observed in many areas remote from sources are also crucial for evaluating the performance of three-dimensional,

1 chemical transport models of oxidant and acid production in the atmosphere (described in  
2 Section AX2.7 of Annex 2).

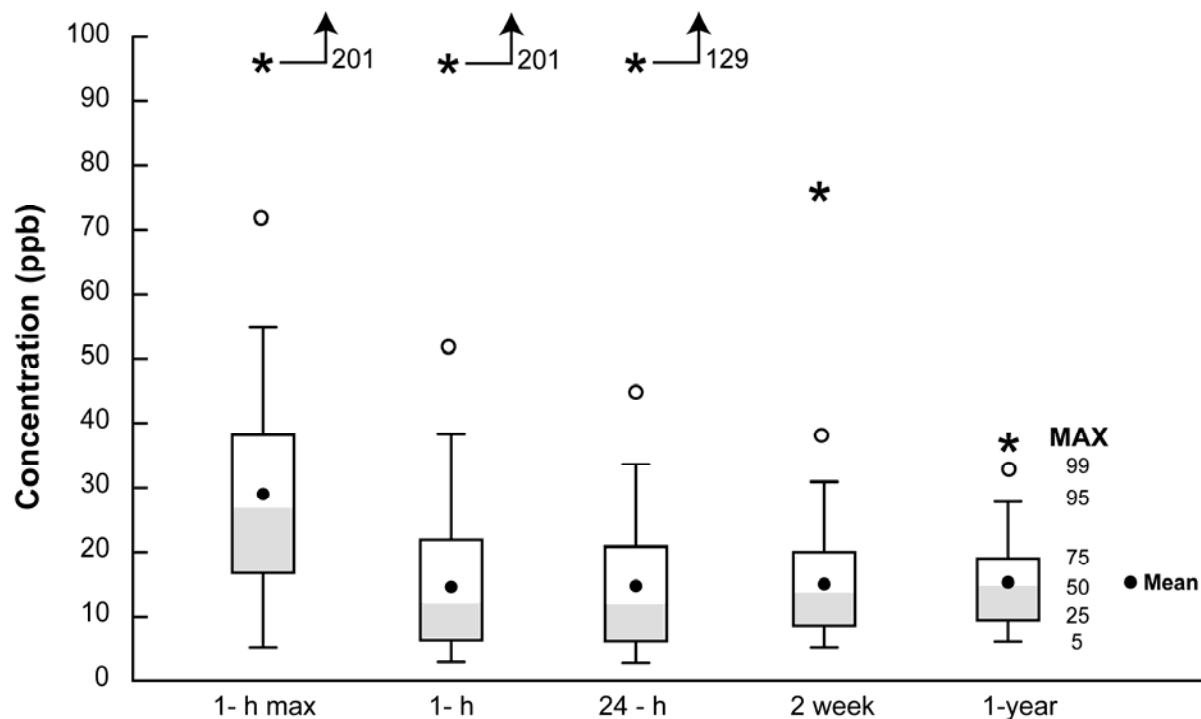
3 There are other approaches to measuring NO<sub>2</sub> that do not suffer from the artifacts  
4 mentioned above. For example, NO<sub>2</sub> can be photolytically reduced to NO, with an efficiency of  
5 about 70%. At present, however, this method requires additional development to ensure its cost  
6 effectiveness and reliability for extensive field deployment. The relatively low and variable  
7 conversion efficiency of this technique, for example, means that increased attention to frequent  
8 calibration exercises would be required for routine operation. Optical methods such as those  
9 using differential optical absorption spectroscopy (DOAS) or laser induced fluorescence (LIF)  
10 are also available, as described in Section AX2.8 of Annex AX2. However, these methods are  
11 even more expensive than either the FRM monitors or photolytic reduction technique and require  
12 specialized expertise to operate as well; moreover, the DOAS is an area-integrated rather than a  
13 point-measured technique.

## 14 15 16 **2.4 AMBIENT CONCENTRATIONS OF NO<sub>2</sub> AND ASSOCIATED** 17 **OXIDIZED NITROGEN SPECIES AND POLICY RELEVANT** 18 **BACKGROUND CONCENTRATIONS**

19 This section provides a brief summary of information on ambient concentrations of NO<sub>2</sub>  
20 and associated oxidized nitrogen compounds in the United States. It also provides estimates of  
21 Policy Relevant Background Concentrations, i.e., background concentrations used to inform  
22 policy-relevant decisions about the NAAQS.

### 23 24 **2.4.1 Ambient Concentrations**

25 Figure 2.4-1 shows ambient concentrations of NO<sub>2</sub> measured at all monitoring sites  
26 located within Metropolitan Statistical Areas (MSAs) in the United States from 2003 through  
27 2005. As can be seen from Figure 2.4-1, mean concentrations of NO<sub>2</sub> are about 15 ppb for  
28 averaging periods ranging from a day to a year, with an interquartile range (IQR) of 10 to  
29 15 ppb. However, the average daily maximum hourly NO<sub>2</sub> concentrations are ~30 ppb. These  
30 values are about twice as high as the 24-h averages. The highest maximum hourly  
31 concentrations (~200 ppb) are more than a factor of ten higher than the mean hourly or 24-h  
32 concentrations.



**Figure 2.4-1. Ambient concentrations of NO<sub>2</sub> measured at all monitoring sites located within Metropolitan Statistical Areas in the United States from 2003 through 2005.**

1 Recall from the discussion above that the FRM for NO<sub>2</sub> is subject to positive interference  
 2 by other oxidized nitrogen compounds (NO<sub>z</sub>), and the degree of interference can be substantial.  
 3 In particular, Dunlea et al. (2007) found an average of about 22% of ambient NO<sub>2</sub> (~9 to 50 ppb)  
 4 measured in Mexico City was due to interference from NO<sub>z</sub> compounds. Comparable levels of  
 5 NO<sub>2</sub> are found in many locations in the United States. The Dunlea et al. (2007) results were  
 6 based on comparison between the chemiluminescent instrument with other (optical) techniques.  
 7 The main sources of interference were HNO<sub>3</sub> and various organic nitrates. Peak interference of  
 8 up to 50% was found during afternoon hours and was associated with O<sub>3</sub> and NO<sub>z</sub> compounds  
 9 such as HNO<sub>3</sub> and the alkyl and multifunctional alkyl nitrates.

10 Data for concentrations of NO<sub>z</sub> constituent species in urban areas in the United States are  
 11 sparse. The most comprehensive set of data for any NO<sub>z</sub> species was obtained for HNO<sub>3</sub> as part  
 12 of the Children's Health Study for which gas-phase HNO<sub>3</sub> was measured at 12 sites in Southern  
 13 California from 1994 through 2001 (Alcorn et al., 2004). Levels ranged from <1 ppb to >10 ppb

1 in general, the highest concentrations of HNO<sub>3</sub> and the highest ratio of HNO<sub>3</sub>/NO<sub>2</sub> were found  
2 downwind of central Los Angeles in the San Bernadino Valley during summer, as one would  
3 expect for this more oxidized nitrogen product. Measurements of HONO in urban areas are very  
4 limited; however, data from Stutz et al., (2004) and Wang et al., (2006) indicate that levels of  
5 HONO are <1 ppb even under heavily polluted conditions (with the highest levels found during  
6 the night and just after dawn and lowest values found in the afternoon). Several field studies  
7 such as Hayden et al. (2003) in rural Quebec, Williams et al. (1987) near Boulder, CO, and Singh  
8 et al. (2007) in aircraft flights over eastern North America have also found much higher levels of  
9 NO<sub>z</sub> compounds than NO<sub>x</sub> in relatively unpolluted rural air.

10 Calculations with EPA's Community Multiscale Air Quality (CMAQ) modeling system  
11 for the mid-Atlantic region in a domain from Virginia-Southern New Jersey showed that the  
12 highest levels of HNO<sub>3</sub> and organic nitrates occur during mid-afternoon, consistent with their  
13 formation by photochemical processes that also produce O<sub>3</sub>. Model calculations during an O<sub>3</sub>  
14 episode in July 2002 made for the Maryland State O<sub>3</sub> Implementation Plan (SIP) showed episode  
15 averages of the ratio NO<sub>z</sub>/NO<sub>2</sub> ranging from 0.26 to 3.6 in rural Virginia, with the highest ratios  
16 in rural areas and lowest ratios in urban centers nearer the sources of fresh NO<sub>x</sub> emissions. The  
17 capabilities of three-dimensional transport models like CMAQ and issues associated with their  
18 use are presented in Annex Section AX2.7.

19

#### 20 **2.4.2 Policy Relevant Background Concentrations of Nitrogen Dioxide**

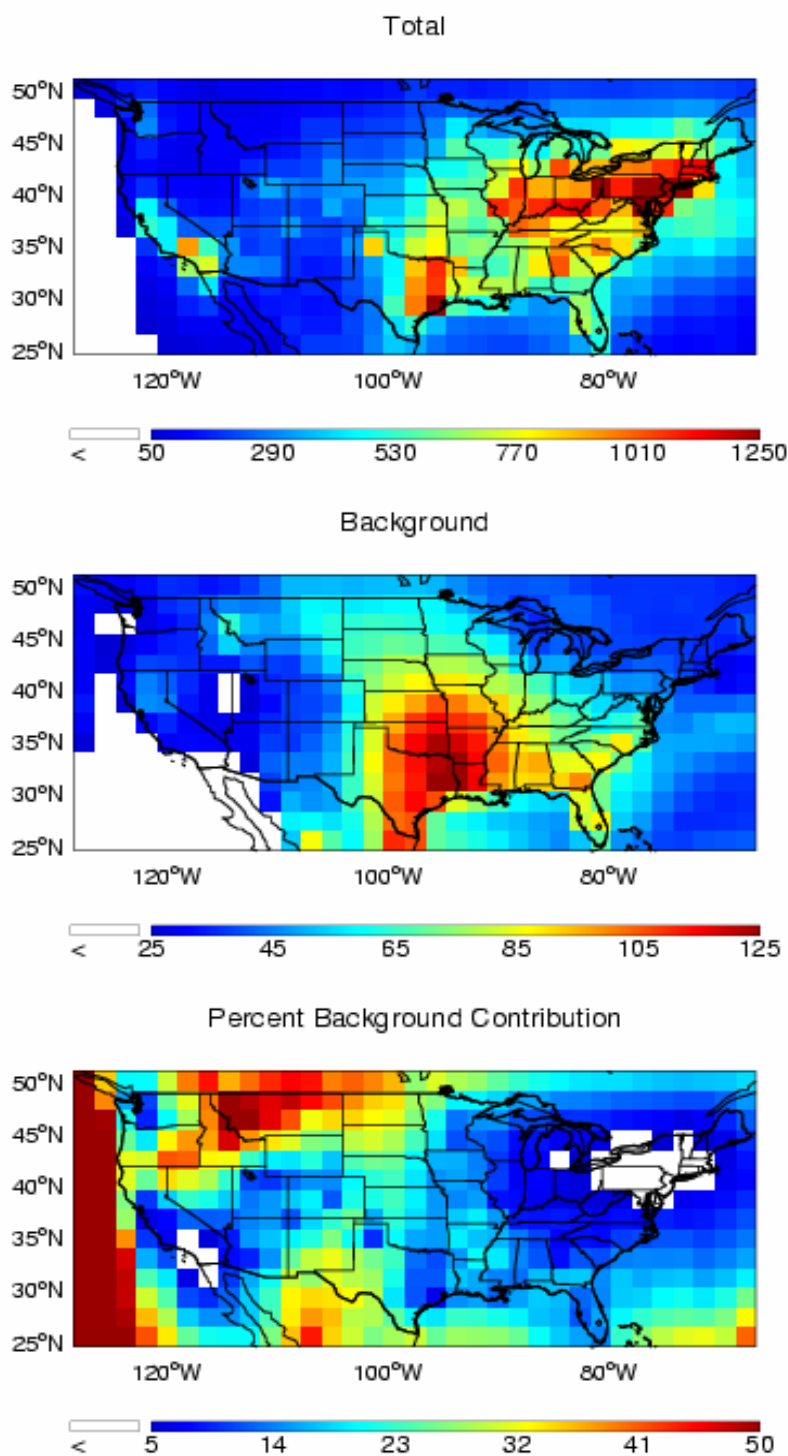
21 Background concentrations of NO<sub>2</sub> used for purposes of informing decisions about  
22 NAAQS are referred to as Policy Relevant Background (PRB) concentrations. Policy Relevant  
23 Background concentrations are those concentrations that would occur in the United States in the  
24 absence of anthropogenic emissions in continental North America (defined here as the United  
25 States, Canada, and Mexico). Policy Relevant Background concentrations include contributions  
26 from natural sources everywhere in the world and from anthropogenic sources outside these  
27 three countries. Background levels so defined facilitate separation of pollution levels that can be  
28 controlled by U.S. regulations (or through international agreements with neighboring countries)  
29 from levels that are generally uncontrollable by the United States. The EPA assesses risks to  
30 human health and environmental effects from NO<sub>2</sub> levels in excess of PRB concentrations.

1 Contributions PRB concentrations include photochemical actions involving natural  
2 emissions of NO, NO<sub>2</sub>, and reduced nitrogen (NH<sub>x</sub>) compounds; as well as their long-range  
3 transport from outside North America. Natural sources of NO<sub>2</sub> and its precursors include  
4 biogenic emissions, wildfires, lightning, and the stratosphere. Biogenic emissions from  
5 agricultural activities are not considered in the formation of PRB concentrations. Discussions of  
6 the sources and estimates of emissions are given in Annex Section AX2.6.2.

7  
8 *Analysis of Policy Relevant Background Contribution to Nitrogen Dioxide Concentrations over*  
9 *the United States*

10 The MOZART-2 global model of tropospheric chemistry (Horowitz et al., 2003) was  
11 used to diagnose the PRB contribution to NO<sub>2</sub> concentrations. The model setup for the present-  
12 day simulation has been published in a series of papers from a recent model intercomparison  
13 (Dentener et al., 2006ab; Shindell et al., 2006; Stevenson et al., 2006; van Noije et al., 2006).  
14 MOZART-2 is driven by National Center for Environmental Prediction meteorological fields  
15 and IIASA 2000 emissions at a horizontal resolution of 1.9° × 1.9° with 28 sigma levels in the  
16 vertical, and it includes gas-phase and aerosol chemistry. Results shown in Figure 2.4-2 are for  
17 the meteorological year 2001. An additional “PRB” simulation was conducted in which  
18 continental North American anthropogenic emissions were set to zero.

19 We first examine the role of PRB in contributing to NO<sub>2</sub> concentrations in surface air.  
20 Figure 2.4-2 shows the annual mean NO<sub>2</sub> concentrations in surface air in the base case  
21 simulation (top panel) and the PRB simulation (middle panel), along with the percentage  
22 contribution of the background to the total base case NO<sub>2</sub> (bottom panel). Maximum  
23 concentrations in the base case simulation occur along the Ohio River Valley and in the  
24 Los Angeles basin. While present-day concentrations are often above 5 ppbv, PRB is less than  
25 300 pptv over most of the continental United States, and less than 100 pptv in the eastern United  
26 States. The distribution of PRB (middle panel of Figure 2.4-2) largely reflects the distribution of  
27 soil NO emissions, with some local enhancements due to biomass burning such as in western  
28 Montana. In the northeastern United States, where present-day NO<sub>2</sub> concentrations are highest,  
29 PRB contributes <1% to the total. Thus, it appears that PRB levels of NO<sub>2</sub> are much smaller  
30 than observed levels.



**Figure 2.4-2. Annual mean concentrations of NO<sub>2</sub> (ppbv) in surface air over the United States in the present-day (upper panel) and policy relevant background (middle panel) MOZART-2 simulations. The bottom panel shows the percentage contribution of the background to the present-day concentrations. See text in Annex Section AX2.9 for details.**



## 2.5 EXPOSURE ISSUES

### 2.5.1 Personal Exposures

#### 2.5.1.1 General Concepts

Human exposure to an airborne pollutant consists of contact between the human and the pollutant at a specific concentration for a specified period of time. People spend various amounts of time in different microenvironments (Figure 2.5-1) characterized by different pollutant concentrations. The figure represents a composite average across the United States across all age groups. Different cohorts, e.g., the elderly might be expected to exhibit different activity patterns. The integrated exposure of a person to a given pollutant is the sum of the exposures over all time intervals for all microenvironments in which the individual spent time.

Therefore, the personal exposure concentration to a pollutant, such as  $\text{NO}_2$ , can be represented by the following equation:

$$E_T = \sum_{i=1}^n C_i f_i \quad (2.5-1)$$

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 fraction of time spent in the  $i^{\text{th}}$  microenvironment, and  $C_i$  is the average concentration in the  $i^{\text{th}}$  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:

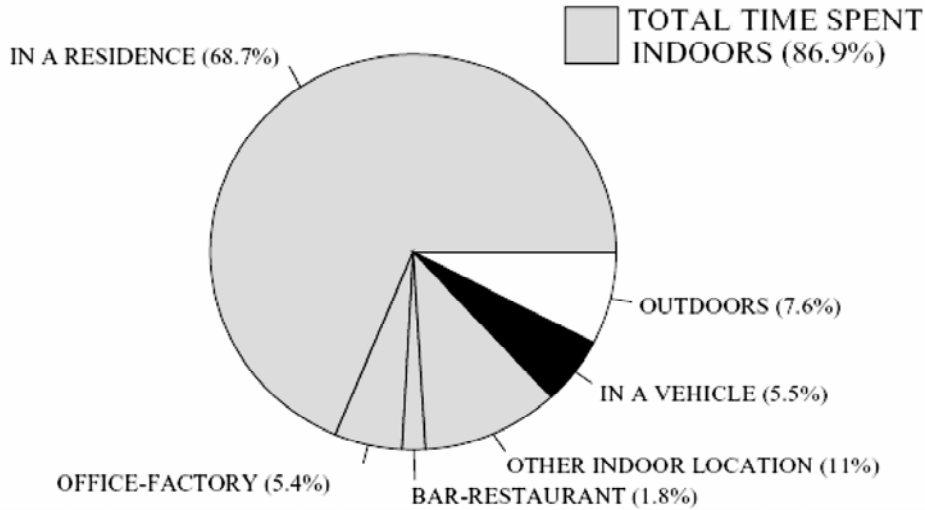
$$E_T = E_a + E_{na} = \{y_o + \sum_i y_i [P_i a_i / (a_i + k_i)]\} C_a + E_{na} = \{y_o + \sum_i y_i F_{inf_i}\} C_a + E_{na} \quad (2.5-2)$$

subject to the constraint

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

## NHAPS - Nation, Percentage Time Spent

Total n = 9,196



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

Source: Klepeis et al. (2001).

1 In the case where microenvironmental exposures occur mainly in one microenvironment,  
 2 Equation 2.5-2 may be approximated by

$$3 \quad E_T = E_a + E_{na} = \{y + (1-y)[Pa/(a+k)]\}C_a + E_{na} = \alpha C_a + E_{na} \quad (2.5-4)$$

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

$$8 \quad C_{me} = C_a + C_{na} = [Pa/(a+k)]C_a + S/[V(a+k)] \quad (2.5-5)$$

9 where  $C_{me}$  is the concentration in a microenvironment;  $C_a$  and  $C_{na}$  are the contributions to  $C_{me}$   
 10 from ambient and nonambient sources;  $S$  is the microenvironmental source strength;  $V$  is the  
 11 volume of the microenvironment, and the symbols in brackets have the same meaning as in  
 12 Equation 2.5-4.

1 Microenvironments in which people are exposed to air pollutants such as NO<sub>2</sub> typically  
2 include residential indoor environments, other indoor locations, near-traffic outdoor  
3 environments, other outdoor locations, and in vehicles as shown in Figure 2.5-1. Indoor  
4 combustion sources such as gas stoves and space heaters need to be considered when evaluating  
5 exposures to NO<sub>2</sub>. Exposure misclassification may result when total human exposure is not  
6 disaggregated between various microenvironments, and this may obscure the true relationship  
7 between ambient air pollutant exposures and health outcomes.

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

- 10 • Ambient concentration
- 11 • The air exchange rate
- 12 • The pollutant specific penetration coefficient
- 13 • The pollutant specific decay rate
- 14 • The fraction of time an individual spends in the microenvironment

15  
16 These factors are in turn determined by the following exposure factors (see Annex AX3.5).

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

28  
29 In general, the relationship between personal exposures and ambient concentrations can  
30 be modified by microenvironments in the following ways: (1) during infiltration, ambient  
31 pollutants can be lost through chemical and physical loss processes, and therefore, the ambient

1 component of a pollutant's concentration in a microenvironment is not the same as its ambient  
2 concentration but the product of the ambient concentration and the infiltration factor ( $F_{inf}$  or  $\alpha$  if  
3 people spend 100% of their time indoors) and (2) exposure to nonambient, microenvironmental  
4 sources.

5 In practice, it is extremely difficult to characterize community exposures by  
6 measurements of each individual's personal exposures. Instead, the distribution of personal  
7 exposures in a community, or the population exposure, is characterized by extrapolating  
8 measurements of personal exposure using various techniques or by stochastic, deterministic or  
9 hybrid exposure modeling approaches such as APEX, SHEDS, and MENTOR (see AX3.7 for a  
10 description of modeling methods). Variations in community-level personal exposures are  
11 determined by cross-community variations in ambient pollutant concentrations and the physical  
12 and exposure factors mentioned above. These factors also determine the strength of the  
13 association between population exposure to NO<sub>2</sub> of ambient origin and ambient NO<sub>2</sub>  
14 concentrations.

## 15 16 **2.5.2 Ambient Monitors and Personal Exposures**

17 Of major concern is the ability of NO<sub>2</sub> measured by ambient monitors to serve as a good  
18 indicator of personal exposure to NO<sub>2</sub> of ambient origin. The key question is what errors are  
19 associated with using NO<sub>2</sub> measured by ambient monitors as a surrogate for personal exposure to  
20 ambient NO<sub>2</sub> in epidemiological studies. There are three aspects of this issue: (1) ambient and  
21 personal sampling issues; (2) the spatial variability of ambient NO<sub>2</sub> concentrations; (3) the  
22 associations between ambient concentrations and personal exposures as influenced by exposure  
23 factors, e.g., indoor sources and sinks, and the time people spend indoors and outdoors. These  
24 issues are treated individually in the following subsections.

### 25 26 **2.5.2.1 Ambient and Personal Sampling Issues**

27 Personal exposures in human exposure and panel studies of NO<sub>2</sub> health effects are  
28 monitored by passive samplers. Their performance is evaluated by comparison to the  
29 chemiluminescence monitoring method. Some form of evaluation is crucial for determining  
30 measurement errors associated with exposure estimates. However, measurements of NO<sub>2</sub> are  
31 subject to artifacts both at the ambient level and at the personal level. As discussed above in  
32 Section 2.3, measurements of ambient NO<sub>2</sub> are themselves subject to variable interference

1 caused by other NO<sub>y</sub> compounds, in particular PANs, organic nitrates, pNO<sub>3</sub><sup>-</sup>, and HONO and  
2 HNO<sub>3</sub>.

3 The most widely used passive samplers are Palmes tubes (Palmes et al., 1976),  
4 Yanagisawa badges (Yanagisawa and Nishimura, 1982), Ogawa samplers (Ogawa and  
5 Company, <http://www.ogawausa.com>) and radial diffusive samplers (Cocheo et al., 1996). The  
6 theories behind and applications of Palmes Tubes and Yanagisawa badges have been described  
7 in the last AQCD for Oxides of Nitrogen (U.S. Environmental Protection Agency, 1993).  
8 Descriptions of the rest of the commercialized samplers will be presented in detail in Annex  
9 Section AX3.3. Briefly, after penetrating into a passive sampler governed by Fick's law,  
10 environmental NO<sub>2</sub> is fixed by the adsorbent (Krupa and Legge, 2000). The sorbent can be  
11 either physically sorptive (e.g., active carbon) or chemisorptive (e.g., triethanolamine [TEA], KI,  
12 and arsenate sodium oxide [AsNaO<sub>2</sub>]); passive samplers for NO<sub>2</sub> are chemisorptive, i.e., a  
13 reagent coated on a support (e.g., metal mesh, filter) chemically reacts with and captures NO<sub>2</sub>.  
14 The sorbent is extracted and analyzed for one or more reactive derivatives; the mass of NO<sub>2</sub>  
15 collected is derived from the concentration of the derivative(s) based on the stoichiometry of the  
16 reaction.

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

23 Another concern for passive sampling is interference from other pollutants. Interference  
24 from other NO<sub>y</sub> species can contribute to NO<sub>2</sub> exposure monitoring errors, but the kinetics and  
25 stoichiometry of interferent compound reactions have not been well established, especially for  
26 passive samplers. In the U.K., an NO<sub>2</sub> monitoring plan using a cost-effective, simpler tube-type  
27 passive sampler has been proposed and implemented countrywide. However, in a comparison of  
28 NO<sub>2</sub> concentrations measured outdoors by the passive samplers with those measured by the  
29 chemiluminescence method, NO<sub>2</sub> concentrations measured by the passive samplers were ~30%  
30 higher than those measured by the chemiluminescence method (Campbell et al., 1994).

1           Although the majority of studies indicate that passive samplers have very good precision,  
2 generally within 5% (Gair et al., 1991; Gair and Penkett, 1995; Plaisance et al., 2004; Kirby  
3 et al., 2001), field evaluation studies showed that the overall average NO<sub>2</sub> concentrations  
4 calculated from diffusion tube measurements were likely to be within 10% of chemiluminescent  
5 measurement data (Bush et al., 2001; Mukerjee et al., 2004). As mentioned before, TEA-based  
6 diffusive sampling methods tend to overestimate NO<sub>2</sub> concentrations in field comparisons with  
7 chemiluminescence analyzers (Campbell et al., 1994). This could be due in part to chemical  
8 reactions between O<sub>3</sub> and NO occurring in the diffusion tube, or differential sensitivity to other  
9 forms of NO<sub>y</sub>, such as HONO, PAN, and HNO<sub>3</sub>, between the passive samplers and the  
10 chemiluminescence analyzers (Gair et al., 1991). Due to spatial and temporal variability of NO  
11 and NO<sub>2</sub> concentrations, especially at roadsides where NO concentrations are relatively high and  
12 when sufficient O<sub>3</sub> is present for interconversion between the species, the lack of agreement  
13 between the passive samplers and ambient monitors can represent differences in sampler  
14 response (Heal et al., 1999; Cox, 2003).

15           A third aspect of passive sampler performance is that, compared with ambient  
16 chemiluminescence monitors, passive samplers give relatively longer time averaged  
17 concentrations (from days to weeks). Consequently, diffusive samplers including those used for  
18 NO<sub>2</sub> monitoring provide integrated but not high time-resolution concentration measurements.  
19 Hourly fluctuations in NO<sub>2</sub> concentrations may be important to the evaluation of exposure-health  
20 effects relationships, and continuous monitors, such as the chemiluminescent monitors, remain  
21 the only approach for estimating short-term peak exposures.

22

## 23 **2.5.2.2     Spatial Variability**

24

### 25 **2.5.2.2.1     *Spatial Variability of Ambient NO<sub>2</sub> Concentrations***

26           Summary statistics for the spatial variability in several urban areas across the United  
27 States are shown in Table 2.5-1. These areas were chosen because they are the major urban  
28 areas with at least five monitors operating from 2003 to 2005. Values in parentheses below the  
29 city name indicate the number of monitoring sites in that particular city. The second column  
30 shows the mean concentration across all sites and the range in means at individual sites. The  
31 third column gives the range of Pearson correlation coefficients between individual site pairs in  
32 the urban area. The fourth column shows the 90th percentile absolute difference in

1 concentrations between site pairs. The fifth column gives the coefficient of divergence (COD),  
2 an indication of the variability across the monitoring sites in each city; a COD value of 0  
3 indicates there are no differences between concentrations at paired sites (spatial homogeneity),  
4 while a COD value approaching 1 indicates extreme spatial heterogeneity.

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

17 The same statistics as shown in Table 2.5-1 have been used to describe the spatial  
18 variability of fine particulate matter (PM<sub>2.5</sub>) (U.S. Environmental Protection Agency, 2004; Pinto  
19 et al., 2005) and O<sub>3</sub> (U.S. Environmental Protection Agency, 2006). However, because of  
20 relative sparseness in data coverage for NO<sub>2</sub>, spatial variability in all cities that were considered  
21 for PM<sub>2.5</sub> and O<sub>3</sub> could not be considered. Thus, the number of cities included here is much  
22 smaller than for either O<sub>3</sub> (24 urban areas) or PM<sub>2.5</sub> (27 urban areas). Even in those cities where  
23 there were monitors for all three pollutants, data may not have been collected at the same  
24 locations, and even if they were, there will be different responses to local sources. For example,  
25 concentrations of NO<sub>2</sub> collected near traffic will be highest in an urban area, but concentrations  
26 of O<sub>3</sub> will tend to be lowest there because of titration by NO forming NO<sub>2</sub>. However, some  
27 general observations can still be made. Mean concentrations of NO<sub>2</sub> at individual monitoring  
28 sites are not as highly variable as for O<sub>3</sub> but are more highly variable than PM<sub>2.5</sub>. Lower bounds  
29 on intersite correlation coefficients for PM<sub>2.5</sub> and for O<sub>3</sub> tend to be much higher than NO<sub>2</sub> in the  
30 same areas shown in Table 2.5-1. CODs for PM<sub>2.5</sub> are much lower than for O<sub>3</sub>, whereas CODs  
31 for NO<sub>2</sub> tend to be the largest among these three pollutants.

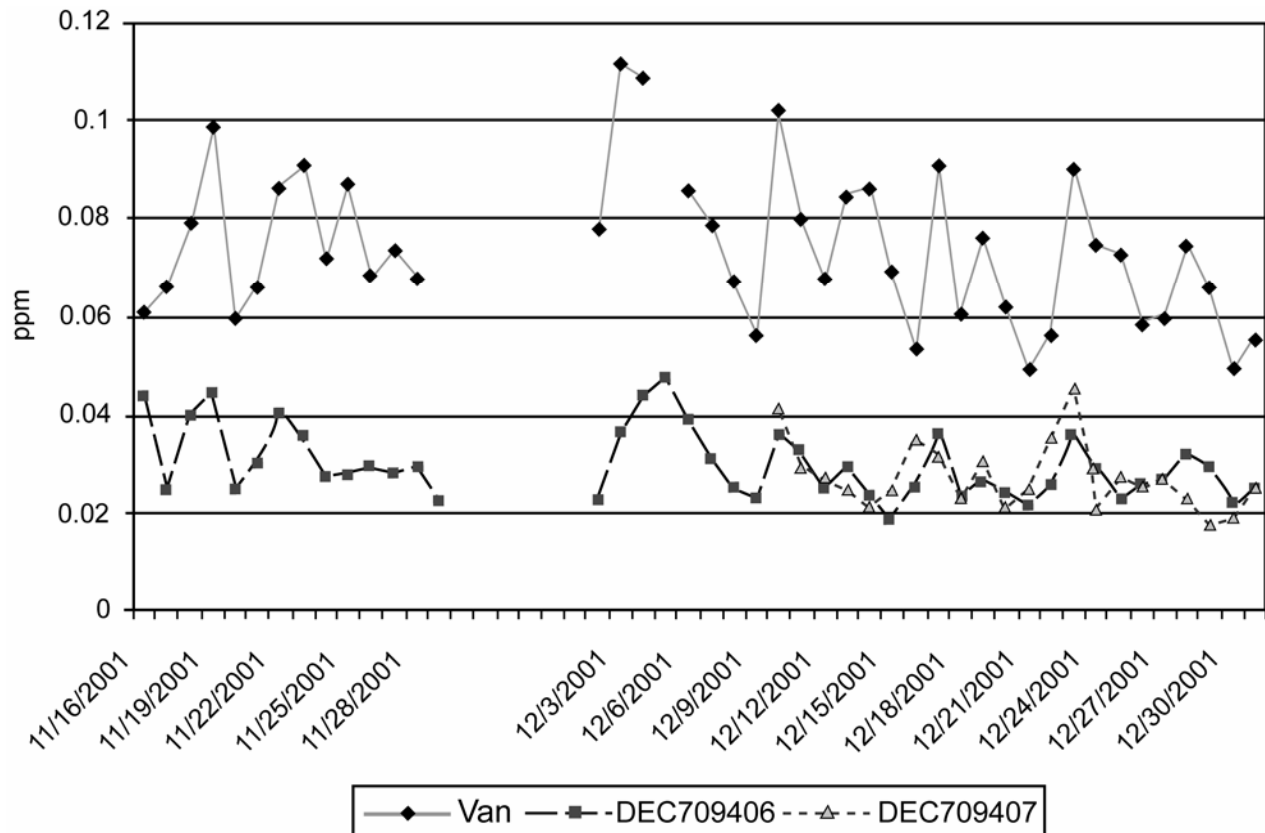
#### 1 2.5.2.2.2 *Small-Scale Vertical Variability*

2 Inlets to instruments for monitoring gas phase criteria pollutants can be located from 3 to  
3 15 m above ground level (CFR 58, Appendix E, 2002). Depending on the pollutant, either there  
4 can be positive, negative, or no vertical gradient from the surface to the monitor inlet. Positive  
5 gradients (i.e., concentrations increase with height) result when pollutants are formed over large  
6 areas by atmospheric photochemical reactions (i.e., secondary pollutants such as O<sub>3</sub>) and  
7 destroyed by deposition to the surface or by reaction with pollutants emitted near the surface.  
8 Pollutants that are emitted by sources at or just above ground level show negative vertical  
9 gradients. Pollutants with area sources (widely dispersed surface sources) and that have minimal  
10 deposition velocities show little or no vertical gradient. Restrepo et al. (2004) compared data for  
11 criteria pollutants collected at fixed monitoring sites at 15 m above the surface on a school  
12 rooftop to those measured by a van whose inlet was 4 m above the surface at monitoring sites in  
13 the South Bronx during two sampling periods in November and December 2001. They found  
14 that CO, SO<sub>2</sub>, and NO<sub>2</sub> showed negative vertical gradients, whereas O<sub>3</sub> showed a positive  
15 vertical gradient and PM<sub>2.5</sub> showed no significant vertical gradient. As shown in Figure 2.5-2,  
16 NO<sub>2</sub> mixing ratios obtained at 4 m (mean ~74 ppb) were about a factor of 2.5 higher than at 15 m  
17 (mean ~30 ppb). Because tail pipe emissions occur at lower heights, NO<sub>2</sub> values could have  
18 been much higher nearer to the surface and the underestimation of NO<sub>2</sub> values by monitoring at  
19 15 m even larger. Restrepo et al. (2004) noted that the use of the NO<sub>2</sub> data obtained by the  
20 stationary monitors underestimates human exposures to NO<sub>2</sub> in the South Bronx. This situation  
21 is not unique to the South Bronx and could arise in other large urban areas in the United States  
22 with populations of similar demographic and socioeconomic characteristics.

23 Thus, weak associations might be found between concentrations at ambient monitors and  
24 other outdoor locations and between concentrations in indoor microenvironments and personal  
25 exposures in part because of the spatial (horizontal and vertical) variability in NO<sub>2</sub>. As  
26 mentioned earlier, there are far fewer monitors for NO<sub>2</sub> than for O<sub>3</sub> or PM<sub>2.5</sub>. Consequently, NO<sub>2</sub>  
27 ambient monitors may be less representative of community or personal exposures than are  
28 ambient monitors O<sub>3</sub> or PM<sub>2.5</sub> for their respective exposures.

29





**Figure 2.5-2. NO<sub>2</sub> concentrations measured at 4 m (Van) and at 15 m at NY Department of Environmental Conservation sites (DEC709406 and DEC709407).**

Source: Restrepo et al. (2004).

1 **2.5.2.3 Relationships of Personal Exposure and Ambient Concentration**

2

3 **2.5.2.3.1 Indoor Sources and Sinks of NO<sub>2</sub> and Associated Pollutants**

4 Indoor sources and indoor air chemistry of NO<sub>2</sub> are important, because they influence the  
 5 indoor NO<sub>2</sub> concentrations to which humans are exposed and alter the association between  
 6 personal exposures and ambient concentrations.

7 Penetration of outdoor NO<sub>2</sub> and combustion in various forms are the major sources of  
 8 NO<sub>2</sub> to indoor environments, e.g., homes, schools, restaurants, and theaters. As might be  
 9 expected, indoor concentrations of NO<sub>2</sub> in the absence of combustion sources are determined by  
 10 the infiltration of outdoor NO<sub>2</sub> (Spengler et al., 1994; Weschler and Shields, 1994; Levy et al.,  
 11 1998b), with potentially significant indoor contributions from chemical reactions of NO in

1 exhaled breath with O<sub>3</sub> (see AX3.4.2 for sample calculations). Indoor sources of nitrogen oxides  
2 have been characterized in several reviews, namely the last AQCD for Oxides of Nitrogen (U.S.  
3 Environmental Protection Agency, 1993); the Review of the Health Risks Associated with  
4 Nitrogen Dioxide and Sulfur Dioxide in Indoor Air for Health Canada (Brauer et al., 2002); and  
5 the Staff Recommendations for revision of the NO<sub>2</sub> Standard in California (California Air  
6 Resources Board, 2006). Mechanisms by which nitrogen oxides are produced in the combustion  
7 zones of indoor sources were reviewed in the last AQCD for Oxides of Nitrogen (U.S.  
8 Environmental Protection Agency, 1993) and will not be repeated here. Sources of ambient NO<sub>2</sub>  
9 are reviewed in AX2.6. It should also be noted that indoor sources can affect ambient NO<sub>2</sub>  
10 levels, particularly in areas in which atmospheric mixing is limited, such as in valleys.

11 Combustion of fossil fuels and biomass is the major primary source of nitrogen oxides.  
12 Combustion of fossil fuels occurs in appliances used for cooking, heating, and drying clothes,  
13 e.g., oil furnaces, kerosene space heaters, coal stoves. Motor vehicles and various types of  
14 generators in structures attached to living areas also contribute NO<sub>2</sub> to indoor environments.  
15 Indoor sources of NO<sub>2</sub> from biomass include wood burning fireplaces and wood stoves and  
16 tobacco.

17 A large number of studies, as described in the reviews cited above, have all noted the  
18 importance of gas cooking appliances as sources of NO<sub>2</sub> emissions. Depending on geographical  
19 location, season, other sources of NO<sub>2</sub>, length of monitoring period, and household  
20 characteristics, homes with gas cooking appliances have approximately 50% to over 400%  
21 higher NO<sub>2</sub> concentrations than homes with electric cooking appliances (Gilbert et al., 2006; Lee  
22 et al., 2000; Garcia-Algar et al., 2003; Raw et al., 2004; Leaderer et al., 1986; Garcia-Algar,  
23 2003). Gas cooking appliances remain significantly associated with indoor NO<sub>2</sub> concentrations  
24 after adjusting for several potential confounders including season, type of community,  
25 socioeconomic status, use of extractor fans, household smoking, and type of heating (Garcia-  
26 Algar et al., 2004; Garrett, 1999). Homes with gas appliances with pilot lights emit more NO<sub>2</sub>  
27 resulting in NO<sub>2</sub> concentrations ~10 ppb higher than in homes with gas appliances with  
28 electronic ignition (Spengler et al., 1994; Lee et al., 1998). Secondary heating appliances are  
29 additional sources of NO<sub>2</sub> in indoor environments, particularly if the appliances are unvented or  
30 inadequately vented. As heating costs increase, the use of these secondary heating appliances  
31 tends to increase.

1 Gas heaters, particularly when unvented or inadequately vented, produce high levels of  
2 indoor NO<sub>2</sub> (Kodoma et al., 2002). Results summarized by Brauer et al. (2001) indicate that  
3 concentrations of NO<sub>2</sub> in homes with unvented gas hot water heaters were 10 to 21 ppb higher  
4 than in homes with vented heaters, which in turn, had NO<sub>2</sub> concentrations 7.5 to 38 ppb higher  
5 than homes without gas hot water heaters.

6 Table 2.5-2 shows short-term average (i.e., minutes to hours) concentrations of NO<sub>2</sub> in  
7 homes with combustion sources (mainly gas fired), and Table 2.5-3 shows long-term average  
8 (i.e., 24 h to 2 weeks) concentrations of NO<sub>2</sub> in homes with mainly gas combustion sources.

9 As can be seen from Tables 2.5-2 and 2.5-3, shorter-term average concentrations tend to  
10 be much higher than longer-term averages. As Triche et al. (2005) indicated, the 90th percentile  
11 concentrations can be substantially greater than the medians, even for 2-week samples. This  
12 finding illustrates the high variability of indoor NO<sub>2</sub> found among homes, reflecting differences  
13 in ventilation of emissions from sources, air exchange rates, the size of rooms, etc. The  
14 concentrations for short averaging periods that are listed in Table 2.5-2 correspond to about 10 to  
15 30 ppb on a 24-h average basis. As can be seen from inspection of Table 2.5-3, these sources  
16 would contribute significantly to the longer-term averages reported there if operated on a similar  
17 schedule on a daily basis. This implies that measurements made with long averaging periods  
18 may not capture the nature of the diurnal pattern of indoor concentrations of NO<sub>2</sub> in homes with  
19 strong indoor sources, a problem that becomes more evident as ambient NO<sub>2</sub> levels decrease  
20 with more efficient controls on outdoor sources.

21 The contribution of NO<sub>2</sub> from combustion of biomass fuels has not been studied as  
22 extensively as that from gas. A main conclusion from the 1993 AQCD for Oxides of Nitrogen  
23 was that properly vented wood stoves and fireplaces would make only minor contributions to  
24 indoor NO<sub>2</sub> levels and several studies conclude that using wood burning appliances does not  
25 increase indoor NO<sub>2</sub> concentrations (Levesque et al., 2001; Triche et al., 2005).

26 Other indoor combustion sources of NO<sub>2</sub> are candle burning and smoking. In a study of  
27 students living in Copenhagen, Sorensen et al. (2005) found that personal exposures to NO<sub>2</sub> were  
28 significantly associated with time exposed to burning candles in addition to other sources (data  
29 not reported). Results of studies relating NO<sub>2</sub> concentrations and exposures to environmental  
30 tobacco smoke (ETS) have been mixed. Several studies found positive associations between

1 NO<sub>2</sub> levels and ETS (e.g., Linaker et al., 1996; Farrow et al., 1997; Alm et al., 1998; Levy, 1998;  
2 Monn et al., 1998; Cyrus et al., 2000; Lee et al., 2000; Garcia-Algar, 2004) whereas others have  
3 not (Madany et al., 1993; Hackney et al., 1992; Kawamoto et al., 1993).

4 Some copollutants could be generated from indoor combustion sources along with NO<sub>2</sub>.  
5 Spicer et al. (1993) compared the measured increase in HONO in a test house resulting from  
6 direct emissions of HONO from a gas range and from production by surface reactions of NO<sub>2</sub>.  
7 They found that emissions from the gas range could account for ~84% of the measured increase  
8 in HONO. In a study of Southern California homes (Lee et al., 2002), indoor levels of NO<sub>2</sub> and  
9 HONO were positively associated with the presence of gas ranges.

10 Rogge et al. (1993) reported that most of the particle mass emitted from a vented natural  
11 gas space heater and a hot water heater was in the form of organic compounds. About 26% of  
12 the mass could be ascribed to single organic compounds, the majority of which were PAHs, oxy-  
13 PAHs, aza arenes, and thia arenes. Brown et al. (2004) characterized emissions of NO<sub>2</sub>,  
14 formaldehyde (HCHO), carbon monoxide (CO) and a number of hydrocarbons, aldehydes, and  
15 acids from unvented gas heaters in a chamber study in Australia. They found highly variable  
16 concentrations of these pollutants depending on the model of heater and operating conditions.  
17 Concentrations of NO<sub>2</sub> in their room-sized test chamber ranged from 180 to 810 ppb; HCHO  
18 ranged from <10 to 2100 ppb; CO ranged from ~1 to 18 ppm along with smaller amounts of  
19 PM<sub>2.5</sub> and hydrocarbons, aldehydes, and acids.

20 Chemistry in indoor settings can be both a source and a sink for NO<sub>2</sub> (Weschler and  
21 Shields, 1997). NO<sub>2</sub> is produced by reactions of NO with O<sub>3</sub> or peroxy radicals, while NO<sub>2</sub> is  
22 removed by gas phase reactions with O<sub>3</sub> and assorted free radicals and by surface-promoted  
23 hydrolysis and reduction reactions. The concentration of indoor NO<sub>2</sub> also affects the  
24 decomposition of PAN. Each of these processes is discussed below.

25 Indoor NO can be oxidized to NO<sub>2</sub> by reacting with O<sub>3</sub> or peroxy radicals. The latter are  
26 generated by indoor air chemistry involving O<sub>3</sub> and unsaturated hydrocarbons such as terpenes  
27 found in air fresheners and other household products (Sawar et al., 2002a,b; Nazaroff and  
28 Weschler, 2004; Carslaw, 2007).

29 At an indoor O<sub>3</sub> concentration of 10 ppb and an indoor NO concentration that is  
30 significantly smaller than that of O<sub>3</sub>, the half-life of NO is 2.5 min (using kinetic data contained  
31 in Jet Propulsion Laboratory, 2006). This reaction is sufficiently fast to compete with even

1 relatively fast air exchange rates. Hence, the amount of NO<sub>2</sub> produced from NO tends to be  
2 limited by the amount of O<sub>3</sub> available (Weschler et al., 1994).

3 NO<sub>2</sub> reacts with O<sub>3</sub> to produce nitrate radicals (NO<sub>3</sub>). To date, there have been no indoor  
4 measurements of the concentration of NO<sub>3</sub> radicals in indoor settings. Modeling studies by  
5 Nazaroff and Cass (1986), Weschler et al. (1992), Sarwar et al. (2002b), and Carslaw et al.  
6 (2007) estimate indoor NO<sub>3</sub> radical concentrations in the range of 0.01 to 5 parts per trillion  
7 (ppt), depending on the indoor levels of O<sub>3</sub> and NO<sub>2</sub>. Once formed, NO<sub>3</sub> can oxidize organic  
8 compounds by either adding to an unsaturated carbon bond or abstracting a hydrogen atom  
9 (Wayne et al., 1991). In certain indoor settings, the nitrate radical may be a more important  
10 indoor oxidant than either O<sub>3</sub> or the hydroxyl radical (Nazaroff and Weschler, 2004; Wayne  
11 et al., 1991). Thus, NO<sub>3</sub> radicals and the products of NO<sub>3</sub> radical chemistry may be meaningful  
12 confounders in NO<sub>2</sub> exposure studies.

13 Reactions between NO<sub>2</sub> and various free radicals can be an indoor source of organo-  
14 nitrates, analogous to the chain-terminating reactions observed in photochemical smog  
15 (Weschler and Shields, 1997). Additionally, based on laboratory measurements and  
16 measurements in outdoor air (Finlayson-Pitts and Pitts, 2000), one would anticipate that NO<sub>2</sub>, in  
17 the presence of trace amounts of HNO<sub>3</sub>, can react with PAHs sorbed onto indoor surfaces to  
18 produce mono- and dinitro-PAHs. Nitrogen dioxide can also be reduced on certain surfaces,  
19 forming NO. Spicer et al. (1989) found that as much as 15% of the NO<sub>2</sub> removed on various  
20 indoor surfaces was reemitted as NO. Weschler and Shields (1996) found that the amount of  
21 NO<sub>2</sub> removed by charcoal filters used in buildings were almost equally matched by the amount  
22 of NO subsequently emitted by the same filters.

23 Nitrogen dioxide can also be converted to HONO indoors through air chemistry. As  
24 noted earlier in this chapter, HONO occurs in the atmosphere mainly through multiphase  
25 processes involving NO<sub>2</sub>. Nitrous acid has been observed to form on surfaces containing  
26 partially oxidized aromatic structures (Stemmler et al., 2006) and on soot particles (Aumann  
27 et al., 1998). Indoors, surface-to-volume ratios are much larger than outdoors, and the surface-  
28 mediated hydrolysis of NO<sub>2</sub> is a major indoor source of HONO (Brauer et al., 1990; Febo and  
29 Perrino, 1991; Spicer et al., 1993; Brauer et al., 1993; Spengler et al., 1993; Wainman et al.,  
30 2001; Lee et al., 2002). Lee et al. (2002) reported average indoor HONO levels were about 6  
31 times higher than outdoor levels (4.6 versus 0.8 ppb). Indoor HONO concentrations averaged

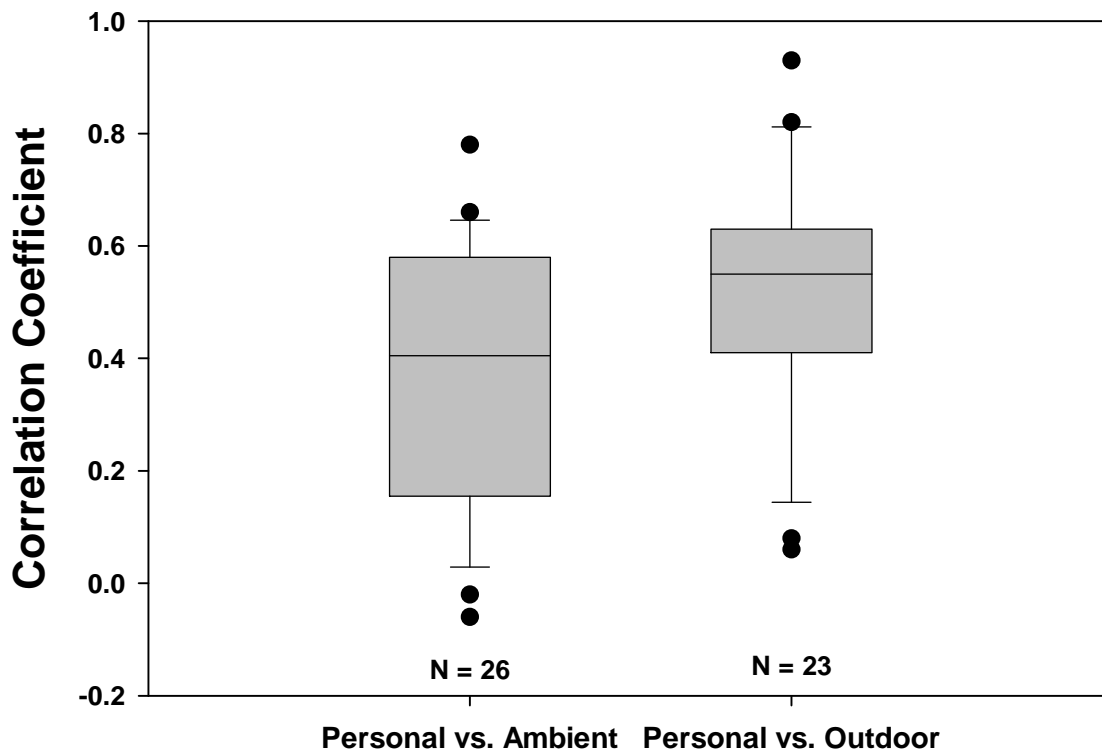
1 17% of indoor NO<sub>2</sub> concentrations, and the two were strongly correlated. Indoor HONO levels  
2 were higher in homes with humidifiers compared to homes without humidifiers (5.9 versus 2.6  
3 ppb). This last observation is consistent with the studies of Brauer et al. (1993) and Wainman  
4 et al. (2001), indicating that the production rate of HONO from NO<sub>2</sub><sup>-</sup> surface reactions is larger at  
5 higher relative humidities. Spicer et al. (1993) reported that an equilibrium between adsorption  
6 of HONO from the gas range (or other indoor combustion sources) and HONO produced by  
7 surface reactions determines the relative importance of these processes in producing HONO in  
8 indoor air.

### 9 10 **2.5.2.3.2 Associations among Ambient and Outdoor Concentrations and Personal** 11 **Exposures**

12 Results of studies showing associations between ambient concentrations and personal  
13 exposures are shown in Table 2.5-4A and results of studies showing associations between  
14 outdoor concentrations and personal exposures are shown in Table 2.5-4B. Figure 2.5-3  
15 summarizes these correlation coefficients with box-whisker plots.

16 The association between personal NO<sub>2</sub> exposure and ambient and outdoor NO<sub>2</sub>  
17 concentrations varies from poor to good as shown in Tables 2.5-4A and B, with stronger  
18 associations generally found when outdoor rather than ambient concentrations are used. This  
19 situation arises in part because outdoor measurements are generally made much closer to study  
20 participants' homes than are measurements of ambient NO<sub>2</sub> concentrations (cf. Section 2.5.2.2).

21 Associations between ambient concentrations and personal exposures were not stratified  
22 by the presence of indoor sources, except in Alm et al. (1998) and Sarnat et al. (2006). The  
23 strength of the association between personal exposures and ambient and/or outdoor  
24 concentrations for a population is determined by variations in indoor or other local sources, air  
25 exchange rate, penetration, and decay rate of NO<sub>2</sub> in different microenvironments and the time  
26 people spend in different microenvironments with different NO<sub>2</sub> concentrations. Alm et al.  
27 (1998) indicated that the association between personal exposure and outdoor concentration was  
28 stronger than the correlation between personal exposure and central site concentration. Kim  
29 et al. (2006) pointed out that the association was not improved using the ambient sampler closest



**Figure 2.5-3. Distribution of correlation coefficients between personal NO<sub>2</sub> exposure and ambient NO<sub>2</sub> concentrations, and between personal NO<sub>2</sub> exposure and outdoor NO<sub>2</sub> concentrations in urban areas. (Note: Data presented here are  $r_p$  and  $r_s$ , and a square root was taken of  $R^2$  when necessary; N is the number of case studies examined.)**

1 to a home. Home ventilation is another important factor modifying the personal-ambient  
 2 relationships; one would expect to observe the strongest associations for subjects spending time  
 3 indoors with open windows. Alm et al. (1998) and Kodama et al. (2002) observed the  
 4 association between personal exposure and ambient concentration became stronger during the  
 5 summer than the winter. However, Sarnat et al. (2006) reported that  $R^2$  values decreased from  
 6 0.34 for a low ventilation population to 0.16 for a high ventilation population in the summer, and  
 7 from 0.47 to 0.34 in the fall.

8 The association between personal exposure and ambient concentration is complicated and  
 9 is determined by many factors. Exposure misclassification might occur if a single factor, such as

1 season or ventilation status, is used as an exposure indicator. Higher personal to ambient  
2 correlation has been found for subjects living in rural areas and lower correlation with subjects  
3 living in urban areas (Rojas-Bracho et al., 2002; Alm et al., 1998). Spengler et al. (1994) also  
4 observed that the relationship between personal exposure and outdoor concentration was highest  
5 in areas with lower ambient NO<sub>2</sub> levels ( $R^2 = 0.47$ ) and lowest in areas with higher ambient NO<sub>2</sub>  
6 levels ( $R^2 = 0.33$ ). This might reflect the highly heterogeneous distribution or the effect of local  
7 sources of NO<sub>2</sub> in an urban area, and personal activities are more diverse in an urban area.  
8 However, it is also possible that indoor sources could explain more personal exposure when  
9 ambient concentrations become lower and more homogeneously distributed.

10         When there is little or no contribution from indoor sources, ambient concentrations  
11 primarily determine exposure; however, if there are indoor sources, the importance of outdoor  
12 levels in determining personal exposures decreases. The association between ambient  
13 concentrations and personal exposures strengthens after controlling for indoor sources.  
14 Raaschou-Nielsen et al. (1997), Spengler et al. (1994), and Gauvin et al. (2001) reported that  $R^2$   
15 values increased by 10 to 40% after controlling for indoor sources, such as gas appliances and  
16 ETS.

17         The correlation coefficient between personal exposures and ambient concentrations has  
18 different meanings for different study designs. There are three types of correlations generated  
19 from different study designs: longitudinal, “pooled,” and daily-average correlations.  
20 Longitudinal correlations are calculated when data from a study includes measurements over  
21 multiple days for each subject (longitudinal study design). Longitudinal correlations describe the  
22 temporal relationship between daily personal NO<sub>2</sub> exposure or microenvironment concentration  
23 and daily ambient NO<sub>2</sub> concentration for each individual subject. The longitudinal correlation  
24 coefficient may differ for each subject. The distribution of correlations across a population could  
25 be obtained with this type of data. Pooled correlations are calculated when a study involves one  
26 or only a few measurements per subject and when different subjects are studied on subsequent  
27 days. Pooled correlations combine individual subject/individual day data for the calculation of  
28 correlations. Pooled correlations describe the relationship between daily personal NO<sub>2</sub> exposure  
29 and daily ambient NO<sub>2</sub> concentration across all subjects in the study. Daily-average correlations  
30 are calculated by averaging exposure across subjects for each day. Daily-average correlations  
31 then describe the relationship between the daily average exposure and daily ambient NO<sub>2</sub>



1 concentration (U.S. Environmental Protection Agency, 2004). The type of correlation analysis  
2 can have a substantial effect on the value of the resultant correlation coefficient. Mage et al.  
3 (1999) showed that very low correlations between personal exposure and ambient concentrations  
4 could be obtained when people with very different non-ambient exposures are pooled, even  
5 though their individual longitudinal correlations are high. Most studies, (employing both cross-  
6 sectional and longitudinal study designs) examined in the current review showed that ambient  
7 NO<sub>2</sub> is associated with personal NO<sub>2</sub> exposure, however, the strength of the association varied  
8 considerably.

### 9 10 **2.5.2.3.3     *Ambient Contribution to Personal NO<sub>2</sub> Exposure***

11         Another aspect of the relationship of personal NO<sub>2</sub> exposure and ambient NO<sub>2</sub> is the  
12 contribution of ambient NO<sub>2</sub> to personal exposures. The infiltration factor ( $F_{inf}$ ) and alpha ( $\alpha$ )  
13 are the keys to evaluate personal NO<sub>2</sub> exposure of ambient origin. As defined in Equations 2.5-2  
14 through 2.5-5, the infiltration factor ( $F_{inf}$ ) of NO<sub>2</sub>, the physical meaning of which is the fraction  
15 of ambient NO<sub>2</sub> found in the indoor environment, is determined by the NO<sub>2</sub> penetration  
16 coefficient ( $P$ ), air exchange rate ( $a$ ), and the NO<sub>2</sub> decay rate ( $k$ ). Alpha ( $\alpha$ ) is a function of  $F_{inf}$   
17 and the fraction of time people spend outdoors ( $y$ ), and the physical meaning of  $\alpha$  is the ratio of  
18 personal ambient exposure concentration to ambient concentration, in the absence of exposures  
19 to non-ambient sources (i.e., when  $E_{na} = 0$ ).

20         The values for  $\alpha$  and  $F_{inf}$  can be calculated physically through Equations 2.5-2 through  
21 2.5-5, if  $P$ ,  $k$ ,  $a$ , and  $y$  are known. However, the values of  $P$  and  $k$  for NO<sub>2</sub> are rarely reported,  
22 and in most mass balance modeling work,  $P$  is assumed to equal 1 and  $k$  is assumed to equal  
23  $0.99 \text{ h}^{-1}$ , (Yamanaka, 1984; Yang et al., 2004; Dimitroulopoulou et al., 2001; Kulkarni et al.,  
24 2002). It is well known that  $P$  and  $k$  are dependent on a large number of indoor parameters, such  
25 as temperature, relative humidity, surface properties, surface-to-volume ratio, the turbulence of  
26 airflow, building type and coexisting pollutants (Lee et al., 1996; Cotterill et al., 1997; Monn  
27 et al., 1998; Garcia-Algar et al., 2003; Sorensen et al., 2005; Zota et al., 2005). As a result, using  
28 a fixed value, as mentioned above, would either over- or underestimate the true  $\alpha$  or  $F_{inf}$ . It  
29 should also be pointed out that both  $P$  and  $k$  are functions of the complicated mass transfer  
30 processes that occur on indoor surfaces, and therefore, are associated with air exchange rate,

1 which has an impact on the turbulence of indoor airflows. However, the relationship between  $P$ ,  
2  $k$ , and  $a$  has not been thoroughly investigated.

3 Alternatively, the ratio of personal exposure to ambient concentration can be regarded as  
4  $\alpha$  in the absence of indoor or nonambient sources. Only a few studies have reported the value  
5 and distribution of the ratio of personal NO<sub>2</sub> exposure to ambient NO<sub>2</sub> concentration, and even  
6 fewer studies reported the value and distribution of  $\alpha$  based on sophisticated study designs.  
7 Rojas-Bracho et al. (2002) reported the median personal/outdoor ratio was 0.64 (with an IQR of  
8 0.45), but the authors reported that  $\alpha$  was overestimated by this ratio because of indoor sources.

9 The random component superposition (RCS) model is an alternative way to calculate  $F_{inf}$   
10 or  $\alpha$  using observed ambient and personal exposure concentrations (Ott et al., 2000). The RCS  
11 statistical model (shown in Equation 2.5-2 through 2.5-5) uses the slope of the regression line of  
12 personal concentration on the ambient NO<sub>2</sub> concentration to estimate the population averaged  
13 attenuation factor and means and distributions of ambient and nonambient contributions to  
14 personal NO<sub>2</sub> concentrations (the intercept of the regression is the averaged nonambient  
15 contribution to personal exposure) (U.S. Environmental Protection Agency, 2004). As shown in  
16 Table 2.5-5,  $\alpha$  calculated by the RCS model ranges from 0.3 to 0.6. Similarly, as shown in Table  
17 2.5-6,  $F_{in}$  ranges from 0.4 to 0.7.

18 The RCS model calculates ambient contributions to indoor concentrations and personal  
19 exposures based on the statistical inferences of regression analysis. However, personal-outdoor  
20 regressions could be affected by extreme values (outliers either on the  $x$  or the  $y$  axis). Another  
21 limitation of the RCS model is that this model is not designed to estimate ambient and  
22 nonambient contributions for individuals, in part because the use of a single value for  $\alpha$  does not  
23 account for the large home-to-home variations in actual air exchange rates and penetration and  
24 decay rates of NO<sub>2</sub>. In the RCS model,  $\alpha$  is also determined by the selection of the predictor.  
25 Using residential outdoor NO<sub>2</sub> concentrations as the model predictor might give a different  
26 estimate of  $\alpha$  than using ambient NO<sub>2</sub> because of the spatial variability of NO<sub>2</sub> mentioned early  
27 in this section.

28 Personal exposure levels in most of the studies considered here were lower than the  
29 corresponding outdoor or ambient levels. In the presence of local sources (indoor or local traffic  
30 sources not accounted for by the ambient monitor), personal exposure levels could be higher than  
31 outdoor or ambient levels (Spengler et al., 1994, 1996; Nakai et al., 1995; Linn et al., 1996;

1 Raaschou-Nielsen et al., 1997; Alm et al., 1998; Levy et al., 1998; Monn et al., 1998; Liard et al.,  
2 1999; Kramer et al., 2000; Linaker et al., 2000; Mukala et al., 2000; Gauvin et al., 2001; Moon  
3 et al., 2001; Rotko et al., 2001; Sarnat et al., 2001, 2005, 2006; Kodama et al., 2002; Mosqueron  
4 et al., 2002; Ramirez-Aguilar et al., 2002; Rojas-Bracho et al., 2002; Lai et al., 2004; Nerriere  
5 et al., 2005; Sorensen et al., 2005; Kim et al., 2006).

6 Nerriere et al. (2005) investigated factors determining the discrepancies between personal  
7 exposure and ambient levels in the Genotox ER study in France (Grenoble, Paris, Rouen, and  
8 Strasbourg). The authors reported that factors affecting the concentration discrepancies between  
9 personal exposure and corresponding ambient monitoring site concentrations were season, city  
10 and land use dependent. During the winter, city and land use account for 31% of the variation of  
11 the discrepancy, and during the summer, 54% of the variation in the discrepancy can be  
12 explained by these factors. When using the ambient site to represent ambient levels, the largest  
13 difference between ambient and personal exposure was found at the “proximity to traffic” site,  
14 while the smallest difference was found at the “background” site. When using urban background  
15 site as ambient level, the largest difference was observed at the “industry” site, and the smallest  
16 difference was observed at the background site, which reflected the heterogeneous distribution of  
17 NO<sub>2</sub> in an urban area. During winter, differences between ambient site and personal exposure  
18 concentrations were larger than those in the summer.

19 In summary, NO<sub>2</sub> is monitored at far fewer sites than either O<sub>3</sub> or PM. Significant spatial  
20 variations in ambient NO<sub>2</sub> concentrations were observed in urban areas. Measurements of NO<sub>2</sub>  
21 are subject to artifacts both at the ambient level and at the personal level. Personal exposure to  
22 ambient and outdoor NO<sub>2</sub> is determined by many factors as listed in Section 2.5.1 and mentioned  
23 previously in Section 2.5.2. These factors all help determine the contribution of ambient NO<sub>2</sub> to  
24 personal exposures. Personal activities determine when, where, and how people are exposed to  
25 NO<sub>2</sub>. The variations of these physical and exposure factors determine the strength of the  
26 association between personal exposure and ambient concentrations both longitudinally and cross-  
27 sectionally. In the absence of indoor and local sources, personal exposures to NO<sub>2</sub> are between  
28 the ambient level and the indoor level. However, personal exposures could be much higher than  
29 either indoor or outdoor concentrations in the presence of these sources. A number of studies  
30 found that personal NO<sub>2</sub> was associated with ambient NO<sub>2</sub>, but the strength of the association  
31 ranged from poor to good.

1           Some researchers concluded that ambient NO<sub>2</sub> may be a reasonable proxy for personal  
2 exposures, while others noted that caution must be exercised if ambient NO<sub>2</sub> is used as a  
3 surrogate for personal exposure. Reasons for the differences in study results are not clear, but  
4 are related in large measure to differences in study design, to the spatial heterogeneity of NO<sub>2</sub> in  
5 study areas, to indoor sources, to the seasonal and geographic variability in the infiltration of  
6 ambient NO<sub>2</sub>, and to differences in the time spent in different microenvironments. Measurement  
7 artifacts at the ambient level and differences in analytical measurement capabilities among  
8 different groups could also have contributed to the mixed results. The collective variability in all  
9 of the above parameters, in general, contributes to exposure misclassification errors in air  
10 pollution-health outcome studies.

11           The association between community average exposures and ambient concentrations is  
12 more directly relevant to epidemiological studies, in which ambient concentrations are used as a  
13 surrogate for community exposure. Liard et al. (1999) conducted an exposure study for office  
14 workers and children in Paris. Three 4-day averaged measurements were conducted for both  
15 adults and children, and personal NO<sub>2</sub> exposures were measured at the same time for each study  
16 participant. The authors reported that the population-averaged exposure during each  
17 measurement fluctuated with the ambient concentration, with an  $r_s$  of 1, although the correlation  
18 coefficient based on individual measurements was low (Table 2.5-4A). The findings in this  
19 study support the assumption in time-series epidemiological studies that ambient concentrations  
20 are a reasonable surrogate for community average exposures. Monn et al. (1998) and Monn  
21 (2001) reported personal NO<sub>2</sub> exposures obtained in the SAPALDIA study (eight study centers  
22 in Switzerland). In each study location, personal exposures for NO<sub>2</sub> were measured  
23 simultaneously for all participants, as well as the residential outdoor concentrations (Table  
24 2.5-4B). Monn (2001) observed a strong association between the average personal exposures in  
25 each study location and corresponding average outdoor concentrations with an  $R^2$  of 0.965. As  
26 pointed out by the author, in an analysis of individual single exposure and outdoor concentration  
27 data, personal versus outdoor  $R^2$  was less than 0.3 (Monn et al., 1998). The results of Monn  
28 (2001) imply that long-term averaged ambient concentrations are a good surrogate for population  
29 exposures.

30

#### 1 **2.5.2.4 Exposure Measurement Error in Epidemiological Studies: NO<sub>2</sub>**

2 In many air pollution epidemiological studies, especially time-series studies with  
3 administrative data on mortality and hospitalization outcomes, data from central ambient  
4 monitoring sites generally are used as the estimate of exposure. Personal exposures of individual  
5 study subjects generally are not directly measured in epidemiological studies. Routinely  
6 collected ambient monitor data, though readily available and convenient, may not represent true  
7 personal exposure, which includes both ambient and nonambient (i.e., indoor) source exposures.  
8 Also, personal exposure measurements may or may not be subject to the same artifacts as the  
9 ambient measurements. Therefore, they may not be measuring the same quantities. Zeka and  
10 Schwartz (2004) state that each pollutant, as measured at a central site in each city, is a surrogate  
11 for exposure to the same pollutant in personal exposure measurements.

12 In considering exposure error, it should be noted that total personal exposure can be  
13 partitioned into two types of sources, ambient and nonambient. Sheppard (2005) notes that  
14 nonambient source exposures typically vary across individuals, but the community averages do  
15 not vary across communities. In addition, nonambient exposures are not likely to have strong  
16 temporal correlations. In contrast, ambient concentrations across individuals should be highly  
17 correlated, as they tend to vary over time similarly for everyone because of changes in source  
18 generation, weather, and season. The independence of ambient and nonambient exposure  
19 sources has important implication. Sheppard et al. (2005) observes that when ambient and  
20 nonambient sources are independent, exposure variation due to nonambient source exposures  
21 behaves like Berkson measurement error (i.e., statistically independent from the observed  
22 variable) and does not bias the effect estimates.

23 A simulation study by Sheppard et al. (2005) also considered attenuation of the risk based  
24 on personal behavior, their microenvironment, and qualities of the pollutant in time-series  
25 studies. Of particular interest is their finding that significant variation in nonambient exposure or  
26 in ambient source exposure that is independent of ambient concentration does not further bias the  
27 effect estimate. In other words, risk estimates were not further attenuated in time-series studies  
28 even when the correlations between personal exposures and ambient concentrations were weak.

29 In the case of NO<sub>2</sub>, there are exposures to nonambient indoor sources to consider.  
30 Exposures to nonambient sources are largely independent of ambient exposures for a number of  
31 sources such as exposures associated with cooking or smoking. However, the relationship

1 between exposure to some nonambient sources and to ambient concentrations may not be  
2 entirely straightforward. If the indoor source strength is driven by outdoor parameters that also  
3 determine ambient levels, then exposures to these sources could be associated with ambient  
4 concentrations. For example, use of natural gas or other fuels for heating varies with outdoor  
5 temperatures and are a source of nonambient exposures to NO<sub>2</sub>. Of course, the contribution to  
6 personal exposures from indoor heating depends to a large extent on how efficiently the  
7 emissions are vented. Ambient levels will also vary with emissions from local facilities, such as  
8 power plants, that respond to changes in temperature. Indoor sources could also be affecting  
9 ambient levels. This situation is found in many areas where there can be trapping of emissions  
10 within topographic features. Again, the contribution of the nonambient sources depends largely  
11 on how efficiently the emissions are vented.

12 Other complications for NO<sub>2</sub> in the relationship between personal exposures and ambient  
13 concentrations include expected strong seasonal variation of personal behaviors and building  
14 ventilation practices that can modify exposure. Also, there may be potential differential errors  
15 based on different measurement techniques for ambient and personal measurement. In addition,  
16 the relationship may be affected by temperature (e.g., high temperature may increase air  
17 conditioning use, which may reduce NO<sub>2</sub> penetration indoors), further complicating the role of  
18 temperature as a confounder of NO<sub>2</sub> health effects. It should be noted that the pattern of  
19 exposure misclassification error and influence of confounders may differ across the outcomes of  
20 interest as well as in susceptible populations and by study design. For example, those who may  
21 be suffering from chronic cardiovascular or respiratory conditions may be in a more protective  
22 environment (i.e., with less exposure to both NO<sub>2</sub> and its confounders such as temperature and  
23 PM) than those who are healthy.

24 As discussed thoroughly in the 2004 PM AQCD (Section 8.4.5), the resulting exposure  
25 measurement error and its effect on the estimates of relative risk must be considered to include  
26 both Berkson type and classical-type error (i.e., statistically independent of the true variable).  
27 Errors of the classical type arise when a quantity is measured by some device and repeated  
28 measurements vary around the true value. Error of the Berkson type is involved when a group's  
29 average is assigned to each individual suiting the group's characteristics. The group's average is  
30 thus the "measured value," that is the value that enters the analysis, and the individual latent  
31 value is the "true value" (Heid et al., 2004)

1           In theory, there are three components to exposure measurement error in time-series  
2 studies as described by Zeger et al. (2000): (1) the use of average population rather than  
3 individual exposure data, (2) the difference between average personal ambient exposure and  
4 ambient concentrations at central monitoring sites, and (3) the difference between true and  
5 measured ambient concentrations. The first error component, having aggregate rather than  
6 individual exposure data, is a Berkson measurement error, which in a simple linear model  
7 increases the standard error, but does not bias the risk estimate. The second error component  
8 resulting from the difference between average personal ambient exposure and outdoor ambient  
9 concentration level has the greatest potential to introduce bias. If the error is of a fixed amount  
10 (i.e., absolute differences do not change with increasing concentrations), there is no bias.  
11 However, if the error is not a fixed difference, this error will likely attenuate the NO<sub>2</sub> risk  
12 estimate, as personal NO<sub>2</sub> exposures are generally lower than ambient NO<sub>2</sub> concentrations in  
13 homes without sources while they are higher in homes with sources. The third error component,  
14 the instrument measurement error in the ambient levels, is referred to as nondifferential  
15 measurement error and, while unlikely to cause substantial bias, can lead to a bias toward  
16 the null.

17           Sheppard (2005) stated that the time-series design is an ecologic study design and, thus,  
18 suffers from loss of information (i.e., sources of variation) in the analysis. In air pollution  
19 studies, it only uses information about the ambient concentrations, which represent only a  
20 fraction of the total personal exposure variation over time and individuals in a population. Thus,  
21 there is less power in time-series studies than there would be if the time-series design could use  
22 all the exposure variation in the population. Sheppard concluded that the size of the populations  
23 that can be feasibly studied in time-series studies, even with the lower exposure variation from  
24 using only ambient concentration data, overwhelms the benefits of using total personal exposure  
25 on a subset of the population in a feasible panel study. Relative to panel studies, time-series  
26 studies are immensely more powerful, because they can consider all the events over time in  
27 entire populations.

28           Interpretation of the results observed in epidemiological studies using NO<sub>2</sub> measurements  
29 from ambient monitoring sites needs to consider the impact of exposure measurement error.  
30 Results from a simulation study by Sheppard et al. (2005) seem to suggest that effect estimates  
31 were not further biased in time-series studies even when the correlations between personal

1 exposures and ambient concentrations were weak. Zeger et al. (2000) indicated that realistic  
2 models for estimating air pollution health effects have elements of both classical and Berkson  
3 error models, which generally lead to effect estimates biased toward the null. However, they  
4 also noted that when a pollutant with no health effect is correlated with at least one pollutant  
5 having a nonzero effect, regression coefficients can be biased away from the null; that is,  
6 positive associations can be observed.

### 7 8 **2.5.3 NO<sub>2</sub> as a Component of Mixtures**

#### 9 10 **2.5.3.1 Correlations between Ambient NO<sub>2</sub> and Ambient Copollutants**

11 Confounding of NO<sub>2</sub> health effects is often examined at the ambient level, as ambient  
12 concentrations are generally used to reflect exposures in epidemiological studies. The majority  
13 of studies examining pollutant associations in the ambient environment have focused on ambient  
14 NO<sub>2</sub>, PM<sub>2.5</sub> (and its components), and CO, with fewer studies reporting the relationship between  
15 ambient NO<sub>2</sub> and ambient O<sub>3</sub> or SO<sub>2</sub>.

16 Data were compiled from EPA's Air Quality System and a number of exposure studies.  
17 Correlations between ambient concentrations of NO<sub>2</sub> and other pollutants, PM<sub>2.5</sub> (and its  
18 components where available), CO, O<sub>3</sub>, and SO<sub>2</sub> are summarized in Table 2.5-7. Mean values of  
19 paired, site-wise correlations are shown. As can be seen from the table, NO<sub>2</sub> is moderately  
20 correlated with PM<sub>2.5</sub> (range: 0.37 to 0.78) and with CO (0.41 to 0.76) in suburban and urban  
21 areas. At locations such as Riverside, CA, associations between ambient NO<sub>2</sub> and ambient CO  
22 concentrations (both largely traffic-related pollutants) are much lower, likely as the result of  
23 other sources of both CO and NO<sub>2</sub> increasing in importance in moving away from the urban  
24 core. These sources include oxidation of CH<sub>4</sub> and other biogenic compounds, residential wood  
25 burning and prescribed and wild land fires for CO and soil emissions, lightning, and residential  
26 wood burning and wild land fires for NO<sub>2</sub>. In urban areas, the ambient NO<sub>2</sub>-CO correlations  
27 vary widely. The strongest correlations are seen between NO<sub>2</sub> and elemental carbon. Note that  
28 the results of Hochadel et al. (2006) for PM<sub>2.5</sub> optical absorbance have been interpreted in terms  
29 of elemental carbon (EC). Correlations between ambient NO<sub>2</sub> and ambient O<sub>3</sub> are mainly  
30 negative, owing to the chemical relation between the two, with again considerable variability in  
31 the observed correlations. Only one study (Sarnat et al., 2001) examined associations between



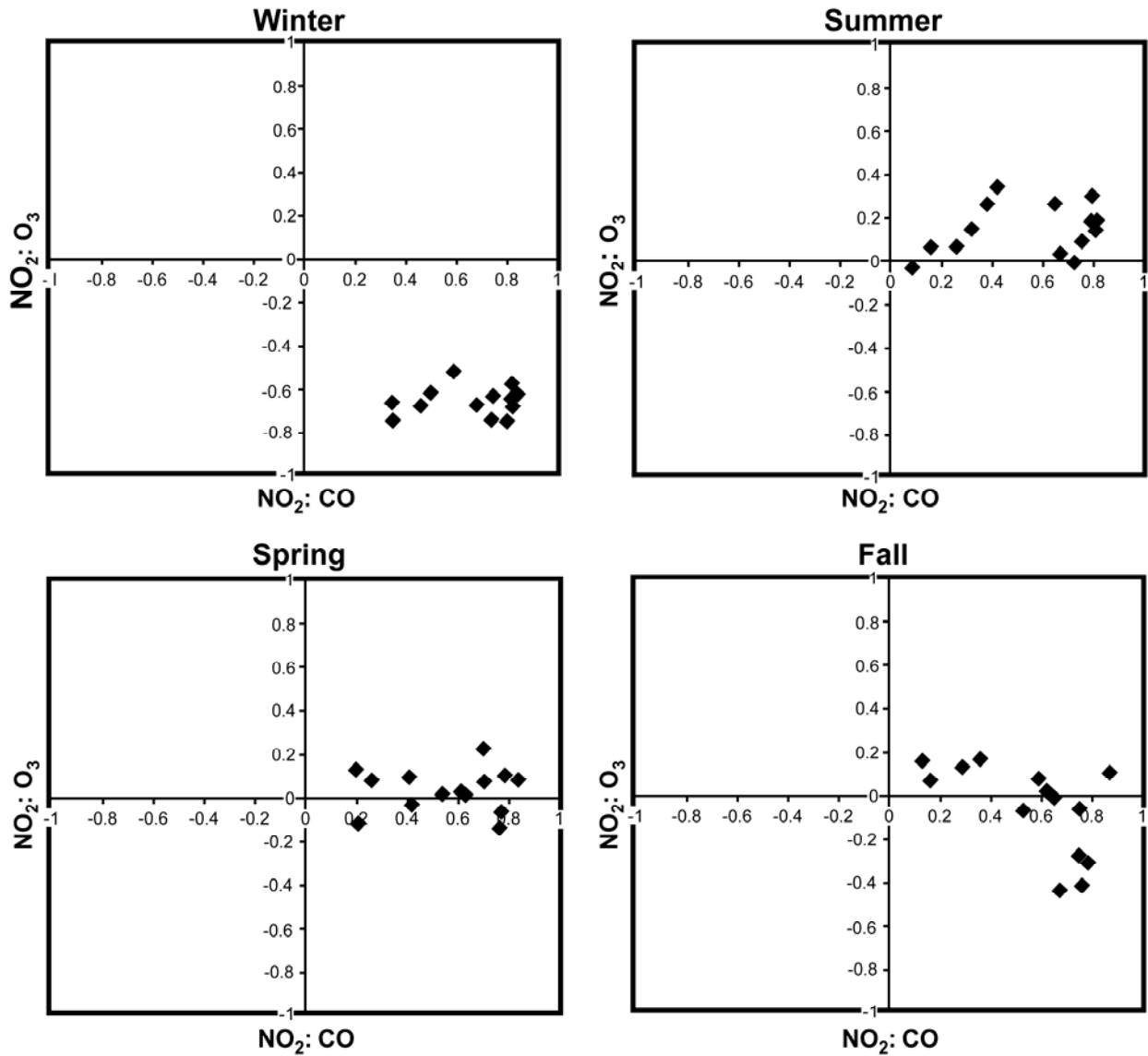
1 ambient NO<sub>2</sub> and ambient SO<sub>2</sub> concentrations, and it showed a negative correlation during  
2 winter. This analysis needs to be extended to other cities.

3       Figures 2.5-4a-d show seasonal plots of correlations between NO<sub>2</sub> and O<sub>3</sub> versus  
4 correlations between NO<sub>2</sub> and CO. As can be seen from the figures, NO<sub>2</sub> is positively correlated  
5 with CO during all seasons at all sites. However, the sign of the correlation of NO<sub>2</sub> with O<sub>3</sub>  
6 varies with season, ranging from negative during winter to slightly positive during summer.  
7 There are at least two main factors contributing to the observed seasonal behavior. Ozone and  
8 radicals correlated with it tend to be higher during the summer, thereby tending to increase the  
9 ratio of NO<sub>2</sub> to NO. Nitrogen oxide compounds formed by further the oxidation of NO<sub>x</sub> are also  
10 expected to be correlated with O<sub>3</sub> and increased summertime photochemical activity. Because  
11 some of these additionally oxidized nitrogen compounds create a positive artifact in the FRM for  
12 NO<sub>z</sub>, they may also tend to increase the correlation of NO<sub>2</sub> with O<sub>3</sub> during the warmer months.

13       A number of case studies show similar correlations between ambient NO<sub>2</sub> and other  
14 pollutants presented above. Particulate and gaseous copollutants data were analyzed at 10 sites  
15 in St. Louis Regional Air Pollution Study dataset (1975-1977) by Kim et al. (2005). This study  
16 examined the spatial variability in source contributions to PM<sub>2.5</sub>. Table 2.5-8 shows correlations  
17 between NO<sub>x</sub> and traffic pollutants measured in ambient air.

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

25       In the Restrepo et al. (2004) study, NO<sub>2</sub> behaved as if traffic was its main source, as NO<sub>2</sub>  
26 behaved similarly to CO and PM<sub>2.5</sub>, i.e., their concentrations decreased with height. Ozone  
27 showed the opposite vertical gradient, i.e., its concentration increased with height. Seaton and  
28 Dennekamp (2003) suggested that NO<sub>2</sub> may be a surrogate for ultrafine particles, in particular



**Figure 2.5-4a-d. Correlations of NO<sub>2</sub> to O<sub>3</sub> versus correlations of NO<sub>2</sub> to CO for Los Angeles, CA (2001-2005).**

1 for particle number concentrations. The results from the measurements made at a background  
 2 site in Aberdeen city over the course of 6 months showed very high correlation between the  
 3 number concentration of particles less than 100 nm in diameter and NO<sub>2</sub>. The correlation  
 4 between NO<sub>2</sub> and the particle number concentration ( $r = 0.89$ ) was much higher than that  
 5 between NO<sub>2</sub> and PM<sub>2.5</sub>

1 (r = 0.55) and that between NO<sub>2</sub> and PM<sub>10</sub> (r = 0.45). A time-series mortality study (Wichmann  
2 et al., 2000; re-analysis by Stölzel et al., 2003) conducted in Erfurt, Germany, measured and  
3 analyzed ultrafine particle number and mass concentrations as well as NO<sub>2</sub>. Unlike Seaton and  
4 Dennekamp's data, in this data set, the correlation between NO<sub>2</sub> and various number  
5 concentration indices were not much stronger than those between PM<sub>2.5</sub> and number  
6 concentration indices or those between PM<sub>10</sub> and number concentration indices. For example,  
7 the correlation between NC<sub>0.01-0.10</sub> (particle number concentration for particle diameter between  
8 10 and 100 nm) and NO<sub>2</sub>, PM<sub>2.5</sub>, and PM<sub>10</sub> were 0.66, 0.61, and 0.61, respectively.

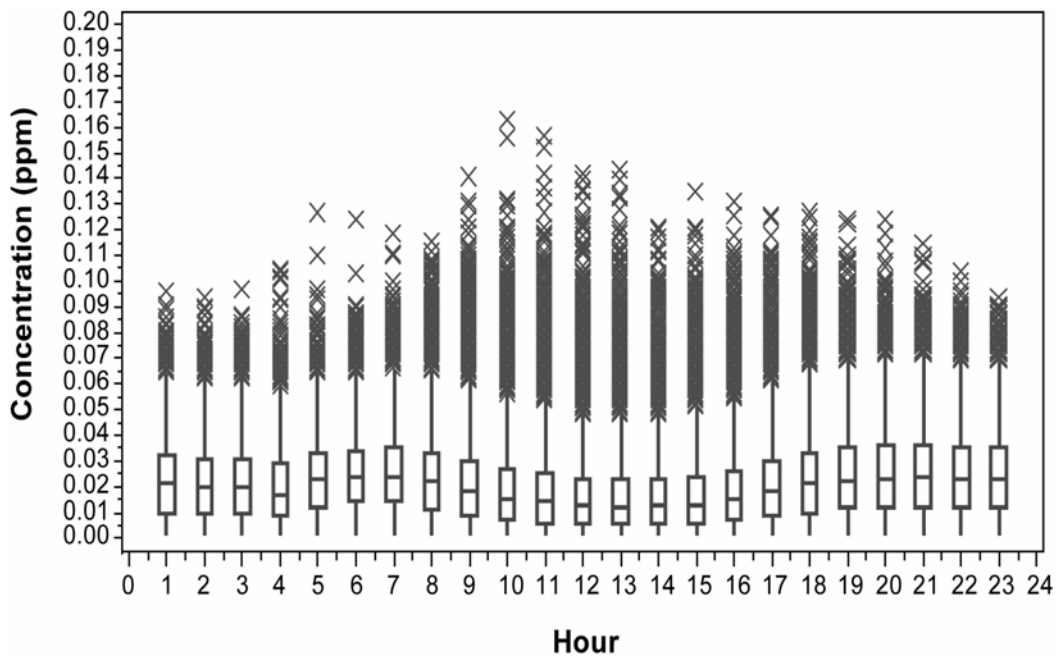
9  
10 **2.5.3.2 Correlations of Personal and Ambient NO<sub>2</sub> and Personal and Ambient**  
11 **Copollutants**

12 Correlations between ambient concentrations of NO<sub>2</sub> and personal copollutants, PM<sub>2.5</sub>  
13 (and its components where available), CO, O<sub>3</sub>, and SO<sub>2</sub> are summarized in Table 2.5-9.  
14 Correlations between personal concentrations of NO<sub>2</sub> and ambient copollutants, PM<sub>2.5</sub> (and its  
15 components where available), CO, O<sub>3</sub>, and SO<sub>2</sub> are summarized in Table 2.5-10, and correlations  
16 between personal NO<sub>2</sub> concentrations and personal copollutant concentrations are shown in  
17 Table 2.5-11.

18 Most studies examined above show that personal NO<sub>2</sub> concentrations are significantly  
19 correlated with either ambient or personal level PM<sub>2.5</sub> or other combustion generated pollutants,  
20 e.g., CO and EC.

