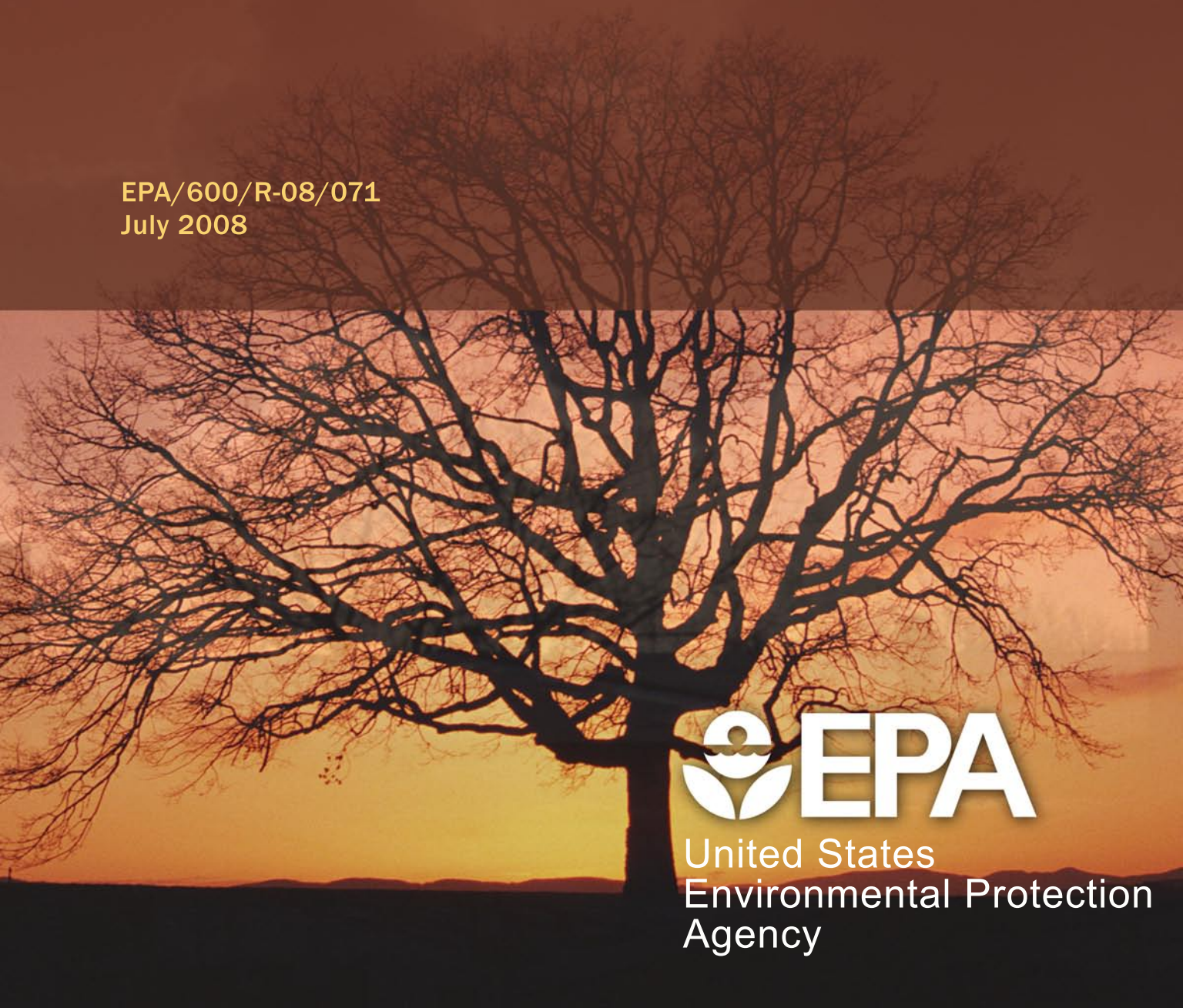
# Integrated Science Assessment for Oxides of Nitrogen — Health Criteria

EPA/600/R-08/071
July 2008



United States
Environmental Protection
Agency

July 2008
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# Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

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

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# Acronyms and Abbreviations

| | |
|---|---|
| 1NP | 1-nitropyrene |
| 2NF | 2-nitrofluoranthene |
| 2NP | 2-nitropyrene |
| α | Alpha |
| ACS | American Cancer Society |
| $a_i$ | air exchange rate (for microenvironment *i*) |
| AIRE | (Italian Study) Asma Infantile Ricerca in Emilia-Romagna |
| AM | alveolar macrophages |
| APEX | Air Pollution Exposure (model) |
| APHEA | Air Pollution on Health: a European Approach (study) |
| AQCD | Air Quality Criteria Document |
| AQS | EPA's Air Quality System |
| ATS | American Thoracic Society |
| β | beta; the calculated health effect parameter |
| BAL | bronchoalveolar lavage |
| BALF | bronchoalveolar lavage fluid |
| BHPN | *N*-bis (2-hydroxy-propyl) nitrosamine |
| BLF | bronchial lavage fluid |
| Br | bromide |
| BTEX | benzene, toluene, ethylbenzene, and o-, m-, p-xylene |
| C | carbon |
| CAA | Clean Air Act |
| CALINE4 | California line source dispersion (model) |
| CAMP | Childhood Asthma Management Program |
| CAP(s) | concentrated ambient particle(s) |
| CARB | California Air Resources Board |
| CASAC | Clean Air Scientific Advisory Committee |
| CASTNet | Clean Air Status and Trends Network |
| CDC | Centers for Disease Control and Prevention |
| CDPFs | catalyzed diesel particle filters |
| CFD | computational fluid dynamics |
| $CH_4$ | methane |
| CHAD | Consolidated Human Activities Database |
| CHF | congestive heart failure |
| CHS | Children's Health Study |
| CI | confidence interval |
| CMAQ | EPA's Community Multiscale Air Quality (CMAQ) model |
| CMSA | consolidated metropolitan statistical area |
| CO | carbon monoxide |
| $CO_2$ | carbon dioxide |

| | |
|---|---|
| COD | coefficient of divergence |
| CoH | coefficient of haze |
| COPD | chronic obstructive pulmonary disease |
| CRP | C-reactive protein |
| CTM | chemical transport model |
| CVD | cardiovascular disease |
| DEP | diesel exhaust particle |
| DEPcCBP | diesel exhaust particle extract-coated carbon black particles |
| DMA | dimethylamine |
| DMN | dimethylnitrosamine |
| DOAS | differential optical absorption spectroscopy |
| EC | elemental carbon |
| ECP | eosinophil cationic protein |
| ED | emergency department |
| ECG | electrocardiography; electrocardiogram |
| EGU(s) | electricity generating unit(s) |
| ELF | epithelial lining fluid |
| EPA | U.S. Environmental Protection Agency |
| EPO | eosinophil peroxidase |
| ETS | environmental tobacco smoke |
| FEF | forced expiratory flow |
| $FEF_{75}$ | forced expiratory flow after exhaling 75% of FVC |
| $FEF_{25-75}$ | average forced expiratory flow over middle 50% of FVC |
| FeNO | fractional exhaled NO |
| FEMs | Federal Equivalent Methods |
| $FEV_{0.5}$ | forced expiratory volume in 0.5 seconds |
| $FEV_1$ | forced expiratory volume in 1 second |
| $F_{inf_i}$ | infiltration factor (for microenvironment *i*) |
| FRM | Federal Reference Method |
| FVC | forced vital capacity |
| GAM | Generalized Additive Model(s) |
| GIS | Geographic Information System |
| GLM | Generalized Linear Model(s) |
| GSH | glutathione; reduced glutathione |
| GST | glutathione *S*-transferase (e.g., GSTM1, GSTP1, GSTT1) |
| $H^+$ | hydrogen ion |
| $H_2O$ | water |
| $H_2SO_4$ | sulfuric acid |
| HCHO | formaldehyde |
| HDL | high-density lipoprotein cholesterol |
| $HNO_3$ | nitric acid |
| HONO | nitrous acid |
| HR | heart rate |
| HRV | heart rate variability |

| | |
|---|---|
| HS | hemorrhagic stroke |
| $H_2S$ | hydrogen sulfide |
| $HSO_4^-$ | bisulfate ion |
| $H_2SO_4$ | sulfuric acid |
| h$\nu$ | solar ultraviolet photon |
| *i* | microenvironment |
| IARC | International Agency for Research on Cancer |
| ICAM-1 | intercellular adhesion molecule-1 |
| ICD9 | International Classification of Diseases, Ninth Revision |
| ICDs | implanted cardioverter defibrillators |
| Ig | immunoglobulin (e.g., IgA, IgE, IgG) |
| IHD | ischemic heart disease |
| IIASA | International Institute for Applied Systems Analysis |
| IL | interleukin (e.g., IL-4, IL-6, IL-8) |
| IOM | Institute of Medicine |
| IQR | interquartile range |
| IS | ischemic stroke |
| ISA | Integrated Science Assessment |
| ISAAC | International Study of Asthma and Allergies in Children |
| K | mass transfer coefficient |
| $k_i$ | decay rate (for microenvironment i) |
| KI | potassium iodide |
| LIF | laser induced fluorescence |
| LOESS | locally estimated smoothing splines |
| LRD | lower respiratory disease |
| $MEF_{25}$ | maximal expiratory flow at 25% |
| $MEF_{50}$ | maximal expiratory flow at 50% |
| MENTOR | Modeling Environment for Total Risk for One-Atmosphere |
| MI | myocardial infarction |
| MMEF | maximal midexpiratory flow |
| $MoO_X$ | molybdenum oxide |
| MOZART-2 | Model for Ozone and Related Chemical Tracers, version 2 |
| MPP | multiphase processes |
| MSA | metropolitan statistical area |
| N, n | number of observations |
| NAAQS | National Ambient Air Quality Standards |
| $NaAsO_2$ | sodium arsenite |
| NAL | inflammatory nasal lavage markers |
| NAMS | National Air Monitoring Stations |
| NAPAP | National Acid Precipitation Assessment Program |
| NAS | National Academy of Sciences |
| NCEA | National Center for Environmental Assessment |
| NCEP | National Center for Environmental Prediction |
| NCICAS | National Cooperative Inner-City Asthma Study |

| | |
|---|---|
| NDMA | *N*-nitrosodimethylamine |
| NEI | National Emissions Inventory |
| NERL | National Exposure Research Laboratory |
| NHAPS | National Human Activity Pattern Survey |
| nitro-PAHs | nitro-polycylic aromatic hydrocarbons |
| NK | natural killer cells |
| NLCS | Netherlands Cohort Study on Diet and Cancer |
| NMMAPS | National Morbidity, Mortality, and Air Pollution Study |
| NMOR | *N*-nitrosomorpholine |
| NN | nitronapthalene |
| NO | nitric oxide |
| $NO_2^-$ | nitrite |
| $NO_2$ | nitrogen dioxide |
| $NO_3^-$ | nitrate ion |
| $NO_3$ | nitrate radical |
| NOAA | National Oceanic and Atmospheric Administration |
| $NO_X$ | oxides of nitrogen |
| $NO_Y$ | total oxidized nitrogen |
| $NO_Z$ | oxidized *N* species |
| NR | not reported |
| NRC | National Research Council |
| NSA | nitrosating agent |
| $O_3$ | ozone |
| OAQPS | Office of Air Quality Planning and Standards |
| OC | organic carbon |
| OH | hydroxyl radical |
| OR | odds ratio |
| ORD | Office of Research and Development |
| OVA | ovalbumin |
| P, p | probability value |
| PAARC | Air Pollution and Chronic Respiratory Diseases (study) |
| PAF | paroxysmal atrial fibrillation |
| PAH(s) | polycyclic aromatic hydrocarbon(s) |
| PAMS | Photochemical Assessment Monitoring Stations |
| PAN(s) | peroxyacyl nitrate(s) |
| Pb | lead |
| PD20 | provocative dose that produces a 20% decrease in $FEV_1$ |
| PD100 | provocative dose that produces a 100% increase in sRAW |
| PEACE | Pollution Effects on Asthmatic Children in Europe (study) |
| PEF | peak expiratory flow |
| $P_i$ | penetration coefficient (for microenvironment *i*) |
| PIH | primary intracerebral hemorrhage |
| PM | particulate matter |

| | |
|---|---|
| $PM_{2.5}$ | particulate matter with 50% upper cut point aerodynamic diameter of 2.5 μm for sample collection; surrogate for fine PM |
| $PM_{10}$ | particulate matter with 50% upper cut point aerodynamic diameter of 10 μm for sample collection |
| $PM_{10-2.5}$ | particulate matter with 10 μm as upper cut point aerodynamic diameter and 2.5 μm as lower cut point for sample collection; surrogate for thoracic coarse PM (does not include fine PM) |
| PMN(s) | polymorphonuclear leukocyte(s) |
| $PNO_3^-$ | particulate nitrate |
| POM | particulate organic matter |
| ppb | parts per billion |
| ppm | parts per million |
| ppt | parts per trillion |
| PRB | policy-relevant background |
| PT | prothrombin time |
| PS | passive sample |
| R, r | correlation coefficient |
| RADS | reactive airway dysfunction syndrome |
| RAPS | (St. Louis) Regional Air Pollution Study |
| RCS | random component superposition (model) |
| $RONO_2$ | organic nitrates |
| RR | rate ratio; relative risk |
| RSV | respiratory syncytial virus |
| RTP | Research Triangle Park |
| SAPALDIA | Study of Air Pollution and Lung Diseases in Adults |
| SCC | Source Classification Codes |
| SCE(s) | sister chromatid exchange(s) |
| SD | standard deviation |
| SES | socioeconomic status |
| SHEDS | Simulation of Human Exposure and Dose System |
| SIDS | sudden infant death syndrome |
| SNP | single nucleotide polymorphism$^{35}$S sulfur-35 radionuclide |
| SLAMS | State and Local Air Monitoring Stations |
| SO | sulfur monoxide |
| $SO_2$ | sulfur dioxide |
| $SO_4^{2-}$ | sulfate ion |
| $SO_X$ | sulfur oxides |
| sRaw | specific airway resistance |
| STN | Speciation Trends Network |
| τ | tau; atmospheric lifetime |
| TEA | triethanolamine |
| TNF | tumor necrosis factor (e.g., TNF-α) |
| TSP | total suspended particles |
| UFP | Ultrafine particles (<100 nm) |
| URI | upper respiratory infections |

| | |
|---|---|
| UV | ultraviolet |
| VIII-C factor | Classic hemophilia A (factor VIII:C deficiency) |
| VOC(s) | volatile organic compound(s) |
| VWF | von Willibrand Factor |
| WBC | white blood cell |

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# Preface

National Ambient Air Quality Standards (NAAQS) are promulgated by the U.S. Environmental Protection Agency (EPA) to meet requirements set forth in Sections 108 and 109 of the Clean Air Act (CAA). These sections require the EPA Administrator (1) to list widespread air pollutants that reasonably may be expected to endanger public health or welfare; (2) to issue air quality criteria that assess the latest available scientific information on the nature and effects of ambient exposure to the criteria pollutants; (3) to set "primary" NAAQS to protect human health with adequate margin of safety and to set "secondary" NAAQS to protect against welfare effects (e.g., effects on vegetation, ecosystems, visibility, climate, manmade materials, etc); and (4) to periodically review and revise, as appropriate, the criteria and NAAQS for a given listed pollutant or class of pollutants.

The purpose of this Integrated Science Assessment (ISA) for Oxides of Nitrogen ($NO_X$) – Health Criteria is to critically evaluate and assess the latest scientific information published since the 1993 $NO_X$ Air Quality Criteria Document (AQCD), with the main focus on pertinent new information useful in evaluating health effects data associated with ambient air nitrogen oxides exposures. A First External Review Draft of this ISA (dated August 2007) was released for public comment and was reviewed by the Clean Air Scientific Advisory Committee (CASAC) in October 2007; a Second External Review Draft was made available to the public in March 2008. Public comments and CASAC recommendations have been taken into account in making revisions to the document for incorporation into this final ISA. This document will provide inputs to the risk and exposure analyses prepared by EPA's Office of Air Quality Planning and Standards (OAQPS), which will lead to the proposal and, ultimately, promulgation of decisions on potential retention or revision, as appropriate, of the current Nitrogen Dioxide ($NO_2$) NAAQS by the EPA Administrator.

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

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

## Legislative Requirements

Two sections of the CAA govern the establishment and revision of the 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."[1] 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."[2]

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

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

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

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

## History of Reviews of the Primary NAAQS for $NO_2$

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

[1] 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].

[2] 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."

On July 22, 1987, EPA announced it was undertaking plans to revise the 1982 $NO_X$ air quality criteria (Federal Register, 1987). In November 1991, EPA released an updated draft AQCD for CASAC and public review and comment (Federal Register, 1991). The draft document provided a comprehensive assessment of the available scientific and technical information on health and welfare effects associated with $NO_2$ and other oxides of nitrogen. 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 $NO_2$" (Wolff, 1993).

EPA prepared a draft Staff Paper that summarized and integrated the key studies and scientific evidence contained in the revised AQCD and identified the critical elements to be considered in the review of the $NO_2$ NAAQS. The 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, 1996). 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 $NO_2$ (Federal Register, 1995). The decision not to revise the $NO_2$ NAAQS was finalized after careful evaluation of the comments received on the proposal. The level for both the existing primary and secondary NAAQS for $NO_2$ is 0.053 ppm annual arithmetic average, calculated as the arithmetic mean of the 1-h $NO_2$ concentrations.

The current review was initiated on December 9, 2005 (70 FR 73236) with a request for submission of recent scientific information on specified topics. EPA's draft Integrated Review Plan for the Primary National Ambient Air Quality Standard for Nitrogen Dioxide was made available in February, 2007 for public comment and was discussed by the Clean Air Science Advisory Committee (CASAC) via a publicly accessible teleconference consultation on May 11, 2007 (72 FR 20336). The first external review draft of this ISA was released for public comment and review by CASAC on August 31, 2007 (72 FR 50107), and was reviewed by CASAC at a public meeting held on October 24-25, 2007. The second draft of this ISA was released for public comment and review by CASAC in March 2008 (73 FR 11916), and was reviewed by CASAC at a public meeting held on May 1-2, 2008.

# Chapter 1. Introduction

This concise evaluation and synthesis of the most policy-relevant science forms the scientific foundation for the review of the primary (health-based) NAAQS for nitrogen dioxide ($NO_2$) currently set at 0.053 ppm, annual average. Its intent is to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutant in ambient air" (Clean Air Act, Section 108, 2003).[1] Key information and judgments from the previous AQCDs for $NO_X$ are incorporated in this assessment. Details of the pertinent scientific literature published since the last review and selected older studies of particular interest are included in annexes.

The terms "oxides of nitrogen" or "nitrogen oxides" refer to all forms of oxidized nitrogen compounds, including nitric oxide (NO), $NO_2$, and all other oxidized nitrogen-containing compounds transformed from NO and $NO_2$ (defined further in Chapter 2, Section 2.1). Descriptions of the atmospheric chemistry of $NO_X$ include both gaseous and particulate species; a meaningful analysis would not be possible otherwise. Most studies on the health effects of gaseous $NO_X$ focus on $NO_2$; effects of other gaseous species are considered as information is available. The health effects of particulate $NO_X$ are included in the review of the NAAQS for particulate matter (PM). In evaluating the health evidence, possible influences of other co-occurring atmospheric pollutants such as PM, sulfur dioxide ($SO_2$), carbon monoxide (CO), and ozone ($O_3$) are considered.

The Integrated Plan for the Review of the Primary National Ambient Air Quality Standard for Nitrogen Dioxide (U.S. Environmental Protection Agency, 2007) identifies key policy-relevant questions which provide a framework for review of the scientific evidence. These questions are:

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

## 1.1. Document Development

The EPA initiated the current review of the $NO_2$ NAAQS in the Federal Register with a call for information (U.S. Environmental Protection Agency, 2005). Publications were identified through an extensive literature search process; additional publications were identified by EPA scientists in a variety of disciplines. In addition to peer-reviewed literature, previous EPA reports and materials obtained from scouring reference lists were examined. All relevant epidemiologic, human clinical, animal toxicological, and in vitro studies, including those related to exposure-response relationships, mechanism(s) of action,

[1]The secondary $NO_x$ NAAQS, in conjunction with a review of the secondary NAAQS for $SO_x$, is underway independently, as is a review of the primary NAAQS for $SO_x$ and a review of the primary and secondary effects of PM.

or susceptible subpopulations published since the last review were considered. In addition, EPA conducts analyses of air quality and emissions data, and evaluates studies on atmospheric chemistry, transport, and fate of these emissions, as well as issues related to exposure. Further information was acquired from consultation with content and area experts, CASAC and the public. Annex AX1 has more discussion of search strategies and considerations for study inclusion.

## 1.2. Document Organization

The ISA has five chapters. The introduction presents background information, discusses the ISA's purpose, search and study evaluation process, and sets the framework for causal determination. Chapter 2 highlights key concepts for understanding the atmospheric chemistry, sources, exposure, and dosimetry of $NO_X$, following a "source-to-exposure" paradigm. Chapter 3 evaluates and integrates epidemiologic, human clinical, and toxicological data as it pertains to review of the primary NAAQS. Chapter 4 deals with the public health impact of ambient $NO_X$ exposure, with an emphasis on susceptible and vulnerable population groups. Lastly, Chapter 5 summarizes key findings and conclusions from the atmospheric sciences, ambient air data analyses, exposure assessment, dosimetry, and health effects.

The annexes supplement the ISA with additional details from the recent literature, as well as selected older studies of particular interest. They contain information on:

- framework for causal determination (Annex 1);
- atmospheric chemistry of $NO_X$, sampling, and analytic methods (Annex 2);
- environmental concentrations and human exposure (Annex 3);
- toxicological studies of health effects in laboratory animals (Annex 4);
- human clinical studies of health effects related to short-term exposure (Annex 5); and
- epidemiologic studies of health effects from short- and long-term exposure (Annex 6).

## 1.3. EPA Framework for Causal Determinations

A consistent and transparent basis for evaluating the causal nature of air pollution-induced health effects is important. EPA's framework uses standardized language, drawing on other agencies and the scientific community, especially from the National Academy of Sciences (NAS) Institute of Medicine (IOM) document, *Improving the Presumptive Disability Decision-Making Process for Veterans* (Institute of Medicine, 2007).

This section:

- describes the type of scientific evidence used in establishing a causal relationship between exposure and health effects;
- defines cause, in contrast to statistical association;
- discusses the sources of evidence necessary to reach a conclusion about the existence of a causal relationship;
- highlights the issue of multifactorial causation;
- identifies issues and approaches related to uncertainty; and

- provides a framework for classifying and characterizing the weight of evidence in support of a general causal relationship.

Approaches to assessing the separate and combined lines of evidence (e.g., epidemiologic, animal toxicological, human clinical, and in vitro studies) have been formulated by a number of regulatory and science agencies in addition to the IOM, including the International Agency for Research on Cancer (IARC, 2006), EPA Guidelines for Carcinogen Risk Assessment (U.S. Environmental Protection Agency, 2005), Centers for Disease Control and Prevention (2004), and the National Acid Precipitation Assessment Program (NAPAP, 1991). (See Annex AX1 for excerpts from these documents.) These approaches are similar in nature, although adapted to different purposes, and have proven effective in providing a uniform structure and language for causal determinations, and support decision-making under conditions of uncertainty.

## 1.3.1. Scientific Evidence Used in Establishing Causality

The most compelling evidence of a causal relationship between pollutant exposure and health effects comes from human clinical studies, which evaluate health effects of administered exposure under controlled laboratory conditions.

In epidemiologic or observational studies of humans, the investigator does not control exposure or intervene with the study population. Observational studies can describe associations between exposure and effect; study designs include cross-sectional, case-control, cohort, time-series, and panel studies. "Natural experiments" occur occasionally, and compare health effects before and after an exposure change, such as closure or elimination of a pollution source. They can provide compelling evidence of causality.

Experimental animal data complement clinical and observational data. These studies help characterize effects of concern, exposure-response relationships, sensitive subpopulations, and modes of action. In the absence of clinical or epidemiologic data in cases where humans are assumed or known to respond similarly to the experimental species, animal data alone may be sufficient to support a likely causal determination.

## 1.3.2. Moving from Association to Causation

"Cause" explains a significant, effectual relationship between an agent and an associated disorder or disease. "Association" is the statistical dependence among events, characteristics, or other variables. An association is prima facie evidence for causation; alone, however, it is insufficient proof of a causal relationship between exposure and disease. Unlike an association, a causal claim supports the creation of counterfactual claims; that is, a claim about what the world would have been like under different or changed circumstances (Institute of Medicine, 2007). Much of the newly available health information evaluated in this ISA comes from epidemiologic studies that report a statistical association between exposure and health outcome.

Many of the health outcomes reported in these studies have complex etiologies. The diseases, such as asthma, coronary heart disease or cancer are typically initiated by a web of multiple agents. Outcomes depend on a variety of factors, such as age, genetic susceptibility, nutritional status, immune competence, and social factors, as shown in Figure 1.3-1 (Gee and Payne-Sturges, 2004; Institute of Medicine, 2007). Further, exposure to a combination of agents could cause synergistic or antagonistic effects. Thus, net effects are the result of many actions and counteractions.

Moving from association to causation involves eliminating alternative explanations for the association. Controlled human exposure studies, or human clinical studies, randomly allocate subjects groups, usually called study and control groups, and exposed to a pollutant or a sham, respectively. Results are assessed by rigorous comparison of rates of relevant outcomes between the groups. This type

of study is generally regarded as the most scientifically rigorous method of hypothesis testing. By assigning exposure randomly, the study design attempts to remove the effect of factors that influence exposure. Only a causal relationship between exposure and health outcome should produce observed associations in randomized clinical trials.

In another type of human clinical study, a subject is exposed to a pollutant and a sham at different points in time, and the responses are compared. This design effectively controls for potential confounders, since the subject serves as his or her own control.

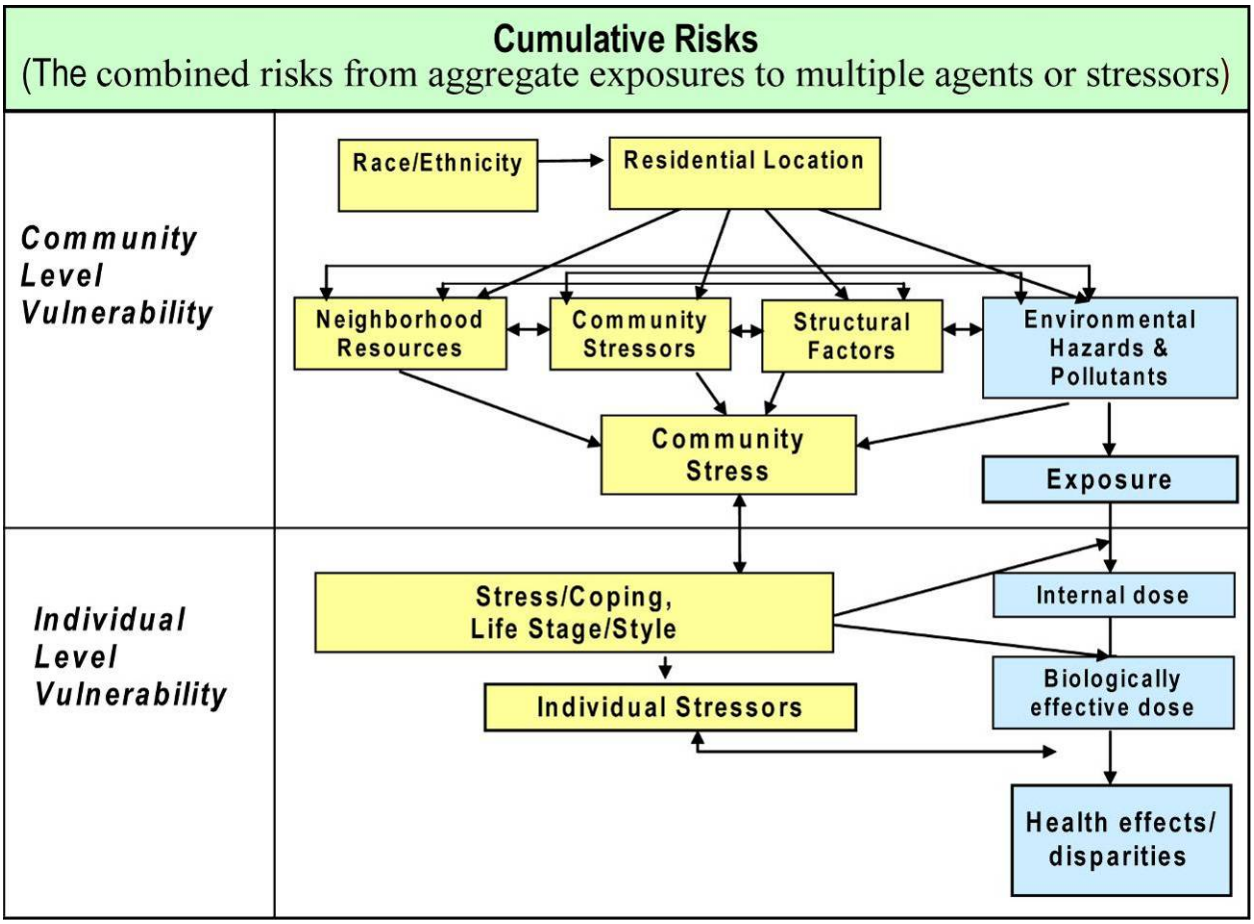


**Figure 1.3-1. Exposure–disease–stress model for environmental health disparities.**

A lack of observable effects from human clinical studies does not necessarily mean that a causal relationship does not occur. One limitation is a small study population, which restricts the ability to discern statistically significant findings. These studies are also confined to limited real-world conditions that can be feasibly studied. In addition, the most susceptible individuals or groups may be explicitly excluded, such as those with nutritional deficits, for practical and ethical reasons.

Inferring causation from epidemiologic studies requires consideration of uncertainties, particularly potential confounders. One way to remove spurious association is through statistical control of these potential confounders, a method termed "adjustment." Multivariable regression models are an example of a tool for estimating the association between exposure and outcome that involves such adjustment. Study designs that include matching of case and control exposure groups can also address confounding.

Likewise, stratified analysis, i.e., examining the association within homogeneous groups of the confounding variable, controls for confounders. Stratified analyses have an additional benefit: the examination of effect modification through comparison of the effect estimates across different groups. If investigators successfully measure characteristics that distort results, the method's adjustment helps separate a spurious from a true causal association. Appropriate statistical adjustment for confounders requires identification and measurement of all reasonably expected confounders.

Measurement error is another problem encountered when adjusting for spurious associations. In multivariate analyses in the time series study design, the effects of a well-measured covariate may be overestimated, in contrast to a more poorly measured covariate. Several components contribute to exposure measurement error in these studies, including differences between true and measured ambient concentrations, differences between average personal exposure to ambient pollutants and ambient concentrations at central monitoring sites, and the use of average population exposure rather than individual exposure estimates.

Confidence that unmeasured confounders are not biasing the results is increased when multiple studies are conducted in various settings using different subjects or exposures. Thus, multicity studies which use a consistent method to analyze data from across locations with different levels of covariates can provide insight on potential confounding in associations. The number and degree of diversity of covariates, as well as their relevance to the potential confounders, remain matters of scientific judgment. Intervention studies, because of their experimental nature, can be particularly useful in characterizing causation.

In addition to clinical and epidemiologic studies, the tools of experimental biology are valuable for providing insight into human physiology and pathology. Laboratory tools have been extended to explore the effects of putative toxicants on human health, especially through the study of model systems in other species. Background knowledge of the biological mechanisms involved can prove crucial in establishing, or negating, a causal claim. On the other hand, species can differ from each other in fundamental aspects of physiology and anatomy (e.g., metabolism, airway branching, hormonal regulation) that may hamper extrapolation. Testable hypotheses about the causal nature of proposed mechanisms or modes of action are central to utilizing experimental data in causal determinations.

## 1.3.3. Multifactorial Causation

Scientific judgment regarding likely sources and magnitude of confounding, as well as the pros and cons of various existing study designs, results, and analyses is crucial. One key consideration in this ISA was the evaluation of the potential contribution of $NO_X$ to health effects, when it is a component of a complex air pollutant mixture. There are multiple ways by which $NO_X$ might cause or be associated with adverse health effects. First, the reported $NO_X$ effect estimates in epidemiologic studies may reflect independent $NO_X$ effects on respiratory health. Second, ambient $NO_X$ may be serving as an indicator of complex ambient air pollution mixtures that share the same source, such as motor vehicles or electricity generation. Finally, copollutants may mediate the effects of $NO_X$, or $NO_X$ may influence the toxicity of copollutants. These relationships are illustrated in Figure 1.3-2.

Epidemiologists use the terms "interaction" and "effect modification" to denote the departure of the observed joint risk from expectations based on the separate effects of the factors. These possibilities are not necessarily exclusive. In addition, confounding can result in the fabrication of an association between adverse health effects and $NO_X$ that is actually attributable to another factor closely associated with $NO_X$. Multivariate models are the most widely used strategy to address confounding in epidemiologic studies, but such models are not readily interpreted when assessing effects of covarying pollutants such as PM, CO, $O_3$, and $SO_2$.

## 1.3.4. Uncertainty

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

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

Assessment of model uncertainty involves: (1) whether exposure causes the health outcome; (2) the set of confounders associated with exposure and health outcome; (3) which parametric forms best describe the relationships among exposure, confounders, and outcome; and (4) whether other forms of bias could be affecting the association.

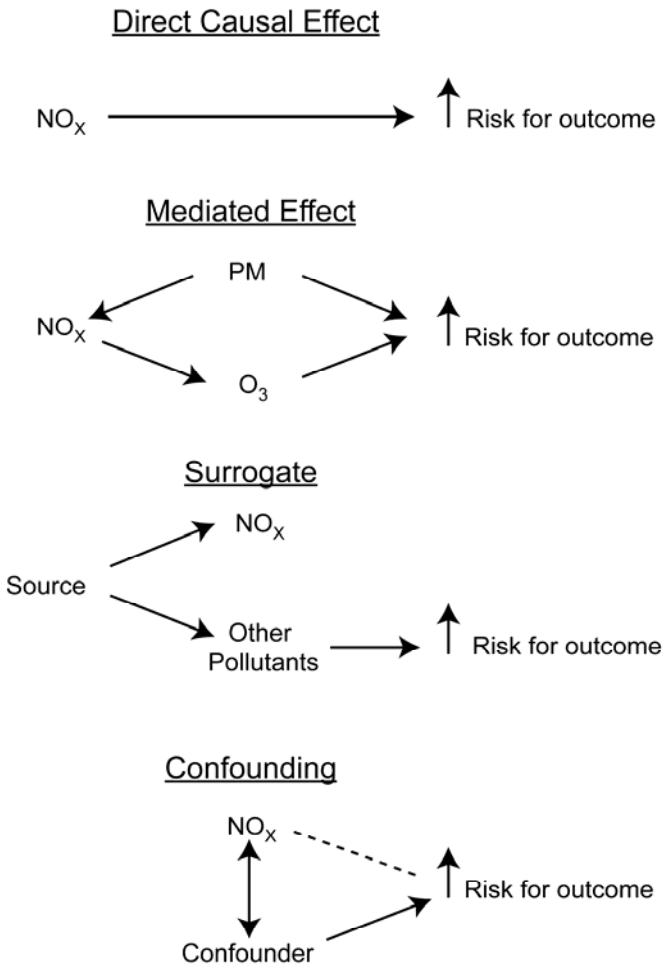


**Figure 1.3-2. Potential relationships of $NO_X$ with adverse health effects.**

## 1.3.5. Application of Framework

EPA uses a two-step approach to evaluate the scientific evidence on health effects of exposure to criteria pollutants. These two steps address two policy-relevant questions noted above – what are (if any) the effects of $NO_X$ on susceptible populations, given the total body of evidence, and at what levels of $NO_X$ exposure do health effects of concern occur. The first step determines the weight of evidence in support of causation and characterizes the strength of any resulting causal classification. The second step includes further evaluation of the quantitative evidence regarding the concentration-response relationships and the levels, duration and pattern of exposures at which effects are observed.