21 As might be expected from a pollutant having a major traffic source, the diurnal cycle of  
22 NO<sub>2</sub> in typical urban areas is characterized by traffic emissions, with peaks in emissions  
23 occurring during morning and evening rush hour traffic. Motor vehicle emissions consist mainly  
24 of NO, with only about 10% of primary emissions in the form of NO<sub>2</sub>. The diurnal pattern of  
25 NO and NO<sub>2</sub> concentrations are also strongly influenced by the diurnal variation in the mixing  
26 layer height. Thus, during the morning rush hour when mixing layer heights are still low, traffic  
27 produces a peak in NO and NO<sub>2</sub> concentrations. As the mixing layer height increases during the  
28 day, dilution of emissions occurs, and NO and NO<sub>2</sub> are converted to NO<sub>2</sub>. During the afternoon  
29 rush hour, mixing layer heights are often still at, or are near, their daily maximum values  
30 resulting in dilution of traffic emissions through a larger volume than in the morning. Starting  
31 near sunset, the mixing layer height drops and conversion of NO to NO<sub>2</sub> occurs without  
32 subsequent photolysis of NO<sub>2</sub> recreating NO.

1 The composite diurnal variability of NO<sub>2</sub> in selected urban areas with multiple sites  
 2 (New York, NY; Atlanta, GA; Baton Rouge, LA; Chicago, IL; Houston, TX; Riverside, CA; and  
 3 Los Angeles, CA) is shown in Figure 2.5-5. Figure 2.5-5 shows that lowest hourly median  
 4 concentrations are typically found at around midday and that highest hourly median  
 5 concentrations are found either in the early morning or in mid-evening. Median values range by  
 6 about a factor of two from about 13 ppb to about 25 ppb. However, individual hourly  
 7 concentrations can be considerably higher than these typical median values, and hourly NO<sub>2</sub>  
 8 concentrations of >0.10 ppm can be found at any time of day.



**Figure 2.5-5 Composite, diurnal variability in 1-h average NO<sub>2</sub> 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. Asterisks denote individual values above the 95th percentile.**

9 Information concerning the seasonal variability of ambient NO<sub>2</sub> concentrations is given  
 10 in the Section AX3.3. NO<sub>2</sub> levels are highest during the cooler months of the year and still show  
 11 positive correlations with CO. Mean NO<sub>2</sub> levels are lowest during the summer months, though  
 12 of course, there can be large positive excursions associated with the development of high-

1 pressure systems. In this regard, NO<sub>2</sub> behaves as a primary pollutant, although there is no good  
2 reason to suspect strong seasonal variations in its emissions.

## 3 4 5 **2.6 DOSIMETRY OF INHALED NITROGEN OXIDES**

6 This section provides a brief overview of NO<sub>2</sub> dosimetry and updates information  
7 provided in the 1993 AQCD for Oxides of Nitrogen. A more extensive discussion of NO<sub>2</sub>  
8 dosimetry appears in Annex 4. Nitrogen dioxide, classified as a reactive gas, interacts with  
9 surfactants, antioxidants, and other compounds in the epithelial lining fluid (ELF). The  
10 compounds thought to be responsible for adverse pulmonary effects of inhaled NO<sub>2</sub> are the  
11 reaction products themselves or the metabolites of these products in the ELF.

12 Acute NO<sub>2</sub> uptake in the lower respiratory tract is thought to be rate-limited by chemical  
13 reactions of NO<sub>2</sub> with ELF constituents rather than by gas solubility in the ELF (Postlethwait and  
14 Bidani, 1990). Postlethwait and Bidani (1994) concluded that the reaction between NO<sub>2</sub> and  
15 water does not significantly contribute to the absorption of inhaled NO<sub>2</sub>. Rather, uptake is a  
16 first-order process for NO<sub>2</sub> concentrations of <10 ppm, is aqueous substrate-dependent, and is  
17 saturable. Postlethwait et al. (1991) reported that inhaled NO<sub>2</sub> (<10 ppm) does not penetrate the  
18 ELF to reach underlying sites and suggested that cytotoxicity may be due to NO<sub>2</sub> reactants  
19 formed in the ELF. Related to the balance between reaction product formation and removal, it  
20 was further suggested that cellular responses may be nonlinear with greater responses being  
21 possible at low levels of NO<sub>2</sub> uptake versus higher levels of uptake.

22 Ascorbate and glutathione (GSH) are the primary NO<sub>2</sub> absorption substrates in rat ELF  
23 (Postlethwait et al., 1995). Velsor and Postlethwait (1997) investigated the mechanisms of acute  
24 epithelial injury from NO<sub>2</sub> exposure. Membrane oxidation was not a simple monotonic function  
25 of GSH and ascorbic acid levels. The maximal levels of membrane oxidation were observed at  
26 low antioxidant levels versus null or high antioxidant levels. Glutathione and ascorbic acid-  
27 related membrane oxidation were superoxide and hydrogen peroxide dependent, respectively.  
28 The authors suggested that increased absorption of NO<sub>2</sub> occurred at the higher antioxidant  
29 concentrations, but little secondary oxidation of the membrane occurred because the reactive  
30 species (e.g., superoxide and hydrogen peroxide) generated during absorption were quenched. A  
31 lower rate of NO<sub>2</sub> absorption occurred at the low antioxidant concentrations, but oxidants were  
32 not quenched and so were available to interact with the cell membrane. Illustrating the complex

1 interaction of antioxidants, some studies suggest that NO<sub>2</sub>-oxidized GSH may be again reduced  
2 by uric acid and/or ascorbic acid (Kelly et al., 1996; Kelly and Tetley, 1997).

3       Very limited work related to the quantification of NO<sub>2</sub> uptake has been reported since the  
4 1993 AQCD for Oxides of Nitrogen. In both humans and animals, the uptake of NO<sub>2</sub> uptake by  
5 the upper respiratory tract decreases with increasing ventilator rates. This causes a greater  
6 proportion of inhaled NO<sub>2</sub> to be delivered to the lower respiratory tract. In humans, the  
7 breathing pattern shifts from nasal to oronasal during exercise relative to rest. Since the nasal  
8 passages absorb more inhaled NO<sub>2</sub> than the mouth, exercise (with respect to the resting state)  
9 delivers a disproportionately greater quantity of the inhaled mass to the pulmonary region of the  
10 lung, where the NO<sub>2</sub> is readily absorbed. Bauer et al. (1986) reported a statistically significant  
11 increase in uptake from 72% during rest to 87% during exercise in a group of 15 asthmatic  
12 adults. The minute ventilation also increased from 8.1 L/min during rest to 30.4 L/min during  
13 exercise. Hence, exercise increased the dose rate of NO<sub>2</sub> by 5-fold in these subjects. Similar  
14 results have been reported for beagle dogs where the dose rate of NO<sub>2</sub> was 3-fold greater for the  
15 dogs during exercise than rest (Kleinman and Mautz, 1991).

16  
17

## 18 **2.7 INDOOR AND PERSONAL EXPOSURE HEALTH STUDIES**

19       At the time of the 1993 AQCD for Oxides of Nitrogen, many of the available health  
20 effects studies consisted predominately of indoor NO<sub>2</sub> exposure studies. Although indoor  
21 sources in these studies include both gas-fueled cooking and heating appliances, in most of the  
22 older studies the focus was primarily on cooking stoves. Indoor studies evaluated in the 1993  
23 AQCD for Oxides of Nitrogen include Neas et al. (1991), Dijkstra et al. (1990), Ekwo et al.  
24 (1983), Ware et al. (1984), Melia et al. (1977, 1979, 1982a,b, 1990), and Keller et al. (1979a,b).  
25 Indoor studies examining children 2 years old or younger include Samet et al. (1993, 1992),  
26 Ogston et al. (1985), and Margolis et al. (1992). Available outdoor studies with ambient NO<sub>2</sub>  
27 measures include Dockery et al. (1989), Braun-Fahrlander et al. (1992), Schwartz (1989),  
28 Schwartz et al. (1991), Schwartz and Zeger (1990), and Vedal et al. (1987). Although there was  
29 some evidence suggesting that increased NO<sub>2</sub> exposure was associated with increased respiratory  
30 symptoms in children aged 5 to 12 years, the main conclusion was that there was insufficient  
31 epidemiological evidence for an association between short-term exposure and health effects.

32

## 2.7.1 Recent Indoor Studies of Exposures to Nitrogen Oxides and Health Outcomes

These studies consist of NO<sub>2</sub> exposures that may differ from ambient exposure in relation to pattern, levels, and associated copollutants (see Annex Table AX6.1 for details). Samet and Bell (2004) state that, while “evidence from studies of outdoor air pollution cannot readily isolate an effect of NO<sub>2</sub> because of its contribution to the formation of secondary particles and ozone, observational studies of exposure indoors can test hypothesis related to NO<sub>2</sub> specifically although confounding by combustion sources in the home is a concern.” Thus, indoor NO<sub>2</sub> sources are not likely confounded by other ambient pollutants such as PM, O<sub>3</sub>, CO, and SO<sub>2</sub>.

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; Garrett et al., 1998; Smith et al., 2000). Several indoor exposure studies have also been conducted in Europe (Farrow et al., 1997; Simoni et al., 2002, 2004), one in Singapore (Ng et al., 2001), and one cohort study in the United States (Belanger et al., 2006; van Strien et al., 2004). The key results from these studies are summarized in the Annex Table AX6.1. These include one key intervention study (Pilotto et al., 2004) that provides strong evidence of a detrimental effect of exposure to indoor levels of NO<sub>2</sub>.

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 homes. For the 114 children enrolled, symptoms were recorded daily and reported in fortnightly telephone interviews during 12 weeks in the winter. Passive diffusion badges were used to measure NO<sub>2</sub> exposure in classrooms (6 h/day) and in the children’s homes. Schools in the intervention group (with new heaters) averaged with overall means (SD) of 15.5 (6.6) ppb NO<sub>2</sub>, while control schools (with unflued heaters) averaged 47.0 (26.8) ppb. Exposure to NO<sub>2</sub> 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

1 reductions in several symptoms: difficulty breathing during the day (rate ratio [RR] = 0.41  
2 [95% CI: 0.07, 0.98]) and at night (RR = 0.32 [95% CI: 0.14, 0.69]); chest tightness during the  
3 day (RR = 0.45 [95% CI: 0.25, 0.81]) and at night (RR = 0.59 [95% CI: 0.28, 1.29]); and  
4 asthma attacks during the day (RR = 0.39 [95% CI: 0.17, 0.93]).

5 Samet and Bell (2004) state that Pilotto et al. (2004) provides persuasive evidence of an  
6 association between exposure to NO<sub>2</sub> from in-class heaters and the respiratory health of children  
7 with asthma and further that the study provides evidence from an intervention and, thus, avoids  
8 some potential limitations at observational studies. The two groups of children studied had  
9 similar baseline characteristics. In addition, the concentrations in the home environment were  
10 similar for the two groups, implying that exposure at school was likely to be the primary  
11 determinant of a difference in indoor NO<sub>2</sub> exposure between the two groups. Samet and Utell  
12 (1990) concluded that, the “absence of significant differences between the groups for lung  
13 function tests and bronchial responsiveness are consistent with the majority of chamber study  
14 results.”

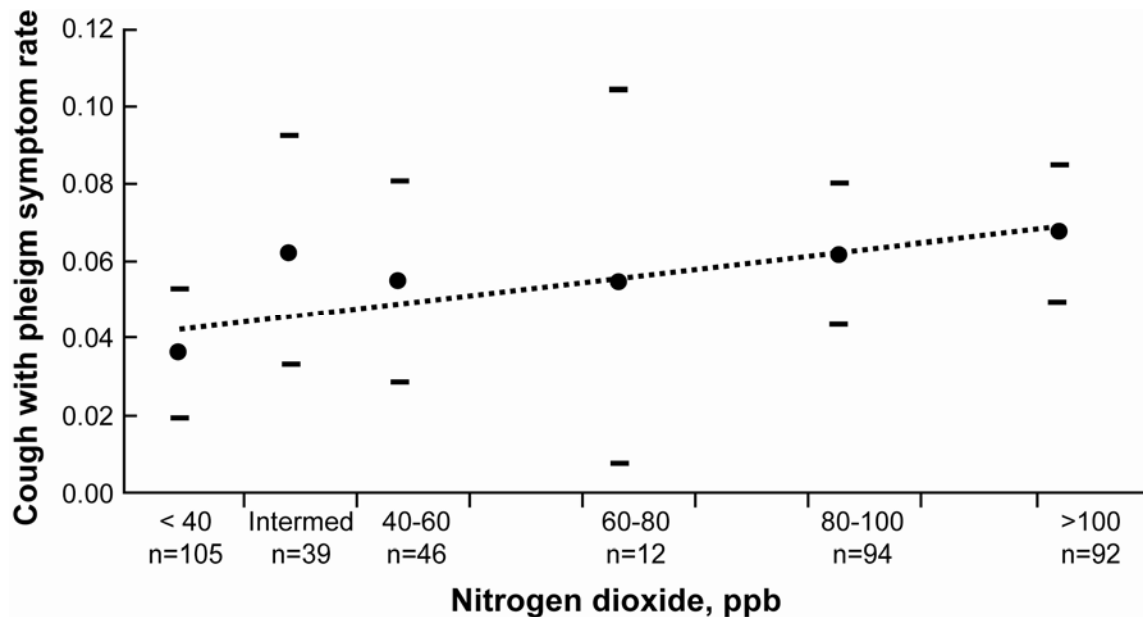
15 In an earlier study of the health effects of unflued gas heaters on wintertime respiratory  
16 symptoms of 388 Australian schoolchildren, Pilotto et al. (1997a) measured NO<sub>2</sub> in  
17 41 classrooms in 8 schools, with half using unflued gas heaters and half using electric heat.  
18 Although similar methods were used to measure NO<sub>2</sub> levels (passive diffusion badge monitors  
19 exposed for 6 h at a time), there were three major differences between this study and the 2003  
20 study: (1) the 1997 study was not a randomized trial, (2) enrollment was not restricted to  
21 asthmatic children, and (3) enrollment was not restricted to children from homes without unflued  
22 gas heaters. In Pilotto et al. (1997a), only children from nonsmoking homes were enrolled and a  
23 subset of children (n = 121) living in homes with unflued gas heaters were given badges to be  
24 used at home. Symptoms were recorded daily by each child’s parents. Children were classified  
25 into low- and high-exposure groups based on their measured exposure at school, their measured  
26 exposure at home (if they lived in homes with unflued gas heaters), or their reported use of  
27 electric heat at home. Maximum hourly concentration in these classrooms each day over  
28 2 weeks of hourly monitoring were highly correlated with their corresponding 6-h concentrations  
29 measured over the same 2 weeks (r = 0.85). Hourly peaks of NO<sub>2</sub> of the order of ≥80 ppb were  
30 associated with 6-h average levels of approximately ≥40 ppb. They inferred that children in  
31 classrooms with gas heaters that had 6-h average levels of ≥40 ppb were experiencing



1 approximately 4-fold or higher 1-h peaks of exposure than the NO<sub>2</sub> levels experienced by  
2 children who had no gas exposure (6-h average levels of 20 ppb). The importance of this study  
3 is that it examines the effect of repeated peaks over time as have been used in toxicological  
4 infectivity studies (e.g., Miller et al., 1987).

5 Pilotto et al. (1997a) report that during the winter heating season, children in the high  
6 exposure category (NO<sub>2</sub> > 40 ppb) had higher rates of sore throat, colds, and absenteeism than all  
7 other children. In models adjusted for personal risk factors including asthma, allergies, and  
8 geographic area, classroom NO<sub>2</sub> level and school absence were significantly associated (odds  
9 ratio [OR] = 1.92 [95% CI: 1.13, 3.25]). Increased likelihood of individual respiratory  
10 symptoms was not significantly associated with classroom level of NO<sub>2</sub> (e.g., cough with  
11 phlegm: adjusted OR = 1.28 (95% CI: 0.76, 2.15). Dose-response relationships are illustrated  
12 in Figure 2.7-1 for symptom rates for cough and in Figure 2.7-2 for school absence. Pilotto et al.  
13 (1997b) notes that this study “provides evidence that short-term exposure to the peak levels of  
14 NO<sub>2</sub> produced by unflued gas appliances affects respiratory health and that the significant dose-  
15 response relationship seen with increasing NO<sub>2</sub> exposure strengthens the evidence for a cause-  
16 effect relationship.”

17 One recent birth cohort study in the United States measured indoor exposure to NO<sub>2</sub>  
18 (Belanger et al., 2006; van Strien et al., 2004). Families were eligible for this study if they had a  
19 child with physician-diagnosed asthma (asthmatic sibling) and a newborn infant (birth cohort  
20 subject). NO<sub>2</sub> levels were measured using Palmes tubes left in the homes for 2 weeks. Higher  
21 levels of NO<sub>2</sub> were measured in homes with gas stoves (mean [SD], 26 [18] ppb) than in homes  
22 with electric ranges (9 [9] ppb). Children living in multifamily homes were exposed to more  
23 NO<sub>2</sub> (23 [17] ppb) than children in single-family homes (10 [12] ppb). The authors examined  
24 associations between NO<sub>2</sub> concentrations and respiratory symptoms experienced by the  
25 asthmatic sibling in the month prior to sampling (Belanger et al., 2005). For children living in  
26 multifamily homes, each 20-ppb increase in NO<sub>2</sub> concentration increased the likelihood of any  
27 wheeze or chest tightness (OR for wheeze = 1.52 [95% CI: 1.04, 2.21]; OR for chest  
28 tightness = 1.61 [95% CI: 1.04, 2.49]) as well as increasing the risk of suffering additional days  
29 of symptoms. No significant associations were found between level of NO<sub>2</sub> and symptoms for  
30 children living in single-family homes. The authors suggested that the low levels of exposure  
31 may have been responsible for the lack of association observed in single-family homes. In these

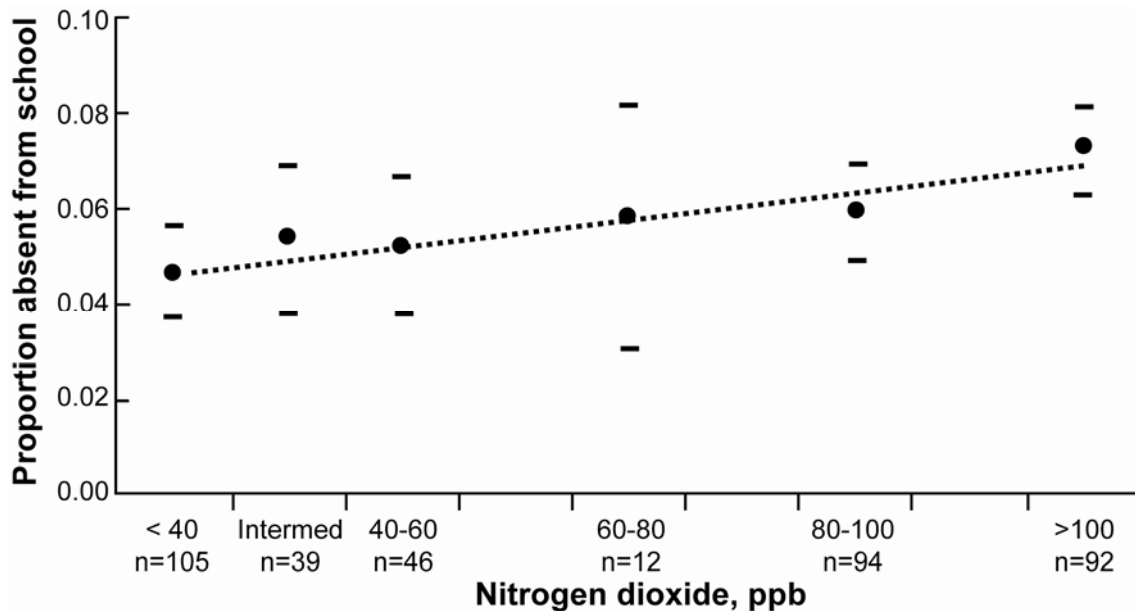


**Figure 2.7-1. Geometric mean symptom rates and 95% confidence intervals for cough with phlegm during the winter heating period for 388 children grouped according to estimated amount of NO<sub>2</sub> exposure at home and at school. Group means and trends (p = 0.02) estimated from mixed models allowing for correlation between children within classrooms (unadjusted for confounding).**

Source: Pilotto et al. (1997a).

1 same families, van Strien et al. (2004) compared the measured NO<sub>2</sub> concentrations with  
 2 respiratory symptoms experienced by the birth cohort infants during the first year of life.  
 3 Although wheeze was not associated with NO<sub>2</sub> concentration, persistent cough was associated  
 4 with increasing NO<sub>2</sub> concentration in a dose-response relationship as shown in Figure 2.7-3  
 5 (van Strien et al., 2004).

6 An important consideration in the evaluation of these study results is that NO<sub>x</sub> is part of a  
 7 complex mixture of chemicals emitted from unvented gas heaters. In addition to NO and NO<sub>2</sub>,  
 8 indoor combustion sources such as unvented gas heaters emit other pollutants that are present in  
 9 the fuel or are formed during combustion. The major products from the combustion of natural  
 10 gas are carbon dioxide (CO<sub>2</sub>) and CO followed by HCHO with smaller amounts of other  
 11 oxidized organic compounds in the gas phase. In a study of pollutants emitted by unvented gas  
 12 heaters, Brown et al. (2004) found that CO in a room test chamber ranged from 1 to 18 ppm for

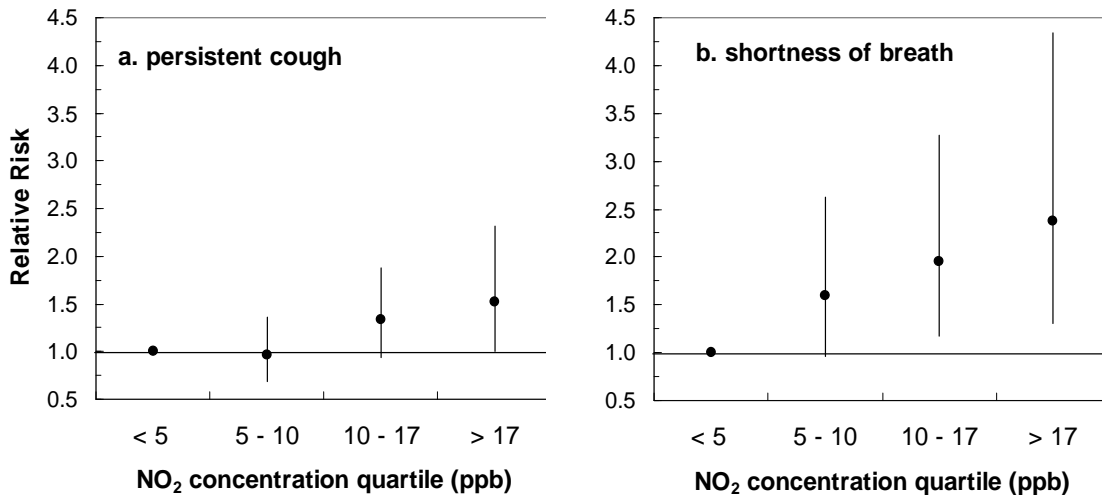


**Figure 2.7-2. Proportions (and 95% confidence intervals) of children absent from school for at least 1 day during the winter heating period grouped according to estimated amount of NO<sub>2</sub> exposure at home and at school (n = 388). Group means and trend (p < 0.001) estimated from Generalized (binomial) Linear Mixed Models (GLMM) allowing for correlation between children with classrooms (unadjusted for confounding).**

Source: Pilotto et al. (1997a).

1 NO<sub>2</sub> ranging from 100 to 300 ppb; corresponding levels of HCHO were highly variable, ranging  
 2 from <10 ppb to a few hundred ppb (with an outlier at >2 ppm).

3 PM in the sub-micrometer size range is also produced during natural gas combustion.  
 4 Ristovski et al. (2000) concluded that particulate mass emissions from natural gas heaters are  
 5 low but that natural gas heaters are larger sources of organic compounds, such as HCHO. They  
 6 also measured emission rates for individual particles, which are expected to be present mainly in  
 7 the ultrafine size range, but concluded that these rates are low and they could not detect an  
 8 increase in particle number from one of the two model heaters tested. However, Rogge et al.  
 9 (1993) found that at least 22% of the fine particle mass emitted by natural gas heaters consists of  
 10 PAHs, oxy-PAHs, and aza- and thia-arenes. They also identified emissions of speciated alkanes,  
 11 n-alkanoic acids, polycyclic aromatic ketones, and quinones. However, these accounted for only  
 12 about another 4% of the fine PM emitted. Although the rates of emission of PM are low and are



**Figure 2.7-3. Data taken from Table 3 in van Strien et al. (2004). Adjusted association of increasing indoor NO<sub>2</sub> concentration 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.**

1 not likely to affect PM levels, their PAH content indicates that natural gas combustion could be a  
 2 significant source of PAHs in indoor environments.

3 Overall, the recent studies build upon the evidence available from personal and indoor  
 4 exposure studies in the 1993 AQCD, showing consistent evidence of respiratory effects with  
 5 exposure to NO<sub>2</sub>. These studies can serve as a bridge between epidemiological studies and  
 6 controlled human exposure studies, as noted above, and provide some evidence of coherence for  
 7 respiratory effects. As is true for NO<sub>x</sub> in the ambient air, indoor NO<sub>x</sub> concentrations may be  
 8 correlated with a mixture of other pollutants. The major products of combustion of natural gas  
 9 include CO<sub>2</sub> and CO, followed by HCHO, with smaller amounts of other oxidized organic  
 10 compounds in the gas phase and sub-micrometer PM whose major identifiable components are  
 11 PAHs, possibly complicating the interpretation of associations between health effects and indoor  
 12 NO<sub>2</sub> levels.

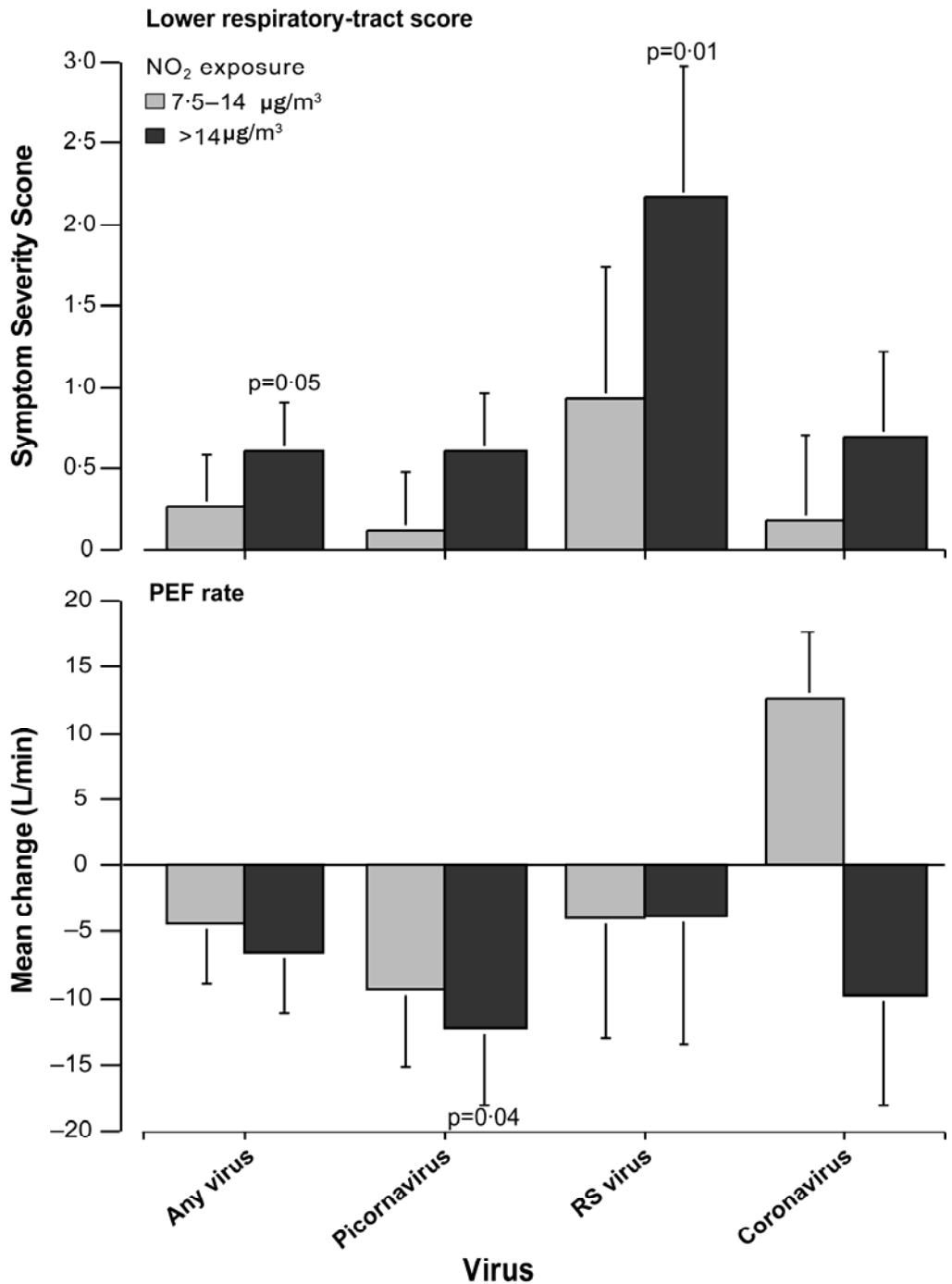
13

## 2.7.2 Recent Studies of Personal NO<sub>x</sub> Exposure

Several studies collected personal exposure data for NO<sub>2</sub>. Personal exposure to NO<sub>2</sub> 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 clipped to their clothing during the day and placed in the 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 (Chauhan et al., 2003). The authors found significant increases in the 4 point symptom severity score associated with exposure to NO<sub>2</sub> levels greater than 14 µg/m<sup>3</sup> (7.4 ppb) in the week preceding any viral infection (score increase of 0.6 [95% CI: 0.01, 1.18]) or respiratory syncytial virus alone (score increase of 2.1 [95% CI: 0.52, 3.81]). Chauhan et al. 2003 also found a significant reduction in PEF associated with exposure greater than 14 µg/m<sup>3</sup> (by 12 L/min [95% CI: -23.6, -0.80]). Exploration of the relationship between PEF and NO<sub>2</sub> 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<sub>2</sub> greater than 28 µg/m<sup>3</sup> (14.9 ppb) (RR = 1.9 [95% CI: 1.1, 3.4]) (Linaker et al., 2000). See Figure 2.7-4. Thus, high personal NO<sub>2</sub> 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.

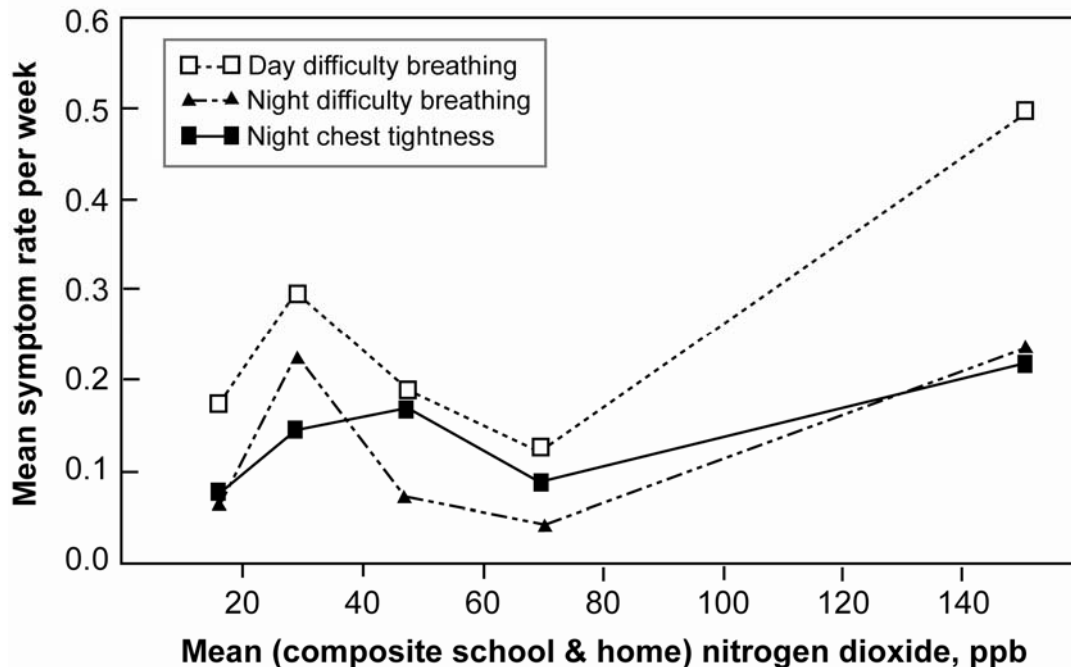
Nitschke et al. (2006) used passive diffusion badges for measuring NO<sub>2</sub> exposures in 6-h increments at home and school for 174 asthmatic children in Australia. School and home measurements were based on 3 consecutive days of sampling. The maximum of 9 days of sampling (for 6 h each day) NO<sub>2</sub> value was selected as the representative daily exposure for dose-response analyses. Children kept a daily record of respiratory symptoms for the 12-week study period. Significant associations were found between the maximum NO<sub>2</sub> level at school or home and respiratory symptom rates (see Annex Table AX 6-1). The dose response relationship is illustrated in Figure 2.7-5.

In a cross-sectional survey of 344 children in Australia, Ponsonby et al. (2001) used passive gas samplers to measure personal exposure to NO<sub>2</sub>. 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



**Figure 2.7-4. Mean change in respiratory-tract symptom scores and PEF rates after viral infection for children in medium and high NO<sub>2</sub> exposure tertiles compared with children in the low exposure tertile.**

Source: Chauhan et al. (2003).



**Figure 2.7-5. Mean symptom rates per week (difficulty breathing during the day and night, and chest tightness at night) plotted against mean maximum nitrogen dioxide levels (composite of school and home exposure) groups as <20 ppb (n = 12), 20-39 ppb (n = 51), 40-50 ppb (n = 25), 60-79 ppb (n = 18), and 80+ ppb (n = 68).**

Source: Nitschke et al. (2006).

1 next day. School exposures were measured with passive samplers placed in each child's  
 2 classroom. Sampling took place for 2 consecutive days. Mean (SD) personal exposure was  
 3 10.4 (11.1) ppb and mean total NO<sub>2</sub> exposure (personal plus schoolroom) was 10.1 (8.6) ppb.  
 4 Of the health outcomes measured (recent wheeze, asthma ever, lung function measured when  
 5 NO<sub>2</sub> sampling stopped), only the FEV<sub>1</sub>/FVC ratio following cold air challenge was significantly  
 6 associated with NO<sub>2</sub> levels measured with the personal badges (-0.12 [95% CI: -0.23, -0.01])  
 7 per 1 ppb increase in personal exposure).

8 In Finland, Mukula et al. (1999, 2000) studied 162 preschool-age children. Mukula et al.  
 9 (2000) used passive monitors exposed for 1-week periods over the course of 13 weeks both  
 10 indoors, outdoors, and on the clothing of preschool children attending 8 day care centers in  
 11 Helsinki. The only significant association between NO<sub>2</sub> measured personally and symptoms was  
 12 for cough during the winter (relative risk [RR] = 1.86 [95% CI: 1.15, 3.02] for NO<sub>2</sub> at levels

1 above 27.5  $\mu\text{g}/\text{m}^3$  [14.5 ppb]). Similar results were obtained when data were analyzed  
2 unstratified by season, but including a factor for season (RR = 1.52 [95% CI: 1.00, 2.31] for  
3  $\text{NO}_2$  at levels above 27.5  $\mu\text{g}/\text{m}^3$  [14.5 ppb], Mukala et al., 1999).

4

### 5 **2.7.3 Summary Indoor and Personal Exposure Studies**

6 Overall, the recent studies build upon the evidence available from personal and indoor  
7 exposure studies in the 1993 AQCD, showing consistent evidence of respiratory effects with  
8 exposure to  $\text{NO}_2$ . There is convincing evidence for a direct effect of  $\text{NO}_2$  exposure on  
9 respiratory health from the randomized intervention study by Pilotto et al. (2003) and from other  
10 studies enrolling asthmatic children (Pilotto et al., 1997; Nitschke et al., 2006; Smith et al., 2000;  
11 Belanger et al., 2006). From indoor and personal exposure studies, effects observed in these  
12 studies all occurred at ambient levels and are relatively unconfounded by copollutants found in  
13 ambient air that make unambiguous interpretation of many of the health effects studies of  
14 ambient exposure problematic. Chauhan et al. (2003) shows an association between increased  
15 personal exposure to  $\text{NO}_2$  and the severity of virus-induced asthma exacerbations in children.  
16 The study design reduced potential bias from misclassification of other pollutant exposure or  
17 health outcomes. As is true for  $\text{NO}_2$  in the ambient air, indoor  $\text{NO}_2$  concentrations may be  
18 correlated with a mixture of other pollutants, as the major products of combustion of natural gas  
19 includes  $\text{CO}_2$ , CO, and HCHO, along with smaller amounts of other oxidized organic compounds  
20 in the gas phase and sub-micrometer PM, particularly PAHs, thus complicating the interpretation  
21 of associations between health effects and indoor  $\text{NO}_2$  levels. Nonetheless, the findings of these  
22 recent indoor and personal exposure studies, combined with studies available in the previous  
23 AQCD, provide strong evidence that  $\text{NO}_2$  exposure is associated with respiratory effects. These  
24 studies can serve as a bridge between epidemiological studies and controlled human exposure  
25 studies, as noted above, and provide some evidence of coherence for respiratory effects.



**TABLE 2.5-1. SPATIAL VARIABILITY OF NO<sub>2</sub> IN SELECTED UNITED STATES URBAN AREAS**

	<b>Mean Concentration (ppb)</b>	<b>r</b>	<b>P90 (ppb)</b>	<b>COD</b>
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

**TABLE 2.5-2. NO<sub>2</sub> CONCENTRATIONS NEAR INDOOR SOURCES:  
SHORT-TERM AVERAGES**

<b>Avg Concentration (ppb)</b>	<b>Peak Concentration (ppb)</b>	<b>Comment</b>	<b>Reference</b>
191 kitchen, 195 living room, 184 bedroom	375 kitchen, 401 living room, 421 bedroom	Cooked full meal with use of gas stove and range for 2 h and 20 min; 7 h TWA	Fortman et al. (2001)
400 kitchen, living room, bedroom	673 bedroom	Automatic oven cleaning of gas stove. Avgs are over the entire cycle.	Fortman 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 <sup>3</sup> ).	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 operating in a 1400 ft <sup>2</sup> house, 1.0 h <sup>-1</sup> for air exchange rate.	Girman et al. (1982)

N/R = not reported

TWA = time-weighted avg

<sup>1</sup> Unvented are not permitted in many areas such as California.

**TABLE 2.5-3. NO<sub>2</sub> CONCENTRATIONS NEAR INDOOR SOURCES:  
LONG-TERM AVERAGES**

<b>Avg Concentration (ppb)</b>	<b>Comment</b>	<b>Reference</b>
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 %-ile)	No indoor combustion source	
80 (90th %-ile)	Fireplaces	
84 (90th %-ile)	Kerosene heaters	
147 (90th %-ile)	Gas space heaters	
52 (90th %-ile)	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	

**TABLE 2.5-4A. THE ASSOCIATION BETWEEN PERSONAL EXPOSURES AND AMBIENT CONCENTRATIONS**

Study	Study Design	Association Variable	Location	Season	$r_p$ , $r_s$ , or $R^2$
Linn et al. (1996)	Longitudinal, Southern California, 269 School Children, fall, winter, and spring 1992-1994, 24-h avg, 1-wk consecutive measurement for each season for each child.	Personal vs. central	Pooled	Pooled	0.63 ( $r_p$ ) (n = 107)
Alm et al. (1998)	Longitudinal, Helsinki, 246 children aged 3-6 yrs old, winter and spring of 1991, 1-wk averaged sample for each person, 6 consecutive wks in the winter and 7 consecutive wks in the spring.	Personal vs. central	Downtown	Spring	0.64 ( $r_p$ ), $p < 0.001$ (Sample size was not reported.)
		Personal vs. central	Suburban	Spring	0.78 ( $r_p$ ), $p < 0.001$ (Sample size was not reported.)
		Personal vs. central	Downtown	Winter	-0.06 ( $r_p$ ), $p > 0.05$ (Sample size was not reported.)
		Personal vs. central	Suburban	Winter	0.32 ( $r_p$ ), $p > 0.05$ (Sample size was not reported.)
		Personal vs. central	Downtown (electric stove home)	Pooled	0.42 ( $r_p$ ), $p < 0.01$ (Sample size was not reported.)
		Personal vs. central	Downtown (gas stove home)	Pooled	0.16 ( $r_p$ ), $p > 0.01$ (Sample size was not reported.)
		Personal vs. central	Suburban (electric stove home)	Pooled	0.55 ( $r_p$ ), $p < 0.001$ (Sample size was not reported.)
		Personal vs. central	Downtown (nonsmoking home)	Pooled	0.47 ( $r_p$ ), $p < 0.001$ (Sample size was not reported.)
		Personal vs. central	Downtown (smoking home)	Pooled	0.23 ( $r_p$ ), $p > 0.01$ (Sample size was not reported.)
		Personal vs. central	Suburban (nonsmoking home)	Pooled	0.53 ( $r_p$ ), $p < 0.001$ (Sample size was not reported.)
		Personal vs. central	Suburban (smoking home)	Pooled	0.52 ( $r_p$ ), $p < 0.001$ (Sample size was not reported.)
		Personal vs. central	Pooled	Pooled	0.37 ( $R^2$ ) (n = 24)

**TABLE 2.5-4A (cont'd). THE ASSOCIATION BETWEEN PERSONAL EXPOSURES AND AMBIENT CONCENTRATIONS**

Study	Study Design	Association Variable	Location	Season	$r_p$ , $r_s$ , or $R^2$
Liard et al. (1999)	Daily avg/cross-sectional, Paris, 55 adults and 39 children, May-June 1996, three 4-day avg measurements for each person, during each measurement session, all subjects were measured at the same time.	Adults vs. central	Urban	Summer	0.41 ( $R^2$ ), $p < 0.0001$ (Sample size was not reported.)
		Children vs. central	Urban	Summer	0.17 ( $R^2$ ), $p = 0.0004$ (Sample size was not reported.)
Gauvin et al. (2001)	Daily avg/cross-sectional, three French metropolitan areas, 73 children, April-June 1998 in Grenoble, May-June 1998 in Toulouse, and June-October 1998 in Paris, one 48-h avg measurement for each child, all children in the same city were measured on the same day.	Personal vs. central (Grenoble)	Urban	Pooled	0.01 ( $R^2$ ) (Sample size was not reported.)
		Personal vs. central (Toulouse)	Urban	Pooled	0.04 ( $R^2$ ) (Sample size was not reported.)
		Personal vs. central (Paris)	Urban	Pooled	0.02 ( $R^2$ ) (Sample size was not reported.)
Kim et al. (2006)	Longitudinal, Toronto, 28 adults with coronary artery disease, Aug 1999 to Nov 2001, 1 day/wk, 24-h avg, for a maximum of 10 wks for each person.	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. (2001)	Longitudinal, Baltimore, 56 seniors, schoolchildren, and people with COPD, summer of 1998 and winter of 1999, 14 of 56 subjects participated in both sampling seasons; all subjects were monitored for 12 consecutive days (24-h avg samples) in each of the one or two seasons, with the exception of children who were measured for 8 consecutive days during the summer.	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)	Longitudinal, Boston, 43 seniors and schoolchildren, summer of 1999 and winter of 2000, Similar study design as Sarnat et al. (2001).	Personal vs. central (subject wise)	Urban	Summer	-0.25 to 0.5 ( $r_s$ ) with a median of 0.3* (Sample size was not reported in the text.). Slope = 0.19, 0.08-0.30
				Winter	-0.5 to 0.9 ( $r_s$ ) with a median of 0.4* (Sample size was not reported in the text.) Slope = -0.03, -0.21-0.15
Sarnat et al. (2006)	Longitudinal, Steubenville, 15 senior subjects, summer and fall of 2000, two consecutive 24-h samples were collected for each subject for each wk, 23 wks total	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.

**TABLE 2.5-4B. THE ASSOCIATION BETWEEN PERSONAL EXPOSURES AND OUTDOOR CONCENTRATIONS**

Study	Study Design	Association Variable	Location	Season	$r_p$ , $r_s$ , or $R^2$
Kramer et al. (2000)	West Germany, 191 children. March and Sept 1996, 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)	Santiago, 20 children, winters of 1998 and 1999, 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)	Copenhagen and rural areas, 204 children, Oct 1994, April, May, and June 1995, 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)	Helsinki, 246 children aged 3-6 yrs old, winter and spring of 1991, 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 ( $r_p$ ) (Sample size was not reported.)
		Personal vs. outdoor	Suburban	Winter	0.49 ( $r_p$ ) (Sample size was not reported.)
		Personal vs. outdoor	Downtown	Spring	0.80 ( $r_p$ ) (Sample size was not reported.)
		Personal vs. outdoor	Suburban	Spring	0.82 ( $r_p$ ) (Sample size was not reported.)
		Personal vs. outdoor	Downtown (electric stove home)	Pooled	0.55 ( $r_p$ ) (Sample size was not reported.)
		Personal vs. outdoor	Downtown (gas stove home)	Pooled	0.59 ( $r_p$ ) (Sample size was not reported.)
		Personal vs. outdoor	Suburban (electric stove home)	Pooled	0.63 ( $r_p$ ) (Sample size was not reported.)

**TABLE 2.5-4B (cont'd). THE ASSOCIATION BETWEEN PERSONAL EXPOSURES AND OUTDOOR CONCENTRATIONS**

Study	Study Design	Association Variable	Location	Season	$r_p$ , $r_s$ , or $R^2$
Alm et al. (1998) (cont'd)		Personal vs. outdoor	Downtown (nonsmoking home)	Pooled	0.73 ( $r_p$ ) (Sample size was not reported.)
		Personal vs. outdoor	Downtown (smoking home)	Pooled	0.51 ( $r_p$ ) (Sample size was not reported.)
		Personal vs. outdoor	Suburban (nonsmoking home)	Pooled	0.59 ( $r_p$ ) (Sample size was not reported.)
		Personal vs. outdoor	Suburban (smoking home)	Pooled	0.46 ( $r_p$ ) (Sample size was not reported.)
		Personal vs. outdoor	Pooled	Pooled	0.86 ( $R^2$ ) (n = 23)
Monn et al. (1998)	Geneva, Basel, Lugano, Aarau, Wald, Payerne, Montana, and Davos (SAPALDIA study, Switzerland), 140 subjects, Dec 1993 to Dec 1994, each home was monitored for 3 periods of 1 mo; in the 1st wk of each period, personal, indoor and 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. (1998)	18 cities across 15 countries, 568 adults, Feb or March 1996, 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)

**TABLE 2.5-4B (cont'd). THE ASSOCIATION BETWEEN PERSONAL EXPOSURES AND OUTDOOR CONCENTRATIONS**

Study	Study Design	Association Variable	Location	Season	$r_p$ , $r_s$ , or $R^2$
Kodama et al. (2002)	Tokyo, 150 junior-high school students and their family members,	Personal vs. outdoor	Urban	Summer	0.24 ( $r_p$ ) (Sample size was not reported.)
	Feb 24-26, Jun 2-4, July 13-15, and Oct 14-16 in 1998 and Jan 26-28 in 1999, 3-day avg, personal exposures were monitored on the same day.	Personal vs. outdoor	Urban	Winter	0.08 ( $r_p$ ) (Sample size was not reported.)
Spengler et al. (1994)	Los Angeles Basin, probability-based sample, 70 subjects, May 1987 to May 1988, 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 ( $R^2$ ) (Sample size was not reported.)
Linaker et al. (2000)	Southampton, 114 asthmatic children, Oct 1994 to Dec 1995, 13 mos (1-wk avgs) for each child.	Personal vs. outdoor (overall measurements across children and time)	Pooled, urban, no major indoor sources	Pooled	Not significant (Sample size was not reported.)
		Personal vs. outdoor (subject-wise)	By person	Pooled	-0.77 to 0.68 and median -0.02 ( $r_p$ ) (Sample size was not reported.)
Lai et al. (2004)	Oxford, 50 adults, Dec 1998 to Feb 2000, one 48-h avg measurement per person.	Personal vs. outdoor	Urban	Pooled	0.41 ( $r_p$ ) (Sample size was not reported.)

\* Values were estimated from figures in the original paper.



**TABLE 2.5-5. SUMMARY OF REGRESSION MODELS OF PERSONAL EXPOSURE TO AMBIENT/OUTDOOR NO<sub>2</sub>**

Study	Location	Season	Model Type	Slope (SE)	Intercept / ppb	R <sup>2</sup>
Rojas-Bracho et al. (2002)	Santiago, 20 children, winters of 1998 and 1999, 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)	Helsinki, 246 children aged 3-6 yrs, winter and spring of 1991, 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)	Geneva, Basle, Lugano, Aarau, Wald, Payerne, Montana, and Davos (SAPALDIA study, Switzerland), 140 subjects, Dec 1993 to Dec 1994, each home was monitored for 3 periods of 1 mo; in the 1st wk of each period, personal, indoor and 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. (1998)	18 cities across 15 countries, 568 adults, Feb or March 1996, 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)	Los Angeles Basin, probability-based sample, 70 subjects, May 1987 to May 1988, in the microenvironmental component of the study, each participant was monitored for 48 hours during each of 8 sampling cycles throughout the yr.	All	Personal vs. outdoor	0.56	15.8	0.51

**TABLE 2.5-5 (cont'd). SUMMARY OF REGRESSION MODELS OF PERSONAL EXPOSURE TO AMBIENT/OUTDOOR NO<sub>2</sub>**

Study	Location	Season	Model Type	Slope (SE)	Intercept / ppb	R <sup>2</sup>
Sorensen et al. (2005)	Copenhagen, 30 subjects (20-33 yrs old) in each measurement campaign, fall 1999, and winter, spring and summer of 2000, four measurement campaigns in 1 yr; each campaign lasted 5 wks with 6 subjects each wk; one 48-h avg NO <sub>2</sub> measurement for each subject.	All	Personal vs. outdoor (n = 73)	0.60 (0.07)	—	—
		(>8 °C)	Personal vs. outdoor (n = 35)	0.68 (0.09)	—	—
		(<8 °C)	Personal vs. outdoor (n = 38)	0.32 (0.13)	—	—
Sorensen et al. (2005)	Copenhagen, 30 subjects (20-33 yrs old) in each measurement campaign, fall 1999, and winter, spring and summer of 2000, four measurement campaigns in 1 yr; each campaign lasted 5 wks with 6 subjects each wk; one 48-h avg NO <sub>2</sub> measurement for each subject .	All	Personal vs. central (n = 66)	0.56 (0.09)	—	—

**TABLE 2.5-5 (cont'd). SUMMARY OF REGRESSION MODELS OF PERSONAL EXPOSURE TO AMBIENT/OUTDOOR NO<sub>2</sub>**

Study	Location	Season	Model Type	Slope (SE)	Intercept / ppb	R <sup>2</sup>
Alm et al. (1998)	Helsinki, 246 children aged 3-6 yrs, winter and spring of 1991, 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)	Baltimore, 56 seniors, Schoolchildren, and people with COPD, summer of 1998 and winter of 1999, 14 of 56 subjects participated in both sampling seasons; all subjects were monitored for 12 consecutive days (24-h avg 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)	Boston, 43 seniors and schoolchildren, summer of 1999 and winter of 2000, Similar study design as Sarnat et al., 2001.	Summer	Personal vs. central (n = 341)	0.19	—	—
		Winter	Personal vs. central (n = 298)	-0.03*	—	—
Sarnat et al. (2006)	Steubenville, 15 senior subjects, summer and fall of 2000, two consecutive 24-h samples were collected for each subject for each wk, 23 wks total.	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
Mosqueron et al. (2002)	Paris, 62 Paris office workers, Dec 1999 to Sept 2000, 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 $R^2$ is 0.14, and ambient $NO_2$ and indoor cooking account for 0.07 each
			Office indoor vs. ambient and floor height	None	0.56 (n = 62)	The overall $R^2$ is 0.24, partial $R^2$ for ambient and floor height were 0.18 and 0.06, respectively
Lee et al. (1999)	Hong Kong, 14 public places with mechanical ventilation systems, Oct 1996 to March 1997, Teflon bags were used to collect indoor and outdoor NO and $NO_2$ 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
Monn et al. (1997)	Switzerland, 17 homes across Switzerland, winter 1994 to summer 1995, 48- to 72-h indoor, outdoor and personal $NO_2$ were measured.	Overall study seasons	Indoor/outdoor ratio	Without gas cooking	0.4, -0.7 (n = 26)	—
Lee et al. (1995)	Boston area, 517 residential homes, Nov 1984 to Oct 1986, 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

**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
Garrett et al. (1999)	The Latrobe Valley, Victoria, Australia, 80 homes, March-April 1994, and Jan-Feb, 1995, 4-day averaged indoor (bedroom, living room, and kitchen) and outdoor NO <sub>2</sub> 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)	Geneva, Basle, Lugano, Aarau, Wald, Payerne, Montana, and Davos (SAPALDIA study, Switzerland), 140 subjects, Dec 1993 to Dec 1994, each home was monitored for 3 periods of 1 mo; in the 1st wk of each period, personal, indoor and outdoor levels were measured, and in the next 3 consecutive wks, only outdoor levels were measured (1-wk averaged measurement).	Overall study seasons	Residential indoor vs. residential outdoor	All homes	0.47 (n = 1544)	R <sup>2</sup> was 0.37.
				Homes without smokers and gas-cooking	0.40 (n = 968)	R <sup>2</sup> was 0.33.
Spengler et al. (1994)	Los Angeles Basin, probability-based sample, 70 subjects, May 1987 to May 1988, 48-h averaged, in the microenvironmental component of the study, each participant was monitored during each of eight sampling cycles throughout the yr.	Overall study seasons	Residential indoor vs. residential outdoor	Gas range with pilot light	0.49 (n = 314)	R <sup>2</sup> was 0.44.
				Gas range without pilot light	0.4 (n = 148)	R <sup>2</sup> was 0.39.
				Electric stove	0.4 (n = 170)	R <sup>2</sup> was 0.41.

**TABLE 2.5-7. CORRELATIONS (PEARSON CORRELATION COEFFICIENT)  
BETWEEN AMBIENT NO<sub>2</sub> AND AMBIENT COPOLLUTANTS**

Study (ambient)	Location	PM <sub>2.5</sub>	CO	O <sub>3</sub>	SO <sub>2</sub>
This Assessment	Los Angeles	0.49 (u <sup>3</sup> ), 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	0.49 (s)	0.53 (u), 0.46 (s)	-0.20 (u)	
This Assessment	New York City	0.58 (u)	0.46 (u)	-0.06 (u)	
Kim et al. (2006)	Toronto	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 (RAPS)		0.641		
Sarnat et al. (2001) <sup>4</sup>	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 <sup>2</sup> )			
Arx et al. (2004)	21 European cities	0.75			
Cyrus et al. (2003)	Ehrfurt, Germany	0.50	0.74		
Mosqueron et al. (2002)	Paris	0.69			
Rojas-Bracho et al. (2002)	Santiago, Chile	0.77			

<sup>1</sup>Value with respect to NO<sub>x</sub>.

<sup>2</sup>Inferred based on EC as dominant contributor to PM<sub>2.5</sub> absorbance.

<sup>3</sup>u: urban; s: suburban; and r: rural

<sup>4</sup>Spearman correlation coefficient was reported

**TABLE 2.5-8. PEARSON CORRELATION COEFFICIENTS BETWEEN NO<sub>x</sub> AND TRAFFIC-GENERATED POLLUTANTS**

NO <sub>x</sub> : PM <sub>2.5</sub> (MV component)	0.48 < r < 0.75 <sup>1</sup>	0.48 < r < 0.75 <sup>2</sup>
NO <sub>x</sub> : CO	0.30 < r < 0.77 <sup>1</sup>	0.54 < r < 0.77 <sup>2</sup>
NO <sub>x</sub> : Pb	0.42 < r < 0.76 <sup>1</sup>	0.48 < r < 0.76 <sup>2</sup>
NO <sub>x</sub> : Br	0.55 < r < 0.73 <sup>1</sup>	0.58 < r < 0.73 <sup>2</sup>
NO <sub>2</sub> : EC <sup>3</sup>	0.93	
NO <sub>2</sub> : EC <sup>4</sup>	0.82 autumn, 0.24 summer	

<sup>1</sup>St. Louis RAPS (Kim et al., 2006), all sites

<sup>2</sup>St. Louis RAPS (Kim et al., 2006), all sites with upwind background site removed

<sup>3</sup>Ruhr Valley (Hochadel et al., 2006)

<sup>4</sup>Steubenville, OH (Sarnat et al., 2006)

**TABLE 2.5-9. CORRELATIONS (PEARSON CORRELATION COEFFICIENT) BETWEEN AMBIENT NO<sub>2</sub> AND PERSONAL COPOLLUTANTS**

Study	Location	PM <sub>2.5</sub>	Sulfate	EC	Ultrafine particle
Sarnat et al. (2006)	Steubenville, Fall	0.71	0.52	0.70	—
Sarnat et al. (2006)	Steubenville, Summer	0.00	0.1 not significant	0.26	—
Vinzents et al. (2005)	Copenhagen	—	—	—	0.49 (R <sup>2</sup> ) explained by ambient NO <sub>2</sub> and ambient temperature

**TABLE 2.5-10. CORRELATIONS (PEARSON CORRELATION COEFFICIENT) BETWEEN PERSONAL NO<sub>2</sub> AND AMBIENT COPOLLUTANTS**

Study	Location	PM <sub>2.5</sub>	Sulfate	EC	PM <sub>10</sub>	CO
Sarnat et al. (2006)	Steubenville, Fall	0.46	0.35	0.57	—	—
Sarnat et al. (2006)	Steubenville, Summer	0.00	0.1 not significant	0.17	—	—
Kim et al. (2006)	Toronto	0.30	—	—	—	0.20
Rojas-Bracho et al. (2002)	Santiago	0.65	—	—	0.39	—

**TABLE 2.5-11. CORRELATIONS (PEARSON CORRELATION COEFFICIENT)  
BETWEEN PERSONAL NO<sub>2</sub> AND PERSONAL COPOLLUTANTS**

<b>Study</b>	<b>Location</b>	<b>PM<sub>2.5</sub></b>	<b>CO</b>	<b>VOCs</b>	<b>HONO</b>
Kim et al. (2006)	Toronto	0.41	0.12		—
Modig et al. (2004)	Umea	—	—	0.06 for 1, 3-butadiene; and 0.10 for benzene	—
Mosqueron et al. (2002)	Paris	0.12 but not significant	—	—	—
Jarvis et al. (2005)	21 European cities	—	—	—	0.77 for indoor NO <sub>2</sub> and indoor HONO
Lee et al. (2002)	—	—	—	—	0.51 for indoor NO <sub>2</sub> and indoor HONO
Lai et al. (2004)	Oxford	-0.1	0.3	-0.11 for TVOCs	—



### 3. INTEGRATED HEALTH EFFECTS OF NO<sub>2</sub> EXPOSURE

This chapter integrates epidemiological, human clinical, and toxicological evidence for adverse health effects associated with exposure to NO<sub>2</sub>, alone or in combination with other pollutants. The body of epidemiological and experimental evidence is evaluated for strength, consistency, coherence, and plausibility. Judgments are made about the extent to which causal inferences can be made on the observed associations between health effects and exposure to oxides of nitrogen. The focus is on studies conducted at environmentally relevant concentrations, i.e., primarily studies that identify effects associated with NO<sub>2</sub> levels  $\leq 5$  ppm. The evaluations of those studies incorporate the science and conclusions from the 1993 AQCD for Oxides of Nitrogen. More detailed information is summarized in the Annexes, highlighting key study findings. The chapter first presents a brief overview of the toxicological evidence for potential mechanisms of injury. Morbidity and mortality associated with short-term exposures to NO<sub>2</sub> are presented next, followed by morbidity and mortality associated with long-term exposures. The chapter concludes with discussions of the limited literature on health effects associated with other oxides of nitrogen, including NO, HONO, and HNO<sub>3</sub>.

Issues relevant to the evaluation of epidemiological study findings were discussed in previous documents, particularly in the AQCDs for PM (U.S. Environmental Protection Agency, 2004) and O<sub>3</sub> (U.S. Environmental Protection Agency, 2006). These include the influence of model specification on study findings, the evaluation of lag periods used in epidemiological analyses, and general considerations regarding confounding or effect modification. In evaluating NO<sub>2</sub> epidemiological studies, the consideration of measurement and exposure errors are of particular relevance. Chapter 2 describes the extent and significance of the positive artifacts from other oxidized nitrogen compounds in the FRM-reported NO<sub>2</sub> values found in standard regulatory networks. Because nearly all epidemiological studies use FRM-reported NO<sub>2</sub> as the population exposure estimates, these estimates represent the effects of other oxidized nitrogen compounds in addition to NO<sub>2</sub>.

In the 1993 AQCD for Oxides of Nitrogen, human clinical evidence indicated that NO<sub>2</sub> caused decrements in lung function, particularly increased airways resistance in healthy subjects

1 with exposures of >2.0 ppm for 2 h. Other studies showed increased airways responsiveness in  
2 healthy subjects at concentrations of >1 ppm for 1 h. Asthmatics and COPD patients  
3 demonstrated increased decrements in lung function that were dependent on exposure conditions.  
4 However, concentration-response relationships were not observed for changes in lung function,  
5 airways responsiveness, or symptoms, and no association was apparent between lung function  
6 responses and respiratory symptoms. Epidemiological evidence was somewhat mixed for the  
7 effects of NO<sub>2</sub> exposure on lower respiratory symptoms and disease, but supportive for effects in  
8 children aged 5 to 12 years. However, at the time, data were inadequate to determine a  
9 quantitative relationship between estimates of exposure and symptoms. There was similarly  
10 insufficient epidemiological evidence regarding the long- or short-term effects of NO<sub>2</sub> on  
11 pulmonary function. Animal toxicology studies evaluated in the 1993 AQCD identified  
12 biochemical and cellular mechanisms whereby NO<sub>2</sub> induces effects. The ability of NO<sub>2</sub> to  
13 modulate host defenses and enhance susceptibility to bacterial and viral disease was attributed to  
14 alterations in alveolar macrophage (AM) structure, function, and metabolic activity. Animal  
15 infectivity models also demonstrated decreased resistance to bacterial infections associated with  
16 NO<sub>2</sub> exposure. Analysis of exposure regimens showed the dependence of effects on the  
17 concentration and duration and the exposure profile, rather than the cumulative product of  
18 concentration times duration of exposure (C × T).

19  
20

### 21 **3.1 POTENTIAL MECHANISMS OF INJURY**

22 The effects of NO<sub>2</sub> on respiratory tract function account for most of the currently  
23 available literature relevant to this evaluation of the effects of gaseous NO<sub>x</sub>, and the evidence  
24 includes a variety of endpoints ranging from biochemical effects to morphological and functional  
25 changes. Limited relevant data are available for effects of other gaseous oxides of nitrogen, such  
26 as NO and HNO<sub>3</sub> vapor. This evidence is briefly discussed in Section 3.7 with further details  
27 available in Annex Chapters 4, 5, and 6.

28 Biochemical studies on the effects of NO<sub>2</sub> on the lung focus on the possible  
29 mechanism(s) of toxicity and/or on detection of indicators of tissue and cellular damage. The  
30 biochemical effects observed in the respiratory tract after NO<sub>2</sub> exposure include chemical  
31 alteration of lipids, amino acids, proteins, and enzymes and changes in oxidant/antioxidant  
32 homeostasis. Membrane polyunsaturated fatty acids and thiol groups are the main biochemical

1 targets for NO<sub>2</sub> exposure: data available in the 1993 AQCD indicated that NO<sub>2</sub> induces lipid  
2 peroxidation and changes in lipid content of cell membranes. These effects appear to occur at  
3 concentrations as low as 0.04 ppm. Another likely mechanism involves the oxidation of water-  
4 soluble low-molecular-weight reducing substances and proteins, resulting in enzyme dysfunction  
5 that manifests itself as toxicity (Freeman and Mudd, 1981). Mechanisms of respiratory tract  
6 toxicity may relate to NO<sub>2</sub> metabolites or reaction products resulting in local pH changes or to  
7 direct damage to target cells via reactive metabolites. The underlying mechanisms are complex,  
8 because their effects may occur directly through the action of nitrogen or oxygen radicals  
9 generated via NO<sub>2</sub>-mediated chemical reactions or may be secondary to release of reactive  
10 oxygen species (ROS) by leukocytes responding to local irritation caused by cell damage. For a  
11 detailed description of mechanism studies, see Annex Chapter 4.

12  
13

## 14 **3.2 MORBIDITY ASSOCIATED WITH SHORT-TERM NO<sub>2</sub>** 15 **EXPOSURE**

### 16 17 **3.2.1 Respiratory Effects Associated with Short-Term NO<sub>2</sub> Exposure**

#### 18 19 **3.2.1.1 Lung Host Defenses and Immunity**

20  
21 Lung host defenses are sensitive to NO<sub>2</sub> exposure, with numerous measures of such  
22 effects observed at concentrations of <1 ppm. According to Chauhan et al. (2003), potential  
23 mechanisms include “direct effects on the upper and lower airways by ciliary dyskinesia (Carson  
24 et al., 1993), epithelial damage (Devalia et al., 1993a), increases in pro-inflammatory mediators  
25 and cytokines (Devalia et al., 1993b), rises in IgE concentration (Siegel et al., 1997), and  
26 interaction with allergens (Tunnicliffe et al., 1994), or indirectly through impairment of  
27 bronchial immunity (Sandstrom et al., 1992).” Table 3.2-1 summarizes a range of proposed  
28 mechanisms by which exposure to NO<sub>2</sub> in conjunction with viral infections may exacerbate  
29 upper and lower airways symptoms (Chauhan et al., 1998). A major concern has been the  
30 potential for NO<sub>2</sub> exposure to enhance susceptibility to, or the severity of, illness resulting from  
31 respiratory infections and asthma, especially in children. The following discussion focuses on  
32 studies published since the 1993 AQCD and conducted at near-ambient exposure concentrations.

1           One new epidemiological field study (Chauhan et al., 2003) discussed in Section 2.7  
2 provided evidence that increased personal exposure to NO<sub>2</sub> worsens virus-associated symptoms  
3 and lung function in children with asthma. Personal exposure concentrations were low, with  
4 medians for the exposure quartiles ranging from 2.6 to 10.9 ppb. These concentrations are at  
5 least 2 orders of magnitude lower than the lowest concentrations demonstrated to have  
6 measurable effects on airways inflammation in association with allergen challenge in clinical  
7 studies. Differences that can influence the interaction of NO<sub>2</sub> and infectious agents include  
8 exercise (Illing et al., 1980), the presence of O<sub>3</sub> (Ehrlich et al., 1977; Gardner, 1980; Gardner  
9 et al., 1982; Graham et al., 1987), and elevated temperatures (Gardner et al., 1982).

10           Several clinical studies have attempted to address the question of whether NO<sub>2</sub> exposures  
11 impaired host defenses and/or increased susceptibility to infection and produced mixed results  
12 (Rehn et al., 1982; Goings et al., 1989; Rubinstein et al., 1991; Sandström et al. 1990, 1991,  
13 1992a,b; Devlin 1992, 1999; Frampton et al., 2002: from Samet and Bell, 2004, review) (see the  
14 1993 AQCD for details of older studies and Annex Table AX5-1 for additional details on newer  
15 studies). One approach has been to examine the effects of in vivo NO<sub>2</sub> exposure on the function  
16 of AMs obtained by bronchoalveolar lavage, including the susceptibility of these cells to viral  
17 infection in vitro. Two studies since 1993 involved 2.0-ppm NO<sub>2</sub> exposures for 4 or 6 h with  
18 intermittent exercise and found no effect on AM inactivation of influenza virus either  
19 immediately or 18 h after exposure (Azadniv et al., 1998; Devlin et al., 1999). However, the  
20 Devlin et al. (1999) study found reduced AM phagocytic capacity after NO<sub>2</sub> exposure,  
21 suggesting a reduced ability to clear inhaled bacteria or other infectious agents. Frampton et al.  
22 (2002) examined NO<sub>2</sub> effects on viral infectivity of airways epithelial cells. Subjects were  
23 exposed to air, or 0.6- or 1.5-ppm NO<sub>2</sub> for 3 h, and bronchoscopy was performed 3.5 h after  
24 exposure. Epithelial cells were harvested from the airways by brushing and then challenged in  
25 vitro with influenza virus and respiratory syncytial virus (RSV). NO<sub>2</sub> exposure did not alter viral  
26 infectivity, but appeared to enhance epithelial cell injury in response to infection with RSV  
27 ( $p = 0.024$ ). Similar results were seen with influenza virus. These findings suggest that prior  
28 exposure to NO<sub>2</sub> may increase the susceptibility of the respiratory epithelium to injury by  
29 subsequent viral challenge. Over all results from clinical studies are equivocal but suggestive of  
30 the potential for NO<sub>2</sub> effects.

1 Animal studies provide clearer evidence that host defense system components such as  
2 mucociliary transport and AMs (see Annex Tables AX.4.3 and 4.4) are targets for inhaled NO<sub>2</sub>.  
3 Animal studies further show that NO<sub>2</sub> can impair the respiratory host defense system sufficiently  
4 to render the host more susceptible to respiratory infections (See Annex Table 4.5). Ciliated  
5 epithelial cells involved in mucociliary transport in the conducting airways exhibit  
6 morphological changes at NO<sub>2</sub> concentration as low as 0.5 ppm with 7 months of exposure  
7 (Yamamoto and Takahashi, 1984). However, mucociliary clearance is not affected by NO<sub>2</sub>  
8 exposure as low as 3 ppm. In a 1994 study, exposure of guinea pigs to 5640- or 16,920-μg/m<sup>3</sup>  
9 (3 or 9 ppm) NO<sub>2</sub> 6 h/day, 6 days/week for 2 weeks resulted in concentration-dependent  
10 decreases in ciliary activity of 12 and 30% of control values at NO<sub>2</sub> concentrations of  
11 5640 μg/m<sup>3</sup> (3 ppm) and 16,920 μg/m<sup>3</sup> (9 ppm), respectively (Ohashi et al., 1994). These  
12 concentration-dependent decreases are accompanied by a concentration-dependent increase in  
13 eosinophil accumulation on the epithelium and submucosal connective tissue layer of the nasal  
14 mucosa. For foreign agents such as some bacteria and viruses that deposit below the mucociliary  
15 region in the gas-exchange region of the lung, AMs primarily provide host defenses by acting to  
16 remove or kill viable particles, remove nonviable particles, and process and present antigens to  
17 lymphocytes for antibody production. AMs are one of the sensitive targets for NO<sub>2</sub>, as  
18 evidenced by in vivo acute and long-term animal exposures and in vitro studies (see Annex  
19 Table AX4.4 for details of studies related to each of these morphological or functional  
20 parameters in exposed animals). The susceptibility to bacterial and viral pulmonary infections in  
21 animals also increases with NO<sub>2</sub> exposures of as low as 0.5 ppm. No new studies published  
22 since 1993 were identified that evaluated this endpoint. Annex Table AX4.5 summarizes the  
23 effects of NO<sub>2</sub> exposure and infectious agents in animal studies as compiled in the 1993 AQCD  
24 for Oxides of Nitrogen. It is important to note that the 1993 AQCD provides evidence that the  
25 host's response to inhaled NO<sub>2</sub> can be significantly influenced by the duration and temporal  
26 patterns of exposure. This is important in considering continuous versus intermittent exposures  
27 and attempting to understanding observed differences in reported results.

28 In summary, the evidence for altered host defense is coherent across disciplines and  
29 plausible. Taken as a whole, however, the body evidence lacks consistency and robustness. The  
30 epidemiologic, clinical, and animal data provide supportive evidence of impaired host-defense  
31 systems and increased risk of susceptibility to both viral and bacterial infections. In particular,

1 the Pilotto et al. (2004) and the Chauhan et al. (2003) studies add to the weight of evidence  
2 produced since the last AQCD. Their findings indicate that exposure to NO<sub>2</sub> before the start of a  
3 respiratory infection is associated with an increase in respiratory symptoms and exacerbation of  
4 asthma. These effects are reported to occur at levels near and below the current NAAQS. These  
5 indoor/personal NO<sub>2</sub>-exposure studies all were controlled for some variable associated with  
6 ambient NO<sub>2</sub> exposure; however, confounding with ultrafine emissions remains a concern.

7

### 8 **Clinical Studies on Host Defense and Immunity**

9       Clinical studies have attempted to address the question of whether NO<sub>2</sub> exposure  
10 increases susceptibility to infection. Goings et al. (1989) exposed healthy volunteers to either  
11 1- to 3 ppm NO<sub>2</sub> or to air for 2 h/day for 3 consecutive days. A live, genetically engineered  
12 influenza A vaccine virus was administered intranasally to all subjects after exposure on day 2.  
13 Infection was determined by virus recovery from nasal washings, a 4-fold or greater increase in  
14 antibody titer, or both. The findings of this study were inconclusive, in part, because of  
15 limitations in sample size. In addition, the attenuated, cold-adapted virus used in the study was  
16 incapable of infecting the lower respiratory tract, where NO<sub>2</sub> may have the most important  
17 impact on host defense.

18       There is evidence from both animal and human studies that exposure to NO<sub>2</sub> may alter  
19 lymphocyte subsets in the lung and possibly in the blood. Lymphocytes, particularly T cells and  
20 NK cells, play a key role in the innate immune system and host defense against respiratory  
21 viruses. Sandström et al. (1990, 1991) observed a significant, dose-related increase in  
22 lymphocytes and mast cells recovered by bronchoalveolar lavage (BAL) 24-h after a 20-min  
23 exposure to NO<sub>2</sub> at 2.25 to 5.5 ppm. Rubinstein et al. (1991) found that a series of 4 daily, 2-h  
24 exposures to 0.60 ppm NO<sub>2</sub> resulted in a small increase in NK cells recovered by BAL. In  
25 contrast, repeated exposures to 1.5- or 4 ppm NO<sub>2</sub> for 20 min every second day on six occasions  
26 resulted in decreased CD16<sup>+</sup>56<sup>+</sup> (NK cells) and CD19<sup>+</sup> cells (B lymphocytes) in BAL fluid, 24-h  
27 after the final exposure (Sandström et al., 1992a,b). No effects were seen on polymorphonuclear  
28 leukocytes (PMN) or total lymphocyte numbers. Solomon et al. (2000) found a decrease in  
29 CD4<sup>+</sup> T lymphocytes in BAL fluid 18-h after 4 daily, 4-h exposures to 2.0 ppm NO<sub>2</sub>. Azadniv  
30 et al. (1998) observed a small but significant reduction in CD8<sup>+</sup> T lymphocytes in peripheral  
31 blood, but not BAL, 18-h following single 6-h exposures to 2.0 ppm NO<sub>2</sub>. Frampton et al.

1 (2002) found small increases in BAL lymphocytes and decreases in blood lymphocytes with  
2 exposures to 0.6 and 1.5 ppm NO<sub>2</sub> for 3 h.

3 The observed effects on lymphocyte responses, as described above, have not been  
4 consistent among studies. Differing exposure protocols and small numbers of subjects among  
5 these studies may explain the varying and conflicting findings. Furthermore, the clinical  
6 significance of transient, small changes in lymphocyte subsets is unclear. It is possible that the  
7 inflammatory response to NO<sub>2</sub> exposure involves both lymphocytes and PMNs, with lymphocyte  
8 responses occurring transiently and at lower concentrations and PMN responses predominating  
9 at higher concentrations or more prolonged exposures. The airways lymphocyte responses do  
10 not provide convincing evidence of impairment in host defense.

11 One study found that 20-min exposures to NO<sub>2</sub> at 1.5 to 3.5 ppm transiently reduced  
12 airways mucociliary activity, assessed by fiberoptic bronchoscopy (Helleday et al., 1995).  
13 Reduced mucus clearance would be expected to increase susceptibility to infection by reducing  
14 the removal rate of microorganisms from airways. However, the study was weakened by a lack  
15 of a true air control exposure as well as by the absence of randomization and blinding. As a  
16 clarification, Helleday et al. (1995) did not measure mucus clearance rates directly using  
17 radiolabeled particles; rather they utilized an optical technique to characterize ciliary activity.  
18 Rehn et al. (1982) examined the effect of NO<sub>2</sub> exposure on mucociliary clearance of a  
19 radiolabeled Teflon aerosol. After a 1-h exposure to either 0.27- or 1.06-ppm (500 or  
20 2000 µg/m<sup>3</sup>) NO<sub>2</sub>, there were no changes in airways clearance rates.

21 Another approach has been to examine the effects of in vivo NO<sub>2</sub> exposure on the  
22 function of AMs obtained by bronchoalveolar lavage, including the susceptibility of these cells  
23 to viral infection in vitro. Several NO<sub>2</sub> exposure scenarios, including continuous low-level  
24 exposure or intermittent peak exposures have been examined (Frampton et al., 1989). AMs  
25 obtained by BAL 3.5-h after a 3-h continuous exposure to 0.60 ppm NO<sub>2</sub> tended to inactivate  
26 influenza virus in vitro less effectively than cells collected after air exposure. The effect was  
27 observed in cells from 4 of the 9 subjects studied; AMs from these 4 subjects increased release of  
28 interleukin-1 (IL-1) after exposure to NO<sub>2</sub>, whereas cells from the remaining 5 subjects  
29 decreased release of IL-1 following exposure. However, two subsequent studies (Azadniv et al.,  
30 1998; Devlin et al., 1999) involving 2.0 ppm NO<sub>2</sub> exposures for 4 or 6 h, with intermittent  
31 exercise, found no effect on AM inactivation of influenza virus either immediately or 18-h after

1 exposure. However, the Devlin et al. (1999) study found reduced AM phagocytic capacity after  
2 NO<sub>2</sub> exposure, suggesting a reduced ability to clear inhaled bacteria or other infectious agents.

3 Frampton et al. (2002) examined NO<sub>2</sub> effects on viral infectivity of airways epithelial  
4 cells. Subjects were exposed to air, or 0.6- or 1.5-ppm NO<sub>2</sub> for 3 h, and bronchoscopy was  
5 performed 3.5-h after exposure. Epithelial cells were harvested from the airways by brushing  
6 and then challenged in vitro with influenza virus and respiratory syncytial virus (RSV). NO<sub>2</sub>  
7 exposure did not alter viral infectivity, but appeared to enhance epithelial cell injury in response  
8 to infection with RSV (p = 0.024). A similar nonsignificant change was seen with influenza  
9 virus. These findings suggest that prior exposure to NO<sub>2</sub> may increase the susceptibility of the  
10 respiratory epithelium to injury by subsequent viral challenge.

## 11 **Toxicological Studies on Host Defense and Immunity**

### 13 *Mucociliary Clearance*

14 Substances capable of disrupting or impairing mucociliary clearance can result in an  
15 excess accumulation of cellular secretions, increased acute bacterial and viral infections, chronic  
16 bronchitis, and prolonged pulmonary complications (Schlesinger et al., 1987). The respiratory  
17 tract often responds to irritants by increasing mucus secretion. Ideally, this would enhance the  
18 capture of harmful substances to be removed to the upper respiratory tract through the action of  
19 the ciliated epithelium. The ciliated epithelial cells lining the respiratory tract (tracheobronchial  
20 region) can respond to insults by changing cilia beat frequency, cessation of beating, and/or  
21 development of abnormal forms of cilia. With even greater exposures, loss of cilia and ciliated  
22 epithelial cells can be found in animals exposed to NO<sub>2</sub>, and a description of such  
23 histopathologic changes can be found in the Section 3.2.1.1 on morphological changes.

24 Changes in the functional impairment of mucociliary clearance are observed at high  
25 concentrations of NO<sub>2</sub> ( $\geq 5.0$  ppm) (Giordano and Morrow, 1972; Kita and Omichi, 1974). At  
26 lower exposures (2 h/day for 2, 7, and 14 days to 564- and 1880- $\mu\text{g}/\text{m}^3$  [0.3 and 1.0 ppm] NO<sub>2</sub>),  
27 the mucociliary clearance of inhaled tracer particles deposited in the tracheobronchial tree of  
28 rabbits was not altered (Schlesinger et al., 1987). Vollmuth et al. (1986) studied the clearance of  
29 strontium-85-radiolabelled polystyrene latex spheres from the lungs of rabbits following a single  
30 2-h exposure to NO<sub>2</sub> at 564, 1880, 5640, or 18,800  $\mu\text{g}/\text{m}^3$  (0.3, 1.0, 3.0, or 10.0 ppm). An  
31 acceleration in clearance occurred immediately after exposure to the two lowest NO<sub>2</sub>  
32



1 concentrations; a similar effect was found by Schlesinger and Gearhart (1987). At the higher  
2 levels of NO<sub>2</sub>, acceleration in clearance was not evident until midway through the 14-day  
3 postexposure period. Repeated exposure for 14 days (2 h/day) to 1880- or 18,800-μg/m<sup>3</sup> (1.0 or  
4 10.0 ppm) NO<sub>2</sub> produced a response similar to a single exposure at the same concentration.

5 Exposure of guinea pigs to 5640- or 16,920-μg/m<sup>3</sup> (3 or 9 ppm) NO<sub>2</sub> 6 h/day,  
6 6 days/week for 2 weeks resulted in concentration-dependent decreases in ciliary activity of 12  
7 and 30% of control values at NO<sub>2</sub> concentrations of 5640 μg/m<sup>3</sup> (3 ppm) and 16,920 μg/m<sup>3</sup>  
8 (9 ppm), respectively, (Ohashi et al., 1994) accompanied by concentration-dependent increase in  
9 eosinophil accumulation on the epithelium and submucosal connective tissue layer of the nasal  
10 mucosa. Morphological changes (i.e., compound cilia, cytoplasmic vacuolization, sloughing)  
11 were observed only in the nose of animals in the high-concentration group.

### 12 13 *Effects on AMs and Mast Cells*

14 The effectiveness of AMs depends on the type, number, and viability of the cells. To  
15 perform their primary function of detoxifying and/or clearing the lung of infectious and  
16 noninfectious particles, AMs must maintain an intact membrane, mobility, and phagocytic  
17 activity, and have functioning enzyme systems as well as secrete cellular mediators that recruit  
18 and activate inflammatory cells in the lungs (Fels and Cohn, 1986). AMs are one of the sensitive  
19 targets for NO<sub>2</sub>, as evidenced by in vivo acute and long-term animal exposures and in vitro  
20 studies, and there are studies (see Annex Table AX4.4) related to each of these morphological or  
21 functional parameters in exposed animals.

22 Structural changes, including the loss of surface processes, appearance of fenestrae, bleb  
23 formation, and denuded surface areas, have been observed in AMs isolated from mice  
24 continuously exposed to 3760-μg/m<sup>3</sup> (2.0 ppm) NO<sub>2</sub> or to 940-μg/m<sup>3</sup> (0.5 ppm) NO<sub>2</sub>  
25 continuously with a 1-h peak to 3760 μg/m<sup>3</sup> (2.0 ppm) for 5 days/week. The AMs showed  
26 distinctive morphological changes after 21 weeks of exposure that would be expected to interfere  
27 with cellular functions such as chemotaxis and phagocytosis (Aranyi et al., 1976). Continuous  
28 exposure to lower NO<sub>2</sub> concentrations, i.e., to 940 μg/m<sup>3</sup> (0.5 ppm) continuous or to 1.8 μg/m<sup>3</sup>  
29 (0.1 ppm) continuous with a 3-h peak to 1880 μg/m<sup>3</sup> (1.0 ppm) for periods up to 24 weeks, did  
30 not result in any significant morphological or biochemical changes.

31 Mochitate et al. (1986) reported a significant increase in the total number of AMs isolated  
32 from rats during 10 days of exposure to 7520-μg/m<sup>3</sup> (4.0 ppm) NO<sub>2</sub>, but the number of PMNs

1 did not increase. The AMs from exposed animals also exhibited increased metabolic activity, as  
2 measured by the activities of glucose-6-phosphate dehydrogenase, glutathione peroxidase, and  
3 pyruvate kinase. The AMs also showed increased rates of synthesis of protein and DNA. All  
4 responses peaked on day 4 and returned to control levels by the day 10. Increased numbers and  
5 metabolic activity of AMs would be expected to have a positive influence on host defenses.  
6 However, AMs are rich in proteolytic enzymes and increased numbers could result in some  
7 tissue destruction when the enzymes are released. Schlesinger (1987a,b) found no significant  
8 changes in the number or the viability of AMs in BAL fluid from rabbits exposed to 564- or  
9 1880- $\mu\text{g}/\text{m}^3$  (0.3 or 1.0 ppm)  $\text{NO}_2$ , 2 h/day for 13 days. Although there were no effects on the  
10 numbers of AMs that phagocytosed latex spheres, 2 days of exposure to 564  $\mu\text{g}/\text{m}^3$  (0.3 ppm)  
11 decreased the phagocytic capacity (i.e., number of spheres phagocytosed per cell). The higher  
12 level of  $\text{NO}_2$  increased phagocytosis, whereas longer exposures had no effect. In rats,  
13 continuous exposure at 7520- $\mu\text{g}/\text{m}^3$  (4.0 ppm) or 15,000- $\mu\text{g}/\text{m}^3$  (8.0 ppm)  $\text{NO}_2$  for 10 days  
14 significantly increased the number of AMs in the BAL fluid, with the increase becoming  
15 significant by the fifth day of exposure. Viability of these isolated cells decreased on day 1 and  
16 remained depressed throughout exposure. However, phagocytic activity of AMs was  
17 significantly depressed (after 5 days of exposure to 15,000  $\mu\text{g}/\text{m}^3$  [8.0 ppm] and 7 days of  
18 exposure to 7520  $\mu\text{g}/\text{m}^3$  [4.0 ppm]), but returned to the control value at 10 days of exposure  
19 (Suzuki et al., 1986). There may be a species difference in responsiveness, because Lefkowitz  
20 et al. (1986) did not observe a depression in phagocytosis in mice exposed for 7 days to  
21 9400- $\mu\text{g}/\text{m}^3$  (5.0 ppm)  $\text{NO}_2$ .

22 Suzuki et al. (1986) proposed that the inhibition of phagocytosis might be due to  $\text{NO}_2$   
23 effects on membrane lipid peroxidation. Studies by Dowell et al. (1971) and Goldstein et al.  
24 (1977) add support to this hypothesis. Acute exposure to 5640 to 7520  $\mu\text{g}/\text{m}^3$  (3.0 to 4.0 ppm)  
25 caused swelling of AMs (Dowell et al., 1971) and increased agglutination of AMs with  
26 concanavalin A (Goldstein et al., 1977), suggesting damage to membrane functions.

27  $\text{NO}_2$  exposure appears to decrease the ability of rat AMs to produce superoxide anion,  
28 which may limit antibacterial activity (Amoruso et al., 1981). Amoruso et al. (1981) presented  
29 evidence of such an effect at  $\text{NO}_2$  concentrations ranging from 1.3 to 17.0 ppm. The duration of  
30 the  $\text{NO}_2$  exposure was not given; all exposures were expressed in terms of parts per million  $\times$  h  
31 (ppm-h). A 50% decrease of superoxide anion production began after exposure to

1 54,700- $\mu\text{g}/\text{m}^3\text{-h}$  (29.1 ppm-h)  $\text{NO}_2$ . Suzuki et al. (1986) reported a marked decrease in the  
2 ability of rat AMs to produce superoxide anion following a 10-day exposure to either 7520- or  
3 15,000- $\mu\text{g}/\text{m}^3$  (4.0 or 8.0 ppm)  $\text{NO}_2$ . At the highest concentration, the effect was significant  
4 each day, but at the lower concentration, the depression was significant only on exposure days 3,  
5 5, and 10. Superoxide production in AMs from rat BAL fluid, stimulated by phorbol myristate  
6 acetate (PMA), was decreased after 0.5 days of exposure to 940- $\mu\text{g}/\text{m}^3$  (0.5 ppm)  $\text{NO}_2$  and  
7 continued to be depressed after 1, 5, and 10 days of exposure (Robison et al., 1993).

8 Kumae and Arakawa (2006) compared the female offspring of Brown-Norway rats that  
9 were exposed continuously to  $\text{NO}_2$  at 376, 940, or 3760  $\mu\text{g}/\text{m}^3$  (0.2, 0.5, or 2.0 ppm) during  
10 breeding and gestation and up through 12 weeks of age to female offspring who were exposed  
11 continuously to 376, 940, or 3760  $\mu\text{g}/\text{m}^3$  (0.2, 0.5, or 2.0 ppm) only during the weanling period  
12 (from weeks 5 to 12). The ROS generation from AMs was significantly suppressed in the  
13 940- and 3760- $\mu\text{g}/\text{m}^3$  (0.5 and 2.0 ppm)  $\text{NO}_2$ -exposed weanling animals; no change in ROS-  
14 generating capability was observed in the embryonic-exposed animals compared to the air  
15 controls.

16 The AMs obtained by BAL from baboons exposed to 3760- $\mu\text{g}/\text{m}^3$  (2.0 ppm)  $\text{NO}_2$  for  
17 8 h/day, 5 days/week for 6 months had impaired responsiveness to migration inhibitory factor  
18 produced by sensitized lymphocytes (Green and Schneider, 1978). This substance affects the  
19 behavior of AMs by inhibiting free migration, which in turn, interferes with AM functional  
20 capacity. In addition, the random mobility of AMs was significantly depressed in rabbits  
21 following a 2 h/day exposure for 13 days to  $\text{NO}_2$  at 564  $\mu\text{g}/\text{m}^3$  (0.3 ppm) but not at 1880  $\mu\text{g}/\text{m}^3$   
22 (1.0 ppm) (Schlesinger, 1987b).

23 Mast cells also play an important role in modulating lung inflammatory responses. IgE-  
24 mediated histamine release from lung mast cells was significantly increased in guinea pigs, but  
25 not rats, exposed to 7520- $\mu\text{g}/\text{m}^3$  (4.0 ppm)  $\text{NO}_2$ , 24 h/day for 12 weeks (Fujimaki and Nohara,  
26 1994). No effect of  $\text{NO}_2$  on histamine release was observed at the lower concentrations of 1880-  
27 or 3760- $\mu\text{g}/\text{m}^3$  (1 or 2 ppm)  $\text{NO}_2$ .

28 Several newer studies provide information on the concentration at which effects on the  
29 recruitment and infiltration of PMNs into the lung occur following  $\text{NO}_2$  exposure. When  
30 Robison et al. (1993) exposed rats to 0 or 0.5-ppm  $\text{NO}_2$ , 8 h/day, 5 days/week for 0.5, 1, 5, or  
31 10 days, no effects were observed on neutrophil, lymphocyte, or macrophage/monocyte levels or

1 cell population percentages in BAL. Results, therefore, suggest no significant influx of  
2 inflammatory cells into lung airways and alveolar spaces. In rats exposed to 0 or 1.2-ppm NO<sub>2</sub>,  
3 there were no significant differences in cell viability and percentages of pulmonary AMs or  
4 PMNs between animals exposed to 1.2-ppm NO<sub>2</sub> and nonexposed controls (Bermudez, 2001).  
5 However, when Pagani et al. (1994) exposed rats to NO<sub>2</sub> at 0, 5, or 10 ppm, 24-h or 24 h/day for  
6 7 days, exposure to 10 ppm caused maximal influx of PMN at 24 h, but no influx was observed  
7 after 7 days of exposure. Likewise, no significant changes in lymphocyte counts were observed.

8

### 9 ***Humoral Immunity and Response to Challenge Agents***

10 As noted by U.S. Environmental Protection Agency (1993), it is most relevant to assess  
11 the effects of inhaled compounds on cell-mediated and antibody responses in the lung itself,  
12 because this is the primary site of defense against respiratory infections. However, because of  
13 technical obstacles, many older studies have assessed the responses in inhaled pollutants or NO<sub>2</sub>  
14 in the spleen or peripheral blood. These studies are more difficult to interpret in terms of  
15 enhanced risk of respiratory infections. Some studies suggest little effect, whereas others  
16 suggest suppression or activation, depending not only on concentration but also on length of  
17 exposure, species tested, and specific endpoints measured. Annex Table AX4.3 summarizes the  
18 various humoral and cell-mediated effects seen in animals exposed to NO<sub>2</sub>.

19

### 20 ***Interaction with Infectious Microorganisms***

21 Suppression of host defense mechanisms by NO<sub>2</sub> as described in the studies above would  
22 be expected to result in an increased incidence and severity of pulmonary infections (Miller  
23 et al., 1987; Gardner et al., 1979; Coffin and Gardner, 1972). Various experimental approaches  
24 have been employed using animals in an effort to determine the overall functional efficiency of  
25 the host's pulmonary defenses following NO<sub>2</sub> exposure. In the most commonly used infectivity  
26 model, animals are exposed to either NO<sub>2</sub> or filtered air and the treatment groups are combined  
27 and exposed briefly to an aerosol of a viable agent, such as *Streptococcus* spp., *Klebsiella*  
28 *pneumoniae*, *Diplococcus pneumoniae*, or influenza virus and mortality rates are determined  
29 (Ehrlich, 1966; Henry et al., 1970; Coffin and Gardner, 1972; Ehrlich et al., 1979; Gardner,  
30 1982). Although the endpoint is mortality, this experimental test is considered a sensitive  
31 indicator of the depression of the defense mechanisms and is a commonly used assay for  
32 assessing immunotoxicity.

1 Annex Table AX4.5 summarizes the effects of NO<sub>2</sub> exposure and infectious agents in  
2 animal studies as compiled in the 1993 AQCD for Oxides of Nitrogen. No new studies  
3 published since 1993 were identified that evaluated this endpoint. The susceptibility to bacterial  
4 and viral pulmonary infections in animals increases with NO<sub>2</sub> exposure. After acute exposure,  
5 the lowest observed concentration that increased lung susceptibility to bacterial infections was  
6 3750-μg/m<sup>3</sup> (2 ppm) NO<sub>2</sub> in a 3-h exposure study with mice (Ehrlich et al., 1977; Ehrlich, 1980).  
7 Acute (17 h) exposures to greater than 4250-μg/m<sup>3</sup> (2.3 ppm) NO<sub>2</sub> also decreased pulmonary  
8 bactericidal activity in mice (Goldstein et al., 1974). Long-term exposure studies have  
9 demonstrated that NO<sub>2</sub> exposure reduces the efficiency of defense against infections at  
10 concentrations as low as 940 μg/m<sup>3</sup> (0.5 ppm). Mice challenged with influenza A/PR/8 virus  
11 after continuous exposure for 39 days had increased mortality (Ito, 1971); a 6-month exposure  
12 to the same NO<sub>2</sub> concentration likewise resulted in increased bacterial-induced mortality in mice  
13 (Ehrlich and Henry, 1968). Gardner et al. (1977a,b) also reported an increase in mortality with  
14 increasing length of exposure in mice exposed to NO<sub>2</sub> from 940 to 52,640 μg/m<sup>3</sup> (0.5 to  
15 28 ppm).

16 The influence of a wide variety of exposure regimens has been evaluated using the  
17 infectivity model (Annex Table AX4.5). For example, the effect of varying durations of  
18 continuous exposure on the mortality of mice exposed to NO<sub>2</sub> was determined for varying  
19 durations of time (Gardner et al., 1977b). When the product of C × T was held constant, the  
20 relationship between concentration and time produced significantly different mortality responses.  
21 Concentration had more influence than duration on the outcome. A more complete discussion of  
22 the C × T relationship issues for NO<sub>2</sub> is summarized in a later section. The effect of continuous  
23 versus intermittent exposure to NO<sub>2</sub> followed by bacterial challenge has been studied (Ehrlich  
24 and Henry, 1968; Gardner et al., 1979); results suggest that fluctuating levels may ultimately be  
25 as toxic as sustained higher levels (Gardner et al., 1979). Extensive investigations have also  
26 been made on the response to airborne infections in mice breathing spike exposures to NO<sub>2</sub>  
27 superimposed on a lower continuous background level of NO<sub>2</sub>, which simulates the pattern  
28 (although not the NO<sub>2</sub> concentrations) of exposure in the urban environment in the United States  
29 (Gardner 1980; Gardner et al., 1982; Graham et al., 1987). The pattern of exposure determined  
30 the response and that the response was found not to be predictable based on a simple C × T  
31 relationship. Miller et al. (1987) further investigated the effects of chronic exposure to NO<sub>2</sub>

1 spikes on murine antibacterial lung defenses using a spike-to-baseline ratio of 4:1, which is not  
2 uncommon in the urban environment in the United States. Mice were exposed 23 h/day,  
3 7 days/week for 1 year to a baseline of 376  $\mu\text{g}/\text{m}^3$  (0.2 ppm) or to this baseline level on which  
4 was superimposed a 1-h spike of 1500- $\mu\text{g}/\text{m}^3$  (0.8 ppm)  $\text{NO}_2$ , twice a day, 5 days/week. There  
5 was significantly greater mortality in mice exposed to peak plus baseline compared to baseline-  
6 exposed animals.

7 A dose-related decrease in pulmonary antibacterial defenses occurs from  $\text{NO}_2$  exposure.  
8 Decreases in antibacterial defenses occurred at concentrations ranging from 7520- $\mu\text{g}/\text{m}^3$   
9 (4.0 ppm)  $\text{NO}_2$  for *Staphylococcus aureus* to 37,500- $\mu\text{g}/\text{m}^3$  (20 ppm)  $\text{NO}_2$  for *Proteus mirabilis*  
10 (Jakab, 1987).

11 Differences in species susceptibility to  $\text{NO}_2$  or to a pathogen may play a role in the  
12 enhancement of mortality seen in experimental animals. Additional factors can influence the  
13 interaction of and infectious agents such as exercise (Illing et al., 1980), the presence of  $\text{O}_3$   
14 (Ehrlich et al., 1977; Gardner, 1980; Gardner et al., 1982; Graham et al., 1987), or elevated  
15 temperatures (Gardner et al., 1982). Table 3.2-1 summarizes a range of proposed mechanisms  
16 by which exposure to  $\text{NO}_2$  in conjunction with viral infections may exacerbate upper and lower  
17 airways symptoms (Chauhan et al., 1998).

18

### 19 **3.2.1.2 Effects of Short-Term $\text{NO}_2$ Exposure on Lung Function**

20

#### 21 **Epidemiological Studies of Lung Function**

22

##### 23 ***Spirometry ( $FEV_1$ )—Children***

24 Reliable, repeatable measurement of lung function in children presents special  
25 challenges. The method that seems to produce the most accurate results is spirometry, but  
26 because it requires special equipment and trained testers, it is not generally used for large-scale  
27 studies. Of the three studies reviewed here that did use spirometry (Hoek and Brunekreef, 1994;  
28 Linn et al., 1996; Timonen et al., 2002), all conducted repeat lung function measurements in  
29 schoolchildren. All found significant associations between small decrements in lung function  
30 and increases in ambient  $\text{NO}_2$  levels. Hoek and Brunekreef (1994) enrolled 1,079 children in the  
31 Netherlands to examine the effects of low-level winter air pollution on FVC,  $FEV_1$ , MMEF, and  
32 PEF. A significant effect was found only for the PEF measure: the mean (over all subjects)

1 slope (SE) was a reduction of 52 mL/s (95% CI: 21, 83) for 20-ppb increase in the previous  
2 day's NO<sub>2</sub>. The authors do not give mean values for lung function measurements, so it is not  
3 possible to calculate what percentage of PEF this decrement represents. Linn et al. (1996)  
4 examined 269 Los Angeles-area schoolchildren and short-term air pollution exposures. The  
5 authors found statistically significant associations between previous-day 24-h NO<sub>2</sub>  
6 concentrations and FVC the next morning (mean decline of 8 mL [95% CI: 2, 14] per 20-ppb  
7 increase in NO<sub>2</sub>), and current-day 24-h NO<sub>2</sub> concentrations and morning to evening changes in  
8 FEV<sub>1</sub> (mean decline of 8 mL [95% CI: 2, 14] per 20-ppb increase in NO<sub>2</sub>). Timonen et al.  
9 (2002) enrolled 33 Finnish children with chronic respiratory symptoms to study the effects of  
10 exercise-induced lung function changes and ambient air pollution. No significant effects were  
11 observed for lung function changes due to exercise, but significant associations were observed  
12 for level of NO<sub>2</sub> lagged by 2 days and baseline FVC (mean decline of 21 mL [95% CI: -29, -12]  
13 for 20-ppb NO<sub>2</sub>) and FEV<sub>1</sub> (mean decline of 20 mL [95% CI: -26, -13] for 20-ppb NO<sub>2</sub>).

#### 14 15 ***Supervised Peak Flow Meter Measurements—Children***

16 Other studies conducted supervised lung function measurements in schoolchildren using  
17 peak flow devices (Scarlett et al., 1996; Peacock et al., 2003; Steerenberg et al., 2001). Scarlett  
18 et al. (1996) used portable peak flow meters to measure lung function in 154 pupils in a school in  
19 southern England. No significant associations were found between level of ambient NO<sub>2</sub> and  
20 FEV<sub>0.75</sub>, FVC, or the ratio of FEV<sub>0.75</sub> to FVC. They also reported that lung function of children  
21 with current wheeze (n = 14) was not differentially affected. In a second study by the same  
22 group of investigators, Peacock et al. (2003) measured peak flow rates for 177 children in three  
23 schools in southern England. Although no significant associations were found between level of  
24 NO<sub>2</sub> and peak flow, there was a significant association for peak flow decrements of 20% or more  
25 with NO<sub>2</sub> lagged by 2 days or averaged over the previous 4 days. For all children, the OR  
26 (95% CI) for each 20-ppb increase in NO<sub>2</sub> was 1.91 (95% CI: 1.52, 2.76) and 2.32 (95% CI:  
27 1.00, 5.50) for a 2-day lag and 1 to 4 day lag, respectively. Odds ratios (OR) were similar for a  
28 subset of 43 children with current wheeze (as determined by a questionnaire administered to  
29 parents) (OR = 1.70 [95% CI: 1.00, 2.86] and OR = 2.81 [95% CI: 0.98, 8.06], for a 2-day lag  
30 and 1 to 4 day lag, respectively). Steerenberg et al. (2001) enrolled 82 children (38 urban,  
31 44 suburban) in the Netherlands and collected supervised peak flow measurements at their

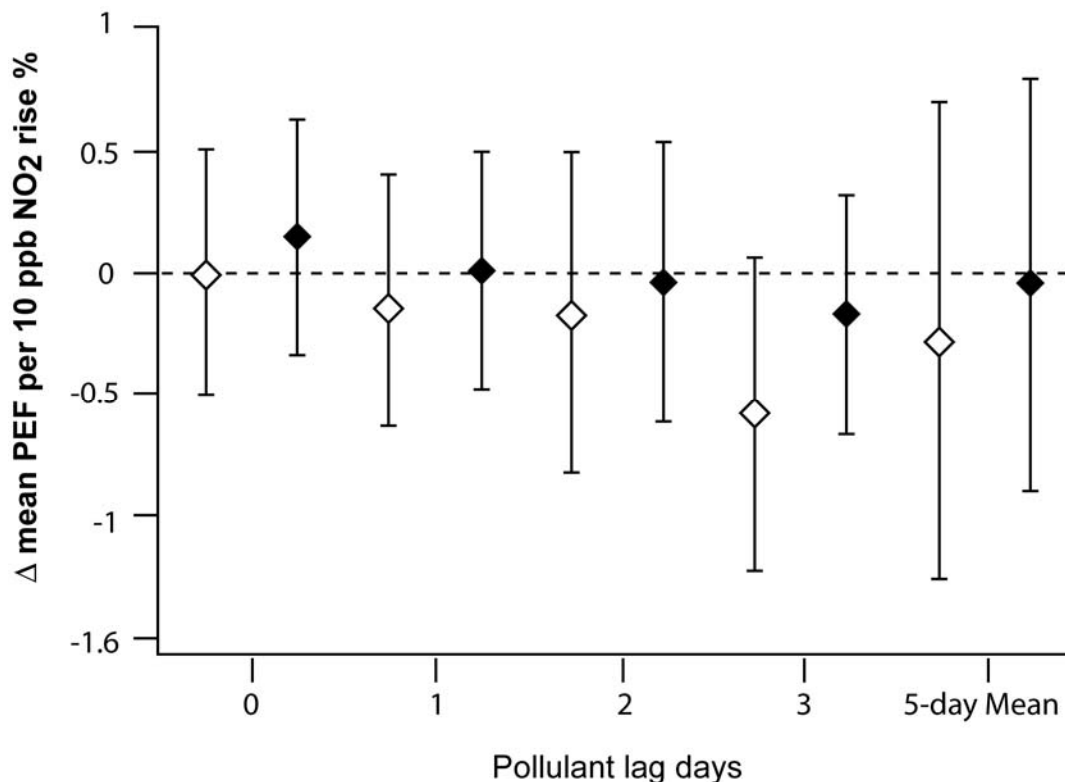
1 schools. Significant inverse associations were found between PEF and NO<sub>2</sub>: each 20-ppb  
2 increase in NO<sub>2</sub> lagged by 1 day was associated with a 3.1% decrease in PEF. Ward et al. (2002)  
3 studied the effects of air pollutants on PEF on a panel of 162 nine-year-old children in England  
4 for winter and summer periods and reported no significant associations between NO<sub>2</sub> and lung  
5 functions or symptoms.

### 6 7 ***Home-Use Peak Flow Meter Measurements—Children***

8         Reliable data are notoriously difficult to come by using portable peak flow measuring  
9 devices (for example, see Wensley and Silverman, 2001). This may help explain why, in  
10 contrast to studies with supervised measurements, none of the nine studies using home peak flow  
11 measurements reported any significant associations with ambient NO<sub>2</sub> (Roemer et al., 1998  
12 [2,010 children in the PEACE study in Europe]; Roemer et al., 1999 [a subset of 1,621 children  
13 from the PEACE study with chronic respiratory symptoms]; Mortimer et al., 2002  
14 [846 asthmatic children from the NCICAS]; Van der Zee et al., 1999 [633 children in the  
15 Netherlands]; Timonen and Pekkanen, 1997 [169 children including asthmatics in Finland];  
16 Ranzi et al., 2004 [118 children, some with asthma, in the Italian AIRE study]; Segala et al.,  
17 1998 and Just et al., 2002 [over 80 asthmatic children in Paris]; Delfino et al., 2003a  
18 [22 asthmatic children in southern California]).

19         Ward et al. (2000) examined the effect of correcting peak flow for nonlinear errors on  
20 NO<sub>2</sub> effects estimates in a panel study of 147 (47% female) 9-year olds. The correction resulted  
21 in a small increase in the group mean PEF (1.1 L·min<sup>-1</sup>). For the entire panel, NO<sub>2</sub> effect  
22 estimates were all corrected in the positive direction with a narrowing of the 95% confidence  
23 interval, and all but the result for 0-day lag were decreased in absolute size by up to 73% (effect  
24 estimate for NO<sub>2</sub> lagged 3 days corrected from -0.56 to -0.15% per 10 ppb). When only the  
25 symptomatic/atopic children (i.e., reported wheezing and positive skin test) were considered, the  
26 estimates for associations with 5-day average NO<sub>2</sub> decreased in size from -2.53% to -0.90% per  
27 10 ppb. In addition, lag 0 became significant with an increase in magnitude from -0.51% to  
28 -1.22% per 10 ppb. Figures 3.2-1 and 3.2-2 illustrate the results for the whole panel and the  
29 symptomatic/atopic children, respectively. The authors concluded that correction for PEF meter  
30 measurements resulted in small but important shifts in the direction and size of effect estimates





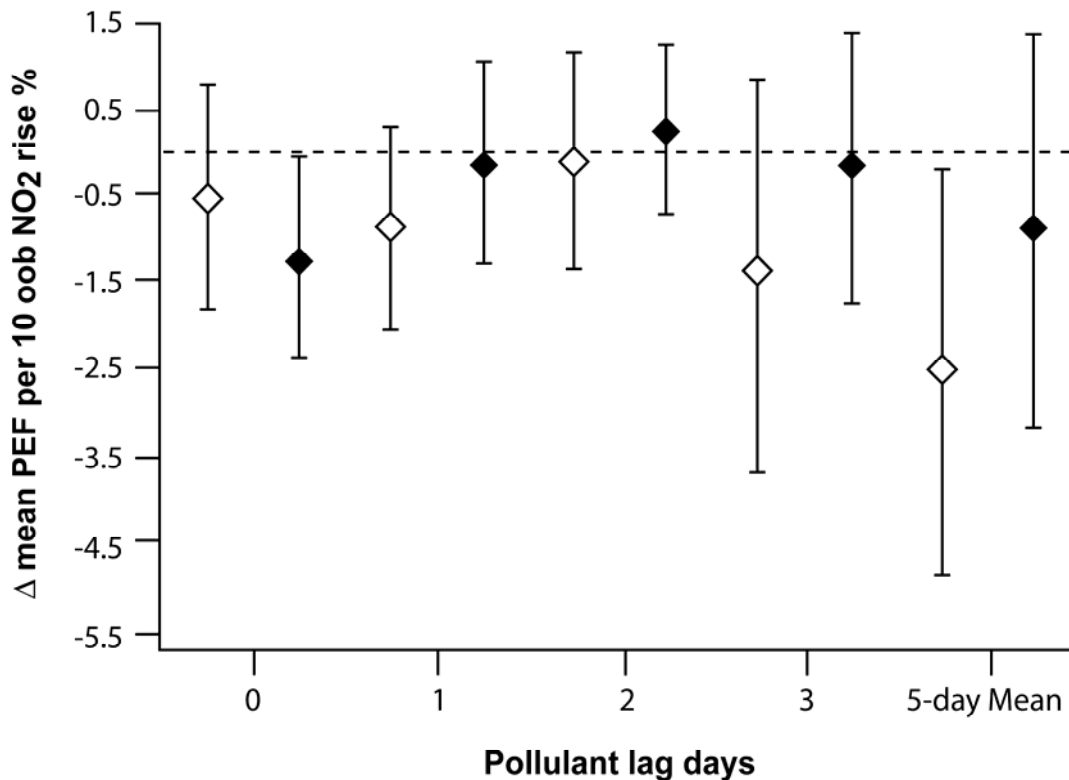
**Figure 3.2-1. Effect estimates with 95% confidence intervals calculated for both uncorrected (◇) and corrected (◆) PEF: change in 5-day mean = lag 0 to lag 4 days.**

Source: Ward et al. (2000).

1 and probable interpretation of results. The effects of correction were, however, not consistent  
 2 across pollutants or lags and could not be easily predicted (Ward et al., 2000).

3  
 4 ***Spirometry (FEV<sub>1</sub>)—Adults***

5 Spirometry was used in a large cross-sectional study in Switzerland (Schindler et al.,  
 6 2001). A subset of 3,912 lifetime nonsmoking adults participated in the spirometric lung  
 7 function measurements in the SAPALDIA study (Study of Air Pollution and Lung Diseases in  
 8 Adults). Significant inverse relationships were found between increases in NO<sub>2</sub> and decreases in  
 9 FVC (by 2.74% [95% CI: 0.83, 4.62]) and FEV<sub>1</sub> (by 2.52% [95% CI: 0.49, 4.55]) for a 20-ppb  
 10 increase in NO<sub>2</sub> on the same day as the examination. FEF<sub>25-75</sub> (forced expiratory flow at 25% to  
 11 75% of FVC) was found to decrease by 6.73% (95% CI: 0.038, 13.31) for each 20-ppb increase



**Figure 3.2-2. Effect estimates with 95% confidence intervals for subjects with both reported wheezing and a positive skin test only, calculating for both uncorrected (◇) and corrected (◆) PEF: change in 5-day mean: lag 0 to lag 4 days.**

Source: Ward et al. (2000).

1 in average NO<sub>2</sub> concentration over the previous 4 days. Spirometry was also used in a panel  
 2 study enrolling 29 adults with COPD (n = 11), asthma (n = 11) or IHD (ischemic heart disease,  
 3 n = 7) in Rome (Lagorio et al., 2006). Patients were followed for two 1-month periods during a  
 4 spring and winter. Significant inverse relationships were also found for FEV<sub>1</sub> in this study for  
 5 both COPD and asthmatic patients. For each 20-ppb increase in NO<sub>2</sub> concentration FEV<sub>1</sub>  
 6 decreased by 4.36% (95% CI: 1.18, 7.54) for previous day's NO<sub>2</sub> or by 5.19% (95% CI: 1.58,  
 7 8.80) for the mean of the previous 2 days' NO<sub>2</sub> levels for COPD patients. Decreases were  
 8 similar for asthmatic patients: 4.14% (95% CI: 1.55, 6.73) decrease in FEV<sub>1</sub> for previous day's  
 9 NO<sub>2</sub> concentration and 4.81% (95% CI: 2.09, 7.53) for the mean of the previous 2 days.  
 10 A study of 34 patients with severe COPD in Denver used self-administered, home spirometry

1 measurements to examine the effects of winter air pollution on lung function (Silkoff et al.,  
2 2005). Subjects were enrolled in one of two winters (n = 16 and 18 per winter panel). The  
3 authors observed no adverse effects of ambient air pollution on lung function for the first winter,  
4 but in the second winter did see a significant decrease in morning PEF associated with same day  
5 and previous day NO<sub>2</sub> level (quantitative results not provided).

## 6 7 ***Home-Use Peak Flow Meter Measurements—Adults***

8 Of the studies reviewed that employed portable peak flow meters for subject-measured  
9 lung function, none reported significant associations with NO<sub>2</sub> levels (van der Zee et al., 2000  
10 [489 adults in the Netherlands]; Higgins et al., 1995 [153 adults in the UK including COPD and  
11 asthma patients]; Park et al., 2005a [64 asthmatic adults in Korea]; Hiltermann et al., 1998  
12 [60 asthmatic adults in the Netherlands]; Harre et al., 1997 [40 adults with COPD in New  
13 Zealand]; Forsberg et al., 1998 [38 adult asthmatics in Sweden]; and Higgins et al., 2000  
14 [35 adults in the UK with COPD or asthma]).

## 15 16 **Clinical Studies of Lung Function**

### 17 18 ***Healthy Adults***

19 Studies examining responses of healthy volunteers to acute exposure to NO<sub>2</sub> have  
20 generally failed to show alterations in lung mechanics such as airways resistance (Hackney et al.,  
21 1978; Kerr et al., 1979; Linn et al., 1985a; Mohsenin, 1987a, 1988; Frampton et al., 1991; Kim  
22 et al., 1991; Morrow et al., 1992; Rasmussen et al., 1992; Vagaggini et al., 1996; Azadniv et al.,  
23 1998; Devlin et al., 1999). Exposures ranging from 75 minutes to 5 h at concentrations up to  
24 4.0-ppm NO<sub>2</sub> did not alter pulmonary function. Bylin et al. (1985) found increased airways  
25 resistance after a 20-min exposure to 0.25-ppm NO<sub>2</sub> and decreased airways resistance after a  
26 20-min exposure to 0.5-ppm NO<sub>2</sub>, but no change in airways responsiveness to aerosolized  
27 histamine challenge in the same subjects. These effects have not been confirmed in other  
28 laboratories.

29 Few human clinical studies of NO<sub>2</sub> have included elderly subjects. Morrow et al. (1992)  
30 studied the responses of 20 healthy volunteers, 13 smokers, and 7 nonsmokers, of mean age  
31 61 years, following exposure to 0.3-ppm NO<sub>2</sub> for 4 h with light exercise. There was no  
32 significant change in lung function related to NO<sub>2</sub> exposure for the group as a whole. However,

1 the 13 smokers experienced a slight decrease in FEV<sub>1</sub> during exposure, and their responses were  
2 significantly different from the 7 nonsmokers (% change in FEV<sub>1</sub> at end of exposure:  
3 -2.25 versus +1.25%, p = 0.01). The post-hoc analysis and small numbers of subjects,  
4 especially in the nonsmoking group, limits the interpretation of these findings.

5 The controlled studies reviewed in O<sub>3</sub> AQCD (U.S. Environmental Protection Agency,  
6 2006) generally reported only small pulmonary function changes after combined exposures of  
7 NO<sub>2</sub> or HNO<sub>3</sub> with O<sub>3</sub>, regardless of whether the interactive effects were potentiating or additive.  
8 Hazucha et al. (1994) found that preexposure of healthy women to 0.6-ppm NO<sub>2</sub> for 2 h  
9 enhanced spirometric responses and methacholine airways responsiveness induced by a  
10 subsequent 2-h exposure to 0.3-ppm O<sub>3</sub>, with intermittent exercise. Following a 1-h exposure  
11 with heavy exercise, Adams et al. (1987) found no differences between spirometric responses to  
12 0.3-ppm O<sub>3</sub> and the combination of 0.6-ppm NO<sub>2</sub> + 0.3-ppm O<sub>3</sub>. However, the increase in  
13 airways resistance was significantly less for NO<sub>2</sub> + O<sub>3</sub> than for O<sub>3</sub> alone.

14 Gong et al. (2005) studied 6 healthy elderly subjects (mean age 68 years) and 18 patients  
15 with COPD (mean age 71 years), all exposed to: (a) air, (b) 0.4-ppm NO<sub>2</sub>, (c) ~200 µg/m<sup>3</sup>  
16 concentrated ambient fine particles (CAPs), and (d) CAPs + NO<sub>2</sub>. Exposures were for 2-h with  
17 exercise for 15 min of each half hour. CAPs exposure was associated with small reductions in  
18 mid-expiratory flow rates on spirometry, and reductions in oxygen saturation, but there were no  
19 effects of NO<sub>2</sub> on lung function, oxygen saturation, or sputum inflammatory cells. However, the  
20 exposures were not fully randomized or blinded, and most of the NO<sub>2</sub> exposures took place  
21 months after completion of the CAPs and air exposures. In addition, the small number of healthy  
22 subjects severely limits the statistical power for this group.

23

#### 24 ***Chronic Obstructive Pulmonary Disease Patients***

25 Few studies have examined responses to NO<sub>2</sub> in subjects with chronic obstructive  
26 pulmonary disease (COPD). Hackney et al. (1978) found no lung function effects of exposure to  
27 0.3-ppm NO<sub>2</sub> for 4-h with intermittent exercise in smokers with symptoms and reduced FEV<sub>1</sub>.  
28 In a group of 22 subjects with moderate COPD, Linn et al. (1985b) found no pulmonary effects  
29 of 1-h exposures to 0.5-, 1.0-, or 2.0-ppm NO<sub>2</sub> with 30 min of exercise.

30 In a study by Morrow et al. (1992), 20 subjects with COPD were exposed for 4-h to  
31 0.3-ppm NO<sub>2</sub> in an environmental chamber, with intermittent exercise. Progressive decrements

1 in forced vital capacity (FVC) occurred during the exposure, becoming statistically significant  
2 only at the end of the exposure. The decrements in FVC occurred without changes in flow rates.  
3 These changes in lung function were typical of the “restrictive” pattern seen with O<sub>3</sub> rather than  
4 the obstructive changes described by some studies of NO<sub>2</sub> exposure in asthmatics.

5 Gong et al. (2005) exposed 6 elderly healthy adults and 10 COPD patients to four  
6 separate atmospheres: (a) air, (b) 0.4-ppm NO<sub>2</sub>, (c) ~200-μg/m<sup>3</sup> CAPs, or (d) CAPs + NO<sub>2</sub>. As  
7 noted above, there were no significant effects of NO<sub>2</sub> in either the healthy or the COPD subjects.

### 8 9 *Asthmatic Individuals*

10 Kleinman et al. (1983) evaluated the response of lightly exercising asthmatic subjects to  
11 inhalation of 0.2-ppm NO<sub>2</sub> for 2 h, during which resting minute ventilation doubled. Forced  
12 expiratory flows and airways resistance were not altered by the NO<sub>2</sub> exposure. Bauer et al.  
13 (1986) studied the effects of mouthpiece exposure to 0.3-ppm NO<sub>2</sub> for 30 min (20 min at rest  
14 followed by 10 min of exercise at ~40 L/min) in 15 asthmatics. At this level, NO<sub>2</sub> inhalation  
15 produced significant decrements in forced expiratory flow rates after exercise, but not at rest.  
16 Jörres and Magnussen (1991) found no effects on lung function in 11 patients with mild asthma  
17 exposed to 0.25-ppm NO<sub>2</sub> for 30-min, including 10-min of exercise. However, small reductions  
18 in FEV<sub>1</sub> were observed following 1-ppm NO<sub>2</sub> exposure for 3-h with intermittent exercise in  
19 12 mild asthmatics. Koenig et al. (1994) found no pulmonary function effects of exposure to  
20 0.3-ppm NO<sub>2</sub> in combination with 0.12-ppm O<sub>3</sub>, with or without sulfuric acid (H<sub>2</sub>SO<sub>4</sub>)  
21 (70 μg/m<sup>3</sup>) or HNO<sub>3</sub> (0.05 ppm), in 22 adolescents with mild asthma. However, 6 additional  
22 subjects dropped out of the study citing uncomfortable respiratory symptoms.

23 Jenkins et al. (1999) examined FEV<sub>1</sub> decrements and airways responsiveness to allergen  
24 in a group of mild, atopic asthmatics. The subjects were exposed during rest for 6 h to filtered  
25 air, NO<sub>2</sub> (200 ppb), O<sub>3</sub> (100 ppb), or NO<sub>2</sub> (200 ppb) + O<sub>3</sub> (100 ppb). The subjects were also  
26 exposed for 3 h to NO<sub>2</sub> (400 ppb), O<sub>3</sub> (200 ppb), or NO<sub>2</sub> (400 ppb) + O<sub>3</sub> (200 ppb) to provide  
27 doses identical to those in the 6-h protocols (i.e., equal C × T). Immediately following the 3-h  
28 exposure, but not after the 6-h exposure, there were significant decrements in FEV<sub>1</sub> following  
29 O<sub>3</sub> and NO<sub>2</sub> + O<sub>3</sub> exposures.

30

1 **Summary**

2 Epidemiological studies using data from supervised lung function measurements or  
3 spirometry report small decrements in lung function (Hoek and Brunekreef, 1994; Linn et al.,  
4 1996; Schindler et al., 2001) or peak flow meters (Peacock et al., 2003). Each 20-ppb increase in  
5 same-day NO<sub>2</sub> concentration was associated with FVC deficits of 0.3% (Linn et al., 1996) to  
6 2.7% (Schindler et al., 2001). No significant associations were reported in any studies using  
7 unsupervised, self-administered peak flow measurements with portable devices.

8 Clinical studies have not provided compelling evidence of NO<sub>2</sub> effects on pulmonary  
9 function. Acute exposures of young, healthy volunteers to NO<sub>2</sub> at levels as high as 4.0 ppm do  
10 not alter lung function as measured by spirometry or airways resistance. The small number of  
11 studies of COPD patients prevents any conclusions about effects on pulmonary function. The  
12 Morrow et al. (1992) study, performed in Rochester, NY, suggested restrictive type effects of  
13 0.3-ppm NO<sub>2</sub> exposure for 4 h. However, three other studies, performed in Southern California  
14 at similar exposure concentrations, found no effects. The contrasting findings in these studies  
15 may, in part, reflect the difference in duration of exposure or the differing levels of background  
16 ambient air pollution to which the subjects were exposed chronically, as there were much lower  
17 background levels in Rochester, NY than in Southern California. For asthmatics, the effects of  
18 NO<sub>2</sub> on pulmonary function have also been inconsistent at exposure concentrations of less than  
19 1-ppm NO<sub>2</sub>. Overall, clinical studies have failed to show effects of NO<sub>2</sub> on pulmonary function  
20 at exposure concentrations relevant to ambient exposures. However, highly variable findings in  
21 COPD and asthmatic patients suggest that some individuals may be particularly susceptible to  
22 NO<sub>2</sub> effects.

23

24 **3.2.1.3 Respiratory Symptoms**

25 Since the 1993 AQCD, results have been published from several single-city and multicity  
26 studies, including three large longitudinal studies in urban areas covering the continental United  
27 States and southern Ontario: the Harvard Six Cities study (Six Cities; Schwartz et al., 1994), the  
28 National Cooperative Inner-City Asthma Study (NCICAS; Mortimer et al., 2002), and the  
29 Childhood Asthma Management Program (CAMP; Schildcrout et al., 2006). Because of similar  
30 analytic techniques (i.e., multistaged modeling and generalized estimating equations [GEE]), one  
31 strength of all three of these studies is that, as Schildcrout et al. (2006) stated, they could each be  
32 considered as a meta-analysis of “large, within-city panel studies” without some of the

1 limitations associated with meta-analyses, e.g., “between-study heterogeneity and obvious  
2 publication bias.”

3 The report from the Six Cities study includes 1,844 schoolchildren who were followed  
4 for 1 year (Schwartz et al., 1994). Symptoms (in 13 categories, analyzed as cough, lower or  
5 upper respiratory symptoms), were recorded daily. Cities included Watertown (MA), Baltimore,  
6 Kingston-Harriman (TN), Steubenville, Topeka, and Portage (WI). In Mortimer et al. (2002),  
7 864 asthmatic children were followed daily for four 2-week periods over the course of 9 months.  
8 The eight NCICAS cities were New York City (Bronx, E. Harlem), Baltimore, Washington  
9 (DC), Cleveland, Detroit, St Louis, and Chicago. Morning and evening asthma symptoms  
10 (analyzed as none versus any) and peak flow were recorded. Schildcrout et al. (2006) reported  
11 on 990 asthmatic children living within 50 miles of one of 31 NO<sub>2</sub> monitors located in eight  
12 North American cities (Boston, Baltimore, Toronto, St. Louis, Denver, Albuquerque, San Diego,  
13 and Seattle). Symptoms (analyzed as none versus any per day) and rescue medication use  
14 (analyzed as number of uses per day) were recorded daily for 2 months. All three studies found  
15 significant associations between level of NO<sub>2</sub> exposure and risk of respiratory symptoms in  
16 children (Schwartz et al., 1994), and in particular, asthmatic children (Mortimer et al., 2002;  
17 Schildcrout et al., 2006).

18 In Schwartz et al. (1994), a significant association was found between a 4-day mean of  
19 NO<sub>2</sub> exposure and incidence of cough among all children in single-pollutant models: the odds  
20 ratio (OR) was reported for each 10-ppb increase in NO<sub>2</sub> as OR = 1.27 (95% CI: 1.04, 1.56)  
21 (given in Annex Table AX6.2 for a 20-ppb increase). Cough incidence was not significantly  
22 associated with NO<sub>2</sub> on the previous day. The local nonparametric smooth of the 4-day mean  
23 concentration showed increased (p = 0.01) cough incidence up to approximately the mean  
24 concentration (~13 ppb), after which no further increase was observed. The significant  
25 association between cough and 4-day mean NO<sub>2</sub> remained unchanged in models that included  
26 O<sub>3</sub>, but was attenuated and lost significance in two-pollutant models including PM<sub>10</sub> (OR for  
27 10-ppb increase in NO<sub>2</sub> = 1.17 [95% CI: 0.94, 1.46]) or SO<sub>2</sub> (OR for NO<sub>2</sub> = 1.19 [95% CI: 0.95,  
28 1.51]).

29 In Mortimer et al. (2002), the greatest effect of the pollutants studied for morning  
30 symptoms was for a 6-day moving average. For increased NO<sub>2</sub>, the risk of any asthma  
31 symptoms (cough, wheeze, shortness of breath) among the asthmatic children in the NCICAS

1 was somewhat higher than for the healthy children in the Six Cities study: OR = 1.48 (95% CI:  
2 1.02, 2.16). Effects were attenuated in multipollutant models that included O<sub>3</sub> (OR for 20-ppb  
3 increase in NO<sub>2</sub> = 1.40 [95% CI: 0.93, 2.09]), O<sub>3</sub> and SO<sub>2</sub> (OR for NO<sub>2</sub> = 1.31 [95% CI: 0.87,  
4 2.09]), or O<sub>3</sub>, SO<sub>2</sub>, and PM<sub>10</sub> (OR for NO<sub>2</sub> = 1.45 [95% CI: 0.63, 3.34]).

5 In the CAMP study (Shildcrout et al., 2006), the strongest association between NO<sub>2</sub> and  
6 increased risk of cough was found for a 2-day lag: each 20-ppb increase in NO<sub>2</sub> occurring 2 days  
7 before measurement increased risk of cough (OR = 1.09 [95% CI: 1.03, 1.15]). Two-pollutant  
8 models including CO, PM<sub>10</sub>, or SO<sub>2</sub> produced similar results. (See Figure 3.2-3.) Further,  
9 increased NO<sub>2</sub> exposure was associated with increased use of rescue medication in the CAMP  
10 study, with the strongest association for a 2-day lag, both for single- and multipollutant models  
11 (e.g., for an increase of 20-ppb NO<sub>2</sub> in the single-pollutant model, the RR for increased inhaler  
12 usage was 1.05 (95% CI: 1.01, 1.09)). (See Figure 3.2-4.)

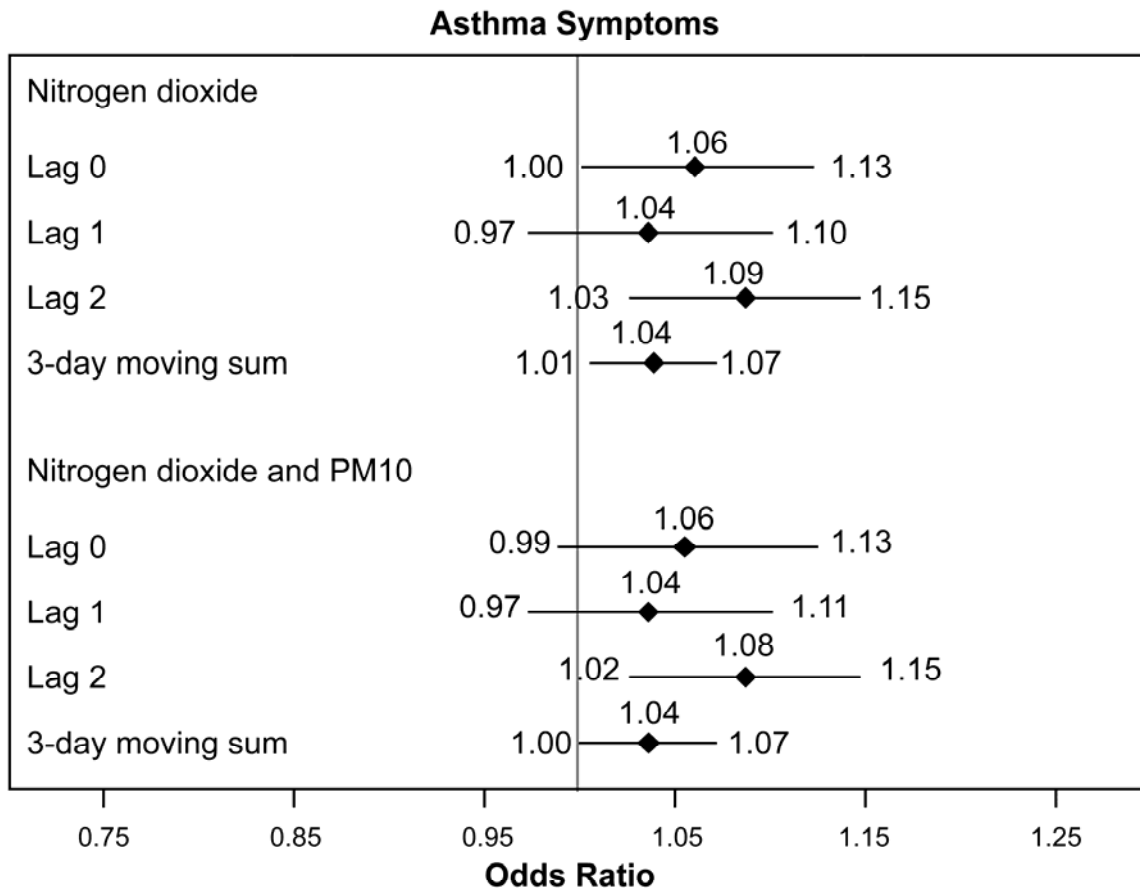
13 Two 3-month-long panel studies recruited asthmatic children from the one outpatient  
14 clinic in Paris: one study followed 84 children in the fall of 1992 (Segala et al., 1998), and the  
15 other followed 82 children during the winter of 1996 (Just et al., 2002). GEE in logistic  
16 regression analyses found significant associations between respiratory symptoms and level of  
17 NO<sub>2</sub> and are shown in Annex Table AX6.2 for each 20-ppb increase in NO<sub>2</sub>. No multipollutant  
18 models were shown.

19 In metropolitan Sydney, 148 children with a history of wheeze were followed for  
20 11 months (Jalaludin et al., 2004). Daily symptoms, medication use, and doctor visits were  
21 examined. In regression models using GEE, significant associations were found between  
22 increased likelihood of wet cough and each 8.2-ppb increase in NO<sub>2</sub> (OR = 1.05 [95% CI: 1.00,  
23 1.10]). The authors report that estimates did not change in multipollutant models including O<sub>3</sub> or  
24 PM<sub>10</sub>. Ward et al. (2002) examined respiratory symptoms in a panel of 162 children in the  
25 United Kingdom.

26 No significant associations were reported for the winter period, but a significant  
27 association was reported for the summer period for cough and NO<sub>2</sub> (lag 0; OR = 1.09 [95% CI:  
28 1.17, 1.01]).

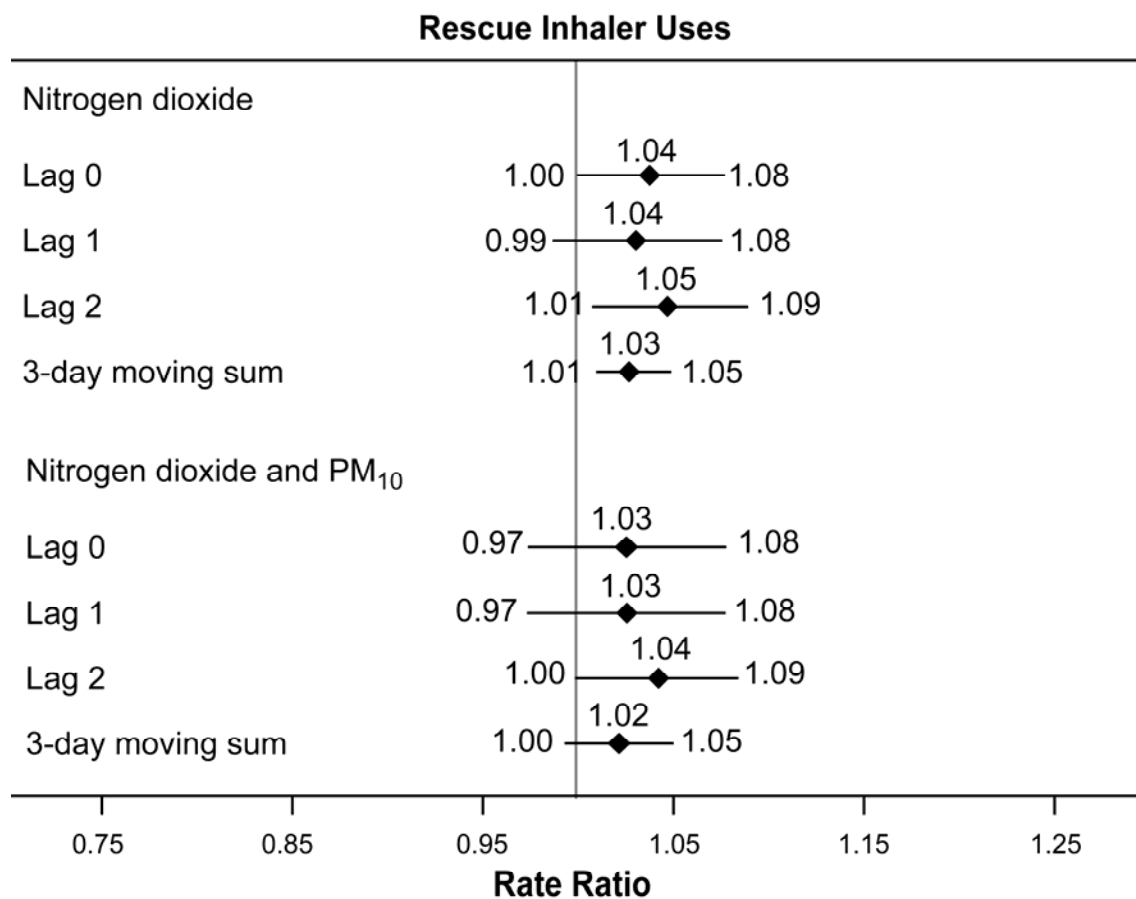
29 For adults, most studies examining associations between ambient NO<sub>2</sub> pollution and  
30 respiratory symptoms were conducted in Europe. Various studies have enrolled older adults





**Figure 3.2-3. Results for single- and two-pollutant models: Childhood Asthma Management Program, November 1993-September 1995. Odds ratios for daily asthma symptoms associated with shifts in within-subject concentrations.**

Source: Schildcrout et al. (2006).



**Figure 3.2-4. Results for single- and two-pollutant models: Childhood Asthma Management Program, November 1993-September 1995. Odds ratios for daily rescue inhaler use associated with shifts in within-subject concentrations. All city-specific estimates of pollutant effects were included in calculations of study-wide effects except nitrogen dioxide in Seattle, Washington. Horizontal lines represent the 95% confidence interval (with limits specified at ends).**

Source: Schildcrout et al. (2006).

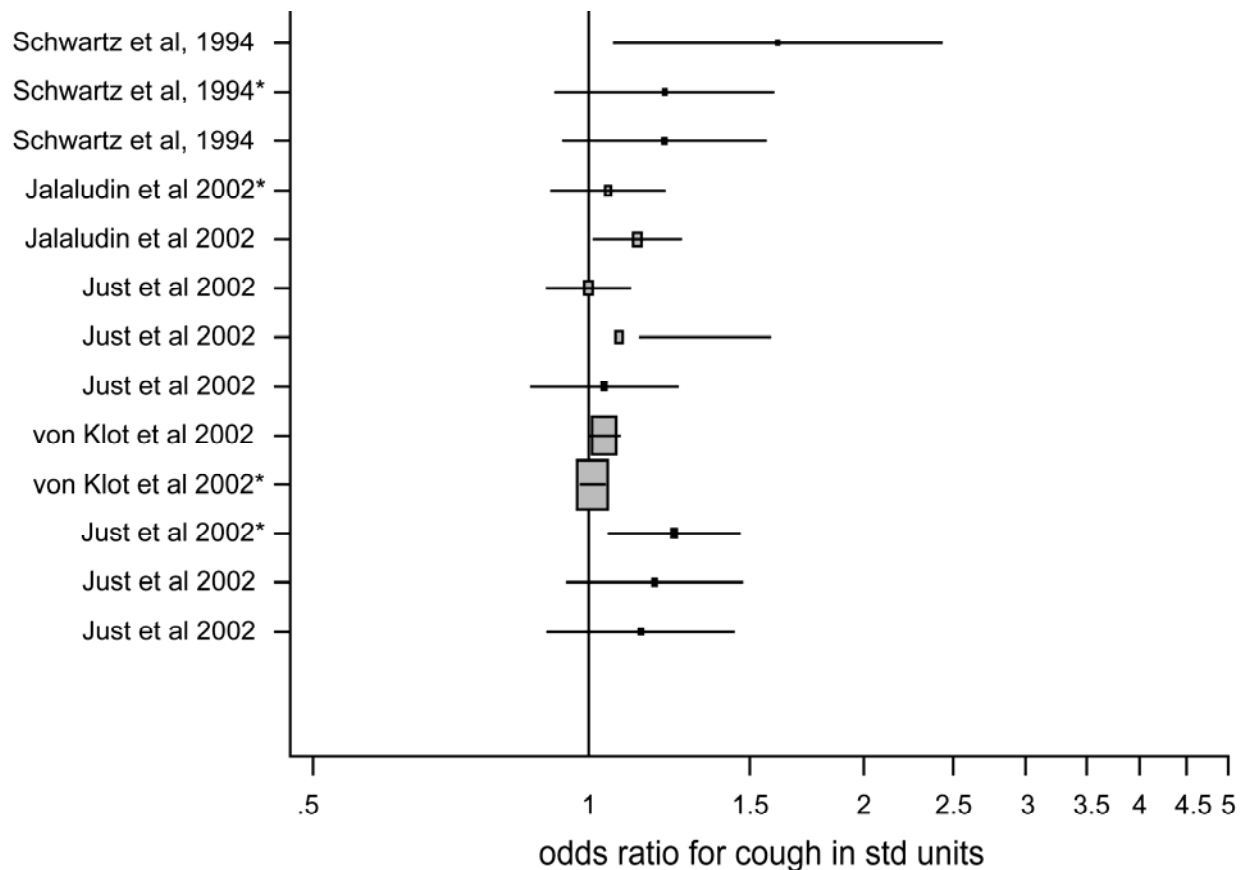
- 1 (van der Zee et al., 2000; Harre et al., 1997; Silkoff et al., 2005), nonsmoking adults (Segala
- 2 et al., 2004), patients with COPD (Higgins et al., 1995; Desqueyroux et al., 2002), bronchial
- 3 hyperresponsiveness (Boezen et al., 1998), or asthma (Hiltermann et al., 1998; Forsberg et al.,
- 4 1998; von Klot et al., 2002). Associations were found between NO<sub>2</sub> and either respiratory
- 5 symptoms or inhaler use in a number studies (van der Zee et al., 2000; Harre et al., 1997; Silkoff

1 et al., 2005; Segala et al., 2004; Hiltermann et al., 1998), but not in all studies (Desqueyroux  
2 et al., 2002; von Klot et al., 2002).

3  
4 ***Summary Analysis Methodology of Respiratory Symptom Studies***

5 Of the ambient exposure studies reviewed above, it is striking that the studies using  
6 generalized estimating equations (GEE) in the analysis also report significant associations  
7 between daily exposure to NO<sub>2</sub> and respiratory effects (see list of these studies in Annex  
8 Table AX6.2). It is possible that the development of the GEE extension to generalized linear  
9 models (GLM) for analysis of longitudinal data (Liang and Zeger, 1986) and subsequent  
10 availability of GEE in statistical analysis packages permitted a much more accurate estimate of  
11 within-subjects variability in repeated-measures designs. This may explain, in part, why so  
12 many of the studies using GEE in the analysis show associations between daily exposure and  
13 symptoms, while other studies using alternative methods to estimate (and perhaps overestimate)  
14 autocorrelation do not (e.g., Roemer et al., 1998 and the PEACE study). Among the studies  
15 using GEE, with the exception of Mortimer et al. (2002) where the strongest association was  
16 with a mean of the previous 6 days, studies enrolling asthmatics, children or adults, found  
17 significant associations between ambient NO<sub>2</sub> exposure and respiratory symptoms for lags of  
18 0, 1, or 2 days (see Annex Table AX6.2). Interestingly, for the three studies enrolling healthy  
19 subjects (Schwartz et al., 1994; Pino et al., 2004; Segala et al., 2004) significant associations are  
20 only found for longer lag times (of 4 to 6 days). All significant associations between ambient  
21 NO<sub>2</sub> and respiratory symptoms occurred in locations with 24-h average NO<sub>2</sub> levels below the  
22 annual EPA standard of 53 ppb.

23 Odds ratios and 95% confidence limits for associations with cough and asthma symptoms  
24 in children are presented in Figures 3.2-5 and 3.2-6, respectively. These figures are called forest  
25 plots, and the area of the square denoting the odds ratio is the proportional to the weight of the  
26 study. When combined in a random effect meta-analysis, the results for cough showed a  
27 significant association with NO<sub>2</sub> exposure (OR = 1.09 [95% CI: 1.05, 1.24]; p value in test for  
28 heterogeneity = 0.110). For asthma symptoms, the combined odds ratio from a meta-analysis  
29 was 1.14, (95% CI: 1.05, 1.24), and the test for heterogeneity had a p value of 0.055. The  
30 effects used in the analysis were selected as follows. Those studies having 0 lag were preferred  
31 to 1-day lags and moving averages, longer single-day lags were not included; if a study had both

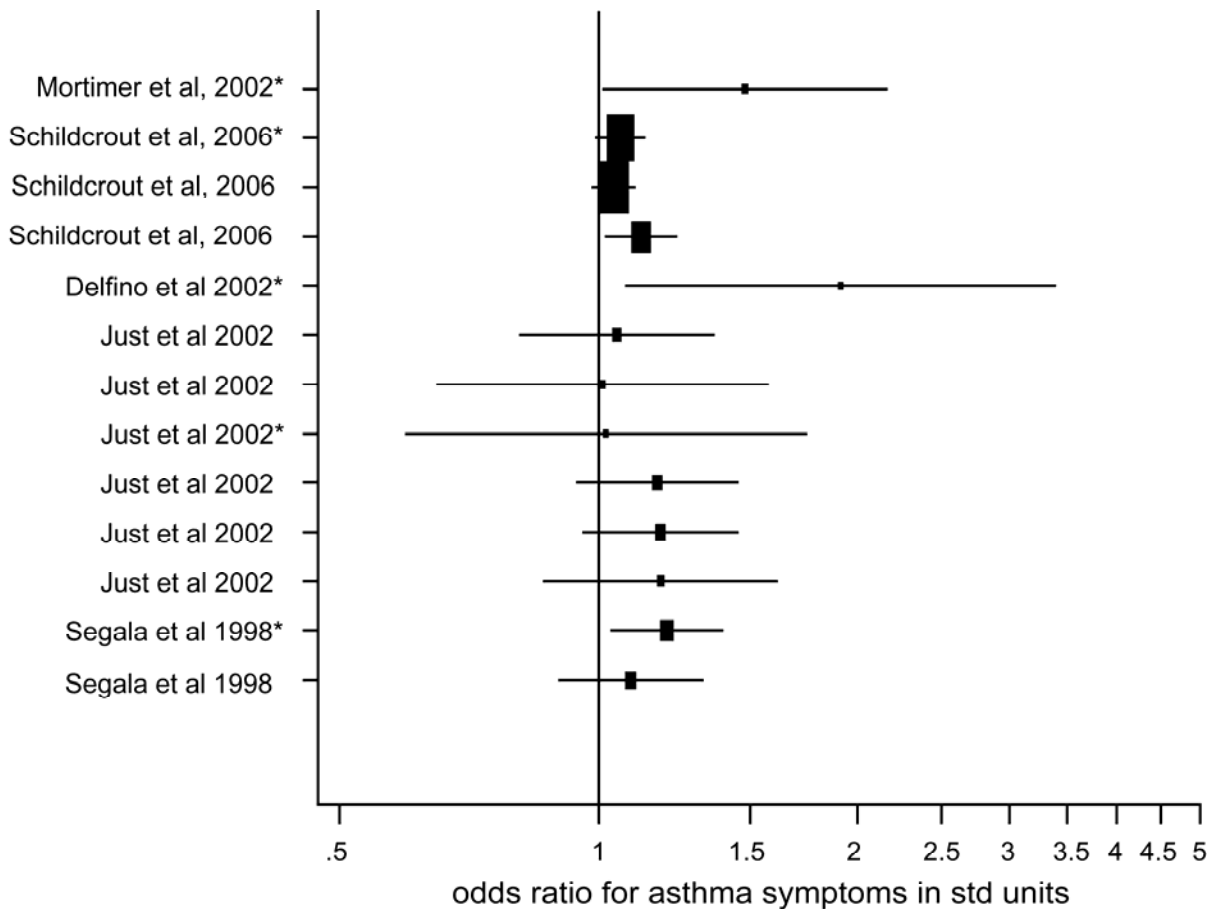


**Figure 3.2-5. Odds ratios (95% CI) for associations between cough and 24-h average NO<sub>2</sub> concentrations (per 20 ppb).**

**Schwartz et al. (1994): incidence; lags: 1-4 day moving average 0, and 1. Jalaludin et al. (2002): prevalence; dry cough, wet cough; lags 0, 0, 0. Just et al. (2002): prevalence; nocturnal cough; lags 0, 0-2, 0-4 day moving average, 0. Von Klot et al. (2002): prevalence; cough; lags 1-5 day moving average, 0. Just et al. (2002): incidence; nocturnal cough; lags 0, 0-2, 0-4. The effects used in the meta-analysis are denoted by \*.**

1 incidence and prevalence, then the incidence effect was to be used; and “dry cough” was  
 2 preferred to “wet cough.”

3 The results of multipollutant analyses for the three U.S. multicity studies are presented in  
 4 Figure 3.2-7. Associations with NO<sub>2</sub> were generally robust to adjustment for copollutants, as  
 5 stated previously. Odds ratios were often unchanged with the addition of copollutants, though



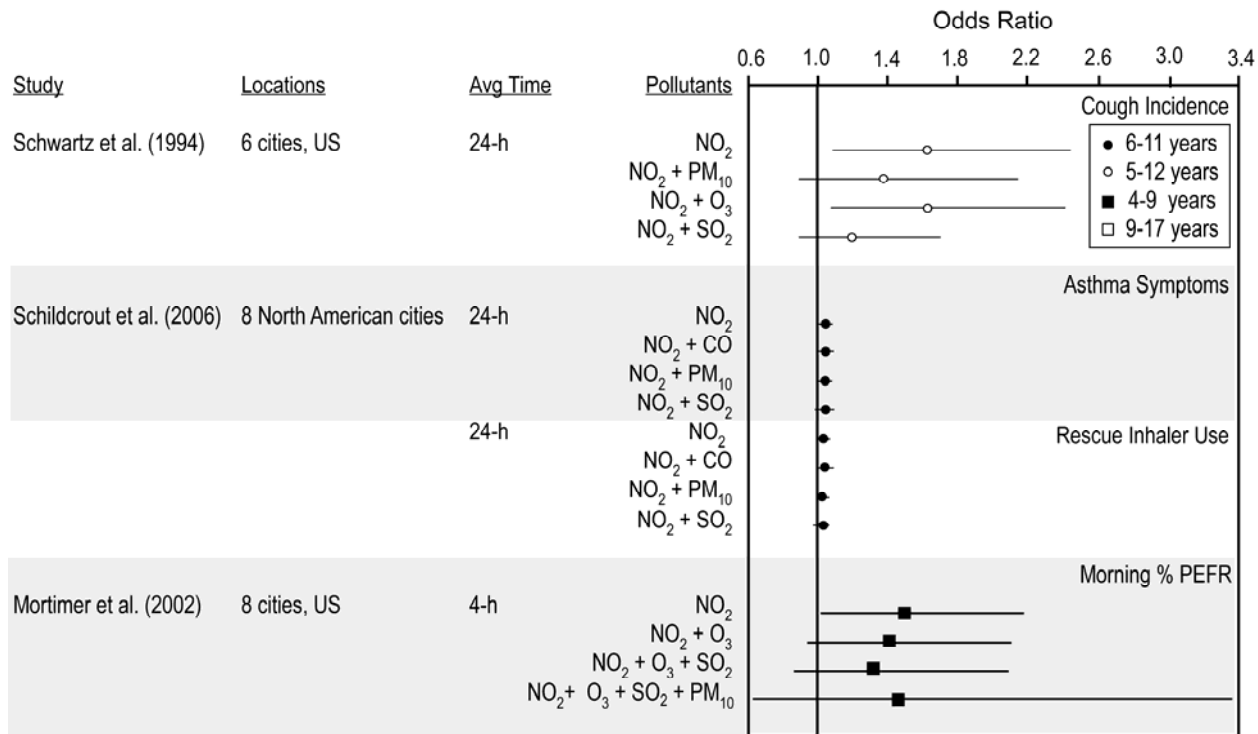
**Figure 3.2-6. Odds ratios (95% CI) for associations between asthma symptoms and 24-h average NO<sub>2</sub> concentrations (per 20 ppb).**

**Mortimer et al. (2002): prevalence; lag: 1-6 day moving average.**  
**Schildcrout et al. (2006): prevalence; lags 0, 1, 3 day moving average.**  
**Delfino et al. (2002): prevalence; lag 0. Just et al. (2002): prevalence;**  
**lags 0, 0-2, 0-4; incidence; lags 0, 0-2, 0-4. Segala et al. (1998): incidence;**  
**lags 0, 1. The effects used in the meta-analysis are denoted by \*.**

1 reductions in magnitude are apparent in certain models, such as with adjustment for SO<sub>2</sub> in the  
 2 Six Cities study results (Schwartz et al., 2004).

3  
 4 ***School Absence***

5 The few studies available that used school absence as a health endpoint did not find a  
 6 significant association with increased levels of ambient NO<sub>2</sub> (Gilliland et al., 2001; Rondeau



**Figure 3.2-7. Odds ratios and 95% confidence intervals for associations between asthma symptoms and 24-h average NO<sub>2</sub> concentrations (per 20 ppb) from multipollutant models. Details about effects from the top of the figure to the bottom entries are: Mortimer et al. (2002): prevalence; lag: 1-6 day moving average. Schildcrout et al. (2006): prevalence; lags 0, 1, 3 day moving average. Delfino et al. (2002): prevalence; lag 0. Just et al. (2002): prevalence; lags 0, 0-2, 0-4; incidence; lags 0, 0-2, 0-4. Segala et al. (1998): incidence; lags 0, 1.**

1 et al., 2005; Park et al., 2002). As part of the Children's Health Study, Gilliland et al. (2001)  
 2 examined school absence among 2,081 schoolchildren in 12 communities in Southern California  
 3 and found significant associations between 20-ppb increases in O<sub>3</sub> and respiratory illness related  
 4 absences, but no association in single-pollutant models with NO<sub>2</sub> or PM<sub>10</sub>. Annual mean daily  
 5 NO<sub>2</sub> in the 12 communities ranged from 5 to 45 ppb. Park et al. (2002) studied school  
 6 absenteeism in an elementary school in Seoul, Korea, and found significant risks associated with  
 7 increases of PM<sub>10</sub> (RR = 1.06 [95% CI: 1.04, 1.09] for each 42.1- $\mu\text{g}/\text{m}^3$  increase), SO<sub>2</sub>  
 8 (RR = 1.09 [95% CI: 1.07, 1.12] for each 5.68-ppb increase), and O<sub>3</sub> (RR = 1.08 [95% CI: 1.06,

1 1.11] for each 15.94-ppb increase) but none with NO<sub>2</sub> (although there is a suggestion of an  
2 association with an RR of 1.02 (95% CI: 0.99, 1.04) for each 14.51-ppb increase).

3  
4 **Summary**

5 Taken together, these studies indicate that short-term exposure to NO<sub>2</sub> is associated with  
6 respiratory symptoms in children and adults. For children, the results of new multicity studies  
7 provide substantial support for associations with respiratory symptoms, particularly in asthmatic  
8 children. In adults, the recent studies link short-term NO<sub>2</sub> exposure with various respiratory  
9 symptoms or medication use, but the findings are not always consistent.

10  
11 **3.2.1.4 Airways Inflammation**

12  
13 **Epidemiological Studies of Airways Inflammation**

14 A number of studies have examined biological markers for inflammation (exhaled NO  
15 and inflammatory nasal lavage [NAL] markers [Steerenberg et al., 2001, 2003]; exhaled NO  
16 [Adamkiewicz et al., 2004]) and lung damage (urinary Clara cell protein CC16 [Timonen et al.,  
17 2004]). Steerenberg et al. (2001) studied 126 schoolchildren from urban and suburban  
18 communities in the Netherlands. Sampling of exhaled air and NAL fluid was performed seven  
19 times, once per week over the course of 2 months. On average, the ambient NO<sub>2</sub> levels were  
20 1.5 times higher and ambient NO levels 7.8 times higher in the urban compared to suburban  
21 community. Compared to children in the suburban community, urban children had significantly  
22 greater levels of inflammatory NAL markers (IL-8, urea, uric acid, albumin) but not greater  
23 levels of exhaled NO. However, within the urban group, a concentration-response relationship  
24 was seen. For increases of 20 ppb in NO<sub>2</sub> lagged by 1 or 3 days, exhaled NO increased  
25 significantly by 6.4 to 8.8 ppb. Exhaled NO also increased for suburban children versus  
26 comparable increases in NO<sub>2</sub>, but not significantly. Another study by Steerenberg et al. (2003)  
27 of 119 schoolchildren in the Netherlands found associations between ambient NO<sub>2</sub> and level of  
28 exhaled NO, but quantitative regression results are not given. The authors concluded from their  
29 data that an established, ongoing inflammatory response to pollen was not exacerbated by  
30 subsequent exposure to high levels of air pollution or pollen Steerenberg et al., (2003).  
31 Adamkiewicz et al. (2004) studied 29 elderly adults in Steubenville and found significant

1 associations between increased exhaled NO and increased daily levels of PM<sub>2.5</sub>, but no  
2 association was found with ambient NO<sub>2</sub>.

3 Timonen et al. (2004) collected biweekly urine samples for 6 months from 131 adults  
4 with coronary heart disease living in Amsterdam, Helsinki, and Erfurt, Germany. Estimates  
5 using data from all three communities showed significant associations between urinary levels of  
6 Clara cell protein CC16 (a marker for lung damage) with elevations in daily PM<sub>2.5</sub> concentration,  
7 but not ambient NO<sub>2</sub>. In Helsinki, however, there was a significant association between a  
8 10- $\mu\text{g}/\text{m}^3$  increase in NO<sub>2</sub> lagged by 3 days and a 9.2% increase (95% CI: 0.1, 18.3) in  
9 ln(CC16). Interestingly, the correlation between NO<sub>2</sub> and PM<sub>2.5</sub> was lower in Helsinki ( $r = 0.35$ )  
10 compared to this correlation in Amsterdam ( $r = 0.49$ ) or Erfurt ( $r = 0.82$ ).

11 Bernard et al. (1998) examined personal exposure to NO<sub>2</sub> and its effect on plasma  
12 antioxidants in a group of 107 healthy adults in Montpellier, France. Subjects wore passive  
13 monitors for 14 days. When subjects were divided into two exposure groups (above and below  
14 40  $\mu\text{g}/\text{m}^3$  [21.3 ppb]), those in the high-exposure group had significantly lower plasma  
15  $\beta$ -carotene levels. This difference was even greater when analysis was stratified by dietary  
16  $\beta$ -carotene intake: exposure to >40- $\mu\text{g}/\text{m}^3$  NO<sub>2</sub> had the largest effect on plasma  $\beta$ -carotene level  
17 among subjects who ate <4 mg/day  $\beta$ -carotene ( $p < 0.005$ ). No other pollutants were included in  
18 this study.

19

## 20 **Clinical Studies of Airways Inflammation**

21

### 22 *Healthy Adults*

23 Helleday et al. (1994) performed BAL before and 24 h after exposure to 3.5-ppm NO<sub>2</sub> for  
24 20 min, with 15 min of light exercise in 8 smokers and 8 nonsmokers. The recovery of PMNs in  
25 the bronchial portion of BAL was slightly increased in the nonsmokers, while only the alveolar  
26 portion showed increased PMN numbers in smokers. A significant weakness of this study was  
27 the failure to include a true air exposure with a randomized, double-blind design.

28 The 1993 AQCD for Oxides of Nitrogen cited preliminary findings from two studies  
29 showing modest airways inflammation, as indicated by increased PMN numbers in BAL fluid  
30 after exposure to 2.0-ppm NO<sub>2</sub> for 4 to 6-h with intermittent exercise. Both of those studies have  
31 now been published in complete form Azadniv et al. (1998); Devlin et al. (1999), and additional



1 studies summarized below provided a clearer picture of the airways inflammatory response to  
2 NO<sub>2</sub> exposure.

3 Healthy volunteers exposed to 2.0-ppm NO<sub>2</sub> for 6-h with intermittent exercise (Azadniv  
4 et al., 1998) showed a slight increase in the percentage of PMNs obtained in BAL fluid 18-h  
5 after exposure (air, 2.2 ± 0.3%; NO<sub>2</sub>, 3.1 ± 0.4%). In a separate group of subjects exposed using  
6 the same protocol but assessed immediately after exposure Gavras et al., (1994), no effects were  
7 found in AM phenotype or expression of the cell adhesion molecule CD11b or receptors for IgG.  
8 Blomberg et al. (1997) reported that 4-h exposures to 2.0-ppm NO<sub>2</sub> resulted in an increase in  
9 IL-8 and PMNs in the proximal airways of healthy subjects, although no changes were seen in  
10 bronchial biopsies. This group also studied the effects of repeated 4-h exposures to 2-ppm NO<sub>2</sub>  
11 on 4 consecutive days, with BAL, bronchial biopsies, and BAL fluid antioxidant levels assessed  
12 1.5-h after the last exposure Blomberg et al., (1999). The bronchial wash fraction of BAL fluid  
13 showed a 2-fold increase in PMNs and a 1.5-fold increase in myeloperoxidase, indicating  
14 persistent mild airways inflammation with repeated NO<sub>2</sub> exposure.

15 Devlin et al. (1999) exposed 8 healthy nonsmokers to 2.0-ppm NO<sub>2</sub> for 4-h with  
16 intermittent exercise. BAL performed the following morning showed a 3.1-fold increase in  
17 PMNs recovered in the bronchial fraction, indicating small airways inflammation. These  
18 investigators also observed a reduction in AM phagocytosis and superoxide production,  
19 indicating possible adverse effects on host defense.

20 Pathmanathan et al. (2003) conducted four repeated daily exposures of healthy subjects to  
21 4-ppm NO<sub>2</sub> or air for 4 h, with intermittent exercise. Exposures were randomized and separated  
22 by 3 weeks. Bronchoscopy and bronchial biopsies were performed 1-h after the last exposure.  
23 Immunohistochemistry of the respiratory epithelium showed increased expression of IL-5, IL-10,  
24 and IL-13, as well as intercellular adhesion molecule-1 (ICAM-1). These interleukins are  
25 upregulated in Th2 inflammatory responses, which are characteristic of allergic inflammation.  
26 The findings suggest repeated NO<sub>2</sub> exposures may drive the airways inflammatory response  
27 toward a Th2 or allergic-type response. Unfortunately, the report provided no data on  
28 inflammatory cell responses in the epithelium or on cells or cytokines in BAL fluid. Thus, the  
29 findings cannot be considered conclusive regarding allergic inflammation. Furthermore, the  
30 exposure concentrations of 4 ppm are considerably higher than ambient outdoor concentrations.

1           Recent studies provide evidence for airways inflammatory effects at concentrations  
2 <2.0 ppm. Frampton et al. (2002) examined NO<sub>2</sub> concentration responses in 21 healthy  
3 nonsmokers. Subjects were exposed to air or 0.6- or 1.5-ppm NO<sub>2</sub> for 3 h, with intermittent  
4 exercise, with exposures separated by at least 3 weeks. BAL was performed 3.5-h after  
5 exposure. PMN numbers in the bronchial lavage fraction increased slightly (<3-fold) but  
6 significantly (p = 0.0003) after exposure to 1.5-ppm NO<sub>2</sub>; no increase was evident at 0.6-ppm  
7 NO<sub>2</sub>. Lymphocyte numbers increased in the bronchial lavage fraction after 0.6-ppm NO<sub>2</sub>, but  
8 not 1.5 ppm. CD4<sup>+</sup> T lymphocyte numbers increased in the alveolar lavage fraction, and  
9 lymphocytes decreased in blood. These findings suggest a lymphocytic airways inflammatory  
10 response to 0.6-ppm NO<sub>2</sub>, which changes to a mild neutrophilic response at 1.5-ppm NO<sub>2</sub>.

11           Jörres et al. (1995) found that 3-h exposures to 1-ppm NO<sub>2</sub> with intermittent exercise  
12 altered levels of eicosanoids, but not inflammatory cells, in BAL fluid collected 1-h after  
13 exposure. Eicosanoids are chemical mediators of the inflammatory response; their increase in  
14 BAL fluid in this study suggests inflammation. The absence of an increase in PMN numbers  
15 may reflect the timing of bronchoscopy (1 h after exposure). The peak influx of PMNs may  
16 occur several hours after exposure, as it does following O<sub>3</sub> exposure.

17           The studies summarized in this section provide evidence for airways inflammation at  
18 NO<sub>2</sub> concentrations of <2.0 ppm; separately analyzing the bronchial fraction of BAL appears to  
19 increase the sensitivity for detecting airways inflammatory effects of NO<sub>2</sub> exposure. The onset  
20 of inflammatory responses in healthy subjects appears to be between 100 and 200 ppm-min, i.e.,  
21 1 ppm for 2 to 3 h.

22

### 23 ***Toxicological Studies of Airways Inflammation***

24           Numerous studies demonstrate changes in protein and enzyme levels in the lung  
25 following inhalation of NO<sub>2</sub> (see Annex Table AX4.2). These observations reflect the ability of  
26 NO<sub>2</sub> to cause lung inflammation associated with concomitant infiltration of serum protein,  
27 enzymes, and inflammatory cells. However, interpretation of the array of changes observed may  
28 also reflect other factors. For example, NO<sub>2</sub> exposure may induce differentiation of some cell  
29 populations in response to damage-induced tissue remodeling. Thus, some changes in lung  
30 enzyme activity and protein content may reflect changes in cell types, rather than the direct  
31 effects of NO<sub>2</sub> on protein infiltration. Furthermore, some direct effects of NO<sub>2</sub> on enzymes are

1 possible because NO<sub>2</sub> can oxidize certain reducible amino acids or side chains of proteins in  
2 aqueous solution (Freeman and Mudd, 1981).

3         Increased BAL fluid protein levels have been observed at low concentrations of NO<sub>2</sub>.  
4 Exposure to 752-μg/m<sup>3</sup> (0.4 ppm) NO<sub>2</sub> continuously for 1 week resulted in increases in BAL  
5 protein in vitamin c-deficient guinea pigs (Sherwin and Carlson, 1973). A slight increase in  
6 albumin, indicating a mild degree of injury to the pulmonary capillary membrane, was observed  
7 in mice exposed to 9400-μg/m<sup>3</sup> (5.0 ppm) NO<sub>2</sub>, 6 h/day for 6 days Rose et al., (1989). Guinea  
8 pigs demonstrated significantly increased lactate dehydrogenase (LDH) content of the lower  
9 lobes of the lung following exposure to 3760-μg/m<sup>3</sup> (2.0 ppm) NO<sub>2</sub> for 1, 2, or 3 weeks Sherwin  
10 et al., (1972). However, in rats, increases in LDH in BAL fluid were noted at exposure to 1880  
11 to 9400-μg/m<sup>3</sup> (1.0 to 5.0 ppm) NO<sub>2</sub>, 7-h/day, 5-days/week for 2.7 weeks, but values returned to  
12 control levels after 15 weeks of exposure while histological changes persisted (Gregory et al.,  
13 1983).

14         Numerous studies in rats and mice published since the 1993 AQCD for Oxides of  
15 Nitrogen have investigated the ability of NO<sub>2</sub> to induce protein level changes consistent with  
16 inflammation. Muller et al. (1994) exposed rats to 0, 0.8-, 5-, or 10-ppm NO<sub>2</sub> continuously for 1  
17 or 3 days and reported that BAL protein content significantly increased in a concentration- and  
18 exposure duration-dependent manner, with the change becoming significant at 5 ppm for 3 days  
19 and at 10 ppm for ≥1 day of exposure. Pagani et al. (1994) exposed rats to 0, 9-, or 18-mg/m<sup>3</sup> (0,  
20 5, or 10 ppm) NO<sub>2</sub>, 24 h or 24-h/day for 7 days. In their study, protein content in BAL fluid  
21 increased significantly only after 24 h of exposure to 10-ppm NO<sub>2</sub>.

22         Overall, these newer studies suggest that markers of inflammation measured in BAL fluid  
23 such as total protein content and content of markers of cell membrane permeability (e.g., LDH)  
24 increase only at or above 5-ppm exposure. Based on the new studies, rats and mice appear to  
25 respond in a similar fashion.

26         It has also been reported that protein content changes in BAL fluid can be dependent on  
27 dietary antioxidant status, further clouding the interpretation of such effects. NO<sub>2</sub> exposure  
28 increases the protein content of BAL fluid in vitamin C-deficient guinea pigs at NO<sub>2</sub> levels as  
29 low as 1880 μg/m<sup>3</sup> (1.0 ppm) after a 72-h exposure, but a 1-week exposure to 752 μg/m<sup>3</sup>  
30 (0.4 ppm) did not increase protein levels (Selgrade et al., 1981). The results of this 1-week  
31 exposure apparently conflict with those of Sherwin and Carlson (1973), who found increased

1 protein content of BAL fluid from vitamin C-deficient guinea pigs exposed to 752- $\mu\text{g}/\text{m}^3$   
2 (0.4 ppm)  $\text{NO}_2$  for 1 week. Differences in exposure techniques, protein measurement methods,  
3 and/or degree of vitamin C deficiencies may explain the difference between the two studies.  
4 Hatch et al. (1986) found that the  $\text{NO}_2$ -induced increase in BAL protein in vitamin C-deficient  
5 guinea pigs was accompanied by an increase in lung content of nonprotein sulfhydryls and  
6 ascorbic acid and a decrease in vitamin E content. The increased susceptibility to  $\text{NO}_2$  was  
7 observed when lung vitamin C was reduced (by diet) to levels <50% of normal.

## 8 9 **Summary**

10 Recent epidemiological studies provide some evidence that short-term exposure to  $\text{NO}_2$   
11 can result in inflammatory responses in the airways, but the findings are not consistently  
12 positive. The controlled human exposure studies summarized in this section provide evidence  
13 for airways inflammation at  $\text{NO}_2$  concentrations of <2.0 ppm; separately analyzing the bronchial  
14 fraction of BAL appears to increase the sensitivity for detecting airways inflammatory effects of  
15  $\text{NO}_2$  exposure. The onset of inflammatory responses in healthy subjects appears to be between  
16 100 and 200 ppm-min, i.e., 1 ppm for 2 to 3 h. Biological markers of inflammation are reported  
17 in antioxidant-deficient laboratory animals with exposures to 0.4-ppm  $\text{NO}_2$ . Normal animals do  
18 not respond until exposed to much higher levels, i.e., 5-ppm  $\text{NO}_2$ . Together, the available  
19 evidence indicates that short-term exposure to  $\text{NO}_2$  may result in airways inflammation  
20 particularly among the more susceptible, such as those with antioxidant deficiencies.

### 21 22 **3.3.1.5 Airways Hyperresponsiveness**

#### 23 24 **Clinical Studies of Airways Responsiveness**

25 Inhaled pollutants such as  $\text{NO}_2$  may have direct effects on lung function, or they may  
26 enhance the inherent responsiveness of the airways to challenge with a bronchoconstricting  
27 agent. Several drugs and other stimuli that cause bronchoconstriction have been used in  
28 challenge testing, including the cholinergic drugs methacholine and carbachol, as well as  
29 histamine, hypertonic saline, cold air, and  $\text{SO}_2$ . Challenge with “specific” allergens is  
30 considered in asthmatics.

31 Asthmatics are generally much more sensitive to nonspecific bronchoconstricting agents  
32 than non-asthmatics, and airways challenge testing is used as a diagnostic test in asthma. There

1 is a wide range of airways responsiveness in healthy people, and responsiveness is influenced by  
2 many factors, including medications, cigarette smoke, pollutants, respiratory infections,  
3 occupational exposures, and respiratory irritants. Standards for airways challenge testing have  
4 been developed for the clinical laboratory (American Thoracic Society, 2000a). However,  
5 variations in methods for administering the bronchoconstricting agents may substantially affect  
6 the results (Cockcroft et al., 2005).

7         Increases in nonspecific airways responsiveness in response to pollutant exposure mean  
8 that the pollutant causes the airways to be more sensitive to other stimuli, and in asthmatics, is  
9 one indicator of increased severity of disease. In addition, increases in airways responsiveness  
10 are correlated with worsened asthma control, and effective treatment often reduces airways  
11 responsiveness.

12

### 13 *Nonspecific Responsiveness in Healthy Adults*

14         Several observations indicate that NO<sub>2</sub> exposures in the range of 1.5 to 2.0 ppm cause  
15 small but significant increases in airways responsiveness in healthy subjects. Mohsenin (1988)  
16 found that a 1-h exposure to 2-ppm NO<sub>2</sub> increased responsiveness to methacholine, as measured  
17 by changes in specific airways conductance, without directly affecting lung function.  
18 Furthermore, pretreatment with ascorbic acid prevented the NO<sub>2</sub>-induced increase in airways  
19 responsiveness (Mohsenin, 1987a). A mild increase in responsiveness to carbachol was  
20 observed following a 3-h exposure to 1.5-ppm NO<sub>2</sub>, but not to intermittent peaks of 2.0 ppm  
21 (Frampton et al. 1991). Thus, the lower threshold concentration of NO<sub>2</sub> for causing increases  
22 in nonspecific airways responsiveness in healthy subjects appears to be in the 1- to 2-ppm range.

23

### 24 *Nonspecific Responsiveness in Asthmatic Individuals*

25         The 1993 AQCD for Oxides of Nitrogen reported results from some early studies that  
26 suggested that NO<sub>2</sub> might enhance subsequent responsiveness to challenge by  
27 bronchoconstricting agents. This increase in airways responsiveness in asthmatics has been  
28 observed in some, but not all studies, at relatively low NO<sub>2</sub> concentrations within the range of  
29 0.2 to 0.3 ppm. Appearing in Tables 15-9 and 15-10 of the 1993 AQCD (U.S. Environmental  
30 Protection Agency, 1993), the meta-analysis by Folinsbee (1992) also provided suggestive  
31 evidence of increased airways responsiveness in asthmatics exposed to NO<sub>2</sub> concentrations of as

1 low as 0.1 ppm for 1 hour during rest. However, numerous studies had not reported independent  
2 effects of NO<sub>2</sub> on lung function in asthmatic individuals.

3 Roger et al. (1990), in a comprehensive, concentration-response experiment, were unable  
4 to confirm the results of a pilot study suggesting airways responses occur in asthmatic subjects.  
5 Twenty-one male asthmatics exposed to NO<sub>2</sub> at 0.15, 0.30, or 0.60 ppm for 75 min did not  
6 experience significant effects on lung function or airways responsiveness compared with air  
7 exposure. Bylin et al. (1985) found significantly increased bronchial responsiveness to histamine  
8 challenge compared with sham exposure in 8 atopic asthmatics exposed to 0.30-ppm NO<sub>2</sub> for  
9 20 min. Five of 8 asthmatics demonstrated increased reactivity, while 3 subjects showed no  
10 change, as assessed by specific airways resistance. Mohsenin (1987b) reported enhanced  
11 responsiveness to methacholine in 8 asthmatic subjects exposed to 0.50-ppm NO<sub>2</sub> at rest for 1 h;  
12 airways responsiveness was measured by partial expiratory flow rates at 40% vital capacity,  
13 which may have increased the sensitivity for detecting small changes in airways responsiveness.  
14 Jörres and Magnussen (1991) found no effects on lung function or methacholine responsiveness  
15 in 11 patients with mild asthma exposed to 0.25-ppm NO<sub>2</sub> for 30 min with 10 min of exercise.  
16 Strand et al. (1996) performed a series of studies in mild asthmatics exposed to 0.26 ppm for  
17 30 min and found increased responsiveness to histamine as well as to allergen challenge (see  
18 below).

19 The effects of NO<sub>2</sub> exposure on SO<sub>2</sub>-induced bronchoconstriction have been examined,  
20 but with inconsistent results. Jörres and Magnussen (1990) found an increase in airways  
21 responsiveness to SO<sub>2</sub> in asthmatic subjects following exposure to 0.25-ppm NO<sub>2</sub> for 30 min at  
22 rest, yet Rubinstein et al. (1990) found no change in responsiveness to SO<sub>2</sub> inhalation following  
23 exposure of asthmatics to 0.30-ppm NO<sub>2</sub> for 30 min with 20 min of exercise.