To aid judgment, various "aspects"[1] of causality have been discussed by many philosophers and scientists; the most widely cited were articulated by Sir Austin Bradford Hill in 1965 (Centers for Disease Control and Prevention, 2004; EPA, 2005; IARC, 2006; Institute of Medicine, 2007). These elements (Hill, 1965) have been modified (below) for use in causal determinations specific to health and environmental effects and pollutant exposures.[2]

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**Table 1.3-1. Aspects to aid judging causality.**

1. ***Consistency of the observed association.*** An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.

2. ***Strength of the observed association.*** The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. A modest risk, however, does not preclude a causal association and may reflect a lower level of exposure, an agent of lower potency, or a common disease with a high background level.

3. ***Specificity of the observed association.*** As originally intended, this refers to increased inference of causality if one cause is associated with a single effect or disease. Based on our current understanding this is now considered one of the weaker guidelines for causality; for example, many agents cause respiratory disease and respiratory disease has multiple causes. The ability to demonstrate specificity under certain conditions remains, however, a powerful attribute of experimental studies. Thus, although the presence of specificity may support causality, its absence does not exclude it.

4. ***Temporal relationship of the observed association.*** A causal interpretation is strengthened when exposure is known to precede development of the disease.

5. ***Biological gradient (exposure-response relationship).*** A clear exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times). There are, however, many possible reasons that a study may fail to detect an exposure-response relationship. Thus, although the presence of a biological gradient may support causality, the absence of an exposure-response relationship does not exclude a causal relationship.

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[1] The "aspects" described by Hill (1965) have become, in the subsequent literature, more commonly described as "criteria." The original term "aspects" is used here to avoid confusion with 'criteria' as it is used, with different meaning, in the Clean Air Act.

[2] The Hill apects were developed for use with epidemiology data. They have been modified here for use with a broader array of data, i.e., epidemiologic, human clinical, and animal toxicologic studies, as well as *in vitro* data, and to be more consistent with EPA's Guidelines for Carcinogen Risk Assessment.

6. ***Biological plausibility***. An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A lack of biological understanding, however, is not a reason to reject causality.

7. ***Coherence.*** An inference of causality may be strengthened by other lines of evidence that support a cause-and-effect interpretation of the association. For instance, similar findings between clinical and animal studies, or closely related health effects, which are expected to be associated with exposure, are in fact observed together. The absence of other lines of evidence, however, is not a reason to reject causality.

8. ***Experimental evidence (from human populations).*** Experimental evidence is generally available from human populations for the criteria pollutants. The strongest evidence for causality can be provided when a change in exposure brings about a change in adverse health effect or disease frequency in either clinical or observational studies (e.g., natural experiments, intervention studies).

9. ***Analogy.*** Structure activity relationships and information on the agent's structural analogs can provide insight into whether an association is causal. Similarly, information on mode of action for a chemical, as one of many structural analogs, can inform decisions regarding likely causality.

While these aspects provide a framework for assessing the evidence, they do not lend themselves to consideration in terms of simple formulas or fixed rules of evidence leading causality conclusions. A tallying of studies reporting statistically significant or nonsignificant results does not point toward credible conclusions about the relative weight of the evidence and the likelihood of causality. Rather, these considerations are taken into account with the goal of producing an objective appraisal of the evidence, informed by peer and public comment and advice. The principles in Table 1.3-1 cannot be used as a strict checklist, but rather as a determination of the weight of the evidence for inferring causality. In particular, the absence of one or more of the principles does not automatically exclude a study from consideration (e.g., see discussion in Centers for Disease Control and Prevention, 2004).

## 1.3.6. First Step—Determination of Causality

To draw conclusions on the causal relationships between relevant pollutant exposures and health outcomes, EPA assessed results from recent publications, in light of evidence available from the previous NAAQS review. Using a five-level hierarchy to classify the overall weight of evidence for causation, not just association (see Table 1.3-2), EPA drew on the work of previous evaluations, most prominently the IOM's Improving the Presumptive Disability Decision-Making Process for Veterans (Institute of Medicine, 2007), EPA's Guidelines for Carcinogen Risk Assessment (U.S. Environmental Protection Agency, 1986), and the U.S. Surgeon General's report on the benefits of smoking cessation (Centers for Disease Control and Prevention, 2004). These efforts are presented in more detail in Annex AX1. The weight of evidence evaluation is based on various lines of evidence from human clinical, epidemiologic, animal studies, and in vitro studies. The separate judgments are then integrated into a qualitative statement about the overall weight of the evidence and causality.

## 1.3.7. Second Step—Evaluation of Population Response

Beyond judgments regarding causality are questions relevant to characterizing exposure and risk to populations; in other words, at what levels do health effects occur? Such questions include:

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

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**Table 1.3-2. Weight of evidence for causal determination (adapted from Institute of Medicine, 2007).**

| | |
|---|---|
| **Sufficient to infer a causal relationship** | Evidence is sufficient to conclude that there is a causal relationship between relevant pollutant exposure and the outcome. Causality is supported when an association has been observed between the pollutant and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. That is, human clinical studies provide the strongest evidence for causality. Causality is also supported by findings from epidemiologic "natural experiments" or observational studies supported by other lines of evidence. Generally, determination is based on multiple studies from more than one research group. |
| **Sufficient to infer a likely causal relationship (i.e., more likely than not).** | Evidence is sufficient to conclude that there is a likely causal association between relevant pollutant exposures and the outcome. That is, an association has been observed between the pollutant and the outcome in studies in which chance, bias and confounding are minimized, but uncertainties remain. For example, observational studies show associations but confounding and other issues are difficult to address and/or other lines of evidence (human clinical, animal, or mechanism of action information) are limited or inconsistent. Generally, determination is based on multiple studies from more than one research group. |
| **Suggestive, but not sufficient to infer a causal relationship** | Evidence is suggestive of an association between relevant pollutant exposures and the outcome, but is weakened because chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows an association, while the results of other studies are inconsistent. |
| **Inadequate to infer the presence or absence of a causal relationship** | The available studies are inadequate to infer the presence or absence of a causal relationship. That is, studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association between relevant pollutant exposure and the outcome. For example, studies which fail to control for confounding or which have inadequate exposure assessment, fall into this category. |
| **Suggestive of no causal relationship** | The available studies are suggestive of no causal relationship. That is, several adequate studies, examining relationships between relevant population exposures and outcomes, and considering sensitive subpopulations, are mutually consistent in not showing an association between exposure and the outcome at any level of exposures. In addition, the possibility of a small elevation in risk at the levels of exposure studied can never be excluded. |

On the population level, causal and likely causal claims typically characterize how risk—the probability of health effects—changes in response to exposure. Generally, the response is evaluated within the range of observation, which is determined by the type of study and methods of exposure measurement. Extensive human data to inform risk analyses exists for all criteria pollutants, unlike most other environmental pollutants. Animal data also can inform concentration-response, particularly relative to dosimetry, mechanisms of action, and characteristics of sensitive subpopulations.

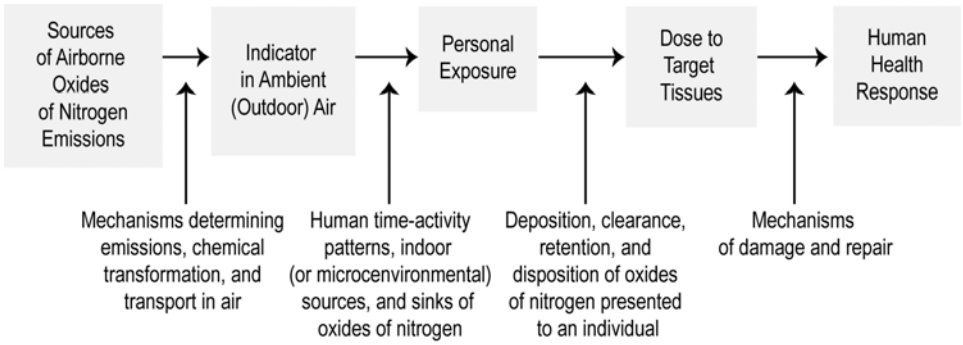
An important consideration in characterizing the public health impacts associated with exposure to a pollutant is whether the concentration-response relationship is linear across the full concentration range encountered, or whether nonlinear relationships exist along any part of this range. Of particular interest is the shape of the concentration-response curve at and below the level of the current standard. The complex molecular and cellular events that underlie cancer and noncancer toxicity are likely to be both linear and nonlinear, and vary depending on concentration. Additionally, many factors may act by perturbing naturally occurring background processes related to disease.

At the human population level, various sources of variability and uncertainty tend to smooth and "linearize" the concentration-response function, such as low data density in the lower concentration range, possible influence of measurement error, and individual differences in susceptibility to air pollution health effects. These attributes of population concentration-response may explain why the available human data at ambient concentrations for some environmental pollutants (e.g., $O_3$, lead [Pb], PM, secondhand tobacco smoke, radiation) do not exhibit evident thresholds for health effects, even though likely mechanisms of action include nonlinear processes. These attributes of human population concentration-response relationships have been extensively discussed in the broader epidemiologic literature (e.g., Rothman and Greenland, 1998).

# Chapter 2. Source to Exposure

## 2.1. Introduction

This chapter provides concepts and findings relating to emissions sources, atmospheric science, human exposure assessment, and human dosimetry. The order of these topics essentially follows that given in the National Research Council paradigm for integrating air pollutant research (NRC, 2004) as shown in Figure 2.1-1. This chapter is meant to serve as a prologue for detailed discussions on the evidence on health effects that follow in Chapters 3 and 4, and as a source of information to help interpret those effects against data about atmospheric concentrations and exposures.




Source: Adapted from National Research Council (2004).

**Figure 2.1-1. A generalized conceptual model for integrating research on $NO_X$ pollution and human health effects.**

The definition of "nitrogen oxides," as it appears in the NAAQS legislation, differs from the one commonly used in air pollution research and control communities. In this document, the terms "oxides of nitrogen" and "nitrogen oxides" ($NO_X$) refer to all forms of oxidized nitrogen (*N*) compounds, including NO, $NO_2$, and all other oxidized *N*-containing compounds formed from NO and $NO_2$.[1]

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

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

# 2.2. Sources and Atmospheric Chemistry

The role of $NO_X$ in $O_3$ formation was reviewed in the Air Quality Criteria for Ozone and Related Photochemical Oxidants (U.S. Environmental Protection Agency, 2006a). Mechanisms for transporting $O_3$ precursors including $NO_X$, the factors controlling the efficiency of $O_3$ production from $NO_X$, methods for calculating $O_3$ from its precursors, and methods for measuring total oxidized nitrogen ($NO_Y$) were all reviewed the 2006 $O_3$ AQCD. The chemistry of reactive, oxidized *N* compounds in the atmosphere is summarized in Figure 2.2-1.

## 2.2.1. Sources of $NO_X$

Both anthropogenic and natural (biogenic) processes emit $NO_X$. $NO_X$ is emitted by combustion sources as mainly NO with smaller quantities of $NO_2$. The major sources of $NO_X$ in the U.S. are listed in Table 2.2-1 (see Annex Table AX2-3 for more detail). On-road mobile sources constitute the largest source of $NO_X$ followed by electricity generating units (EGUs) and non-road mobile sources. Stationary engines and industrial facilities also emit $NO_X$, but because they are fewer in number or burn less fuel, their mass contribution is relatively smaller. It should be remembered in viewing Table 2.2-1 that the values shown are nationwide averages and may not reflect relative contributions of the different sources to ambient $NO_2$ at any given location and to an individual's exposures to $NO_2$.

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**Table 2.2-1. Annual 2002 average anthropogenic $NO_X$ emissions in the U.S. (million metric tons).**

| SOURCE CATEGORY | EMISSIONS |
|---|---|
| On-Road Mobile Sources | 7.4 |
| Electricity-Generating Units | 4.3 |
| Non-Road Mobile Sources | 4.0 |
| Industrial/Commercial/Residential Fuels | 2.3 |
| Industrial Processes | 1.1 |
| Prescribed Fires | 0.19 |
| Waste Disposal | 0.10 |
| Residential Wood | 0.04 |
| Fertilizers and Livestock | 0.019 |
| Miscellaneous | 0.011 |
| Road Dust | <0.01 |
| Solvent Use | 0.0082 |
| TOTAL | 19.4 |

Source: NEI 2002 Emissions Booklet (U.S. Environmental Protection Agency, 2006b)

As defined above, $NO_X$ is a complex mixture of many oxides of nitrogen, so many factors can contribute to ambient $NO_X$ concentrations at any given time or location. Relatedly, there are several methods for determining $NO_X$ emissions from these many sources. One method is to consider the ratio of components of $NO_X$ to each other or to the total concentration of $NO+NO_2$. The ratio of $NO_2$ to the sum of NO and $NO_2$ in the exhaust from gasoline fueled vehicles is variable, but generally of the order of a few percent (Heeb et al., 2008; Hilliard and Wheeler, 1979) as determined by dynamometer studies. Catalyzed diesel particle filters (CDPFs) can increase the $NO_2$ to $NO+NO_2$ ratio in diesel exhaust from <0.1 to around 0.3 to 0.7, depending on the engine, design of the CDPF and mode of operation. For example, Shorter et al. (2005) in a study of public transit buses in New York City found that ratios in emissions from retrofitted diesel engines range from 0.3 to 0.6.

Sources of $NO_X$ are distributed with height, some are at or near ground level (e.g., motor vehicles) and others aloft (e.g., electric utilities stacks). Figure 2.2-1 shows schematically on-road motor vehicles and electric utilities, the two largest $NO_X$ sources in the U.S., along with $NO_X$ species and major reaction pathways. Because the prevailing winds aloft are generally stronger than those at the surface, emissions from elevated sources can be distributed over a wider area than those emitted at the surface. The elevated emissions besides being widely dispersed are diluted to much lower levels than near their source.

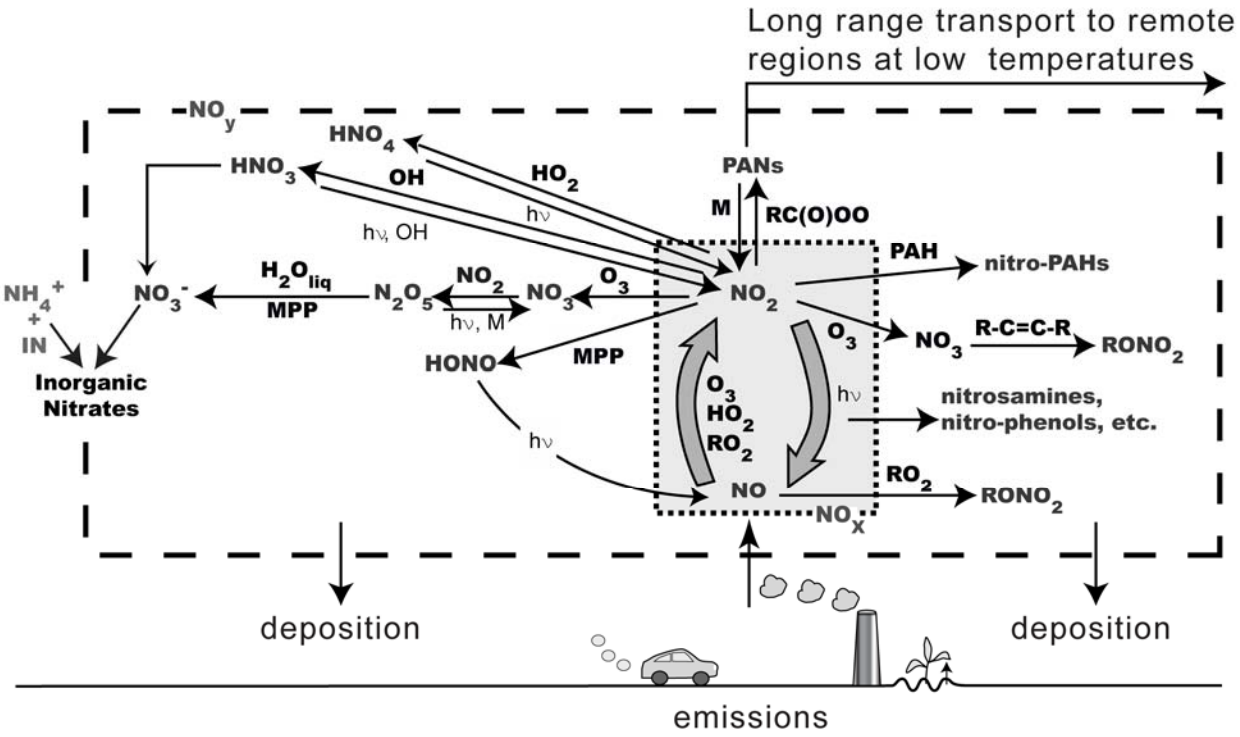



**Figure 2.2-1. Schematic diagram of the cycle of reactive oxidized *N* species in the atmosphere. $NO_Y$ refers to all the species shown within the inner and outer box; $NO_X$ to NO and $NO_2$ (in the inner box); and $NO_Z$ to all the species outside of the inner box. IN refers to inorganic particulate species (e.g., sodium [$Na^+$], calcium [$Ca^{++}$]), MPP to multiphase processes, h$\nu$ to a solar photon and R to an organic radical. Particle-phase $RONO_2$ are formed from the species shown on the right side. For the purposes of this EPA document, "$NO_X$" is defined as the group of all nitrogen-containing compounds inside the large dashed-line box, the same group generally termed "$NO_Y$" by atmospheric scientists.**

Biomass burning also produces $NO_X$. Apart from these anthropogenic sources, there are also smaller natural sources which include microbial activity in soils (particularly fertilized soils) and lightning. Wildfires can be large but episodic and highly variable sources of $NO_X$. $NO_X$ sources and emissions are described in greater detail in Annex Section AX2.4.