24 The inconsistent results of these studies have not been satisfactorily explained. It is  
25 evident that a wide range of responses occurs among asthmatics exposed to NO<sub>2</sub>. This variation  
26 may in part reflect differences in subjects and exposure protocols: mouthpiece versus chamber,  
27 obstructed versus non-obstructed asthmatics, sedentary versus exercise, and varying use of  
28 medication(s) among subjects. Identification of factors that predispose to NO<sub>2</sub> responsiveness  
29 requires further investigation. These studies have typically involved volunteers with mild  
30 asthma; data are needed from more severely affected asthmatics who may be more susceptible.  
31 Overall, there is only suggestive evidence that short-term exposures to NO<sub>2</sub> at outdoor ambient

1 concentrations (<0.25 ppm) significantly alter lung function or nonspecific airways  
2 responsiveness in most people with mild asthma. However, it remains possible that more severe  
3 asthmatics, or individuals with particular sensitivity to NO<sub>2</sub> airways effects, would experience  
4 reductions in lung function or increased airways responsiveness when exercising outdoors at  
5 NO<sub>2</sub> concentrations of <0.25 ppm. Furthermore, outdoor levels influence indoor concentrations,  
6 which may reach peak levels that are clinically important for some adults and children with  
7 asthma.

8  
9 *Allergen Responsiveness in Asthmatic Individuals*

10 In asthmatics, inhalation of an allergen to which an individual is sensitized can cause  
11 bronchoconstriction and increased allergic airways inflammation, and this an important cause of  
12 asthma exacerbations. Aerosolized allergens can be used in controlled airways challenge testing  
13 in the laboratory, either clinically to identify specific allergens to which the individual is  
14 responsive or in research to investigate the pathogenesis of the airways allergic response or the  
15 effectiveness of treatments. The degree of responsiveness is a function of the concentration of  
16 inhaled allergen, the degree of sensitization as measured by the level of allergen-specific  
17 immunoglobulin E, and the degree of nonspecific airways responsiveness (Cockcroft and Davis,  
18 2006).

19 It is difficult to predict the level of responsiveness to an allergen, and rarely, severe  
20 bronchoconstriction can occur with inhalation of very low concentrations of allergen. Allergen  
21 challenge testing, therefore, involves greater risk than nonspecific airways challenge with drugs  
22 such as methacholine. Asthmatics may experience both an “early” response, with declines in  
23 lung function within minutes after the challenge, and a “late” response, with a decline in lung  
24 function hours after the exposure. The early response primarily reflects release of histamine and  
25 other mediators by airways mast cells; the late response reflects enhanced airways inflammation  
26 and mucous production. Responses to allergen challenge are typically measured as changes in  
27 pulmonary function, such as declines in FEV<sub>1</sub>. However, the airways inflammatory response can  
28 also be assessed using BAL, induced sputum, or exhaled breath condensate.

29 The potential for NO<sub>2</sub> exposure to enhance responsiveness to allergen challenge in  
30 asthmatics deserves special mention. Several recent studies, summarized in Annex Table AX5.3,  
31 have reported that low-level exposures to NO<sub>2</sub>, both at rest and with exercise, enhance the  
32 response to specific allergen challenge in mild asthmatics.

1 Tunnicliffe et al. (1994) exposed 8 subjects with mild asthma to 0.1- or 0.4-ppm NO<sub>2</sub> for  
2 1-h at rest and reported that 0.4-ppm NO<sub>2</sub> exposure slightly increased responsiveness to a fixed  
3 dose of allergen during both the early and late phases of the response. In two U.K. studies  
4 (Devalia et al., 1994; Rusznak et al., 1996), exposure to the combination of 0.4-ppm NO<sub>2</sub> and  
5 0.2-ppm SO<sub>2</sub> increased responsiveness to subsequent allergen challenge in mild atopic  
6 asthmatics, whereas, neither pollutant alone altered allergen responsiveness.

7 A series of studies from the Karolinska Institute in Sweden have explored airways  
8 responses to allergen challenge in asthmatics. Strand et al. (1997) demonstrated that single  
9 30-min exposures to 0.26-ppm NO<sub>2</sub> increased the late phase response to allergen challenge 4-h  
10 after exposure. In a separate study (Strand et al., 1998), 4 daily repeated exposures to 0.26-ppm  
11 NO<sub>2</sub> for 30 min increased both the early and late-phase responses to allergen. Barck et al. (2002)  
12 used the same exposure and challenge protocol in the earlier Strand studies (0.26 ppm for 30  
13 min, with allergen challenge 4-h after exposure), and performed BAL 19-h after exposure to  
14 determine NO<sub>2</sub> effects on the inflammatory response to allergen challenge. NO<sub>2</sub> (0.26 ppm for  
15 30 min) followed by allergen caused increases in the BAL recovery of PMN and eosinophil  
16 cationic protein (ECP), with reduced volume of BAL fluid and reduced cell viability, compared  
17 with air followed by allergen. ECP is released by degranulating eosinophils, is toxic to  
18 respiratory epithelial cells, and is thought to play a role in the pathogenesis of airways injury in  
19 asthma. These findings indicate that NO<sub>2</sub> enhanced the airways inflammatory response to  
20 allergen. Subsequently, Barck et al. (2005a) exposed 18 mild asthmatics to air or NO<sub>2</sub> for 15  
21 min on day 1, followed by two 15-min exposures separated by 1-h on day 2, with allergen  
22 challenge after exposures on both days 1 and 2. Sputum was induced before exposure on day  
23 1 and after exposures (morning of day 3). NO<sub>2</sub> + allergen, compared to air + allergen, treatment  
24 resulted in increased levels of ECP in both sputum and blood and increased myeloperoxidase  
25 levels in blood. A separate study examined NO<sub>2</sub> effects on nasal responses to nasal allergen  
26 challenge (Barck et al., 2005b). Single 30-min exposures to 0.26-ppm NO<sub>2</sub> did not enhance  
27 nasal allergen responses. All exposures in the Karolinska Institute studies (Barck et al., 2002,  
28 2005a; Strand et al., 1997, 1998) used subjects at rest. These studies utilized an adequate  
29 number of subjects, included air control exposures, randomized exposure order, and separated  
30 exposures by at least 2 weeks. Together, they appear to demonstrate convincingly effects of  
31 quite brief exposures to 0.26 ppm on allergen responsiveness in asthmatics. The level of



1 confidence in the findings from the Karolinska Institute would be further increased with  
2 confirmation from other laboratories. However, the findings may shed some light on the variable  
3 results in earlier studies of NO<sub>2</sub> effects on nonspecific airways responsiveness. It is possible that  
4 some prior studies may have been variably confounded by environmental allergen exposure,  
5 increasing the variability in subject responses to NO<sub>2</sub> and perhaps explaining some of the  
6 inconsistent findings.

7         Several studies have been conducted using longer NO<sub>2</sub> exposures. Wang et al. (1995a,b,  
8 1999) found that more intense (0.4 ppm) and prolonged (6 h) NO<sub>2</sub> exposures enhanced allergen  
9 responsiveness in the nasal mucosa in subjects with allergic rhinitis. Jenkins et al. (1999)  
10 examined FEV<sub>1</sub> decrements and airways responsiveness to allergen in a group of mild, atopic  
11 asthmatics. The subjects were exposed for 3-h to NO<sub>2</sub> (400 ppb), O<sub>3</sub> (200 ppb), and NO<sub>2</sub>  
12 (400 ppb) + O<sub>3</sub> (200 ppb). The subjects were also exposed for 6-h to produce exposure  
13 concentrations that would provide identical doses to the 3-h protocols (i.e., equivalent C × T).  
14 Significant increases in airways responsiveness to allergen occurred following all the 3-h  
15 exposures, but not following the 6-h exposures.

16         Lastly, one study examined the effects on allergen responsiveness of exposure to traffic  
17 exhaust in a tunnel (Svartengren et al., 2000). Twenty mild asthmatics sat in a stationary vehicle  
18 within a busy tunnel for 30 min. Allergen challenge was performed 4-h later. The control  
19 exposure was in a hotel room in a suburban area with low air pollution levels. Exposures were  
20 separated by 4 weeks and the order was randomized. Median NO<sub>2</sub> levels in the vehicle were  
21 313 µg/m<sup>3</sup> or 0.166 ppm, PM<sub>10</sub> levels were 170 µg/m<sup>3</sup>, and PM<sub>2.5</sub> levels were 95 µg/m<sup>3</sup>. Median  
22 NO<sub>2</sub> levels outside the hotel were 11 µg/m<sup>3</sup>. Subjects in the tunnel experienced increased cough,  
23 and also reported awareness of noise and odors. More importantly, there was a greater allergen-  
24 induced increase in specific airways resistance after the tunnel exposure than after the control  
25 exposure (44% versus 31% respectively). Thoracic gas volume was also increased to a greater  
26 degree after the tunnel exposure, suggesting increased gas trapping within the lung. These  
27 findings were most pronounced in the subjects exposed to the highest levels of NO<sub>2</sub>. This study  
28 suggests that exposure to traffic exhaust, and particularly the NO<sub>2</sub> component, increases allergen  
29 responsiveness in asthmatics, and the results fit well with the findings in studies of clinical  
30 exposures of NO<sub>2</sub> (Barck et al., 2002, 2005a). However, it was not possible to blind the  
31 exposures, and the control exposure (hotel room, presumably quiet and relaxed) was not well

1 matched to the experimental exposure (vehicle, noisy, odorous). It remains possible that factors  
2 other than NO<sub>2</sub> contributed to, or were responsible for, the observed differences in allergen  
3 responsiveness.

4         These recent studies involving allergen challenge suggest that NO<sub>2</sub> may enhance the  
5 sensitivity to allergen-induced decrements in lung function, and increase the allergen-induced  
6 airways inflammatory response. Enhancement of allergic responses in asthmatics occurs at  
7 exposure levels more than an order of magnitude lower than those associated with airways  
8 inflammation in healthy subjects. The dosimetry difference is even greater when considering  
9 that the allergen challenge studies were generally performed at rest, while the airways  
10 inflammation studies in healthy subjects were performed with intermittent exercise.  
11 Enhancement of allergen responses has been found at exposures as low as 8 ppm-min, i.e.,  
12 0.26 ppm for 30 min. Additional work is needed to understand more completely the exposure-  
13 response characteristics of NO<sub>2</sub> effects on allergen responses, as well as the effects of exercise,  
14 relationship to the severity of asthma, the role of asthma medications, and other clinical factors.  
15 Additional animal and in vitro studies are needed to establish the precise mechanisms involved.

16

### 17 **Toxicological Studies of Airways Responsiveness**

18         The 1993 AQCD found airways responsiveness to be a key health response to NO<sub>2</sub>  
19 exposure. Although the mechanisms are not fully known, many studies have demonstrated the  
20 ability of NO<sub>2</sub> exposure to increase bronchial sensitivity to various challenge agents.

21         Acute exposures of Brown-Norway rats to NO<sub>2</sub> at a concentration of 9400 µg/m<sup>3</sup> (5 ppm)  
22 for 3-h resulted in increased specific immune response to house dust mite allergen and increased  
23 immune-mediated pulmonary inflammation (Gilmour et al., 1996). Higher levels of antigen-  
24 specific serum IgE, local IgA, IgG, and IgE were observed when rats were exposed to NO<sub>2</sub> after  
25 both the immunization and challenge phase, but not after either the immunization or challenge  
26 phase alone. Increases in the number of inflammatory cells in the lungs and lymphocyte  
27 responsiveness to house dust mite allergen in the spleen and mediastinal lymph node were  
28 observed. The authors concluded that this increased immune responsiveness to house dust mite  
29 allergen may be the result of the increased permeability of the lung caused by NO<sub>2</sub> exposure,  
30 enhancing translocation of the antigen to local lymph nodes and circulation to other sites in the  
31 body.

1 A delayed bronchial response, seen as increased respiration rate (tachypnea), occurred in  
2 NO<sub>2</sub>-exposed, *Candida albicans*-sensitized guinea pigs 15 to 42-h after a challenge dose of  
3 *C. albicans* (Kitabatake et al., 1995). Guinea pigs were given an intraperitoneal injection of  
4 *C. albicans*, followed by a second injection 4 weeks later. Two weeks after the second injection,  
5 the animals were given an inhalation exposure of killed *C. albicans*. Animals were also exposed  
6 4 h/day to 8955- $\mu\text{g}/\text{m}^3$  (4.76 ppm) NO<sub>2</sub> from the same day as the first injection of *C. albicans* for  
7 a total of 30 exposures (5 days/week).

8 Pulmonary function (lung resistance, dynamic compliance) was not affected in  
9 NO<sub>2</sub>-exposed rabbits immunized intraperitoneally within 24-h of birth until 3 months of age to  
10 either *Alternaria tenuis* or house dust mite antigen. The rabbits were given intraperitoneal  
11 injections once weekly for 1 month, and then every 2 weeks thereafter, and exposed to  
12 7520- $\mu\text{g}/\text{m}^3$  (4 ppm) NO<sub>2</sub> for 2-h daily (Douglas et al., 1994).

13 Kobayashi and Miura (1995) studied the concentration- and time-dependency of airways  
14 hyperresponsiveness to inhaled histamine aerosol in guinea pigs exposed subchronically to NO<sub>2</sub>.  
15 In one experiment, guinea pigs were exposed by inhalation to 0, 113, 940, or 7520- $\mu\text{g}/\text{m}^3$   
16 (0, 0.06, 0.5, or 4.0 ppm) NO<sub>2</sub>, 24 h/day for 6 or 12 weeks. Immediately following the last  
17 exposure, airways hyperresponsiveness was assessed by measurement of specific airways  
18 resistance as a function of increasing concentrations of histamine aerosol. Animals exposed to  
19 7520- $\mu\text{g}/\text{m}^3$  (4 ppm) NO<sub>2</sub> for 6 weeks exhibited increased airways response to inhaled histamine  
20 aerosol; airways response at 12 weeks was not determined. No effects were observed at the  
21 lower exposure levels. In another experiment conducted in this study (Kobayashi and Miura,  
22 1995), guinea pigs were exposed by inhalation to 0, 1880-, 3760-, or 7520- $\mu\text{g}/\text{m}^3$  (0, 1.0, 2.0, or  
23 4.0 ppm) NO<sub>2</sub>, 24 h/day for 6 or 12 weeks, and the airways hyperresponsiveness was determined.  
24 Increased hyperresponsiveness to inhaled histamine was observed in animals exposed to  
25 7520  $\mu\text{g}/\text{m}^3$  (4 ppm) for 6 weeks; 3760  $\mu\text{g}/\text{m}^3$  (2 ppm) for 6 and 12 weeks; and 1880  $\mu\text{g}/\text{m}^3$   
26 (1 ppm) for 12 weeks only. The results also showed that at 1880- or 3760- $\mu\text{g}/\text{m}^3$  (1 or 2 ppm)  
27 NO<sub>2</sub>, airways hyperresponsiveness developed to a higher degree with the passage of time.  
28 Therefore, a higher concentration of NO<sub>2</sub> induces airways hyperresponsiveness faster than a  
29 lower concentration. When the specific airways resistance was compared to values determined  
30 1 week prior to initiation of the NO<sub>2</sub> exposure, values were increased in the 3760- and

1 7520- $\mu\text{g}/\text{m}^3$  (2.0 and 4.0 ppm) animals at 12 weeks only. Specific airways resistance was also  
2 increased to a higher degree with the passage of time.

3  
4 **Summary**

5 Exposure to  $\text{NO}_2$  enhances the inherent responsiveness of the airways to subsequent  
6 specific and nonspecific challenges. Hyperresponsiveness to a challenge agent is typically  
7 characterized by bronchoconstriction subsequent to  $\text{NO}_2$  compared to clean air exposure.  
8 Subchronic exposures (6 to 12 weeks) of animals to  $\text{NO}_2$  (1 to 4 ppm) increases responsiveness  
9 to nonspecific challenge. Healthy humans exposed to  $\text{NO}_2$  in the range of 1.5 to 2.0 ppm for a  
10 few hours also develop small but significant increases in nonspecific airways responsiveness.  
11 There is limited evidence that asthmatics may experience increased airways responsiveness to  
12 nonspecific challenge following exposure to between 0.2- and 0.3-ppm  $\text{NO}_2$  for 30 min. A meta-  
13 analysis of four studies provided suggestive evidence of increased airways responsiveness in  
14 asthmatics exposed to 0.1-ppm  $\text{NO}_2$  for 1 h. Data supporting increased airways responsiveness  
15 to specific allergen challenges following  $\text{NO}_2$  exposure is more compelling. Bronchoconstriction  
16 following an allergen challenge occurs in asthmatics exposed during rest to 0.26-ppm  $\text{NO}_2$  for 30  
17 min relative to clean air. However, inflammatory responses to allergen challenge in asthmatics  
18 may be a more sensitive endpoint and have been reported subsequent to exposure at 0.26-ppm  
19  $\text{NO}_2$  for 30 min. These inflammatory responses to the allergen challenge were not accompanied  
20 by any changes in pulmonary function or subjective symptoms. Increased immune-mediated  
21 pulmonary inflammation also occurs in rats exposed to house dust mite allergen following  
22 exposure to 5-ppm  $\text{NO}_2$  for 3 h. Overall, studies involving allergen challenge suggest that  $\text{NO}_2$   
23 exposure increases the allergen-induced airways inflammatory response and may also enhance  
24 the sensitivity to allergen-induced decrements in lung function.

25  
26 **3.2.1.6 Hospital Admissions and Emergency Department Visits for Respiratory**  
27 **Outcomes**

28 Total respiratory causes for emergency department (ED) visits typically include asthma,  
29 COPD (including pneumonia, bronchitis, and emphysema), upper and lower respiratory  
30 infections such as influenza, and other minor categories. Morbidities that result in ED visits are  
31 closely related to, but are generally less severe than, those that result in unscheduled hospital  
32 admissions. In many cases, acute health problems are successfully treated in the ED; however, a

1 subset of more severe cases that present initially to the ED may require hospital admission and  
2 are then classified as hospital admissions. ED visits represent an important acute outcome that  
3 may be affected by NO<sub>2</sub> exposures.

4 Many studies have been published in the past decade that examined temporal associations  
5 between NO<sub>2</sub> exposures and ED visits and hospital admissions for respiratory diseases. Asthma  
6 visits typically dominate the daily incidence counts. Chronic bronchitis and emphysema often  
7 are combined to define COPD, which is a prominent diagnosis among older adults with lung  
8 disease.

#### 9 10 **3.3.1.6.1 All Respiratory Outcomes (ICD9: 460-519)**

11 Overall, the majority of studies that have examined all respiratory outcomes as a single  
12 group have focused on hospital admission data. Those studies are summarized here, along with a  
13 single study of ED visits and all respiratory outcomes.

14 Two multicity studies that combine the effects of ambient air pollution (including NO<sub>2</sub>)  
15 in several cities and describe similar response rates and respiratory health outcomes as measured  
16 by increased hospital admissions are available (Barnett et al., 2005); (Simpson et al., 2005a).  
17 These studies are summarized in Table 3.2-2.

18 Barnett et al. (2005) used a case-crossover method to study ambient air pollution effects  
19 on respiratory hospital admissions of children (age groups 0, 1 to 4, and 5 to 14 years) in  
20 multiple cities in both Australia and New Zealand during the study period 1998-2001. For NO<sub>2</sub>  
21 the interquartile ranges for 1-h and 24-h NO<sub>2</sub> were 9.0 and 5.1 ppb, respectively. No significant  
22 associations were reported between NO<sub>2</sub> and hospital admission for infants or children 1 to 4  
23 years old in these cities. For all respiratory admissions among children 1 to 4 years, a 2.8%  
24 (95% CI: 0.7, 4.9) increase was found for a 9-ppb increment in the daily maximum 1-h  
25 concentration of NO<sub>2</sub>, and for children aged 5 to 14 years the same increase in NO<sub>2</sub> resulted in a  
26 4.7% increase in admission for all respiratory disease (95% CI: 1.6, 7.9) both lagged 0 to 1 day  
27 (Barnett et al., 2005). Multipollutant models in the study showed that the results for NO<sub>2</sub> were  
28 often independent of the effects of other pollutants, although some impact caused by particles  
29 and SO<sub>2</sub> could not be separated from those found for NO<sub>2</sub>. For respiratory admissions in the  
30 5- to 14-year age group, a significant association with PM<sub>10</sub> disappeared after adjusting for NO<sub>2</sub>,  
31 indicating that this result could not be separated from that for NO<sub>2</sub>. However, the association  
32 with NO<sub>2</sub> remained after adjusting for PM<sub>10</sub>.

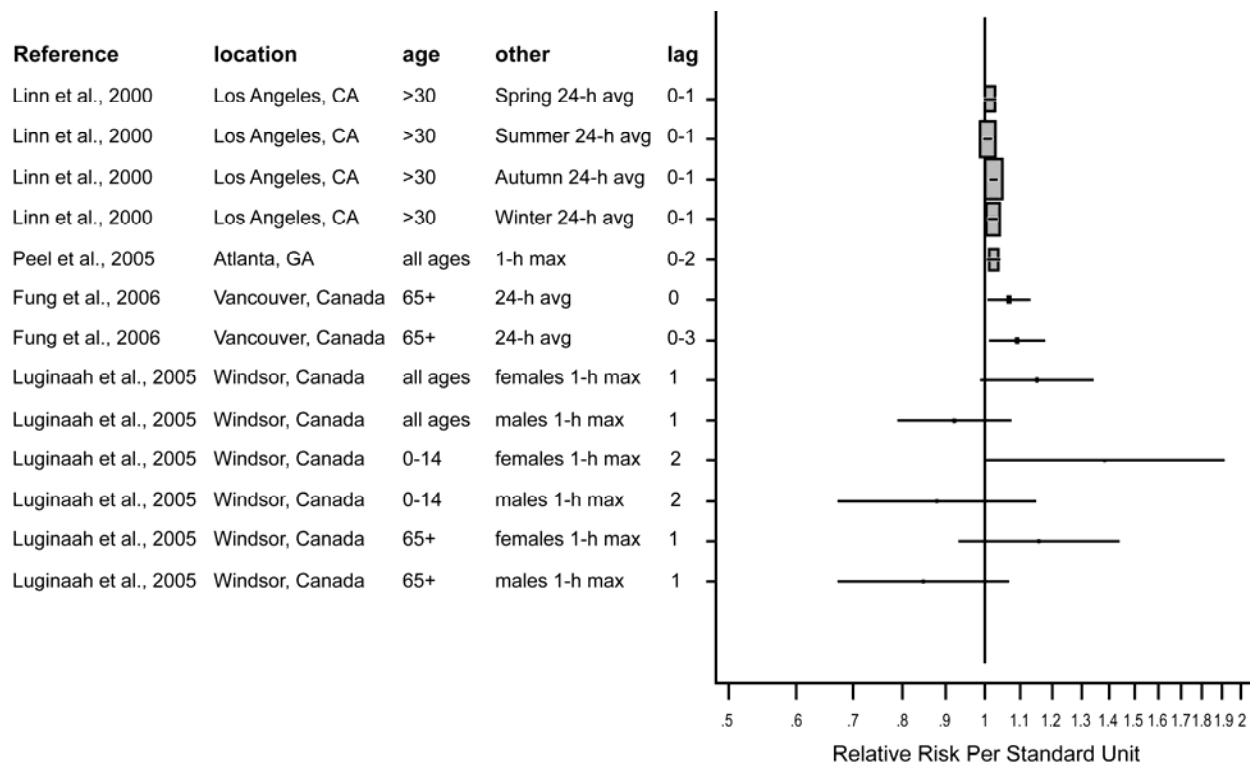
1 In a multicity study of all hospitalizations for respiratory disease (ICD9 460 to 519) for  
2 people ages  $\geq 65$  years, Simpson et al. (2005a) examined the response to a change in the  
3 maximum daily 1-h concentration equivalent to the average IQR of the four cities (54.5 ppb).  
4 The calculated relative risk (RR, expressed per ppb) (1.0027 [95% CI: 1.0015, 1.0039] lag 0 to  
5 1) was small, but statistically significant. The authors present results from three statistical  
6 models that produced similar results overall for the four cities. Perth generally experienced  
7 much lower 1-h maximum concentrations of NO<sub>2</sub> than the other Australian cities.

8 In their analysis of two-pollutant models, Simpson et al. (2005a) reported that  
9 concentrations of NO<sub>2</sub> and particulate matter (PM<sub>10</sub>) may be associated with similar outcomes or  
10 effects. There was clear evidence of heterogeneity of response across different cities within  
11 similar age groups to the same pollutant mixtures. For respiratory hospitalization the city that  
12 provided the greatest source of heterogeneity, Perth, was the same in each of the three statistical  
13 model approaches applied. Simpson et al. (2005a) suggest that a possible source of variation of  
14 response could lie in the population characteristics (age, structure, etc.) that differentiate one  
15 urban population from another. They concluded that it might not be reasonable to generalize  
16 health outcomes in response to pollutants experienced in one urban location to another location.

17 Several North American studies have examined ED visits and hospital admissions for all  
18 respiratory causes and ambient NO<sub>2</sub> concentrations (Linn et al., 2000; Peel et al., 2005; Luginaah  
19 et al., 2005; Fung et al., 2006). These studies have generally focused on adults and the elderly.  
20 (See Figure 3.2-8.)

21 Among adults ( $>30$  years of age) living in a large area of Los Angeles, Linn et al. (2000)  
22 noted seasonal associations between NO<sub>2</sub> levels (mean 24-h average NO<sub>2</sub>: 34 ppb) and the  
23 frequency of hospitalization for all pulmonary disease. Though associations were positive for  
24 each of the four seasons, the associations for autumn and winter were markedly higher. It was  
25 noted that these single-pollutant results could not be distinguished from effects related to  
26 copollutants PM<sub>10</sub> and CO (Linn et al., 2000).

27 Peel et al. (2005) examined ED visits for all respiratory causes among all ages in relation  
28 to ambient NO<sub>2</sub> concentrations in Atlanta, GA; they found a 1.6% (95% CI: 0.6, 2.7) increase in  
29 respiratory ED visits associated with a 20-ppb increase in 1-h maximum NO<sub>2</sub> concentrations.



**Figure 3.2-8 Relative risks (95% CI) for hospital admissions and ED visits for all respiratory causes with 24-h NO<sub>2</sub> concentrations (per 20 ppb).**

1 In Vancouver, Fung et al. (2006) used time-series analysis, the method of Dewanji and  
2 Moolgavkar (2000), and case-crossover analysis of all respiratory hospitalizations for adults aged  
3 65 and older. All three methods showed positive associations between incremental changes in  
4 NO<sub>2</sub> of 5.43 ppb (IQR) from a mean concentration of 16.83 ppb. Using a time-series analysis  
5 Fung et al. (2006) reported a RR of 1.018 ([95% CI: 1.003, 1.034] lag 0) while the case-  
6 crossover analysis showed a significant change in the relative rate of 1.028 ([95% CI: 1.010,  
7 1.04] lag 0). These represented percent changes of 1.8% and 2.8% respectively. The Dewanji  
8 and Moolgavkar model did not produce a statistically significant association between NO<sub>2</sub> and  
9 hospitalization for the IQR of 5.43 ppb (RR = 1.012 [95% CI: 0.997, 1.027] lag 0)]. Results of  
10 multipollutant models were not given, but there were strong correlations of NO<sub>2</sub> with CO  
11 (r = 0.74), SO<sub>2</sub>, PM<sub>10</sub>, and PM<sub>10-2.5</sub> (Fung et al., 2006).

12 In the Windsor/Detroit border area of Canada, Luginaah et al. (2005) noted a positive  
13 trend between an incremental change in NO<sub>2</sub> of 16 ppb (mean 1-h maximum: 38.9 ppb) and

1 respiratory admissions. These authors used two approaches that included both time-series and  
2 case-crossover analyses segregated by sex. Though associations for females in each of the age  
3 groups examined were positive, the authors found only one statistically significant association in  
4 females aged 0 to 14 years that identified an increased percent of hospitalization of 18.9% using  
5 the case-crossover analysis (RR = 1.189 [95% CI: 1.002, 1.411] lag 2). In this study, CO and  
6 NO<sub>2</sub> were correlated (r = 0.38) and thought to represent motor vehicle emissions.

7 Studies from Europe on associations with respiratory hospitalization were conducted in  
8 London, Paris, and in Drammen, Norway. A detailed analysis of respiratory hospitalization by  
9 age group and by seasonal temperature was carried out in London using the APHEA protocol  
10 (Ponce de Leon et al., 1996). In this study, significant positive relative risks were reported for all  
11 ages and for children (0 to 14 year olds), but the presence of O<sub>3</sub> during summer months may  
12 have also contributed to a change in the rate of hospitalization. Respiratory hospitalizations for  
13 adults (15 to 64 years) examined separately were not statistically significantly increased. The  
14 increased hospitalization rates were based on an incremental change for NO<sub>2</sub> of 27 ppb (similar  
15 to the difference of the 90th and 10th percentiles of the annual concentration) and an annual  
16 mean 24-h concentration of 37.3 ppb in London.

17 In Paris, France (mean 24-h average NO<sub>2</sub> of 23.6 ppb), Dab et al. (1996) determined that  
18 there was no statistically significant association between admissions for all respiratory causes  
19 combined based on an incremental change of 52.35 ppb, though the estimates were positive.

20 In Drammen, Norway, Oftedal et al. (2003) reported associations between respiratory  
21 hospitalizations and NO<sub>2</sub>. Oftedal et al. (2003) reported that both NO<sub>2</sub> and benzene were  
22 associated with an increase in hospital admission for all respiratory disease. In a single-pollutant  
23 model, the relative rate of hospitalization for all respiratory disease increased based on an  
24 increment of 11-ppb NO<sub>2</sub> (RR = 1.060 [95% CI: 1.017, 1.105] lag 3 days). This finding was  
25 robust, since in two-pollutant models NO<sub>2</sub> remained associated with a significant increase in  
26 admissions after adjusting for PM<sub>10</sub> (RR = 1.063 [95% CI: 1.008, 1.120]) or for benzene  
27 concentration (RR = 1.046 [95% CI: 1.002, 1.091]). Other studies outside the United States  
28 found positive outcomes (Llorca et al., 2005; Braga et al., 2001; Wong et al., 1999).

### 29 30 **3.2.1.6.2 Asthma (ICD9: 493)**

31 In North America, the most recent studies to investigate for evidence of an association  
32 between ambient concentrations of NO<sub>2</sub> and hospitalizations or ED visits were conducted by



1 Linn et al. (2000); Lin et al. (2003, 2004); Jaffe et al. (2003); Peel et al. (2005); and Tolbert  
2 et al. (2000). Mean concentrations of NO<sub>2</sub> in studies of hospitalizations and ED visits for asthma  
3 in North America varied from city to city. The mean daily concentrations were relatively low in  
4 Canada, recorded at 25.24 ppb (SD 9.04) in Toronto, ON from 1981 to 1993, and 18.65 ppb (SD  
5 5.59) in Vancouver, BC from 1987 to 1991. In Atlanta, GA between 1993 and 1995, the mean  
6 of the daily 1-h maximum concentration was 81.7 ppb (SD 53.8) (Tolbert et al., 2000) but  
7 decreased between 1993 and 2000 to 45.9 ppb (SD 17.3) (Peel et al., 2005). During studies  
8 carried out between 1991 and 1996, the mean of the 24-h average NO<sub>2</sub> concentration in  
9 Cincinnati was 50 ppb (SD 15) and 48 ppb (SD 16) in Cleveland (Jaffe et al., 2003).  
10 Surprisingly, the lowest concentrations were reported by Linn et al (2000), who calculated the  
11 overall mean in Los Angeles, CA from 1992 to 1995 to be 3.4 ppb (SE 1.3).

12 Linn et al. (2000) found significant increases (1.14% [95% CI: 0.9, 1.9]) in hospital  
13 admissions for asthma with a 10 ppb change in the 24-h average concentration of NO<sub>2</sub> in  
14 Los Angeles (mean 24-h NO<sub>2</sub>: 34 ppb). When seasonal differences in hospitalization frequency  
15 were examined, higher rates of hospitalization for asthma in Los Angeles were found for the  
16 cooler months of autumn (1.9% [95% CI: 1.1, 2.7]), and winter (2.8% [95% CI: 2.7, 2.9]) based  
17 on a 10 ppb change in the concentration of NO<sub>2</sub> (Linn et al., 2000).

18 Lin et al. examined the data for hospital admissions due to asthma in the Canadian cities  
19 of Toronto (Linn et al., 2003) and Vancouver (Linn et al., 2004). Lin et al. (2004) studied  
20 gaseous air pollutants and 3,822 asthma hospitalizations (2,368 boys, 1,454 girls) among  
21 children 6 to 12 years of age with low household income in Vancouver, Canada between 1987  
22 and 1998. NO<sub>2</sub> levels were derived from 30 monitoring stations. Exposures to NO<sub>2</sub> were found  
23 to be significantly and positively associated with asthma hospitalization for males in the low  
24 socioeconomic group but not in the high socioeconomic group. This effect did not persist among  
25 females. Lin et al. (2003) conducted a case-crossover analysis of the effect of short-term  
26 exposure to gaseous pollution on 7,319 asthma hospitalizations (4,629 boys, 2,690 girls) in  
27 children in Toronto between 1980 and 1994. NO<sub>2</sub> concentrations measured from four  
28 monitoring stations were positively associated with asthma admissions in both sexes. The effects  
29 of NO<sub>2</sub> on asthma hospitalization remained after adjustment for PM. Differences in the results of  
30 these two studies might be attributed to differences in the study designs.

1 A study in Paris showed an association for hospitalization for asthma based on both the  
2 mean 24-h average concentration and the maximum daily 1-h concentration of NO<sub>2</sub> (mean  
3 38.6 ppb) Dab et al., (1996). For the 24-h NO<sub>2</sub> concentration, the estimate was 17.5%  
4 (RR = 1.175 [95% CI: 1.059, 1.304] lag 0 to 1); while for a similar incremental change in the  
5 1-h maximum concentration of NO<sub>2</sub>, the increase in admissions for asthma was 8.1%  
6 (RR = 1.081 [95% CI: 1.019, 1.148] lag 0 to 1).

7 In Atlanta, GA, Peel et al. (2005) examined various respiratory ED visits in relation to  
8 pollutant levels from 1 January 1993 to 31 August 2000. The pollutants and metrics for this  
9 analysis were selected a priori based on current hypotheses regarding potentially causal  
10 pollutants and components with a focus on PM aspects (Albritton and Greenbaum, 1998;  
11 Schlesinger, 2000) as well as useful models for primary traffic related pollutants. The mean  
12 daily count of asthma ED visits for asthma was 39.0 ± 20.5 over the entire study period. Results  
13 for the a priori single-pollutant models examining a 3-day moving average (lag 0, 1, and 2) of  
14 NO<sub>2</sub> showed a small but not statistically significant associations with asthma visits (RR = 1.014  
15 [95% CI: 0.997, 1.030) for all age groups. In secondary analysis of patients ages 2 to 18 years, a  
16 20-ppb increase in the day 5 lag of the NO<sub>2</sub> concentration yielded an RR of 1.027 (95% CI:  
17 1.005, 1.000).

18 Wade et al. (2006) examined the effects of instrument precision and spatial variability on  
19 assessment of the temporal variation of ambient air pollution (including NO<sub>2</sub>) in Atlanta. The  
20 use of calculated instrument data yielded an estimate of instrument imprecision equal to 20% of  
21 the temporal variation for NO<sub>x</sub> and PM<sub>2.5</sub> mass and 10% of O<sub>3</sub> and CO. The spatial variability  
22 was approximately 80% of the temporal variation for NO<sub>x</sub>. Population-weighted uncertainty in  
23 primary pollutant levels because of instrument imprecision and spatial variation was found to be  
24 60 to 70% of the temporal variation. Note that these ambient air pollutant error estimates have  
25 not been incorporated into the health risk models by Peel et al., (2005) and are expected to  
26 appear in a later publication.

27 Jaffe et al. (2003) examined the effects of ambient pollutants during the summer months  
28 (June through August) on the daily number of ED visits for asthma among Medicaid recipients  
29 aged 5 to 34 years from 1 July 1991 to 30 June 1996 in Cincinnati and Cleveland. The percent  
30 change in ED visits for asthma as the primary diagnosis per 10-ppb increase in 24-h average NO<sub>2</sub>

1 concentration was 6% (95% CI: -1, 13) in Cincinnati and 4% (95% CI: -1, 8) in Cleveland,  
2 with an overall percent increase in ED visits of 3% (95% CI: -1, 7).

3 A number of studies outside of North America have examined the association between  
4 NO<sub>2</sub> and hospitalization or ED visits for asthma. Barnett et al., (2005) examined specific  
5 respiratory disease outcomes and did not find associations between incremental changes in NO<sub>2</sub>  
6 concentration and respiratory admissions for asthma among children 1 to 4 years old. The  
7 largest association found in this study was a 6.0% increase in asthma admissions in the 5- to  
8 14-year age group related to a 5.1-ppb increase in 24-h NO<sub>2</sub>, with evidence of a seasonal impact  
9 that resulted in larger increases in admissions during the warm season. When the same groups  
10 were examined for the effect of a 9.0-ppb change in the maximum 1-h concentration of NO<sub>2</sub>,  
11 there were no significant associations between NO<sub>2</sub> and hospitalization for asthma.

12 Tenias et al. (1998) used the APHEA design and analysis approach in Valencia, Spain, to  
13 examine the association between hospital ED visits for asthma among patients over 14 years old  
14 and air pollution for the period 1 January 1993 to 31 December 1995, yielding 734 cases. The  
15 mean 24-h NO<sub>2</sub> level was 57.7 µg/m<sup>3</sup> and the mean 1-h NO<sub>2</sub> level was 100.1 µg/m<sup>3</sup>. There were  
16 7.6% and 3.7% increases in ED visits associated with the 24-h average NO<sub>2</sub> concentration at lag  
17 0 (1.076 [95% CI: 1.020, 1.134]) and the 1-h maximum NO<sub>2</sub> concentration (1.037 [95% CI:  
18 1.008, 1.066]), respectively. Examination of single- and two-pollutant models shows that the  
19 addition O<sub>3</sub>, smoke, or SO<sub>2</sub> into the model results in little variation in the NO<sub>2</sub> effect estimates,  
20 thus diminishing the effect of confounding on the NO<sub>2</sub> effect estimates.

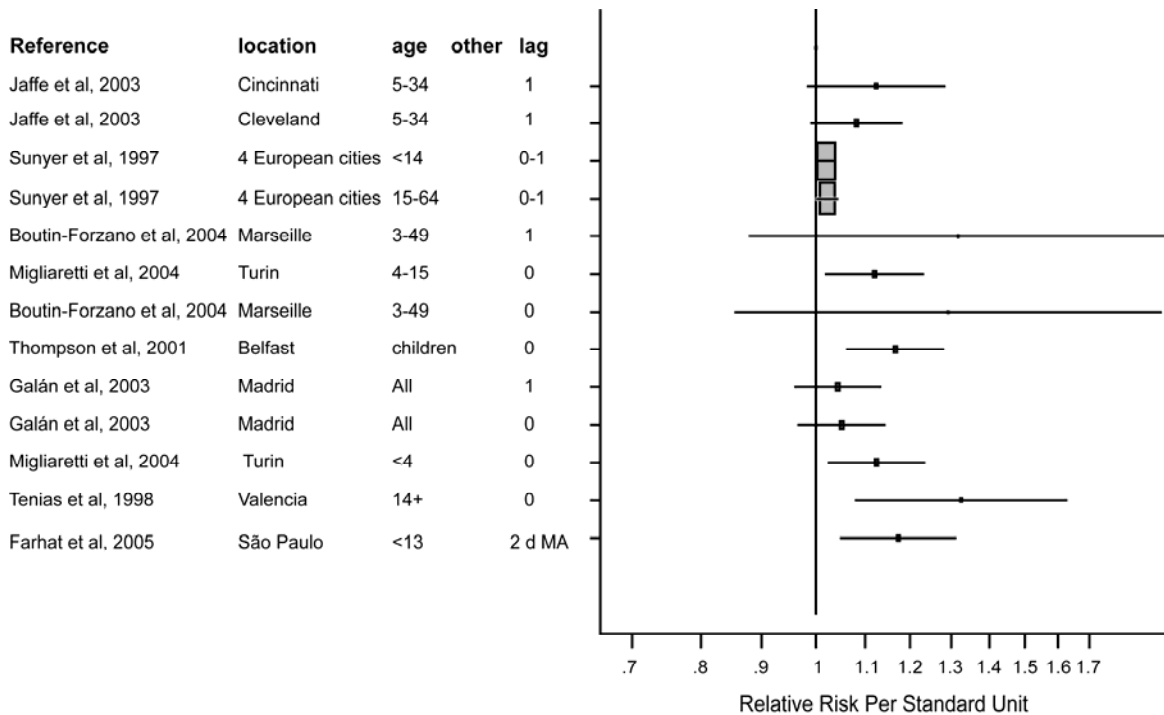
21 Castellsague et al. (1995) examined the association between hospital emergency visits for  
22 asthma and air pollutants during the winter and summer months from 1985 to 1989 in Barcelona,  
23 Spain for the 14 to 65 year age group. Barcelona traffic density on working day shows little  
24 variability during the year, suggesting a steady emission of vehicle exhaust, which is the main  
25 source of NO<sub>2</sub> in the city. There were 460 summer asthma visits and 452 winter visits. Mean  
26 NO<sub>2</sub> levels averaged 104.0 µg/m<sup>3</sup> (95th percentile = 183 µg/m<sup>3</sup>) during the summer, and  
27 100.8 µg/m<sup>3</sup> (95th percentile = 153 µg/m<sup>3</sup>) during the winter. The increase in asthma visits for a  
28 25-µg/m<sup>3</sup> increase of current day levels of NO<sub>2</sub> was 4.5% (95% CI: 0.9, 8.1) in summer and  
29 5.6% (95% CI: 1.1, 10.4) in winter. A cumulative measure of NO<sub>2</sub> yielded a slightly stronger  
30 association.

1 A time-series analysis in Sydney examined respiratory outcomes in children and adults,  
2 but reported no association between changes in NO<sub>2</sub> (24-h average) for asthma admissions  
3 (Morgan et al., 1998a). For children aged 1 to 14, a 5.3% increase in hospital admissions for  
4 asthma ([95% CI: 1.1, 9.7] lag 0) was associated with the daily 1-h maximum value based on  
5 15-ppb incremental change. This association with the 1-h maximum daily concentration  
6 remained robust in a multiple pollutant model (5.95% [95% CI: 1.11, 11.02] lag 0) which was  
7 only marginally different from the single-pollutant model (Morgan et al., 1998a). The  
8 association with adults also was positive, but not statistically significant.

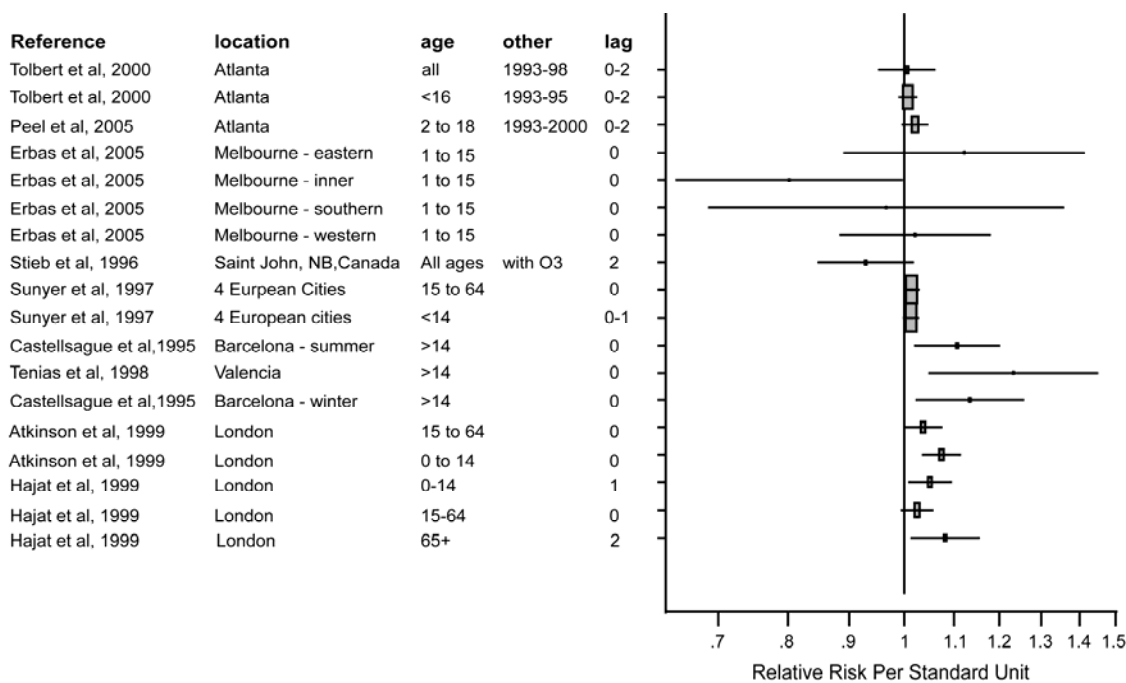
9 Studies of ED visits for asthma have been reported from cities in Europe including  
10 London (Atkinson et al., 1999a,b; Hajat et al., 1999); Belfast (Thompson et al., 2001); Valencia,  
11 Barcelona, and Madrid, Spain (Tenias et al., 1998; Galan et al., 2003; Castellsague et al., 1995);  
12 Turin, Italy (Migliaretti et al., 2004, 2005); Marseille, France (Boutin-Forzano et al., 2004); and  
13 Amsterdam and Rotterdam (Schouten et al., 1996). Sunyer et al. (1997) have described a meta-  
14 analysis of several cities under the umbrella of the APHEA protocol (Katsouyanni et al., 1996).  
15 Additional cities where associations between ED visits for asthma and ambient concentrations of  
16 NO<sub>2</sub> have been examined include Melbourne, Brisbane and Perth, Australia (Erbas et al., 2005;  
17 Hinwood et al., 2006), and São Paulo, Brazil (Farhat et al., 2005).

18 Figures 3.2-9 and 3.2-10 show the percent increases (and 95% confidence limits) in visits  
19 to the ED for asthma associated with daily NO<sub>2</sub> 1-h peaks and 24-h averages for each study,  
20 respectively. Meta-analysis and meta-regression were used to summarize these results. The  
21 results of meta-regression show that the percent increases did not vary significantly for adults  
22 versus children, the sampling time of NO<sub>2</sub>, or the daily NO<sub>2</sub> concentration for each sampling  
23 time. The lags presented in the figures vary depending on reported results. Most studies  
24 reported effect estimates from a short lag period (i.e., 0 to 2 days).

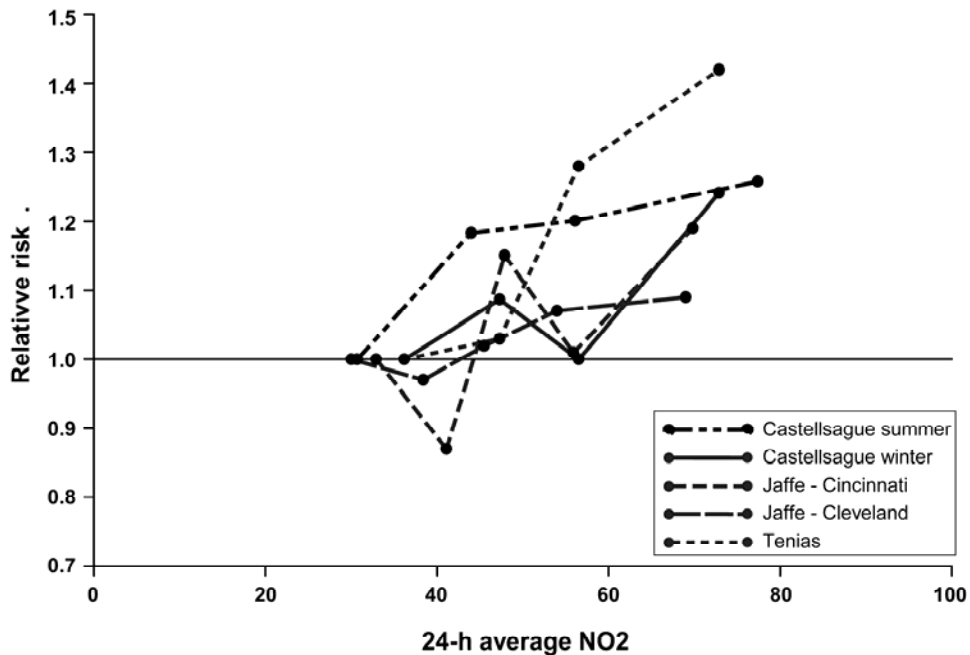
25 Figure 3.2-11 provides three examples of dose response relationships for the effect  
26 estimates of asthma visits to the ED and NO<sub>2</sub> concentrations. Jaffe et al. (2003) found a positive  
27 association between ambient NO<sub>2</sub> and asthma ED visits among Medicaid-enrolled asthmatics in  
28 two urban cities in Ohio. When a concentration-response relationship was examined by quintile  
29 of NO<sub>2</sub> concentration, risk decreased in the second quintile and increased monotonically in the  
30 third and fourth quintiles in Cleveland, but were less smooth in Cincinnati. The lack of  
31 consistency in results may be due to the uncontrolled interaction effects of copollutants,



**Figure 3.2-9. Relative Risks (95% CI) for ED visits for asthma per 30-ppb increase in 1-h peak NO<sub>2</sub>.**



**Figure 3.2-10. Relative Risk (95% CI) in ED visits for asthma per 20-ppb increase in 24-h average NO<sub>2</sub>.**



**Figure 3.2-11. Dose response presentation of data from three studies for asthma ED visits: (a) Relative risk for an ED visit for asthma in Cincinnati and Cleveland, OH by quintile of NO<sub>2</sub>. (b) A monotonic increase in Valencia, Spain. (c) Increased risk in Barcelona, Spain, but no consistent linear trend evident.**

Source: (a) Jaffe et al., 2003; (b) Tenias et al., 1998; (c) Castellsague et al., 1995.

1 uncontrolled confounding by variables such as pollen and influenza epidemics, and incomplete  
 2 data. Tenias et al. (1998) reported a positive and significant association between ambient NO<sub>2</sub>  
 3 and ED visits in Valencia's Hospital Clinic Universitari from 1994-1995. Castellsague et al.  
 4 (1995) found a small but significant association of NO<sub>2</sub> and ED visits due to asthma in  
 5 Barcelona. Specifically, the adjusted risk estimates of asthma visits for each quartile of NO<sub>2</sub>  
 6 showed increased risks in each quartile, although the increase was not monotonic. Increased  
 7 trends were apparent in both summer and winter for the second quartile, suggesting that if any  
 8 threshold level exists, it may be quite low.

9  
 10 **COPD (ICD9: 490-496)**

11 Studies examining COPD outcomes have focused on hospital admission data, including  
 12 multicity studies in the United States (Moolgavkar, 2000), Europe (Anderson et al., 1997) and

1 Australia (Simpson et al., 2005a), and single-city studies in Canada (Yang et al., 2005), Europe  
2 (Dab et al., 1996), and Australia (Morgan et al., 1998).

3 Moolgavkar (2003) reported statistically significant associations between NO<sub>2</sub> and COPD  
4 admissions in two U.S. counties, with approximately 2% increases in Cook County, IL and Los  
5 Angeles County, CA associated with a 10-ppm increase in NO<sub>2</sub>. Multipollutant models adjusted  
6 for PM<sub>10</sub> and PM<sub>2.5</sub> attenuated these estimates slightly, though they remained statistically  
7 significant.

8 Anderson et al. (1997) examined COPD admissions in six European cities with mean  
9 24-h average and daily 1-h maximum NO<sub>2</sub> concentrations ranging from 22 to 35 ppb and 33.5 to  
10 51.3 ppb, respectively. Admissions in Amsterdam, Barcelona, London, Paris, and Rotterdam  
11 during different periods from 1977 to 1991 were analyzed for association with NO<sub>2</sub> by season  
12 (warm or cool) or for the entire year and using an incremental change of 26 ppb for either the  
13 daily 1-h maximum or the 24-h average concentration. The APHEA protocol (time series) was  
14 employed in data analysis. The authors reported associations between hospital admissions for  
15 COPD and 24-h average NO<sub>2</sub> during the warm season (RR = 1.03 [95% CI: 1.00, 1.06] lag 1)  
16 and 1-h maximum NO<sub>2</sub> (RR = 1.02 [95% CI: 1.00, 1.05] lag 1). Significant risks for  
17 hospitalization for obstructive respiratory diseases were found year round for both the 24-h  
18 average and the daily 1-h maximum value for NO<sub>2</sub> (Anderson et al., 1997). No multipollutant  
19 models were described for this meta-analysis, but black smoke, O<sub>3</sub>, and SO<sub>2</sub> all appeared to be  
20 responsible for an increased frequency of admissions. The authors reported some heterogeneity  
21 of association between cities. When the authors investigated individual cities, only London, with  
22 a 26-ppb increase in NO<sub>2</sub> was clearly significantly positive on its own for increased hospital  
23 admissions for COPD. Amsterdam showed no association between NO<sub>2</sub> and COPD admissions.

24 Simpson et al. (2005a) report small but statistically significant associations between  
25 incremental changes in NO<sub>2</sub> and COPD among patients ≥65 years using hospitalization data  
26 from four Australian cities (0.3% increase [95% CI: 0.15, 0.39]). The analysis of admissions in  
27 Sydney, Melbourne, Brisbane, and Perth sought to compare three modeling approaches for  
28 outcomes including generalized additive models (GAM), GLM and a penalized spline model.  
29 The authors found significant heterogeneity of response among results in different cities.

30 In a time-series study in Vancouver, an area with low pollution concentrations (24-h  
31 mean NO<sub>2</sub> of 17.03 ppb), Yang et al. (2005) reported associations between NO<sub>2</sub> and hospital

1 admissions for COPD in patients  $\geq 65$  years for both the lag 1 day (RR = 1.05; 95% CI: 1.01,  
2 1.09) and 7-day extended lag period (RR = 1.11 [95% CI: 1.04, 1.20]). Yang et al. (2005)  
3 reported that NO<sub>2</sub> was the strongest predictor of hospital admissions for COPD in single-  
4 pollutant models; however, in two-pollutant models with either PM<sub>10</sub> or CO, the effect of NO<sub>2</sub>  
5 was attenuated and lost significance.

6 A time-series analysis in Sydney, Australia, examined respiratory outcomes in children  
7 and adults, but generally failed to show an association between changes in NO<sub>2</sub> (24-h average)  
8 for increased hospital admissions among COPD patients  $\geq 65$  years (Morgan et al., 1998a).  
9 Similarly, a study in Paris, France, of COPD and related obstructive respiratory disease found  
10 that NO<sub>2</sub> was not statistically significantly associated with increased hospital admissions (Dab  
11 et al., 1996).

12

### 13 ***Multipollutant Modeling Results***

14 Several studies of the relationship between ambient NO<sub>2</sub> concentrations and ED visits  
15 evaluated copollutant models (Sunyer et al., 1997; Atkinson et al., 1999b; Galan et al., 2003).  
16 Individual models including NO<sub>2</sub> and black smoke (Sunyer et al., 1997; Atkinson et al., 1999b),  
17 SO<sub>2</sub> (Sunyer et al., 1997; Atkinson et al., 1999b; Galan et al., 2003), CO (Atkinson et al., 1999b),  
18 PM<sub>10</sub> (Atkinson et al., 1999b; Galan et al., 2003), or O<sub>3</sub> (Atkinson et al., 1999b) did not produce  
19 effect estimates that were significantly different than those produced when using the single-  
20 pollutant model.

21 Respiratory ED visit and hospital admission studies observed consistent NO<sub>2</sub> risk  
22 estimates with the inclusion of SO<sub>2</sub>, O<sub>3</sub>, and PM constituents (Burnett et al., 1997b, 1999; Lee  
23 et al., 2006). In one of these studies (Burnett et al., 1997), the effect of NO<sub>2</sub> was adjusted for  
24 SO<sub>4</sub><sup>2-</sup> and coefficient of haze (CoH). With the addition of SO<sub>4</sub><sup>2-</sup> in the model, the risk estimate  
25 for NO<sub>2</sub> on respiratory hospitalizations remained relatively stable; however, the inclusion of the  
26 CoH term in the model yielded an attenuated risk estimate.

27 In field studies, power to assess independent NO<sub>2</sub> effects may be limited by small sample  
28 sizes and short follow-up times. Yet, the NO<sub>2</sub> effect was not as robust to the addition of  
29 copollutants in multipollutant models, with a few exceptions. For example, in Schwartz et al.  
30 (1994), the significant association between cough and 4-day mean NO<sub>2</sub> remained unchanged in  
31 models that included O<sub>3</sub> but was attenuated and lost significance in two-pollutant models



1 including PM<sub>10</sub> or SO<sub>2</sub>. In Mortimer et al. (2002), effects were attenuated in multipollutant  
2 models that included O<sub>3</sub>; O<sub>3</sub> and SO<sub>2</sub>; or O<sub>3</sub>, SO<sub>2</sub>, and PM<sub>10</sub>. In Schildcrout et al. (2006), each  
3 20-ppb increase in NO<sub>2</sub> increased risk of cough (OR 1.09 [95% CI: 1.03, 1.15]). This result was  
4 unchanged in two-pollutant models with CO, PM<sub>10</sub>, or SO<sub>2</sub>.

5 Multipollutant regression analyses indicated that NO<sub>2</sub> risk estimates, in general, were not  
6 sensitive to the inclusion of copollutants, including CO and SO<sub>2</sub>. There is limited evidence that  
7 PM<sub>10</sub> or other ambient particle constituents do have an effect on NO<sub>2</sub> risk estimates. These  
8 results suggest that the effect of NO<sub>2</sub> on respiratory health outcomes appears to be robust and  
9 independent of the effects of other gaseous copollutants but that ambient particles may confound  
10 NO<sub>2</sub> effects on health.

## 11 12 **Summary**

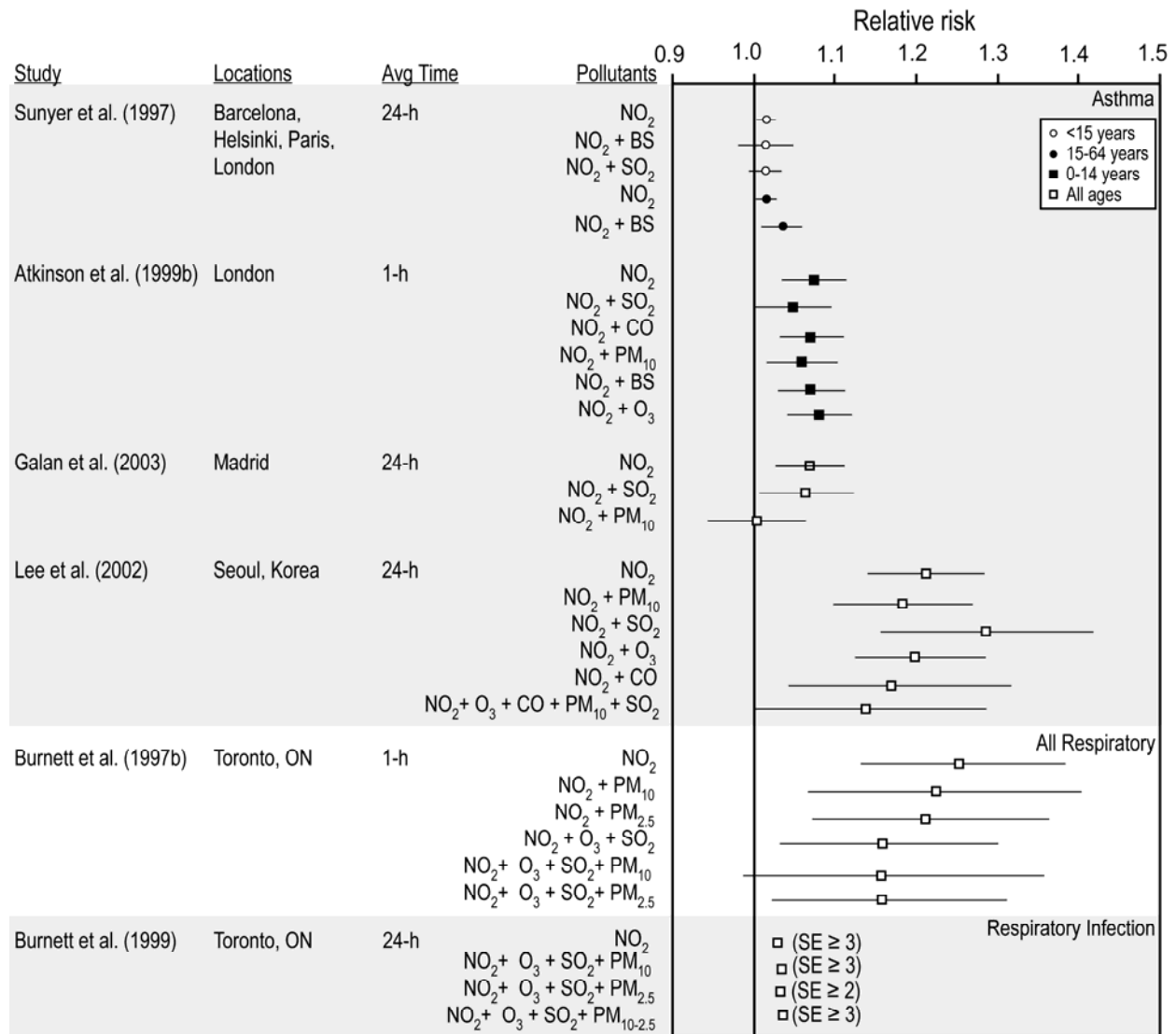
13 Overall, there is strong evidence that increased ED visits and hospital admissions for  
14 respiratory causes, including asthma and COPD, are associated with ambient concentrations of  
15 NO<sub>2</sub>. Still, it is important to note that there uncertainty remains regarding the role of NO<sub>2</sub> as a  
16 surrogate for other pollutants, which could confound results presented in this section. In nearly  
17 all of these studies, there was evidence of correlations between NO<sub>2</sub> and CO and PM measures.  
18 Some authors found statistically significant associations between asthma ED visits or hospital  
19 admissions and NO<sub>2</sub> in single-pollutant models and subsequently examined these associations in  
20 two- or multipollutant models. In São Paulo, asthma remained strongly associated with NO<sub>2</sub>  
21 after adjustment for PM<sub>10</sub> and SO<sub>2</sub>, but not when CO was included in the model (Farhat et al.,  
22 2005). In Madrid, significant association with NO<sub>2</sub> remained after adjustment for SO<sub>2</sub> but not  
23 PM<sub>10</sub> (Galan et al., 2003). Similarly, in Turin, adjustment for total suspended particulate (TSP)-  
24 attenuated effects of NO<sub>2</sub> (Migliaretti et al., 2004) demonstrating that the responses to individual  
25 pollutant species were not independent. In a meta-analysis of four cities in the APHEA project,  
26 NO<sub>2</sub> remained associated with asthma for adults after adjustment for the effects of black smoke  
27 (Sunyer et al., 1997). In associations between ED visits to hospitals and NO<sub>2</sub>, Atkinson et al.  
28 (1999a) found that effects of NO<sub>2</sub> remained after adjustment for SO<sub>2</sub>, CO, PM<sub>10</sub>, or black smoke.  
29

### 3.2.1.8 Integration of Evidence and Biological Plausibility for Associations between NO<sub>2</sub> Exposure and Respiratory Health Effects

Taken together, recent studies provide strong evidence that NO<sub>2</sub> is associated with a range of respiratory effects, from biochemical effects or biological markers of inflammation to hospitalization for respiratory diseases. This conclusion is based on findings from numerous new epidemiological studies, including multipollutant studies that control for the effects of other pollutants, and is supported by evidence from toxicological and controlled human exposure studies.

The body of evidence from epidemiological studies has grown substantially since the 1993 AQCD. The strongest new epidemiological evidence is for associations with increased ED visits and hospital admissions for respiratory causes, especially asthma and COPD, with ambient concentrations of NO<sub>2</sub>. In nearly all of these studies, there were high correlations between ambient measures of NO<sub>2</sub> and CO and PM. The effect estimates for NO<sub>2</sub> were robust after the inclusion of CO and PM in multipollutant models, as shown in Figure 3.2-12. Looking within the new epidemiological findings, there is evidence of coherence for respiratory effects in the associations between short-term NO<sub>2</sub> exposure and respiratory symptoms and ED visits or hospital admissions for respiratory diseases, particularly asthma. Recent studies reporting associations between indoor and personal exposure to NO<sub>2</sub> and respiratory symptoms or lung function provide key support for epidemiological findings of associations with ambient NO<sub>2</sub> concentrations (e.g., Pilotto et al., 2004). In particular, an intervention study (Pilotto et al., 2004) provides strong evidence of a detrimental effect of exposure to NO<sub>2</sub>.

Evidence from experimental studies provides plausibility for effects on the respiratory system with NO<sub>2</sub> exposure. Toxicological studies have shown that lung host defenses, including mucociliary clearance and AM and other immune cell functions, are sensitive to NO<sub>2</sub> exposure, with numerous measures of such effects observed at concentrations below 1 ppm. These are potential mechanisms underlying more frank effects observed in epidemiological studies, such as hospital admissions or ED visits for respiratory diseases, including asthma, COPD, or respiratory infections. A recent epidemiological study (Chauhan et al., 2003) provided evidence that increased personal exposures to NO<sub>2</sub> worsen virus-associated symptoms and lung function in



**Figure 3.2-12. Relative risks and 95% confidence intervals for associations between ED visits and hospital admissions for respiratory diseases and 24-h average NO<sub>2</sub> concentrations (per 20 ppb).**

1 children with asthma. The limited evidence from controlled human exposure studies indicates  
 2 that NO<sub>2</sub> may increase susceptibility to injury by subsequent viral challenge.

3 Controlled human exposure studies provide strong evidence for airways responsiveness  
 4 with short-term exposure to NO<sub>2</sub>; however, they do not provide compelling evidence for other  
 5 respiratory effects, such as changes in lung function or subjective respiratory symptoms.

1 Biological markers of inflammation are reported in antioxidant-deficient laboratory animals with  
2 exposures to 0.4-ppm NO<sub>2</sub>. Normal animals do not respond until exposed to much higher levels,  
3 i.e., 5-ppm NO<sub>2</sub>. Recent epidemiological studies provide somewhat mixed evidence on short-  
4 term exposure to NO<sub>2</sub> and inflammatory responses in the airways. The controlled human  
5 exposure studies provide evidence for airways inflammation at NO<sub>2</sub> concentrations of <2.0 ppm;  
6 the onset of inflammatory responses in healthy subjects appears to be between 100 and  
7 200 ppm-min, i.e., 1 ppm for 2 to 3 h.

8 The biochemical effects observed in the respiratory tract following exposure to NO<sub>2</sub>  
9 include chemical alteration of lipids, amino acids, proteins, enzymes, and changes in  
10 oxidant/antioxidant homeostasis, with membrane polyunsaturated fatty acids and thiol groups as  
11 the main biochemical targets for NO<sub>2</sub> exposure. However, the biological implications of such  
12 alterations are unclear.

13 Asthma is the respiratory illness for which most evidence is available. The following  
14 section provides further integrative discussion with a particular focus on the epidemiological and  
15 experimental study findings relevant to asthmatics.

## 16 17 ***Integration with a Focus on Asthma***

### 18 19 *Asthmatic Children*

20 There is strong evidence from epidemiological studies for an association between NO<sub>2</sub>  
21 exposure and children's hospital admissions, ED visits, and calls to doctors for asthma. This  
22 evidence came from large longitudinal studies, panel studies, and time-series studies. NO<sub>2</sub>  
23 exposure is associated with aggravation of asthma effects that include symptoms, medication  
24 use, and lung function. Effects of NO<sub>2</sub> on asthma were most evident with cumulative lag of 2 to  
25 6 days, rather than same-day levels of NO<sub>2</sub>. Time-series studies also demonstrated a relationship  
26 in children between hospital admissions or ED visits for asthma and NO<sub>2</sub> exposure, even after  
27 correcting for PM and CO concentrations.

28 As discussed in Section 3.2.1.3, large, longitudinal cohort studies in the United States,  
29 Canada and Europe have reported significant associations between level of NO<sub>2</sub> and risk of  
30 respiratory symptoms in children, particularly asthmatic children. A number of recent panel  
31 studies of asthmatic children have also generally reported significant associations between  
32 respiratory symptoms and NO<sub>2</sub> exposure. The effects were observed with lag periods ranging

1 from 2 days to a 6-day moving average for NO<sub>2</sub>, suggesting that NO<sub>2</sub> may not only be directly  
2 triggering asthma attack, but may also be acting indirectly as a primer for subsequent antigen  
3 exposure.

4       Important evidence is also available from epidemiological studies of indoor NO<sub>2</sub>  
5 exposures. A number of recent studies show associations with wheeze, chest tightness, and  
6 length of symptoms (Belanger et al., 2006); respiratory symptom rates (Nitschke et al., 2006);  
7 school absences (Pilotto et al., 1997a); respiratory symptoms, likelihood of chest tightness, and  
8 asthma attacks (Smith et al., 2000); and severity of virus-induced asthma (Chauhan et al., 2003).  
9 However, several studies (Mukala et al., 1999, 2000; Farrow et al., 1997) evaluating younger  
10 children found no association between indoor NO<sub>2</sub> and respiratory symptoms.

11       Human clinical studies of the health effects of NO<sub>2</sub> have not been conducted on children;  
12 however, toxicological studies provide strong biological plausibility of the effects of NO<sub>2</sub>  
13 exposure on asthma exacerbation in children. Several endpoints in these studies point to  
14 mechanisms by which NO<sub>2</sub> can produce these adverse health effects. These mechanisms include  
15 reduced mucociliary clearance, AM function, such as depressed phagocytic activity and altered  
16 humoral- and cell-mediated immunity. NO<sub>2</sub> effects on AMs at levels as low as 1.0 ppm are  
17 especially relevant to effects seen with asthmatics. This exposure causes decreased bactericidal  
18 activity, reduced cell viability, disruption of membrane integrity and reduced cell number. These  
19 are all mechanisms that can provide biological plausibility for the NO<sub>2</sub> effects in asthmatic  
20 children observed in epidemiological studies. Chauhan et al. (2003) have reviewed potential  
21 mechanisms by which NO<sub>2</sub> exacerbates asthma in the presence of viral infections. They include  
22 “direct effects on the upper and lower airways by ciliary dyskinesia, epithelial damage, increases  
23 in pro-inflammatory mediators and cytokines, rises in IgE concentration, and interactions with  
24 allergens, or indirectly through impairment of bronchial immunity.”

25       As stated above, asthma is a chronic inflammatory disorder. Animal studies provide  
26 strong evidence that NO<sub>2</sub> can produce inflammation and lung permeability changes. One  
27 limitation of this work is that effects on markers of inflammation, such as BAL fluid levels of  
28 total protein and lactate dehydrogenase, and recruitment or proliferation of leukocytes, occur  
29 only at exposure levels of ≥5 ppm. Studies conducted at these higher exposure concentrations  
30 may elicit mechanisms of action and effects that do not occur at near-ambient levels of NO<sub>2</sub>.

1 *Asthmatic Adults*

2 One of the key health effects of concern at near-ambient concentrations of NO<sub>2</sub> is  
3 increases in airways responsiveness of asthmatic individuals after short-term exposures.  
4 Epidemiological studies show a strong association between NO<sub>2</sub> exposures and asthma  
5 symptoms in adult asthmatics. Outdoor NO<sub>2</sub> studies in Europe found an increased risk of  
6 shortness of breath (Hiltermann et al., 1998); prevalence for wheeze, phlegm, cough, and  
7 breathing problems upon waking (Von Klot et al., 2002); and severe asthma symptoms (Forsberg  
8 et al., 1998) associated with NO<sub>2</sub> levels. Several indoor NO<sub>2</sub> exposure studies have shown  
9 associations, as well. Endpoints include likelihood of cough (Smith et al., 2000) and rescue  
10 medication use (Ng et al., 2001).

11 Controlled human exposure studies are limited to acute, fully reversible functional and/or  
12 symptomatic responses and are further limited to exposures of only mild asthmatics. Increased  
13 airways responsiveness, the most sensitive indicator of response, occurred with resting exposures  
14 of 0.2 to 0.5-ppm NO<sub>2</sub>. Other studies showed an absence of effects on airways responsiveness at  
15 much higher concentrations, up to 4 ppm. Lung function effects are variable and inconsistent;  
16 however, there is little evidence for effects at <0.25 ppm. There is no obvious explanation for  
17 the apparent lack of concentration-response relationship; therefore, the findings do not provide  
18 clear quantitative conclusions about the health effects of short-term exposures to NO<sub>2</sub>. Effects at  
19 lower levels are seen in the epidemiological studies described above.

20  
21

22 **3.2 CARDIOVASCULAR EFFECTS ASSOCIATED WITH SHORT-  
23 TERM NO<sub>2</sub> EXPOSURE**

24

25 **3.2.2.1 Studies of Hospital Admissions and Emergency Department Visits for  
26 Cardiovascular Disease (CVD)**

27 Our current review includes approximately 40 studies published since 1992 that address  
28 the effect of NO<sub>x</sub> exposure on hospitalizations or ED visits for CVD. No studies were reviewed  
29 that linked CVD hospital admissions or emergency visits with exposure to NO<sub>x</sub> prior to the  
30 release of the document in 1993. Cases of CVD are typically identified using ICD codes  
31 recorded on hospital discharge records. However, counts of hospital or ED admissions are also  
32 used. Studies of ED visits include cases that are less severe than those that have been  
33 documented to require hospitalization via discharge records and these studies are clearly

1 distinguished in the annex tables. All CVD diagnoses or selected diagnoses for diseases or  
2 disease grouping such as myocardial infarction (MI), ischemic heart disease (IHD), congestive  
3 heart failure (CHF), angina pectoris, cardiac arrhythmia, cerebrovascular diseases, or stroke are  
4 outcomes considered in the analyses.

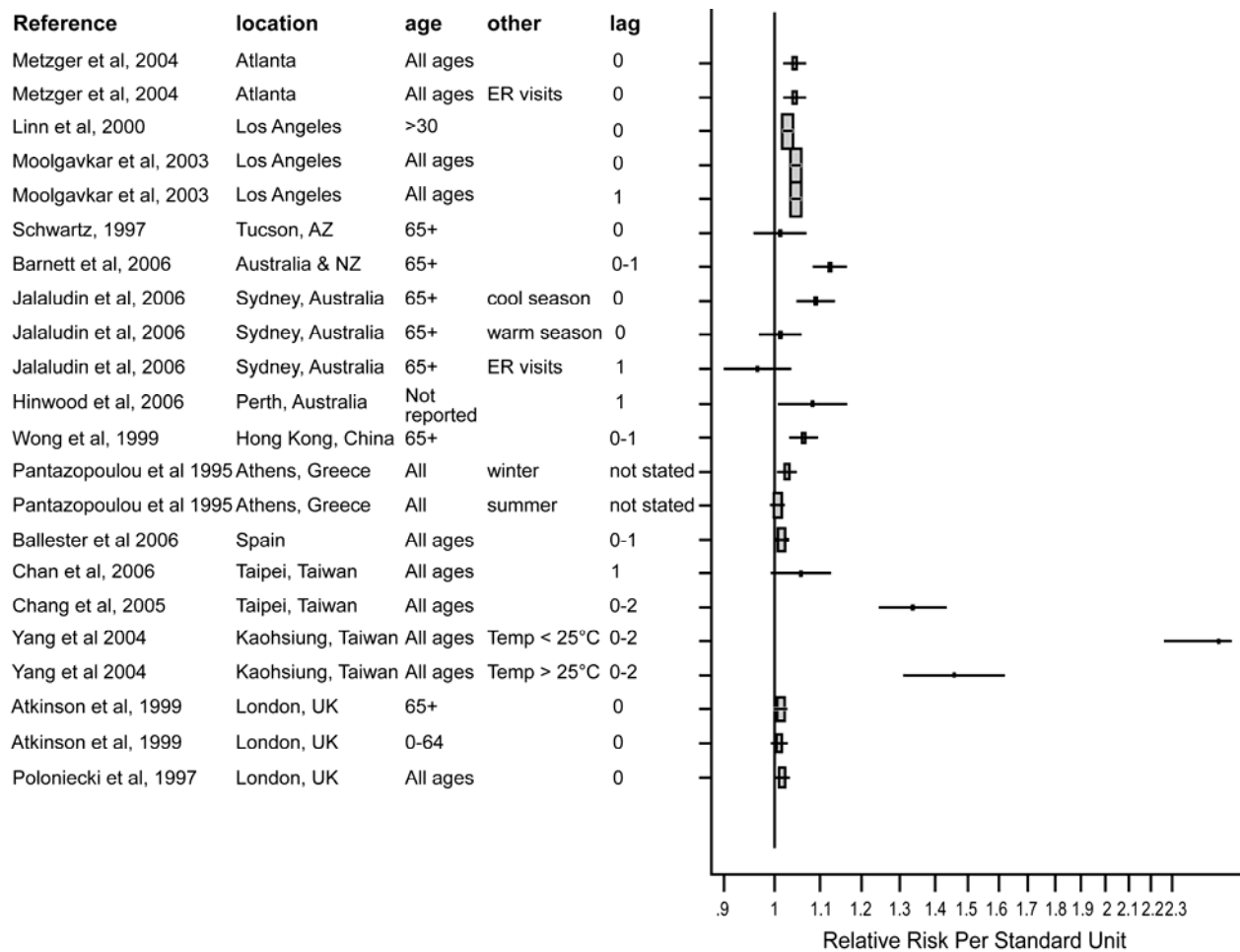
#### 5 6 ***All CVD (ICD9 390-459)***

7 All studies of the association of hospitalizations or ED visits are positive and most  
8 confidence limits exclude the null value, with the exception of the lag 1 results for the elderly  
9 reported by Jalaludin et al., 2006. Results from these studies are summarized in Figure 3.2-13.  
10 However, findings from multicity studies conducted in Spain (Ballester et al., 2006) and  
11 Australia (Barnett et al., 2006) indicate weak associations in single-pollutant models, which are  
12 attenuated in multipollutant models. Analyses from a study conducted in Los Angeles and Cook  
13 Counties (Moolgavkar et al., 2003), also show an increase in hospital admissions for CVD  
14 associated with NO<sub>2</sub> that was diminished in multipollutant models. Associations were also  
15 diminished with the use of increasingly stringent convergence criteria applied for subsequent  
16 reanalyses (Moolgavkar, 2003). Another large multiyear study conducted in Los Angeles  
17 County reports a small increase in CVD admissions, but authors could not distinguish  
18 independent effects of specific pollutants (Linn et al., 2000).

19 Pekkanen et al. (2000) reports an association between plasma fibrinogen, a risk factor and  
20 possible biomarker for cardiovascular disease, and NO<sub>2</sub> (See Section 3.1.2.3). In addition,  
21 findings from controlled human exposure and animal studies may provide limited biological  
22 plausibility and mechanistic evidence for the epidemiology findings. These studies evaluated  
23 cardiovascular endpoints such as blood pressure, cardiac output and hematological parameters  
24 (Folinsbee et al., 1978; Linn et al., 1985b; Posin et al., 1978; Frampton et al., 2002; Suzuki et al.,  
25 1981, 1984; Mersch et al., 1973; Kunitomo et al., 1984; Takano et al., 2004).

#### 26 27 ***Heart Disease (ICD9 390-429)***

28 Some investigators distinguish heart diseases from diseases of the cerebrovascular  
29 system, involving blood vessels supplying blood to the brain, in their research. Findings from  
30 studies conducted in Canada and the Detroit area report positive associations of heart disease  
31 with NO<sub>2</sub> that are diminished in two-pollutant models (Fung et al., 2005; Burnett et al., 1997a,  
32 1999).



**Figure 3.2-13. Relative risks (95% CI) for associations between 24-h NO<sub>2</sub> exposure (per 20 ppb) and hospitalizations or emergency department visits for all cardiovascular diseases (CVD). Primary author and year of publication, city, stratification variable(s), and lag are listed. Results for lags 0 or 1 are presented, as available.**

1            However, findings from several European and Australian multicity studies indicate robust  
2 associations between NO<sub>2</sub> and hospitalization for heart disease (Von Klot et al., 2005; Barnett  
3 et al., 2006; Simpson et al., 2005a). Von Klot et al. analyzed prospective cohort data from five  
4 European cities (Augsburg, Barcelona, Helsinki, Rome, and Stockholm) to determine if  
5 readmissions for cardiac-related disorders were associated with ambient NO<sub>2</sub> level. The range in  
6 24-h NO<sub>2</sub> level was 15.8 to 26 ppb in the five cities studied. Von Klot reports a 3.2% (95% CI:  
7 1.4, 5.1) increase in re-admissions among cardiac patients, which was independent of the effect



1 of PM<sub>10</sub> and O<sub>3</sub> in two-pollutant models. A 20-ppb increase in 24-h average NO<sub>2</sub> level was  
2 associated (RR = 1.14 (95% CI: 1.08, 1.21) with an increase in hospital admissions among the  
3 elderly in five cities in Australia and New Zealand (Barnett et al., 2006). Daily maximum NO<sub>2</sub>  
4 level was associated with a similar increase in hospitalizations (2.8% (95% CI: 1.38, 4.26) per  
5 increase of 9.3-ppb NO<sub>2</sub>) among the elderly of Sydney, Australia (Jalaludin et al., 2006). Daily  
6 1-h maximum NO<sub>2</sub> level was associated with increases in hospitalizations among the elderly  
7 (RR: 1.06 [95% CI: 1.03, 1.08] per 30-ppb increase in NO<sub>2</sub>) (Simpson et al., 2005a). Increases  
8 in admissions were also reported for all ages (Jalaludin et al., 2006; Simpson et al., 2005a). An  
9 earlier study also yielded positive results with an increase of 20 ppb in the 24-h average NO<sub>2</sub>  
10 level associated with a RR of 1.09 (95% CI: 1.06, 1.14) increase in cardiac admissions among  
11 all ages and similar increase among the elderly (Morgan et al., 1998a). Results were diminished  
12 slightly when the 1-h maximum NO<sub>2</sub> level was used (Morgan et al., 1998a).

13 Some results remained robust in two-pollutant models (Simpson et al., 2005a; Morgan  
14 et al., 1998a) while results reported in other studies were attenuated by the inclusion of CO in  
15 multipollutant models (Jalaludin et al., 2006; Barnett et al., 2006). Two Asian case crossover  
16 studies (Chang et al., 2005; Yang et al., 2004) report increases in cardiac disease that are robust  
17 in multipollutant models. However, the effects reported by Yang et al. were orders of magnitude  
18 above results reported in other studies (Yang et al., 2006). A time-series analysis conducted in  
19 Hong Kong reported small associations that were not robust in multipollutant models (Wong  
20 et al., 1999).

## 21 22 *Arrhythmia (ICD9 427)*

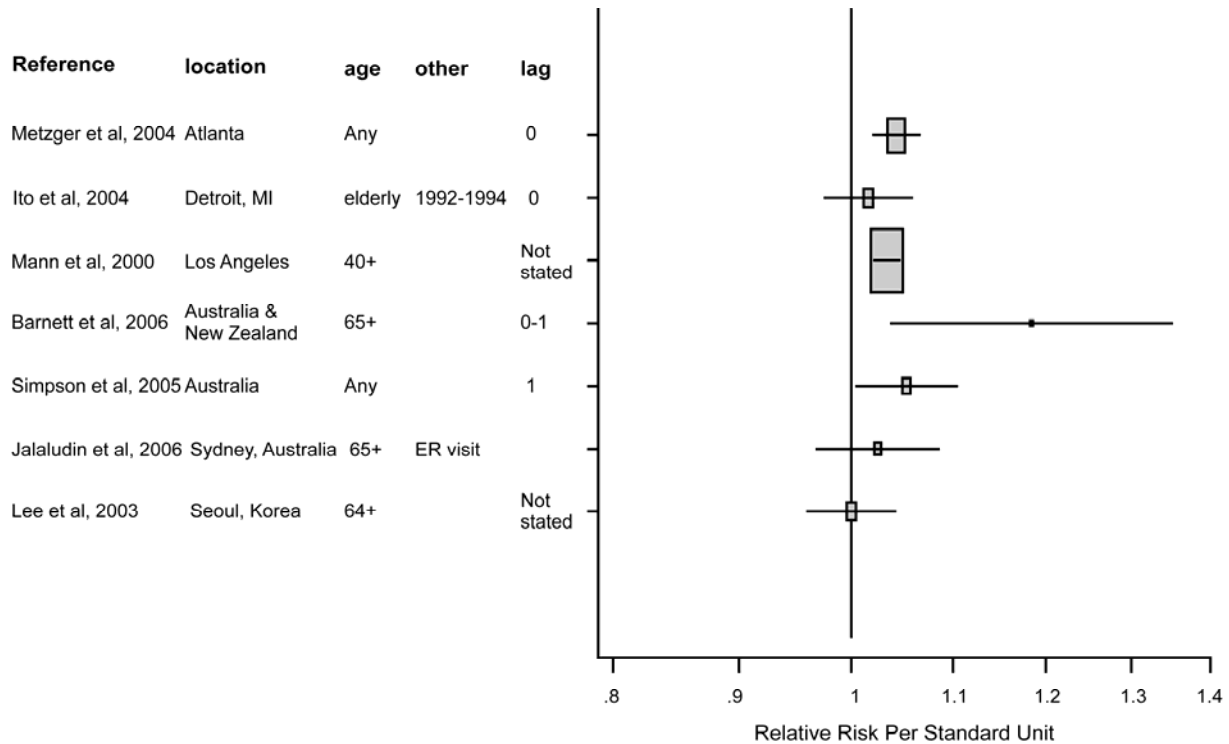
23 Arrhythmia is variation from the normal heart rhythm. Ventricular arrhythmias cause  
24 most sudden cardiac deaths while atrial fibrillation or supraventricular arrhythmia, the most  
25 common type of arrhythmia, is not a direct threat to life (Dockery et al., 2005). However, risk  
26 factors for atrial fibrillation include hypertension, coronary artery disease and COPD and atrial  
27 fibrillation is associated with increased risk of stroke.

28 Hospital or ED admissions for arrhythmia were inconsistently associated with increases  
29 in ambient NO<sub>2</sub> level. Some studies report positive associations (Rich et al., 2006a; Mann et al.,  
30 2002; Barnett et al., 2006) while others report null associations (Metzger et al., 2004; Lippmann  
31 et al., 2000; reanalysis Ito, 2003, 2004). Studies of heart rate variability (HRV) and implanted

1 cardioverter defibrillators provide limited evidence to support a possible association between  
 2 arrhythmias and NO<sub>2</sub> or ambient pollution levels (See Section 3.1.2.3).

3  
 4 ***Ischemic Heart Disease (IHD) ICD9 410-414***

5 Some studies further delineate cardiac disease by using groupings of specific conditions  
 6 such as IHD, which includes acute MI, previous MI, angina pectoris, and other chronic IHD.  
 7 Figure 3.2-14 summarizes studies that include hospitalization for IHD as an outcome. Two U.S.  
 8 studies report associations of IHD hospitalizations or ED visits with ambient NO<sub>2</sub> level (Mann  
 9 et al., 2002; Metzger et al., 2004), while another reports no association (Lippmann et al., 2000;  
 10 reanalysis Ito, 2003, 2004). The study by Mann et al. (2002) was novel, because exposures were  
 11 assigned based on proximity to the monitoring station and results were pooled across air basins.  
 12 Independent NO<sub>2</sub> effects were not distinguished in these studies, however (Mann et al., 2002;  
 13 Metzger et al., 2004).