## 2.2.2. Chemical Transformations

NO and $NO_2$ are often grouped together and given the category label "$NO_X$" because they are emitted together and can rapidly interconvert as shown in the inner box in Figure 2.2-1. The NO emitted from the sources shown in Figure 2.2-1 can be oxidized to form $NO_2$, meaning that atmospheric $NO_2$ concentrations nearly always have a large fraction created by secondary formation in the atmosphere, not direct emission. The timescale for the conversion of NO to $NO_2$ is on the order of a minute.[1] $NO_2$ reacts with $O_3$ and various free radicals in the gas phase and on surfaces in multiphase processes to form the oxidation products shown in Figure 2.2-1. These products include inorganic species (shown on the left side of the outer box in Figure 2.2-1) and organic species (shown on the right side of the outer box in Figure 2.2-1). The oxidized *N* species in the outer box are often collectively termed $NO_Z$; thus, $NO_X+NO\text{-}_Z=NO_Y$.

The concentrations and atmospheric lifetimes ($\tau$) of inorganic and organic products from reactions of $NO_X$ vary widely in space and time. Inorganic reaction products include nitrous acid (HONO), $HNO_3$, pernitric acid, and particulate nitrate ($PNO_3^-$). While a broad range of organic *N* compounds are emitted by combustion sources (e.g., nitrosamines and nitro-PAHs), they are also formed in the atmosphere from reactions of NO and $NO_2$. These include PANs and isoprene nitrates, other nitro-PAHs, and the more recently identified nitrated organic compounds in the quinone family. Most of the mass of products shown in the outer box of Figure 2.2-1 is in the form of PAN and $HNO_3$, although other organic nitrates, e.g., isoprene nitrates and specific biogenic PANs can be important at locations closer to biogenic sources (Horowitz et al., 2007; Singh et al., 2007).

In addition to gas-phase reactions, reactions occurring on surfaces or occurring in multiphase processes (MPP) are important for the formation of HONO and $PNO_3^-$. These reactions can occur on the surfaces of suspended particles, soil, and buildings, and within aqueous media. Further details about these processes can be found in Annex section AX2.2.3. PAN, and other peroxyacyl nitrates, both thermally decompose and photolyze back to reactants. Atmospheric lifetimes with respect to photolysis are a few hours during warm sunlit conditions. For thermal decomposition, they range from ~1 hour at 298 K to ~2.5 days at 273 K, up to several weeks at 250 K. Thus, PAN can provide an effective sink of $NO_X$ at cold temperatures and high solar zenith angles; its lifetime is long enough at low temperatures so that PAN can be transported tens or hundreds of kilometers (depending on meteorological conditions) before decomposing to release $NO_2$, which can then participate in $O_3$ formation in these regions, remote from the original $NO_X$ source. $HNO_3$ can act similarly to some extent, but its high solubility and high deposition rate imply that it is removed from the gas phase faster than PAN, and thus would not be as important as a source of $NO_X$ in remote regions. Characteristic concentrations of many of the $NO_X$ species are given in Annex section AX3.2.

The timescale for reactions of $NO_X$ to form $NO_Z$ products like PAN and $HNO_3$ typically ranges from a few hours during summer to about a day during winter. As a result, morning rush hour emissions of $NO_X$ from motor vehicles can be converted almost completely to $NO_Z$ products by late afternoon during warm, sunny conditions. Because the time required for mixing emissions down to the surface is similar to or longer than the time for oxidation of $NO_X$, emissions of $NO_X$ from elevated sources (like the stacks of electric utilities) tend to be transformed to $NO_Z$ before they reach the surface. However, people live closer to emissions from on-road and off-road motor vehicles, fixed-site combustion engines (e.g., generators), and indoor sources, and so are more likely to be exposed to NO and $NO_2$ from these sources.

[1] This estimate assumes a background concentration of $O_3$ of 40 ppb and a rate coefficient at 298 K of 1.9 X $10^{-14}$ $cm^3$/molec-sec (Jet Propulsion Laboratory, 2003).

Hence, because atmospheric dispersion and chemical reactions in this way determine the partitioning of a person's exposure to $NO_2$ and its reaction products from multiple different sources, a person's total exposure to $NO_X$ cannot be judged solely by the NO and $NO_2$ source strengths given in the national emissions inventories (NEI).

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

### 2.2.2.1. Formation of Nitro-PAHs

Nitro-PAHs are produced either by direct emissions or by atmospheric reactions. Among combustion sources, diesel emissions have been identified as the major source of nitro-PAHs in ambient air (Bezabeh et al., 2003; Gibson, 1983; Schuetzle, 1983; Tokiwa and Ohnishi, 1986). Direct emissions of nitro-PAHs vary with fuel type, vehicle maintenance, and ambient conditions (Arey et al., 1986; 1989; Arey, 1998; Perrini et al., 2005; Pitts, 1987; Sasaki et al., 1997; Zielinska et al., 2004). In addition to direct emission, nitro-PAHs are formed from both gaseous and heterogeneous reactions of PAHs with gaseous *N*-containing pollutants in the atmosphere; reactions of hydroxyl (OH) and nitrate ($NO_3$) radicals with PAHs are the major sources of nitro-PAHs (Arey et al., 1986; 1989; Arey, 1998; Perrini et al., 2005; Pitts, 1987; Sasaki et al., 1997; Zielinska et al., 1989; Bamford and Baker, 2003; Reisen and Arey, 2005). Reactions involving OH radicals occur mainly during the day, while reactions with $NO_3$ radicals occur mainly during the night. The major loss process of nitro-PAHs is photodecomposition (Fan et al., 1996; Feilberg et al., 1999; Feilberg and Nielsen, 2001) with lifetimes on the order of hours, followed by reactions with OH and $NO_3$ radicals. The reaction mechanisms for forming and destroying nitro-PAHs in the atmosphere are described in Annex section AX2.2.4 .

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

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

It should be noted that the first step involved in the multiphase processes noted above is adsorption of $NO_2$. $NO_2$ adsorbed onto particles could then be inhaled along with the products of $NO_2$ reactions such as HONO and nitro-PAHs. However, quantitative details for the fraction of $NO_2$ adsorbed onto particles at ambient levels of $NO_2$ are lacking.

### 2.2.3. $O_3$ Formation

At the low $NO_X$ concentrations found in most environments (ranging from remote continental areas to rural and suburban areas downwind of urban centers), the net production of $O_3$ increases with increasing $NO_X$. At the high $NO_X$ concentrations found in downtown metropolitan areas, and especially near busy streets and roadways and in power plant plumes, net destruction of $O_3$ is initiated with the excess NO found there. In the airshed regimes with high $NO_X$ concentrations, $NO_2$ scavenges OH radicals that would otherwise oxidize VOCs to produce peroxy radicals, which would in turn oxidize NO to $NO_2$. In the airshed regimes with low $NO_X$ concentrations, oxidation of VOCs generates excess free radicals; hence $O_3$ production is more nearly linear with $NO_X$. Between these two regimes, there is a transition zone in which $O_3$ shows only a weak dependence on $NO_X$ concentration.

## 2.3. Measurement Methods

In the EPA regulatory networks as in nearly all large-scale $NO_X$ monitoring networks world-wide, $NO_2$ is the component of most interest. However, in most of these networks, $NO_2$ is not measured directly, but by subtraction following a measurement of the total of NO+$NO_2$ and NO alone. Both these measurements and hence the determination of $NO_2$ by subtraction depend on the same technique for measuring NO. In that technique, NO is measured using the principle of gas-phase chemiluminescence induced by the reaction of NO with $O_3$ at low pressure. The Federal Reference Method (FRM) for $NO_2$ makes use of this technique of NO detection. A prerequisite step is the catalytic reduction of $NO_2$ to NO most often on the surface of a molybdenum oxide ($MoO_X$) substrate, heated to between 300 and 400°C. Because the FRM monitor cannot detect $NO_2$ specifically, the concentration of $NO_2$ is determined as the difference between the air sample passed over the heated $MoO_X$ substrate (the nitrogen oxides total) and the air sample that has not passed over the substrate (the NO).

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

Only recently have attempts been made to systematically quantify the magnitude and variability of the interference by $NO_Z$ species in ambient measurements of $NO_2$. Dunlea et al. (2007) found an average of ~22% of ambient $NO_2$ (~9 to 50 parts per billion [ppb]) measured in Mexico City was due to interference from $NO_Z$ compounds; that is to say, the actual $NO_2$ concentration was ~22% lower than what was reported at monitors using the difference technique. Comparable levels of $NO_2$ are found in many locations in the U.S., but the same comparison for distinct places in the U.S. is difficult to make because significant uncertainty remains in determining the concentrations of the higher oxidation $NO_Z$ products since they are not routinely measured. Dunlea et al. (2007) compared $NO_2$ measured using the conventional chemiluminescent instrument with other (optical) techniques. The main sources of interference were $HNO_3$ and various organic nitrates ($RONO_2$) which can be converted to NO on the

catalyst with varying rates of efficiency. In this study, the efficiency of conversion on the catalyst — that is, how much of the compound introduced to the catalyst was converted to NO — was estimated to be ~38% for $HNO_3$; for PAN, ~95% and ~ 95% for other $RONO_2$. Peak interference (over-estimation) in the reported estimate of $NO_2$ concentrations from the presence of $NO_Z$ compounds of up to 50% was found during afternoon hours and was associated with $O_3$ and $NO_Z$ compounds such as $HNO_3$ and the alkyl and multifunctional alkyl nitrates.

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

Another approach to estimating the measurement interference is to use model calculations in conjunction with known data on the reduction efficiencies of $NO_Z$ species on the $MoO_X$ converters as described above. Lamsal et al. (2008) used the conversion efficiencies noted above along with output for $NO_Y$ species from the GEOS-CHEM global chemical transport model (CTM) to derive seasonal correction factors for the ambient monitoring data across the U.S. These factors range from <10% in winter in the East to >80% in the West, with the highest values found during summer in relatively unpopulated areas. Lamsal et al. (2008) also used these corrected data to determine the feasibility of using satellite data to supplement ground based data. However, the current generation of satellite monitors are in low earth orbiting mode and so the $NO_2$ values are restricted to time of satellite overpass in early afternoon. Future generations of geostationary satellites are planned that will obtain more continuous data across the U.S. throughout the day.

Calculations using EPA's Community Multiscale Air Quality (CMAQ) modeling system for the Mid-Atlantic region in a domain extending from Virginia to southern New Jersey were made at much higher spatial resolution than the GEOS-CHEM simulations (see http://www.mde.state.md.us/Programs/AirPrograms/air_planning/index.asp). The daily average interference for an episode during the summer of 2002 estimated using model-derived concentration fields for $NO_Z$ species and using the conversion efficiencies for $NO_Z$ species given above, ranged from ~20% in Baltimore to ~80% in Madison, VA. Highest values were found during the afternoon, when photochemical activity is highest and production and accumulation of the higher oxidized $NO_Z$ compounds is greatest, and lowest values during the middle of the night when photochemistry stops. The model calculations showed episode averages of the $NO_Z/NO_2$ ratio ranging from 0.26 to 3.6 in rural Virginia; the highest ratios were in rural areas, and lowest were in urban centers closer to sources of fresh $NO_X$ emissions. (The capabilities of three-dimensional CTMs such as GEOS-CHEM and CMAQ and issues associated with their use are presented in Annex section AX2.5.)

In summary, it appears that interference is likely to be on the order of 10% or less during most or all of the day during winter, but much larger interference is likely to be found during summer in the afternoon. In general, the interference in the measurement of $NO_2$ is greater downwind of urban source areas and in relatively remote areas away from concentrated sources as compared to the level of interference at measurements in urban cores with fresh $NO_X$ emissions.

There are approaches to measuring $NO_2$ not affected by the artifacts mentioned above. For example, $NO_2$ can be photolytically reduced to NO with an efficiency of ~70% as used in the Steinbacher et al. (2007) study. This method requires additional development to ensure its cost effectiveness and reliability for extensive field deployment. The relatively low and variable conversion efficiency of this technique would necessitate more frequent calibration. Optical methods such as those using differential optical absorption spectroscopy (DOAS) or laser induced fluorescence (LIF) are also available, as described in Annex section AX2.6. However, these particular methods are more expensive than either the FRM monitors or photolytic reduction technique and require specialized expertise to operate. Moreover, the DOAS obtains an integrated measurement over the instrument path length rather than a point measurement. Cavity attenuated phase shift monitors are an alternative optical approach that is potentially

less costly than DOAS or LIF (Kebabian et al., 2007). However, this technique is not highly specific to $NO_2$ and is subject to interference by other species absorbing at 440 nm, such as the 1,2-dicarbonyl compounds. The extent of this interference and the potential of the cavity attenuated phase shift technique for extensive field deployment have not been evaluated.

Commercially available $NO_X$ monitors have been converted to $NO_Y$ monitors by moving the $MoO_X$ convertor to interface directly with the sample inlet. Because of losses on inlet surfaces and differences in the efficiency of reduction of $NO_Z$ compounds on the heated $MoO_X$ substrate, $NO_X$ cannot be considered as a universal surrogate for $NO_Y$. However, in settings close to relatively high-concentration fresh emissions like those during urban rush hour, most of the $NO_Y$ is present as $NO_X$. To the extent that all the major oxidized *N* species can be reduced quantitatively to NO, measurements of $NO_Y$ should be more reliable than those of $NO_X$, particularly at typical ambient levels of $NO_2$. It is worth reiterating that with the current FRM monitors, the direct measurements of NO are the most specific. Measurements of total $NO_Y$ characterize the entire suite of oxidized *N* compounds to which humans are exposed. Reliable measurements of $NO_Y$ and $NO_2$, especially at the low concentrations observed in many areas remote from sources are also crucial for evaluating the performance of three-dimensional, chemical transport models of oxidant and acid production in the atmosphere (described in Annex section AX2.5).

To summarize this discussion of $NO_2$ measurement techniques and interferences: the current method of determining ambient $NO_X$ and then reporting $NO_2$ concentrations by subtraction of NO is subject to a consistently positive interference by $NO_X$ oxidation products, chiefly $HNO_3$ and peroxyacetyl nitrate (PAN) as well as other oxidized *N*-containing compounds, though the magnitude of this positive bias is largely unknown and can be rapidly changing. Measurements of these oxidation products in urban areas are sparse. Concentrations of these oxidation products are expected to peak in the afternoon because of the continued oxidation of $NO_2$ emitted during the morning rush hours and during conditions conducive to photochemistry in areas well downwind of sources, particularly during summer.

Within the urban core of metropolitan areas, where many of the ambient monitors are sited close to strong $NO_X$ sources such as motor vehicles on busy streets and highways (i.e., where $NO_2$ concentrations are highest), the positive artifacts due to the $NO_2$ oxidation products are much smaller on a relative basis, typically <~10%. Conversely, the positive artifacts are larger in locations more distant from $NO_X$ sources (i.e, where $NO_2$ concentrations are lowest) and could exceed 50%. Therefore, variable, positive artifacts associated with measuring $NO_2$ using the Federal Reference Method (FRM) severely hamper its ability to serve as an accurate and precise indicator of $NO_2$ concentrations at the typical ambient levels generally encountered outside of urban cores.

# 2.4. Atmospheric Concentrations

This section provides a brief overview of ambient concentrations of $NO_2$ and associated oxidized *N* compounds in the U.S.; it also provides estimates of Policy-Relevant Background (PRB) concentrations, i.e., background concentrations used to inform risk and policy assessments for the review of the NAAQS.

## 2.4.1. Ambient Concentrations

Figure 2.4-1 shows the distribution of monitoring sites for $NO_2$ across the U.S. Data for ambient $NO_2$ are not collected or collected at very few sites over large areas of the U.S. Few cities have more than two monitors and several large cities, including Seattle, WA, have none. Note that the number of $NO_2$ monitors has been decreasing in the U.S. as ambient average concentrations have fallen to a few tenths of the level of the NAAQS. There were, for example, 375 $NO_2$ monitors identified in mid-2006, but only 280 in November 2007.

Criteria for siting ambient monitors for NAAQS pollutants are given in the SLAMS / NAMS / PAMS Network Review Guidance (U.S. Environmental Protection Agency, 1998). As might be expected, criteria for siting monitors differ by pollutant. $NO_2$ monitors are meant to be representative of several scales: middle (several city blocks, 300 to 500 m), neighborhood (0.5 to 4 km), and urban (4 to 50 km). Middle- and neighborhood-scale monitors are used to determine highest concentrations and source impacts, while neighborhood- and urban-scale monitors are used for monitoring population exposures. As can be seen, there is considerable overlap between monitoring objectives and scales of representativeness. The distance of neighborhood- and urban-scale monitor inlets from roadways increases with traffic volume and can vary from 10 to 250 m away from roadways as traffic volume increases. Where the distance of an inlet to a road is shorter than the value in this range for the indicated traffic volume on that road, that monitor is classified as middle scale. Vertically, the inlets to $NO_2$ monitors can be set at a height from 2 to 15 m.

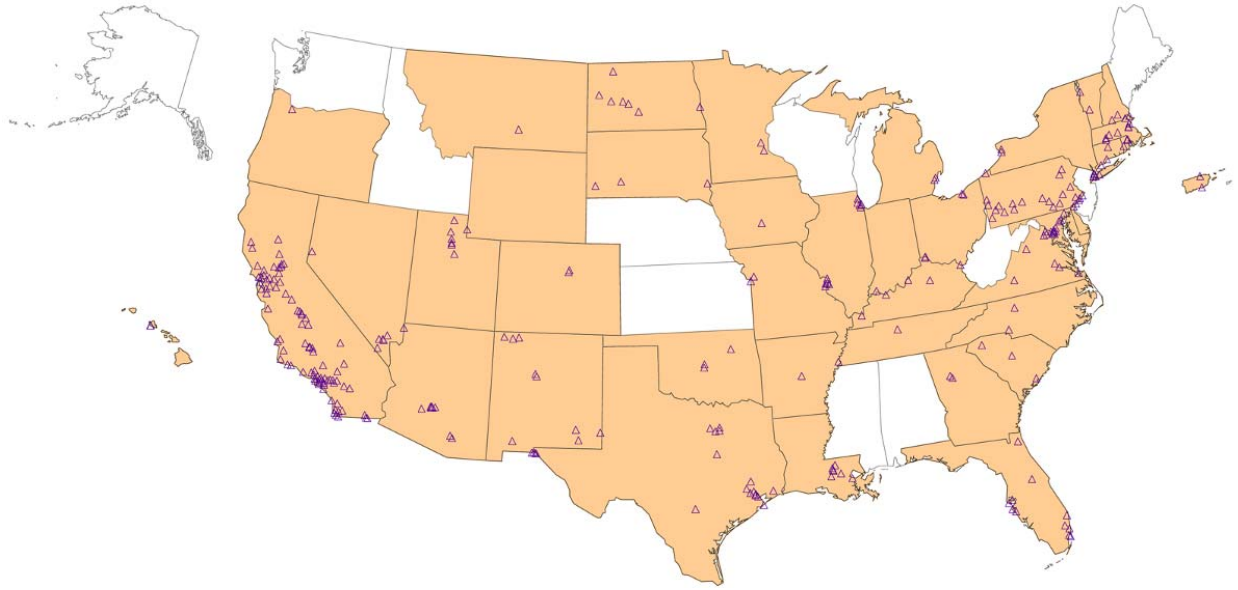
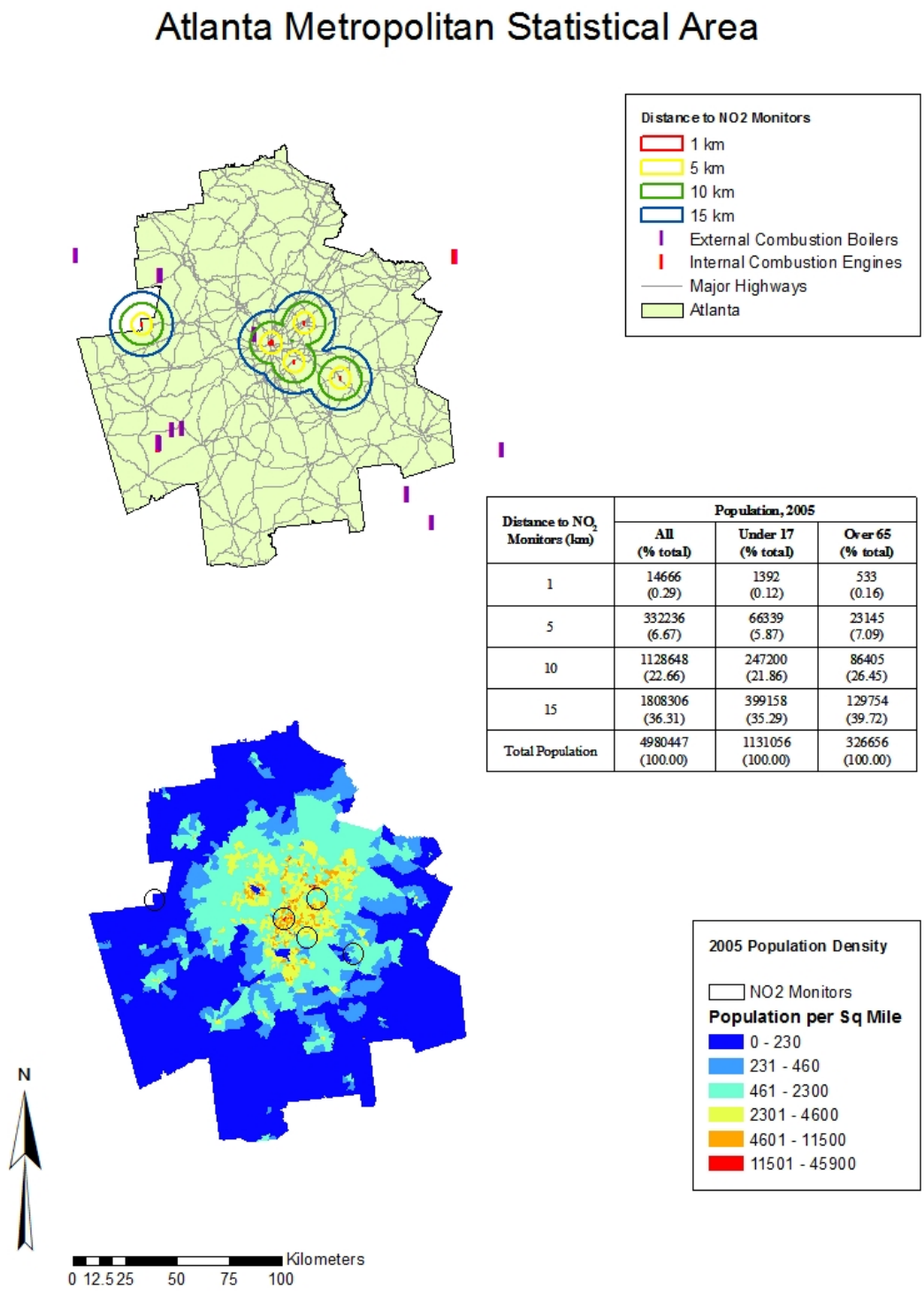


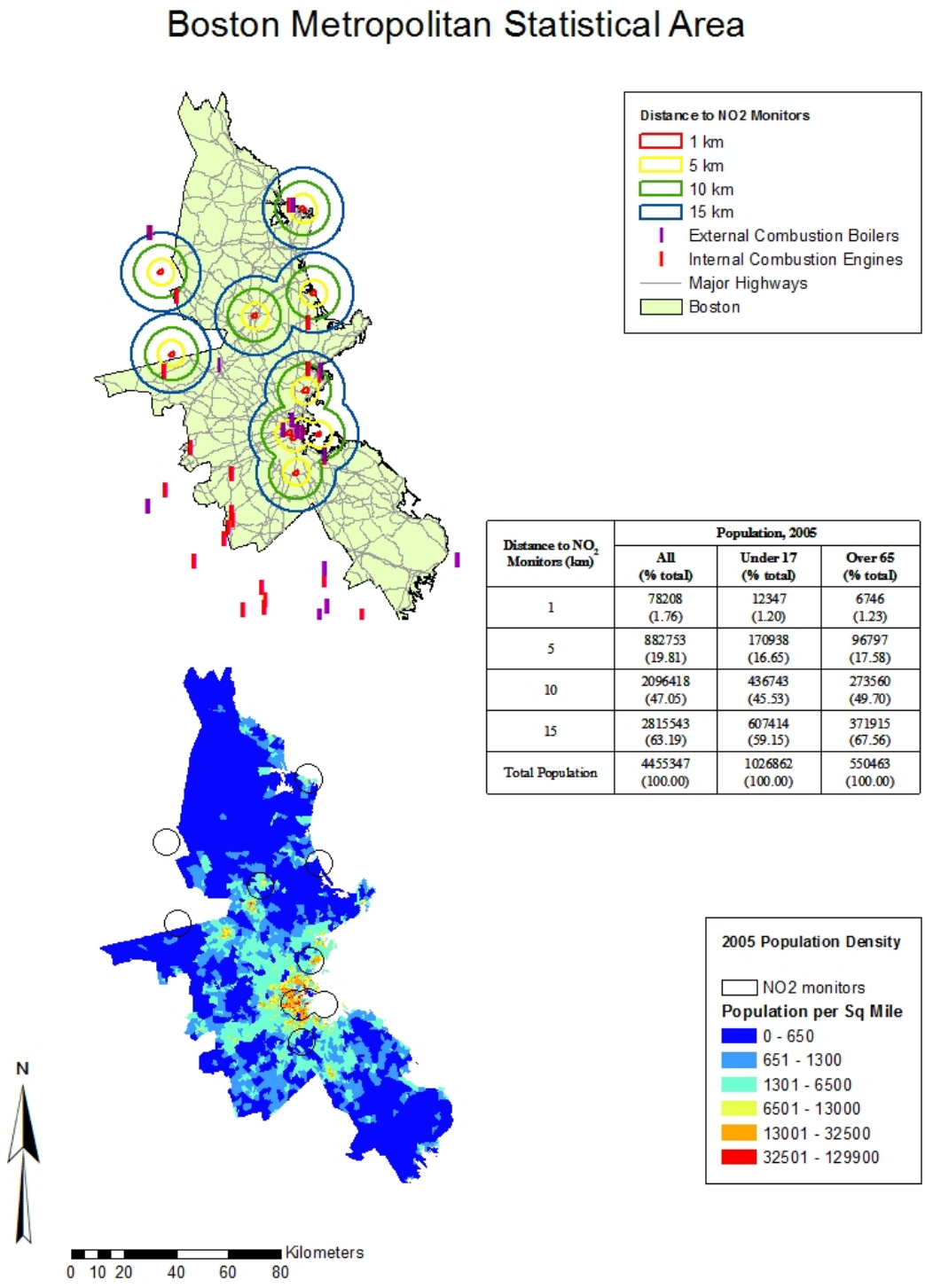
**Figure 2.4-1. Location of ambient $NO_2$ monitors in the U.S. as of November 5, 2007. Shaded states have $NO_2$ monitors; unshaded states have none.**

Figures 2.4-2 through 2.4-12 depict the spatial and population coverage of $NO_2$ monitors in these Consolidated Metropolitan Statistical Areas (CMSAs): Atlanta, GA; Boston, MA; Chicago, IL; Houston, TX; Los Angeles, CA; New York City, NY; Philadelphia, PA; Steubenville, OH; and Baltimore, MD/Washington, DC. (These CMSAs were selected for this depiction to maintain consistency with CMSAs used elsewhere in this assessment for health effects studies or ambient concentration representations.)



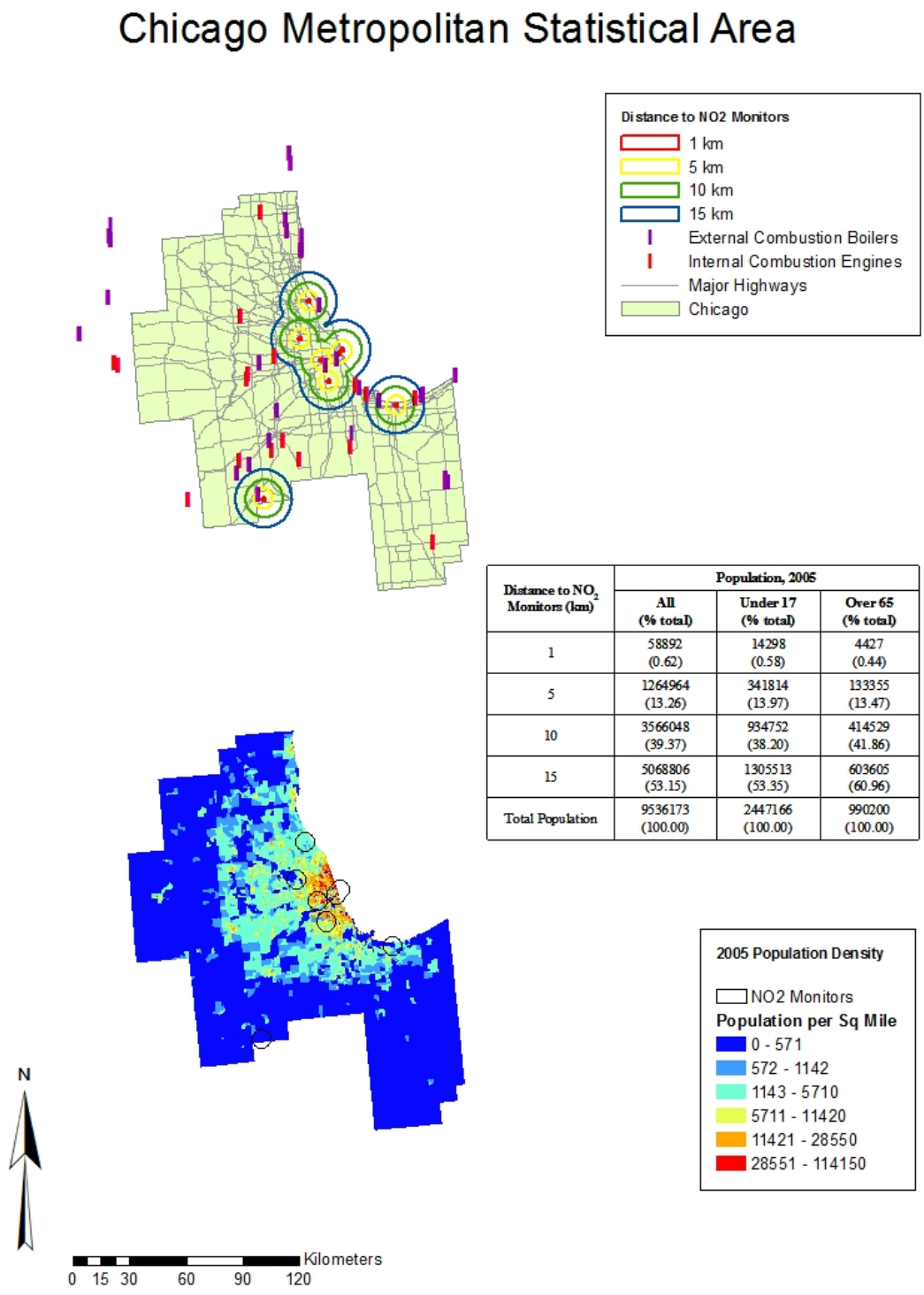

| Distance to $NO_2$ Monitors (km) | Population, 2005 | | |
|---|---|---|---|
| | All (% total) | Under 17 (% total) | Over 65 (% total) |
| 1 | 14666 (0.29) | 1392 (0.12) | 533 (0.16) |
| 5 | 332236 (6.67) | 66339 (5.87) | 23145 (7.09) |
| 10 | 1128648 (22.66) | 247200 (21.86) | 86405 (26.45) |
| 15 | 1808306 (36.31) | 399158 (35.29) | 129754 (39.72) |
| Total Population | 4980447 (100.00) | 1131056 (100.00) | 326656 (100.00) |

**Figure 2.4-2.** **$NO_2$ monitor locations in the Atlanta, GA CMSA shown in relation to major roadways, point-source electric generating units, and population densities for total population, and fractions ≤ 17 years and ≥ 65 years.**