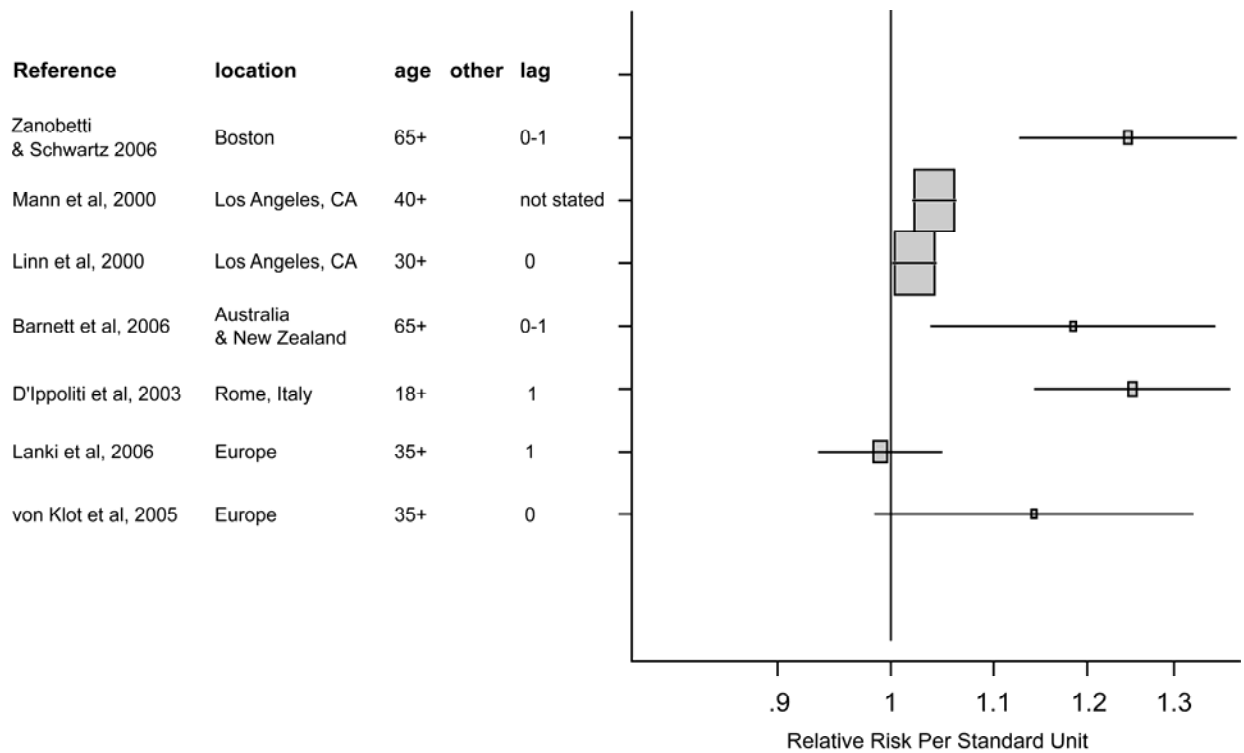
**Figure 3.2-14. Relative risks (95% CI) for associations between 24-h NO<sub>2</sub> exposure (per 20 ppb) and hospitalizations for Ischemic Heart Disease (IHD). Primary author and year of publication, city, stratification variable(s), and lag are listed. Results for lags 0 or 1 are presented, as available.**

1 A European study conducted in Helsinki reports an association of NO with both  
2 hospitalization and ED visits for IHD while no association with NO<sub>2</sub> was observed (Ponka and  
3 Virtanen, 1996). In a multicity study in Europe, a 4.2-ppb increase NO<sub>2</sub> was associated with an  
4 increase in readmission for angina pectoris (ICD9 411, 413) among cardiac patients (von Klot  
5 et al., 2005). O<sub>3</sub> may have been contributed to this observed effect, however (von Klot et al.,  
6 2005). Small associations of IHD admissions with incremental increases in NO<sub>2</sub> have been  
7 observed in Australian populations (Barnett et al., 2006; Jalaludin et al., 2006; Simpson et al.,  
8 2005a). In a study with populations from seven cities in Australia, Barnett et al., (2006) found  
9 that there was no association between NO<sub>2</sub> and IHD admissions for the age group 25 to 64 years.  
10 For persons 65 years and older an increase of 2.5% ([95% CI: 1.0, 4.1] lag 0 to 1) in IHD  
11 hospital admissions per 5.1-ppb increase in NO<sub>2</sub> was reported. A study of four Australian cities  
12 reported a 1-ppb change in the daily maximum 1-h concentration of NO<sub>2</sub> was associated with a  
13 0.17% change in hospitalization for IHD ([95% CI: 0.07, 0.27] lag 0) among the elderly. In a  
14 single-city study of Sydney, Jalaludin et al. (2006) reported a 2.11% ([95% CI: 0.34, 3.01] lag 0)  
15 change in the rate of hospitalization of patients 65 years and older per 9.3-ppb increase in daily  
16 maximum 1-h concentration of NO<sub>2</sub>. A seasonal effect of NO<sub>2</sub> on hospitalization for IHD was  
17 observed (Jalaludin et al., 2006). However, the effect of NO<sub>2</sub> was diminished when it was  
18 modeled with CO (Jalaludin et al., 2006).

19 Wong et al. (1999) reported no association between IHD admissions and 24-h average  
20 NO<sub>2</sub> concentration in Hong Kong (Wong et al., 1999). A Korean study reported an 8% increase  
21 in hospitalization for IHD during all seasons (RR = 1.08 [95% CI: 1.036, 1.14] lag 5) per  
22 14.6-ppb increase in 24-h concentration of NO<sub>2</sub> (Lee et al., 2003a). The relative risk increased  
23 dramatically for those ≥64 years of age in the summer months to 25% for the same incremental  
24 change (RR = 1.25 [95% CI: 1.11, 1.41] lag 5). The effect of NO<sub>2</sub> remained robust in  
25 two-pollutant models with PM<sub>10</sub> (RR = 1.09 [95% CI: 1.02, 1.16] lag 5) but not with CO.

### 26 27 ***Hospital Admissions for Myocardial Infarction (MI) (ICD9 410)***

28 Key studies of hospital admissions for MI are summarized in Figure 3.2-15. Positive  
29 associations of emergency admissions for MI and increases in ambient NO<sub>2</sub> level were reported  
30 in Boston (Zanobetti and Schwartz, 2006) and Southern California (Linn et al., 2000; Mann  
31 et al., 2002). Zanobetti and Schwartz report an increase of 10.21% (3.82-15.61%, lag 0) in



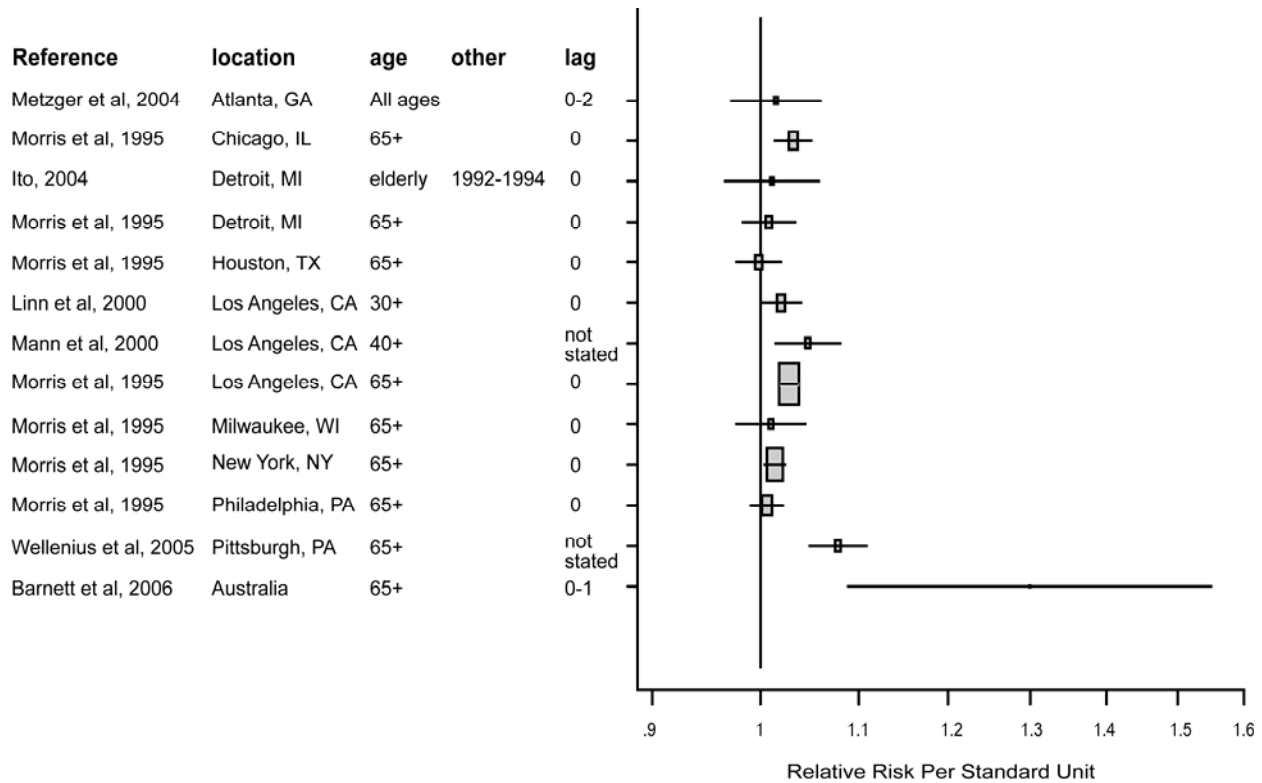
**Figure 3.2-15. Relative risks (95% CI) for associations between 24-h NO<sub>2</sub> exposure (per 20 ppb) and hospitalizations for myocardial infarction (MI). Primary author and year of publication, city, stratification variable(s), and lag are listed. Results for lags 0 or 1 are presented as available.**

1 emergency MI admissions per 16.8-ppb incremental increase in 24-h average NO<sub>2</sub> among the  
 2 elderly. NO<sub>2</sub>, black carbon (BC), and CO were correlated during the warm season making it  
 3 difficult to distinguish the effect of NO<sub>2</sub> (Zanobetti and Schwartz, 2006). Linn et al. reported a  
 4 1.1% ([95% CI: 0.6, 1.6%], lag 0) increase in admissions for MI per 10-ppb increase in NO<sub>2</sub> and  
 5 Mann et al. reported a 2.04% ([95% CI: 1.05, 3.02%], lag 0-1) increase per 10-ppb increase in  
 6 NO<sub>2</sub> in Southern California. Again, NO<sub>2</sub> and CO were highly correlated making it difficult to  
 7 distinguish an independent effect of NO<sub>2</sub>. Pooled results from two European multicity studies  
 8 are not consistent. Von Klot et al. report a 2.8% RR of 1.10 (95% CI: 1.01, 1.21) increase in MI  
 9 admissions and Lanki et al. reports a null effect (lag 1). One single-city study in Italy  
 10 (D'Ippoliti et al., 2003) found positive significant associations between 24-h average NO<sub>2</sub> level

1 and admission for MI. D'Ippoliti observed a 2.6% (95% CI: 0.2, 5.2%) increase with a 20-ppb  
 2 increase in NO<sub>2</sub>.

3  
 4 **Congestive Heart Failure (CHF) (ICD9 428)**

5 Studies of hospital admissions and ED visits for CHF have produced mixed results  
 6 (Figure 3.2-16). A seven city study conducted in the US among the elderly found positive  
 7 associations in Los Angeles (RR: = 1.32 [1.21, 1.43]), Chicago (RR: = 1.37 [1.14, 1.61]) and  
 8 New York (RR: = 1.14 [1.04, 1.28]) per 20-ppb increase in NO<sub>2</sub> (Morris et al., 1995). Estimates  
 9 were close to the null value in Philadelphia, Detroit, Houston, and Milwaukee and only the  
 10 estimate for New York remained significant in multi-pollutant models (Morris et al., 1995).



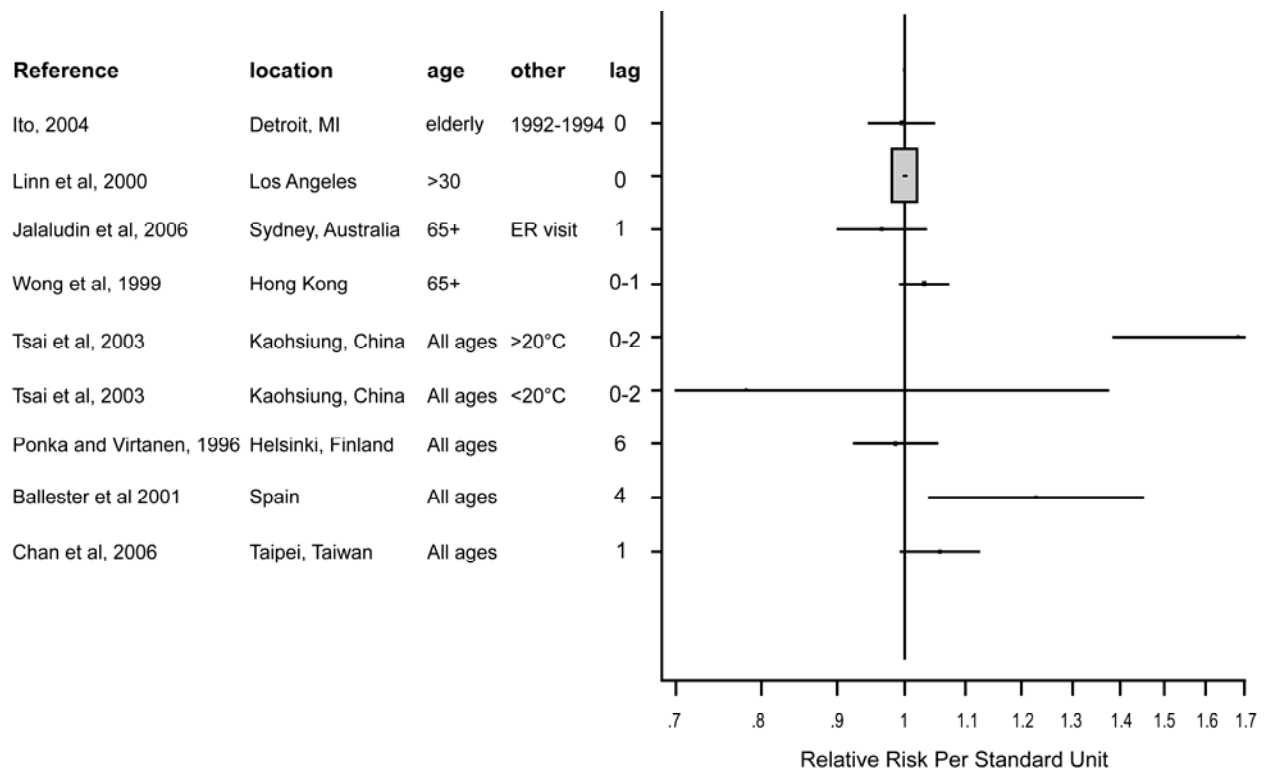
**Figure 3.2-16. Relative risks (95% CI) for associations between 24-h NO<sub>2</sub> exposure (per 20 ppb) and hospitalizations for congestive heart failure (CHF). Primary author and year of publication, city, stratification variable(s), and lag are listed. Results for lags 0 or 1 are presented as available.**

1 A more recent study of an elderly population conducted in Pittsburgh and Allegheny  
2 County reported a OR = 1.08 increase in CHF admissions with a 20-ppb increase in NO<sub>2</sub>  
3 (Wellenius et al., 2005). The result for NO<sub>2</sub> was not affected by PM<sub>10</sub> but was diminished in a  
4 two-pollutant model containing CO. A 6.9% (OR = 1.3 [95% CI: 1.09, 1.55], lag 0) increase in  
5 CHF admissions was observed in a seven city Australian study (pooled results) per 20-ppb  
6 increase in 24-h average NO<sub>2</sub> concentration among the elderly (Barnett et al., 2006).

### 7 8 ***Hospital Admissions for Stroke and Cerebrovascular Disease (ICD9 430-448)***

9 Cerebrovascular diseases include ICD9 codes 430-448 and may be more narrowly  
10 defined to capture ischemic stroke (IS) (ICD9 433-435) and hemorrhagic stroke (HS) (ICD9  
11 430). Studies that have evaluated the association between all cerebrovascular disease and  
12 ambient NO<sub>2</sub> concentration are summarized in Figure 3.2-17. Results from these studies are  
13 inconsistent. The largest study described in the figure, conducted by Linn et al. (2000), did not  
14 find an effect for NO<sub>2</sub> on cerebrovascular disease admission (Linn et al., 2000). However, these  
15 authors report an increase in hospitalizations of 2.7% (95% CI: 2.6, 2.8) for occlusive stroke  
16 during the winter months (year round effect also observed). Wellenius et al. (2005) found a  
17 2.94% increase in IS admissions per 11.93% increase in 24-h average NO<sub>2</sub> level (multipollutant  
18 models were not examined) (Wellenius et al., 2005). In a Canadian study, Villeneuve et al.  
19 (2006) reported an association between NO<sub>2</sub> exposure and IS during the winter months, among  
20 the elderly (OR = 1.26 [95% CI: 1.09, 1.46], lag 3).

21 Results from Europe are also inconsistent with Ponka and Virtanen (1996) reporting null  
22 results and Ballester et al. (2001) reporting a 1.15 ([95% CI: 1.02, 1.29], lag 4) increase in  
23 cerebrovascular admissions per 20-ppb increase in 24-h NO<sub>2</sub> level. No association was found in  
24 Sydney between daily 1-h maximum NO<sub>2</sub> concentration and cerebrovascular disease (Jalaludin  
25 et al., 2006). No associations between air pollutants and stroke were reported in a multicity  
26 study conducted in Australia and New Zealand (Barnett et al., 2006). Investigations of NO<sub>2</sub>  
27 cerebrovascular disease and stroke have been conducted in populations in Asia (Chan et al.,  
28 2006; Tsai et al., 2003). An increase in 24-h average concentration NO<sub>2</sub> of 20 ppb resulted in  
29 increased risk of hospitalization (OR = 1.67 [95% CI: 1.48, 1.87] lag 0 to 2) in Taiwan (Tsai  
30 et al., 2003). The associations were stronger on warm days. Using multipollutant models that  
31 were adjusted for PM<sub>10</sub>, CO, O<sub>3</sub>, and SO<sub>2</sub>, Tsai et al. (2003) found the association between NO<sub>2</sub>  
32 and IS as well as PIH remained significant (p < 0.01). By contrast, a study by Chan et al. in



**Figure 3.2-17. Relative risks (95% CI) for associations between 24-h NO<sub>2</sub> exposure (per 20 ppb) and hospitalizations for 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.**

1 Taiwan, failed to demonstrate statistically significant associations between NO<sub>2</sub> and rates of  
 2 hospital admissions for cerebrovascular disease, stroke (IS or HS) (Chan et al., 2006).

3  
 4 ***Vaso-occlusion in Sickle Cell***

5 A recent study evaluated the association of pain in Sickle Cell patients, which is thought  
 6 to be caused by vaso-occlusion, with air pollution (Yallop et al., 2007). A time series analysis  
 7 was performed to link daily hospital admissions for acute pain among sickle cell patients with  
 8 daily air pollution levels in London using the cross correlation function. No association was  
 9 reported for NO<sub>2</sub>. However, Yallop et al. observed an association (CCF = -0.063, lag 0) for NO,  
 10 CO, and O<sub>3</sub>.

1 ***Multipollutant Modeling Results***

2 The majority of studies of CVD hospital and ED admissions reported results from  
3 multipollutant models. Since results from multipollutant models in single-city studies are  
4 generally less stable because of smaller sample sizes, results for multicity studies are discussed  
5 in this section. Burnett et al. (1997a) report robust estimates for cardiac disease hospital  
6 admissions and NO<sub>2</sub>, whereas the observed association for cardiac hospitalizations and PM were  
7 explained by gaseous pollutants. In another multicity study conducted in the same area,  
8 associations of NO<sub>2</sub> with cardiac disease were not attenuated when CO, SO<sub>2</sub>, and PM variables  
9 were included in the models (Burnett et al., 1999). Relative risks for NO<sub>2</sub> with CHF were  
10 diminished in multipollutant models used in a multicity study including six U.S. cities (Morris  
11 et al., 1995). Wellenius et al. (2005a) did not report multipollutant results for a study of  
12 ischemic and HS. In this study, only ischemic stroke was associated with NO<sub>2</sub> exposure.

13 Investigators conducting a multicity study in Australia observed a different effect with  
14 the NO<sub>2</sub> association, with CVD weakening after inclusion of CO in the model (Barnett et al.,  
15 2006). The authors hypothesized that NO<sub>2</sub> is a good surrogate for PM, which may explain the  
16 observed effect of NO<sub>2</sub> on admissions for CVD (Barnett et al., 2006). Results from another  
17 multicity study in Australia are similar with authors suggesting that NO<sub>2</sub> effects on cardiac  
18 disease and IHD may be confounded by PM (Simpson et al., 2005b). Multicity studies from  
19 Europe are inconsistent with regard to the results of multipollutant models. Von Klot et al.  
20 reported that the effect of NO<sub>2</sub> on MI, angina, and cardiac disease was independent of PM<sub>10</sub> and  
21 O<sub>3</sub> (von Klot et al., 2005), while Ballester et al. (2006) reported that the effect of NO<sub>2</sub> on cardiac  
22 disease was diminished in two-pollutant models. Copollutant model results for NO<sub>2</sub> were not  
23 reported for a third multicity study in Europe (Lanki et al., 2006).

24 Results from multipollutant models have been inconsistent in large multicenter studies  
25 that have evaluated the effect NO<sub>2</sub> on hospital and ED visits for CVD. In general, investigators  
26 acknowledge the limitations of multipollutant models to tease out independent contributions of  
27 individual and highly correlated pollutants. In addition, most researchers generally acknowledge  
28 the possibility that observed effects on the cardiovascular system are related to traffic pollutants.  
29 See Table 3.2-3 for the effects of including a copollutant with NO<sub>2</sub> in multipollutant models.

30



### 3.2.2.2 Heart Rate Variability, Repolarization, Arrhythmia, and Other Measures Cardiovascular Function Associated with Short-Term NO<sub>2</sub> Exposure

#### *Heart Rate Variability*

HRV, a measure of the beat-to-beat change in heart rate (HR), 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-MI population. Lower time domain as well as frequency domain variables (i.e., 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 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). However, acute changes in HRV parameters do not necessarily occur immediately prior to sudden fatal ventricular arrhythmias (Waxman et al., 1994). HRV itself is not the causative agent, nor has it been implied to be a causative agent in any of the studies performed to date. Altered HRV, including changes in HRV associated with exposure to criteria pollutants, may be a marker for enhanced risk.

The potentially adverse effects of air pollutants on cardiac autonomic control were examined in a large population-based study, among the first in this field. Liao et al. (2004) investigated short-term associations between ambient pollutants and cardiac autonomic control from the fourth cohort examination (1996 to 1998) of the population-based Atherosclerosis Risk in Communities (ARIC) Study. PM<sub>10</sub>, NO<sub>2</sub>, and other gaseous air pollutants were examined in this study. PM<sub>10</sub> (24-h average) and NO<sub>2</sub> exposures (24-h average) 1 day prior to the randomly allocated examination date were used. The mean (SD) NO<sub>2</sub> level was 21 (8) ppb. They calculated 5-min HRV indices between 8:30 a.m. and 12:30 p.m. and used logarithmically-transformed data on high-frequency (0.15 to 0.40 Hz) and low-frequency (0.04 to 0.15 Hz)

1 power, standard deviation of normal R-R intervals (SDNN), and mean HR. The effective sample  
2 sizes for NO<sub>2</sub> and PM<sub>10</sub> were 4,390 and 4,899, respectively, from three U.S. study centers in  
3 North Carolina, Minnesota, and Mississippi. PM<sub>10</sub> concentrations measured 1 day prior to the  
4 HRV measurements were inversely associated with both frequency- and time-domain HRV  
5 indices. Ambient NO<sub>2</sub> concentrations were inversely associated with high-frequency power and  
6 SDNN. In single-pollutant models, a 20-ppb increase in ambient NO<sub>2</sub> was associated with a  
7 5% reduction (95% CI: 0.7, 9.2), in mean SDNN. Consistently more pronounced associations  
8 were suggested between PM<sub>10</sub> and HRV among persons with a history of hypertension.

9 The Liao et al. (2004) findings were cross-sectionally derived from a population-based  
10 sample and reflect the short-term effects of air pollution on HRV. When the regression  
11 coefficients for each individual pollutant model were compared, the effects for PM<sub>10</sub> were  
12 considerably larger than the effects for gaseous pollutants such as NO<sub>2</sub>. Because of the  
13 population-based sample, this study is more generalizable than other smaller panel studies. The  
14 findings are suggestive of short-term effects of air pollutants, including NO<sub>2</sub>, on HRV at the  
15 population level.

16 Various measures of HRV have been examined in relation to daily levels of ambient air  
17 pollution in other studies (Chan et al., 2005; Wheeler et al., 2006; Holguin et al., 2003;  
18 Luttmann-Gibson et al., 2006; Schwartz et al., 2005). Chan et al. (2005) recruited 83 patients  
19 from the cardiology section of a hospital in Taiwan. Patients included 39 with coronary heart  
20 disease (CHD) and 44 with more than one risk factor for CHD. The authors reported finding  
21 significant associations between increases in NO<sub>2</sub> and decline in SDNN (NO<sub>2</sub> lagged 4 to 8 h)  
22 and LF (NO<sub>2</sub> lagged 5 or 7 h) (see Annex Table AX6.4.1 for quantitative results). There were no  
23 significant associations for r-MSSD or HF and NO<sub>2</sub>. None of the other pollutants tested (PM<sub>10</sub>,  
24 CO, SO<sub>2</sub>, O<sub>3</sub>) were significantly associated with any of the HRV measured. Wheeler et al.  
25 (2006) examined HRV and ambient air pollution in Atlanta in 12 patients who had an MI from  
26 3 to 12 months prior to enrollment and 18 COPD patients. The results in the two patient groups  
27 were quite different: increasing concentration of NO<sub>2</sub> in the previous 4-h significantly reduced  
28 SDNN in MI patients and significantly increased SDNN in COPD patients (see Annex Table  
29 AX6.10). Similar significant associations were seen with increases in 4-h ambient PM<sub>2.5</sub>. The  
30 PM<sub>2.5</sub> concentrations were moderately correlated with NO<sub>2</sub> levels ( $r = 0.4$ ).

1 In contrast, Holguin et al. (2003) PM<sub>2.5</sub> concentrations were moderately correlated with  
2 NO<sub>2</sub> levels ( $r = 0.04$ ) in 34 elderly adults in Mexico City and found no significant associations  
3 with increases in NO<sub>2</sub>, but did find significant effects of PM<sub>2.5</sub> on HF, particularly among  
4 hypertensive subjects. Similarly, Luttmann-Gibson et al. (2006) also found significant effects of  
5 PM<sub>2.5</sub> and SO<sub>4</sub> on HRV measured in a panel of 32 senior adults in Steubenville, OH, but  
6 observed no effect of increasing NO<sub>2</sub>. Likewise, Schwartz et al. (2005) found significant effects  
7 of increases in PM<sub>2.5</sub> on measures of HRV, while no associations with NO<sub>2</sub> were observed. A  
8 population-based study of air pollutants and HRV was conducted in Boston, MA on 497 men  
9 from the VA Normative Aging Study (NAS) (Park et al., 2005b). The mean (SD) 24-h  
10 average NO<sub>2</sub> concentration was 22.7 (6.2) ppb. Associations with HRV outcomes were observed  
11 with a 4-h moving average of O<sub>3</sub> and PM<sub>2.5</sub> concentrations, but not with NO<sub>2</sub>.

### 12 13 ***Repolarization Changes***

14 In addition to the role played by the autonomic nervous system in arrhythmogenic  
15 conditions, myocardial vulnerability and repolarization abnormalities are believed to be key  
16 factors contributing to the mechanism of such diseases. Measures of repolarization include QT  
17 duration, T-wave complexity, variability of T-wave complexity, and T-wave amplitude. A  
18 prospective panel study, conducted in East Germany, analyzed 12 repeat ECG recordings for  
19 56 males with IHD (Henneberger et al., 2005). Ambient air pollutants measured at fixed  
20 monitoring sites were used to assign individual exposures for 0 to 5, 5 to 11, 12 to 17, 18 to 23,  
21 0 to 23 h and for 2 to 5 days prior to the EEG. Pollutants considered were ultrafine particles  
22 (UFP), accumulation mode particle (ACP), PM<sub>2.5</sub>, elemental carbon (EC), organic carbon (OC),  
23 SO<sub>2</sub>, NO<sub>2</sub>, NO, and CO. Associations were observed between (1) QT duration and EC and OC;  
24 (2) T-wave amplitude and UFP, ACP and PM<sub>2.5</sub>; and (3) T-wave complexity and PM<sub>10</sub>, EC, and  
25 OC. NO ( $r = 0.83$ ) and NO<sub>2</sub> (0.76) were highly correlated with UFP but were not associated  
26 with repolarization abnormalities.

### 27 28 ***Arrhythmias Recorded on Implanted Defibrillators***

29 Implanted cardioverter defibrillators (ICDs) are often used in cardiac patients to detect  
30 life-threatening arrhythmias. Among patients with ICDs in eastern Massachusetts, increases in  
31 ambient NO<sub>2</sub> was significantly associated with defibrillator discharges (Peters et al., 2000) and  
32 ventricular arrhythmias (Dockery et al., 2005; Rich et al., 2005), but not with paroxysmal atrial

1 fibrillation (PAF) episodes (Rich et al., 2006a). In a pilot study, Peters et al. (2000) abstracted  
2 device records for 3 years for each of 100 patients with ICDs. Defibrillator discharge events  
3 were positively associated with the previous day and 5-day mean NO<sub>2</sub> concentrations: each  
4 20-ppb increase in the previous day's NO<sub>2</sub> level was associated with an increased risk of a  
5 discharge event (OR = 1.55 [95% CI: 1.05, 2.29]) (see Annex Table AX6.4.2 for the increase  
6 associated with a 20-ppb increase in NO<sub>2</sub>).

7 Two separate analyses of the same cohort of patients examined the association between  
8 air pollution and the incidence of ventricular arrhythmias (Dockery et al., 2005; Rich et al.,  
9 2005). A total of 203 patients with ICDs who lived within 25 miles of the ambient monitoring  
10 site in Boston were monitored. Data included a total of 635 person-years of follow-up or an  
11 average of 3.1 years per subject. The median (IQR) 48-h average NO<sub>2</sub> concentration was  
12 22.7 (7.7) ppb. In the analysis by Dockery et al. (2005), positive associations were observed  
13 between ventricular arrhythmias within 3 days of a prior event and a 2-day mean of several air  
14 pollutants including PM<sub>2.5</sub>, BC, NO<sub>2</sub>, CO, and SO<sub>2</sub>. Rich et al. (2005, 2006a) examined  
15 associations between ambient air pollution levels and two other cardiac endpoints recorded by  
16 the ICDs, namely ventricular arrhythmias (Rich et al., 2005) and PAF episodes (Rich et al.,  
17 2006a). In single-pollutant models, each 20-ppb increase in the mean NO<sub>2</sub> level over the  
18 previous 2 days was associated with an increased likelihood of ventricular arrhythmia, OR = 1.54  
19 (95% CI: 1.11, 2.18). The association with NO<sub>2</sub> was not significant in two pollutant models  
20 with PM<sub>2.5</sub>, but remained marginally significant in models with O<sub>3</sub> (2.0-ppb increase in 24-h  
21 moving average NO<sub>2</sub> was associated with an OR = 1.36 [95% CI: 1.00, 1.80]). There was a  
22 strong association between an increase of NO<sub>2</sub> (by 20 ppb) and ventricular arrhythmia in the  
23 presence of ventricular arrhythmia within the previous 72 h (OR = 2.09 [95% CI: 1.26, 3.51]).  
24 No association was found between NO<sub>2</sub> levels and PAF (Rich et al., 2006b).

25

## 26 ***Plasma Fibrinogen, Biomarker for Cardiovascular Disease***

27

### 28 *Epidemiological Studies*

29 In a large cross-sectional study of 7,205 office workers in London, Pekkanen et al. (2000)  
30 collected blood samples and analyzed the association between plasma fibrinogen, a risk factor  
31 for CVD, and ambient levels of air pollution. In models adjusting for weather and demographic  
32 and socioeconomic factors, there was an increased likelihood of blood levels of fibrinogen

1 >3.19 g/l (90th percentile) for each 20-ppb increase in NO<sub>2</sub> lagged by 3 days (OR = 1.14 [95%  
2 CI: 1.03, 1.25]). The correlation between daily NO<sub>2</sub> and other traffic-related pollutants were  
3 high: daily levels of black smoke (r = 0.75), PM<sub>10</sub> (r = 0.76), SO<sub>2</sub> (r = 0.62), CO (r = 0.81). The  
4 authors suggest that the increased concentrations of fibrinogen, a mediator of cardiovascular  
5 morbidity and mortality, may be an indicator of inflammatory reactions caused by air pollution.

6 Pekkanen et al. (2002) enrolled a panel of 45 adults with coronary heart disease in order  
7 to examine associations between heart function as measured by risk of ST-segment depression  
8 and particulate pollution. Level of particulate and gaseous pollutants, including NO<sub>2</sub>, lagged by  
9 2 days was found to have the strongest effect on risk of ST-segment depression during mild  
10 exercise tests (OR = 14.1 [95% CI: 3.0, 65.4] for ST-segment depression of >0.1mV with a  
11 20-ppb increase in NO<sub>2</sub> lagged by 2 days). A large (n = 863) cross-sectional study of resting  
12 heart rate (HR) of adults in France found significant associations between elevated levels of NO<sub>2</sub>  
13 within 8-h of measurement and resting HR of ≥75 beats per minute (bpm) (OR = 2.7 [95% CI:  
14 1.2, 5.4] for resting HR >75 bpm for each 20-ppb increase in NO<sub>2</sub>) (Ruidivets et al., 2005).

#### 15 16 *Controlled Human Exposure and Animal Studies*

17 Folinsbee et al. (1978) studied three groups of 5 healthy males exposed to 0.62-ppm NO<sub>2</sub>  
18 for 2 h. The groups differed by duration of exercise during exposure: 15, 30, or 60 min. In  
19 addition to pulmonary function, outcome measures included indirect calorimetry, cardiac output  
20 using the CO<sub>2</sub> rebreathing technique, blood pressure, HR, and diffusing capacity of the lung for  
21 carbon monoxide (DLCO). There were no significant effects for the individual groups, or for the  
22 15 subjects analyzed together. However, the small number of subjects in each group limited  
23 statistical power.

24 Drechsler-Parks (1995) assessed changes in cardiac output using noninvasive impedance  
25 cardiography. Eight older adults (56 to 85 years of age) were exposed to 0.60-ppm NO<sub>2</sub>,  
26 0.45-ppm O<sub>3</sub>, and the combination of 0.60-ppm NO<sub>2</sub> + 0.45-ppm O<sub>3</sub> for 2-h with intermittent  
27 exercise. The exercise-induced increase in cardiac output was smaller with the NO<sub>2</sub> + O<sub>3</sub>  
28 exposures than with the filtered air or O<sub>3</sub> exposures alone. There were no significant differences  
29 in minute ventilation, HR, or cardiac stroke volume, although the mean stroke volume was lower  
30 for NO<sub>2</sub> + O<sub>3</sub> than for air. The author speculated that chemical interactions between O<sub>3</sub> and NO<sub>2</sub>

1 at the level of the epithelial lining fluid led to the production of nitrite, leading to vasodilatation,  
2 with reduced cardiac preload and cardiac output. This study has not been repeated.

3 One previous study (Linn et al., 1985a) reported small but statistically significant  
4 reductions in blood pressure after exposure to 4-ppm NO<sub>2</sub> for 75 min, a finding consistent with  
5 systemic vasodilatation in response to the exposure. However, many subsequent studies at  
6 concentrations generally less than 4 ppm have not reported changes in blood pressure in response  
7 to NO<sub>2</sub> exposure.

8 There is also evidence that NO<sub>2</sub> exposure may affect circulating red blood cells. Posin  
9 et al. (1978) exposed 10 healthy males to 1- or 2-ppm NO<sub>2</sub> for 2.5 to 3.0-h daily for 2 days.  
10 Blood obtained immediately after the second exposure showed a reduced hemoglobin and  
11 hematocrit (NO<sub>2</sub>: 41.96 ± 2.75; sham exposure: 43.18 ± 2.83, p = 0.001) and reduced red blood  
12 cell acetyl cholinesterase levels. However, the control air exposures were not identical to and  
13 concurrent with the NO<sub>2</sub> exposures, a potential flaw in the study design.

14 In the study by Frampton et al. (2002), healthy subjects were exposed to air or 0.6- or  
15 1.5-ppm NO<sub>2</sub> for 3-h with intermittent exercise, and blood was obtained 3.5-h after exposure.  
16 There was a significant, concentration-related reduction in hematocrit and hemoglobin in both  
17 males and females, confirming the findings of Posin et al. (1978). These studies suggest that  
18 NO<sub>2</sub> exposure in the range of 1- to 2-ppm for a few hours is sufficient to alter the red blood cell  
19 membrane. The reductions in blood hemoglobin were not sufficiently large to result in health  
20 effects for these healthy subjects. However, in the Frampton study, the reduction in hemoglobin  
21 represented the equivalent of about 200 mL of blood loss for a 70-kg male. This could  
22 conceivably have adverse cardiovascular consequences for someone with significant underlying  
23 lung disease, heart disease, or anemia.

24 These few studies suggest systemic effects of NO<sub>2</sub> exposure at concentrations below  
25 2.0 ppm, but the observations require confirmation. The results on the effect of NO<sub>2</sub> on various  
26 hematological parameters in animals are inconsistent and thus, provide little biological  
27 plausibility for the epidemiology findings. There have also been reported changes in the red  
28 blood cell membranes of experimental animals following NO<sub>2</sub> exposure. Red blood cell  
29 D-2,3-diphosphoglycerate was reportedly increased in guinea pigs following exposure to  
30 0.36-ppm NO<sub>2</sub> for 1 week (Mersch et al., 1973). An increase in red blood cell sialic acid,  
31 indicative of a younger population of red blood cells, was reported in rats exposed to 4.0-ppm

1 NO<sub>2</sub> continuously for 1 to 10 days (Kunimoto et al., 1984). However, in another study, exposure  
2 to the same concentration of NO<sub>2</sub> resulted in a decrease in red blood cells (Mochitate and Miura,  
3 1984). A more recent study (Takano et al., 2004) using an obese rat strain found changes in  
4 blood triglycerides, high-density lipoprotein cholesterol (HDL), and HDL/total cholesterol ratios  
5 with a 24-week exposure to 0.16-ppm NO<sub>2</sub>.

6 In the only study conducted below 5-ppm NO<sub>2</sub> that evaluated methemoglobin formation,  
7 Nakajima and Kusumoto (1968) reported that, in mice exposed to 0.8-ppm NO<sub>2</sub> for 5 days, the  
8 amount of methemoglobin was not increased. This is in contrast to some (but not all) in vitro  
9 and high concentrations of NO<sub>2</sub> in vivo studies, which have found methemoglobin effects  
10 (U.S. Environmental Protection Agency, 1993).

### 11 12 **3.2.2.3 Integration for Effects of Short-Term NO<sub>2</sub> Exposure on Cardiovascular Outcomes**

13 Cardiac rhythm disorders are the leading cause of hospital admissions for CVD in the  
14 United States (Henneberger et al., 2005). Results from a Boston area study of ventricular  
15 arrhythmias indicate an association of arrhythmia with short-term exposure to ambient (Peters  
16 et al., 2000; Dockery et al., 2005; Rich et al., 2005; see also Annex Table AX2.6.4-1). However,  
17 arrhythmias were also associated with PM exposure and high correlations among ambient  
18 pollutants were reported. A study of repolarization changes and air pollution also points to PM  
19 as a possible causative agent (Henneberger et al., 2005). Results from studies of HRV are also  
20 inconclusive with regard to the effect of NO<sub>2</sub> on the cardiovascular system (Liao et al., 2004;  
21 Chan et al., 2005; Wheeler et al., 2006; Holguin et al., 2003; Luttmann-Gibson et al., 2006;  
22 Schwartz et al., 2005).

23 Numerous studies have shown an association between NO<sub>2</sub> exposure and hospital or ED  
24 admissions for CVD including IHD, MI, CFH, cardiac disease not involving the peripheral  
25 circulation, and cerebrovascular disease. Both incremental changes in daily 1-h maximum  
26 concentrations and 24-h averages of NO<sub>2</sub> are associated with IHD admissions worldwide.  
27 Associations between hospital admissions for MI and ambient NO<sub>2</sub> are reported in both the  
28 United States and Europe. Associations between ambient NO<sub>2</sub> and CHF were found in several  
29 U.S. cities and in an Australian multicity meta-analysis. Studies of ambient NO<sub>2</sub> and other  
30 cardiac disease or cerebrovascular disease are fewer and provide less consistent results.  
31 However, evidence from multipollutant models is inconsistent and does not suggest that the  
32 effects of NO<sub>2</sub> are robust when adjusted for other traffic-related pollutants.

1 A small number of controlled human exposure studies have evaluated cardiovascular  
2 responses to NO<sub>2</sub> exposure. Typically, the studies utilize short exposure durations and small  
3 numbers of subjects, resulting in poor characterization of NO<sub>2</sub> concentration-response and, thus,  
4 are of limited value in providing corroborating evidence for the epidemiological findings. Early  
5 work (Folinsbee et al., 1978) using exposures of 0.62 ppm for 2-h found no changes in HR and  
6 cardiac output in healthy males. Another early study (Linn et al., 1985a) demonstrated  
7 reductions in blood pressure (BP) following an exposure of 4-ppm NO<sub>2</sub> for 75 min. A more  
8 recent study (Gong et al., 2005) demonstrated reductions in diastolic BP following a 2-h  
9 exposure to 0.4-ppm NO<sub>2</sub>. Another cardiovascular endpoint affected by NO<sub>2</sub> is circulating red  
10 blood cells. Posin et al. (1978) found reduced hemoglobin, hematocrit, and RBC  
11 acetylcholinesterase levels following exposures to 1- or 2-ppm NO<sub>2</sub> for 2.5 to 3-h daily for 2  
12 days. This was confirmed in a study (Frampton et al., 2002) exposing healthy subjects to 0.6 and  
13 1.5 ppm for 3-h with intermittent exercise. These alterations in hemoglobin and hematocrit do  
14 not pose a risk to healthy individuals, but could account for the observed cardiovascular  
15 morbidity and mortality in individuals with underlying IHD, CHF, and other heart and lung  
16 disease.

17 There are limited experimental data on the effects of ambient NO<sub>2</sub> on the heart. Two  
18 early studies (Suzuki et al., 1981, 1984) showed reductions in PaO<sub>2</sub> at 4 ppm for 3 months and  
19 reduced HR at 1.2 and 4 ppm for 1 month. Data on the effects of NO<sub>2</sub> on hematological  
20 endpoints are inconsistent; however, two early studies (Mersch et al., 1973; Kunimoto et al.,  
21 1984) found changes in RBC membranes and sialic acid. A more recent study (Takano et al.,  
22 2004) using an obese rat strain found changes in blood triglycerides, HDL, and HDL/total  
23 cholesterol ratios with a 24-week exposure to 0.16-ppm NO<sub>2</sub>. These studies may provide limited  
24 biological plausibility and mechanistic evidence for an effect on the cardiovascular system.

25  
26

### 27 **3.3 MORTALITY WITH SHORT-TERM EXPOSURE TO NO<sub>2</sub>**

28 Since the 1993 AQCD, a number of studies, mostly using time-series analyses, reported  
29 short-term mortality risk estimates for NO<sub>x</sub>, in most cases, (see Annex Table AX6.7). There  
30 was no epidemiological study reviewed in the 1993 AQCD that examined the mortality effects of  
31 ambient NO<sub>x</sub>. However, since most of these studies' original focus or hypothesis was on PM, a  
32 quantitative interpretation of the NO<sub>x</sub> mortality risk estimates requires caution.

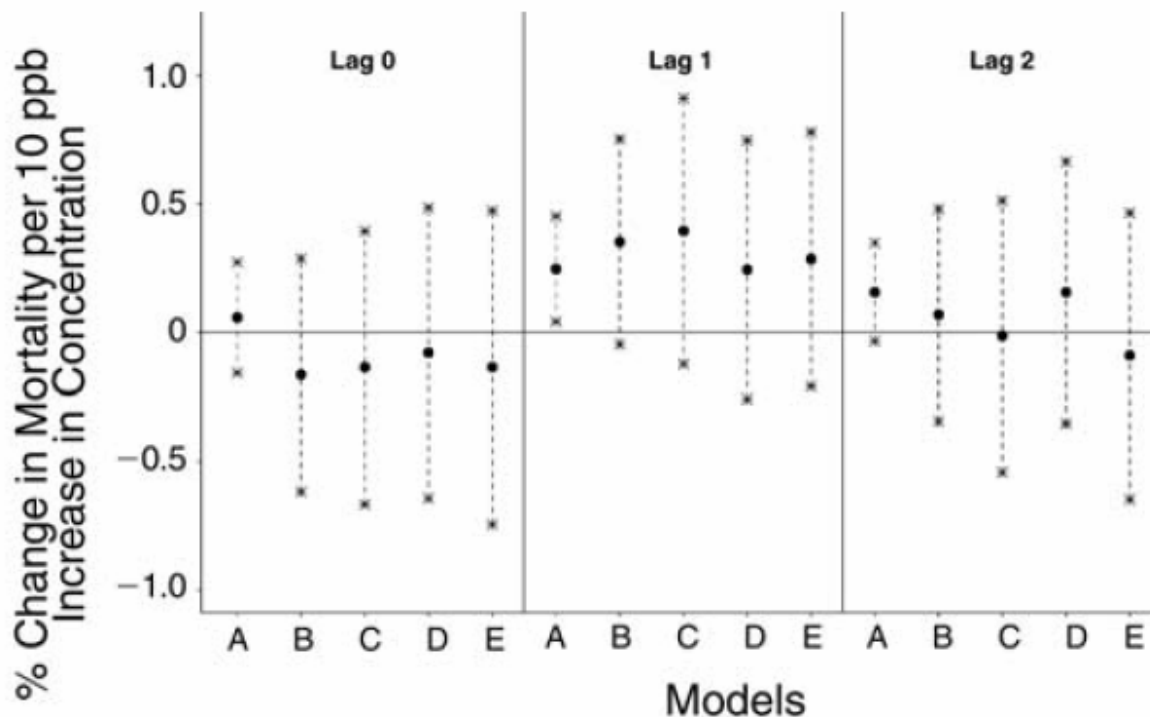


### 1 **3.3.1 Multicity Studies and Meta-Analyses**

2 In reviewing the range of mortality risk estimates, multicity studies provide the most  
3 useful information because they analyze multiple cities data in a consistent method, avoiding  
4 potential publication bias. Risk estimates from multicity studies are also usually reported for  
5 consistent lag days, further reducing potential bias caused by choosing the “best” lag in  
6 individual studies. There have been several multicity studies from the United States, Canada,  
7 and Europe. Meta-analysis studies also provide useful information on describing heterogeneity  
8 of risk estimates across studies, but unlike multicity studies, the heterogeneity of risk estimates  
9 seen in meta-analysis may also reflect the variation in analytical approaches across studies.  
10 Multicity studies and meta-analyses are reviewed in the following section, and effect estimates  
11 from these studies are summarized. Discussion will focus on the studies that were not affected  
12 by GAM with convergence issues (Dominici et al., 2002; Ramsay et al., 2003) unless otherwise  
13 noted when the studies raise relevant issues.

#### 14 **3.3.1.1 United States Largest 90 Cities Study**

15 The time-series analysis of the largest 90 U.S. cities (Samet et al., 2000; reanalysis  
16 Dominici et al., 2003) in the National Morbidity, Mortality, and Air Pollution Study (NMMAPS)  
17 is by far the largest multicity study conducted to date to investigate the mortality effects of air  
18 pollution, but its primary interest was PM (i.e., PM<sub>10</sub>). It should also be noted that, according to  
19 the table of mean pollution levels in the original report (Samet et al., 2000), NO<sub>2</sub> was not  
20 measured in 32 of the 90 cities. The analysis in the original report used GAMs with default  
21 convergence criteria and Dominici et al. (2003) reanalyzed the data using GAM with stringent  
22 convergence criteria as well as using GLM. It should be noted that this model’s adjustment for  
23 weather effects employs more terms than other time-series studies in the literature, suggesting  
24 that the model adjusts for potential confounders more aggressively than the models in other  
25 studies. PM<sub>10</sub> and O<sub>3</sub> (in summer) appeared to be more strongly associated with mortality than  
26 the other gaseous pollutants. Regarding NO<sub>2</sub>, SO<sub>2</sub>, and CO, the authors stated, “The results did  
27 not indicate associations of these pollutants with total mortality.” However, it should be noted  
28 that, as with PM<sub>10</sub>, NO<sub>2</sub>, SO<sub>2</sub>, and CO, each showed the strongest association at lag 1 day (for  
29 O<sub>3</sub>, it was lag 0 day), and as with PM<sub>10</sub>, addition of other copollutants in the model at lag 1 day  
30 hardly affected the mortality risk estimates of these gaseous pollutants. Figure 3.3-1 shows the  
31



**Figure 3.3-1. Posterior means and 95% posterior intervals of national average estimates for NO<sub>2</sub> 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<sub>2</sub> alone; B = NO<sub>2</sub> + PM<sub>10</sub>; C = NO<sub>2</sub> + PM<sub>10</sub> + O<sub>3</sub>; D = NO<sub>2</sub> + PM<sub>10</sub> + SO<sub>2</sub>; E = SO<sub>2</sub> + PM<sub>10</sub> + CO.**

Source: Dominici et al. (2003).

1 total mortality risk estimates for NO<sub>2</sub> from Dominici et al. (2003). The NO<sub>2</sub> risk estimates in the  
 2 multipollutant models were about the same or larger. Thus, these results do not indicate that the  
 3 NO<sub>2</sub>-mortality association was confounded by PM<sub>10</sub> or other pollutants (and vice versa).

#### 4 **3.3.1.2 Canadian Multicity Studies**

5 There have been four Canadian multicity studies: (1) analysis of gaseous pollutants in  
 6 11 cities from 1980 to 1991 (Burnett et al., 1998); (2) analysis of PM<sub>2.5</sub>, PM<sub>10-2.5</sub>, and gaseous  
 7 pollutants in 8 cities from 1986 to 1996 (Burnett et al., 2000); (3) analysis of PM<sub>2.5</sub>, PM<sub>10-2.5</sub>, and  
 8 gaseous pollutants in 12 cities from 1981 to 1999 (Burnett et al., 2004); and, (4) analysis of NO<sub>2</sub>,  
 9 NO, PM<sub>2.5</sub> and its selected components, PM<sub>10-2.5</sub>, PM<sub>10</sub>, as well as an examination of correlation

1 between these pollutants and selected traffic-related species including VOCs and PAHs with  
2 between 1984 and 2000 (Brook et al., 2007). Since the first two studies were affected by the  
3 GAM issue (only the PM indices were reanalyzed for the second study in Burnett and Goldberg,  
4 2003), and the third study is most extensive both in terms of the length and coverage of cities, the  
5 discussion will focus on the third study.

6 Total (nonaccidental), cardiovascular, and respiratory mortality were analyzed in the  
7 Burnett et al. (2004) study. Daily 24-h average as well as 1-h max values were analyzed for all  
8 the gaseous pollutants and CoH. For PM<sub>2.5</sub>, PM<sub>10-2.5</sub>, PM<sub>10</sub>, CoH, SO<sub>2</sub>, and CO, the strongest  
9 mortality association was found at lag 1, whereas for NO<sub>2</sub>, it was the 3-day moving average  
10 (i.e., average of 0-, 1-, and 2-day lags), and for O<sub>3</sub>, it was the 2-day moving average. Of the  
11 single- day lag estimates for NO<sub>2</sub>, lag 1-day showed the strongest associations, which is  
12 consistent with the NMMAPS result. The 24-h average values showed stronger associations than  
13 the 1-h max values for all the gaseous pollutants and CoH except for O<sub>3</sub>. The pooled NO<sub>2</sub>  
14 mortality risk estimate in a single-pollutant model (for all available days) was 2.0% (95% CI:  
15 1.1, 2.9) per 20-ppb increase in the 3-day moving average of NO<sub>2</sub>. NO<sub>2</sub> was most strongly  
16 correlated with CoH (r = 0.60), followed by PM<sub>2.5</sub> (r = 0.48). However, the NO<sub>2</sub>-mortality  
17 association was insensitive to adjustment for these or any of other pollutants in the two-pollutant  
18 models. For example, the NO<sub>2</sub> mortality risk estimate with CoH in the model was 2.6% (95%  
19 CI: 1.3, 3.9) per 20-ppb increase in the 3-day moving average of NO<sub>2</sub>. The model with O<sub>3</sub>  
20 resulted in the largest reduction in the NO<sub>2</sub> risk estimate, 1.8% (95% CI: 0.9, 2.7). For the data  
21 subset for days when PM<sub>2.5</sub> data were available (every 6th day), the NO<sub>2</sub> risk estimate was 2.4%  
22 (95% CI: 0.7, 4.1) and 3.1% (95% CI: 1.2, 5.1) per 20-ppb increase in 1-day lag NO<sub>2</sub>, without  
23 and with PM<sub>2.5</sub> in the model, respectively. The risk estimates for cardiovascular (2.0% [95% CI:  
24 0.5, 3.5]) and respiratory deaths (2.1% [95% CI: -0.2, 4.4] per 20-ppb increase in the 3-day  
25 moving average) were similar to that for total mortality. In their sensitivity analysis, larger risk  
26 estimates were observed for warmer months. Older age groups also showed larger risk  
27 estimates.

28 The results from the above 12-city study appear to be similar to those from the 8-city  
29 study (Burnett et al., 2000) in that NO<sub>2</sub>-mortality associations were stronger than those for the  
30 associations between the size-fractionated PM indices and mortality, and simultaneous inclusion  
31 of NO<sub>2</sub> and the size-fractionated PM indices in the regression model resulted in reductions in the

1 PM risk estimates. However, Burnett et al. (2004) mentioned, in their discussion section, results  
2 from additional data collection and analysis in which daily PM<sub>2.5</sub> was collected in 11 of the  
3 12 cities between 1998 and 2000. In that analysis, simultaneous inclusion of the PM<sub>2.5</sub> and NO<sub>2</sub>  
4 in the model resulted in a considerable reduction of the NO<sub>2</sub> risk estimates. Thus, while the NO<sub>2</sub>  
5 risk estimates were not sensitive to adjustment for the PM indices collected every-6th-day, it was  
6 sensitive to adjustment for the daily PM<sub>2.5</sub>. Burnett et al. (2004) discussed that reducing  
7 combustion would result in public health benefits because NO<sub>2</sub> or its products originate from  
8 combustion sources but cautioned that they could not implicate NO<sub>2</sub> as a specific causal  
9 pollutant.

10 Brook et al. (2007) further examined data from ten Canadian cities with a special focus  
11 on the NO<sub>2</sub> and the role of other traffic-related air pollutants. Again, NO<sub>2</sub> showed the strongest  
12 associations with mortality among the pollutants examined including NO, and none of the other  
13 pollutants substantially reduced NO<sub>2</sub> risk estimates in multi-pollutant models. The analysis also  
14 confirmed the 2004 Burnett et al. study result that NO<sub>2</sub> risk estimate was larger in the warm  
15 season. Generally, NO showed stronger correlation with the primary VOCs (e.g., benzene,  
16 toluene, xylenes, etc.) than NO<sub>2</sub> or PM<sub>2.5</sub>. NO<sub>2</sub> was more strongly correlated with the organic  
17 compounds than it is with the PM mass indices or trace metals in PM<sub>2.5</sub>. Brook et al. concluded  
18 that the strong NO<sub>2</sub> effects seen in Canadian cities could be a result of it being the best indicator,  
19 among the pollutants monitored, of fresh combustion as well as photochemically processed  
20 urban air.

21 In summarizing the Canadian multicity studies, NO<sub>2</sub> was most consistently associated  
22 with mortality among the air pollutants examined, especially in warm season. Adjustments for  
23 PM indices and its components did not reduce NO<sub>2</sub> risk estimates. NO<sub>2</sub> was also shown to be  
24 associated with organic compounds that are indicative of combustion products (traffic-related air  
25 pollution) and photochemical reactions

26

### 27 **3.3.1.3 Air Pollution and Health: A European Approach (APHEA) Studies**

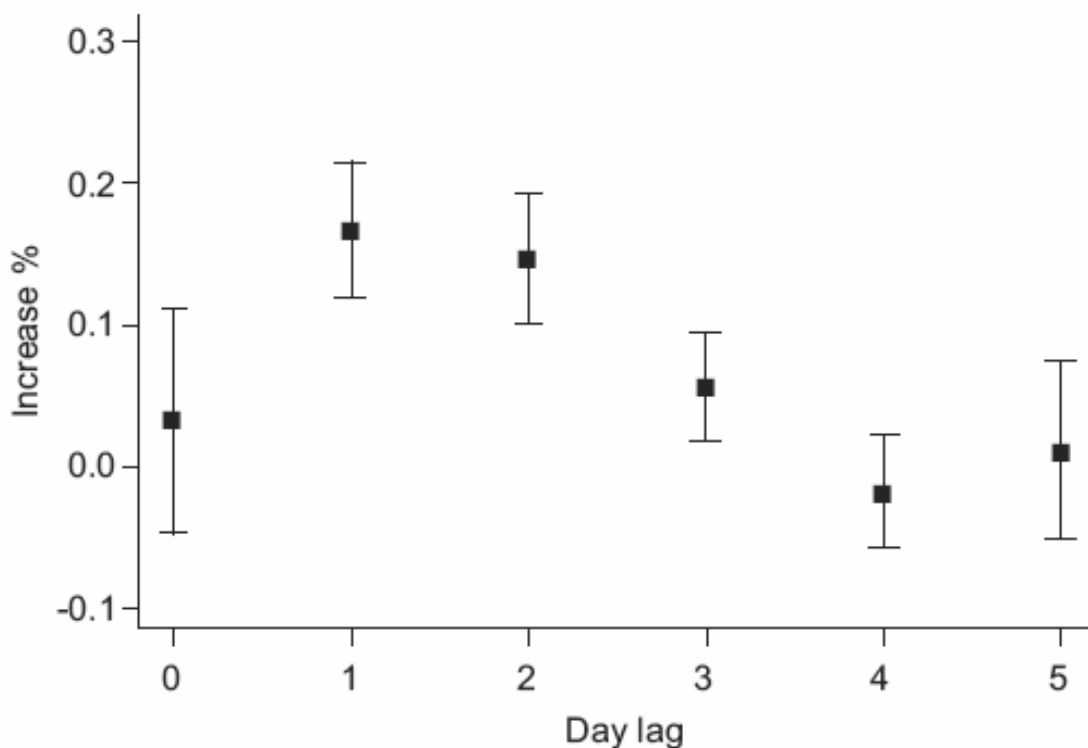
28 The first report (Touloumi et al., 1997) on NO<sub>2</sub> and O<sub>3</sub> effects on mortality from the Air  
29 Pollution and Health: a European Approach (APHEA1) project included six cities (Athens,  
30 Barcelona, Paris, Lyon, Koln, and London). The data were analyzed by each center separately  
31 following a standardized methodology, but the lag for the “best” model was allowed to vary in  
32 these cities from 0 to 3 days. A 30-ppb increase in 1-h max NO<sub>2</sub> was associated with a 1.5%

1 (95% CI: 1.0, 2.0) increased risk in nonaccidental mortality. There was a tendency for larger  
2 effects of NO<sub>2</sub> in cities with higher levels of black smoke. The pooled estimate for NO<sub>2</sub> was  
3 almost halved when black smoke was included in the model. The author suggested that the NO<sub>2</sub>  
4 effects on mortality could have been confounded by other “vehicle-derived pollutants.” Zmirou  
5 et al. (1998) analyzed (broad) cause-specific mortality (cardiovascular and respiratory causes) in  
6 ten European cities including the four cities (Barcelona, Paris, Lyon, and London) for which NO<sub>2</sub>  
7 was available, but they reported that “NO<sub>2</sub> did not show consistent relationships” with these  
8 mortality categories.

9 One of the extended APHEA2 project studies (Katsouyanni et al., 2001; reanalysis, 2003)  
10 analyzed data from 29 European cities and reported risk estimates for PM<sub>10</sub> and not for NO<sub>2</sub>, but  
11 found that the cities with higher NO<sub>2</sub> levels tended to have larger PM<sub>10</sub> risk estimates.  
12 Furthermore, simultaneous inclusion of PM<sub>10</sub> and NO<sub>2</sub> reduced the PM<sub>10</sub> risk estimate by half.  
13 An analysis of the elderly mortality in the same 28 cities (Aga et al., 2003) also found a similar  
14 effect modification of PM by NO<sub>2</sub>. Thus, combined with the Touloumi et al. study result  
15 described above, PM and NO<sub>2</sub> risk estimates in these European cities may be reflecting the  
16 health effects of the same air pollution source and/or effect modifiers of each other.

17 Samoli et al. (2005) investigated the concentration-response relationship between NO<sub>2</sub>  
18 and total nonaccidental mortality in nine of the APHEA2 cities where medians were >110 µg/m<sup>3</sup>  
19 (57 ppb) and the third quartiles were >130 µg/m<sup>3</sup> (68 ppb). Two methods, the nonparametric  
20 meta-smooth method and the parametric cubic spline method, were applied to estimate the shape  
21 of the concentration-response relationship. Both methods suggested a monotonic increase in the  
22 relationship, and the investigators concluded that the linear model was adequate to describe the  
23 NO<sub>2</sub>-mortality relationship.

24 In another APHEA2 study, Samoli et al. (2006) analyzed 29 APHEA2 cities to estimate  
25 NO<sub>2</sub> associations for total, cardiovascular, and respiratory deaths. Unlike the APHEA1 method,  
26 the average of lags 0 and 1 days were chosen a priori to avoid potential bias with the “best” lag  
27 approach. In addition, to estimate multiday effects, a cubic polynomial distributed lag with lags  
28 up to 5 days before deaths was used. The figure for the total mortality risk estimates in the fitted  
29 distributed lag model is shown in Figure 3.3-2, which suggests multiday effects. The strongest  
30 association shown at lag 1 day is also consistent with the results from NMMAPS and Canadian  
31 multicity studies. The estimated increase in total deaths was 1.7% (95% CI: 1.3, 2.2) per 30-ppb



**Figure 3.3-2. Shape of the association of total mortality with NO<sub>2</sub> over 6 days (lags 0 through 5) summarized over all cities using a cubic polynomial distributed lag model. The percent increase is for 10-µg/m<sup>3</sup> increase in the 1-h maxima of NO<sub>2</sub>.**

Source: Samoli et al. (2006).

1 increase in 1-h max NO<sub>2</sub>. The risk estimates for cardiovascular and respiratory deaths were  
 2 2.3% (95% CI: 1.7, 3.0) and 2.2% (95% CI: 1.0, 3.4) per 30-ppb increase, respectively. The  
 3 estimates using the distributed lag models were higher than those for the average of 0- and 1-day  
 4 lags by 23%, 22%, and 45% for total, cardiovascular, and respiratory mortality, respectively.  
 5 However, such a pattern was not consistently clear on the city-to-city basis (in 17 out of  
 6 29 cities, this was the case). Samoli et al. presented the shape of the association of total and  
 7 respiratory mortality (they mentioned that the shape for the cardiovascular mortality was similar  
 8 to that for total mortality) using the cubic polynomial distributed lag model. In the two-pollutant  
 9 models with black smoke, PM<sub>10</sub>, SO<sub>2</sub>, and O<sub>3</sub>, the risk estimates for total and cardiovascular  
 10 mortality were not affected. The largest reduction in the NO<sub>2</sub> risk estimate for total mortality

1 was for the model with SO<sub>2</sub>, reducing the estimate to 1.5% (95% CI: 1.0, 2.0). For respiratory  
2 mortality, only the risk estimate with SO<sub>2</sub> was substantially reduced (by ~50%). In a second-  
3 stage analysis, the city-specific effect estimates were regressed on potential effect modifiers by  
4 weighted regression, with weights inversely proportional to their city-specific variances. For  
5 total and cardiovascular mortality, the geographical area (defined as western, southern, and  
6 central eastern European cities) was the most important effect modifier (estimates were lower in  
7 eastern cities), followed by the smoking prevalence (NO<sub>2</sub> risk estimates were higher in cities  
8 with a lower prevalence of smoking). For cardiovascular mortality, the cities with higher natural  
9 gas consumption had higher NO<sub>2</sub> risk estimates. The authors concluded that the results showed  
10 effects of NO<sub>2</sub> on mortality, but that the role of NO<sub>2</sub> as a surrogate of other unmeasured  
11 pollutants could not be completely ruled out.

12 In summarizing the series of APHEA studies, the NO<sub>2</sub> risk estimates were somewhat  
13 sensitive to the inclusion of PM in the model in the APHEA1 (six cities), but not in the analysis  
14 of a larger set in the APHEA2 (29 cities). The fact that PM risk estimates tend to be higher in  
15 the cities with higher NO<sub>2</sub>, and vice-versa, appears to suggest that the mortality risk estimates for  
16 NO<sub>2</sub> and PM share the same source type(s) in these European cities. An examination of the  
17 concentration-response function in nine cities suggested no evidence of threshold. Multiday  
18 lagged effects were suggested.

#### 19 20 **3.3.1.4 The Netherlands Study**

21 While the Netherlands studies for the 1986 to 1994 data (Hoek et al. 2000 and 2001;  
22 reanalysis in Hoek, 2003) are not multicity studies and the Netherlands data were also analyzed  
23 as part of APHEA2 (Samoli et al., 2006), the results from the reanalysis (Hoek, 2003) are  
24 discussed here, because the database comes from a large population (14.8 million for the entire  
25 country) and a more extensive analysis was conducted than in the multicity studies. PM<sub>10</sub>, black  
26 smoke, O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>, CO, sulfate (SO<sub>4</sub><sup>2-</sup>), and nitrate (NO<sub>3</sub><sup>-</sup>) were analyzed at lags 0, 1, and  
27 2 days and the average of lags 0-6 days. PM<sub>10</sub>, SO<sub>4</sub><sup>2-</sup>, and NO<sub>3</sub><sup>-</sup> had less than 1/3 of the  
28 available days for other pollutants. All the pollutants were associated with total mortality, and  
29 for single-day models, lag 1 day showed strongest associations for all the pollutants. The NO<sub>2</sub>  
30 risk estimate in a single-pollutant model was 1.9% (95% CI: 1.2, 2.7) per 20-ppb increase in  
31 1-day lag 24-h average NO<sub>2</sub>, and 1.5% (95% CI: 0.7, 2.4) per 20-ppb increase in the average of

1 0-6 day 24-h average NO<sub>2</sub>. NO<sub>2</sub> was most highly correlated with black smoke ( $r = 0.87$ ), and the  
2 simultaneous inclusion of NO<sub>2</sub> and black smoke reduced both pollutants' risk estimates (NO<sub>2</sub>  
3 risk estimate = 0.8% [95% CI: -0.5, 2.1] per 20-ppb increase in the average of 0-6 day NO<sub>2</sub>).  
4 PM<sub>10</sub> was less correlated with NO<sub>2</sub> ( $r = 0.62$ ), and the simultaneous inclusion of these pollutants  
5 resulted in an increase in the NO<sub>2</sub> risk estimate. Cause-specific analysis showed larger risk  
6 estimates for COPD (6.1% [95% CI: 2.7, 9.7] per 20-ppb increase in the average of 0-6 day  
7 daily average NO<sub>2</sub>) and pneumonia (11.5% [95% CI: 6.7, 16.5]) deaths, but because essentially  
8 all of the pollutants showed larger risk estimates for these subcategories, it is difficult to interpret  
9 these estimates as effects of NO<sub>2</sub> alone. Likewise, the analysis of more specific cardiovascular  
10 mortality categories (Hoek et al., 2001; reanalysis in Hoek, 2003) showed larger NO<sub>2</sub> risk  
11 estimates than that for the overall cardiovascular mortality, but again, since the same pattern was  
12 seen for other pollutants as well, it is difficult to interpret these cause-specific risk estimates as  
13 due to NO<sub>2</sub> alone.

14

### 15 **3.3.1.5 Other European Multicity Studies**

16 There are also other European multicity studies, conducted in eight Italian cities (Biggeri  
17 et al., 2005), nine French cities (Le Tertre et al., 2002) and seven Spanish cities (Saez et al.,  
18 2002). The studies by Le Tertre et al. (2002) and Saez et al. (2002) were conducted using GAM  
19 methods with the default convergence setting.

20 Biggeri et al. (2005) analyzed eight Italian cities (Turin, Milan, Verona, Ravenna,  
21 Bologna, Florence, Rome, and Palermo) from 1990 to 1999. Only single-pollutant models were  
22 examined in this study. The NO<sub>2</sub> risk estimates were 3.6% (95% CI: 2.3, 5.0), 5.1% (95% CI:  
23 3.0, 7.3), and 5.6% (95% CI: 0.2, 11.2) per 20-ppb increase in the average of 0- and 1-day lag  
24 24-h average NO<sub>2</sub>, for total, cardiovascular, and respiratory deaths, respectively. Since all the  
25 pollutants showed positive associations with these mortality categories, and the correlation  
26 among the pollutants were not presented, it is not clear how much of the observed associations  
27 are shared or confounded. The mortality risk estimates were not heterogeneous across cities for  
28 all the gaseous pollutants.

29 The French nine cities study examined black smoke, SO<sub>2</sub>, NO<sub>2</sub>, and O<sub>3</sub> by generally  
30 following the APHEA protocol but using GAM and the average of lags 0 and 1 day for  
31 combined estimates. All four pollutants were positively associated with mortality outcomes,



1 with a 50- $\mu\text{g}/\text{m}^3$  (26 ppb) increase in pollutants being associated with an increase of 2.7 to 3.8%  
2 in total mortality. The study did not report description of correlation among the pollutants or  
3 conduct multipollutant models; therefore, it is difficult to assess the potential extent of  
4 confounding among these pollutants. The  $\text{NO}_2$  risk estimates were reported to be homogeneous  
5 across cities.

6 The Spanish Multi-center Study on Air Pollution and Mortality (whose Spanish acronym  
7 is EMECAM) published a study with a focus on PM indices ( $\text{PM}_{10}$ , TSP, and black smoke) and  
8  $\text{SO}_2$  in 12 cities (Ballester et al., 2002) and a study that focused on  $\text{O}_3$  and  $\text{NO}_2$  in seven cities  
9 (Saez et al., 2002). These studies followed the APHEA protocol but using the GAM approach.  
10 The Ballester et al. study did not consider  $\text{NO}_2$ , and, while the Saez et al. study did consider  
11  $\text{SO}_2$  and CO in the multipollutant model, they did not consider PM indices. Thus, the extent of  
12 correlation between  $\text{NO}_2$  and PM indices, or the extent of possible confounding between these  
13 pollutants is not known. The Saez et al. (2002) study reported that  $\text{NO}_2$  was positively  
14 associated with total and cardiovascular mortality in the model with all the gaseous pollutants  
15 included simultaneously. The  $\text{NO}_2$  risk estimates were reported to be heterogeneous across the  
16 cities.

#### 17 **3.3.1.6 Australian Four Cities Study**

18 Simpson et al. (2005b) analyzed data from four Australian cities (Brisbane, Melbourne,  
19 Perth, and Sydney) using methods similar to the APHEA2 approach. They also examined  
20 sensitivity of results to three statistical models: (1) GAM with a single nonparametric smoother  
21 (to adjust for temporal trends) and parametric smoothers to adjust for other covariates and using  
22 stringent convergence criteria as implemented in the statistical package, Splus; (2) GLM with  
23 natural splines; and (3) GAM with a penalized spline algorithm in conjunction with multiple  
24 smoothing parameter estimation by generalized cross-validation, which avoids the back-fitting  
25 issues, as implemented in the statistical package, R. Associations between mortality and  $\text{NO}_2$ ,  
26  $\text{O}_3$ , and nephelometer readings were examined at single day lag 0, 1, 2, and 3 days and using the  
27 average of 0- and 1-day lags. Among the three pollutants, correlation was strongest between  
28  $\text{NO}_2$  and nephelometer readings, ranging from ( $r \sim$  up to 0.62 among the four cities). Of the  
29 three pollutants,  $\text{NO}_2$  showed the largest mortality risk estimates per inter-quartile-range. The  
30 authors state that the results using the three statistical methods “yield similar results,” although  
31 the figure of the results for the three methods appear to show some 20% difference in risk  
32

1 estimates between the smallest (the GLM approach) and the largest (the GAM with R). The  
2 authors presented numerical results from the GAM/Splus approach. The estimated risk for  
3 30-ppb increase in 1-h maximum increase of the average of 0- and 1-day lag NO<sub>2</sub> was 3.4%  
4 (95% CI: 1.1, 5.7), 4.3% (95% CI: 0.9, 7.8), and 11.4% (95% CI: 3.5, 19.9) for total,  
5 cardiovascular, and respiratory deaths, respectively. The NO<sub>2</sub> risk estimates were not sensitive  
6 to the addition of nephelometer readings (3.1% [95% CI: 0.3, 5.9]) or O<sub>3</sub> (3.67% [95% CI: 1.2,  
7 6.2]) in the two-pollutant models for total mortality, but the nephelometer risk estimate was  
8 greatly reduced in the model with NO<sub>2</sub>.

9

### 10 ***Multipollutant Modeling Results***

11 The results from multipollutant models in the multicity studies (i.e., NMMAPS, Canadian  
12 cities, APHEA2, and Australian 4 cities studies) suggest that NO<sub>2</sub> mortality risk estimates  
13 were generally not sensitive to the inclusion of copollutant(s) (mostly PM indices) in the models.  
14 The Netherlands study (Hoek et al., 2003), with a large population database, showed a reduction  
15 in NO<sub>2</sub> mortality risk estimates when black smoke was included in the model. Examining this  
16 issue in single-city studies is more difficult because of generally wider confidence intervals  
17 owing to smaller sample size. Also, many of the available single-city studies that presented  
18 multipollutant model results were those that used GAM analyses with default convergence  
19 criteria. Furthermore, because a large majority of these single-city studies focused on PM (and  
20 less frequently, O<sub>3</sub>), very few studies examined multipollutant models with NO<sub>2</sub> and other  
21 gaseous pollutants and the combinations of copollutants examined were not usually consistent  
22 across studies. Thus, a systematic evaluation of the multipollutant results from single-city  
23 studies is limited, and we only briefly summarize these results qualitatively, with focus on larger  
24 cities below.

25 The single-city analyses that examined NO<sub>2</sub> and PM indices together and did not find  
26 major reductions (i.e., more than 50% reduction in excess risk estimates) in NO<sub>2</sub> risk estimates  
27 include analyses of data from Cook County, IL, with PM<sub>10</sub> (Moolgavkar, 2003; GAM analysis);  
28 Los Angeles, CA, with PM<sub>2.5</sub> (Moolgavkar, 2003; GAM analysis); Maricopa County, AZ, with  
29 PM<sub>10</sub> (Moolgavkar, 2000; GAM analysis); and, Vancouver, Canada, with PM<sub>10</sub> (Vedal et al.,  
30 2003). The single-city studies that analyzed NO<sub>2</sub> and PM indices together and did find major  
31 reductions in NO<sub>2</sub> risk estimates include analyses of data from Philadelphia, PA, with TSP

1 (Kelsall et al., 1997; GAM analysis); Santa Clara County, CA, with PM<sub>2.5</sub> and NO<sub>3</sub><sup>-</sup> (Fairley,  
2 1999 with GAM; reanalysis, 2003); Mexico City with PM<sub>2.5</sub> (Borja-Aburto et al., 1998); Sydney,  
3 Australia, with bsp (Morgan et al., 1998). Thus, it is difficult to find a consistent pattern of  
4 evidence of confounding with PM from these single-city results. It is also possible that the  
5 constituents of PM (e.g., relative contribution of traffic-related pollution to PM mass) vary from  
6 city to city and hence correlations of PM with NO<sub>2</sub> vary, contributing to apparently inconsistent  
7 results.

8 A fewer single-city studies examined multipollutant models with NO<sub>2</sub> and other gaseous  
9 pollutants. Those that examined NO<sub>2</sub> and O<sub>3</sub> simultaneously and did not find major reductions in  
10 NO<sub>2</sub> risk estimates include analyses of data from Los Angeles, CA (Kinney and Özkaynak,  
11 1991); Philadelphia, PA (Kelsall et al., 1997; GAM analysis); Philadelphia, PA (Lipfert et al.,  
12 2000b); London, England (Bremner et al., 1999). The studies in which adding O<sub>3</sub> did reduce  
13 NO<sub>2</sub> risk estimates include analyses of data from Barcelona, Spain (Saez et al., 2002, asthma  
14 mortality); and Sydney, Australia (Morgan et al., 1998). In Toronto data (Burnett et al., 1998),  
15 including both CO and NO<sub>2</sub> reduced the NO<sub>2</sub> risk estimate; however, in the Canadian 12-cities  
16 study, the combined NO<sub>2</sub> risk estimate was not sensitive to inclusions of CO. In the analyses of  
17 data from Philadelphia, PA (Kelsall et al., 1997; GAM analysis); Vancouver, Canada (Vedal  
18 et al., 2003); and London, England (Bremner et al., 1999), two-pollutant models with SO<sub>2</sub> did  
19 not reduce NO<sub>2</sub> risk estimates, whereas in the analyses of Seoul, Korea (Kwon et al., 2001) and  
20 Hong Kong, China (Wong et al., 2001), adding SO<sub>2</sub> in the model did reduce NO<sub>2</sub> risk estimates.  
21 Again, the results from these single-city studies are too limited to allow a consistent pattern to  
22 emerge.

23 In summary, because of the lack of consistency in the way multipollutants were examined  
24 (e.g., lags examined, combination of pollutants examined, model specification) and because of  
25 the limited statistical power in individual cities, it is difficult to extract information that help  
26 elucidate a pattern of confounding between NO<sub>2</sub> and other pollutants from these single-city  
27 studies. Therefore, the multipollutant results from multicity studies provide more useful  
28 information on this issue. As noted before, the results from the multicity studies from the United  
29 States, Canada, and Europe generally suggest that NO<sub>2</sub> mortality risk estimates are not very  
30 sensitive to the addition of copollutants. However, this does not resolve the issue of surrogacy

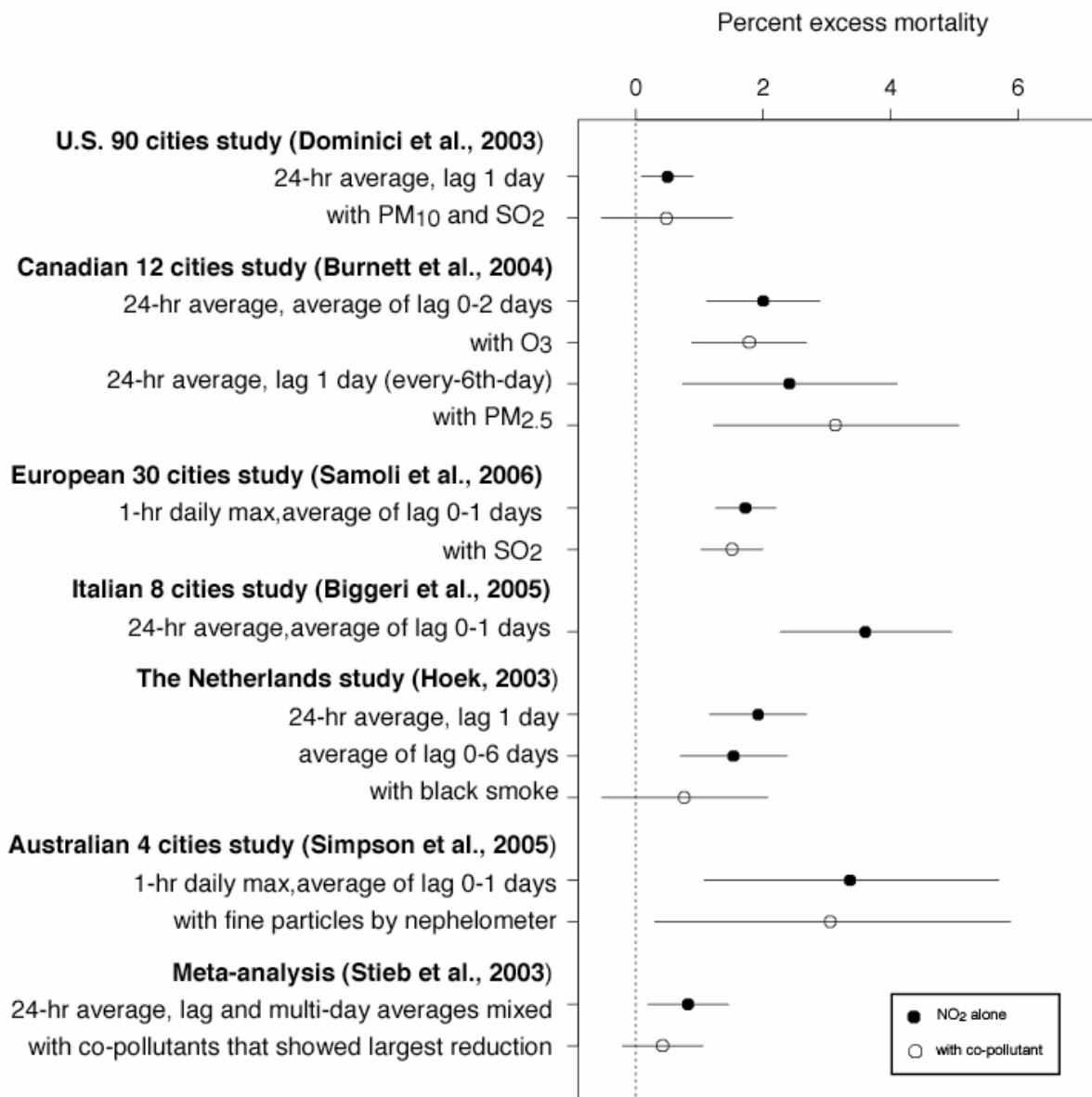
1 and its interpretation is also complicated by the possible influence of varying extent of exposure  
2 characterization error across multiple pollutants.

### 3 4 **3.3.1.7 Meta-analyses of NO<sub>2</sub> Mortality Studies**

5 Stieb et al. (2002) reviewed time-series mortality studies published between 1985 and  
6 2000, and conducted meta-analysis to estimate combined effects for each of PM<sub>10</sub>, CO, NO<sub>2</sub>, O<sub>3</sub>,  
7 and SO<sub>2</sub>. Since many of the studies reviewed in that analysis were affected by the GAM  
8 convergence issue, Stieb et al. (2003) updated the estimates by separating the GAM versus non-  
9 GAM studies and by single- versus multipollutant models. There were more GAM estimates  
10 than non-GAM estimates for all the pollutants except SO<sub>2</sub>. For NO<sub>2</sub>, there were 11 estimates  
11 from single-pollutant models and only 3 estimates from multipollutant models. The lags and  
12 multiday averaging used in these estimates varied. The combined estimate for total mortality  
13 was 0.8% (95% CI: 0.2, 1.5) per 20-ppb increase in the daily average NO<sub>2</sub> from the single-  
14 pollutant models, and 0.4% (95% CI: -0.2, 1.1). Note that, although the estimate from the  
15 multipollutant models was smaller than that from the single-pollutant models, the number of the  
16 studies for the multipollutant models was small (three), also, the data extraction procedure of this  
17 meta-analysis for the multipollutant models was to extract from each study the multipollutant  
18 model that resulted in the greatest reduction in risk estimate compared with that observed in  
19 single-pollutant models. It should also be noted that all the multicity studies whose combined  
20 estimates have been discussed above were published after this meta-analysis.

### 21 22 **3.3.1.8 Summary of Risk Estimates for Mortality from Short-Term NO<sub>2</sub> Exposure** 23 **Studies**

24 Figure 3.3-3 shows combined estimates for total mortality per the standardized  
25 increments (20 ppb for 24-h average or 30 ppb for daily 1-h maximum) from the multicity  
26 studies and meta-analysis discussed above. The estimates from single-pollutant models range  
27 from 0.5 (the NMMAPS study) to 3.6 (the Italian 8 cities study) percent. The heterogeneity of  
28 estimates in these studies may be due to several factors including the differences in: (1) model  
29 specification, (2) averaging/lag time, (3) NO<sub>2</sub> levels, and (4) effect modifying factors.  
30 Interestingly, the Canadian 12-city study showed combined risk estimates (average of 0-1 day or  
31 single 1-day lag) about 4 times larger than that for the U.S. estimate, despite the fact that the  
32 range of Canadian NO<sub>2</sub> (10 to 26 ppb) was somewhat lower than that for the U.S. data (9 to



**Figure 3.3-3. Combined NO<sub>2</sub> 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<sub>2</sub> concentrations. For multipollutant models, results from the models that resulted in the greatest reduction in NO<sub>2</sub> risk estimates are shown.**

1 39 ppb for the 10%-trimmed data). In fact, the NMMAPS estimate is the smallest among the  
 2 multicities studies. Since a similar pattern (i.e., the NMMAPS estimate being the smallest

1 among multicities study) was seen for PM<sub>10</sub> mortality risk estimates (U.S. Environmental  
2 Protection Agency, 2004), it is possible that this may be due to the difference in model  
3 specifications. The NMMAPS study used more smoothing terms (two terms for temperature  
4 [same-day and average of lag 1 to 3] and two terms for dewpoint [same-day and average of lag  
5 1 to 3]) and more degrees of freedom for the smoothing terms (up to 6) than other studies, which  
6 usually include up to two smoothing terms for weather variables.

7 The multipollutant models in these studies generally did not alter NO<sub>2</sub> risk estimates,  
8 except for the Netherlands study. The meta-analysis by Stieb et al. (2003) shows a smaller  
9 combined risk estimate for the multipollutant models than that for single-pollutant models, but  
10 since these are not from the same set of studies (11 studies for single-pollutant models and  
11 3 studies for multipollutant models), it is not clear how much of the difference was due to the  
12 addition of copollutants. Thus, the evidence of confounding, in the sense of instability of risk  
13 estimates in multipollutant models, is not clear from these studies. The difference in risk  
14 estimates due to lag/averaging time also was not clear from these studies.

15 In the Canadian study, the estimate for the 3-day average (2.0%) and that for 1-day lag  
16 (2.4%, though this was based on every-6th-day data, to match with PM<sub>2.5</sub> data) were similar in  
17 magnitude. In the Netherlands study, the estimate for the 1-day lag (1.9%) and that for the  
18 average of 0 to 6 days (1.5%) were not very different. In the Samoli et al. (2006) study, they  
19 examined a polynomial distributed lag, and reported that the combined risk estimate for total  
20 mortality was 23% larger (45% larger for respiratory mortality) than that for the average of  
21 0- and 1-day lags. However, such a pattern was not consistently clear on the city-to-city basis.  
22 Thus, while the risk estimates for multiday effects may be larger than the single-day or 1- to  
23 2-day average risk estimates, the evidence so far indicates that the magnitude of such multiday  
24 risk estimates are not much bigger than the 1-or 2-day average estimates. Among the 1-day risk  
25 estimates, the association at 1-day lag was generally the strongest in these multicity studies.

26 In summary, the range of NO<sub>2</sub> total mortality risk estimates is 0.5 to 3.6% per 20-ppb  
27 increase in the 24-h average NO<sub>2</sub> (or 30-ppb increase in the daily 1-h maximum). The risk  
28 estimates are generally insensitive to the inclusion of copollutants. Multiday effects have been  
29 suggested, but their magnitude, when expressed per the same increment, is not very different  
30 from those for 1-or 2-day average exposure indices. A few studies examined association

1 between cause-specific mortality and NO<sub>2</sub>. While NO<sub>2</sub> risk estimates for some specific causes  
2 were found to be larger than for all-cause mortality, such a pattern was not unique to NO<sub>2</sub>.

### 3 4 **3.3.1.9 Cause-Specific Mortality from Short-Term Exposure to NO<sub>2</sub>**

5 Risk estimates for specific causes of death would be useful in evaluating consistency of  
6 the association with causal inference. However, comparing relative size of risk estimates across  
7 categories of different mean daily counts (e.g., all-cause versus respiratory) requires caution  
8 when the “best lag” estimates are chosen from several lags. This is because the range of risk  
9 estimates for the smaller daily mean counts are expected to be larger due to larger standard error  
10 of estimates, and the “best lag” choice would result in a larger bias for the category with smaller  
11 mean counts. Thus, it would be more appropriate to compare risk estimates across different  
12 cause-specific categories using the same lag (unless there is a strong indication that lag structure  
13 of associations would be different among the different causes).