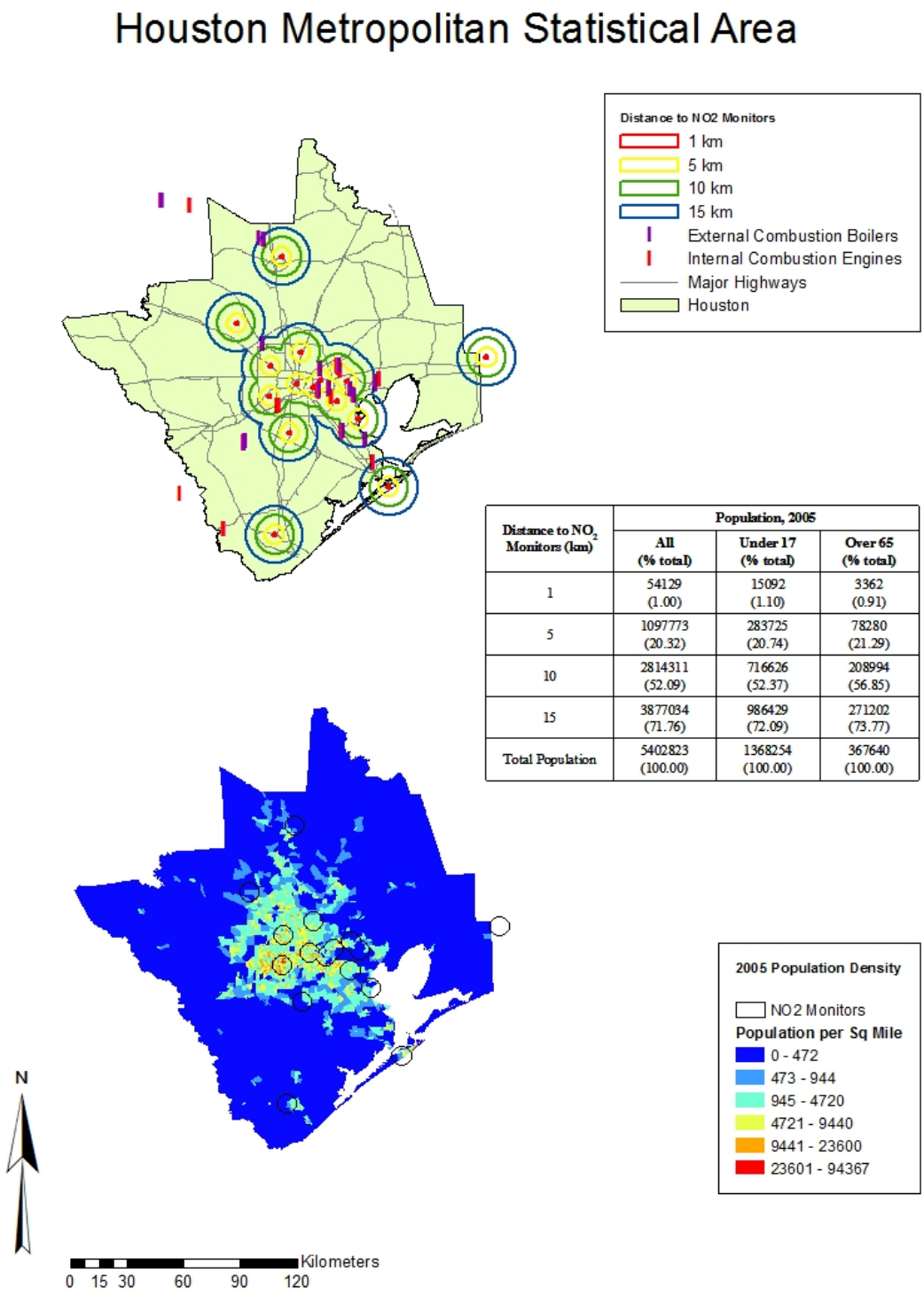

| Distance to $NO_2$ Monitors (km) | Population, 2005 | | |
|---|---|---|---|
| | All (% total) | Under 17 (% total) | Over 65 (% total) |
| 1 | 78208 (1.76) | 12347 (1.20) | 6746 (1.23) |
| 5 | 882753 (19.81) | 170938 (16.65) | 96797 (17.58) |
| 10 | 2096418 (47.05) | 436743 (45.53) | 273560 (49.70) |
| 15 | 2815543 (63.19) | 607414 (59.15) | 371915 (67.56) |
| Total Population | 4455347 (100.00) | 1026862 (100.00) | 550463 (100.00) |

**Figure 2.4-3. $NO_2$ monitor locations in the Boston, MA CMSA shown in relation to major roadways, point-source electric generating units, and population densities for total population, and fractions ≤ 17 years and ≥ 65 years.**



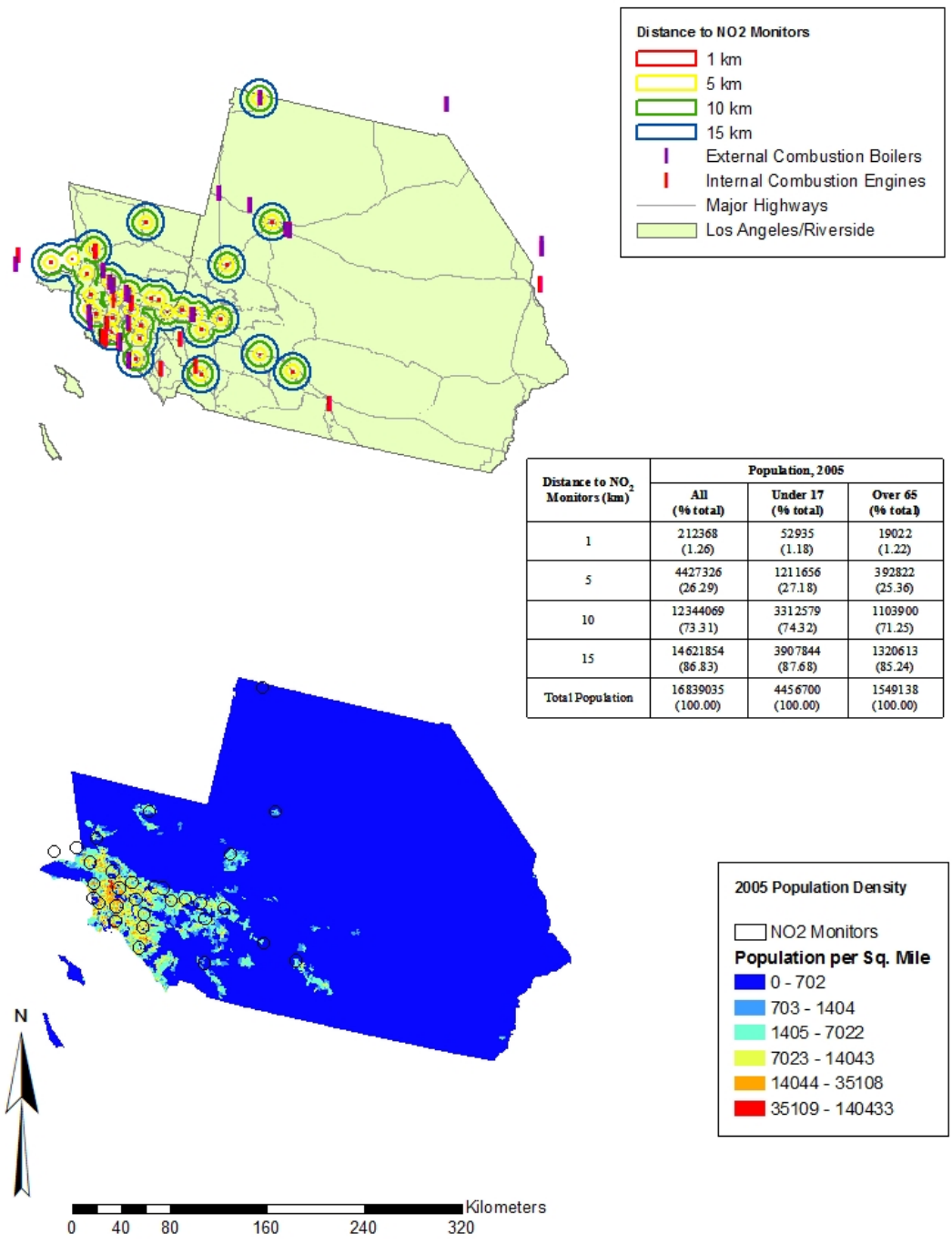

| Distance to $NO_2$ Monitors (km) | Population, 2005 | | |
|---|---|---|---|
| | All (% total) | Under 17 (% total) | Over 65 (% total) |
| 1 | 58892 (0.62) | 14298 (0.58) | 4427 (0.44) |
| 5 | 1264964 (13.26) | 341814 (13.97) | 133355 (13.47) |
| 10 | 3566048 (39.37) | 934752 (38.20) | 414529 (41.86) |
| 15 | 5068806 (53.15) | 1305513 (53.35) | 603605 (60.96) |
| Total Population | 9536173 (100.00) | 2447166 (100.00) | 990200 (100.00) |

**Figure 2.4-4.** **$NO_2$ monitor locations in the Chicago, IL CMSA shown in relation to major roadways, point-source electric generating units, and population densities for total population, and fractions ≤ 17 years and ≥ 65 years.**




| Distance to $NO_2$ Monitors (km) | Population, 2005 | | |
|---|---|---|---|
| | All (% total) | Under 17 (% total) | Over 65 (% total) |
| 1 | 54129 (1.00) | 15092 (1.10) | 3362 (0.91) |
| 5 | 1097773 (20.32) | 283725 (20.74) | 78280 (21.29) |
| 10 | 2814311 (52.09) | 716626 (52.37) | 208994 (56.85) |
| 15 | 3877034 (71.76) | 986429 (72.09) | 271202 (73.77) |
| Total Population | 5402823 (100.00) | 1368254 (100.00) | 367640 (100.00) |

**Figure 2.4-5.** **$NO_2$ monitor locations in the Houston, TX CMSA shown in relation to major roadways, point-source electric generating units, and population densities for total population, and fractions ≤ 17 years and ≥ 65 years.**




| Distance to $NO_2$ Monitors (km) | Population, 2005 | | |
|---|---|---|---|
| | All (% total) | Under 17 (% total) | Over 65 (% total) |
| 1 | 212368 (1.26) | 52935 (1.18) | 19022 (1.22) |
| 5 | 4427326 (26.29) | 1211656 (27.18) | 392822 (25.36) |
| 10 | 12344069 (73.31) | 3312579 (74.32) | 1103900 (71.25) |
| 15 | 14621854 (86.83) | 3907844 (87.68) | 1320613 (85.24) |
| Total Population | 16839035 (100.00) | 4456700 (100.00) | 1549138 (100.00) |

**Figure 2.4-6. $NO_2$ monitor locations in the Los Angeles, CA CMSA shown in relation to major roadways, point-source electric generating units, and population densities for total population, and fractions ≤ 17 years and ≥ 65 years.**

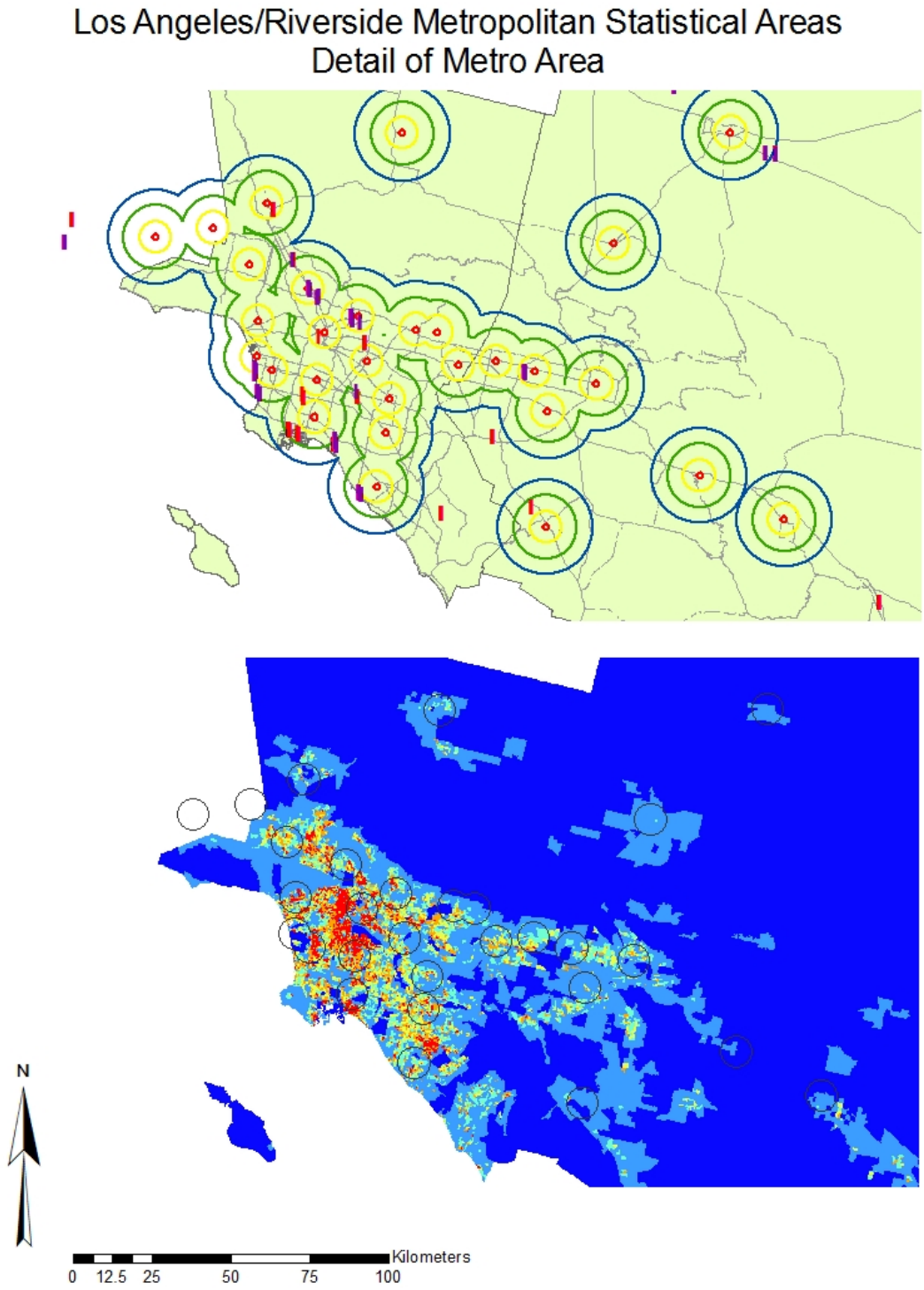
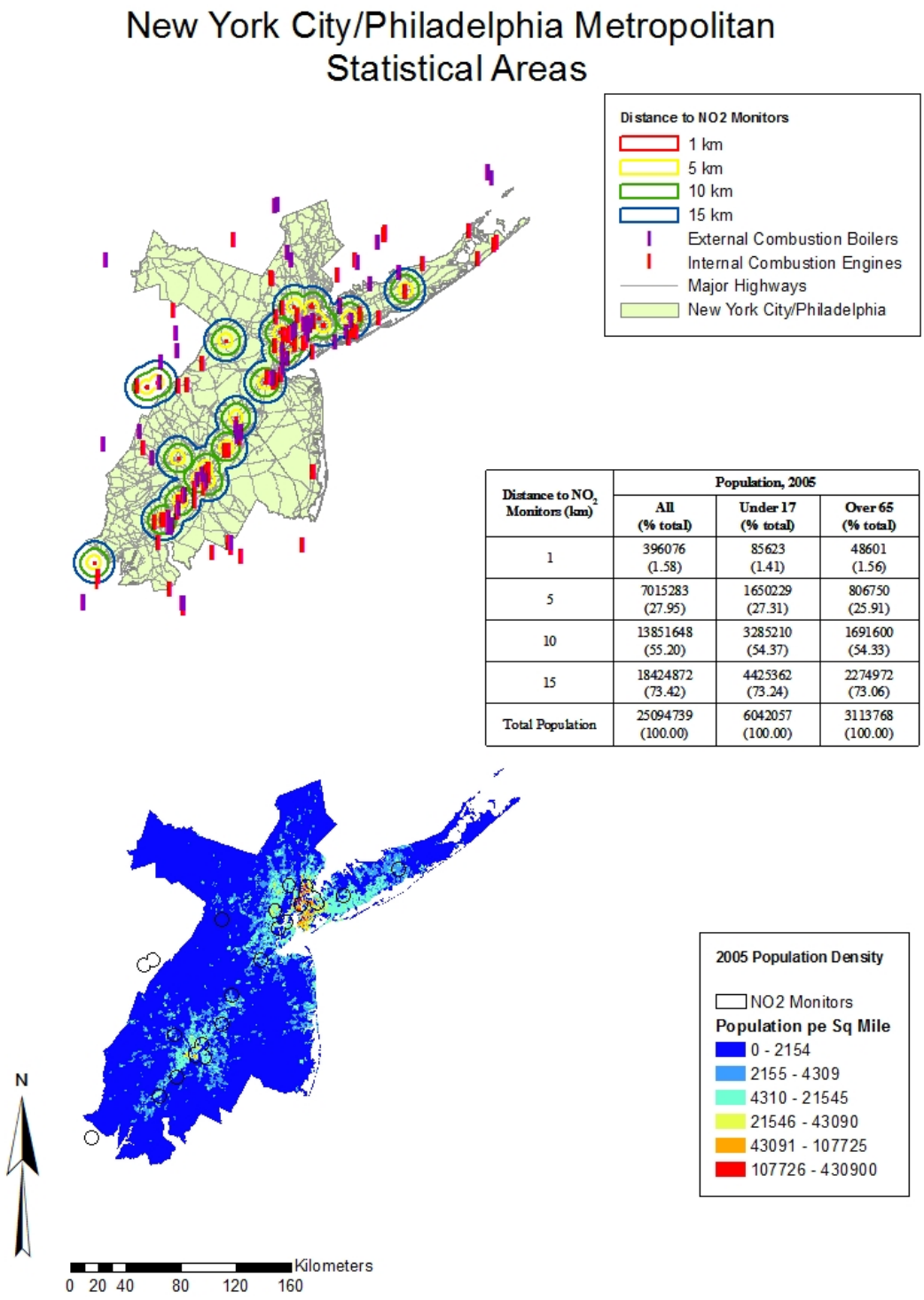



**Figure 2.4-7. Detail of $NO_2$ monitor locations in the Los Angeles, CA CMSA shown in relation to major roadways, point-source electric generating units, and total population density.**




| Distance to $NO_2$ Monitors (km) | Population, 2005 | | |
|---|---|---|---|
| | All (% total) | Under 17 (% total) | Over 65 (% total) |
| 1 | 396076 (1.58) | 85623 (1.41) | 48601 (1.56) |
| 5 | 7015283 (27.95) | 1650229 (27.31) | 806750 (25.91) |
| 10 | 13851648 (55.20) | 3285210 (54.37) | 1691600 (54.33) |
| 15 | 18424872 (73.42) | 4425362 (73.24) | 2274972 (73.06) |
| Total Population | 25094739 (100.00) | 6042057 (100.00) | 3113768 (100.00) |

**Figure 2.4-8. $NO_2$ monitor locations in the New York City, NY and Philadelphia, PA CMSAs shown in relation to major roadways, point-source electric generating units, and population densities for total population, and fractions ≤ 17 years and ≥ 65 years.**