14 Several multicity studies provided risk estimates for broad cause-specific categories  
15 (typically all-cause, cardiovascular, and respiratory) using consistent lags/averaging for broad  
16 specific causes. In the Canadian 12-city study (Burnett et al., 2004), the NO<sub>2</sub> excess risk  
17 estimates for all-cause, cardiopulmonary, and respiratory mortality were 2.0% (95% CI: 1.1,  
18 2.9), 2.0% (95% CI: 0.5, 3.53), and 2.1% (95% CI: -0.2, 4.4) per 20-ppb increase in the  
19 average of 0 to 2 day lags of 24-h average NO<sub>2</sub>, respectively, suggesting no difference in risk  
20 estimates among these categories. In the Samoli et al. (2006) APHEA2 analysis of 30 European  
21 cities, estimated increases in all-cause, cardiovascular, and respiratory deaths were 1.7%  
22 (95% CI: 1.3, 2.2), 2.3% (95% CI: 0.7, 3.0), and 2.2% (95% CI: 1.0, 3.4) per 30-ppb increase  
23 in the average of 0- and 1-day lag daily 1-h max NO<sub>2</sub>, respectively. In Biggeri et al. (2005)  
24 analysis of eight Italian cities, the NO<sub>2</sub> risk estimates for all-cause, cardiovascular, and  
25 respiratory mortality were 3.6% (95% CI: 2.3, 5.0), 5.1% (95% CI: 3.0, 7.3), and 5.6% (95%  
26 CI: 0.2, 11.2), respectively, per 20-ppb increase in the average of 0- and 1-day lags of 24-h  
27 average NO<sub>2</sub>. In the Australian four-city study (Simpson et al., 2005b), the risk estimates for all-  
28 cause, cardiovascular, and respiratory mortality were 3.4% (95% CI: 1.1, 5.7), 4.3% (95% CI:  
29 0.9, 7.8), and 11.4% (95% CI: 3.5, 19.9), respectively, per 20-ppb increase in the average of  
30 0- and 1-day lags of 24-h average NO<sub>2</sub>. In the Netherlands study, the risk estimates for all-cause  
31 (2.6% [95% CI: 1.2, 4.0] per 20-ppb increase in the average of 0 through 6 day lags of daily

1 24-h average NO<sub>2</sub>) and cardiovascular (2.7% [95% CI: 0.7, 4.7]) deaths were similar, but those  
2 for COPD (10.4% [95% CI: 4.5, 16.7]) and pneumonia (19.9% [95% CI: 11.5, 29.0]) were  
3 much larger. These results suggest that, with some exceptions, the risk estimates for  
4 cardiovascular and respiratory causes are larger than that for all-cause mortality. However, it  
5 should be noted that this pattern was not unique to NO<sub>2</sub>—other pollutants often showed similar  
6 patterns. There are numerous single-city studies (see the annex table) that also examined broad  
7 specific causes (cardiovascular and respiratory), but the patterns are not always consistent, likely  
8 due to smaller sample size, or the lags reported were not consistent across the specific causes  
9 examined.

10 Some of the single-city studies examined more specific causes within cardiovascular or  
11 respiratory causes. In the Netherlands study (Hoek et al., 2001; reanalysis Hoek, 2003), the risk  
12 estimates for heart failure (7.6% [95% CI: 1.4, 14.2] per the average of 0- through 6-day lags of  
13 24-h average NO<sub>2</sub>) and cerebrovascular disease were larger than those for total cardiovascular  
14 (2.7% [95% CI: 0.7, 4.7]) causes. However, such a pattern was seen for PM<sub>10</sub>, CO, and SO<sub>2</sub> as  
15 well. In the Goldberg et al. (2003) analysis of Montreal data, the risk estimates for the death  
16 with underlying cause of CHF and those deaths classified as having CHF 1 year before death  
17 (through the universal insurance plan) were compared. They did not find associations between  
18 air pollution and those with underlying cause of CHF, but they found associations between some  
19 of the air pollutants examined (i.e., CoH, SO<sub>2</sub>, NO<sub>2</sub>) and the deaths that were classified as having  
20 CHF 1 year before death. Again, the association with the specific cause of death was not unique  
21 to NO<sub>2</sub>. This pattern of association between multiple pollutants, including but not specific to  
22 NO<sub>2</sub>, and specific causes of deaths were seen for asthma mortality (Saez et al., 1999), mortality  
23 in a cohort with COPD (Garcia-Aymerich et al., 2000; Sunyer and Basagana, 2001), mortality in  
24 a cohort with severe asthma (Sunyer et al., 2002), infant mortality (Loomis et al., 1999),  
25 intrauterine mortality (Pereira et al., 1998), and mortality in a cohort of patients with CHF  
26 (Kwon et al., 2001). While NO<sub>2</sub> may have contributed to these associations as part of the  
27 mixture of pollutants or as a surrogate index, these studies cannot be used to evaluate specificity  
28 of NO<sub>2</sub> effects on these specific causes of death.

29 In summary, both broad specific (cardiovascular and respiratory) and more specific  
30 causes/categories of death have been shown to be associated with NO<sub>2</sub>. However, since other



1 pollutants also showed similar associations with these causes or categories, it is difficult to  
2 discuss consistency with causal inference that is specific to NO<sub>2</sub>.

### 3 4 **3.3.3 Summary of Effects of Short-Term Exposure to NO<sub>x</sub> on Mortality**

5 Range of mortality risk estimates: In the short-term studies, the range of NO<sub>2</sub> total  
6 mortality risk estimates is 0.5 to 3.6% per 20-ppb increase in the 24-h average NO<sub>2</sub> (or 30-ppb  
7 increase in the daily 1-h maximum). Various lag/averaging days and distributed lags do not  
8 appear to alter the estimates substantially.

9 Confounding: In the large multicity time-series studies, the NO<sub>2</sub> risk estimates were  
10 generally insensitive to the inclusion of copollutants in the models. In that sense, strong  
11 evidence of confounding is not indicated in the short-term studies' results.

12 NO<sub>2</sub> (or NO<sub>x</sub>) as a surrogate marker: The issue of NO<sub>2</sub> being a surrogate marker of  
13 another pollutant or for a pollution type is probably the most important one in interpreting NO<sub>2</sub>  
14 risk estimates, but currently available information is not sufficient to establish quantitative  
15 characterization of such surrogacy. NO<sub>2</sub> has been suggested to be a surrogate marker of traffic-  
16 related air pollution, ultrafine particles, fine particles, and weather conditions. The fact that NO<sub>2</sub>  
17 plays a critical role in the photochemical reactions that produce other potentially harmful  
18 pollutants make it difficult to treat NO<sub>2</sub> simply as a surrogate marker or confounder. More  
19 characterization of the surrogate marker is needed from different geographic locations.  
20 Increasingly available PM speciation data may help this effort.

21 Concentration-response function: One multicity time-series study (Samoli et al., 2006)  
22 examined this issue. There was no indication of a threshold, and the concentration-response  
23 curves were consistent with linear hypothesis.

24 Effect modification: Only few studies in the short-term effects studies examined possible  
25 effect modifiers. The APHEA2 time-series analysis found that the most important effect  
26 modifier was the geographical area (eastern cities had lower NO<sub>2</sub> risk estimates than western or  
27 southern cities). For respiratory mortality, cities with high median PM<sub>10</sub> showed higher risk  
28 estimates. The Canadian 12 cities study reported that the risk estimate was higher in summer  
29 than in winter. Older age groups also showed larger risk estimates.

30 Sensitivity of risk estimates to model specification: Most time-series studies examined  
31 the sensitivity of risk estimates to alternative model specifications by changing the degrees of

1 freedom for smoothing terms to adjust for temporal trends and weather effects, and the changes  
2 in risk estimates were typically not substantial (i.e., <30%). However, these studies did not  
3 apply qualitatively different alternative models (i.e., different number of smoothing terms) that  
4 are found across studies. One study using the NMMAPS data did find that varying degrees of  
5 freedom for temporal adjustment made a 2-fold change in the PM mortality risk estimate.  
6 Similar attempts should be made to examine sensitivity of risk estimates to qualitatively different  
7 weather model specifications.

### 8 9 **3.3.4 Integration of Evidence Related to Mortality and Short-Term** 10 **Exposure to NO<sub>2</sub>**

11 In evaluating the risk estimates for mortality, the main focus is on multicity studies and  
12 meta-analyses. These studies of short-term mortality effects include the NMMAPS, Canadian  
13 multi-cities studies, APHEA, Italian 8 cities study, the Netherlands study, the Australian 4 cities  
14 study, and the Stieb et al. (2002, 2003) meta-analyses. The largest U.S. study of 90 cities  
15 showed a NO<sub>2</sub>-mortality association with a total mortality risk estimate at lag 1 of 0.25% per  
16 10 ppb or 0.50% per 20 ppb. A Canadian 12-city study (Burnett et al., 2004) showed an NO<sub>2</sub>  
17 mortality risk estimate of 2.0% per 20-ppb increase in the 3-day moving average of NO<sub>2</sub>. These  
18 acute mortality studies are described in detail in Annex Table AX6.7 and summarized in Figure  
19 3.3-3. The range of NO<sub>2</sub> total mortality risk estimates is 0.5 to 3.6% per 20-ppb increase in the  
20 24-h average of NO<sub>2</sub> (or 30-ppb increase in the daily 1-h maximum).

21 As stated above, controlled human exposure studies, by necessity, are limited to acute,  
22 fully reversible functional and/or symptomatic responses in healthy or mildly asthmatic subjects.  
23 Animal studies have not used mortality as an endpoint in acute exposure studies. However, a  
24 number of animal studies (described in Section 2.3) have shown biochemical, lung host defense,  
25 permeability, and inflammation effects with acute exposures that may provide limited biological  
26 plausibility for mortality in susceptible individuals. A 5-ppm NO<sub>2</sub> exposure for 24 h in rats  
27 caused increases in blood and lung total GSH and a similar exposure resulted in impairment of  
28 alveolar surface tension of surfactant phospholipids due to altered fatty acid content. A fairly  
29 large body of literature describes the effects of NO<sub>2</sub> on lung host defenses at low exposures.  
30 However, most of these effects are seen only with subchronic or chronic exposure, and therefore,  
31 do not correlate well with the short lag times evidenced in the epidemiological studies. Acute  
32 exposures to ≤5ppm NO<sub>2</sub> show increased BAL protein, increased epithelial cell proliferation,

1 increased neutrophils, and decreased pulmonary eosinophils; however, these effects, similarly,  
2 do not correlate well with the short lag times in mortality studies.

### 3 4 5 **3.4 MORBIDITY ASSOCIATED WITH LONG-TERM NO<sub>2</sub> EXPOSURE**

#### 6 7 **3.4.1 Respiratory Effects Associated with Long-Term NO<sub>2</sub> Exposure**

##### 8 9 **3.4.1.1 Lung Function Growth**

###### 10 11 *Epidemiologic Studies*

12 Studies of lung function demonstrate some of the strongest effects of chronic exposure to  
13 NO<sub>2</sub>. Six studies are listed in Annex Table AX6.6-1, three from the United States and three from  
14 Europe. Three of the studies involved lung function in children and three report lung function  
15 studies in adults.

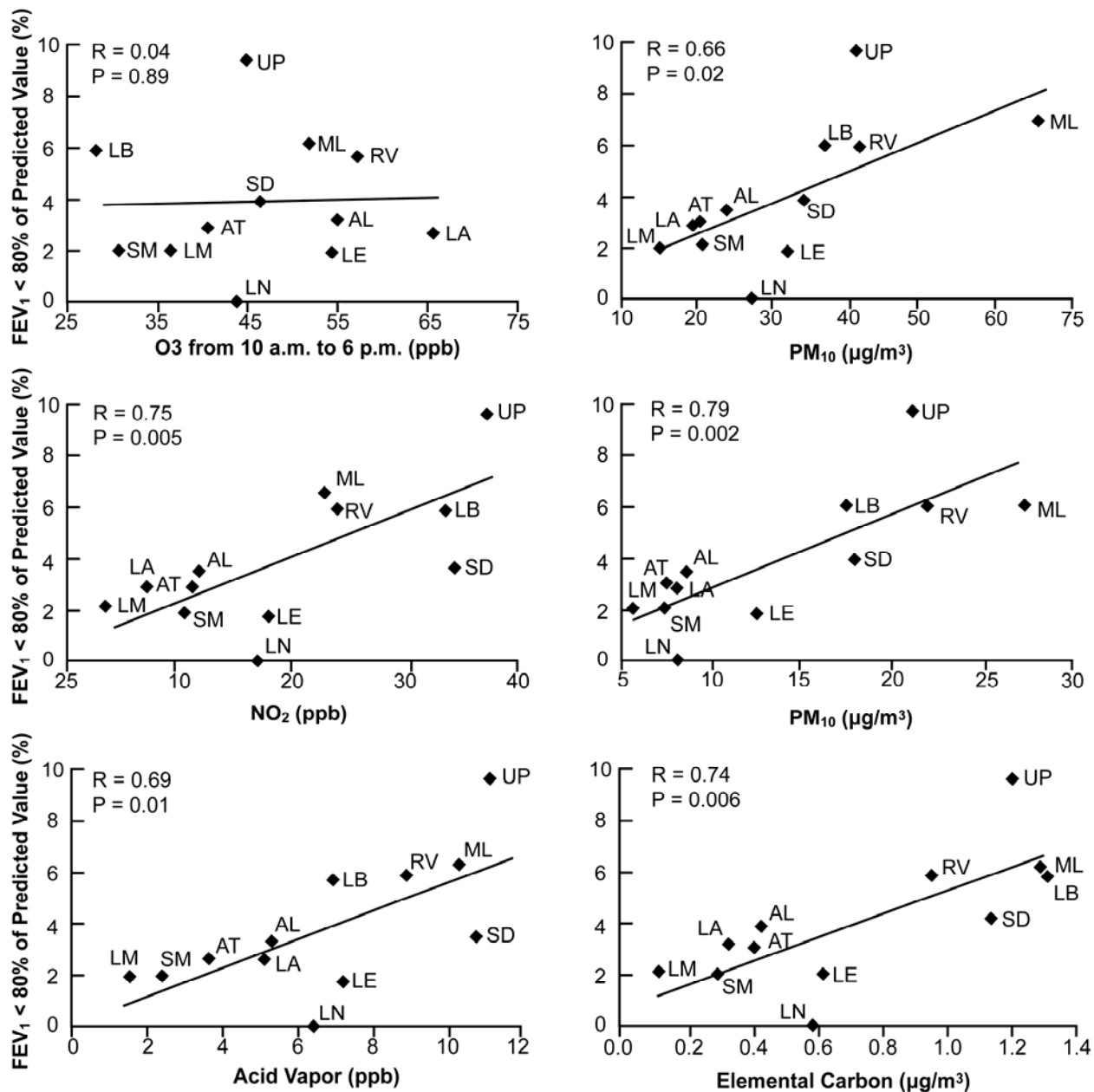
16 The Children's Health Study (CHS) in California is a longitudinal cohort study designed  
17 to investigate the effect of chronic exposure to several air contaminants (including NO<sub>2</sub>) on  
18 respiratory health in children. Twelve California communities were selected based on historical  
19 data indicating different levels of specific pollutants. In each community, monitoring sites were  
20 set up to measure NO<sub>2</sub>, O<sub>3</sub>, and PM<sub>10</sub> hourly and average PM<sub>2.5</sub> and acid vapor every 2 weeks.  
21 Children were recruited through local schools in grades 4, 7, and 10. Questionnaires were  
22 distributed through the schools and answered with parental help. Lung function was measured for  
23 each child using portable equipment at the school. The study followed children for 10 years,  
24 with annual questionnaires and lung function measurement.

25 In 2004, Gauderman reported results for 8-year follow up of the children enrolled in  
26 grade 4 (n = 1759). Exposure to NO<sub>2</sub> was significantly associated with deficits in lung growth  
27 over the 8-year period. The difference in FVC for children exposed to the lowest versus the  
28 highest levels of NO<sub>2</sub> (34.6 ppb) was -95.0 mL. (95% CI: -189.4 to -0.6). For FEV<sub>1</sub> the  
29 difference was 101.4 mL (95% CI: -165.5 to -38.4) and for MMEF the difference was  
30 -221.0 mL/s (95% CI: -377.6, -44.4). Results were similar for boys and girls and among  
31 children who did not have a history of asthma. These deficits in growth of lung function resulted  
32 in clinically significant differences in FEV<sub>1</sub> at age 18. The study had the following important  
33 characteristics: it was prospective; exposure and outcome data were collected in a consistent

1 manner over the duration of the study; and confounding by SES was controlled in the models and  
2 by selecting communities similar in demographic characteristics at the outset. In addition, the  
3 NO<sub>2</sub> concentration associated with deficits in lung growth was 34.6 ppb (39.0 ppb highest mean  
4 -4.4 ppb lowest mean), a level below the current standard. Similar results were reported for acid  
5 vapor (resulting primarily from photochemical conversions of NO<sub>x</sub> to HNO<sub>3</sub>), with a difference  
6 in FVC of 105.2 mL (95% CI: -105.2, -15.9); FEV<sub>1</sub> 105.8 (95% CI: -168.8, -42.7); and  
7 MMEF -165.0 (95% CI: -344.8, -14.7). These results are depicted in Figure 3.4-1. The  
8 authors concluded that the effects of NO<sub>2</sub> could not be distinguished from the effects of particles  
9 (PM<sub>2.5</sub> and PM<sub>10</sub>). NO<sub>2</sub> was strongly correlated with these other contaminants (0.79, and 0.67,  
10 respectively). For example, exposure to the highest versus the lowest PM<sub>2.5</sub> concentrations was  
11 associated with a difference in FEV<sub>1</sub> of -79.7 mL (95% CI: -153.0, -6.4). The effects on  
12 growth in lung function in this study cannot be attributed to O<sub>3</sub>. O<sub>3</sub> was not correlated with NO<sub>2</sub>  
13 (-0.11), and no significant effects of O<sub>3</sub> were detected (difference in FEV<sub>1</sub> -22.8 (95% CI:  
14 -122.3, 76.6).

15 Gauderman et al. (2007) has reported results of an 8-year follow-up on 3,677 children  
16 who participated in the CHS in California. Briefly, this study recruited schoolchildren in  
17 12 California communities with differing levels of air pollution. Each child had lung function  
18 measurements taken at school each year for 8 years. Children living <500 m from a freeway  
19 (n = 440) had significant deficits in lung growth over the 8-year follow-up compared to children  
20 who lived at least 1500 m from a freeway. The difference in FVC was -63 mL (-131 to 5); the  
21 difference in FEV<sub>1</sub> -81 mL (-143 to -18); and the difference in MMEF -127 mL/s (-243 to  
22 -11). This study did not attempt to measure specific pollutants near freeways or to estimate  
23 exposure to specific pollutants for study subjects. Thus, while the study presents important  
24 findings with respect to traffic pollution and respiratory health in children, it does not provide  
25 evidence that NO<sub>2</sub> is responsible for these deficits in lung growth.

26 Avol et al. (2001) studied the effect of relocating to areas of differing air pollution levels  
27 in 110 10-year-old children who were participating in the CHS. As a group, subjects who had  
28 moved to areas of lower PM<sub>10</sub> showed increased growth in lung function and the same  
29 relationship was observed for NO<sub>2</sub>. In general, the authors focused on associations with PM,  
30 where larger and significant effects were observed; associations were reported with NO<sub>2</sub>, but  
31 they did not reach statistical significance.



**Figure 3.4-1. Proportion of 18-year olds with a FEV<sub>1</sub> 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).

1 Overall, the studies discussed above are substantiated by cross sectional studies that  
2 examined effects of exposure to NO<sub>2</sub> on lung function. Peters (1999) reported the initial results  
3 from the CHS. This was a cross-sectional analysis of lung function tests conducted on  
4 3,293 children in the first year of the study. Both NO<sub>2</sub> and PM<sub>10</sub> were associated with decreases  
5 in FVC, FEV<sub>1</sub>, and MMEF. O<sub>3</sub> was associated with decreases in MMEF and PEF. For all  
6 pollutants, the decreases were only significant for girls.

7 In the United States, a study was conducted of students attending the University of  
8 California (Berkeley) who had been lifelong residents of the Los Angeles or San Francisco areas  
9 (Tager, 2005). Using geocoded address histories, a lifetime exposure to air pollution was  
10 constructed for each student. Increasing lifetime exposure to NO<sub>2</sub> was associated with decreased  
11 FEF<sub>75</sub> and FEF<sub>25-75</sub>. Controlling for O<sub>3</sub> in the models, however, substantially reduced the effect  
12 of NO<sub>2</sub>.

13 In Germany, Moseler (1994) measured NO<sub>2</sub> outside the homes of 467 children, including  
14 106 who had physician-diagnosed asthma. Five of six lung function parameters were reduced  
15 among asthmatic children exposed to NO<sub>2</sub> at concentrations >21 ppb. No significant reductions  
16 in lung function were detected among children without asthma.

17 The SAPALDIA (Study of Air Pollution and Lung Diseases in Adults) study  
18 (Ackermann-Lieblich, 1997) compared 9,651 adults (age 18 to 60) in eight different regions in  
19 Switzerland. Significant associations of NO<sub>2</sub>, SO<sub>2</sub>, and PM<sub>10</sub> with FEV<sub>1</sub> and FVC were found  
20 with a 10-μg/m<sup>3</sup> increase in annual average exposure. Due to the high correlations between NO<sub>2</sub>  
21 and the other pollutants (SO<sub>2</sub> = 0.86, PM<sub>10</sub> = 0.91), it was difficult to assess the effect of a  
22 specific pollutant. A random subsample of 560 adults from SAPALDIA recorded personal  
23 measurements of NO<sub>2</sub> and measurements of NO<sub>2</sub> outside their homes (Schindler, 1998). Using  
24 the personal and home measurements of NO<sub>2</sub>, similar associations were reported between NO<sub>2</sub>  
25 with FEV<sub>1</sub> and FVC.

26 Goss et al. (2004) examined the relationship of ambient pollutants on individuals with  
27 cystic fibrosis using the Cystic Fibrosis Foundation National Patient Registry in 1999 and 2000.  
28 Exposure was assessed by linking air pollution values from the Aerometric Information Retrieval  
29 System with the patient's home zip code. Associations were reported between PM and  
30 exacerbations or lung function changes, but no clear associations were found for NO<sub>2</sub>, SO<sub>2</sub>, O<sub>3</sub>,

1 and CO. The odds of patients with cystic fibrosis having two or more pulmonary exacerbations  
2 during 2000 per 10 ppb NO<sub>2</sub> is 0.98 (95% CI: 0.91, 1.01).

#### 3 4 ***Toxicology Studies***

5 A limited number of animal studies, especially those using spikes of NO<sub>2</sub>, have shown  
6 decrements in vital capacity and lung distensibility, which may provide biological plausibility for  
7 these lung function findings. NO<sub>2</sub> concentrations in many urban areas of the United States and  
8 elsewhere consist of spikes superimposed on a relatively constant background level. Miller et al.  
9 (1987) evaluated this urban pattern of NO<sub>2</sub> exposure in mice using continuous 7 days/week,  
10 23 h/day exposures to 0.2-ppm NO<sub>2</sub> with twice daily (5 days/week) 1-h spike exposures to  
11 0.8-ppm NO<sub>2</sub> for 32 and 52 weeks. Mice exposed to clean air and to the constant background  
12 concentration of 0.2-ppm NO<sub>2</sub> served as controls. Vital capacity tended to be lower (p = 0.054)  
13 in mice exposed to NO<sub>2</sub> with diurnal spikes than in mice exposed to air. Lung distensibility,  
14 measured as respiratory system compliance, also tended to be lower in mice exposed to diurnal  
15 spikes of NO<sub>2</sub> compared with constant NO<sub>2</sub> exposure or air exposure. These changes suggest  
16 that ≤52 weeks of low-level NO<sub>2</sub> exposure with diurnal spikes may produce a subtle decrease in  
17 lung distensibility, although part of this loss in compliance may be a reflection of the reduced  
18 vital capacity. Vital capacity appeared to remain suppressed for at least 30 days after exposure.  
19 Lung morphology in these mice was evaluated only by light microscopy (a relatively insensitive  
20 method) and showed no exposure-related lesions. The decrease in lung distensibility suggested  
21 by this study is consistent with the thickening of collagen fibrils in monkeys (Bils, 1976) and the  
22 increase in lung collagen synthesis rates of rats (Last et al., 1983) after exposure to higher levels  
23 of NO<sub>2</sub>.

24 Tepper et al. (1993) exposed rats to 0.5-ppm NO<sub>2</sub>, 22 h/day, 7 days/week, with a 2-h  
25 spike of 1.5-ppm NO<sub>2</sub>, 5 days/week for up to 78 weeks. No effects on pulmonary function were  
26 observed between 1 and 52 weeks of exposure. However, after 78 weeks of exposure, flow at  
27 25% forced vital capacity was decreased, perhaps indicating airways obstruction. A significant  
28 decrease in the frequency of breathing was also observed at 78 weeks that was paralleled by a  
29 trend toward increased expiratory resistance and expiratory time. Taken together, these results  
30 suggest that few, if any, significant effects were seen that suggest incipient lung degeneration.

1           The age sensitivity to exposure to diurnal spikes of NO<sub>2</sub> was studied by Stevens et al.  
2 (1988), who exposed 1-day- and 7-week-old rats to continuous baselines of 0.5-, 1.0-, and  
3 2.0-ppm NO<sub>2</sub> with twice daily 1-h spikes at three times these baseline concentrations for 1, 3, or  
4 7 weeks. In neonatal rats, vital capacity and respiratory system compliance increased following  
5 3 weeks, but not 6 weeks, of exposure to the 1.0- and 2.0-ppm NO<sub>2</sub> baselines with spikes. In  
6 young adult rats, respiratory system compliance decreased following 6 weeks of exposure, and  
7 body weight decreased following 3 and 6 weeks of exposure to the 2-ppm baseline with spike.  
8 In the young adult rats, pulmonary function changes returned to normal values 3 weeks after  
9 exposure ceased. A correlated morphometric study (Chang et al., 1986) is summarized in  
10 Section 3.4.1.2 below.

11           Lafuma et al. (1987) exposed 12-week-old hamsters with and without laboratory-induced  
12 (elastase) emphysema to 2.0-ppm NO<sub>2</sub>, 8 h/day, 5 days/week for 8 weeks. Vital capacity and  
13 pulmonary compliance were not affected by NO<sub>2</sub> exposure.

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

19

### 20 **3.4.1.2 Morphological Effects**

21           Animal toxicology studies demonstrate morphological changes to the respiratory tract  
22 from exposure to NO<sub>2</sub> that may provide further biological plausibility for the decrements in lung  
23 function growth observed in epidemiological studies discussed above. The centriacinar region is  
24 most sensitive to NO<sub>2</sub> and is where injury is first noted. This region includes the terminal  
25 conducting airways (terminal bronchioles), respiratory bronchioles, and adjacent alveolar ducts  
26 and alveoli. The upper respiratory tract (i.e., nasal cavity) does not appear to be much affected  
27 by NO<sub>2</sub> exposure. Within the centriacinar region, cell injury occurs in the ciliated cells of the  
28 bronchiolar epithelium and the type 1 cells of the alveolar epithelium, which are then replaced  
29 with nonciliated bronchiolar (Clara) cells and type II cells, respectively. Permanent alterations  
30 resembling emphysema-like disease may result from chronic exposure.

31           There is a large degree of interspecies variability in responsiveness to NO<sub>2</sub>; this is clearly  
32 evident from those few early studies where different species were exposed under identical



1 conditions (Wagner et al., 1965; Furiosi et al., 1973; Azoulay-Dupuis et al., 1983). This  
2 variability may be due to dosimetric differences in effective dose of NO<sub>2</sub> reaching target sites,  
3 but other species differences may play a role. Guinea pigs, hamsters, and monkeys all appear to  
4 be more severely affected morphologically by equivalent exposure to NO<sub>2</sub> than are rats, the most  
5 commonly used experimental animal. However, in most cases, similar types of histological  
6 lesions are produced when similar effective concentrations are used.

7  
8 ***Time Course***

9         Several investigators have studied the temporal progression of early events due to NO<sub>2</sub>  
10 exposure in the rat (e.g., Freeman et al., 1966, 1968, 1972; Stephens et al., 1971, 1972; Evans  
11 et al., 1972, 1973a,b, 1974, 1975, 1976, 1977; Cabral-Anderson et al., 1977; Rombout et al.,  
12 1986) and guinea-pig (Sherwin et al., 1973). These studies observed increased AM aggregation,  
13 desquamation of type I cells and ciliated bronchiolar cells, and accumulation of fibrin in small  
14 airways as the earliest alterations resulting from exposure to NO<sub>2</sub>. These alterations were seen  
15 within 24 to 72-h of exposure to NO<sub>2</sub> concentrations of ≥2.0 ppm. However, repair of injured  
16 tissue and replacement of destroyed cells begins within 24 to 48-h of continuous exposure. The  
17 new cells in the bronchiolar are derived from nonciliated bronchiolar (Clara) cells, whereas in  
18 the alveoli, the damaged type I cells are replaced with type II cells. One feature of the new cells  
19 is that they are relatively resistant to effects of continued NO<sub>2</sub> exposure.

20         The time course of alveolar lesions was also investigated by Kubota et al. (1987) in rats  
21 continuously exposed to 0.04- to 4.0-ppm NO<sub>2</sub>, 24 h/day for up to 27 months. One phase, which  
22 lasted for 9 to 18 months of exposure, consisted of a decrease in number and an increase in cell  
23 volume of type I epithelium, an increase in the number and volume of type II cells, and an  
24 increase in the relative ratio of type II to type I cells. A second phase, between 18 to 27 months  
25 of exposure, showed some recovery of the alveolar epithelium, but the total volume of interstitial  
26 tissue decreased, while collagen fibers in the interstitium increased. These findings indicate that  
27 some lesions, i.e., epithelial changes, tend to resolve, at least partially, with continued chronic  
28 exposure to low concentrations and to resolve rapidly during postexposure periods. At 0.4 ppm,  
29 the authors reported that the lesion typically was milder and its initiation delayed, compared to  
30 the higher concentration. At 0.4 and 4.0 ppm, morphometric increases in the mean alveolar  
31 thickness of the air-blood tissue barrier in the rats were also observed. According to the authors,

1 these interstitial changes were considered to be progressive and leading to fibrosis, rather than  
2 resolving as do epithelial changes.

3 In a more recent study, Barth et al., (1994a) evaluated cell proliferation at three different  
4 levels (bronchial, bronchiolar epithelium, and type II cells) in the lungs of rats exposed to 0, 0.8-,  
5 5-, or 10-ppm NO<sub>2</sub>, 24 h/day for 1 or 3 days. The highest rate of cell proliferation occurred in  
6 the bronchiolar epithelium. Cell proliferation was increased in type II cells after exposure to  
7 5-ppm NO<sub>2</sub> for 3 days and 10-ppm NO<sub>2</sub> for 1 or 3 days. In the bronchiolar epithelium, cell  
8 proliferation was increased at 0.8 ppm and above for both 1 and 3 days. Increased cell  
9 proliferation (AgNOR-number only) in the bronchial epithelium was observed in animals  
10 exposed to 10 ppm for 3 days.

11 Rats were also exposed continuously to NO<sub>2</sub> at 0, 5, 10, or 20 ppm continuously for 3 or  
12 25 days (Barth et al., 1994b, 1995; Barth and Muller, 1999). The highest proliferative activity  
13 was in the respiratory bronchiolar epithelium (Barth et al., 1994b; Barth and Muller, 1999).  
14 After 3 days of exposure, cell proliferation in the bronchiolar epithelium was increased 3-fold in  
15 the 5-ppm exposure group and remained elevated at the same level in the next two higher-  
16 concentration groups. The bronchial epithelium showed a different pattern, with a dose-  
17 dependent increase in the 10- and 20-ppm exposure groups. After 25 days, cell proliferation  
18 levels were increased in both the bronchiolar and bronchial epithelium in the 10- and 20-ppm  
19 groups. The increase was dose-dependent and there was no significant difference in the levels  
20 between the two tissues.

21 Pulmonary tissue damage, vascular alterations, Clara cell proliferation, and tissue-  
22 specific localization of NO<sub>2</sub> effects were all found to be both exposure duration- and  
23 concentration-dependent (Barth et al., 1995; Barth and Muller, 1999). After 3 days of exposure,  
24 there were histopathological changes extending from slight interstitial edema after exposure to  
25 5 ppm, to epithelial necrosis and interstitial inflammatory infiltration after exposure to 10 ppm,  
26 and an additional intra-alveolar edema after 20 ppm. Clara cells from the lungs of all  
27 NO<sub>2</sub>-exposed groups lost the apical intraluminal projections, and the damaged epithelium was  
28 covered by a layer of CC10 reactive material. These changes in Clara cells were not observed  
29 after 25 days of exposure. Exposure for 25 days to 10- and 20-ppm NO<sub>2</sub> resulted in a dose-linear  
30 increase of cell proliferation in the bronchial and bronchiolar epithelium. Double labeling of

1 CC10 and BrdU showed that cell proliferation was restricted to Clara cells, an indication of the  
2 progenitor role of Clara cells in oxidative stress injury in the lung tissue.

3 Morphometry studies showed that alveolar circumference was increased and alveolar  
4 surface density was decreased after an exposure to 20 ppm after 3 days and to 10 and 20 ppm  
5 after 25 days (Barth et al., 1994b, 1995). No significant alveolar changes were observed in the  
6 5-ppm exposure groups. The average medial thickness (AMT) of the pulmonary arteries was  
7 decreased in the 5-ppm group at both 3 and 25 days; AMT was increased in the 10-ppm group  
8 after 25 days and in the 37,600- $\mu\text{g}/\text{m}^3$  (20 ppm) group after 3 and 25 days (Barth et al., 1994b,  
9 1995). The AMT and alveolar density were negatively correlated (coefficient of correlation:  
10  $-0.56$ ), suggesting that pulmonary tissue damage and vascular alterations are closely related  
11 (Barth et al., 1995). These high exposure studies undoubtedly initiate mechanisms of injury that  
12 do not occur at more relevant near-ambient exposures, so little insight can be gained with these  
13 histopathology and morphometry studies in animals regarding these epidemiological findings.

#### 14 15 *Effects of NO<sub>2</sub> as a Function of Exposure Pattern*

16 Few morphological studies have been designed to evaluate modifying factors to NO<sub>2</sub>  
17 exposures, such as the exposure duration and concentration relationship, short-term peaks in  
18 concentration, or cycles of exposure and postexposure.

19 The relative roles of concentration and time in response to subchronic exposure have  
20 been investigated by Rombout et al. (1986). Rats were exposed from 0.53 to 10.6 ppm for up to  
21 28 days; or to 10.2 ppm for either a single 6-h exposure, 6 h/day for 28 days, or 24 h/day for  
22 28 days. Exposure concentration played a more important role in inducing lung epithelial cell  
23 lesions than did exposure duration provided  $C \times T$  was constant. The effect of concentration was  
24 stronger with intermittent exposure than with continuous exposure.

25 Few studies have examined ambient NO<sub>2</sub> patterns consisting of a low baseline level with  
26 transient spikes of NO<sub>2</sub>, as exists in the environment. However, in some cases, there was no  
27 group at the baseline exposure, preventing evaluation of the contribution of peaks to the  
28 responses. Gregory et al. (1983) exposed rats (14 to 16 weeks old) for 7 h/day, 5 days/week for  
29 up to 15 weeks to NO<sub>2</sub> at 1.0 or 5.0 or 1.0 ppm with two 1.5-h spikes of 5.0 ppm per day. After  
30 15 weeks of exposure, histopathologic changes were minimal, with focal hyperinflation and

1 areas of subpleural accumulation of macrophages found in some of the animals exposed either to  
2 the baseline of 5.0 ppm or to 1.0 ppm with the 5.0-ppm spikes.

3 Port et al. (1977) observed dilated respiratory bronchioles and alveolar ducts in mice  
4 exposed to 0.1-ppm NO<sub>2</sub> with daily 2-h peaks to 1.0 ppm for 6 months. Miller et al. (1987)  
5 found no morphological effects in mice exposed for 1 year, although host defense functional  
6 changes were noted (see Section 4.3.2).

7 Changes in the proximal alveolar and terminal bronchiolar regions in response to  
8 exposure to baseline NO<sub>2</sub> concentration plus NO<sub>2</sub> spikes were also investigated in the rat. Crapo  
9 et al. (1984) and Chang et al. (1986) exposed rats for 6 weeks to a baseline concentration of  
10 0.5- or 2.0-ppm NO<sub>2</sub>, 23 h/day for 7 days/week, onto which were superimposed two daily 30-  
11 min spikes of three times the baseline concentration for 5 days/week. Morphometric analyses  
12 showed increases in the volumes of the type 2 epithelium, surface area of type II cells, interstitial  
13 matrix, and AMs; no changes were seen in the volume of fibroblasts at the lower concentration.  
14 Most of the changes were also noted at the higher exposure level, and in some cases, the change  
15 was greater than that at the lower level (i.e., increase in type 1 and type 2 epithelial volume). At  
16 both levels of exposure, the increase in the volume of type II cells and interstitial fibroblasts  
17 were not accompanied by significant changes in their numbers, but the number of AMs  
18 decreased. At the highest exposure, the number of type I cells decreased and their average  
19 surface area increased. Generally, there was a spreading and hypertrophy of type II cells. A  
20 correlation between decreased compliance (Stevens et al., 1988) and thickening of the alveolar  
21 interstitium was found (see Section 3.3.1.1 for details of the pulmonary function portion of the  
22 study). Examination of the terminal bronchiolar region revealed no effects at the lower exposure  
23 level. At the higher level, there was a 19% decrease in ciliated cells per unit area of the  
24 epithelial basement membrane and a reduction in the mean ciliated surface area. The size of the  
25 dome protrusions of nonciliated bronchiolar (Clara) cells was decreased, giving the bronchial  
26 epithelium a flattened appearance, but there was no change in the number of cells.

27

### 28 ***Factors Affecting Susceptibility to Morphological Changes***

29 Susceptibility to morphological effects may be influenced by many factors, such as age,  
30 compromised lung function, and acute infections. Age of the animal at the time of exposure may  
31 be responsible for some of the variability in morphological response seen in the same species  
32 exposed to comparable concentrations.

1           It appears that neonates, prior to weaning, are relatively resistant to NO<sub>2</sub>, and that  
2           responsiveness then increases (Stevens et al., 1978). Furthermore, the responsiveness of mature  
3           animals appears to decline somewhat with age, until an increase in responsiveness occurs at  
4           some point in senescence. However, the morphological response to NO<sub>2</sub> in animals of different  
5           ages involves similarities in the cell types affected and in the nature of the damage incurred.  
6           Age-related differences occur in the extent of damage and in the time required for repair, the  
7           latter taking longer in older animals. The reasons for age differences in susceptibility are not  
8           known but may involve toxicokinetic and toxicodynamic differences during different growth  
9           phases.

10           Kyono and Kawai (1982) exposed rats at 1, 3, 12, and 21 months of age continuously for  
11           1 month to 0.11-, 0.46-, 2.8-, or 8.8-ppm NO<sub>2</sub>. Light and electron microscopic analyses were  
12           used, and various morphometric parameters were assessed, including arithmetic mean thickness  
13           of the air-blood barrier and the volume density of various alveolar wall components. Because  
14           these investigators were interested in the effect of the overall gas-exchange area, they  
15           deliberately excluded the centriacinar alveolar region, site of main damage. Analysis of  
16           individual results was complex, but depending upon the animal's age and the specified endpoint,  
17           exposure levels as low as 0.11 ppm changed specific morphometric parameters. There was a  
18           trend towards a concentration-dependent increase in air-blood barrier thickness in all age groups,  
19           with evidence of age-related differences in response. At any concentration, the response of this  
20           endpoint decreased in rats from 1 to 12 months old, but increased again in 21-month-old animals.  
21           Type I and II cells showed various degrees of response, depending on both age at onset of  
22           exposure and exposure concentration. The response of each lung component did not always  
23           show a simple concentration-dependent increase or decrease, but suggested a multiphasic  
24           reaction pattern.

25           Kyono and Kawai (1982) may not have used the most susceptible animal model.  
26           Azoulay-Dupuis et al. (1983) investigated the species and age-related susceptibility to  
27           morphological changes by exposing both rats and guinea pigs aged 5 to >60 days old to 2.0 and  
28           10 ppm for 3 days. There was no mortality in the rats; however, mortality increased with  
29           increasing age in guinea pigs exposed to 10 ppm. In both species, older animals showed greater  
30           effects of exposure than did neonates. Rats at all ages and guinea pigs less than 45 days old were  
31           not affected. The 45-day-old guinea pigs showed thickening of alveolar walls, alveolar edema,

1 and inflammation; animals older than 45 days showed similar, but more frequent, alterations that  
2 seemed to increase with age. Adults also had focal loss of cilia in bronchioli.

3 Age-related responsiveness to an urban pattern of NO<sub>2</sub> was evaluated by Chang et al.  
4 (1986, 1988) using 1-day- or 6-week-old rats exposed for 6 weeks to a baseline of 0.5-ppm NO<sub>2</sub>  
5 for 23 h/day, 7 days/week, with two 1-h spikes (given in the morning and afternoon) of 1.5 ppm  
6 5 days/week. Electron microscopic morphometric analysis of the proximal alveolar regions  
7 showed an increase in the surface density of the alveolar basement membrane in the older  
8 animals that was not seen in the younger animals. Although both age groups responded in a  
9 generally similar manner, the 6-week-old rats seemed to be generally more susceptible to injury  
10 than were the 1-day-olds, as the 6-week old animals had more variables that were significantly  
11 different from their control group. There was no qualitative evidence of morphological injury in  
12 the terminal bronchioles of the younger rats, but there was a 19% increase in the average ciliated  
13 cell surface that was not evident in the older rats. In addition, there was a 13% increase in the  
14 mean luminal surface area of Clara cells in the younger versus control animals of the same age.  
15 Pulmonary function was also altered in similarly exposed rats (Stevens et al., 1988) (see Section  
16 3.3.1.1). Interpretation of the neonatal effects is difficult. Assuming that rats prior to weaning  
17 are more resistant to NO<sub>2</sub> (Stevens et al., 1978) (see below), effects observed after a 6-week  
18 exposure from birth may have resulted from the last 3 weeks of exposure, as the first 3 weeks  
19 may constitute a more resistant period. In contrast, effects observed in young adults probably  
20 reflect the impact of the entire 6-week exposure. These findings may parallel the effects  
21 observed in the CHS studies reviewed above, identifying school-age children as vulnerable to the  
22 effects of NO<sub>2</sub>.

23 Few studies have been conducted on effects in individuals with preexisting respiratory  
24 disease with exposure to environmental levels of NO<sub>2</sub>. These studies include animals with  
25 laboratory-induced emphysema or infections. Morphometric analyses of lungs from normal and  
26 elastase-induced emphysematous hamsters (2 months old) that had been exposed to 2.0-ppm  
27 NO<sub>2</sub> for 8 h/day, 5 days/week, for 8 weeks, indicated that emphysematous lesions were  
28 exacerbated by NO<sub>2</sub> (i.e., NO<sub>2</sub> increased pulmonary volume and decreased internal alveolar  
29 surface area) (Lafuma et al. (1987). The investigators suggested that these results may imply a  
30 role for NO<sub>2</sub> in enhancing pre-existing emphysema. A study by Fenters et al. (1973) also  
31 reported that acute infectious (influenza) lung disease enhanced the morphological effects of

1 NO<sub>2</sub> in squirrel monkeys when these animals were exposed continuously to 1.0-ppm NO<sub>2</sub> for 16  
2 months.

### 3 4 **3.4.1.3 Asthma Prevalence and Incidence—Children**

5 Among the studies reporting results from the United States in regard to asthma  
6 prevalence incidence associated with NO<sub>2</sub> exposure, several publications from the CHS in  
7 California report results. Gauderman et al., 2005 conducted a study of children randomly  
8 selected from the CHS with exposure measured at children's homes. Although only 208 were  
9 enrolled, exposure to NO<sub>2</sub> was strongly associated with both lifetime history of asthma, and  
10 asthma medications use. Gauderman et al. (2005) measured ambient NO<sub>2</sub> with Palmes tubes  
11 attached at the subjects' homes at the roofline eaves, signposts, or rain gutters at an approximate  
12 height of 2 m above the ground. Samples were deployed for 2-week periods in both summer and  
13 fall. Traffic-related pollutants were characterized by 3 metrics: (1) proximity of home to  
14 freeway, (2) average number of vehicles within 150 meters, and (3) model-based estimates.  
15 Yearly average NO<sub>2</sub> levels within the 10 communities ranged from 12.9 to 51.5 ppb. The  
16 average NO<sub>2</sub> concentration measured at home was associated with asthma prevalence (OR = 8.33  
17 [95% CI: 1.15, 59.87] per 20 ppb) with similar results by season and when taking into account  
18 several potential confounders. Tables 3.4-1 and 3.4-2 show associations with several indicators  
19 of traffic-related air pollution and asthma. In each community measured, NO<sub>2</sub> was more strongly  
20 correlated with estimates of freeway-related pollution than with non-freeway-related pollution.  
21 In a related CHS study, McConnell et al. (2006) studied the relationship of proximity to major  
22 roads and asthma and found a positive relationship.

23 Further evaluation of exposure estimation was done in this cohort of schoolchildren  
24 (Molitor et al., 2007). Several models of interurban air pollution exposure were used to classify  
25 and predict FVC in an integrated Bayesian modeling framework, using three interurban  
26 predictors: distance to a freeway; traffic density; and predicted average NO<sub>2</sub> exposure from the  
27 California line source dispersion (CALINE4) model. Results suggested that the inclusion of  
28 residual spatial terms can reduce uncertainty in the prediction of exposures and associated health  
29 effects (Molitor et al., 2007).

30 Islam et al. (2007) studied whether lung function is associated with new onset asthma and  
31 whether this relationship varies by exposure to ambient air pollutants by examining a cohort of  
32 2,057 fourth-grade children who were asthma- and wheeze-free at the start of the CHS and

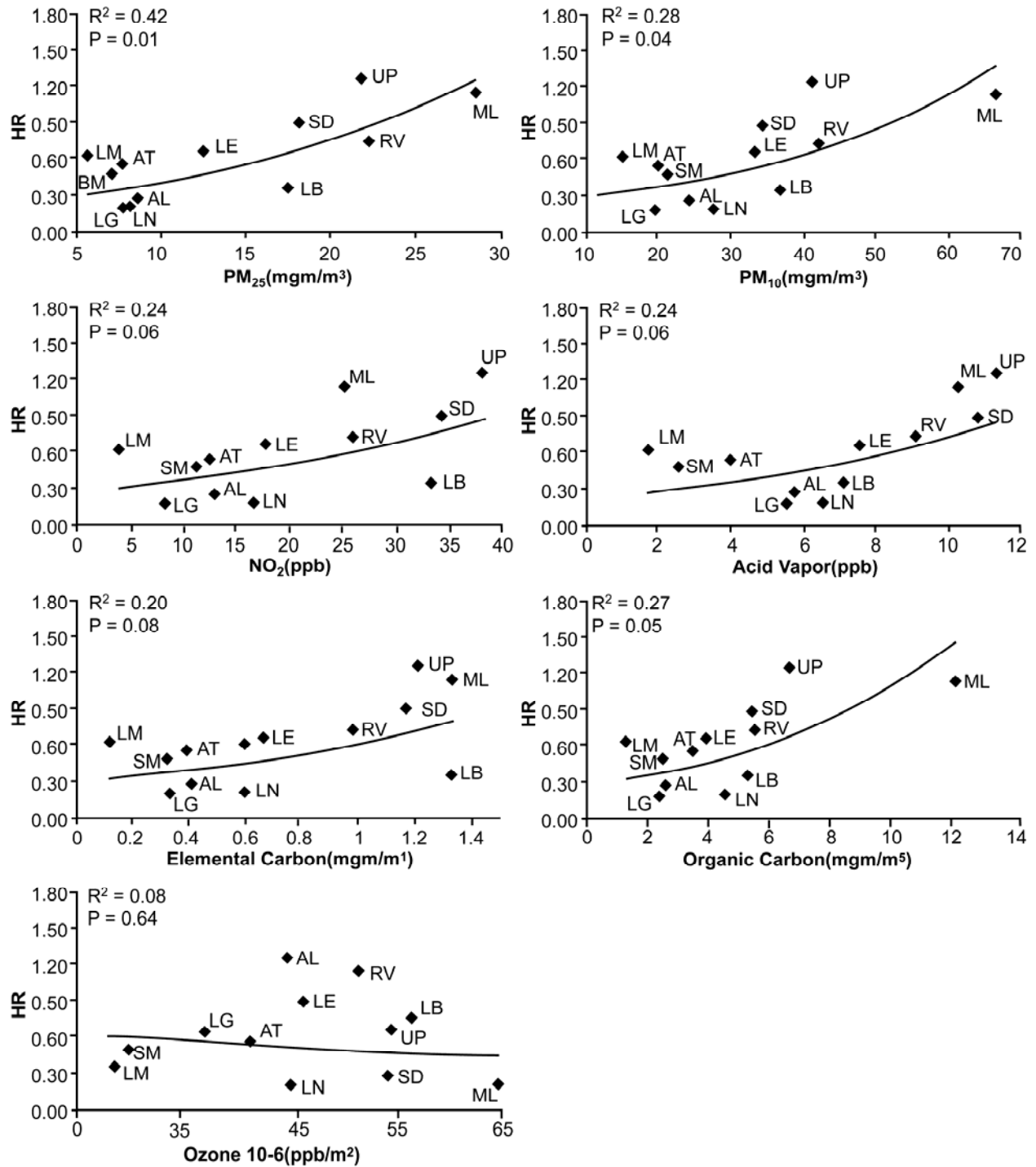
1 followed them for 8 years. A hierarchical model was used to evaluate the effect of individual air  
2 pollutants (NO<sub>2</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>, and acid vapor, O<sub>3</sub>, EC, and OC) on the association of lung  
3 function with asthma as shown in Figure 3.4-2. The loss of the protective effect from better lung  
4 function can be appreciated from these graphs. PM indicators were significantly related, and  
5 NO<sub>2</sub> was marginally significant (p = 0.06). This study shows that better airflow, characterized  
6 by higher FEF<sub>25-75</sub> and FEV<sub>1</sub> during childhood was associated with decreased risk of new onset  
7 asthma during adolescence. However, exposure to high levels of ambient pollutants (NO<sub>2</sub> and  
8 others) attenuated this protective association of lung function on asthma occurrence.

9 Brauer et al. (2007) assessed the development of asthmatic/allergic symptoms and respiratory  
10 infections during the first 4 years of life in a birth cohort study (n = 4,000, but the number of  
11 participants decreased over the study to ~3,500) in the Netherlands. The mean NO<sub>2</sub> concentration  
12 was 13.1 ppb. Air pollution concentrations at the home address at birth were calculated by a  
13 model combining air pollution measurements with a Geographic Information System (GIS).  
14 This exposure model was validated. The association between exposure and health outcomes was  
15 analyzed by multiple logistic regression in the adjustment for confounding variables. The  
16 interquartile range in increase in NO<sub>2</sub> was 10.6 µg/m<sup>3</sup>.

17 Wheeze, doctor-diagnosed asthma, and flu and serious colds were associated with air  
18 pollutants (considered traffic-related: NO<sub>2</sub>, PM<sub>2.5</sub>, soot); for example, NO<sub>2</sub> was associated with  
19 doctor-diagnosed asthma (OR = 1.28 [95% CI: 1.04, 1.56] for a cumulative lifetime indicator.  
20 Jerrett (2007) comments on this study that (1) the effects are larger and more consistent than in  
21 participants of the same study at age 2; (2) these effects suggest that onset and persistence of  
22 respiratory disease formation begins at an early age and continues; and (3) the more sophisticated  
23 method for exposure assessment used based on spatially and temporally representative field  
24 measurements and land use regression is capable of capturing small area variations in traffic  
25 pollutants. Importantly, this study is one of the few assessing disease incidence in the same  
26 manner as the CHS discussed above.

27 Kim et al. (2004a) reported positive associations for girls to both NO<sub>2</sub> and NO<sub>x</sub> in the San  
28 Francisco bay area. They studied 1,109 students (grades 3 to 5) at 10 school sites for bronchitis  
29 symptoms and asthma in relation to ambient pollutant levels to include NO, NO<sub>2</sub>, and NO<sub>x</sub>  
30 measured at the school site. Mean levels ranged for schools from 33 to 69 ppb for NO<sub>x</sub>; 19 to 31





**Figure 3.4-2. Effect of individual pollutants on the association of lung function with asthma.**

Source: Islam et al. (2007).

1 for NO<sub>2</sub>; and 11 to 38 ppb for NO. NO<sub>x</sub> and NO<sub>2</sub> measurements at school sites away from traffic  
2 were similar to levels measured at the regional site. They found associations between traffic-  
3 related pollutants and asthma and bronchitis symptoms, which is consistent with previous reports  
4 of traffic and respiratory outcomes. Some U.S. studies had previously shown inconsistent  
5 results, possibly due to exposure misclassification as the studies used only a single fixed site.  
6 The higher effect estimates with black carbon, NO<sub>x</sub>, and NO compared with NO<sub>2</sub> and PM<sub>2.5</sub>  
7 suggest that primary or fresh traffic emissions may play an etiologic role in these relationships  
8 and that while NO<sub>x</sub> and NO may serve as indicators of traffic exposures, they may also act as  
9 etiologic agents themselves.

10 Millstein et al. (2004) studied the effects of ambient air pollutants on asthma medication  
11 use and wheezing among 2,034 fourth-grade schoolchildren from the CHS. Included in the  
12 pollutants examined were NO<sub>2</sub> and HNO<sub>3</sub>. They observed that monthly average pollutant levels  
13 produced primarily by photochemistry (i.e., O<sub>3</sub>, HNO<sub>3</sub>, and acetic acid) were associated with  
14 asthma medication use among children with asthma—especially among children who spent more  
15 than the calculated median time outdoors. The March-August OR for HNO<sub>3</sub> (IQR 1.64 ppb) was  
16 1.62 (95% CI: 0.94, 2.80) and for NO<sub>2</sub> (IQR 5.74 ppb) was 0.96 (95% CI: 0.68, 1.37).

17 Other studies (see Annex Table AX6.2) have investigated asthma prevalence in children  
18 associated with NO<sub>2</sub> exposure. Although several of these studies have reported positive  
19 associations, the large number of comparisons made and the limited number of positive results  
20 do not suggest a strong relationship between chronic NO<sub>2</sub> exposure and asthma. Exposure in  
21 these studies varied, but medians were often greater than 20 ppb. Most of the studies did not  
22 report correlations of NO<sub>2</sub> exposure with other air pollutants; therefore, it is not possible to  
23 determine whether some of these associations were related to other air contaminants.

24 Annex Table AX6.6-2 lists several studies from Europe where the International Study of  
25 Asthma and Allergies in Children (ISAAC) protocol was used. Children were interviewed in  
26 school and results of the questionnaire were compared with air pollution measurements in their  
27 communities. These studies included thousands of children in several European countries and  
28 Taiwan, and all but one were negative. In Austria (Studnicka, 1997) the highest level of  
29 exposure (14.7- to 17.0-ppb NO<sub>2</sub>) was associated with increased risk of asthma.

30 Two studies (Shima and Adachi, 2000; Kim et al., 2004a) reported positive associations  
31 for girls, but negative associations for boys. It is difficult to interpret these studies since the level

1 of exposure did not vary by gender. The children surveyed were 9 to 11 years old. In this age  
2 range, asthma is more common among girls, perhaps due to hormonal influences, while asthma  
3 is more common in boys at younger ages.

#### 4 5 **3.4.1.4 Respiratory Symptoms**

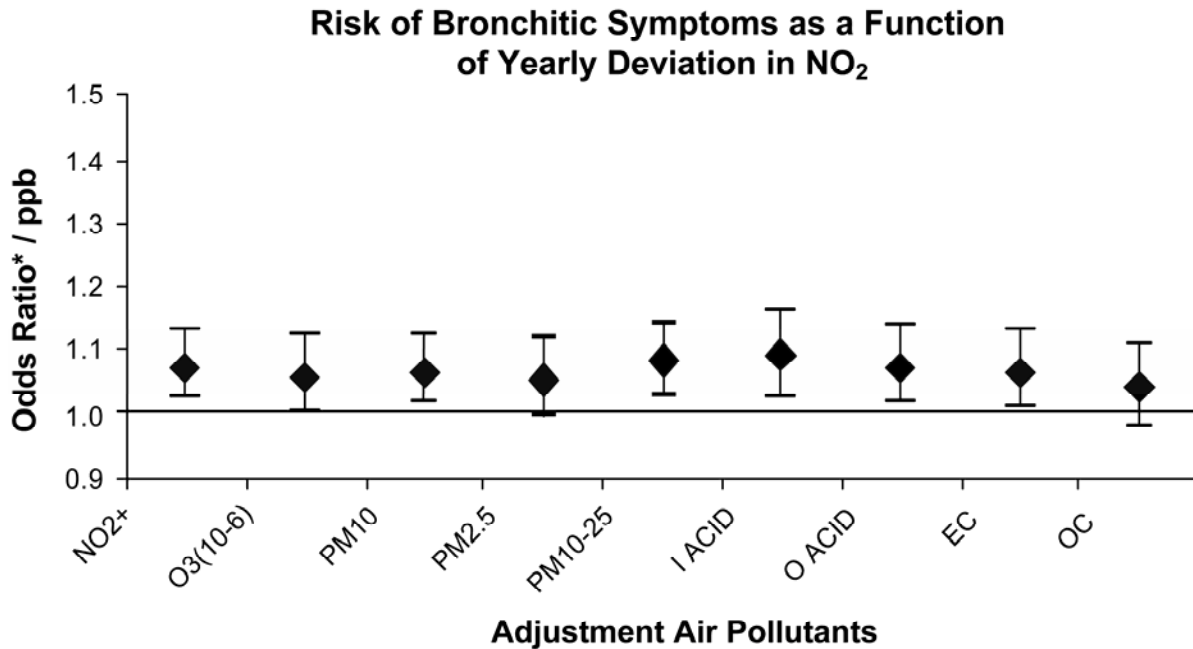
6 Although a large number of studies have investigated effects of chronic exposure to NO<sub>2</sub>  
7 on respiratory symptoms, the validity of these studies is uncertain. More appropriately,  
8 symptoms should be compared to acute exposures. In some of these studies, a symptom (e.g.  
9 wheeze) may be used as a surrogate for disease that is difficult to define or diagnose, (e.g.  
10 asthma). This confusion between acute and chronic symptoms or acute and chronic exposure  
11 may explain some of the inconsistency in results of these studies.

12 Annex Table AX6.6-3 lists nine studies, most of which report some positive associations  
13 with NO<sub>2</sub> exposure and symptoms, but all report a large number of negative results. Only one of  
14 these studies (Peters et al., 1999) reported an association of NO<sub>2</sub> exposure with wheeze, and in  
15 boys. This was despite the fact that wheeze was investigated in a large number of studies,  
16 including several studies that included thousands of children.

17 McConnell et al. (2003) studied the relationship between bronchitis symptoms and  
18 pollutants in the CHS. Symptoms assessed yearly by questionnaire from 1996 to 1999 were  
19 associated with the yearly variability for the pollutants for NO<sub>2</sub> (OR = 1.071 ppb [95% CI: 1.02,  
20 1.13]). In two-pollutant models, the effects of yearly variation in NO<sub>2</sub> were only modestly  
21 reduced by adjusting for other pollutants except for OC and NO<sub>2</sub>. (See Figure 3.4-3).

22 McConnell et al. (2006) evaluated whether the association of exposure to air pollution  
23 with annual prevalence of chronic cough, phlegm production, or bronchitis was modified by dog  
24 or cat ownership indicators or allergen and endotoxin exposure. Subjects consisted of  
25 475 children from the CHS. Among children owning a dog, there was strong association  
26 between bronchitis symptoms and all pollutants studied. Odds ratio for NO<sub>2</sub> were 1.49 (95% CI:  
27 1.14, 1.95), indicating that dog ownership may worsen the relationship between air pollution and  
28 respiratory symptoms in asthmatic children.

29 Cough and difficulty breathing were more commonly reported in association with NO<sub>2</sub>  
30 exposure. Interestingly, both Garrett et al., 1999 and Hirsch et al., 1999 report positive  
31 associations between NO<sub>2</sub> exposure and symptoms when symptoms are less common. Garrett



**Figure 3.4-3. Odds ratios for within-community bronchitis symptoms associations with NO<sub>2</sub>, adjusted for other pollutants in two-pollutant models.**

Source: McConnell et al. (2003).

1 indicates a positive associations only during the summer months and Hirsch reports a significant  
2 association with cough, particularly cough among non-atopic children.

3 Three studies (Mukala et al., 1999; van Strien et al., 2004; Nitschke et al., 2006)  
4 compared exposure to NO<sub>2</sub> measured by personal monitors, or monitors in the home, with  
5 respiratory symptoms. Mukala et al. (1999) reported a significant association of the highest level  
6 of weekly NO<sub>2</sub> exposure and cough. Both cough and shortness of breath were reported by  
7 van Strien et al. (2004) associated with measured home exposure to NO<sub>2</sub> among infants. This  
8 relationship appeared to be dose dependent. Nitschke et al. (2006) reported difficulty breathing  
9 and chest tightness in asthmatic children that was associated with 10-ppb increases in NO<sub>2</sub>  
10 measured in school classrooms. Further discussion of these studies was provided earlier in  
11 Section 6.2.

12 Two studies of infants were conducted in Germany and the Netherlands using the same  
13 exposure protocol (Gehring et al., 2002; Brauer et al., 2002). In Munich, 1,756 infants were  
14 enrolled and followed for 2 years. Outcomes of interest were asthma, bronchitis, and respiratory

1 symptoms including wheeze, cough, and nasal symptoms. To determine exposure, 40 measuring  
2 sites were selected in Munich, including sites along main roads, side streets and background  
3 sites. At each site, NO<sub>2</sub> was measured four times (once in each season) for 14 days using Palmes  
4 tubes. Regression modeling was used to relate annual average pollutant concentrations to a set  
5 of predictor variables (i.e., traffic density, heavy vehicle density, household density, population  
6 density) obtained from GIS. The percentage of variability explained by the model (R<sup>2</sup>) was  
7 0.62 for NO<sub>2</sub>. Using geocoded birth addresses, values for the predictor variables were obtained  
8 for each child, and the model was used to assign an estimate of NO<sub>2</sub> exposure. At 1 year of age,  
9 an increase of 8.5 µg/m<sup>3</sup> of NO<sub>2</sub> was associated with cough (OR = 1.40 [95% CI: 1.12, 1.75])  
10 and dry cough at night (OR = 1.36 [95% CI: 1.07, 1.74]). NO<sub>2</sub> exposure was not associated  
11 with wheeze, bronchitis, or respiratory infections. Estimated PM<sub>2.5</sub> exposure was also associated  
12 with cough and dry cough at night, with nearly identical odds ratios.

13 In the Netherlands (Brauer et al., 2002), the same protocol was used to estimate NO<sub>2</sub>  
14 exposure in a birth cohort of 3,730 infants. However, these study subjects lived in many  
15 different communities from rural areas to large cities in northern, central and western parts of the  
16 Netherlands. Forty sites were selected to represent different exposures and measurements were  
17 taken as in the Gehring et al. (2002) study. In this study, ear, nose, and throat infections  
18 (OR = 1.16 [95% CI: 1.00, 1.34]) and physician-diagnosed flu (OR = 1.11 [95% CI: 1.00,  
19 1.23]) were marginally significant. The association of NO<sub>2</sub> with dry cough at night could not  
20 be replicated, nor was NO<sub>2</sub> associated with asthma, wheeze, bronchitis, or eczema.

21 In both of these studies, the 40 monitoring sites set up to measure NO<sub>2</sub> also measured  
22 PM<sub>2.5</sub> with Harvard Impactors. Estimates of NO<sub>2</sub> and PM<sub>2.5</sub> were highly correlated in Brauer  
23 et al., correlation = 0.97). The correlation was not reported in Gehring et al.; however, the  
24 similarity of odds ratios for each pollutant suggests that the estimated exposures were also highly  
25 correlated. Thus, a major limitation of these studies is the inability to distinguish the effects of  
26 different pollutants.

27 In a study of 3,946 Munich schoolchildren, Nicolai et al. (2003) assessed traffic exposure  
28 using two different methods. First, all street segments within 50 m of each child's home were  
29 identified and the average daily traffic counts were totaled. Second, a model was constructed  
30 based on measurement of NO<sub>2</sub> at 34 sites throughout the city using traffic counts and street  
31 characteristics (R<sup>2</sup> = 0.77). The model was then used to estimate NO<sub>2</sub> exposure at each child's

1 home address. When traffic counts of  $\leq 50\text{m}$  were used as an exposure variable, a significant  
2 association was found with current asthma (OR = 1.79 [95% CI: 1.05, 3.05]), wheeze  
3 (OR = 1.66 [95% CI: 1.07, 2.57]), and cough (OR = 1.62 [95% CI: 1.16, 2.27]). Similar results  
4 were found when modeled NO<sub>2</sub> exposure was substituted as the exposure variable (current  
5 asthma OR = 1.65 [95% CI: 0.94, 2.90], wheeze OR = 1.58 [95% CI: 1.05, 2.48], cough  
6 OR = 1.60 [95% CI: 1.14, 2.23]). Asthma, wheeze, and cough were also associated with  
7 estimated exposures to soot and benzene derived from models, suggesting that some component  
8 of traffic pollution is increasing risk of respiratory conditions in children, but making it difficult  
9 to determine whether NO<sub>2</sub> is the cause of these conditions.

#### 10 11 **3.4.1.5 Integration of Evidence on Long-Term NO<sub>2</sub> Exposure and Respiratory Illness** 12 **and Lung Function Decrements**

13 There is strong evidence for the increased occurrence of respiratory illness in children  
14 associated with long-term exposures to NO<sub>2</sub>. An earlier U.S. Environmental Protection Agency  
15 meta-analysis of indoor NO<sub>2</sub> studies supported an effect of estimated exposure to NO<sub>2</sub> on  
16 respiratory symptoms and disease in children ages 5 to 12. A similar relationship was not seen  
17 with infants and younger children ages 0 to 2. Recent evidence from cohort studies from  
18 California, examining NO<sub>2</sub> exposure in children over an 8-year period, demonstrated deficits in  
19 lung function growth. Deficits in lung function growth is a known risk factor for chronic  
20 respiratory disease and possibly for premature mortality in later life stages. Lung growth  
21 continues from early development through early adulthood, reaches a plateau, and then  
22 eventually declines with advancing age. Dockery and Brunekreef (1996) have hypothesized that  
23 the risk for chronic respiratory disease is associated with maximum lung size, the length of time  
24 the lung size has been at the plateau, and the rate of decline of lung function. Therefore,  
25 exposures to NO<sub>2</sub> in childhood may reduce maximum lung size by limiting lung growth and  
26 subsequently increase the risk in adulthood for chronic respiratory disease.

27 Animal toxicological studies provide biological plausibility for the observed increased  
28 incidence of respiratory illness among children. A number of defense system components such  
29 as AMs and the humoral and cell-mediated immune system have been demonstrated to be targets  
30 for inhaled NO<sub>2</sub>. The animal studies described above show that NO<sub>2</sub> exposure impairs the host  
31 defense system, causing animals to be more susceptible to respiratory infections. Morphological  
32 changes are elicited in ciliated epithelial cells at NO<sub>2</sub> concentrations as low as 0.5 ppm for

1 7 months; however, early studies showed that mucociliary clearance is not affected by exposures  
2 <5 ppm. A more recent study in guinea pigs showed a concentration-dependent decrease in  
3 ciliary activity at 3-ppm NO<sub>2</sub>.

4 A second line of defense in the lung, the AMs, are affected by NO<sub>2</sub> in a concentration-  
5 and species-dependent manner with both acute and chronic exposures. Mechanisms whereby  
6 NO<sub>2</sub> affects AM function include membrane lipid peroxidation, decreased ability to produce  
7 superoxide anion, inhibition of migration, and decreased phagocytic activity. Decreases in  
8 bactericidal and phagocytic activities are likely related to increased susceptibility to pulmonary  
9 infections. More recent studies have confirmed that AMs are a primary target for NO<sub>2</sub> at  
10 exposure levels <1 ppm.

11 Humoral and cell-mediated immune systems comprise a third line of defense that has  
12 been shown to be suppressed by NO<sub>2</sub> exposure. The use of animal infectivity studies provides  
13 key biological plausibility evidence for the effects of NO<sub>2</sub> on respiratory morbidity and  
14 mortality. For these studies, the animals are exposed to NO<sub>2</sub>, followed by exposure to an aerosol  
15 containing the infectious agent. This body of work shows that NO<sub>2</sub> decreases intrapulmonary  
16 bactericidal activity in mice in a concentration-dependent manner, with no concurrent changes to  
17 mucociliary clearance.

18 Thus, strong evidence indicates that the reduced efficacy of lung defense systems is an  
19 important mechanism for the observed increase in incidence and severity of respiratory  
20 infections. Overall, the NO<sub>2</sub> toxicological literature suggests a linear concentration-response  
21 relationship that exists in an exposure range of 0.5 to >5 ppm and mortality resulting from  
22 pulmonary infection. NO<sub>2</sub> exposure reduces the efficiency of defense against infections at  
23 concentrations as low as 0.5 ppm. The exposure protocol is important, with concentration being  
24 more important than duration of exposure and with peak exposures being important in the overall  
25 response. The effect of concentration is stronger with intermittent exposure than with continuous  
26 exposure. Repeated exposures of low levels of NO<sub>2</sub> are necessary for many respiratory effects.  
27 The animal toxicological studies also demonstrate differences in species sensitivity to NO<sub>2</sub> and  
28 differences in responses to the microbes used for the infectivity tests. Animal to human  
29 extrapolation is limited by a poor understanding of the quantitative relationship between NO<sub>2</sub>  
30 concentrations and effective doses between animals and humans. However, animals and humans

1 share many host defense components, making the infectivity model useful for understanding the  
2 mechanisms whereby NO<sub>2</sub> elicits adverse respiratory health effects.

3 The 1993 AQCD for Oxides of Nitrogen stated that an increase of reported respiratory  
4 symptoms in some epidemiology studies may be an indication of the ability of the respiratory  
5 host-defense mechanism to either overcome an infection or to limit its severity. NO<sub>2</sub> may affect  
6 the immune system in such a way that one or several aspects of the immune system do not  
7 function at a level sufficient to limit the extent or occurrence of infection.

8 Toxicological and human clinical studies demonstrating altered host defenses provide  
9 plausibility for the observed increase in frequency and severity of respiratory symptoms and/or  
10 infections in humans. Increased severity or rate of respiratory illness may result from altered  
11 host defenses in an NO<sub>2</sub> exposed lung subsequently infected with an infectious microorganism.  
12 Although the host defense system reacts both very specifically and generally to the challenge, the  
13 overall response in humans is expressed as a generalized demonstration of signs and symptoms  
14 that may be associated with a site such as the lower respiratory tract and also may be reported or  
15 objectively discerned as a general outcome such as a chest cold, cough, or an incident of asthma  
16 or bronchitis (U.S. Environmental Protection Agency, 1993).

17 Other important biochemical mechanisms examined in animals may provide biological  
18 plausibility for chronic effects of NO<sub>2</sub> observed in epidemiology studies. The main biochemical  
19 targets of NO<sub>2</sub> exposure appear to be antioxidants, membrane polyunsaturated fatty acids, and  
20 thiol groups. NO<sub>2</sub> effects include changes in oxidant/antioxidant homeostasis and chemical  
21 alterations of lipids and proteins. Lipid peroxidation has been observed at NO<sub>2</sub> exposures as low  
22 as 0.04 ppm (for 9-months) and at exposures of 1.2 ppm for 1 week, suggesting lower effect  
23 thresholds with longer durations of exposure. Other studies show decreases in the formation of  
24 key arachidonic acid metabolites in AMs following NO<sub>2</sub> exposures of 0.5 ppm. NO<sub>2</sub> has also  
25 been shown to increase collagen synthesis rates at concentrations as low as 0.5 ppm. This could  
26 indicate increases in total lung collagen, which are associated with pulmonary fibrosis.  
27 Morphological effects following chronic NO<sub>2</sub> exposures have been identified in animal studies  
28 that link to these increases in collagen synthesis and may provide plausibility for the deficits in  
29 lung function growth described in epidemiological studies.



### 3.4.2 Cardiovascular Effects Associated with Long-Term NO<sub>2</sub> Exposure

Limited toxicology data exist on the effect of NO<sub>2</sub> on the heart. Alterations in vagal responses have been shown to occur in rats exposed to 10-ppm NO<sub>2</sub> for 24 h; however, exposure to 0.4-ppm NO<sub>2</sub> for 4 weeks revealed no change (Tsubone and Suzuki, 1984). NO<sub>2</sub>-induced effects on cardiac performance are suggested by a significant reduction in PaO<sub>2</sub> in rats exposed to 4.0-ppm NO<sub>2</sub> for 3 months. When exposure was decreased to 0.4-ppm NO<sub>2</sub> over the same exposure period, PaO<sub>2</sub> 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<sub>2</sub> for 1 month (Suzuki et al., 1984). Whether these effects are the direct result of NO<sub>2</sub> 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<sub>2</sub>.

No effect on hematocrit and hemoglobin have been reported in squirrel monkeys exposed to 1.0-ppm NO<sub>2</sub> for 16 months (Fenters et al., 1973) or in dogs exposed to ≤5.0-ppm NO<sub>2</sub> for 18 months (Wagner et al., 1965). There was, however, polycythemia and an increased ratio of PMNs to lymphocytes in rats exposed to 2.0 + 1.0 ppm NO<sub>2</sub> for 14 months (Furiosi et al., 1973). No additional studies were found in the literature since the 1993 AQCD for Oxides of Nitrogen.

### 3.4.3 Adverse Birth Outcomes Associated with Long-Term NO<sub>2</sub> Exposure

The effects of maternal exposure during pregnancy to air pollution have been examined by several investigators in recent years (2000 through 2006). 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.

The reliability and validity of birth certificate data has been recently reviewed (DiGiuseppe et al., 2002). The authors found that specific variables had different degrees of reliability. Variables rated the most reliable included birth weight, maternal age, race, and insurance status. Gestational age, parity, and delivery type (vaginal versus cesarean) were reasonably reliable, while obstetrical complications and personal exposures, e.g., smoking and alcohol consumption, were not.

1 Mothers who have a low birth weight or preterm infant are at high risk to have an adverse  
2 outcome in a subsequent pregnancy. Similarly, mothers who have a normal infant are at low risk  
3 for an adverse outcome in the next pregnancy. Statistically, births to the same mother are not  
4 independent observations. As most women in the United States have two or more births and  
5 these births often occur within a few years, birth certificate data, which include several years of  
6 observations, have a very large number of non-independent observations. None of the studies  
7 reviewed considered this problem, and all analyzed births as independent events. For studies  
8 using only 1 (or at most 2) years of birth certificates, the effects are small; for studies using  
9 several years of birth certificates, the variance estimates would be reduced.

10 While most studies analyzed average NO<sub>2</sub> exposure for the whole pregnancy, many also  
11 considered exposure during specific trimesters or other time periods. Fetal growth, for example,  
12 is much more variable during the third trimester. Thus, studies of fetal growth might anticipate  
13 that exposure during the third trimester would have the greatest likelihood of an association, as is  
14 true for the effect of maternal smoking during pregnancy. However, growth can also be affected  
15 through placentation, which occurs in the first trimester. Similarly, preterm delivery might be  
16 expected to be related to exposure early in pregnancy affecting placentation, or through acute  
17 effects occurring just before delivery.

18 Of the three studies conducted in the United States, one (Bell et al., 2007) reported a  
19 significant decrease in birthweight associated with exposure to NO<sub>2</sub> among mothers in  
20 Connecticut and Massachusetts. The two studies conducted in California did not find  
21 associations between NO<sub>2</sub> exposure with any adverse birth outcome (Ritz et al., 2000; Salam  
22 et al., 2005). Differences in these studies that may have contributed to the differences in results  
23 include the following: sample size; average NO<sub>2</sub> concentration; and different pollution mixtures.  
24 The results reported by Bell et al. (2007) had the largest sample size and therefore greater power  
25 to assess small increases in risk. The two California studies reported higher mean concentrations  
26 of NO, but also strong correlations of NO<sub>2</sub> exposure with PM mass and CO.

27 Annex Table AX6.5-1 lists seven studies that investigated the relationship of ambient  
28 NO<sub>2</sub> exposure with birth weight. Since low birth weight may result from either inadequate  
29 growth in utero or delivery before the usual 40 weeks of gestation, three of the authors only  
30 considered low birth weight (<2500 g) in full-term deliveries (>37 weeks), the other four  
31 controlled for gestational age in the analysis. When correlations with other pollutants were

1 reported in these studies, they ranged from 0.5 to 0.8. All of these studies reported strong effects  
2 for other pollutants.

3 Lee et al. (2003) reported a significant association between NO<sub>2</sub> and low birth weight,  
4 and the association was only for exposure in the second trimester. It is difficult to hypothesize  
5 any biological mechanism relating NO<sub>2</sub> exposure and fetal growth specifically in the second  
6 trimester. Bell et al. (2007) reported an increased risk of low birth weight with NO<sub>2</sub> exposure  
7 averaged over pregnancy (OR = 1.027 [95% CI: 1.002, 1.051]) and a deficit in birthweight  
8 specific to the first trimester. In addition, the deficit in birthweight appeared to be greater among  
9 black mothers (-12.7 g per IQR increase in NO<sub>2</sub> [95% CI: -18.0, -7.5]) than for white mothers  
10 (-8.3 g per IQR increase in NO<sub>2</sub> [95% CI: -10.4, -6.3]).

11 Six studies investigated NO<sub>2</sub> exposure related to preterm delivery (Annex Table  
12 AX6.5.2). Three reported positive associations (Bobak, 2000; Marozienne et al., 2002; Leem  
13 et al., 2006) and three reported no association (Liu et al., 2003; Ritz et al., 2000; Hansen et al.,  
14 2006). Among the studies reporting an association, two (Bobak, 2000; Leem et al., 2006)  
15 reported significant associations for both the first trimester and the third trimester of pregnancy.  
16 The third (Marozienne et al., 2002) reported significant increases in risk for exposure in the first  
17 trimester and averaged over all of pregnancy. In two (Bobak, 2000; Leem et al., 2006) of the  
18 positive studies, NO<sub>2</sub> exposure was correlated with SO<sub>2</sub> exposure (r = 0.54, 0.61 for the two  
19 studies); the third study did not report correlations.

20 Three studies (see details in Annex Table AX6.5-3) specifically investigated fetal growth  
21 by comparing birth weight for gestational age with national standards. Two of these studies  
22 reported associations of small for gestational age with NO<sub>2</sub> exposure. Mannes et al. (2004)  
23 determined increased risk for exposure in trimesters 2 and 3, while Liu et al. (2003) reported  
24 risks associated only with NO<sub>2</sub> exposure in the first month of pregnancy. In all three studies,  
25 NO<sub>2</sub> exposure was correlated with CO exposure (r = 0.69, 0.57, 0.72 in the three studies).

26

### 27 ***Reproductive and Developmental Effects of NO<sub>2</sub> Exposure in Animal Studies***

28 Only a few studies have investigated the effects of NO<sub>2</sub> on reproduction and development  
29 of NO<sub>2</sub>. Exposure to 1.0-ppm NO<sub>2</sub> for 7 h/day, 5 days/week for 21 days, resulted in no  
30 alterations in spermatogenesis, germinal cells, or interstitial cells of the testes of 6 rats (Kripke  
31 and Sherwin, 1984). Similarly, breeding studies by Shalamberidze and Tsereteli (1971) found

1 that long-term NO<sub>2</sub> exposure had no effect on fertility. However, there was a statistically  
2 significant decrease in litter size and neonatal weight when male and female rats exposed to  
3 1.3-ppm NO<sub>2</sub>, 12 h/day for 3 months were bred. In utero death due to NO<sub>2</sub> exposure resulted in  
4 smaller litter sizes, but no direct teratogenic effects were observed in the offspring. In fact, after  
5 several weeks, NO<sub>2</sub>-exposed litters approached weights similar to those of controls.

6 Following inhalation exposure of pregnant Wistar rats to 0.5- and 5.3-ppm NO<sub>2</sub> for  
7 6 h/day throughout gestation (21 days), maternal toxic effects and developmental disturbances in  
8 the progeny were reported (Tabacova et al., 1984; Balabaeva and Tabacova, 1985; Tabacova and  
9 Balabaeva, 1988). Maternal weight gain during gestation was significantly reduced at 5.3 ppm,  
10 with findings of pathological changes, e.g., desquamative bronchitis and bronchiolitis in the  
11 lung, mild parenchymal dystrophy and reduction of glycogen in the liver, and blood stasis and  
12 inflammatory reaction in the placenta. At gross examination, the placentas of the high-dose  
13 dams were smaller in size than those of control rats. A marked increase of lipid peroxides was  
14 found in maternal lungs and particularly in the placenta at both exposure levels by the end of  
15 gestation (Balabaeva and Tabacova, 1985). Disturbances in the prenatal development of the  
16 progeny were registered, such as 2- to 4-fold increase in late post-implantation lethality at 0.5  
17 and 5.3 ppm, respectively, as well as reduced fetal weight at term and stunted growth at 5.3 ppm.  
18 These effects were significantly related to the content of lipid peroxides in the placenta, which  
19 was suggestive of a pathogenetic role of placental damage. Teratogenic effects were not  
20 observed, but dose-dependent morphological signs of embryotoxicity and retarded intrauterine  
21 development, such as generalized edema, subcutaneous hematoma, retarded ossification, and  
22 skeletal aberrations, were found at both exposure levels.

23 In a developmental neurotoxicity study, Wistar rats were exposed by inhalation to 0-,  
24 0.025-, 0.05-, 0.5-, or 5.3-ppm NO<sub>2</sub> during gestational days 0 through 21. It is unclear whether  
25 the study was conducted at two separate times. Maternal toxicity was not reported. Viability  
26 and physical development (i.e., incisor eruption and eye opening) were significantly affected in  
27 the group exposed only to 5.3 ppm. There was a concentration-dependent change in  
28 neurobehavioral endpoints, including disturbances in early neuromotor development, including  
29 coordination deficits, retarded locomotor development, and decreased activity and reactivity.  
30 Statistical significance was observed in some or all of the endpoints at the time point(s)  
31 measured in the 0.05-, 0.5-, and 5.3-ppm exposure groups.

1 Di Giovanni et al. (1994) investigated whether in utero exposure of rats to NO<sub>2</sub> changed  
2 ultrasonic vocalization, a behavioral response indicator of the development of emotionality.  
3 Pregnant Wistar female rats were exposed by inhalation to 0, 1.5-, and 3-ppm NO<sub>2</sub> from day 0 to  
4 20 of gestation. Dam weight gain, pregnancy length, litter size at birth, number of dams giving  
5 birth, and postnatal mortality were unaffected by NO<sub>2</sub>. There was a significant decrease in the  
6 duration of ultrasonic signals elicited by the removal of the pups from the nest in the 10-day and  
7 15-day-old male pups in the 3-ppm NO<sub>2</sub>-exposed group. No other parameters of ultrasonic  
8 emission, or of motor activity, were significantly affected in these prenatally exposed pups.  
9 Since prenatal exposure to NO<sub>2</sub> did not significantly influence the rate of calling, the authors  
10 concluded that this decrease in the duration of ultrasounds in the 3-ppm NO<sub>2</sub> exposed group does  
11 not necessarily indicate altered emotionality, and the biological significance of these findings  
12 remains to be determined.

#### 13 14 **3.4.3.1 Integration and Biological Plausibility for Reproductive and Developmental** 15 **Effects**

16 Integration of epidemiological and toxicological findings is limited by the dearth of  
17 studies in both disciplines. In epidemiological studies of birth outcomes, generally, birth  
18 certificate data were compared to NO<sub>2</sub> measured by routine monitoring. Only a small number of  
19 studies looked at low birth weight or preterm delivery. Of the seven studies that examined  
20 associations between low birth weight and ambient NO<sub>2</sub>, only two reported a significant  
21 association (Bell et al., 2007; Lee et al., 2003). Two studies of fetal growth reported associations  
22 of small for gestational age with NO<sub>2</sub> exposure. Overall, exposure in the third trimester may  
23 have the strongest association with evaluating effects on fetal growth. In evaluations of preterm  
24 delivery, three studies reported positive associations and three studies reported no association.  
25 Exposure early and late in the pregnancy may be associated more strongly with effects on  
26 preterm delivery. These results are confounded by prior pregnancy history (i.e., multiple births  
27 to the same mother are not independent observations), smoking, and poor quality of birth  
28 certificate data.

29 The small body of toxicological literature examining the effects of NO<sub>2</sub> on birth  
30 outcomes is somewhat inconclusive, but NO<sub>2</sub> does not appear to be a reproductive toxicant. One  
31 early study found a decrease in litter size and neonatal weight when male and female rats were  
32 exposed to 1.3 ppm for 3 months and then bred. Earlier studies suggested that exposures of

1 ≤10 ppm did not induce mutagenesis in rats. The few toxicological studies discussed that  
2 evaluated the effects of NO<sub>2</sub> on reproduction and development show that NO<sub>2</sub> at ~5 ppm  
3 throughout gestation reduced maternal weight gain. A 5-ppm exposure resulted in smaller  
4 placentas, increased maternal lipid peroxides, increased late post-implantation mortality,  
5 embryotoxicity, and retarded intrauterine development. Gestational exposure to 3-ppm NO<sub>2</sub>  
6 caused a decrease in duration, but not rate, of ultrasonic vocalization in pups.

7 In summary, epidemiological evidence is not strong for associations between NO<sub>2</sub>  
8 exposure and grown retardation; however, some evidence is accumulating for effects on preterm  
9 delivery. Similarly, scant animal evidence supports a weak association between NO<sub>2</sub> exposure  
10 and adverse birth outcomes and provides little mechanistic information or biological plausibility  
11 for the epidemiology findings.

#### 12 13 **3.4.4 Cancer Incidence Associated with Long-Term NO<sub>2</sub> Exposure**

14 Two studies (see Annex Table AX6.5-6) have investigated the relationship between NO<sub>2</sub>  
15 exposure and lung cancer and reported positive associations. Although this literature review has  
16 concentrated on studies that measured exposure to NO<sub>2</sub>, modeled exposures will be considered  
17 for cancer studies. This is necessary because the relevant exposure period for lung cancer may  
18 be 30 years or more.

19 Nyberg et al. (2000) reported results of a case control study of 1,043 men age 40 to  
20 75 years with lung cancer and 2,364 controls in Stockholm County. They mapped residence  
21 addresses to a GIS database indicating 4,300 traffic-related line sources and 500 point sources of  
22 NO<sub>2</sub> exposure. Exposure was derived from a model validated by comparison to actual  
23 measurements of NO<sub>2</sub> at six sites. Exposure to NO<sub>2</sub> at 10 µg/m<sup>3</sup> was associated with an OR of  
24 1.10 (95% CI: 0.97, 1.23). Exposure to the 90th percentile (≥29.26 µg/m<sup>3</sup>) of NO<sub>2</sub> was  
25 associated with an OR of 1.44 (95% CI: 1.05, 1.99).