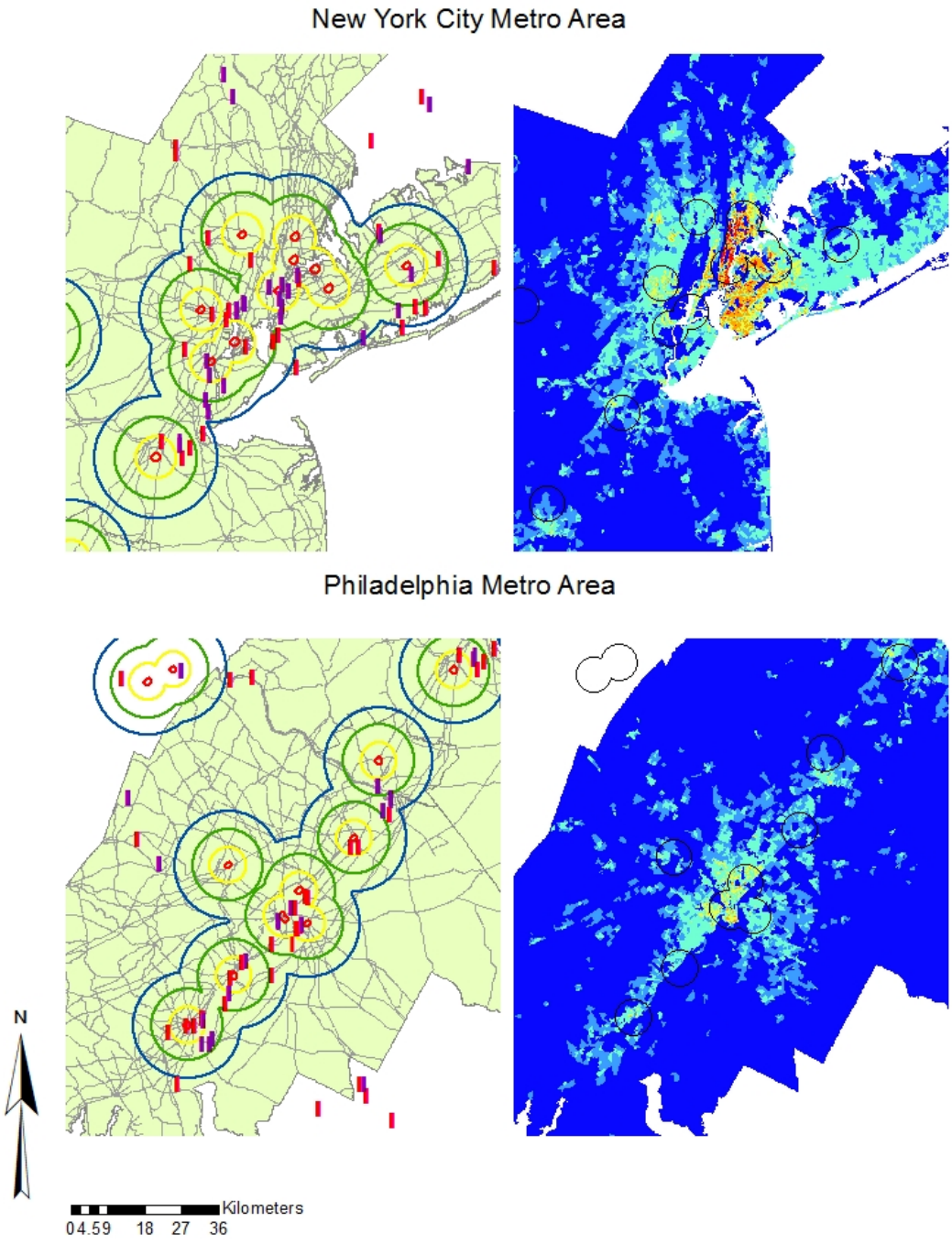
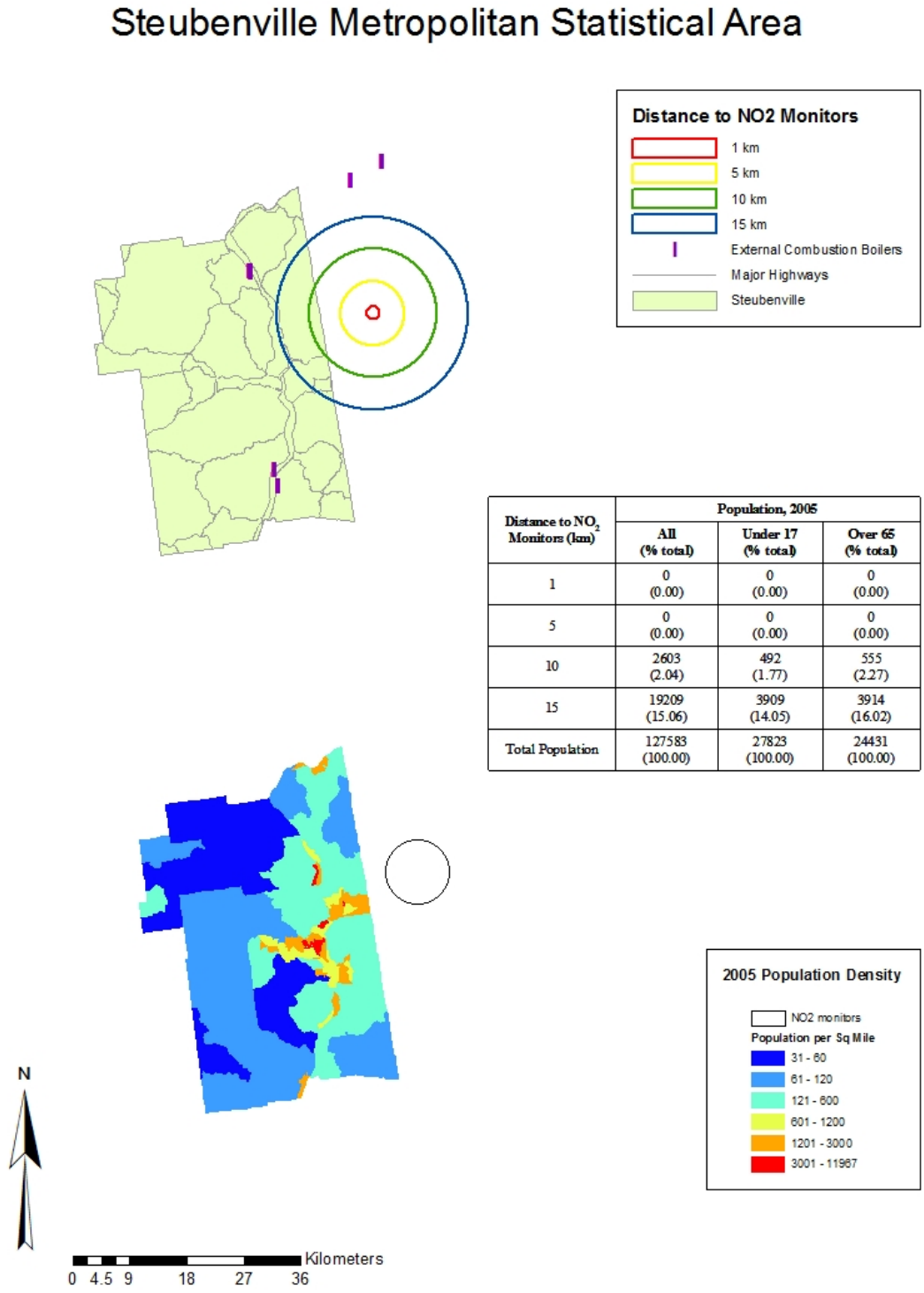
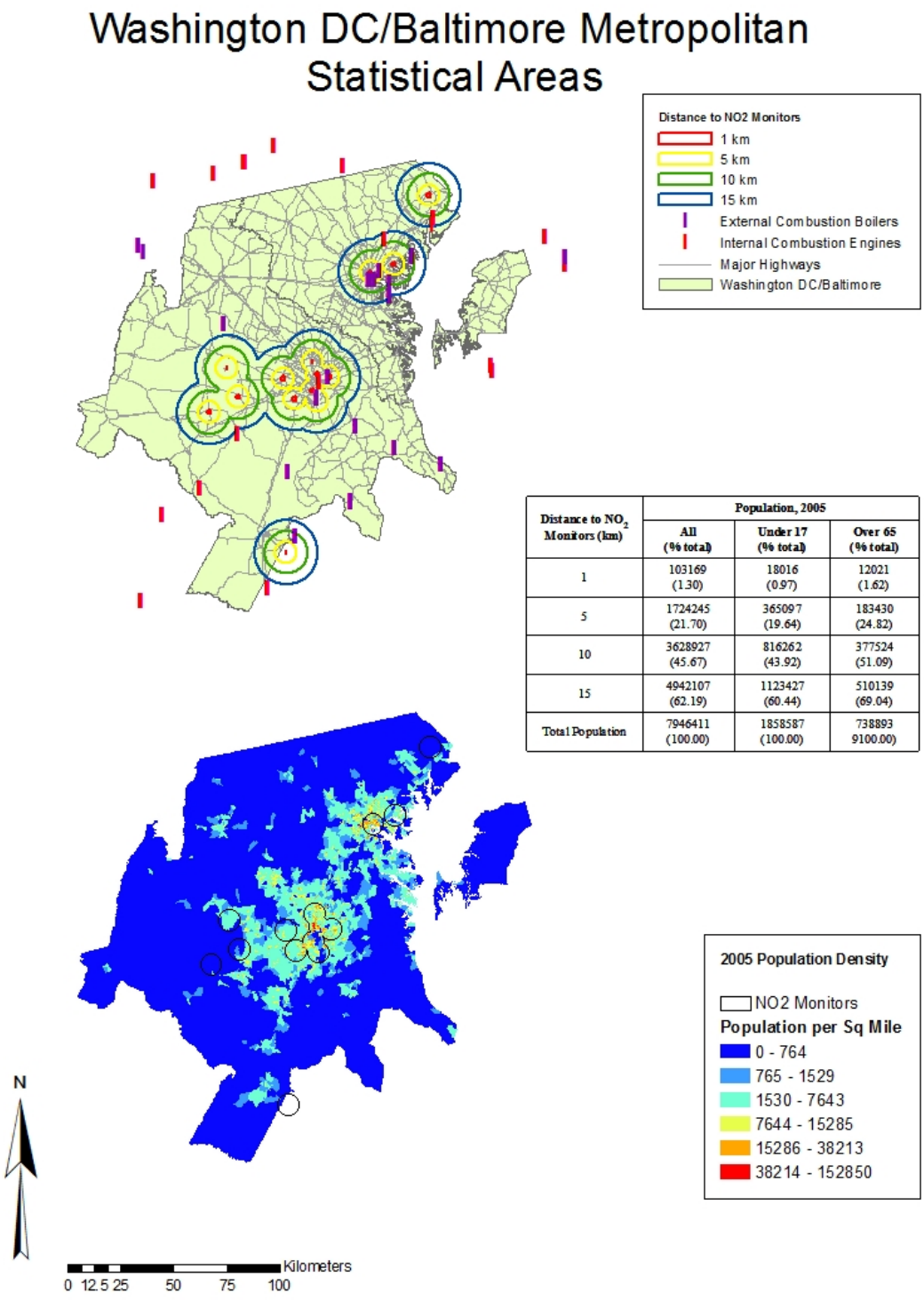



**Figure 2.4-9.** **Detail of $NO_2$ monitor locations in the New York City, NY and Philadelphia, PA CMSAs shown in relation to major roadways, point-source electric generating units, and total population density.**




| Distance to $NO_2$ Monitors (km) | Population, 2005 | | |
|---|---|---|---|
| | All (% total) | Under 17 (% total) | Over 65 (% total) |
| 1 | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| 5 | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| 10 | 2603 (2.04) | 492 (1.77) | 555 (2.27) |
| 15 | 19209 (15.06) | 3909 (14.05) | 3914 (16.02) |
| Total Population | 127583 (100.00) | 27823 (100.00) | 24431 (100.00) |

**Figure 2.4-10. $NO_2$ monitor locations in the Steubenville, OH CMSA shown in relation to major roadways, point-source electric generating units, and population densities for total population, and fractions ≤ 17 years and ≥ 65 years.**




| Distance to $NO_2$ Monitors (km) | Population, 2005 | | |
|---|---|---|---|
| | All (% total) | Under 17 (% total) | Over 65 (% total) |
| 1 | 103169 (1.30) | 18016 (0.97) | 12021 (1.62) |
| 5 | 1724245 (21.70) | 365097 (19.64) | 183430 (24.82) |
| 10 | 3628927 (45.67) | 816262 (43.92) | 377524 (51.09) |
| 15 | 4942107 (62.19) | 1123427 (60.44) | 510139 (69.04) |
| Total Population | 7946411 (100.00) | 1858587 (100.00) | 738893 9100.00) |

**Figure 2.4-11. $NO_2$ monitor locations in the Washington, DC and Baltimore, MD CMSAs shown in relation to major roadways, point-source electric generating units, and population densities for total population, and fractions ≤ 17 years and ≥ 65 years.**

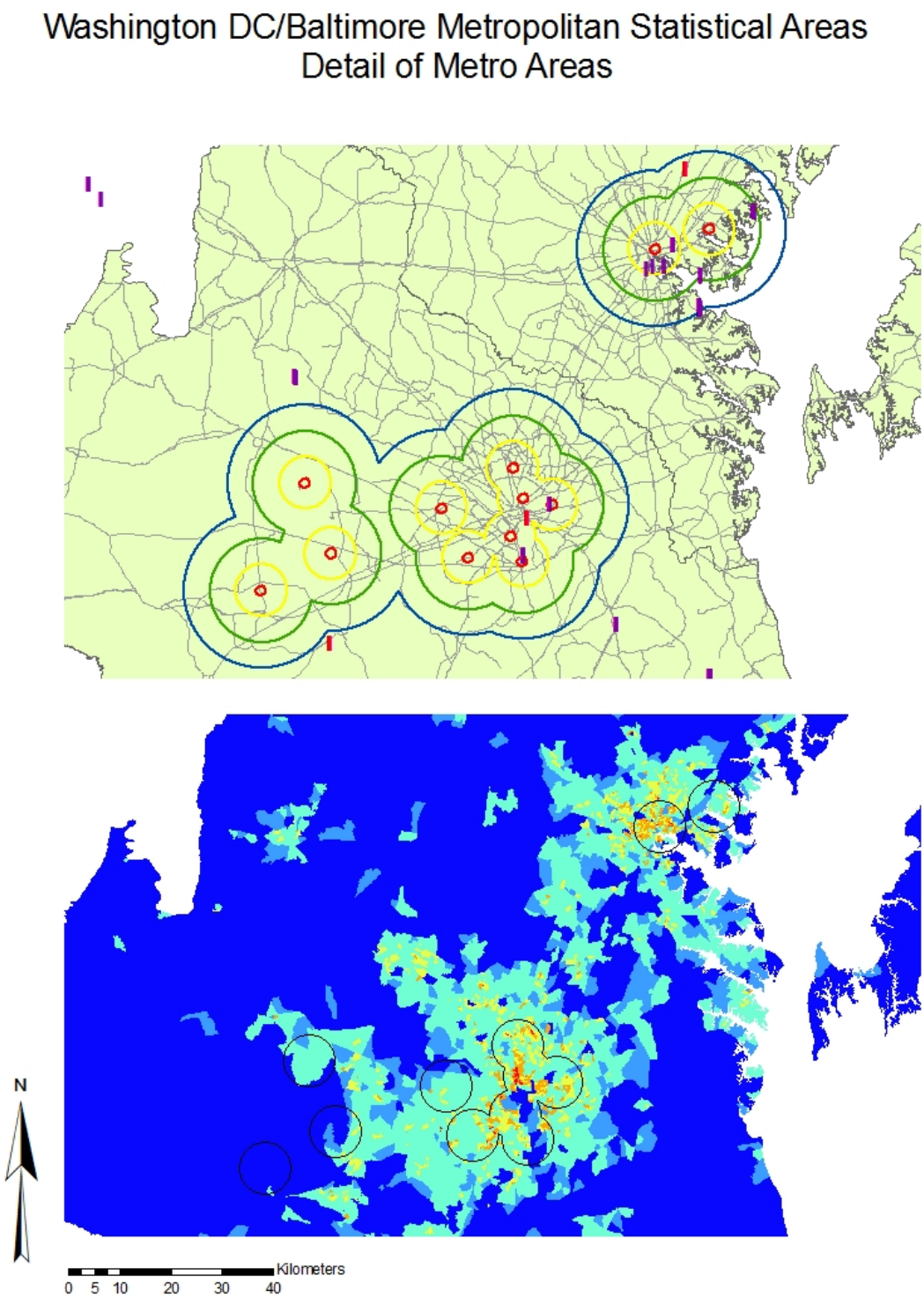



**Figure 2.4-12. Detail of $NO_2$ monitor locations in the Washington, DC and Baltimore, MD CMSAs shown in relation to major roadways, point-source electric generating units, and total population density.**

The study areas included 8 regions comprising 11 metropolitan statistical areas (MSAs), as defined by the U.S. Census Bureau (http://www.census.gov/): Atlanta, Boston, Chicago, Houston, Steubenville, Los Angeles/Riverside, Washington DC/Baltimore, and New York City/Philadelphia. All pertinent census data (state, Metropolitical Statistical Area [MSA], county, and census block maps) were obtained from the ArcGis 9.2 Media Kit provided by ESRI (2006). Census blocks served as the unit of analysis for population calculations. All geospatial analyses were performed in ArcMap (Build 1324). $NO_2$ monitor location data (i.e., latitude/longitude) for 2004 were obtained from EPA's AirData website (http://www.epa.gov/air/data/). Monitors were mapped for a particular region if they were within 15 kms of its boundary. Information on point sources (i.e., fossil fueled electrical power generators) for 2002 was obtained from the National Emissions Inventory (U.S. Environmental Protection Agency, 2006b). Point sources were classified by their Source Classification Codes (SCC): 1010xxxx for electric generation: external combustion boilers, and 2010xxxx for electric generation: internal combustion engines. Point sources were mapped for a particular region if they were within 30 kms from its boundary.