26 Very similar results were reported in a Norwegian study (Nafstad et al., 2003). The study  
27 population is a cohort of 16,209 men who enrolled in a study of cardiovascular disease in 1972.  
28 The Norwegian cancer registry identified 422 incident cases of lung cancer. Exposure data was  
29 modeled based on residence, estimating exposure for each person in each year from 1974 to  
30 1998. Each 10 µg/m<sup>3</sup> of NO<sub>2</sub> was associated with an OR of 1.08 (95% CI: 1.02, 1.15). Cancer

1 incidence with exposure of  $\geq 30 \mu\text{g}/\text{m}^3$  was associated with an OR of 1.36 (95% CI: 1.01, 1.83);  
2 however, controlling for  $\text{SO}_2$  exposure did appreciably change the effect estimates for  $\text{NO}_2$ .

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

8

### 9 ***Animal and In Vitro Carcinogenicity and Genotoxicity Studies***

10       There is no clear evidence that  $\text{NO}_2$  acts as a complete carcinogen. No studies were  
11 found on  $\text{NO}_2$  using classical carcinogenesis whole-animal bioassays. Of the existing studies  
12 that have evaluated the carcinogenic and cocarcinogenic potential of  $\text{NO}_2$ , results are often  
13 unclear or conflicting. Witschi et al. (1988) critically reviewed some of the important theoretical  
14 issues in interpreting these types of studies.  $\text{NO}_2$  does appear to act as a tumor promoter at the  
15 site of contact (i.e., in the respiratory tract from inhalation exposure), possibly due to its ability to  
16 produce cellular damage and, thus, promote regenerative cell proliferation. This hypothesis is  
17 supported by observed hyperplasia of the lung epithelium from  $\text{NO}_2$  exposure (see Lung  
18 Morphology section, U.S. Environmental Protection Agency, 1993), which is a common  
19 response to lung injury, and enhancement of endogenous retrovirus expression (Roy-Burman  
20 et al., 1982). However, these findings were considered by U.S. Environmental Protection  
21 Agency (1993) to be inconclusive.

22       When studied using in vivo assays, no inductions of recessive lethal mutations were  
23 observed in *Drosophila* exposed to  $\text{NO}_2$  (Inoue et al., 1981; Victorin et al., 1990).  $\text{NO}_2$  does not  
24 increase chromosomal aberrations in lymphocytes and spermatocytes or micronuclei in bone  
25 marrow cells (Gooch et al., 1977; Victorin et al., 1990). No increased stimulation of poly(ADP-  
26 ribose)synthetase activity (an indicator of DNA repair, suggesting possible DNA damage) was  
27 reported in AMs recovered from BAL of rats continuously exposed to 1.2-ppm  $\text{NO}_2$  for 3 days  
28 (Bermudez, 2001).

29        $\text{NO}_2$  has been shown to be positive when tested for genotoxicity in in vitro assays (see  
30 Annex Table AX4.8).  $\text{NO}_2$  is mutagenic in bacteria and in plants. In cell cultures, three studies

1 showed chromosomal aberrations, SCE, and DNA single-strand breaks. However, a fourth study  
2 (Isomura et al., 1984) concluded that NO, but not NO<sub>2</sub>, was mutagenic in hamster cells.

#### 3 4 ***Coexposure Studies with NO<sub>2</sub> and Known Carcinogens***

5 Rats were injected with *N*-bis(2-hydroxy-propyl)nitrosamine (BHPN) and continuously  
6 exposed to 0.04, 0.4, or 4.0-ppm NO<sub>2</sub> for 17 months. Although the data indicated five times as  
7 many lung adenomas or adenocarcinomas in the rats injected with BHPN and exposed to 4-ppm  
8 NO<sub>2</sub> (5/40 compared to 1/10), the results failed to achieve statistical significance (Ichinose et al.,  
9 1991). In a later study, Ichinose and Sagai (1992) reported increased lung tumors in rats injected  
10 with BHPN, followed the next day by either clean air (0%), 0.05-ppm O<sub>3</sub> (8.3%), 0.05-ppm  
11 O<sub>3</sub> + 0.4-ppm NO<sub>2</sub> (13.9%) or 0.4-ppm NO<sub>2</sub> + 1 mg/m<sup>3</sup> H<sub>2</sub>SO<sub>4</sub>-aerosol (8.3%) for 13 months,  
12 and then maintained for another 11 months until study termination. Exposure to NO<sub>2</sub> was  
13 continuous, while the exposures to O<sub>3</sub> and H<sub>2</sub>SO<sub>4</sub>-aerosol were intermittent (exposure for  
14 10 h/day). The increased lung tumors from combined exposure of O<sub>3</sub> and NO<sub>2</sub> were statistically  
15 significant.

16 Ohyama et al. (1999) coexposed rats to diesel exhaust particulates (DEP) extract-coated  
17 carbon black particles (DEPcCBP) once a week for 4 weeks by intratracheal instillation and to  
18 either 6-ppm NO<sub>2</sub>, 4-ppm SO<sub>2</sub>, or 6-ppm NO<sub>2</sub> + 4-ppm SO<sub>2</sub> 16 h/day for 8 months, and  
19 thereafter exposed to clean air for 8 months. Alveolar adenomas were increased in animals  
20 exposed to DEPcCBP and either NO<sub>2</sub> and/or SO<sub>2</sub> compared to animals in the DEPcCBP-only  
21 group and to controls. The incidences of lung tumors for the NO<sub>2</sub>, SO<sub>2</sub>, and NO<sub>2</sub> and/or SO<sub>2</sub>  
22 groups were 6/24 (25%), 4/30 (13%), and 3/28 (11%), respectively. No alveolar adenomas were  
23 observed in animals exposed to DEPcCBP alone or in the controls. Increased alveolar  
24 hyperplasia was elevated in all groups compared to controls. In addition, DNA adducts, as  
25 determined by <sup>32</sup>P- postlabelling, was observed in the 2/3 animals exposed to both DEPcCBP  
26 and either NO<sub>2</sub> and/or SO<sub>2</sub>, but not in animals exposed to DEPcCBP alone or controls. The  
27 authors concluded that the cellular damage induced by NO<sub>2</sub> and/or SO<sub>2</sub> may have resulted in  
28 increased cellular permeability of the DEPcCBP particles into the cells.

#### 29 30 ***Studies in Animals with Spontaneously High Tumor Rates***

31 Three studies evaluated tumor response in strains with high tumor rates. The frequency  
32 and incidence of spontaneously occurring pulmonary adenomas was increased in strain A/J mice



1 (with spontaneously high tumor rates) after exposure to 10.0-ppm NO<sub>2</sub> for 6 h/day, 5 days/week  
2 for 6 months (Adkins et al., 1986). These small, but statistically significant, increases were only  
3 detectable when the control response from nine groups (n = 400) were pooled. Exposure to 1.0-  
4 and 5.0-ppm NO<sub>2</sub> had no effect. In contrast, Richters and Damji (1990) found that an  
5 intermittent exposure to 0.25-ppm NO<sub>2</sub> for up to 26 weeks decreased the progression of a  
6 spontaneous T cell lymphoma in AKR/cum mice and increased survival rates. The investigators  
7 attribute this effect to an NO<sub>2</sub>-induced decrease in the proliferation of T cell subpopulation in the  
8 spleen (especially T-helper/inducer CD<sup>+</sup> lymphocytes), that produce growth factors for the  
9 lymphoma. A study by Wagner et al. (1965) suggested that NO<sub>2</sub> may accelerate the production  
10 of tumors in CAF1/Jax mice (a strain that has spontaneously high pulmonary tumor rates) after  
11 continuous exposure to 5.0-ppm NO<sub>2</sub>. After 12 months of exposure, 7/10 mice in the exposed  
12 group had tumors, compared to 4/10 in the controls. No differences in tumor production were  
13 observed after 14 and 16 months of exposure. A statistical evaluation of the data was not  
14 presented.

#### 15 16 ***Facilitation of Metastases***

17 Whether NO<sub>2</sub> facilitates metastases has been the subject of several experiments by  
18 Richters and Kuraitis (1981, 1983), Richters and Richters (1983), and Richters et al. (1985).  
19 Mice were exposed to several concentrations and durations of NO<sub>2</sub> and were injected  
20 intravenously with a cultured-derived melanoma cell line (B16) after exposure, and subsequent  
21 tumors in the lung were counted. Although some of the experiments showed an increased  
22 number of lung tumors, statistical methods were inappropriate. Furthermore, the experimental  
23 technique used in these studies probably did not evaluate metastases formation, as the term is  
24 generally understood, but more correctly, colonization of the lung by tumor cells.

#### 25 26 ***Production of N-Nitroso Compounds and other Nitro Derivatives***

27 Because of evidence that NO<sub>2</sub> could produce NO<sub>2</sub><sup>-</sup> and NO<sub>3</sub><sup>-</sup> in the blood and the fact  
28 that NO<sub>2</sub><sup>-</sup> is known to react with amines to produce animal carcinogens (nitrosamines), the  
29 possibility that NO<sub>2</sub> could produce cancer via nitrosamine formation has been investigated. Iqbal  
30 et al. (1980) were the first to demonstrate a linear time- and concentration-dependent relationship  
31 between the amount of N-nitrosomorpholine (NMOR, an animal carcinogen) found in whole-  
32 mouse homogenates after the mice were gavaged with 2 mg of morpholine (an exogenous amine

1 that is rapidly nitrosated) and exposure to 15.0- to 50.0-ppm NO<sub>2</sub> for between 1 and 4 h. In a  
2 follow-up study at more environmentally relevant exposures, Iqbal et al. (1981) used  
3 dimethylamine (DMA), an amine that is slowly nitrosated to dimethylnitrosamine (DMN). They  
4 reported a concentration-related increase in biosynthesis of DMN at NO<sub>2</sub> concentrations as low  
5 as 0.1 ppm; however, the rate was significantly greater at concentrations above 10.0-ppm NO<sub>2</sub>.  
6 Increased length of exposure also increased DMN formation between 0.5 and 2 h, but synthesis  
7 of DMN was less after 3 or 4 h of exposure than after 0.5 h.

8 Mirvish et al. (1981) concluded that the results of Iqbal et al. (1980) were technically  
9 flawed, but they found that in vivo exposure to NO<sub>2</sub> could produce a nitrosating agent (NSA)  
10 that would nitrosate morpholine only when morpholine was added in vitro. Further experiments  
11 showed that the NSA was localized in the skin (Mirvish et al., 1983) and that mouse skin  
12 cholesterol was a likely NSA (Mirvish et al., 1986). It has also been reported that only very  
13 lipid-soluble amines, which can penetrate the skin, would be available to the NSA. Compounds  
14 such as morpholine, which are not lipid-soluble, could only react with NO<sub>2</sub> when painted directly  
15 on the skin (Mirvish et al., 1988). Iqbal (1984), responding to the Mirvish et al. (1981)  
16 criticisms, verified their earlier (Iqbal et al., 1980) studies.

17 The relative significance of NO<sub>2</sub><sup>-</sup> from NO<sub>2</sub> compared with other NO<sub>2</sub> sources such as  
18 food, tobacco, and NO<sub>3</sub><sup>-</sup>-reducing oral bacteria is uncertain. Nitrosamines have not been  
19 detected in tissues of animals exposed by inhalation to NO<sub>2</sub> unless precursors to nitrosamines  
20 and/or inhibitors of nitrosamine metabolism are coadministered. Rubenchik et al. (1995) could  
21 not detect *N*-nitrosodimethylamine (NDMA) in tissues of mice exposed to 7.5 to 8.5 mg/m<sup>3</sup> NO<sub>2</sub>  
22 for 1 h. NDMA was found in tissues, however, if mice were simultaneously given oral doses of  
23 amidopyrine and 4-methylpyrazole, an inhibitor of NDMA metabolism. Nevertheless, the main  
24 source of NO<sub>2</sub><sup>-</sup> in the body is formed endogenously, and food is also a contributing source of  
25 nitrite (from nitrate conversion).

26

#### 27 **3.4.4.1 Integration and Biological Plausibility for Cancer Incidence**

28 In summary, two epidemiological studies conducted in Europe showed an association  
29 between long-term NO<sub>2</sub> exposure and cancer incidence, with OR at 10-μg/m<sup>3</sup> NO<sub>2</sub>, ranging from  
30 1.10 to 1.08. Animal studies have provided no clear evidence that NO<sub>2</sub> acts as a carcinogen.  
31 The 1993 AQCD for Oxides of Nitrogen deemed findings of hyperplasia of lung epithelium from

1 NO<sub>2</sub> exposure as inconclusive, though NO<sub>2</sub> does appear to act as a tumor promoter at the site of  
2 contact. There are no in vivo studies that suggest that NO<sub>2</sub> causes teratogenesis or malignant  
3 tumors. Only very high exposure studies, i.e., levels not relevant to ambient NO<sub>2</sub> levels,  
4 demonstrate increased chromosomal aberrations and mutations in in vitro studies.

### 6 **3.4.5 Summary of Morbidity Effects Associated with Long-Term Exposure**

7 This section has presented epidemiological and toxicological studies evaluating  
8 decrements in lung function, asthma prevalence, respiratory symptoms, and morphological  
9 damage associated with long-term NO<sub>2</sub> exposures. It has further presented limited evidence of  
10 cardiovascular effects, adverse birth outcomes, and cancer incidence linked to long-term NO<sub>2</sub>  
11 exposure. Toxicological studies characterizing altered lung host defenses provide convincing  
12 biological plausibility for many of the respiratory effects observed in epidemiological studies,  
13 especially the decrements in lung function observed in the cohort studies. Epidemiology  
14 evidence is less clear for effects of long-term NO<sub>2</sub> exposure on adverse birth outcomes and  
15 cancer incidence. Animal studies do not provide mechanistic information to support these  
16 observational findings. Some toxicological studies have demonstrated an effect of NO<sub>2</sub> exposure  
17 on cardiovascular endpoints; however, whether these effects are the direct result of NO<sub>2</sub>  
18 exposure or secondary responses to lung edema and changes in blood hemoglobin content are not  
19 known. Parallel findings have been reported in the epidemiological literature for short-term  
20 exposures only.

## 22 **3.5 MORTALITY ASSOCIATED WITH LONG-TERM EXPOSURE**

24 There have been several studies that examined mortality associations with long-term  
25 exposure to air pollution, including NO<sub>2</sub>. They all used Cox-proportional hazards regression  
26 models with adjustment for potential confounders. The U.S. studies tended to focus on effects of  
27 PM, while the European studies tended to investigate the influence of traffic-related air pollution.

### 29 **3.5.1 U.S. Studies on the Long-Term Exposure Effects on Mortality**

30 Dockery et al. (1993) conducted a prospective cohort study to study the effects of air  
31 pollution with main focus on PM components in six U.S. cities, which were chosen based on the  
32 levels of air pollution (with Portage, WI being the least polluted and Steubenville, OH, the most

1 polluted). Cox proportional hazards regression was conducted with data from a 14-to-16-year  
2 mortality follow-up of 8,111 adults in the six cities, adjusting for smoking, sex, occupational  
3 exposures, etc. Fine particles were the strongest predictor of mortality, but NO<sub>2</sub> was not  
4 analyzed in their study. Krewski et al. (2000) conducted sensitivity analysis of the Harvard Six  
5 Cities study and examined associations between gaseous pollutants (i.e., O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>, CO) and  
6 mortality. NO<sub>2</sub> showed risk estimates similar to those for PM<sub>2.5</sub> per “low to high” range  
7 increment with total (1.15 [95% CI: 1.04, 1.27] per 10-ppb increase), cardiopulmonary (1.17  
8 [95% CI: 1.02, 1.34]), and lung cancer (1.09 [95% CI: 0.76, 1.57]) deaths; however, in this  
9 dataset NO<sub>2</sub> was highly correlated with PM<sub>2.5</sub> (r = 0.78), SO<sub>4</sub><sup>2-</sup> (r = 0.78), and SO<sub>2</sub> (r = 0.84).

10 Pope et al. (1995) examined PM effects on mortality using the American Cancer Society  
11 (ACS) cohort. Air pollution data from 151 U.S. metropolitan areas in 1980 were linked with  
12 individual risk factors on 552,138 adults who resided in these areas when enrolled in the study in  
13 1982. Mortality was followed up until 1989. As with the Harvard Six Cities Study, the main  
14 hypothesis of this study was focused on fine particles and SO<sub>4</sub><sup>2-</sup>, and gaseous pollutants were not  
15 analyzed. Krewski et al. (2000) examined association between gaseous pollutants (means by  
16 season) and mortality in the Pope et al. (1995) study dataset. NO<sub>2</sub> showed weak but negative  
17 associations with total and cardiopulmonary deaths using either seasonal means. An extended  
18 study of the ACS cohort doubled the follow-up time (to 1998) and tripled the number of deaths  
19 compared to the original study (Pope et al., 2002). In addition to PM<sub>2.5</sub>, all the gaseous  
20 pollutants were examined. SO<sub>2</sub> was associated with all the mortality outcomes (including all  
21 other cause of deaths), but NO<sub>2</sub> showed no associations with the mortality outcomes (RR = 1.00  
22 [95% CI: 0.98, 1.02] per 10-ppb increase in multi-year average NO<sub>2</sub>).

23 Miller et al. (2007) studied 65,893 postmenopausal women between the ages of 50 and  
24 79 years without previous cardiovascular disease in 36 U.S. metropolitan areas from 1994 to  
25 1998. They examined the association between one or more fatal or nonfatal cardiovascular  
26 events and the women’s exposure to air pollutants. Subject’s exposures to air pollution were  
27 estimated by assigning the annual mean levels of air pollutants in 2000 measured at the nearest  
28 monitor to the location of residence based on its five-digit ZIP Code centroid. Thus, the  
29 exposure estimate in this study is spatially more resolved than those in the Harvard Six Cities or  
30 the ACS cohort study. A total of 1,816 women had one or more fatal or nonfatal cardiovascular  
31 events, including 261 deaths from cardiovascular causes. The main focus of the study was

1 PM<sub>2.5</sub>, but the overall CVD events (but not results for death events only) using all the  
2 copollutants (PM<sub>10</sub>, PM<sub>10-2.5</sub>, SO<sub>2</sub>, NO<sub>2</sub>, CO, and O<sub>3</sub>) in both single- and multipollutant models  
3 were presented. The results for the data with non-missing exposure data were included  
4 (N = 28,402 subjects resulting in 879 CVD events) are described here. In the single-pollutant  
5 model results, PM<sub>2.5</sub> showed the strongest associations with the CVD events by far among the  
6 pollutants (hazard ratio = 1.24 [95% CI: 1.04, 1.48] per 10-μg/m<sup>3</sup> increase in annual average),  
7 followed by SO<sub>2</sub> (HR = 1.07 [95% CI: 0.95, 1.20] per 5-ppb increase in the annual average).  
8 NO<sub>2</sub> did not show association with the overall CVD events (HR = 0.98 [95% CI: 0.89, 1.08] per  
9 10-ppb increase in the annual average). In the multipollutant model (apparently, all the  
10 pollutants were included in the model), the PM<sub>2.5</sub>'s association with the overall CVD events was  
11 even stronger and the estimate larger (1.53 [95% CI: 1.21, 1.94]), and the association with SO<sub>2</sub>  
12 also became stronger and the estimate larger (HR = 1.13 [95% CI: 0.98, 1.30]). NO<sub>2</sub> became  
13 negatively associated with the overall CVD events (HR = 0.82 [95% CI: 0.70, 0.95]).  
14 Correlations among these pollutants were not described, and therefore it is not possible to  
15 estimate the extent of confounding among these pollutants in these associations, but it is clear  
16 that PM<sub>2.5</sub> was the best predictor of the CVD events.

17 Lipfert et al. (2000a) conducted an analysis of a national cohort of ~70,000 male U.S.  
18 military veterans who were diagnosed as hypertensive in the mid 1970s and were followed up for  
19 about 21 years (up to 1996). This cohort was 35% black and 81% had been smokers at one time.  
20 TSP, PM<sub>10</sub>, CO, O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>, SO<sub>4</sub><sup>2-</sup>, PM<sub>2.5</sub>, and coarse particles were considered. The county  
21 of residence at the time of entry to the study was used to estimate exposures. Pollution levels  
22 were averaged by year and county. Four exposure periods (1960-74, 1975-81, 1982-88, and  
23 1989-96) were defined, and deaths during each of the three most recent exposure periods were  
24 considered. Lipfert et al. noted that the pollution risk estimates were sensitive to the regression  
25 model specification, exposure periods, and the inclusion of ecological and individual variables.  
26 The authors reported that indications of concurrent mortality risks were found for NO<sub>2</sub> (the  
27 estimate was not given with confidence bands) and peak O<sub>3</sub>. Their subsequent analysis (Lipfert  
28 et al., 2003) reported that the air pollution-mortality associations were not sensitive to the  
29 adjustment for blood pressure. Lipfert et al. (2006a) also examined associations between traffic  
30 density and mortality in the same cohort, whose follow-up period was extended to 2001. The  
31 county-level traffic density was derived by dividing vehicle-km traveled by the county land area.

1 Because of the wide range of the traffic density variable, log-transformed traffic density was  
2 used in their analysis. They reported that traffic density was a better predictor of mortality than  
3 ambient air pollution variables, with the possible exception of O<sub>3</sub>. The log-transformed traffic  
4 density variable was moderately correlated with NO<sub>2</sub> (r = 0.48) and PM<sub>2.5</sub> (r = 0.50) in this data  
5 set. For the 1989 to 1996 data period (the period that showed generally the strongest  
6 associations with exposure variables among the four periods), the estimated mortality relative  
7 risk for NO<sub>2</sub> was 1.025 (95% CI: 0.983, 1.068) per 10-ppb increase in a single-pollutant model.  
8 The two-pollutant model with the traffic density variable reduced NO<sub>2</sub> risk estimates to 0.996  
9 (95% CI: 0.954, 1.040). Interestingly, as the investigators pointed out, the risk estimates due to  
10 traffic density did not vary appreciably across these four periods. They speculated that other  
11 environmental factors such as particles from tire, traffic noise, spatial gradients in socioeconomic  
12 status, etc., might have been involved. Lipfert et al. (2006b) further extended analysis of the  
13 veteran's cohort data to include the U.S. Environmental Protection Agency's Speciation Trends  
14 Network (STN) data, which collected chemical components of PM<sub>2.5</sub>. They analyzed the STN  
15 data for year 2002, again using county-level averages. As in the previous Lipfert et al. (2006a)  
16 study, traffic density was the most important predictor of mortality, but associations were also  
17 seen for elemental carbon, vanadium, NO<sub>3</sub><sup>-</sup>, and nickel. NO<sub>2</sub>, O<sub>3</sub>, and PM<sub>10</sub> also showed  
18 positive but weaker associations. The risk estimate for NO<sub>2</sub> was 1.043 (95% CI: 0.967, 1.125)  
19 per 10-ppb increase in a single-pollutant model. Multi-pollutant model results were not  
20 presented for NO<sub>2</sub>.

21 Abbey et al. (1999) investigated associations between long-term ambient concentrations  
22 of PM<sub>10</sub>, O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>, and CO (1973 to 1992) and mortality (1977 to 1992) in a cohort of  
23 6,338 nonsmoking California Seventh-day Adventists. Monthly indices of ambient air pollutant  
24 concentrations at 348 monitoring stations throughout California were interpolated to zip code  
25 centroids according to home or work location histories of study participants, cumulated, and then  
26 averaged over time. They reported associations between PM<sub>10</sub> and total mortality for males and  
27 non-malignant respiratory mortality for both sexes. NO<sub>2</sub> was not associated with all-cause,  
28 cardiopulmonary, or respiratory mortality for either sex. Lung cancer mortality showed large  
29 risk estimates for most of the pollutants in either or both sexes, but the number of lung cancer  
30 deaths in this cohort was very small (12 for female and 18 for male) and therefore it is difficult to  
31 interpret these estimates.

1           The U.S. studies mentioned above have differences in study population characteristics  
2 and geographic unit of averaging for pollution exposure estimates, and therefore the results  
3 cannot be directly compared. The ACS and Women’s Health Initiative (WHI) cohort studies  
4 found no associations with NO<sub>2</sub>, but in the veterans study, NO<sub>2</sub> was among the pollutants that  
5 showed associations with mortality, though traffic density showed the strongest association. The  
6 geographic resolution of air pollution exposure estimation varied across these studies: the  
7 Metropolitan Statistical Area (MSA)-level averaging in the ACS study; county-level averaging  
8 in the veterans’ study; and assigning the nearest monitor’s annual average to the ZIP code  
9 centroid. Traffic density and other pollutants that showed mortality associations in the veterans  
10 study, including elemental carbon, nickel, and vanadium and NO<sub>2</sub> (but not O<sub>3</sub> or NO<sub>3</sub><sup>-</sup>), are more  
11 localized pollutants, and therefore, using county-level aggregation, rather than MSA-level, may  
12 have resulted in smaller exposure misclassification. However, in the WHI cohort study, despite  
13 its finer resolution of exposure estimation, NO<sub>2</sub> (which is presumably more locally impacted than  
14 PM<sub>2.5</sub>) was not associated with cardiovascular events. It should also be noted that there are  
15 generally fewer NO<sub>2</sub> monitors than PM<sub>2.5</sub> monitors in U.S. cities (nationwide, NO<sub>2</sub> has the  
16 smallest number of monitors among the Criteria pollutants except lead). Therefore, even when  
17 the spatial resolution for exposure estimates is high in the study design, the fewer available  
18 monitors for NO<sub>2</sub> compared to other pollutants, may result in compromised exposure estimation  
19 for NO<sub>2</sub>. Thus, there is uncertainty regarding how the scale of aggregation affects the analyses  
20 that utilize cross-sectional comparisons.

### 21 22 **3.5.2 European Studies on the Long-Term Exposure Effects on Mortality**

23           In contrast to the U.S. studies described above, the European studies described below,  
24 have more spatially resolved exposure estimates, because their hypotheses or study aims  
25 involved mortality effects of traffic-related air pollution. One study from France used a design  
26 similar to the Harvard Six Cities study or ACS in that it was not intended to study of traffic-  
27 related air pollution, and the exposure estimate was not done on an individual basis.

28           Hoek et al. (2002) investigated a random sample of 5,000 subjects from the Netherlands  
29 Cohort Study on Diet and Cancer (NLCS) ages 55 to 69 from 1986 to 1994. Long-term exposure  
30 to traffic-related air pollutants (black smoke and NO<sub>2</sub>) was estimated using 1986 home  
31 addresses. Exposure was estimated with the measured regional and urban background

1 concentration and an indicator variable for living near major roads. Cardiopulmonary mortality  
2 was associated with living near a major road (RR = 1.95 [95% CI: 1.09, 3.52]) and less strongly  
3 with the estimated air pollution levels (e.g., for NO<sub>2</sub>, RR = 1.32 [95% CI: 0.88, 1.98] per 10-ppb  
4 increase). The risk estimate for living near a major road was 1.41 (95% CI: 0.94, 2.12) for total  
5 mortality. For estimated NO<sub>2</sub> (incorporating both background and local impact), the RR was  
6 1.15 (95% CI: 0.60, 2.23) per 10 ppb). Because the NO<sub>2</sub> exposure estimates were modeled,  
7 interpretation of their risk estimates is not straightforward. However, these results do suggest  
8 that NO<sub>2</sub>, as a marker of traffic-related air pollution, was associated with these mortality  
9 outcomes.

10 Filleul et al. (2005) investigated long-term effects of air pollution on mortality in 14,284  
11 adults who resided in 24 areas from seven French cities when enrolled in the PAARC survey (for  
12 air pollution and chronic respiratory diseases) in 1974. Daily measurements of SO<sub>2</sub>, TSP, black  
13 smoke, NO<sub>2</sub>, and NO were made in 24 areas for 3 years (1974 through 76). Cox-proportional  
14 hazards models adjusted for smoking, educational level, BMI, and occupational exposure.  
15 Models were run before and after exclusion of six area monitors influenced by local traffic as  
16 determined by the NO/NO<sub>2</sub> ratio of >3. Before exclusion of the six areas, none of the air  
17 pollutants were associated with mortality outcomes. After exclusion of these areas, analyses  
18 showed associations between total mortality and TSP, black smoke, NO<sub>2</sub>, and NO. The  
19 estimated NO<sub>2</sub> risks were 1.28 (95% CI: 1.07, 1.55), 1.58 (95% CI: 1.07, 2.33), and 2.12  
20 (95% CI: 1.11, 4.03) per 10-ppb increase in NO<sub>2</sub> mean over the study period for total,  
21 cardiopulmonary, and lung cancer mortality, respectively. From these results, the authors noted  
22 that inclusion of air monitoring data from stations directly influenced by local traffic could  
23 overestimate the mean population exposure and bias the results. This point raises a concern for  
24 NO<sub>2</sub> exposure estimates used in other studies (e.g., ACS) in which the average of available  
25 monitors was used to represent the exposure of each city's entire population.

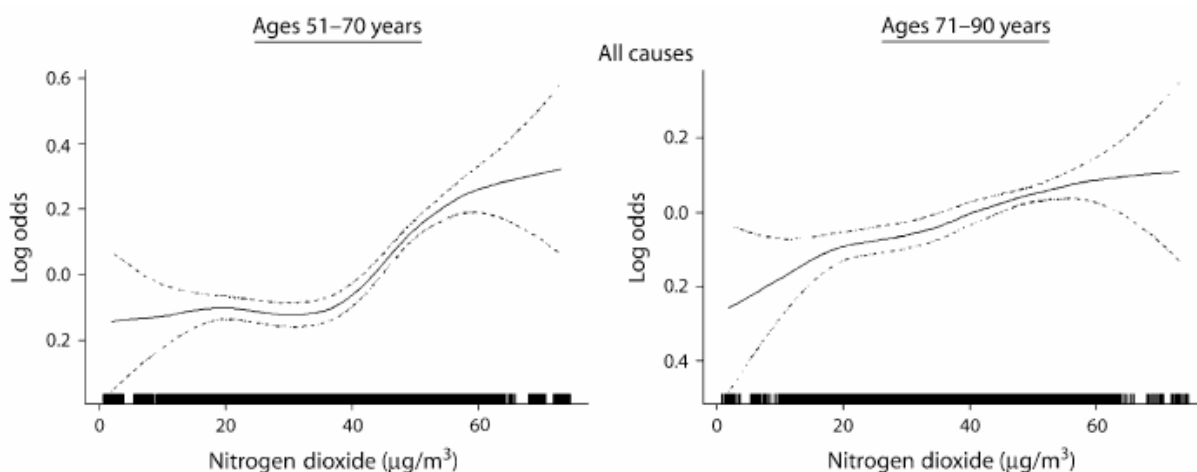
26 Nafstad et al. (2004) investigated the association between mortality and long-term air  
27 pollution exposure in a cohort of Norwegian men followed from 1972/1973 through 1998.  
28 Nafstad et al. also presented the result for lung cancer deaths only in their earlier (Nafstad et al.,  
29 2003) analysis discussed in Section 3.3.4, but their 2004 study includes more mortality  
30 categories and is therefore described here. Data from 16,209 men 40 to 49 years of age living in  
31 Oslo, Norway, in 1972 and 1973 were linked with data from the Norwegian Death Register and



1 with estimates of average yearly air pollution levels at the participants' home addresses from  
2 1974 to 1998. PM was not considered in this study because measurement methods changed  
3 during the study period. NO<sub>x</sub>, rather than NO<sub>2</sub>, was used. Exposure estimates for NO<sub>x</sub> and SO<sub>2</sub>  
4 were constructed using models based on subjects' addresses and emission data for industry,  
5 heating, and traffic and measured concentrations. Addresses linked to 50 of the busiest streets  
6 were given an additional exposure based on estimates of annual average daily traffic. The  
7 adjusted risk estimate for total mortality was 1.08 [95% CI: 1.06, 1.11] for a 10-μg/m<sup>3</sup> increase  
8 in the estimated exposure to NO<sub>x</sub>. Corresponding mortality risk estimates for respiratory causes  
9 other than lung cancer was 1.16 (95% CI: 1.06, 1.26); for lung cancer, 1.11 (95% CI: 1.03,  
10 1.19); and for ischemic heart diseases, 1.08 (95% CI: 1.03, 1.12). SO<sub>2</sub> did not show similar  
11 associations. The risk estimates presented for categorical levels of these pollutants showed  
12 mostly monotonic exposure-response relationships for NO<sub>x</sub>, but not for SO<sub>2</sub>. The authors noted  
13 that the SO<sub>2</sub> levels were reduced by a factor of 7 during the study period, whereas NO<sub>x</sub> did not  
14 show any clear downward trends. These results are suggestive of the effects of traffic-related air  
15 pollution on long-term mortality, but NO<sub>x</sub> likely represented the combined effects of that source,  
16 possibly including PM, which could not be analyzed in this study. Nyberg et al. (2000), a case-  
17 control study of 1,043 men aged 40 to 75 with lung cancer and 2,364 controls in Stockholm  
18 County, reported similar results to this study. They mapped residence addresses to a GIS  
19 database indicating 4,300 traffic-related line sources and 500 point sources of NO<sub>2</sub> exposure.  
20 Exposure was derived from a model validated by comparison to actual measurements of NO<sub>2</sub> at  
21 six sites. Exposure to NO<sub>2</sub> at 10 μg/m<sup>3</sup> was associated with an OR of 1.10 (95% CI: 0.97 1.23).  
22 Exposure to the 90th percentile ( $\geq 29.26$  μg/m<sup>3</sup>) of NO<sub>2</sub> was associated with an OR of 1.44 (95%  
23 CI: 1.05, 1.99).

24 Naess et al. (2007) investigated the concentration-response relationships between air  
25 pollution (i.e., NO<sub>2</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>) and cause-specific mortality using all the inhabitants of Oslo,  
26 Norway, aged 51 to 90 years on January 1, 1992 (n = 143,842), with follow-up of deaths from  
27 1992 to 1998. An air dispersion model was used to estimate the air pollution levels for 1992  
28 through 1995 in all 470 administrative neighborhoods. Correlations among these pollutants were  
29 high (ranged 0.88 to 0.95), but they were not correlated with education and occupation (less than  
30 0.05). All causes of deaths were associated with all indicators of air pollution for both sexes and  
31 both age groups. The investigators reported that the effects appeared to increase at NO<sub>2</sub> levels

1 higher than  $40 \mu\text{g}/\text{m}^3$  (21 ppb) in the younger age (51 to 70 years) group and with a linear effect  
2 in the interval of 20 to  $60 \mu\text{g}/\text{m}^3$  (10 to 31 ppb) for the older age group (see Figure 3.4-4).  
3 However, they also noted that a similar pattern was found for both  $\text{PM}_{2.5}$  and  $\text{PM}_{10}$ . Thus, the  
4 apparent threshold effect was not unique to  $\text{NO}_2$ .  $\text{NO}_2$  risk estimates for all-cause mortality were  
5 presented only in a figure. Associations between these pollutants and cardiovascular causes,  
6 lung cancer, and COPD were also found in both age groups and sexes. The effect estimates were  
7 particularly larger for COPD deaths. The findings are generally consistent with those from  
8 Nafstad et al. (2003 and 2004) studies, in which a smaller number of male-only subjects were  
9 analyzed. Unlike the 2004 Nafstad study, the Naess et al. study (2007) did not adjust for  
10 smoking or physical activities. While  $\text{NO}_2$  effects were suggested, the high correlation among  
11 the PM indices and  $\text{NO}_2$  or  $\text{NO}_x$  makes it difficult to ascribe these associations to  $\text{NO}_2/\text{NO}_x$   
12 alone.



**Figure 3.4-4. Age-adjusted, nonparametric smoothed relationship between  $\text{NO}_2$  and mortality from all causes in Oslo, Norway, 1992 through 1995.**

Source: Naess et al. (2007).

13 Gehring et al. (2006) investigated the relationship between long-term exposure to air  
14 pollution originating from traffic and industrial sources and total and cause-specific mortality in  
15 a cohort of women living in North Rhine-Westphalia, Germany. The area includes the Ruhr  
16 region, one of Europe's largest industrial areas. Approximately 4,800 women (age 50 to

1 59 years) were followed for vital status and migration. Exposure to air pollution was estimated  
2 by GIS models using the distance to major roads, NO<sub>2</sub>, and PM<sub>10</sub> (estimated from 0.71 × TSP,  
3 based on available PM<sub>10</sub> and TSP data in the area) concentrations from air monitoring station  
4 data. Cardiopulmonary mortality was associated with living within a 50-m radius of a major  
5 road (RR = 1.70 [95% CI: 1.02, 2.81]), NO<sub>2</sub> (RR = 1.72 [95% CI: 1.28, 2.29] per 10-ppb  
6 increase in annual average), and PM<sub>10</sub> (RR = 1.34 [95% CI: 1.06, 1.71] per 7-μg/m<sup>3</sup> increase in  
7 annual average). Exposure to NO<sub>2</sub> was also associated with all-cause mortality (1.21 [95% CI:  
8 1.03, 1.42] per 10 ppb). NO<sub>2</sub> was generally more strongly associated with mortality than the  
9 indicator for living near a major road (within versus beyond a 50-m radius) or PM<sub>10</sub>.

### 10 **3.5.3 Estimation of Exposure in Long-Term Exposure Mortality Studies**

11 The long-term exposure mortality studies described above can be categorized into two  
12 types based on the way exposure estimates were made: (1) studies in which the community  
13 average values were assigned to all the subjects in that community; (2) studies in which  
14 individual subject's exposure was estimated based on spatial modeling using emission and  
15 concentration data. The first type is what Kunzli and Tager (1997) called "semi-individual"  
16 study in which the information on potential confounders are collected and adjusted for on an  
17 individual basis, but the air pollution exposure estimate was done on an ecologic basis. The  
18 Harvard Six Cities study, the ACS study, and the French PAARC study are of this type. The  
19 studies that used the latter type of approach are mostly studies that attempted to investigate the  
20 effects of traffic-related pollutants. In the Abbey et al. (1999) Seventh-day Adventist study,  
21 individual exposure estimates were made through interpolation of ambient monitors because a  
22 relatively large number of monitors (348) were available within California, but unlike the  
23 European studies, they did not attempt to address specifically the influence of traffic-related  
24 exposures.

25  
26 The Filleul et al. (2005) French seven cities (24 areas) study found that associations  
27 between NO<sub>2</sub> and mortality outcomes were found only after exclusions of six area monitors that  
28 were highly influenced by local traffic. This raises a question about potential exposure errors  
29 associated with NO<sub>2</sub> or NO<sub>x</sub> in the semi-individual studies. In order for the population average  
30 exposure estimate to be representative in a semi-ecologic study, the data from locally impacted  
31 NO<sub>2</sub> monitors may cause exposure error or, at the least, monitor selection criteria need to be

1 consistent across cities (even if those who live near the source are the ones who are adversely  
2 affected). It is not clear; to what extent such exposure error affected other semi-individual  
3 studies. Unlike regional air pollutants (e.g.,  $\text{SO}_4^{2-}$  and  $\text{PM}_{2.5}$ ) in the eastern United States in  
4 warm seasons when its major constituent is  $\text{SO}_4^{2-}$ ) whose levels are generally uniform within the  
5 scale of the metropolitan area, the within-city variation for more locally impacted pollutants such  
6 as  $\text{NO}_2$ ,  $\text{SO}_2$ , and  $\text{CO}$  are likely to be larger and, therefore, are more likely to have larger  
7 exposure errors in the semi-individual studies. The smaller number of monitors available for  
8  $\text{NO}_2$  in the United States may make the relative error worse for  $\text{NO}_2$  compared to other  
9 pollutants. In the Krewski et al. (2000) sensitivity analysis of the Harvard Six Cities study,  $\text{NO}_2$   
10 was associated with total and cardiopulmonary deaths. However,  $\text{NO}_2$  was highly correlated  
11 with  $\text{PM}_{2.5}$ ,  $\text{SO}_4^{2-}$ , and  $\text{SO}_2$  in this data set, and combined with the relatively small number of  
12 cities studied, it is difficult to interpret the risk estimates. In Krewski et al.'s sensitivity analysis  
13 of the 1995 ACS study, or in the Pope et al.'s (2002) extended ACS study,  $\text{NO}_2$  was not  
14 associated with deaths.

15         In the Hoek et al. study (2002), the indicator of living near a major road was a better  
16 predictor of mortality than the estimated  $\text{NO}_2$  exposures. In the Gehring et al. study (2006) of  
17 the North Rhine-Westphalia, Germany, the estimated  $\text{NO}_2$  was a better predictor of total and  
18 cardiopulmonary mortality than the indicator of living near a major road. Comparing the results  
19 for the indicators of living near a major road (categorical) and the estimated  $\text{NO}_2$  or  $\text{NO}_x$   
20 exposures (continuous) is not straightforward, but it is possible that, depending on the presence  
21 of other combustion sources (e.g., the North Rhine-Westphalia area included highly industrial  
22 areas),  $\text{NO}_2$  may represent more than traffic-related pollution.

23         The second type of studies discussed above, which estimated individual exposures, may  
24 provide more accurate exposure estimates than the semi-individual studies. However, because  
25 they generally involve modeling with such information as traffic volume and other emission  
26 estimates in addition to monitored concentrations, additional uncertainties may be introduced.  
27 Thus, validity and comparability of various methods may need to be examined. In addition,  
28 because the review process, such as this, ultimately needs to link the relationship between the  
29 concentration measured at the community monitors and the health effects, interpreting the risk  
30 estimates based on individual-level exposures will require an additional step to translate the  
31 difference. In addition, the studies with estimated individual exposures will need to deal with

1 within-city spatial confounding with socioeconomic conditions. While most of these studies  
2 adjusted for the socioeconomic variables, residual confounding is always a concern. Finally, a  
3 more accurate exposure estimate does not solve the problem of the surrogate role that NO<sub>2</sub> may  
4 play. Most of these studies do acknowledge this issue and generally treat NO<sub>2</sub> as a surrogate  
5 marker, but the extent of such surrogacy and confounding with other traffic- or combustion-  
6 related pollutant is not clear at this point.

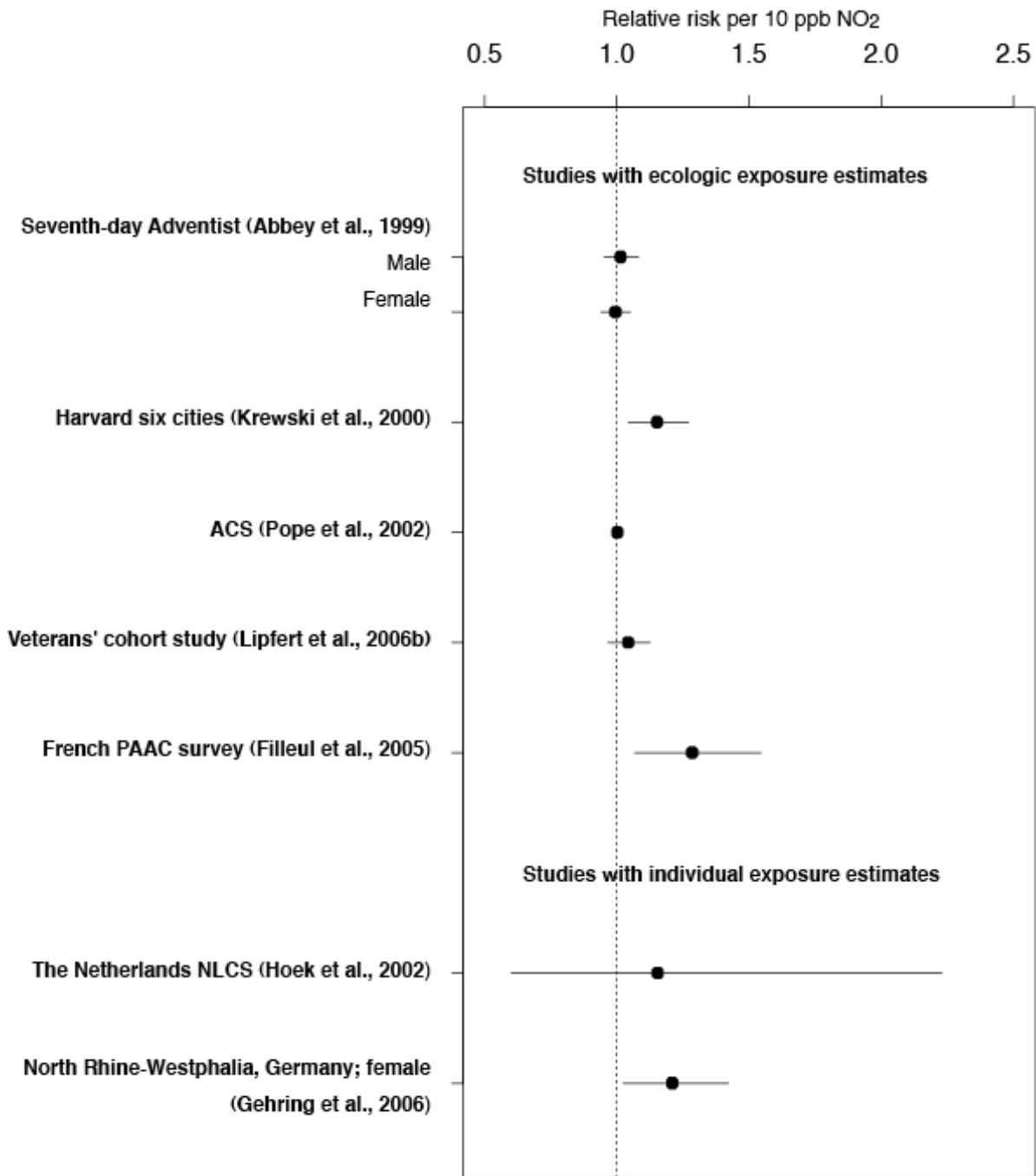
### 7 8 **3.5.4 Summary of Risk Estimates for Mortality with Long-Term Exposure**

9 Figure 3.4-5 summarizes the NO<sub>2</sub> risk estimates for total mortality from the studies  
10 reviewed above. The risk estimates are grouped to those that used ecologic-level exposure  
11 estimates and those that used individual exposure estimates, but because of the small number of  
12 studies listed, no systematic pattern is apparent. Not all of these studies presented correlation  
13 between NO<sub>2</sub> and other pollutants, but those that did present some high correlation coefficients.  
14 For example, in the Harvard Six Cities study, the correlation between NO<sub>2</sub> and PM<sub>2.5</sub> was 0.78.

15 In the French study, the correlation between NO<sub>2</sub> and black smoke was 0.72. In the  
16 German study, the correlation between NO<sub>2</sub> and PM<sub>10</sub> was 0.8 for the 5-year averages.  
17 Therefore, interpretation of the estimates requires additional caution. The risk estimates for total  
18 mortality ranged from 0 to 1.28 per 10-ppb increase in annual or longer averages of NO<sub>2</sub>. The  
19 risk estimates for more specific categories were often larger than these, but such associations  
20 were often not specific to NO<sub>2</sub>, or not consistent across studies.

21 In the long-term studies, those that did report correlation among pollutants suggest that  
22 NO<sub>2</sub> was highly correlated with PM indices to the extent ( $r \sim 0.8$ ) that results from multipollutant  
23 models would be meaningless.

24 Available information on long-term mortality NO<sub>2</sub> risk estimates for more specific causes  
25 is also limited. Among the studies with larger number of subjects, the ACS study (Pope et al.,  
26 2002) examined cardiopulmonary and lung cancer deaths, but as with the all-cause deaths, they  
27 were not associated with NO<sub>2</sub>. In the Naess et al. (2007) analysis of all inhabitants of Oslo,  
28 Norway, age 51 to 90, NO<sub>2</sub> risk estimates for COPD were higher than those for other causes, but  
29 the same pattern was seen for PM<sub>2.5</sub> and PM<sub>10</sub>. In the Gehring et al. (2006) study in North  
30 Rhine-Westphalia, Germany, NO<sub>2</sub> risk estimates for cardiopulmonary mortality were larger than



**Figure 3.4-5. Total mortality risk estimates from long-term studies. The original estimate for the Norwegian study was estimated for NO<sub>x</sub>. Conversion of NO<sub>2</sub> = 0.35 × NO<sub>x</sub> was used.**

1 those for all-cause mortality, but, again, the same pattern was seen for PM<sub>10</sub>. Thus, higher risk  
2 estimates seen for specific causes of deaths were not specific to NO<sub>2</sub> in these studies.

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

9  
10

### 11 **3.6 STUDIES OF NO, HONO, AND HNO<sub>3</sub>**

12 As discussed earlier in Chapter 3, the family of NO<sub>x</sub> contains many other chemicals  
13 besides NO<sub>2</sub>. Of these, chemicals of interest from a toxicology standpoint include nitric oxide  
14 (NO) and HNO<sub>3</sub>. Most of the data is on NO, with many of the studies using high concentrations.  
15 Only the lower concentration studies (i.e., studies that tested concentrations within an order or  
16 two of magnitude above environmental levels) have been included in this update.

17  
18

#### *Nitric Oxide (NO)*

19  
20

#### *Endogenous Formation of NO*

21 Compared with NO<sub>2</sub>, the toxicity database on NO is small. A confounding factor with  
22 the toxicity studies on NO is that it is often difficult to obtain pure NO in air without some  
23 contamination with NO<sub>2</sub>.

24 Endogenous NO is formed in cells from the amino acid L-arginine by at least three  
25 different oxygen-utilizing NO synthetases. Endogenous NO is involved in intracellular signaling  
26 in the nervous system, mediation of vasodilation in both systemic and pulmonary circulation, and  
27 mediation of cytotoxicity and host defense reactions in the immune system (Garthwaite, 1991;  
28 Barinaga, 1991; Moncada et al., 1991, 1992; Snyder and Brecht, 1992). There are two basic  
29 actions of endogenous NO. It is involved in a variety of actions at low concentrations (pico-  
30 nanomolar) within nerve and endothelial cells via activation of guanylate cyclase (Ignarro,  
31 1989). The other action of endogenous NO involves high concentrations (nano- to micromolar)  
32 and is formed during induction of enzymes triggered by exposure of cells to bacterial toxins or to

1 growth-regulating factors (cytokinins). The inducible nitric oxide synthetase (iNOS) formation  
2 occurs especially in macrophages and neutrophil leukocytes and is important for the killing of  
3 bacteria and parasites and possibly also for cytostasis in antitumor reactions (Hibbs et al., 1988;  
4 Ignarro, 1989; Moncada et al., 1991, 1992).

5  
6 ***Effects of NO on Pulmonary Function, Morphology, and Host Lung Defense Function***

7       Murphy et al. (1964) found that respiratory function was not affected in guinea pigs  
8 exposed to NO at 19,600  $\mu\text{g}/\text{m}^3$  (16 ppm) or 61,300  $\mu\text{g}/\text{m}^3$  (50 ppm) for 4 h. Guinea pigs  
9 exposed to 6130- $\mu\text{g}/\text{m}^3$  (5 ppm) NO for 30 min, twice a week for 7 weeks showed increased  
10 airways responsiveness to acetylcholine. Reversal of methacholine-induced bronchoconstriction  
11 by NO has been reported in guinea pigs at 6130  $\mu\text{g}/\text{m}^3$  (5 ppm) (Dupuy et al., 1992), while in  
12 rabbits, full reversal of methacholine-induced bronchoconstriction was seen at 98,100  $\mu\text{g}/\text{m}^3$   
13 (80 ppm) (Högman et al., 1993). This action is in contrast to NO<sub>2</sub> as described above, which  
14 sensitizes the lung to bronchoconstriction following irritant and allergen challenge.

15       Holt et al. (1979) found grossly emphysematous lungs in NO-exposed mice, whereas  
16 comparable exposures to NO<sub>2</sub> resulted in only airspace enlargement. In the study by Azoulay  
17 et al. (1981), rats exposed continuously to 3760- $\mu\text{g}/\text{m}^3$  (2 ppm) NO for 6-h to 6 weeks were  
18 found to have significant enlargement of the airspaces and destruction of alveolar septa.

19       Results from a recent study (Mercer et al. (1995) suggest that the pattern of injury  
20 produced by NO may differ from NO<sub>2</sub>, as well as being more potent in introducing certain  
21 changes in lung morphology. In this study, male rats were exposed to either NO or NO<sub>2</sub> at  
22 0.5 ppm with twice daily 1-h spikes of 1.5 ppm for 9 weeks. The number of pores of Kohn and  
23 detached alveolar septa were evaluated by electron microscopy, using stereological procedures  
24 for the study of lung structure that involved morphometric analyses of electron micrographs.  
25 The average number of pores per lung for the NO group exceeded by approximately 2.5 times  
26 the mean number for the NO<sub>2</sub> groups, which was more than 10 times that for controls. The mean  
27 number of detached septa per lung was significantly higher for the NO group (mean 117) than  
28 the NO<sub>2</sub> group (mean 20) or the controls (mean 4). There was also a statistically significant  
29 30% reduction in interstitial cells in the NO group, but no significant differences in the other  
30 parenchymal cell types were observed between the controls and the NO- or NO<sub>2</sub>-exposed groups.  
31 Lastly, the thickness of the interstitial space was reduced for the NO group (mean 0.24  $\mu\text{m}$



1 versus 0.32  $\mu\text{m}$  for controls) but not for the  $\text{NO}_2$  group (mean 0.29  $\mu\text{m}$ ), and epithelial cell  
2 thickness did not differ between the groups.

3 In a subsequent study, Mercer et al. (1999) exposed rats continuously 22 h/day to 0,  
4 2454, or 7362- $\mu\text{g}/\text{m}^3$  (0, 2, or 6 ppm) NO for 6 weeks. The surface density of the alveolar  
5 basement membrane and the average thickness of the type II alveolar epithelium, although  
6 reduced, did not differ statistically from control animals. Morphometric analysis showed that a  
7 significant greater fraction of the alveolar surface was covered by type II cells in the lungs from  
8 both NO exposure groups. There was a 52% increase in the number of type II cells per surface  
9 area of basement membrane in the 7362- $\mu\text{g}/\text{m}^3$  (6 ppm) NO-exposed animals, as well as an  
10 approximate 3-fold increase in the number of AMs in the airspaces of rat lungs. The mean  
11 number of AMs in the airspaces of lungs from the 2454- $\mu\text{g}/\text{m}^3$  (2 ppm) NO-exposed animals was  
12 elevated but not statistically different from controls. Inhaled NO produced significant  
13 sequestration of platelets in the pulmonary capillaries, as determined from transmission electron  
14 micrographs. The volume density of platelets in the pulmonary capillaries was increased  
15 approximately 2-fold in the NO-exposed groups. Although present in higher numbers, the  
16 platelets did not demonstrate morphologic features of activation such as large, irregular profiles.  
17 Under scanning electron microscopy, fenestrae were found to be distributed throughout the gas-  
18 exchange region of the lungs. Unlike the results of Mercer et al. (1995), there were no  
19 statistically significant differences in the number of lung fenestrae between control and NO-  
20 exposed lungs, as determined by both serial-section counts and scanning electron microscopy.  
21 Thus, it appears that inhaled NO produces a pattern of injury similar to that of  $\text{NO}_2$ , at least in  
22 this regard.

23 Two studies reported the effects of NO on host defense function of the lungs. Mice  
24 exposed to 12,270- $\mu\text{g}/\text{m}^3$  (10 ppm) NO for 2 h/day, 5 days/week for 30 weeks (Holt et al., 1979)  
25 developed immunological alterations that are difficult to interpret due to the duration dependence  
26 of some of the responses (e.g., an enhancement of the humoral immune response to sheep red  
27 blood cells was seen at 10 weeks, but this was not evident at the end of the exposure series). In  
28 the study by Azoulay et al. (1981), mice exposed continuously to 3760- $\mu\text{g}/\text{m}^3$  (2.0 ppm) NO for  
29 6-h to 4 weeks did not show any effect on resistance to infection induced by a bacterial aerosol  
30 administered after each NO exposure. Although the data are limited, NO does not appear to have  
31 the same effect on parameters related to host immune defense as  $\text{NO}_2$ .

1 ***Metabolic Effects in the Lung and Other Tissues***

2 NO has a higher affinity for heme-bound iron than does CO. This affinity leads to the  
3 formation of methemoglobin and the stimulation of guanylate cyclase. NO stimulates guanylate  
4 cyclase in vitro, resulting in smooth muscle relaxation and vasodilation (Katsuki et al., 1977;  
5 Ignarro, 1989; Moncada et al., 1991). This activation pathway via guanylate cyclase is probably  
6 involved in the vasodilation observed in the pulmonary circulation and the acute bronchodilator  
7 effect from inhaled NO. The initial pulmonary vasodilation that occurs during NO inhalation  
8 does not appear to be maintained chronically. Pulmonary cGMP, iNOS, mRNA, and TNF- $\alpha$   
9 were increased in the lungs of rats after a 1-h exposure to 7362- $\mu\text{g}/\text{m}^3$  (6 ppm) NO, but  
10 decreased to control values after 1-day and 1-week exposure periods (Brady et. al., 1998). Lipid  
11 peroxidation (measured as malonyl dialdehyde) was decreased at all time points.

12 It is unclear whether other effects might be exerted from ambient NO via the pathway  
13 involving guanylate cyclase. Since NO is rapidly inactivated by hemoglobin, internal organs  
14 other than the lungs are unlikely to be affected directly by cGMP-mediated vasodilator influence  
15 from ambient concentrations of NO.

16 Methemoglobin formation from inhaled NO, via the formation of nitrosylhemoglobin  
17 (Oda et al., 1975, 1979, 1980a,b; Case et al., 1979; Nakajima et al., 1980) and subsequent  
18 oxidation with oxygen, has been well-characterized (Kon et al., 1977; Chiodi and Mohler, 1985).

19 Levels of reduced glutathione in the lung are not changed in mice exposed to NO  
20 concentrations of 12,300 to 25,800  $\mu\text{g}/\text{m}^3$  (10 to 21 ppm) for 3-h daily for 7 days (Watanabe  
21 et al., 1980).

22 The cytotoxic effects of NO may be explained by the possible mechanism of NO reacting  
23 with thiol-associated iron in enzymes and eventually displacing the iron (Hibbs et al., 1988;  
24 Weinberg, 1992). Other effects of NO with iron and various enzymes and nucleic acids are  
25 listed in Annex AX4.6.

26

27 ***Effects of Short-Term NO Exposure***

28 Research on the role of endogenous NO as a mediator of vascular tone continues to be  
29 active. NO inhalation is used in clinical settings or therapeutically to treat pulmonary  
30 hypertension due to its effects on vascular tone in the pulmonary vascular bed. It is possible that  
31 NO<sub>2</sub> could influence airways or pulmonary vascular availability of NO, with consequences for  
32 the regulation of pulmonary vascular function. Ponka and Virtanen (1996) report an association

1 of hospital and ED admissions with NO. Other studies summarized below were experimental in  
2 design.

3 The effects of inhaled NO are limited to the pulmonary vasculature presumably due to  
4 rapid removal of NO from the circulation arising from reactions with hemoglobin. Although  
5 many studies have used concentrations that are not relevant to environmental levels of air  
6 pollution and were not designed to evaluate the effects of ambient exposures, changes in  
7 pulmonary vascular resistance do occur at concentrations as low as 10 ppm following acute  
8 exposure in pigs (Alving et al., 1993; Holopainen et al., 1999) and 5 ppm in sheep (Fratacci  
9 et al., 1991; Ichinose et al., 1995; DeMarco, et al., 1996). In addition, Jiang et al (2002) reported  
10 in a rodent model of chronic pulmonary hypertension that showed that inhaled NO  
11 concentrations ranging from 0.1 to 2.0 ppm reduced mean pulmonary arterial pressure, while no  
12 such changes were observed in control rats (i.e., normal hypertensive). Thus, changes in  
13 vascular tone from inhaled NO occur in the 5-ppm range, although effects may also be present at  
14 lower concentrations in sensitized animals.

15 Formation of methemoglobin, via the formation of nitrosylhemoglobin (Oda et al., 1975,  
16 1979, 1980a,b; Case et al., 1979; Nakajima et al., 1980) and subsequent oxidation with oxygen  
17 has been well-described (Kon et al., 1977; Chiodi and Mohler, 1985). Methemoglobin in mice  
18 increased exponentially with the NO concentration, from 24,500 to 98,100  $\mu\text{g}/\text{m}^3$  (20 to  
19 80 ppm); levels rapidly decreased after cessation of exposure, with a half-time of only a few  
20 minutes (Oda et al., 1980b). Exposure of mice to 2940- $\mu\text{g}/\text{m}^3$  (2.4 ppm) NO for 23 to 29 months  
21 resulted in nitrosylhemoglobin levels at 0.01%, while the maximal methemoglobin level was  
22 0.3% (Oda et al., 1980b). Exposure to 12,300- $\mu\text{g}/\text{m}^3$  (10 ppm) NO<sub>2</sub> for 6.5 months resulted in  
23 nitrosylhemoglobin level of 0.13% and methemoglobin level of 0.2% (Oda et al., 1976). Rats  
24 exposed to 2450  $\mu\text{g}/\text{m}^3$  (2 ppm) continuously for 6 weeks showed no detectable methemoglobin  
25 (Azoulay et al., 1977). In humans, the ability to reduce methemoglobin varies genetically and is  
26 lower in infants, complicating direct extrapolation of effect levels to human health risk  
27 assessment.

28 The ability of NO to react with iron-containing enzymes has additional ramifications  
29 beyond methemoglobin. Mice exposed to NO at 11,070  $\mu\text{g}/\text{m}^3$  (9 ppm) for 16-h had decreased  
30 iron transferrin (Case et al., 1979). When exposed to 12,300  $\mu\text{g}/\text{m}^3$  (10 ppm) for 6.5 months,  
31 leukocyte count and proportion of PMN cells were increased (Oda et al., 1976). Red blood cell

1 morphology, spleen weight, and bilirubin were also affected. A slight increase in hemolysis was  
2 seen in mice exposed to 2940  $\mu\text{g}/\text{m}^3$  (2.4 ppm) of NO (Oda et al., 1980a).

3  
4 ***Nitrous Acid (HONO)***

5 Two indoor nitrous acid studies were identified that examine health effects and HONO  
6 exposure. One of these was van Strien et al. (2004) discussed above, and the other is Jarvis et al.  
7 (2006). In England, Jarvis et al. (2005) studied 276 adults and related respiratory symptoms and  
8 lung function to home levels of NO<sub>2</sub> and HONO as well as outdoor NO<sub>2</sub> levels. The median  
9 indoor HONO level was 3.10 ppb (IQR 2.05 to 5.09) and 12.76 ppb for NO<sub>2</sub> indoors and  
10 13.83-ppb NO<sub>2</sub> outdoors. The prevalence of wheeze was higher in individuals in the highest  
11 quartile HONO concentration where 33.3% reported wheeze in the previous 12 months versus  
12 those in the lowest concentration quartile where 25.5% reported wheeze. No significant  
13 relationships for NO<sub>2</sub> were noted. An increase in 1 ppb in indoor HONO was associated with a  
14 decrease in FEV<sub>1</sub>, percentages predicted (-0.96% [95% CI: -1.82, -0.09]). After adjustment for  
15 NO<sub>2</sub> measures, the association of HONO with low lung function persisted. In the van Strien  
16 et al. (2004) study of infants in the United States, NO<sub>2</sub> and HONO were moderately correlated  
17 ( $r = 0.40$ ) with higher correlations in homes during autumn and winter ( $r = 0.83$ ). The highest  
18 nitrous acid level was 4.2 ppb. Nitrous acid exposure was not independently associated with  
19 respiratory symptoms.

20 There have also been controlled human exposure studies evaluating the effects of nitrous  
21 acid. Beckett et al. (1995) exposed 11 mild asthmatics to air or 0.65 ppm HONO for 3 h,  
22 including three 20-min exercise periods. Spirometry and symptoms were measured during and  
23 immediately following exposure. HONO caused a small increase in irritant respiratory  
24 symptoms, and a 3% decline in FVC, relative to air exposure. FEV<sub>1</sub> was not significantly  
25 affected. Rasmussen et al. (1995) exposed 15 healthy nonsmokers to air, 0.077, and 0.395-ppm  
26 HONO for 3.5-h including a single 10-min exercise period. HONO caused concentration-related  
27 increases in epithelial cells in eye tear fluid, suggesting eye conjunctival irritation. Specific  
28 airways conductance (the inverse of airways resistance) decreased 10% after HONO and  
29 2% after air. There were no significant effects on FEV<sub>1</sub> or airways responsiveness.

30

1 ***Nitric Acid (HNO<sub>3</sub>)***

2 As discussed in Section 3.4.1, recent reports from the Childrens' Health Study in  
3 Southern California have reported associations between decreased lung function growth and acid  
4 vapor (results primarily from photochemical conversions of oxides of nitrogen to HNO<sub>3</sub> vapor).  
5 Significant associations were reported for long-term exposure to acid vapor with decrements in  
6 measures of lung function, though similar associations were reported with NO<sub>2</sub> and measures of  
7 PM (Gauderman et al., 2004).

8 Very few toxicological studies have been conducted with HNO<sub>3</sub>, even though it exists in  
9 ambient air generally as a water-soluble vapor. The few studies available have examined the  
10 histological response to instilled HNO<sub>3</sub> (usually 1%). This procedure was used to develop  
11 models of bronchiolitis obliterans in various animal species, including dogs, rabbits, and rats  
12 (Totten and Moran, 1961; Greenberg et al., 1971; Gardiner and Schanker, 1976; Mink et al.,  
13 1984). The World Health Organization (WHO, 1997) considered these studies to be informative  
14 for the design of inhalation studies but of questionable relevancy to understanding the pulmonary  
15 response to pure HNO<sub>3</sub> vapor. Based on the limited data available, HNO<sub>3</sub> appears to affect some  
16 respiratory tract parameters in a fashion that is qualitatively similar to NO<sub>2</sub>.

17 In a study by Abraham et al. (1982), normal sheep and allergic sheep (i.e., having airways  
18 responses similar to those occurring in humans with allergic airways disease) were exposed to  
19 4120- $\mu\text{g}/\text{m}^3$  (1.6 ppm) HNO<sub>3</sub> vapor for 4-h using a "head-only" chamber. There was decreased  
20 specific pulmonary flow resistance in both groups of sheep, indicating no bronchoconstriction.  
21 The allergic, but not the normal, sheep showed increased airways reactivity to carbachol, both  
22 immediately and 24-h after HNO<sub>3</sub> exposure. Exposure of rabbits to HNO<sub>3</sub> concentrations of 50,  
23 150, or 450  $\mu\text{g}/\text{m}^3$  (0.02, 0.06, or 0.17 ppm), 4 h/day, 3 days/week for 4 weeks caused no overt  
24 pathology in conducting airways, and airways epithelium was normal in all exposure groups  
25 (Schlesinger et al., 1994). Stimulated superoxide production, however, was reduced in  
26 pulmonary macrophages at all exposure levels. Nadziejko et al. (1992) exposed rats to HNO<sub>3</sub>  
27 vapor for either a single 4-h exposure period to 1000- $\mu\text{g}/\text{m}^3$  (0.39 ppm) HNO<sub>3</sub> vapor or 4 h/day  
28 for 4 days to 250- $\mu\text{g}/\text{m}^3$  (0.1 ppm) HNO<sub>3</sub> vapor. There were no changes in cell populations in  
29 the BAL fluid from rats under either exposure condition. HNO<sub>3</sub> vapor, under either exposure  
30 condition, did not affect zymosan-stimulated respiratory burst activity when pulmonary  
31 macrophages were cultured overnight in order to prevent spontaneous respiratory burst activity.

1 However, when measured using freshly isolated macrophages, both spontaneous and PMA-  
2 stimulated respiratory burst activity was decreased in pulmonary macrophages from rats exposed  
3 to 250- $\mu\text{g}/\text{m}^3$  (0.1 ppm)  $\text{HNO}_3$  vapor for 4 days; results from the single 4-h exposure to  
4 1000- $\mu\text{g}/\text{m}^3$  (0.39 ppm)  $\text{HNO}_3$  vapor were not reported. Lavage fluid protein content was not  
5 affected, but lavage fluid elastase inhibitor capacity was increased in both exposure groups. It is  
6 not known whether this increase was caused by enhanced production of an elastase inhibitor  
7 within the lung or due to increased permeability and leakage of elastase inhibitor from the  
8 plasma into the lung lining layer.

9         Sindhu et al. (1998) reported no effects on lung polyamine metabolism in rats exposed to  
10 50- $\mu\text{g}/\text{m}^3$  (0.02 ppm)  $\text{HNO}_3$  4 h/day, 3 days/week for 40 weeks. No other endpoints were  
11 evaluated.

**TABLE 3.2-1. PROPOSED MECHANISMS WHEREBY NO<sub>2</sub> AND RESPIRATORY VIRUS INFECTIONS MAY EXACERBATE UPPER AND LOWER AIRWAY SYMPTOMS**

<b>Proposed Mechanisms</b>	
<b>Upper Airways</b>	
Epithelium	↓ Ciliary beat frequency ↑ Epithelial permeability ↓ Nasal filtering of inhaled allergen and increased penetration to lower airway ↑ Conditional of inspire air, low temperature/humidity, bronchospasm
<b>Lower Airways</b>	
Epithelium	(as in upper airways)
Cytokines	↓ Epithelial-derived IL-8 ↑ Macrophage-derived IL-1b
Inflammatory cells	
Mast cells	↑ Mast cell tryptase
Lymphocytes	↑ Neutrophils ↑ Total lymphocytes ↑ NK lymphocytes ↓ T-helper/T-cytotoxic cell ratio
Inflammatory mediators	↑ Free radicals, proteases, TXA <sub>2</sub> , TXB <sub>2</sub> , LTB <sub>4</sub>
Allergens	↑ Penetrance due to ciliostasis ↓ PD <sub>20</sub> FEV <sub>1</sub> ↑ Antigen-specific IgE
Peripheral blood	↓ Total macrophages ↓ B and NK lymphocytes ↓ Total lymphocytes

Source: Chauhan et al. (1998).

**TABLE 3.2-2. MULTICITY STUDIES FOR RESPIRATORY DISEASE OUTCOMES AND INCREMENTAL CHANGES IN NO<sub>2</sub>**

Reference		NO <sub>2</sub> (ppb) <sup>1</sup>				95% Confidence Interval		
		Location	Effect	Age	24-h avg (Range of Means Across Cities)	1-h Max (Range of Means Across Cities)	%Change Normalized to 10 ppb <sup>2</sup>	Lower
ANALYSES								
Barnett et al. (2005)	Respiratory	0	7.0, 11.5		6.1	-2.0	14.3	0, 1
Barnett et al. (2005)	Respiratory	1 to 4	7.0, 11.5		4.7	-1.6	11.2	0, 1
Barnett et al. (2005)	Respiratory	1 to 4		15.7, 23.2	3.1	0.8	5.4	0, 1
Barnett et al. (2005)	Respiratory	5 to 14	7.0, 11.5		11.4	3.3	19.8	0, 1
Barnett et al. (2005)	Respiratory	5 to 14		15.7, 23.2	5.2	1.8	8.8	0, 1
Simpson et al. (2005a)	Respiratory	>65		16.3, 24.1	3.0	1.5	3.9	0, 1

<sup>1</sup> Conversion from µg/m<sup>3</sup> to ppb: ÷ 1.91

<sup>2</sup> In order to normalize values for percentage change into a standard unit of 10 ppb, the inverse of the increments identified by the author were multiplied by 10



**TABLE 3.2-3. EFFECTS OF INCLUDING COPOLLUTANTS WITH NO<sub>2</sub> IN MULTIPOLLUTANT MODELS**

Reference, Study Location and Period	Statistical Analysis	NO <sub>2</sub> Averaging Time and Mean Levels (ppb)	Correlation (r) with Other Pollutants						Standardized* Percent Excess Risk (95% CI)
			PM <sub>10</sub>	PM <sub>2.5</sub>	PM <sub>10-2.5</sub>	SO <sub>2</sub>	CO	O <sub>3</sub>	
Samet et al. (2000) (Reanalysis Dominici et al. (2003)) 90 cities, United States 1987-1994	Original two-stage analytic approach that pooled data from multiple locations using GAM, reanalysis with GAM with more stringent criteria and with GLM with natural cubic splines	24-h avg: 11.0-39.4	0.53	NR	NR	0.51	0.64	0.02	Total Mortality: NO <sub>2</sub> alone: 0.50% [0.10, 0.90] NO <sub>2</sub> + PM <sub>10</sub> : 0.60% [-0.10, 1.40] NO <sub>2</sub> + PM <sub>10</sub> + O <sub>3</sub> : 0.64% [-0.20, 1.60] NO <sub>2</sub> + PM <sub>10</sub> + SO <sub>2</sub> : 0.50% [-0.40, 1.40] NO <sub>2</sub> + PM <sub>10</sub> + CO: 0.54% [-0.36, 1.44]
Sunyer et al. (1997) Multi- city, Europe (Barcelona, Helsinki, Paris, London) 1986- 1992	Poisson regression, GEE; followed APHEA protocol	24-h avg: Barcelona: 27.56 Helsinki: 18.2 London: 35.88 Paris: 21.84	NR	NR	NR	NR	NR	NR	Asthma: NO <sub>2</sub> alone, <15 yrs: 1.5% [0.2, 2.6] NO <sub>2</sub> + BS, <15 yrs: 1.4% [-1.8, 4.7] NO <sub>2</sub> + SO <sub>2</sub> , <15 yrs: 1.3% [-0.5, 3.2] NO <sub>2</sub> alone, 15-64 yrs: 1.5% [0.3, 2.7] NO <sub>2</sub> + BS, 15-64 yrs: 3.4% [1.0, 5.9]
Atkinson et al. (1999b) London, United Kingdom, 1/92-12/94	Poisson regression, followed APHEA protocol	1-h max: 50.3 (17.0)	NR	NR	NR	NR	NR	NR	Asthma among 0-14 year olds: NO <sub>2</sub> alone: 7.4% [3.6, 11.3] NO <sub>2</sub> + SO <sub>2</sub> : 4.8% [0.3, 9.4] NO <sub>2</sub> + CO: 6.9% [3.0, 11.0] NO <sub>2</sub> + PM <sub>10</sub> : 5.8% [1.6, 10.1] NO <sub>2</sub> + BS: 6.9% [3.0, 11.0] NO <sub>2</sub> + O <sub>3</sub> : 8.0% [4.2, 12.0]
Galan et al. (2003) Madrid, Spain 1995-1998	Poisson Regression with (1) APHEA protocol, and (2) GAM with strict criteria	24-h avg: 34.89 (9.36)	0.76	NR	NR	0.61	NR	-0.21	Asthma: NO <sub>2</sub> alone: 6.7% [2.6, 11.1] NO <sub>2</sub> + SO <sub>2</sub> : 6.3% [0.8, 12.1] NO <sub>2</sub> + PM <sub>10</sub> : 0.2% [-5.8, 6.3]

**TABLE 3.2-3 (cont'd). EFFECTS OF INCLUDING COPOLLUTANTS WITH NO<sub>2</sub> IN MULTIPOLLUTANT MODELS**

Reference, Study Location and Period	Statistical Analysis	NO <sub>2</sub> Averaging Time and Mean Levels (ppb)	Correlation (r) with Other Pollutants						Standardized* Percent Excess Risk (95% CI)
			PM <sub>10</sub>	PM <sub>2.5</sub>	PM <sub>10-2.5</sub>	SO <sub>2</sub>	CO	O <sub>3</sub>	
McConnell et al. (2003), Southern California, United States 1993-1999	Three-stage regression to yield a logistic mixed-effects model	24-h avg: 19.4 (11.3)	0.2	0.54	-0.22	NR	NR	0.59	Asthma: NO <sub>2</sub> Alone: 7.4% NO <sub>2</sub> + O <sub>3</sub> : 5.9% NO <sub>2</sub> + PM <sub>10</sub> : 6.7% NO <sub>2</sub> + PM <sub>2.5</sub> : 5.5% NO <sub>2</sub> + PM <sub>10-2.5</sub> : 8.2%
Nafstad et al. (2003), Oslo, Norway 1972-1999	Cox-proportional hazard regression	24-h avg (NO <sub>x</sub> ): 5.6	NR	NR	NR	0.63	NR	NR	Lung Cancer Incidence: NO <sub>x</sub> alone: 34.4% [7.9, 71.2] NO <sub>x</sub> + SO <sub>2</sub> : 44.3% [12.0, 82.9] Other Cancer Incidence: NO <sub>x</sub> alone: 7.9% [-3.8, 25.1] NO <sub>x</sub> + SO <sub>2</sub> : 20.6% [3.9, 39.3]
Burnett et al. (1997b) Toronto, ON, Canada	Poisson regression, GEE, GAM	1-h max: 38.5	0.61	NR	NR	0.46	0.25	0.07	All respiratory hospital admissions: NO <sub>2</sub> alone: 25.2% [13.2, 38.2] NO <sub>2</sub> + PM <sub>10</sub> : 22.1% [t = 2.85] NO <sub>2</sub> + O <sub>3</sub> + SO <sub>2</sub> : 15.5% [t = 2.45] NO <sub>2</sub> + O <sub>3</sub> + SO <sub>2</sub> + PM <sub>10</sub> : 15.5% [t = 1.77]
Burnett et al. (1999) Toronto, ON, Canada 1980-1994	Poisson regression	24-h avg: 25.2 (9.1)	0.52	0.5	0.38	0.54	0.55	-0.03	Respiratory infection: NO <sub>2</sub> alone: 3.7% [SE ≥3] NO <sub>2</sub> + SO <sub>2</sub> + O <sub>3</sub> + PM <sub>10</sub> : 3.3% [SE ≥3] NO <sub>2</sub> + SO <sub>2</sub> + O <sub>3</sub> + PM <sub>2.5</sub> : 3.2% [SE ≥2] NO <sub>2</sub> + SO <sub>2</sub> + O <sub>3</sub> + PM <sub>10-2.5</sub> : 3.6% [SE ≥3]

### 3.2-3 (cont'd). EFFECTS OF INCLUDING COPOLLUTANTS WITH NO<sub>2</sub> IN MULTIPOLLUTANT MODELS

Reference, Study Location and Period	Statistical Analysis	NO <sub>2</sub> Averaging Time and Mean Levels (ppb)	Correlation (r) with Other Pollutants						Standardized* Percent Excess Risk (95% CI)
			PM <sub>10</sub>	PM <sub>2.5</sub>	PM <sub>10-2.5</sub>	SO <sub>2</sub>	CO	O <sub>3</sub>	
Lee et al. (2002) Seoul, Korea 12/1/1997- 12/31/1999	Poisson regression, GAM	24-h avg: 31.5 (10.3)	0.74	NR	NR	0.72	0.79	-0.07	Asthma: NO <sub>2</sub> alone: 21.1% [13.9, 28.4] NO <sub>2</sub> + PM <sub>10</sub> : 18.2% [9.7, 26.9] NO <sub>2</sub> + SO <sub>2</sub> : 28.4% [15.4, 41.7] NO <sub>2</sub> + O <sub>3</sub> : 19.7% [12.5, 28.4] NO <sub>2</sub> + CO: 16.8% [4.1, 31.3] NO <sub>2</sub> + O <sub>3</sub> + CO + PM <sub>10</sub> + SO <sub>2</sub> : 13.7% [0.3, 28.7]
Schwartz et al. (1994), Six cities, United States 1984- 1988	Logistic regression, subsequent analysis using GAM	24-h avg: 13.3	0.36	0.35	NR	0.51	NR	-0.28	Cough Incidence: NO <sub>2</sub> alone: 61.3% [8.2, 143.4] NO <sub>2</sub> + PM <sub>10</sub> : 36.9% [-11.6, 113.2] NO <sub>2</sub> + O <sub>3</sub> : 61.3% [8.2, 140.3] NO <sub>2</sub> + SO <sub>2</sub> : 18.8% [-11.6, 69.0]
Mortimer et al. (2002) Eight urban areas, United States 1993	Linear mixed effects models and GEE	4-h avg: 32	NR	NR	NR	NR	NR	0.29	Morning %PEFR NO <sub>2</sub> alone: 48% [2, 116] NO <sub>2</sub> + O <sub>3</sub> : 40% [-7, 109] NO <sub>2</sub> + O <sub>3</sub> + SO <sub>2</sub> : 31% [-13, 109] NO <sub>2</sub> + O <sub>3</sub> + SO <sub>2</sub> + PM <sub>10</sub> : 45% [-37, 234]
Schildcrout et al. (2006) Eight North American Cities 1993-1995	Logistic and Poisson regression with GEE	24-h avg: 17.8-26.0	0.26, 0.64	NR	NR	0.23, 0.68	0.63, 0.92	0.04, 0.47	Asthma symptoms: NO <sub>2</sub> alone: 4.0% [1.0, 7.0] NO <sub>2</sub> + CO: 4.0% [0.0, 8.0] NO <sub>2</sub> + PM <sub>10</sub> : 4.0% [0.0, 7.0] NO <sub>2</sub> + SO <sub>2</sub> : 4.0% [-1.0, 8.0] Rescue Inhaler Use: NO <sub>2</sub> alone: 3.0% [1.0, 5.0] NO <sub>2</sub> + CO: 4.0% [0.0, 7.0] NO <sub>2</sub> + PM <sub>10</sub> : 2.0% [0.0, 5.0] NO <sub>2</sub> + SO <sub>2</sub> : 3.0% [-2.0, 5.0]

\* 24-h avg NO<sub>2</sub> standardized to 20-ppb increment; 1-h max NO<sub>2</sub> standardized to 30-ppb increment

NR: Not Reported

**TABLE 3.4-1. ASSOCIATIONS BETWEEN EXPOSURE TO TRAFFIC AT HOME AND ASTHMA HISTORY**

<b>Exposure Metric</b>	<b>Odds Ratio per IQR OR* (95% CI)</b>
Distance to freeway	1.89 (1.19-3.02)
Traffic volume within 150 meters	1.45 (0.73-2.91)
Model-based pollution from:	
Freeways	2.22 (1.36-3.63)
Other roads	1.00 (0.75-1.33)
Freeways and other roads	1.40 (0.86-2.27)

\*Odds ratio per change of 1 IQR. For distance to freeway, OR for the 25th percentile compared with the 75th percentile (i.e., living closer compared with farther from the freeway). For remaining traffic variables, OR for the 75th percentile compared with the 25th percentile. All models were adjusted for sex, race, Hispanic ethnicity, cohort, and community.

Source: Gaudermann et al. (2005).

**TABLE 3.4-2. ASSOCIATIONS BETWEEN MEASURED NO<sub>2</sub> AND ASTHMA-RELATED OUTCOMES (N = 208)**

<b>Outcome</b>	<b>No.</b>	<b>Measured NO<sub>2</sub> OR* (95% CI)</b>	<b>Distance to Freeway OR* (95% CI)</b>	<b>Model-based Pollution From Freeways OR* (95% CI)</b>
Lifetime history of asthma	31	1.83 (1.04-3.21)	1.89 (1.19-3.02)	2.22 (1.36-3.63)
Recent wheeze†	43	1.72 (1.07-2.77)	1.59 (1.06-2.36)	1.70 (1.12-2.58)
Recent wheeze with exercise†	25	2.01 (1.08-3.72)	2.57 (1.50-4.38)	2.56 (1.50-4.38)
Current asthma medication use	26	2.19 (1.20-4.01)	2.04 (1.25-3.31)	1.92 (1.18-3.12)

\*Odds ratio per change of 1 IQR in exposure (see footnotes to Table 3.4-1).

†Within the last 12 months.

Source: Gaudermann et al. (2005).

## 4. SUSCEPTIBLE AND VULNERABLE POPULATIONS

### 4.1 INTRODUCTION

The previous AQCD for Oxides of Nitrogen (1993) identified certain groups within the population that may be more susceptible to the effects of NO<sub>2</sub> exposure, including persons with preexisting respiratory disease, children, and the elderly. Many other factors such as gender, nutritional status, smoking, and genetic variability also may contribute to the differential effects of environmental pollutants, including NO<sub>x</sub>.

The reasons for paying special attention to these groups were that (1) they may be affected by lower levels of NO<sub>2</sub> than the general populations or that (2) the impact of an effect may be greater for these groups. Finally, epidemiological studies reviewed in the previous AQCD for Oxides of Nitrogen identified children aged 5 to 12 years as a potentially susceptible subpopulation for increases in NO<sub>2</sub> respiratory morbidity.

In the current document, we will focus on the susceptibility of subpopulations with preexisting asthma and cardiovascular disease, age-related susceptibility and vulnerability, high-exposure occupational groups, and genetic factors.

#### 4.1.1 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 of adverse events associated with air pollution. In addition, epidemiological evidence indicates that persons with bronchial hyperresponsiveness (BHR) as determined by methacholine provocation may be at greater risk of 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 are known to be one of the most NO<sub>2</sub>-responsive subgroups in the population; the evidence related to asthmatics is discussed in further detail below.

1 *Asthmatics*

2 Airways hyperresponsiveness in asthmatics to both nonspecific chemical and physical  
3 stimuli and to specific allergens appears to be the most sensitive indicator of response to NO<sub>2</sub>.  
4 Responsiveness is determined using a challenge agent, which causes an abnormal degree of  
5 constriction of the airways as a result of smooth muscle contraction. This response ranges from  
6 mild to severe (spanning orders of magnitude) and is often accompanied by production of  
7 sputum, cough, wheezing, shortness of breath, and chest tightness. Though some asthmatics do  
8 not have this bronchoconstrictor response and some nonasthmatic individuals do (Pattenmore  
9 et al., 1990), increased airways responsiveness is correlated with asthma symptoms and  
10 increased asthma medication usage. Clinical studies have reported increased airways  
11 responsiveness to allergen challenge in asthmatics following exposure to 0.26-ppm NO<sub>2</sub> for  
12 30 min during rest (Barck et al., 2002; Strand et al., 1996, 1998).

13 Epidemiological studies have reported associations with a range of health outcomes with  
14 both short-term and long-term NO<sub>2</sub> exposure in asthmatics; Table 4.1 highlights some of the  
15 findings for asthmatics discussed in Chapter 3. The results reported in these studies generally  
16 report a positive excess risk for asthmatics associated with NO<sub>2</sub>. The recent evidence  
17 strengthens conclusions drawn in the 1993 AQCD for Oxides of Nitrogen that asthmatics are  
18 likely more susceptible to effects from NO<sub>2</sub> exposures than the general public.

19  
20 *Persons with Cardiovascular Diseases*

21 Epidemiological studies consistently have demonstrated an association between ambient  
22 levels of air pollutants and daily hospital admissions, and CVD emergency department (ED)  
23 visits. Recent epidemiological studies also have shown that persons with preexisting  
24 cardiopulmonary conditions are at increased risk for adverse cardiac health events associated  
25 with ambient NO<sub>2</sub> concentrations (Peel et al., 2006; Mann et al., 2002; D'Ippoliti et al., 2003;  
26 von Klot et al., 2005). Peel et al. (2006) reported evidence of effect modification by co-morbid  
27 hypertension and diabetes for the association of ED visits for arrhythmia associated with NO<sub>x</sub>  
28 exposure. In another study, a statistically significant positive relationship was found between  
29 NO<sub>2</sub> concentrations and hospitalizations for ischemic heart disease (IHD) among those with prior  
30 diagnoses of CHF and arrhythmia (Mann et al., 2002). The authors speculated, however that the  
31 vulnerability of the secondary CHF group may be due to differential diagnoses in this group  
32 (Mann et al., 2002). Modification of the association between NO<sub>2</sub> and MI by conduction

1 disorders was observed in another study (D'Ippoliti et al., 2003). Though there is limited  
2 evidence from clinical or toxicological studies on potential susceptibility in those with CVDs, the  
3 epidemiological evidence suggests that these individuals may be more sensitive to effects of NO<sub>2</sub>  
4 exposure.

5

#### 6 **4.1.2 Age-Related Variations in Susceptibility/Vulnerability**

7 Children and elders often are both considered at increase risks from air pollution,  
8 compared to the general population. The American Academy of Pediatrics (2004) notes that  
9 children and infants are among the most susceptible to many air pollutants, including NO<sub>2</sub>.  
10 Eighty percent of alveoli are formed postnatally and changes in the lung continue through  
11 adolescence; the developing lung is highly susceptible to damage from exposure to  
12 environmental toxicants (Dietert et al., 2000). Children also have increased vulnerability as they  
13 spend more time outdoors, are highly active, and have high minute ventilation, which  
14 collectively increase their dose (Plunkett et al., 1992; Wiley et al., 1991a,b). In addition to  
15 children, the elderly are frequently classified as being particularly susceptible to air pollution.  
16 The basis of the increased sensitivity in the elderly is not known, but one hypothesis is that it  
17 may be related to changes in the respiratory tract lining fluid antioxidant defense network (Kelly  
18 et al., 2003). Also, the generally declining health status of many elders may increase their risks  
19 to air pollution induced effects.

20 While evidence is limited for age-specific associations between NO<sub>2</sub> and acute  
21 respiratory ED visits, there is stronger evidence of the association between ambient NO<sub>2</sub>  
22 concentrations and hospital admissions for children and older adults. Peel et al. (2005) and  
23 Atkinson et al. (1999b) each found that the percent increase in ED visits for asthma among  
24 children was twice that found for subjects of all ages. Specifically, Peel et al. (2005) found that  
25 asthma ED visits among children (2 to 18 years) increased by 2.7% in response to a 20-ppb  
26 increase in the 1-h maximum NO<sub>2</sub> concentration, while the increase for all ages was 1.4%.  
27 Similarly, Atkinson et al. (1999b) reported an 8.97% increase in ED visits for asthma among  
28 children aged 0 to 14 years associated with a 36-ppb increase in the 1-h maximum NO<sub>2</sub>  
29 concentration, while the increase for adults aged 15 to 64 and all ages together were 4.44% and  
30 4.37%, respectively. Two additional studies (Sunyer et al., 1997; Migliaretti et al., 2005) found  
31 no difference in the rates of ED visits associated with NO<sub>2</sub> concentrations for children <15 years

1 and adults aged 15 to 64 years. Migliaretti et al. (2005) found that a 5.2-ppb increase in NO<sub>2</sub> was  
2 associated with a 7.7% increase in ED visits for asthma for participants over 64 years of age,  
3 while the same increment was associated with a 2.4% increase among participants of all ages.  
4 Atkinson et al. (1999b) evaluated the effect of a 36-ppb increase in NO<sub>2</sub> on ED visits for all  
5 respiratory causes and found percent increases to be higher among children (1 to 14 years,  
6 2.17%) and the elderly (≥65 years, 3.65%) compared to adults aged 15 to 64 (1.87%).

7 A number of studies investigated the association between ambient NO<sub>2</sub> levels and  
8 hospital admissions for all respiratory causes stratified by age group (Luginaah et al., 2005;  
9 Schouten et al., 1996; Ponce de Leon et al., 1996; Atkinson et al., 1999a; Prescott et al., 1998;  
10 Fusco et al., 2001; Braga et al., 2001; Wong et al., 1999). Of the six studies that evaluated the  
11 elderly population, four found that the percent increase in hospital admissions for all respiratory  
12 causes associated with ambient NO<sub>2</sub> concentrations was higher for the elderly age group  
13 (≥65 years) compared with the adult age group (Schouten et al., 1996; Ponce de Leon et al.,  
14 1996; Atkinson et al., 1999a; Prescott et al., 1998). Luginaah et al. (2005) and Wong et al.  
15 (1999) found no statistically significant difference in the elderly and adult age groups. Braga  
16 et al. (2001) only included subjects aged 0 to 19 years, but further stratified to find the largest  
17 percent increase in hospital admissions associated with NO<sub>2</sub> concentrations in the 0 to 2 age  
18 group (9.4%). Fusco et al. (2001) reported a larger increase in hospital admissions for all  
19 respiratory diseases among children compared with subjects of all ages (4.0% and 2.5%,  
20 respectively). The difference persisted when hospital admissions were limited to asthma only.  
21 Likewise, Fusco et al. (2001) reported a larger increase in hospital admission for asthma among  
22 children compared with subjects of all ages (10.7% and 4.6%, respectively). Hinwood et al.  
23 (2006), Atkinson et al. (1999a), and Anderson et al. (1998) also found larger increases in hospital  
24 admissions for asthma among children (0 to 14 years) and the elderly (≥65 years) compared to  
25 subjects of all ages, though the increases reported in these studies were more modest in  
26 magnitude than that reported by Fusco et al. (2001).

27 In elderly populations, associations between NO<sub>2</sub> and hospitalizations or ED visits for  
28 CVD, including stroke, have been observed in several multicity studies (Barnett et al., 2006;  
29 Simpson et al., 2005; Wellenius et al., 2005; Morris et al., 1995). However, some results were  
30 inconsistent across cities (Morris et al., 1995), and investigators could not distinguish the effect  
31 of NO<sub>2</sub> from the effect of other traffic-related pollutants such as CO and particulate matter (PM).



1 Reductions in blood hemoglobin (~10%) have been reported in healthy subjects following  
2 exposure to NO<sub>2</sub> (1 to 2 ppm) for a few hours during intermittent exercise (Frampton et al.,  
3 2002). The consequence of this hemoglobin reduction in individuals with significant underlying  
4 lung disease, heart disease, or anemia has not been evaluated, but the reductions could lead to  
5 adverse cardiovascular consequences.

6 Many field studies focused on the effect of NO<sub>2</sub> on the respiratory health of children,  
7 while fewer field studies compared the effect of NO<sub>2</sub> in adults and other age groups. In general,  
8 children and adults experienced decrements in lung function associated with short-term ambient  
9 NO<sub>2</sub> exposures (see Section 3.2.1.2 for more details). Importantly, a number of long-term  
10 exposures studies suggest effects in children - impaired lung function growth, increased  
11 respiratory symptoms and infections, and onset of asthma (see Table 4.1 and Section 3.4.1.1).

12 Several mortality studies have investigated age-related differences in NO<sub>2</sub> effects.  
13 Among the studies that observed positive associations between NO<sub>2</sub> and mortality, a comparison  
14 of all age or ≤64 years of age NO<sub>2</sub>-mortality risk estimates to that of the ≥65 years of age  
15 indicates that, in general, the elderly population is more susceptible to NO<sub>2</sub> effects (Biggeri et al.,  
16 2005; Burnett et al., 2004). One study (Simpson et al., 2005) found no difference in increases in  
17 CVD mortality associated with NO<sub>2</sub> concentrations between all ages and those participants  
18 ≥65 years of age.

19 Collectively, there is supporting evidence of age-related differences in susceptibility to  
20 NO<sub>2</sub> health effects. Elders (>65 years of age) appears to be at increased risk of NO<sub>2</sub>-related  
21 hospitalizations. Asthmatic children (<18 years of age) are likely to experience other adverse  
22 respiratory health outcomes with increased NO<sub>2</sub> exposure e.g. airways hyperresponsiveness often  
23 accompanied by production of sputum, cough, wheezing, shortness of breath, chest tightness,  
24 and increased use of asthma medication. Toxicological evidence available in the 1993 AQCD  
25 also provided evidence for age-related differences in NO<sub>2</sub>-induced lung injury. Neonates, prior  
26 to weaning, appeared to be relatively resistant to effects of NO<sub>2</sub>. However, responsiveness  
27 increased in young animals following weaning, appeared to decline in mature animals, then an  
28 increase in responsiveness occurred at some point in senescence. Additionally, new evidence  
29 since the 1993 AQCD raises concerns for increased severity and frequency of respiratory  
30 infections, decreased lung function growth, increased onset of asthma and allergy, increase  
31 hospital and ED visits for asthmatic children.

### 1 **4.1.3 High-Exposure Groups**

2 Lee et al. (2000) reported that NO<sub>2</sub> concentration in heavy traffic (~60 ppb) can be over  
3 twice that of a residential outdoor level (~26 ppb) in North America. Westerdahl et al. (2005)  
4 reported on-road NO<sub>2</sub> concentrations in Los Angeles ranging from 40 to 70 ppb on freeways,  
5 compared to 20 to 40 ppb on residential or arterial roads. People in traffic can potentially  
6 experience high concentrations of NO<sub>2</sub> as a result of the high air exchange rates for vehicles.  
7 Park et al. (1998) observed that the air exchange in cars varied from 1 to 3 times per hour, with  
8 windows closed and no mechanical ventilation, to 36 to 47 times per hour, with windows closed  
9 and the fan set on fresh air. These results imply that the NO<sub>2</sub> concentration inside a vehicle  
10 could rapidly approach those outside the vehicle during commuting. It follows that people with  
11 occupations that require them to be in or close to traffic or roadways (i.e. bus and taxi drivers,  
12 highway patrol officers) could be differentially exposed to NO<sub>2</sub> and, therefore, should be  
13 considered a susceptible population.

14 While driving, concentrations for personal exposure in a vehicle cabin could be  
15 substantially higher than ambient concentrations measured nearby. Sabin et al. (2005) reported  
16 that NO<sub>2</sub> concentrations in the cabins of school buses in Los Angeles ranged from 24 to 120 ppb,  
17 which were typically factors of 2 to 3 (maximum, 5) higher than at ambient monitors in the area.  
18 Lewné et al. (2006) reported work hour exposures to NO<sub>2</sub> for taxi drivers (25.1 ppb), bus drivers  
19 (31.4 ppb), and truck drivers (35.6 ppb). These levels were 1.8, 2.7, and 2.8 times ambient  
20 concentrations. Riediker et al. (2003) studied the exposure to NO<sub>2</sub> inside patrol cars. The  
21 authors found that the mean and maximum NO<sub>2</sub> concentrations in a patrol car were 41.7 and  
22 548.5 ppb compared to 30.4 and 69.5 ppb for the ambient sites. These studies suggest that  
23 people in traffic can be exposed to much higher levels of NO<sub>2</sub> than are obtained at ambient  
24 monitoring sites. Due to the high peak exposures while driving, total personal exposure could be  
25 underestimated if exposures while commuting are not considered; and sometimes exposure in  
26 traffic can dominate personal exposure to NO<sub>2</sub> (Lee et al., 2000; Son et al., 2004). Variations in  
27 traffic-related exposure could be attributed to time spent in traffic, type of vehicle, and distance  
28 from major roads (Sabin et al., 2005; Son et al., 2004; Chan et al., 1999). Sabin et al. (2005)  
29 reported that the intrusion of the vehicle's own exhaust into the passenger cabin is another NO<sub>2</sub>  
30 source contributing to personal exposure while commuting but that the fraction of air inside the

1 cabin from a vehicle's own exhaust was small, ranging from 0.02 to 0.28%, increasing with the  
2 age of the vehicle (CARB, 2007).

3 Distance to major roadways could be another factor affecting indoor and outdoor NO<sub>2</sub>  
4 concentration, and personal NO<sub>2</sub> exposure. Many studies show that outdoor NO<sub>2</sub> levels are  
5 strongly associated with distance from major roads (i.e., the closer to a major road, the higher the  
6 NO<sub>2</sub> concentration) (Gilbert et al., 2005; Roorda-Knape et al., 1998; Lal and Patil, 2001;  
7 Kodama et al., 2002; Gonzales et al., 2005; Cotterill and Kingham, 1997; Nakai et al., 1995).  
8 Meteorological factors (wind direction and wind speed) and traffic density are also important in  
9 interpreting measured NO<sub>2</sub> concentrations (Gilbert et al., 2005; Roorda-Knape et al., 1998;  
10 Rotko et al., 2001; Alm et al., 1998; Singer et al., 2004; Nakai et al., 1995). Singer et al. (2004)  
11 reported results of the East Bay Children's Respiratory Health Study. The authors found that  
12 NO<sub>2</sub> concentrations increased with decreasing downwind distance for school and neighborhood  
13 sites within 350 m downwind of a freeway, and schools located upwind or far downwind of  
14 freeways were generally indistinguishable from one another and regional pollution levels.

15 Most studies show that indoor NO<sub>2</sub> is correlated with outdoor NO<sub>2</sub> and is also a function  
16 of distance to traffic, traffic density, and meteorological parameters. For example,  
17 Roorda-Knape et al. (1998) reported that NO<sub>2</sub> concentrations in classrooms were significantly  
18 correlated with car and total traffic density ( $r = 0.68$ ), percentage of time downwind ( $r = 0.88$ )  
19 and distance of the school from the roadway ( $r = -0.83$ ).

20 Personal exposure is associated with traffic density and proximity to traffic, although  
21 personal exposure is also influenced by indoor sources. Alm et al. (1998) reported that NO<sub>2</sub>  
22 exposures was higher for the children living in the downtown (13.9 ppb) than in the suburban  
23 area (9.2 ppb,  $p = 0.0001$ ) of Helsinki. Within the urban area of Helsinki, Rotko et al. (2001)  
24 observed that the NO<sub>2</sub> exposure was significantly associated with traffic volume near homes.  
25 The average exposure level of 138 subjects having low or moderate traffic near their homes was  
26 12.3 ppb, while the level was 15.8 ppb for the 38 subjects having high traffic volume near home.  
27 Gauvin et al. (2001) reported the ratio of traffic density to distance from a roadway was one of  
28 the significant interpreters of personal exposure in Grenoble, Toulouse, and Paris. After  
29 controlling indoor source impacts on personal exposure, Kodama et al. (2002) and Nakai et al.  
30 (1995) observed that personal exposure decreased with increasing distance from residence home  
31 to major road.

1           Although traffic is a major source of ambient NO<sub>2</sub>, industrial point sources are also  
2 contributors to ambient NO<sub>2</sub>. However, no published reports were found to address the effect of  
3 those sources on population exposure within the United States. Nerriere et al. (2005) measured  
4 personal exposures to fine PM (PM<sub>2.5</sub>), PM<sub>10</sub>, and NO<sub>2</sub> in traffic dominated, urban background  
5 and industrial settings in Paris, Grenoble, Rouen, and Strasbourg, France. They always found  
6 highest ambient concentrations and personal exposures close to traffic. In some cases, traffic  
7 urban background concentrations of NO<sub>2</sub> were higher than in the industrial zone. However, PM  
8 levels and personal exposures tended to be higher in the industrial area than in the traffic-  
9 dominated area. It should be remembered that there can be high traffic emissions in industrial  
10 zones, such as in the Ship Channel in Houston, TX. In rural areas where traffic is sparse, other  
11 sources could dominate. Martin et al. (2003) found pulses of NO<sub>2</sub> release from agricultural areas  
12 occur following rainfall. Other rural contributors to NO<sub>2</sub> include wildfires and residential wood  
13 burning.

#### 14 15 **4.1.4 Genetic Factors for Oxidant and Inflammatory Damage from Air** 16 **Pollutants**

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

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

1 Romieu et al. (2006) investigated the relationships between common polymorphisms in  
2 two genes involved in response to oxidative stress (i.e., GSTM1 and GSTP1) and both  
3 respiratory symptoms and lung function in response to O<sub>3</sub>, NO<sub>2</sub>, and PM<sub>10</sub> among 151 asthmatic  
4 children. The children were genotyped using polymerase chain reaction (PCR) methods and  
5 followed from October 1998 to April 2000. After adjusting for asthma severity, temperature,  
6 environmental tobacco smoke, chronological time and supplementation group, children with the  
7 GSTM1 null polymorphism were more likely to report difficulty breathing in response to O<sub>3</sub> than  
8 GSTM1 positive children. Children with the GSTP1 Val/Val genotype were more likely to  
9 experience breathing difficulty and bronchodilator use in response to O<sub>3</sub> compared with children  
10 with the GSTP1 Ile/Ile and Ile/Val genotypes. This pattern was consistent for O<sub>3</sub> exposure over  
11 various numbers of lag days. Table 4.1-1 shows the results for the effect of a 20-ppb exposure to  
12 NO<sub>2</sub> on respiratory symptom according to genetic polymorphisms of GSTM1 and GSTP1. A  
13 small increase in breathing difficulty was observed with a 20-ppb increase in ambient NO<sub>2</sub> levels  
14 for all of the genotype groups across various numbers of lag days, though none of these  
15 associations was statistically significant. This suggests that ambient NO<sub>2</sub> concentrations may  
16 affect breathing in children regardless of their GSTM1 or GSTP1 genotypes. In contrast to O<sub>3</sub>,  
17 the GSTM1 positive and GSTP1 Ile/Ile and Ile/Val genotype children were more likely to  
18 experience cough and bronchodilator use in response to NO<sub>2</sub> than GSTM1 null and GSTP1  
19 Val/Val children. Contrary to expectations, a 20-ppb increase in ambient NO<sub>2</sub> concentrations  
20 was associated with a decrease in bronchodilator use among GSTP1 Val/Val genotype children.

21 A few studies of genotypes and respiratory health or general air pollution also have been  
22 conducted. Lee et al. (2004) studied ninth grade schoolchildren with asthma in Taiwan for a  
23 gene-environmental interaction between GSTP1105 genotypes and outdoor pollution. While  
24 noting mean NO<sub>2</sub> levels of 41.2 ppb from 1994 to 2001, they examined general district air  
25 pollution levels of low, moderate, and high in the analysis and reported results suggested of such  
26 an interaction of asthma, genotype and air pollution. Gilliland et al. (2002) examined effects of  
27 GSTM1, GSTT1, and GSTP1 genotypes and acute respiratory illness, specifically respiratory  
28 illness related absences from school. The goal was to examine potential susceptibilities on this  
29 basis, but not specifically air pollutants. They concluded that fourth grade school children who  
30 inherited a GSTP1 Val105 variant allele had a decreased risk of respiratory illness related school  
31 absence, indicating that GSTP1 genotype influences the risk and/or severity of acute respiratory

1 infections in school-aged children. Gauderman et al. (2007) described a methodology that uses  
2 principal components (PC) analysis computed on single nucleotide polymorphisms (SNP)  
3 markers for testing association between a disease and a candidate gene. As an example, they  
4 evaluated subjects in the children's health study (CHS) looking at chronic bronchitis symptoms.  
5 The authors observed stronger evidence of an association using the PC approach ( $p = 0.044$ ) than  
6 using either a genotype-based ( $p = 0.13$ ) or haplotype-based ( $p = 0.052$ ) approach. This  
7 methodology may be applied to relationships in this and other databases to evaluate aspects of air  
8 pollutants such as  $\text{NO}_2$ . Khoury et al. (2005) states that while genomics is still in its infancy,  
9 opportunities exist for developing, testing, and applying the tools of genomics to public health  
10 research with possible environmental causes.

11 In summary,  $\text{NO}_2$ -related genetic effects have been presented primarily by Romieu et al.  
12 (2006) and indicate that asthmatic children with GSTM1 null and GSTP1 Val/Val genotypes  
13 appear to be more susceptible to developing respiratory symptoms related to  $\text{O}_3$ , but not  $\text{NO}_2$ ,  
14 concentrations. It was suggested that ambient  $\text{NO}_2$  concentrations may affect breathing in  
15 children regardless of their GSTM1 or GSTP1 genotypes. In contrast to  $\text{O}_3$ , the GSTM1 positive  
16 and GSTP1 Ile/Ile and Ile/Val genotype children were more likely to experience cough and  
17 bronchodilator use in response to  $\text{NO}_2$  than GSTM1 null and GSTP1 Val/Val children.  
18 Contrary to expectations, a 20-ppb increase in ambient  $\text{NO}_2$  concentrations was associated with a  
19 decrease in bronchodilator use among GSTP1 Val/Val genotype children. Understanding a basis  
20 for susceptibility to asthma, will facilitate improve the precision of future studies of air pollution  
21 and health.

22

#### 23 **4.1.5 Vulnerability Related to Socioeconomic Status**

24 Finally, it is possible that individuals with lower socioeconomic status be more  
25 vulnerable to the effects of exposure to  $\text{NO}_2$ . There are a range of potential factors that would  
26 cause increased vulnerability, including reduced access to health care or living in areas with  
27 increased emissions, such as near major sources or roadways. However, the evidence  
28 specifically related to vulnerability is sparse. In one new study, Clougherty et al. (2007)  
29 evaluated the synergistic effects of traffic related air pollutants, including  $\text{NO}_2$ , and the  
30 synergistic effects between social and physical factors in asthma, e.g. stress, violence. The  
31 authors reported an elevated risk of asthma with a 4.3 ppb increase in  $\text{NO}_2$  exposure solely

1 among children with above-median exposure to violence in their neighborhoods, an indicator of  
2 lower socioeconomic status.

## 3 4 5 **4.2 PUBLIC HEALTH IMPACTS**

6 Exposure to ambient NO<sub>x</sub> (primarily NO<sub>2</sub> studied) is associated with a variety of health  
7 outcomes. In protecting public health, a distinction must be made between health effects that are  
8 considered “adverse” and those that are not. What constitutes an adverse health effect varies for  
9 different population groups, with some changes in healthy individuals not being viewed as  
10 adverse but those of similar type and magnitude in other susceptible individuals with preexisting  
11 disease being seen as adverse.

### 12 13 **4.2.1 Concepts Related to Defining of Adverse Health Effects**

14 The American Thoracic Society (ATS) published an official statement on “What  
15 Constitutes an Adverse Health Effect of Air Pollution?” (ATS, 2000b). This statement updated  
16 guidance for defining adverse respiratory health effects published 15 years earlier (ATS, 1985).  
17 The 2000 update takes into account (1) new investigative approaches used to identify the effects  
18 of air pollution; (2) increased focus on quality of life measures more sophisticated considerations  
19 of risks, particularly to susceptible groups; and (3) exposure to air pollution that increases the  
20 risk of an adverse effect to the entire population is viewed as adverse, even though it may not  
21 increase the risk of any identifiable individual to an unacceptable level. For example, if the risk  
22 distribution for asthmatics is shifted toward increased risks, this is considered adverse even if  
23 this shift does not result in clinically observable effects at the lower end of the distribution,  
24 because individuals within the population would have diminished reserve function.

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

31 In an attempt to provide information useful in helping to define adverse health effects  
32 associated with ambient NO<sub>2</sub> exposure by describing the gradation of severity and adversity of

1 respiratory related NO<sub>2</sub> effects, and those definitions are presented here as Tables 4.1-2 and  
2 4.1-3. The severity of effects described in those tables and the approaches taken to define their  
3 relative adversity are adapted from the ATS statements (ATS, 1985, 2000).

4 As assessed in detail in earlier chapters of this document and briefly recapitulated in  
5 preceding sections of this chapter, exposures to a range of NO<sub>2</sub> concentrations have been  
6 reported to be associated with increasing severity of several categories of health effects.

## 7 8 **4.2.2 Estimation of Potential Numbers of Persons in At-Risk Susceptible** 9 **Population Groups in the United States**

### 10 11 **4.2.2.1 Asthma**

12 A recent CDC report (CDC, 2005) on the prevalence of asthma in the United States,  
13 states that the burden of asthma has increased over the past two decades. It is known that a  
14 complex set of factors influence asthma; it is not clear what factors are driving this increase in  
15 prevalence. In 1982, roughly 4% of people younger than 18 years old had asthma. Asthma is  
16 the most prevalent chronic disease among children, and is the number one reason for school  
17 absences. By 1994, this rate had increased to almost 7%, or approximately five million people  
18 under the age of 18. Furthermore, from 1982 through 1994, the overall annual age-adjusted  
19 prevalence rate of asthma for people younger than 18 years old increased by 72%. In 2005,  
20 approximately 22.2 million (or 7.7% of the population) currently had asthma. The incidence was  
21 higher among children (8.9% of children) compared to adults (7.2% of adults.) Prevalence also  
22 is higher among certain ethnic or racial groups, such as Puerto Ricans, American Indians, Alaska  
23 Natives, and African Americans. The asthma prevalence rate for black Americans in 1992 was  
24 just under 6%, representing almost two million people with asthma. The prevalence rate among  
25 white was about 5%, which translates to approximately 12 million people. Gender and age is  
26 also a determinant of prevalence, with adult females having a 40% higher prevalence rate than  
27 adult males, and boys having a 30% higher rate than girls. Additionally a recent study,  
28 Clougherty et al. (2007) evaluated the synergistic effects of traffic relate air pollutants, including  
29 NO<sub>2</sub>, and the synergistic effects between social and physical factors in asthma, e.g. stress,  
30 violence. The difference in prevalence among races may be related to differences in such things  
31 as socioeconomic status, living conditions, diet, and allergen exposures.



1 **4.2.2.2 Heart Disease and Stroke**

2 Heart disease is the leading cause of death in the United States, while death from stroke  
3 ranks third. Survey results published by Centers for Disease Control and Prevention (CDC,  
4 2007 a,b) provide estimates of the prevalence of persons living with heart disease and stroke.  
5 The data used for the analyses was from the 2005 Behavioral Risk Factor Surveillance System  
6 (BRFSS). A random selection of the civilian population aged 18 years or more (n = 356,112)  
7 participated in the survey. Participants were asked if a doctor or other health professional had  
8 ever told them that they had a “heart attack, also called a myocardial infarction,” “angina or  
9 coronary heart disease,” or “stroke.” Differences in prevalence were assessed by age,  
10 race/ethnicity/ sex, education, and state or territory of residence. Approximately 6.5%  
11 (13.6 million people, based on Census 2000 data) of respondents reported a history of MI, angina  
12 or coronary heart disease (CHD). Men reported a higher prevalence of heart disease than  
13 women, and prevalence increased with age. Heart disease decreased with higher education, and  
14 American Indians/Alaska natives and multiracial persons had substantially higher prevalence of  
15 history of heart disease. The prevalence of heart disease also varied depending on state of  
16 residence, with persons from West Virginia reporting the highest prevalence of heart disease.  
17 Approximately 2.6% of participants reported a history of stroke (approximately 5.4 million  
18 people, based on census 2000 data). Again, the prevalence of stroke increased with age, male  
19 gender, and lower educational attainment. American Indians and Alaska natives reported a  
20 higher prevalence of stroke. In addition, residents for southern state reported a higher prevalence  
21 of history of stroke. Approximately 35 million people (12.4%) are above the age of 65 in the  
22 United States (Census 2000). Together, American Indians, Alaska Natives, and multiracial  
23 persons represent approximately 7.2 million people (2.5% of the U.S. population).

**TABLE 4.1. NO<sub>2</sub> EXPOSURE AFFECTS ASTHMATICS**

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An intervention study (Pilotto et al., 2004) of respiratory symptoms of asthmatic children in Australia resulted in reductions in several symptoms (difficulty in breathing during the day and at night, chest tightness during the day and at night, and asthma attacks during the day) related to reduction in NO<sub>2</sub> exposure from in-class heaters. Information on other heater emissions, such as ultrafine particles, was not reported.

Birth cohort studies in the United States (Belanger et al., 2006; Van Strein et al., 2004) and Europe (Brauer et al., 2007) relate NO<sub>2</sub> concentrations to increased respiratory symptoms, infections, and asthma in the very young.

In England, Chauhan et al. (2003) and Linaker et al. (2000) studied personal NO<sub>2</sub> exposure and found NO<sub>2</sub> 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 viruses, RSV and a picorna virus, individually.

Nitschke et al. (2006) reported difficulty breathing and chest tightness associated with 10 ppb increases in NO<sub>2</sub> measured in school classrooms. Lung function tests were performed at the beginning and at the end of the study period, and the authors observed personal NO<sub>2</sub> exposures related in a dose-response manner for reported symptoms in asthmatics.

United States multicity studies of ambient NO<sub>2</sub> exposure examined respiratory symptoms in asthmatics (Mortimer et al., 2002; Schildcrout et al., 2006). In the NCICAS (Mortimer et al., 2002) the greatest effect was seen for morning symptoms (cough, wheeze, shortness of breath) for a 6-day-morning average. In multi-pollutant models, the NO<sub>2</sub> effect was attenuated though remained positive, for O<sub>3</sub>, SO<sub>2</sub>, and combined coarse and fine particulate matter (PM<sub>10</sub>). In the CAMP study (Schildcrout et al., 2006), the strongest association between NO<sub>2</sub> and increased risk of cough and increased use of rescue medication was found for a 2-day lag, which was not attenuated, in two-pollutant models for CO, PM<sub>10</sub>, or SO<sub>2</sub>. Single city panel studies in the Los Angeles area are supportive of these associations for asthmatics (Ostro et al., 2001; Delfino et al., 2002, 2003a,b). Segala et al. (1998) and Just et al. (2002), in Paris both found positive relationships to NO<sub>2</sub> exposure and symptoms in asthmatics.

Few studies of the impact of NO<sub>2</sub> on respiratory symptoms of *adult* asthmatics are available. These find positive associations for NO<sub>2</sub> exposure and respiratory symptoms in European studies (Hiltermann et al., 1998; Von Klot et al., 2002; and Forseberg et al., 1998).

The associations between ambient concentrations of NO<sub>2</sub> and ER visits for asthma in the United States are positive (Jaffe et al., 2003; Peel et al., 2005; Tolbert et al., 2000). Studies conducted outside the United States (Castellsague et al., 1995; Sunyer et al., 1997; Atkinson et al., 1999a,b; Tenias et al., 1998; Erbas et al., 2005) found similar results. A concentration response for NO<sub>2</sub> and asthma ER visits is indicated in these studies (Jaffe et al., 2003; Tenias et al., 1998; Castellsague et al., 1995).

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**TABLE 4.1 (cont'd). NO<sub>2</sub> EXPOSURE AFFECTS ASTHMATICS**

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In relation to *long-term* exposure, Moseler (1994) examined a cohort in Germany and reported decrements in lung function parameters related to NO<sub>2</sub> exposure measures in a group of physician-diagnosed asthmatic children.

The relationship between *long-term* NO<sub>2</sub> exposure and asthma prevalence and incidence has been examined in several studies. In the CHS, Gauderman et al. (2005) report a positive relationship. Further, Islam et al. (2007) studied the CHS cohort to determine whether lung function is associated with new onset asthma. A positive relationship was seen for NO<sub>2</sub> exposure, which was marginally significant while indications for PM were significant. In a separate cohort in the Netherlands, Brauer et al. (2007) provide confirming evidence for this relationship.

Acute mortality related to asthma was examined in Barcelona, Spain (Saez et al., 1999; Sunyer et al., 2002). In the study by Sunyer et al. (2002), severe asthmatics with more than one asthma emergency visit were found to have the strongest mortality associations with NO<sub>2</sub>.

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**TABLE 4.1-1. EFFECT OF NITROGEN DIOXIDE (20 PPB) ON THE RISK OF REPORTING RESPIRATORY SYMPTOMS AND BRONCHODILATOR USE ON A GIVEN DAY ACCORDING TO GSTM1 OR GSTP1 GENOTYPES AMONG 151 ASTHMATIC CHILDREN IN MEXICO CITY**

	<b>GSTM1 positive OR (95% CI)</b>	<b>GSTM1 null OR (95% CI)</b>	<b>GSTP1 Ile/Ile Ile/Val OR (95% CI)</b>	<b>GSTP1 Val/Val OR (95% CI)</b>
<b>Cough</b>				
NO <sub>2</sub> 1 day lag	1.03 (1.00, 1.06)	1.01 (0.97, 1.05)	1.04 (1.01, 1.07)	1.00 (0.96, 1.03)
NO <sub>2</sub> 2 day avg	1.05 (1.01, 1.09)	1.00 (0.96, 1.05)	1.05 (1.02, 1.09)	0.99 (0.95, 1.04)
NO <sub>2</sub> 6 day avg	1.12 (1.07, 1.17)	1.06 (1.00, 1.13)	1.12 (1.07, 1.17)	1.05 (0.99, 1.12)
<b>Difficulty breathing</b>				
NO <sub>2</sub> 1 day lag	1.04 (0.98, 1.10)	1.01 (0.95, 1.07)	1.03 (0.98, 1.07)	1.03 (0.94, 1.13)
NO <sub>2</sub> 2 day avg	1.03 (0.97, 1.10)	1.02 (0.95, 1.10)	1.03 (0.98, 1.09)	1.04 (0.93, 1.16)
NO <sub>2</sub> 6 day avg	1.07 (0.98, 1.17)	1.02 (0.93, 1.12)	1.06 (0.99, 1.13)	1.04 (0.90, 1.20)
<b>Bronchodilator use</b>				
NO <sub>2</sub> 1 day lag	1.02 (0.99, 1.05)	0.97 (0.94, 1.00)	1.02 (0.99, 1.05)	0.96 (0.93, 1.00)
NO <sub>2</sub> 2 day avg	1.03 (1.00, 1.07)	0.96 (0.93, 1.00)	1.03 (0.99, 1.06)	0.96 (0.92, 1.00)
NO <sub>2</sub> 6 day avg	1.06 (1.01, 1.11)	0.96 (0.91, 1.00)	1.05 (1.01, 1.09)	0.96 (0.90, 1.01)

ORs are calculated using GEE models for logistic regression adjusting for asthma severity, previous day temperature, environmental tobacco smoke exposure, chronological time, and supplementation group. Changes in symptoms are shown for an increase of 20 ppb in 1 h nitrogen dioxide (NO<sub>2</sub>) maximum over different averages.

Source: Romieu et al. (2006).

**TABLE 4.1-2. GRADATION OF INDIVIDUAL RESPONSES TO SHORT-TERM NO<sub>2</sub> EXPOSURE IN HEALTHY PERSONS<sup>a</sup>**

<b>Symptomatic Response</b>	<b>Normal</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
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
<b>Functional Response</b>	<b>None</b>	<b>Small</b>	<b>Moderate</b>	<b>Large</b>
FEV <sub>1</sub>	Within normal range (± 3%)	Decrements of 3 to ≤10%	Decrements of >10 but <20%	Decrements of ≥20%
Nonspecific bronchial responsiveness	Within normal range	Increases of <100%	Increases of ≤300%	Increases of >300%
Duration of response	None	<4 h	>4 h but ≤24 h	>24 h
<b>Impact of Responses</b>	<b>Normal</b>	<b>Normal</b>	<b>Mild</b>	<b>Moderate</b>
Interference with normal activity	None	None	A few sensitive individuals choose to limit activity	Many sensitive individuals choose to limit activity

An increase in nonspecific bronchial responsiveness of 100% is equivalent to a 50% decrease in PD<sub>20</sub> or PD<sub>100</sub>.

**TABLE 4.1-3. GRADATION OF INDIVIDUAL RESPONSES TO SHORT-TERM NO<sub>2</sub> EXPOSURE IN PERSONS WITH IMPAIRED RESPIRATORY SYSTEMS**

<b>Symptomatic Response</b>	<b>Normal</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
Wheeze	None	With otherwise normal breathing	With shortness of breath	Persistent with shortness of breath
Cough	Infrequent cough	Cough with deep breath	Frequent spontaneous cough	Persistent uncontrollable cough
Chest pain	None	Discomfort just noticeable on exercise or deep breath	Marked discomfort on exercise or deep breath	Severe discomfort on exercise or deep breath
Duration of response	None	<4 h	>4 h, but ≤24 h	>24 h
<b>Functional Response</b>	<b>None</b>	<b>Small</b>	<b>Moderate</b>	<b>Large</b>
FEV <sub>1</sub> change	Decrements of <3%	Decrements of 3 to ≤10%	Decrements of >10 but <20%	Decrements of ≥20%
Nonspecific bronchial responsiveness	Within normal range	Increases of <100%	Increases of ≤300%	Increases of >300%
Airways resistance (SRaw)	Within normal range (± 20%)	SRaw increased <100%	SRaw increased up to 200% or up to 15 cm H <sub>2</sub> O·s	SRaw increased >200% or more than 15 cm H <sub>2</sub> O·s
Duration of response	None	<4 h	>4 h but ≤24 h	>24 h
<b>Impact of Responses</b>	<b>Normal</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
Interference with normal activity	None	Few individuals choose to limit activity	Many individuals choose to limit activity	Most individuals choose to limit activity
Medical treatment	No change	Normal medication as needed	Increased frequency of medication use or additional medication	Physician or emergency room visit

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

# 5. FINDINGS AND CONCLUSIONS

## 5.1 INTRODUCTION

The previous chapters have presented the most policy-relevant science, integrated across disciplines, as it pertains to oxides of nitrogen. The goal of this chapter is to summarize key findings and draw conclusions from this information. Sections of this chapter are as follows: (1) this introduction, (2) atmospheric sciences, (3) exposure assessment, (4) NO<sub>2</sub> exposure indices, (5) a summary of health effects, and (6) conclusions.

It will be useful at the outset to distinguish between the definitions of “nitrogen oxides” as it appears in the enabling legislation related to the NAAQS and the definition commonly used in the air pollution research and management community. In this document, the terms “oxides of nitrogen” and “nitrogen oxides” refer to all forms of oxidized nitrogen compounds, including NO, NO<sub>2</sub>, and all other oxidized nitrogen-containing compounds transformed from NO and NO<sub>2</sub>. 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 community, the terms “oxides of nitrogen” and “nitrogen oxides” are restricted to refer only to the sum of NO and NO<sub>2</sub>, and this sum is commonly abbreviated as NO<sub>x</sub>. 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<sub>y</sub>.

For the current review, multiple species of many nitrogen oxides are considered as appropriate and as allowed by the available data. For example, descriptions of the atmospheric chemistry of nitrogen oxides include both gaseous and particulate species, because a meaningful analysis would not be possible otherwise. In addition, the health effects of gaseous nitrogen oxides other than NO<sub>2</sub> are evaluated when information on these other species is available. Finally, the possible influence of other atmospheric pollutants on the interpretation of the role of NO<sub>2</sub> in health effects studies is considered, including interactions of NO<sub>2</sub> with other pollutants that co-occur in the environment (e.g., SO<sub>2</sub>, CO, O<sub>3</sub>, particulate matter). The available database for this draft ISA largely provides information on the health effects of NO<sub>2</sub>, with limited information examining other forms of oxides of nitrogen (e.g., HONO). Thus, the review

1 examines a large NO<sub>2</sub> database along with other studies of other gaseous oxides of nitrogen, as  
2 available.

3  
4

## 5 **5.2 ATMOSPHERIC SCIENCES**

6 Atmospheric sciences and exposure assessment are key elements in the causal chain  
7 linking pollutant sources to health effects. Atmospheric chemical processes involving NO<sub>2</sub> result  
8 in the formation of photochemical oxidants such as O<sub>3</sub> and PAN and precursors to acid aerosol  
9 formation such as the strong acid, mutagenic nitro-PAHs and other potentially toxic compounds.  
10 Key findings related to measuring such compounds are listed below.

- 11 • The current method of determining ambient NO<sub>x</sub> (i.e., NO + NO<sub>2</sub>) and then reporting  
12 NO<sub>2</sub> concentrations by subtraction of NO is subject to interference by NO<sub>x</sub> oxidation  
13 products (NO<sub>z</sub>), chiefly HNO<sub>3</sub> and PAN at levels that are largely uncharacterized and  
14 highly variable. Limited evidence suggests that these compounds result in an  
15 overestimate of NO<sub>2</sub> levels by roughly 20 to 25% at typical ambient levels. Smaller  
16 errors are estimated to occur in measurements taken nearer to strong NO<sub>x</sub> sources since  
17 most of the mass emitted as NO<sub>x</sub> would not yet have been further oxidized to NO<sub>z</sub>.  
18 Relatively larger errors, then, appear in locations more distant from strong local NO<sub>x</sub>  
19 sources.
- 20 • Techniques for measuring NO<sub>2</sub> more selectively than the FRM generally involve  
21 expensive and complex systems. As an example, NO<sub>2</sub> could be photolytically reduced to  
22 NO before detection by chemiluminescence in existing networks to eliminate the NO<sub>z</sub>  
23 interference; however, this technique requires further development to ensure its reliability  
24 and cost effectiveness for extensive field deployment.
- 25 • A measurement of total oxidized nitrogen compounds, i.e., the sum of NO, NO<sub>2</sub>, and all  
26 their reaction products, defined as NO<sub>y</sub>, would provide a more physically meaningful  
27 measurement of oxidized nitrogen than do measurements of NO<sub>x</sub> and NO<sub>2</sub> as reported  
28 currently.
- 29 • Existing NO<sub>x</sub> monitors could be converted to NO<sub>y</sub> monitors with relatively  
30 straightforward modifications. However, NO<sub>y</sub> monitors can be subject to relatively  
31 minor positive artifacts from particulate nitrate compounds, and, like the FRM NO<sub>x</sub>



1 monitors, to positive interference by reduced nitrogen compounds if the converter  
2 temperature is not carefully controlled.

- 3 • Because motor vehicles are a large source of urban NO<sub>2</sub>, ambient NO<sub>2</sub> generally behaves  
4 much like a traffic-generated pollutant in urban areas. It is associated with other traffic-  
5 generated pollutants such as CO at ambient levels and shows spatial and temporal  
6 variability consistent with other traffic-generated pollutants.
- 7 • Nitro-PAHs, which are responsible for most of the mutagenicity associated with ambient  
8 PAH samples and other potentially toxic compounds are emitted both directly from  
9 automobile tailpipes and by other NO<sub>x</sub> sources and also are formed secondarily from  
10 atmospheric reactions of NO<sub>2</sub>.
- 11 • Annual average concentrations of NO<sub>2</sub> (~15 ppb) are well below the level of the current  
12 NAAQS (53 ppb). However, daily maximum 1-h average concentrations can be greater  
13 than 100 ppb in a few locations, such as those heavily influenced by traffic.
- 14 • Policy Relevant Background Concentrations of NO<sub>2</sub> are much lower than average  
15 ambient concentrations and are typically less than 0.1 ppb over most of the United States,  
16 with highest values found in agricultural areas.
- 17 • Measurements of NO<sub>y</sub> have the additional benefit of characterizing the entire suite of  
18 oxidized nitrogen compounds in ambient air to which people are exposed.

### 19 20 21 **5.3 EXPOSURE ASSESSMENT**

22 In assessing human exposures to NO<sub>2</sub>, recall that people are exposed to the entire suite of  
23 oxidized nitrogen compounds that are characterized by NO<sub>y</sub> and not just to NO<sub>2</sub> or NO<sub>x</sub>. The  
24 amount of time a person spends in different microenvironments and the infiltration  
25 characteristics of these microenvironments are strong determinants of the association between  
26 ambient NO<sub>2</sub> concentrations and human exposures. In addition to ambient NO<sub>2</sub>, people are also  
27 exposed to NO<sub>2</sub> produced by indoor sources such as gas stoves, to NO<sub>2</sub> and other products of  
28 indoor air reactions, and to NO<sub>2</sub> in vehicles while commuting. Key findings related to assessing  
29 NO<sub>2</sub> exposures are listed below.

- 30 • Spatially, NO<sub>2</sub> is highly variable in urban areas, potentially leading to exposure error  
31 resulting from either a lack of correlation or differences in levels between a central

1 monitoring site and the community average. Intersite correlations for NO<sub>2</sub> concentrations  
2 range from slightly negative to highly positive. The range of spatial variation in NO<sub>2</sub>  
3 concentrations is similar to that for O<sub>3</sub>, but larger than that of PM<sub>2.5</sub>. Twenty-four-hour  
4 concentration differences between individual paired sites in an MSA can be larger than  
5 the annual means at these sites.

- 6 • Rooftop NO<sub>2</sub> measurements, particularly in inner cities, likely underestimate levels  
7 occurring at or near the earth's surface closer to the vehicle emitters.
- 8 • Methods for measuring personal NO<sub>2</sub> generally correlate well with ambient methods in  
9 collocated samples, but they tend to be biased high relative to reported ambient  
10 measurements and are subject to artifacts.
- 11 • In the absence of indoor sources, indoor NO<sub>2</sub> levels are about one-half those found  
12 outdoors. In the presence of indoor sources, particularly unvented combustion sources,  
13 NO<sub>2</sub> levels can be much higher than reported ambient concentrations.
- 14 • Alpha ( $\alpha$ ), the fraction of the ambient NO<sub>2</sub> concentration that contributes to a person's  
15 exposure to ambient NO<sub>2</sub> ranged from ~0.3 to ~0.6 in studies where examined.
- 16 • Indoor exposures to NO<sub>2</sub> are accompanied by exposures to other products of indoor  
17 combustion and to products of NO<sub>2</sub> chemistry occurring indoors and outdoors, such as  
18 HONO.
- 19 • The evidence relating ambient levels to personal exposures is mixed. Most of the  
20 longitudinal studies examined found that ambient levels of NO<sub>2</sub> were reliable proxies of  
21 personal exposures to NO<sub>2</sub>. However, a number of studies found no significant  
22 associations between ambient and personal levels of NO<sub>2</sub>. The differences in study  
23 results are related in large measure to differences in study design, to the spatial  
24 heterogeneity of NO<sub>2</sub> in study areas, to the presence of indoor sources, to seasonal and  
25 geographic differences in the infiltration of ambient NO<sub>2</sub>, and to differences in the time  
26 spent in different microenvironments. Measurement artifacts and differences in  
27 analytical measurement capabilities could also have contributed to the mixed results.
- 28 • The collective variability in all of the above parameters, in general, contributes to  
29 exposure misclassification errors in air pollution-health outcome studies.
- 30 • A few European studies in which community averages of personal exposures were  
31 compared to either ambient or outdoor concentrations support the assumption that

1 ambient concentrations are a reasonable surrogate for community average exposures in  
2 epidemiological studies.

3 The available data are limited, but suggest that the regulatory ambient monitors provide  
4 reasonable proxies for personal exposures to NO<sub>2</sub>. At the same time, variable, positive artifacts  
5 associated with measuring NO<sub>2</sub> using the Federal Reference Method severely limit its ability to  
6 serve as a precise indicator of NO<sub>2</sub> concentrations at typical ambient levels generally  
7 encountered outside of urban cores. Within the urban core, where many of the regulatory  
8 monitors are sited close to strong NO<sub>x</sub> sources such as traffic, the positive artifacts are much  
9 smaller on a relative basis, and the measurement is more precise. Importantly, because the  
10 nitrogen species that introduce the positive artifacts in the FRM NO<sub>2</sub> measurement are present in  
11 ambient air, these artifacts introduce the same error into epidemiological studies. To alleviate  
12 these problems and provide a better understanding of the relationships between nitrogen oxides  
13 and health outcomes, it may be appropriate either to adopt a different indicator for the mixture of  
14 nitrogen oxides, such as NO<sub>y</sub>-NO, or to actively aid continued development of the more specific  
15 techniques for measuring NO<sub>2</sub> with the goal of replacing the current FRM method in the  
16 networks.

#### 17 18 19 **5.4 NO<sub>2</sub> EXPOSURE INDICES**

20 The available NO<sub>2</sub> indices used to indicate short-term ambient NO<sub>2</sub> exposure are daily  
21 maximum 1-h (1-h max); 24-h average; and 2-week average NO<sub>2</sub> concentrations. New data on  
22 short-term exposures have been published since the 1993 AQCD for Oxides of Nitrogen. Some  
23 studies examined only one index, and these studies form an evidence base for that individual  
24 index. A few studies used both 1-h and 24-h data and, thus, allow a comparison of these  
25 averaging periods. These include studies of respiratory symptoms, ED visits for asthma, hospital  
26 admissions for asthma, and mortality.

- 27 • Meta-analysis regression results for asthma ED visits comparing effect estimates for the  
28 1-h and 24-h time periods indicate that effect estimates are slightly, but not significantly,  
29 larger with a 24-h average compared with a 1-h max NO<sub>2</sub>.
- 30 • Experimental studies in both animals and humans provided evidence that short-term NO<sub>2</sub>  
31 exposure (i.e., <1 h to 2–3 h) can result in respiratory effects such as increased airways  
32 responsiveness or inflammation thereby increasing the potential for exacerbation of

1 asthma. These findings generally support epidemiological evidence on short-term  
2 exposures, but do not provide evidence that distinguishes effects for one short-term  
3 averaging period from another.

- 4 • Based on these findings, we have concluded that differences between 1-h and 24-h  
5 exposures are unlikely for several health outcomes.

## 6 7 8 **5.5 HEALTH EFFECTS**

### 9 10 **5.5.1 The 1993 AQCD Findings**

11 The 1993 AQCD for Oxides of Nitrogen found that there were two key health effects of  
12 greatest concern at ambient or near-ambient concentrations of NO<sub>2</sub>: (1) increases in airways  
13 responsiveness of asthmatic individuals after short-term exposures and (2) increased occurrence  
14 of respiratory illness among children associated with longer-term exposures to NO<sub>2</sub>. Evidence  
15 also was found for increased risk of emphysema, but this appeared to be of major concern only  
16 with exposures to levels of NO<sub>2</sub> much higher than current ambient levels of NO<sub>2</sub> (U.S.  
17 Environmental Protection Agency, 1993). The evidence regarding airways responsiveness was  
18 drawn from controlled human exposure and animal toxicological studies showing both airways  
19 responsiveness and lung function changes, though there was a lack of a concentration-response  
20 relationship. Epidemiological studies reported increased respiratory symptoms with increased  
21 indoor NO<sub>2</sub> exposures, and animal toxicological findings of lung host defense system changes  
22 with NO<sub>2</sub> exposure provided a biologically plausible basis for these results. Subpopulations  
23 considered potentially more susceptible to the effects of NO<sub>2</sub> exposure included persons with  
24 preexisting respiratory disease, children, and the elderly. In the 1993 AQCD, the  
25 epidemiological evidence for respiratory health effects was limited, and no studies had  
26 considered effects such as hospital admissions, ED visits, or mortality.

### 27 28 **5.5.2 New Findings**

29 New evidence developed since 1993 has generally confirmed and extended the  
30 conclusions articulated in the 1993 AQCD. Since the 1993 AQCD, the epidemiological  
31 evidence has grown substantially, including new field or panel studies on respiratory health  
32 outcomes, numerous time-series epidemiological studies of effects such as hospital admissions,

1 and a substantial number of studies evaluating mortality risk with short-term NO<sub>2</sub> exposures. As  
2 noted above, no epidemiological studies were available in 1993 that assessed relationships  
3 between oxides of nitrogen and outcomes such as hospital admissions, ED visits, or mortality; in  
4 contrast, there are now dozens of epidemiological studies on such outcomes included in this  
5 evaluation. Several new studies have reported findings from prospective cohort studies on  
6 respiratory health effects with long-term NO<sub>2</sub> exposure. Significant new evidence characterizing  
7 the responses of susceptible and vulnerable populations also has developed since 1993,  
8 particularly concerning children, asthmatics, and those living and working near roadways. While  
9 not as marked as the growth in the epidemiological literature, a number of new toxicological and  
10 controlled human exposure studies provide further insights into relationships between NO<sub>2</sub> and  
11 health effects.

12 In the following subsections, we build upon previous chapters to draw conclusions  
13 regarding the overall strength of the evidence and extent to which causal inferences may be  
14 made. Where the associations observed in epidemiological and experimental studies are strong,  
15 consistent, coherent, and plausible, we have concluded that the relationship is “likely causal.”  
16 Where the epidemiological or clinical findings are generally strong and consistent, but the  
17 available experimental evidence is too limited to draw conclusions regarding coherence or  
18 plausibility of the results, we have concluded that this relationship is “suggestive.” In some  
19 situations, the evidence from epidemiological and experimental studies is not found to be strong  
20 or consistent, and there is limited or no support for coherence and plausibility; these relationships  
21 we judge to be “inconclusive.” Where possible, we have also included observations about the  
22 concentrations at which effects have been observed. A series of tables at the end of this chapter  
23 provide specific information supporting these conclusions. Table 5.5-1 summarizes the key  
24 findings of controlled human exposure studies, and the exposure levels at which those effects  
25 have been observed. Table 5.5-2 summarizes the lowest levels at which effects have been seen  
26 in toxicological studies for a series of effect categories. Table 5.5-3 presents results of  
27 epidemiological studies on respiratory health effects, and it includes information about the  
28 distribution of NO<sub>2</sub> levels used in the study as presented in the study publications (generally  
29 provided as mean and range).

30

### 1 **5.5.2.1 Respiratory Health Effects and Short-Term Exposure to NO<sub>2</sub>**

2 Taken together, recent studies provide strong scientific evidence that NO<sub>2</sub> is associated  
3 with a range of respiratory effects and describe a likely causal relationship between short-term  
4 NO<sub>2</sub> exposure and adverse effects on the respiratory system. This is based on findings from  
5 numerous new epidemiological studies, including multipollutant studies that control for the  
6 effects of other pollutants. This conclusion is supported by evidence from toxicological and  
7 controlled human exposure studies. A number of studies have been conducted in areas where the  
8 full distribution of ambient 24-h average NO<sub>2</sub> concentrations was below the current annual-  
9 average NAAQS level of 53 ppb (see data in Tables 5.5-3A and 5.5-3B). Key findings related to  
10 assessing NO<sub>2</sub> associated health effects are listed below.

- 11 • The strongest new epidemiological evidence exists for associations with increased ED  
12 visits and hospital admissions for respiratory causes, especially asthma and COPD, with  
13 ambient concentrations of NO<sub>2</sub>. In nearly all of these studies, high correlations were  
14 found between ambient measures of NO<sub>2</sub> and of CO and PM. The effect estimates for  
15 NO<sub>2</sub> were robust after the inclusion of CO and PM in multipollutant models. Significant  
16 associations have been reported in some studies conducted in areas such as Vancouver,  
17 Canada, where daily NO<sub>2</sub> concentrations were all below the level of the current annual  
18 NAAQS.
- 19 • Results from recent field and panel studies confirm previous studies that short-term NO<sub>2</sub>  
20 exposure is associated with increased respiratory symptoms (e.g., cough, wheeze),  
21 particularly in children and asthmatics. Few recent epidemiological evaluations of lung  
22 function measures such as FEV<sub>1</sub>, and PEF exist, providing only limited new evidence for  
23 pulmonary effects of NO<sub>2</sub> exposure.
- 24 • Recent studies reporting associations between indoor and personal exposure to NO<sub>2</sub> and  
25 respiratory symptoms or lung function provide key support for epidemiological findings  
26 of associations with NO<sub>2</sub> concentrations (e.g., Pilotto et al., 2004, Chauhan et al., 2004).  
27 In particular, the Pilotto et al. (2004) intervention study provides strong evidence of a  
28 detrimental effect with exposure to NO<sub>2</sub>.
- 29 • A recent epidemiological study (Chauhan et al., 2003) provided evidence that increased  
30 personal exposures to NO<sub>2</sub> worsen virus-associated symptoms and lung function in

1 children with asthma. The limited evidence from controlled human exposure studies  
2 indicates that NO<sub>2</sub> may increase susceptibility to injury by subsequent viral challenge.

- 3 • Controlled human exposure studies provide strong evidence in asthmatics for increased  
4 airways responsiveness to bronchoconstricting agents with short-term exposure to 0.2 to  
5 0.3 ppm NO<sub>2</sub>. The clinical significance of increased airways reactivity is the potential for  
6 a flare-up or exacerbation of asthma or other underlying pulmonary disease following  
7 increased bronchial response to nonspecific airborne irritants. These studies do not  
8 provide compelling evidence for other respiratory effects such as changes in lung  
9 function. Toxicological studies have shown that lung host defenses are sensitive to NO<sub>2</sub>  
10 exposure, with numerous measures of such effects observed at concentrations below  
11 1 ppm.
- 12 • Biological markers of inflammation are reported in antioxidant-deficient laboratory  
13 animals with exposures to 0.4-ppm NO<sub>2</sub>. Normal animals do not respond until exposed  
14 to much higher levels, i.e., ≥5 ppm NO<sub>2</sub>. Recent epidemiological studies provide  
15 somewhat mixed evidence on short-term exposure to NO<sub>2</sub> and inflammatory responses in  
16 the airways. Controlled human exposure studies provide evidence for increased airways  
17 inflammation at NO<sub>2</sub> concentrations of <2.0 ppm; the onset of inflammatory responses in  
18 healthy subjects appears to be between 100 and 200 ppm-min, i.e., 1 ppm for 2 to 3 h.

### 19 **5.5.2.2 Cardiovascular Effects and Short-Term Exposure to NO<sub>2</sub>**

20 Overall, the evidence is inconclusive regarding the effect of NO<sub>2</sub> on the CV system.

- 21 • Numerous epidemiological studies report an association of NO<sub>2</sub> with hospital admissions  
22 or ED visits for CVD (MI and CHF in particular). However, PM and other ambient air  
23 pollutants were also associated with hospitalizations. Further, results from multipollutant  
24 models were inconsistent, with no clear pattern emerging to suggest that the NO<sub>2</sub>  
25 associations observed were robust.
- 26 • Epidemiological evidence from studies of HRV and cardiac rhythm disorders provide  
27 limited evidence of associations with NO<sub>2</sub>. The parameters measured in these studies  
28 were associated most strongly with PM compared to other ambient pollutants, so the  
29 effects observed for NO<sub>2</sub> may have been confounded. Furthermore, a study of  
30

1 repolarization changes found no association between NO<sub>2</sub> and the outcomes measured,  
2 while an effect for PM was observed.

- 3 • The limited evidence from controlled human exposure studies suggests a reduction in  
4 hemoglobin with NO<sub>2</sub> exposure may occur at concentrations between 1.0 and 2.0 ppm  
5 (with 3-h exposures), but the observations require confirmation. The results on the effect  
6 of NO<sub>2</sub> on various hematological parameters in animals are inconsistent and, thus,  
7 provide little biological plausibility for effects on the CV system.

### 8 9 **5.5.2.3 Mortality and Short-Term Exposure to NO<sub>2</sub>**

- 10 • Epidemiological evidence is suggestive of associations between NO<sub>2</sub> and nonaccidental  
11 and cardiopulmonary-related mortality, but additional research is needed to establish  
12 underlying mechanisms by which such effects occur.
- 13 • Results from several large U.S. and European multicity studies and a meta-analysis study  
14 observed positive associations between ambient NO<sub>2</sub> concentrations and risk of all-cause  
15 (nonaccidental) mortality, with effect estimates ranging from 0.5 to 3.6% excess risk in  
16 mortality. In general, the effect estimates were robust to adjustment for copollutants.
- 17 • Both CV and respiratory mortality have been associated with increased NO<sub>2</sub>  
18 concentrations in epidemiological studies; however, similar associations were observed  
19 for other pollutants, including PM and SO<sub>2</sub>.
- 20 • Clinical studies showing hematologic effects (noted above) and animal toxicological  
21 studies showing biochemical, lung host defense, permeability, and inflammation changes  
22 with short-term exposures to NO<sub>2</sub> provide limited evidence of plausible pathways by  
23 which risks of morbidity and, potentially, mortality may be increased, but no coherent  
24 picture is evident at this time.
- 25 • While NO<sub>2</sub> exposure, alone or in conjunction with other pollutants, may contribute to  
26 increased mortality, evaluation of the specificity of this effect is difficult. Limited  
27 experimental evidence exists to prohibits considering biological plausibility at this time,  
28 and the range of mortality risk estimates is smaller than that for other pollutants such as  
29 PM. It is possible that NO<sub>2</sub> is acting as a marker for another pollutants or traffic-related  
30 mixtures.



#### 1 5.5.2.4 Morbidity and Long-Term Exposure to NO<sub>2</sub>

2 The available epidemiological and toxicological data provide *suggestive* evidence that  
3 long-term exposure to NO<sub>2</sub> affects respiratory health.

- 4 • A number of epidemiological studies examined the effects of long-term exposure to NO<sub>2</sub>  
5 and observed associations with decrements in lung function, and partially irreversible  
6 decrements in lung function growth. In one analysis, results were similar for boys  
7 compared to girls and among children who did not have a history of asthma: clinically  
8 significant differences in lung function remained at age 18. These studies, however, are  
9 confounded by other ambient pollutants. In particular, associations are also found for PM  
10 and proximity to traffic (<500 m). As shown in Table 5.5-3C, the mean NO<sub>2</sub>  
11 concentrations in these studies range from 21.5 to 34.6 ppb; thus, all have been conducted  
12 in areas where NO<sub>2</sub> levels are below the level of the NAAQS (53 ppb, annual average).
- 13 • A limited number of epidemiological studies examined the effects of long-term exposure  
14 to NO<sub>2</sub> and observed associations with increases in asthma prevalence. However,  
15 potential confounding by other ambient pollutants introduces uncertainty.
- 16 • Animal toxicological studies demonstrate that exposure to NO<sub>2</sub> results in morphological  
17 changes in the centriacinar region of the lung and in bronchiolar epithelial proliferation,  
18 which may provide biological plausibility for the observed increased incidence of  
19 respiratory illness.
- 20 • Two epidemiological studies conducted in Europe showed an association between long-  
21 term NO<sub>2</sub> exposure and cancer incidence, although animal studies have provided no clear  
22 evidence that NO<sub>2</sub> acts as a carcinogen. There are no in vivo studies suggesting that NO<sub>2</sub>  
23 causes malignant tumors and no evidence of mutagenicity. Substantial evidence exists  
24 that nitro-PAHs are formed via combination of NO<sub>x</sub> and other air pollutants, though  
25 many of these are found in the particulate phase. The PAHs are considered to be known  
26 human carcinogens, and nitration of PAHs is thought to increase carcinogenic potential.
- 27 • No studies have been conducted on potential CV effects of long-term exposure to oxides  
28 of nitrogen.
- 29 • Epidemiological evidence is weak for associations between NO<sub>2</sub> exposure and  
30 intrauterine growth retardation and preterm delivery. Limited toxicological evidence  
31 suggests a weak association between NO<sub>2</sub> exposure and adverse birth outcomes and

1 provides little mechanistic information or biological plausibility for the epidemiological  
2 findings.

#### 3 4 **5.5.2.5 Mortality and Long-Term Exposure to NO<sub>2</sub>**

5 Results from the few available epidemiological studies are inconclusive regarding the  
6 association between long-term exposure to NO<sub>2</sub> and mortality.

- 7 • A limited number of epidemiological studies have investigated the effect of long-term  
8 exposure to NO<sub>2</sub> on mortality. In general, inconsistent associations were observed across  
9 study locations and cause-specific mortality outcomes.
- 10 • Multipollutant analyses were usually not conducted, but studies indicated high  
11 correlations between NO<sub>2</sub> and PM indices ( $r \sim 0.8$ ).

#### 12 13 **5.5.2.6 Concentration-Response Relationships and Thresholds**

14 An important consideration in characterizing the public health impacts associated with  
15 NO<sub>2</sub> exposure is whether the concentration-response relationship is linear across the full  
16 concentration range that is encountered or if nonlinear departures exist along any part of this  
17 range. Of particular interest is the shape of the concentration-response curve at and below the  
18 level of the current annual average standard of 53 ppb (0.053 ppm).

19 Identifying possible “thresholds” in air pollution epidemiological studies is problematic.  
20 Various factors tend to linearize the concentration-response relationships, obscuring any  
21 thresholds that may exist. Exposure measurement error, response measurement error, and low  
22 data density in the lower concentration range are some factors that complicate determining the  
23 shape of the concentration-response curve. Biological characteristics tending to linearize  
24 concentration-response relationships include interindividual variation in susceptibility to health  
25 effects, additivity of pollutant-induced effects to the naturally occurring background disease  
26 processes, and the extent to which health effects are due to other environmental insults having a  
27 mode of action similar to that of NO<sub>2</sub>. Additionally, if the concentration-response relationship is  
28 shallow, identification of any threshold that may exist will be more difficult.

29 The slope of the NO<sub>2</sub> concentration-response relationship has been explored in several  
30 studies. To examine the shape of the concentration-response relationship between NO<sub>2</sub> and daily  
31 physician consultations for asthma and lower respiratory disease in children, Hajat et al. (1999)  
32 used bubble plots to examine residuals of significant models plotted against moving averages of

1 NO<sub>2</sub> concentration. They noted a weak trend for asthma and 0-1 day moving average of NO<sub>2</sub>  
2 and suggested that effects are weaker at low concentrations and stronger at higher concentrations  
3 than predicted by the linear model. These departures are in accord with the sigmoidal dose-  
4 response models. A number of epidemiological studies have reported no evidence for nonlinear  
5 relationships or a threshold response in relationships between NO<sub>2</sub> and mortality or morbidity.  
6 One multicity time-series study (Samoli et al., 2006) examined the relationship between  
7 mortality and NO<sub>2</sub> in 29 European cities. There was no indication of a response threshold, and  
8 the concentration-response curves were consistent with a linear relationship. Kim et al. (2004b)  
9 investigated the presence of a threshold in relationships between air pollutants and mortality in  
10 Seoul, Korea, by analyzing data using a log-linear GAM (linear model), a cubic natural spline  
11 model (nonlinear model), and a B-mode splined model (threshold model). The 24-h average  
12 NO<sub>2</sub> level was 32.5 ppb (SD 10.3); there was no evidence that NO<sub>2</sub> had a nonlinear association  
13 with mortality. Burnett et al. (1997a) used the LOESS smoothing method to present  
14 nonparametric concentration-response curves for respiratory and cardiac hospitalizations. These  
15 smoothed curves did not have significant departures from the linear model. One problem with  
16 this approach is that the LOESS smoothed curve may lack biological rationale. Burnett et al.  
17 (1997b) tested for nonlinearity by testing the significance of the quadratic term in a study of  
18 hospital admissions for respiratory diseases and reported no evidence for nonlinearity for the  
19 association with NO<sub>2</sub>.

20 In studies that have specifically examined concentration-response relationships between  
21 NO<sub>2</sub> and health outcomes, there is little evidence of an effect threshold. Factors that make  
22 difficult identification of any threshold that may exist are noted above.

23

#### 24 **5.5.2.7 Susceptible and Vulnerable Populations**

25 Several susceptible subpopulations can be identified.

- 26 • Based on both short- and long-term studies of an array of respiratory and cardiac health  
27 effects data, asthmatics and persons with preexisting cardiopulmonary conditions are at  
28 greater risk from ambient NO<sub>2</sub> exposures than the general public, with the most extensive  
29 evidence available for asthmatics as a potentially susceptible group. In addition, studies  
30 suggest that upper respiratory viral infections can trigger susceptibility to the effects of  
31 exposure to NO<sub>2</sub>.

- 1 • There is supporting evidence of age-related differences in susceptibility to NO<sub>2</sub> health  
2 effects such that the elderly population (>65 years of age) appears to be at increased risk  
3 of mortality and hospitalizations and that children (<18 years of age) experience other  
4 potentially adverse respiratory health outcomes with increased NO<sub>2</sub> exposure.
- 5 • People with occupations that require them to be in or close to traffic or roadways (i.e.,  
6 bus and taxi drivers, highway patrol officers) may have enhanced exposure to NO<sub>2</sub>  
7 compared to the general population, possibly increasing their vulnerability. Limited  
8 studies, however, provide no evidence that they are more susceptible to the effects of  
9 NO<sub>2</sub> than the general population.
- 10 • In addition to observed increases in NO<sub>2</sub>-exposure-related illnesses, a general shift of the  
11 population response distribution towards greater sensitivity to illness is anticipated. This  
12 shift, in itself is considered adverse.

## 13 14 15 **5.6 CONCLUSIONS**

16 New evidence confirms previous findings in the 1993 AQCD that short-term NO<sub>2</sub>  
17 exposure is associated with increased airways responsiveness, often accompanied by respiratory  
18 symptoms, particularly in children and asthmatics. Additionally, the new body of  
19 epidemiological data provides strong evidence of associations with increased ED visits and  
20 hospital admissions for respiratory causes, especially asthma and COPD, and short-term ambient  
21 exposure to NO<sub>2</sub>. These new findings are based on numerous studies, including panel and field  
22 studies, multipollutant studies that control for the effects of other pollutants, and studies  
23 conducted in areas where the full distribution of ambient 24-h average NO<sub>2</sub> concentrations was  
24 below the current NAAQS of 53 ppb (see data in Table 5.5-3A and 5.5-3B). These conclusions  
25 are supported by evidence from toxicological and controlled human exposure studies.  
26 Individually and together, these data sets form a plausible, consistent, and coherent description of  
27 a relationship between NO<sub>2</sub> exposures and an array of adverse health effects that range from the  
28 onset of respiratory symptoms to hospital admission.

29 It is difficult to determine from these new studies if NO<sub>2</sub> is the causal agent or if NO<sub>2</sub> is a  
30 marker for the effects of another traffic-related pollutant or mix of pollutants (see Chapter 2 and  
31 Section 5.4 for more details on exposure issues). To understand the relationship of NO<sub>2</sub> and  
32 impacts on public health with more certainty, one must turn to other lines of evidence.

1           Other evidence of the effects of NO<sub>2</sub> comes from personal exposure studies of indoor  
2 sources and from clinical and animal studies. Recent studies reporting associations between  
3 personal exposure to NO<sub>2</sub> indoor sources and respiratory symptoms provide key support for  
4 epidemiological findings of associations with ambient NO<sub>2</sub> concentrations. In particular, an  
5 intervention study (Pilotto et al., 2004) provides strong evidence of a detrimental effect on  
6 asthmatic children of exposure to NO<sub>2</sub> from indoor sources. Additionally, a complex set of  
7 recent controlled human exposure studies provides good evidence for increased airways  
8 responsiveness to allergen-induced inflammation and allergen-induced bronchoconstriction  
9 following short-term exposure to levels of NO<sub>2</sub> in the range of 0.26 ppm. The significance of  
10 increased airways responsiveness is the potential for exacerbation of asthma. Increases in  
11 biological markers of inflammation are also reported in antioxidant-deficient laboratory animals  
12 exposed to 0.4-ppm NO<sub>2</sub>; however, it is not clear how these antioxidant-deficient laboratory  
13 animals differ from humans.

14           An argument can be made that NO<sub>2</sub> exacerbates the response to allergen challenge and  
15 worsens virus-associated symptoms in asthmatic children, although data to support this argument  
16 is more limited. A recent epidemiological study (Chauhan et al., 2003) provided evidence that  
17 an increased personal exposure to NO<sub>2</sub> worsens virus-associated symptoms and lung function in  
18 children with asthma. Controlled human exposure studies of healthy adults, conducted at higher  
19 than ambient concentrations, also provide limited evidence that NO<sub>2</sub> may increase inflammation  
20 and increase susceptibility to injury associated with subsequent viral challenge.

21           Lastly, but importantly, large, well-conducted prospective studies provide strong  
22 evidence of partially irreversible decreased lung function growth and lung function capacity  
23 among children with long-term exposure to NO<sub>2</sub> and/or traffic. These studies do not suggest that  
24 NO<sub>2</sub> alone is responsible for these deficits. Chronic animal toxicological studies, at higher than  
25 ambient exposure concentrations, demonstrate that exposure to NO<sub>2</sub> results in morphological  
26 changes in the centriacinar region of the lung and bronchiolar epithelial proliferation and provide  
27 biological plausibility for the lung function growth decrements observed in children.

28           Integrating across the epidemiological, clinical, and animal evidence presented above, we  
29 find that it is plausible, consistent, and coherent that current ambient NO<sub>2</sub> exposures directly  
30 result in adverse impacts to public health at concentrations below the current NAAQS for NO<sub>2</sub>.  
31 In particular, a set of coherent and plausible respiratory health outcomes indicative of

1 exacerbated asthma are associated with NO<sub>2</sub> exposures: increase airways hyperresponsiveness,  
2 inflammation, impair host defense, a progression of respiratory symptoms, worsened virus  
3 infections, emergency room visits, and hospital admission. Additionally, evidence is suggestive  
4 of potentially permanent decreased lung function capacity and increased mortality.

5         The evidence presented in Chapters 2, 3, and 4 also leads us to conclude that NO<sub>2</sub> can be  
6 expected to be an indicator of the effects of traffic-related pollutants. Furthermore, since it  
7 well known that traffic-related pollutants other than NO<sub>2</sub> produce adverse effects on public  
8 health, it is reasonable to conclude that the impact of multiple pollutant mixtures on public health  
9 produce greater impacts on public health than would be expected from NO<sub>2</sub> alone.

**TABLE 5.5-1. KEY HUMAN HEALTH EFFECTS OF EXPOSURE TO NITROGEN DIOXIDE—CLINICAL STUDIES<sup>a</sup>**

<b>NO<sub>2</sub> (ppm) (Exposure Duration)</b>	<b>Observed Effects</b>	<b>References</b>
0.26 (0.5 h)	Asthmatics exposed to NO <sub>2</sub> during rest experienced enhanced sensitivity to allergen-induced decrements in lung function and increase the allergen-induced airways inflammatory response. Inflammatory response to allergen observed in the absence of allergen-induced lung function response. No NO <sub>2</sub> -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 <sub>2</sub> 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) exposures conditions.	Folinsbee (1992)
0.3-0.4 (2-4 h)	Inconsistent effects on FVC and FEV <sub>1</sub> 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 <sub>1</sub> reported for asthmatics.	Azadniv et al. (1998) Blomberg et al. (1997, 1999) Devlin et al. (1999) Frampton et al. (2002) Jorres 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<sub>2</sub> = Nitrogen dioxide

FEV<sub>1</sub> = Functional expiratory volume in 1 s.

FVC = Forced vital capacity.

COPD = Chronic obstructive pulmonary disease.

**TABLE 5.5-2. SUMMARY OF TOXICOLOGICAL EFFECTS FROM NO<sub>2</sub> EXPOSURE  
(LOEL BASED ON CATEGORY)**

<b>Concentration (ppm)</b>	<b>Exposure Duration</b>	<b>Species</b>	<b>Effect</b>	<b>Category</b>	<b>Reference</b>
0.2	From conception to 12 wks post delivery	Rats	Increase in BALF lymphocytes	Inflammation	Kume and Arakawa (2006)
0.5	Weanling period (from 5 wks old to 12 wks)	Rats	Suppression of ROS	Lung host defense	Kume 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)



**TABLE 5.5-3A. EFFECTS OF SHORT-TERM NO<sub>2</sub> EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA**

Reference, Study Location, and Period	Study Population	Averaging time, Mean (SD) NO <sub>2</sub> Levels (ppb)	Statistics for NO <sub>2</sub> 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: NO <sub>2</sub> alone: 61.3% (8.2, 143.4) NO <sub>2</sub> + PM <sub>10</sub> : 36.9% (-11.6, 113.2) NO <sub>2</sub> + O <sub>3</sub> : 61.3% (8.2, 140.3) NO <sub>2</sub> + SO <sub>2</sub> : 18.8% (-11.6, 69.0)
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 %PEFR NO <sub>2</sub> alone: 48% (2, 116) NO <sub>2</sub> + O <sub>3</sub> : 40% (-7, 109) NO <sub>2</sub> + O <sub>3</sub> + SO <sub>2</sub> : 31% (-13, 109) NO <sub>2</sub> + O <sub>3</sub> + SO <sub>2</sub> + PM <sub>10</sub> : 45% (-37, 234)
Schilderout 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: NO <sub>2</sub> alone: 4.0% (1.0, 7.0) NO <sub>2</sub> + CO: 4.0% (0.0, 8.0) NO <sub>2</sub> + PM <sub>10</sub> : 4.0% (0.0, 7.0) NO <sub>2</sub> + SO <sub>2</sub> : 4.0% (-1.0, 8.0) Rescue inhaler use: NO <sub>2</sub> alone: 3.0% (1.0, 5.0) NO <sub>2</sub> + CO: 4.0% (0.0, 7.0) NO <sub>2</sub> + PM <sub>10</sub> : 2.0% (0.0, 5.0) NO <sub>2</sub> + SO <sub>2</sub> : 3.0% (-2.0, 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 5.5-3A (cont'd). EFFECTS OF SHORT-TERM NO<sub>2</sub> EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA**

Reference, Study Location, and Period	Study Population	Averaging time, Mean (SD) NO <sub>2</sub> Levels (ppb)	Statistics for NO <sub>2</sub> 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 <sub>2</sub> 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)
Silkoff et al. (2005) Denver, CO, United States Winters of 1999-2000 and 2000-2001	34 subjects with advanced COPD (≥40 yrs), with a history of more than 10 pack-yrs of tobacco use, airflow limitation with FEV <sub>1</sub> of <70% of predicted value, and FEV <sub>1</sub> /FVC ratio of less than 60%	1999-2000 24-h avg: 16 (17) 2000-2001 24-h avg: 29 (11)	NR	NR	1999-2000: 0, 54 2000-2001: 6, 54	FEV <sub>1</sub> change: 1999-2000 AM, lag 0: 0.012 (-0.001, 0.026) AM, lag 1: 0.022 (0.013, 0.035) AM, lag 2: 0.015 (0.006, 0.028) PM, lag 0: 0.014 (0.001, 0.030) PM, lag 1: 0.013 (-0.002, 0.028) PM, lag 2: 0.011 (-0.005, 0.025) 2000-2001 AM, lag 0: -0.005 (-0.021, 0.018) AM, lag 1: -0.011 (-0.032, 0.008) AM, lag 2: 0.010 (-0.008, 0.024) PM, lag 0: -0.004 (-0.017, 0.006) PM, lag 1: -0.004 (-0.017, 0.006) PM, lag 2: -0.006 (-0.019, 0.003) PEF change:

**TABLE 5.5-3A (cont'd). EFFECTS OF SHORT-TERM NO<sub>2</sub> EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA**

Reference, Study Location, and Period	Study Population	Averaging time, Mean (SD) NO <sub>2</sub> Levels (ppb)	Statistics for NO <sub>2</sub> Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Silkoff (cont'd) et al. (2005) Denver, CO, United States Winters of 1999-2000 and 2000-2001						AM, lag 0: 2.0 (-1.5, 4.0) AM, lag 1: 5.1 (2.5, 7.3) AM, lag 2: 4.0 (1.8, 7.0) PM, lag 0: 2.4 (-1.0, 5.0) PM, lag 1: 2.3 (-1.1, 4.9) PM, lag 2: 2.2 (-1.2, 4.8) 2000-2001 AM, lag 0: -4.9 (-8.0, -2.0) AM, lag 1: -4.7 (-7.8, -0.3) AM, lag 2: 0.8 (-2.0, 4.5) PM, lag 0: -0.5 (-2.7, 2.0) PM, lag 1: -0.8 (-3.0, 1.6) PM, lag 2: -1.3 (-3.3, 0.2)
Gilliand et al. (2001) 200-mile radius of Los Angeles, CA, United States Jan-June 1996	Cohort of 4th grade school children (9-10 yrs) (n = 2,081)	24-h avg 10.9	NR	NR	NR	School absenteeism: All absences: 6.9% (-51.8, 137.2) Non-illness absences: 81.2% (-67.5, 376.1) All illness absences: -9.0% (-66.9, 149.0) Nonrespiratory illness: -61.1% (-90.7, 71.1) Respiratory illness: 43.0% (-59.3, 403.6) URI: -14.3% (-51.4, 51.3) LRI (wet cough): -60.9% (-93.6, 123.2) LRI (wet cough/wheeze or asthma): 10.5% (-91.2, 672.8)
Adamkiewicz et al. (2004) Steubenville, OH. United States Sep-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 (-0.35, 1.41)

**TABLE 5.5-3A (cont'd). EFFECTS OF SHORT-TERM NO<sub>2</sub> EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA**

Reference, Study Location, and Period	Study Population	Averaging time, Mean (SD) NO <sub>2</sub> Levels (ppb)	Statistics for NO <sub>2</sub> Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Rondeau et al. (2005) 200-mile radius of Los Angeles, CA, United States Jan-June 1996	Cohort of 4th grade school children (9-10 yrs) (n = 1,932)	24-h avg: 5-45	NR	NR	NR	School absenteeism: All absences, 5 lag days: -10.6% (-21.0, 1.2) All absences, 15 lag days: -25.4% (-37.3, -11.3) All absences, 30 lag days: -13.2% (-29.0, 5.9) All illness absences, 5 lag days: -9.4% (-15.5, -2.6) All illness absences, 15 lag days: -16.3% (-38.3, 13.4) All illness absences, 30 lag days: -10.4% (-23.5, 33.6) Respiratory illness absences, 5 lag days: 2.8% (-12.2, 35.7) Respiratory illness absences, 15 lag days: -20.3% (-30.0, 16.9) Respiratory illness absences, 30 lag days: -23.8% (-53.9, 25.9)
Linn et al. (1996) Los Angeles, CA, United States 1992-1994	269 school children (during 4th and 5th grade school yrs)	24-h avg: 33 (22)	NR	NR	1, 96	Total symptom score: Previous 24-h, am score: -18.2% (-47.3, 27.1) Current 24-h, pm score: -42.9% (-65.4, -5.9)

\* 24-h avg NO<sub>2</sub> standardized to 20 ppb increment; 1-h max NO<sub>2</sub> standardized to 30 ppb increment

NR = Not reported

**TABLE 5.5-3B. EFFECTS OF SHORT-TERM NO<sub>2</sub> 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 <sub>2</sub> Levels (ppb)	Statistics for NO <sub>2</sub> Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
<b>EMERGENCY DEPARTMENT VISITS—ALL RESPIRATORY</b>						
Peel et al. (2005) Atlanta, GA, United States Jan 1993-Aug 2000	484,830 ER visits, all ages from 31 hospitals	1-h max: 45.9 (17.3)	NR	NR	NR	1.024 (1.009, 1.041)
Stieb* et al. (2000) Saint John, New Brunswick, Canada Jul 1992-Mar 1996	19,821 ER visits	24-h avg: 8.9	NR	NR	0, 82	-14.70%
<b>EMERGENCY DEPARTMENT VISITS—ASTHMA</b>						
Jaffe et al. (2003) 2 cities, Ohio, United States, (Cleveland, Cincinnati) Jul 91-Jun 96	4,416 ER 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 ER 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)	ER visits for asthma	1-h max: 69 (28)	NR	NR	29, 150	48%
Peel et al. (2005) Atlanta, GA, United States Jan 1993-Aug 2000	Asthma ER 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: 4.1% (0.8, 7.6)

**TABLE 5-3B (cont'd). EFFECTS OF SHORT-TERM NO<sub>2</sub> 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 <sub>2</sub> Levels (ppb)	Statistics for NO <sub>2</sub> Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
<b>EMERGENCY DEPARTMENT VISITS—ASTHMA (cont'd)</b>						
Tolbert et al. (2000) Atlanta, GA, United States, 1993-1995	5,934 ER visits for asthma, age 0-16	1-h max: 81.7 (53.8)	NR	NR	5.35, 306	0.7% (-0.8, 2.3)
Cassino* et al. (1999) New York City, NY, United States 1989-1993	1,115 ER 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 ER visits for asthma, ages 0-15, 15 + from 2 hospitals	1-h max: 25.2	NR	NR	0, 120	NO <sub>2</sub> + O <sub>3</sub> : -11%
<b>HOSPITAL ADMISSIONS—ALL RESPIRATORY</b>						
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 <sub>3</sub> , SO <sub>2</sub> and CoH -0.3% (-2.4%, 1.8%)

**TABLE 5-3B (cont'd). EFFECTS OF SHORT-TERM NO<sub>2</sub> 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 <sub>2</sub> Levels (ppb)	Statistics for NO <sub>2</sub> Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
<b>HOSPITAL ADMISSIONS - ALL RESPIRATORY (cont'd)</b>						
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% (11.2, 36.3) ≥65 yrs: 19.1% (7.4, 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 5-3B (cont'd). EFFECTS OF SHORT-TERM NO<sub>2</sub> 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 <sub>2</sub> Levels (ppb)	Statistics for NO <sub>2</sub> Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
<b>HOSPITAL ADMISSIONS - ASTHMA</b>						
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%
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%



**TABLE 5.5-3B (cont'd). EFFECTS OF SHORT-TERM NO<sub>2</sub> 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 <sub>2</sub> Levels (ppb)	Statistics for NO <sub>2</sub> Air Quality Data (ppb)			Standardized Percent Excess Risk (95% CI)
			98th %	99th %	Range	
<b>HOSPITAL ADMISSIONS – COPD</b>						
Moolgavkar (2000) Chicago, Los Angeles, Phoenix, United States 1987-1995	Hospital admissions	24-h avg: Chicago: 25; LA: 38; Phoenix: 19	NR	NR	NR	Chicago: 4.0% Los Angeles: 4.0% Phoenix: 9.0%
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	1.6% ± 0.8%
Yang (2005) Vancouver, BC, Canada, 1994-1998, Days: 1,826	COPD admissions among elderly (65+)	24-h avg: 17.03 (4.48)	NR	NR	4.28, 33.89	32.3% (7.5, 66.2)

\* 24-h avg NO<sub>2</sub> standardized to 20 ppb increment; 1-h max NO<sub>2</sub> standardized to 30 ppb increment

NR = Not reported

**TABLE 5.5-3C. EFFECTS OF LONG-TERM NO<sub>2</sub> EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA**

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO <sub>2</sub> Levels (ppb)	Statistics for NO <sub>2</sub> Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Gauderman et al. (2004) Southern California, United States 1993-2001	1,759 children followed from age 10-18	Annual avg: 34.6	NR	NR	NR	Difference in avg growth in lung function over eight yr study period from the least to most polluted community: FVC: -95.0 ml (-189.4, -0.6) FEV <sub>1</sub> : -101.4 (-164.5, -38.4) MMEF: -211.0 (-377.6, -44.4)
Peters et al. (1999) Southern California, United States 1993	3,293 public school students in grades 4, 7, and 10	24-h avg: 21.5	NR	NR	NR	Regression of pulmonary function tests on NO <sub>2</sub> concentrations (1986-1990): FVC: -42.6 (13.5) Males only: -27.6 (25.9) Females only: -58.5 (15.4) FEV <sub>1</sub> : -23.2 (12.5) Males only: -7.6 (22.1) Females only: -39.9 (13.9) PEFR: -19.0 (43.2) Males only: 48.0 (50.6) Females only: -109.2 (74.8) MMEF: -27.5 (21.7) Males only: 23.0 (27.6) Females only: -90.1 (36.1)  Regression of pulmonary function tests on NO <sub>2</sub> concentrations (1994): FVC: -46.2 (16.0) Males only: -29.9 (29.5) Females only: -63.8 (18.3) FEV <sub>1</sub> : -22.3 (14.8) Males only: -2.1 (25.1)

**TABLE 5.5-3C (cont'd). EFFECTS OF LONG-TERM NO<sub>2</sub> EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA**

Reference, Study Location, and Period	Study Population	Averaging time, Mean (SD) NO <sub>2</sub> Levels (ppb)	Statistics for NO <sub>2</sub> Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Peters et al. (1999) Southern California, United States 1993 (cont'd)						Females only: -44.1 (16.1) PEFR: -29.5 (48.5) Males only: 54.2 (57.3) Females only: -133.4 (83.1) MMEF: -32.9 (24.4) Males only: 30.0 (30.9) Females only: -109.5 (38.9)
Tager et al. (2005) Los Angeles and San Francisco, CA, United States 2000-2002	255 freshman undergraduates between 16-19 yrs old at UC-Berkeley with permanent residence in LA or SF	24-h avg: 28.5	NR	NR	8, 51	Sex-specific effects of estimated lifetime mean exposure to NO <sub>2</sub>  LnFEF75: Men: -0.029 (0.003) Women: -0.032 (0.002)
Millstein et al. (2004) 200 mile radius of Los Angeles 1995	Cohort of 4th grade children (age 9) that entered Children's Health Study in 1995	Monthly avg: NR	NR	NR	NR	Monthly prevalence of asthma medication use: OR: -10.3% (-44.9, 41.4) High time outdoors: -27.8% (-65.9, 51.7) Low time outdoors: -15.2% (-50.5, 43.4)
Kim et al. (2004) San Francisco, CA, United States 2001	1,109 children (grades 3-5) from neighborhoods that span a busy traffic corridor	Annual avg: 23.0	NR	NR	NR	Bronchitis: 5.7% (-2.8, 17.6) Asthma: 5.7% (-8.2, 20.7) Asthma (no outlier): 17.6% (-2.8, 40.4)

**TABLE 5.5-3C (cont'd). EFFECTS OF LONG-TERM NO<sub>2</sub> EXPOSURE ON RESPIRATORY OUTCOMES IN THE UNITED STATES AND CANADA**

Reference, Study Location, and Period	Study Population	Averaging Time, Mean (SD) NO <sub>2</sub> Levels (ppb)	Statistics for NO <sub>2</sub> Air Quality Data (ppb)			Standardized* Percent Excess Risk (95% CI)
			98th %	99th %	Range	
Gauderman et al. (2005) Southern California, United States 2000	208 children originally enrolled in Children's Health Study as 4th graders in 1993 or 1996	Monthly avg: 15.3-51.5	NR	NR	NR	Asthma: 188.7% (7.1, 773.8) Recent wheeze: 158.9% (12.6, 497.4) Recent wheeze with exercise: 240.3% (14.5, 902.2) Current asthma medication use: 295.6% (37.7, 1,043.3)

\* 24-h avg NO<sub>2</sub> standardized to 20 ppb increment; 1-h max NO<sub>2</sub> standardized to 30 ppb increment; monthly and yearly NO<sub>2</sub> avgs standardized to 10 ppb  
NR = Not reported

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