All census maps were projected into ArcMap using the North American Datum of 1983 and the USA Contiguous Lambert Conformal Conic projection coordinate system to allow for calculation of linear distances. $NO_2$ monitor and point source locations for a particular region were then imported into their respective maps and buffer zones of 1, 5, 10, and 15 kms were constructed around the monitor locations. The total population and populations of 2 sensitive subgroups (those $\leq 17$ and those $\geq 65$) were then calculated for those areas using the population data contained within the census block maps.

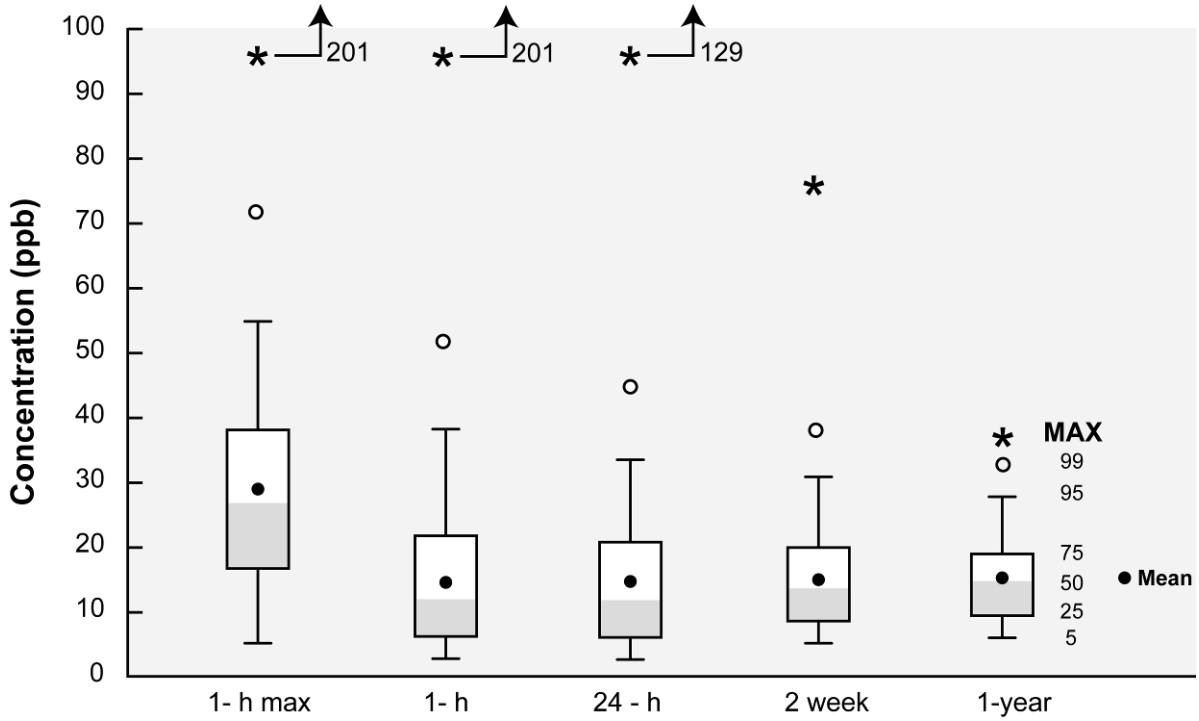



**Figure 2.4-13. Ambient concentrations of $NO_2$ measured at all monitoring sites located within MSAs in the U.S. from 2003 through 2005.**
*** max; • mean**

Figure 2.4-13 shows box plots of ambient concentrations of $NO_2$ measured at all monitoring sites located within MSAs or urbanized areas in the U.S. from 2003 through 2005. As can be seen from Figure

2.4-13 mean $NO_2$ concentrations are ~15 ppb for averaging periods ranging from a day to a year, with an interquartile range (IQR) of 10 to 25 ppb. However, the average of the daily 1-h max $NO_2$ concentration over this 3-year period is ~30 ppb. These values are about twice as high as the 24-h avg. The highest maximum hourly concentration (~200 ppb) found during the period of 2003 to 2005 was more than a factor of ten greater than the overall mean 24-h concentrations. The ratio of the 99th percentile concentration to the mean ranges from 2.1 for the 1-year avgs to 3.5 for the 1-h avgs.

Because ambient $NO_2$ monitoring data are so sparse across the U.S. (see Figure 2.4-1) and particularly so in rural areas, it would not be appropriate to use these data in constructing a map of $NO_2$ concentrations across the continental U.S. The short $\tau$ of $NO_2$ with respect to conversion to $NO_Z$ species and the concentrated nature of $NO_2$ emissions result in steep gradients and low concentrations away from major sources that are not adequately captured by the existing monitoring networks. Model predictions might be more useful for showing large-scale features in the distribution of $NO_2$ and could be used in conjunction with the values shown in Figure 2.4-13 to provide a more complete picture of the variability of $NO_2$ across the U.S. Monthly avg $NO_2$ concentrations for January and July 2002 calculated using EPA's CMAQ model are shown in Figures 2.4-14. (A description of the capabilities of CMAQ and other three-dimensional CTMs is given in Annex section AX2.5.) The high variation in $NO_2$ concentrations of at least a factor of 10 is apparent in these model estimates. As expected, the highest $NO_2$ concentrations are seen in large urban regions, such as the Northeast Corridor, and lowest values are found in sparsely populated regions located mainly in the West. $NO_2$ concentrations tend to be higher in January than in July.

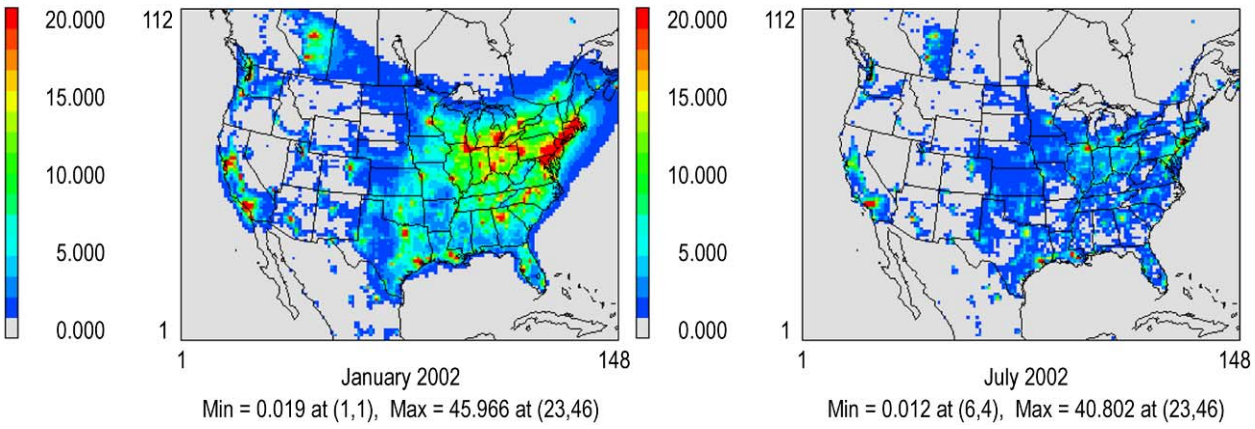



**Figure 2.4-14. Monthly average $NO_2$ concentrations in ppb for January 2002 (left panel) and July 2002 (right panel) calculated by CMAQ (36 X 36 km horizontal resolution).**

## 2.4.2. $NO_2$ Concentrations

Trends in $NO_2$ concentrations across the U.S. from 1980 to 2006 are shown in Figure 2.4-15. The white line shows the mean values and the upper and lower borders of the blue (shaded) areas represent the 10th and 90th percentile values. Information on trends at individual, local air monitoring sites can be found at www.epa.gov/airtrends/nitrogen.html.

Concentrations were substantially higher during earlier years in selected locations and contributed in those years to the "brown clouds" observed in many cities. Residents in Chattanooga, TN, for example, were exposed more than 30 years ago to high levels of $NO_2$ from a munitions plant (Shy and Love, 1980). Annual mean $NO_2$ concentrations there declined from ~102 ppb in 1968 to ~51 ppb in 1972. There was a

strike at the munitions plant in 1973 and levels declined to ~32 ppb. With the implementation of control strategies, values dropped further. In 1988, the annual mean $NO_2$ concentration varied from ~20 ppb in Dallas, TX and Minneapolis, MN to 61 ppb in Los Angeles, CA. However, New York City, with the second-highest annual mean concentration in the U.S. in 1988, the mean $NO_2$ concentration was 41 ppb.

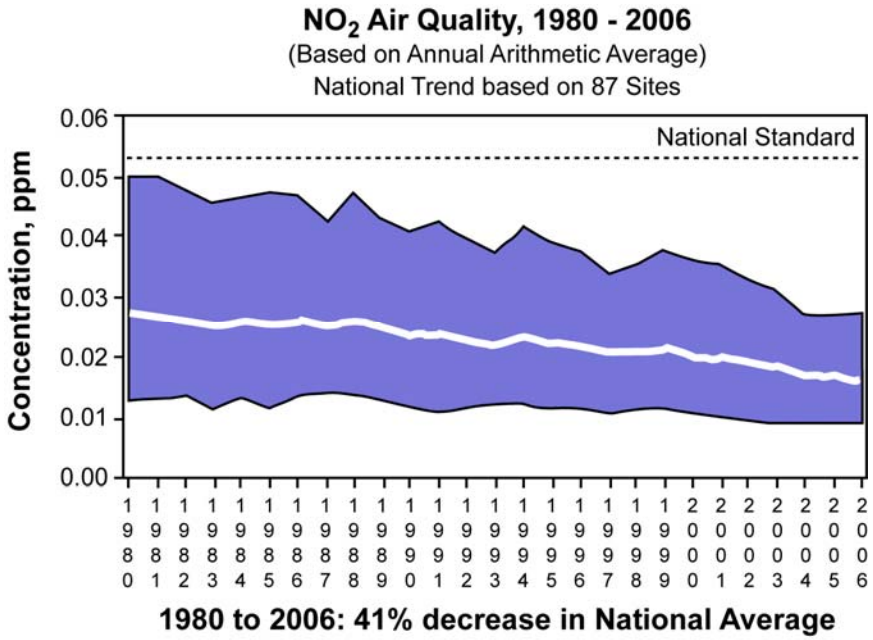



**Figure 2.4-15. Nationwide trend in $NO_2$ concentrations.The white line shows the mean values, and the upper and lower borders of the blue (shaded) areas represent the 10th and 90th percentile values. Information on trends at local air monitoring sites: www.epa.gov/airtrends/nitrogen.html.**

In contrast to most urban areas in the U.S., in other countries, $NO_2$ concentrations have increased. For example, annual mean $NO_2$ concentrations in central London increased during the 1980s from ~25 ppb in 1978 to ~40 ppb in 1989 at the background measurement site and from ~35 to ~45 ppb at the roadside site. Corresponding NO concentrations increased from ~20 ppb to ~40 ppb at the background site and from ~125 to ~185 ppb at the roadside site (Elsom, 2002). Increased use of motor vehicles may have contributed to much of these increases in $NO_2$ levels.

## 2.4.3. Seasonal Variability in $NO_2$ at Urban Sites

The month-to-month variability in 24-h avg $NO_2$ concentrations at two sites in Atlanta, GA is shown in Figure 2.4-16. Variability at other individual sites in selected urban areas is shown in Annex Figures AX3.2-1 to AX3.2-6. As might be expected from an atmospheric species that behaves essentially like a primary pollutant emitted from surface sources, there is strong seasonal variability in $NO_2$ concentrations in the data shown in Figures 2.4-16a-b. Higher concentrations are found during winter, consistent with the lowest mixing layer heights found during the year. Lower concentrations are found during summer, consistent with higher mixing layer heights and increased rates of photochemical oxidation of $NO_2$ to $NO_Z$. Note also the day-to-day variability in $NO_2$ concentration, which also tends to be larger during the winter. There appears to be a somewhat regular pattern for the other southern cities examined with their winter maxima and summer minima.

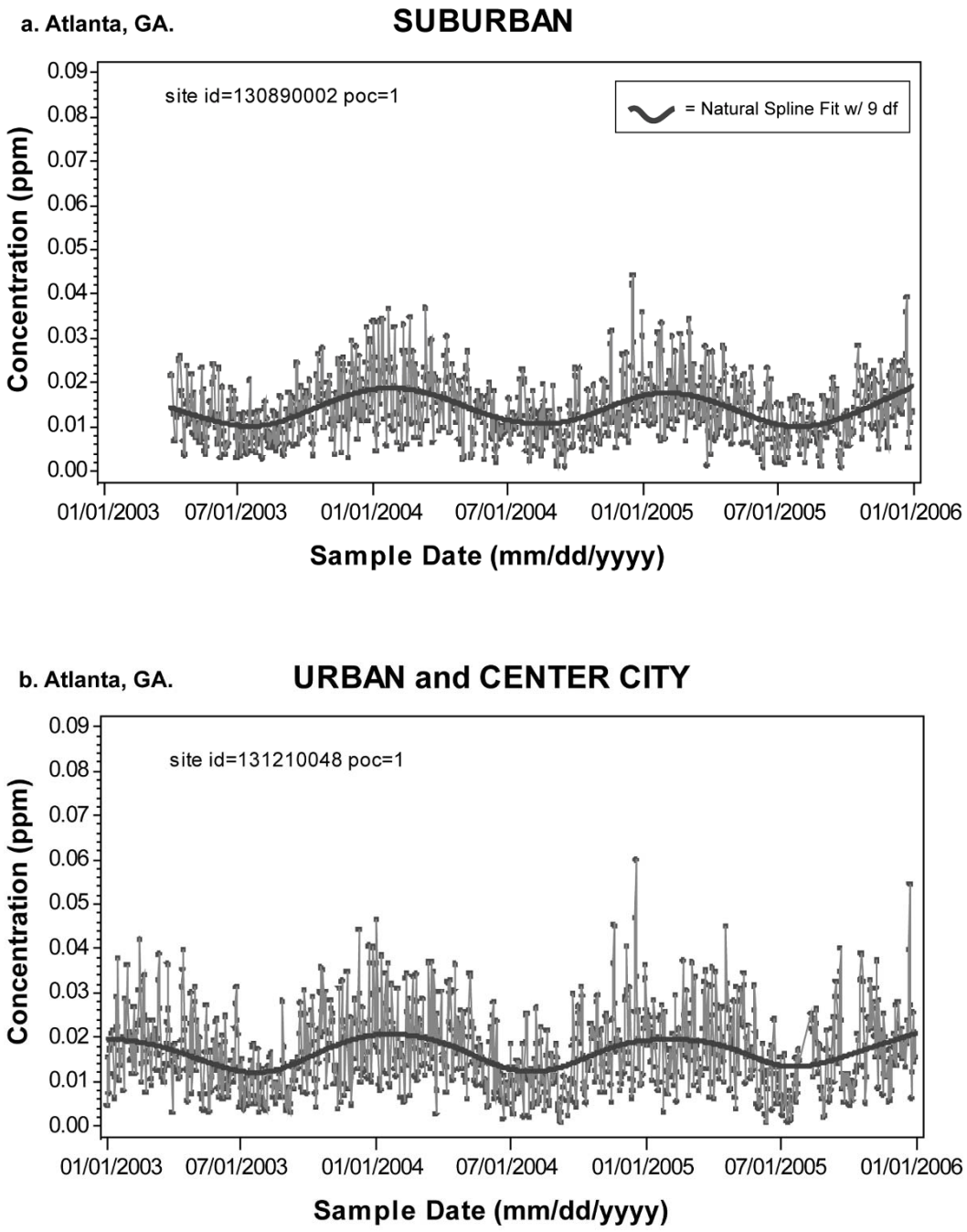



**Figure 2.4-16. Time series of 24-h avg $NO_2$ concentrations at individual sites in Atlanta, GA from 2003 through 2005. A natural spline function (with 9 degrees of freedom) was fit and overlaid to the data (dark solid line).**

Monthly maxima tend to be found from late winter to early spring in Chicago, IL, and New York, NY, with minima occurring from summer through the fall. However, in Los Angeles and Riverside, CA, monthly maxima tend to occur from autumn through early winter, with minima occurring from spring through early summer. Mean and peak $NO_2$ concentrations during winter can be up to a factor of two greater than those during the summer at sites in Los Angeles.

## 2.4.4. Diurnal Variability in $NO_2$ Concentrations

The diurnal variability in $NO_2$ concentrations at the same two sites in the Atlanta metropolitan area shown in Figure 2.4-16 is illustrated in Figure 2.4-17. As can be seen from these figures, $NO_2$ typically exhibits daily maxima during the morning rush hours, although they can occur at other times of day. In addition, there are differences between weekdays and weekends. At both sites, $NO_2$ concentrations are generally lower and the diurnal cycles more compressed on weekends than on weekdays. The diurnal variability of $NO_2$ at these sites is typical of that observed at other urban sites. Monitor siting plays a role in determining diurnal variability in the sense that monitors located farther from traffic will measure lower concentrations and show a flatter overall distribution of data compared to monitors located closer to traffic.

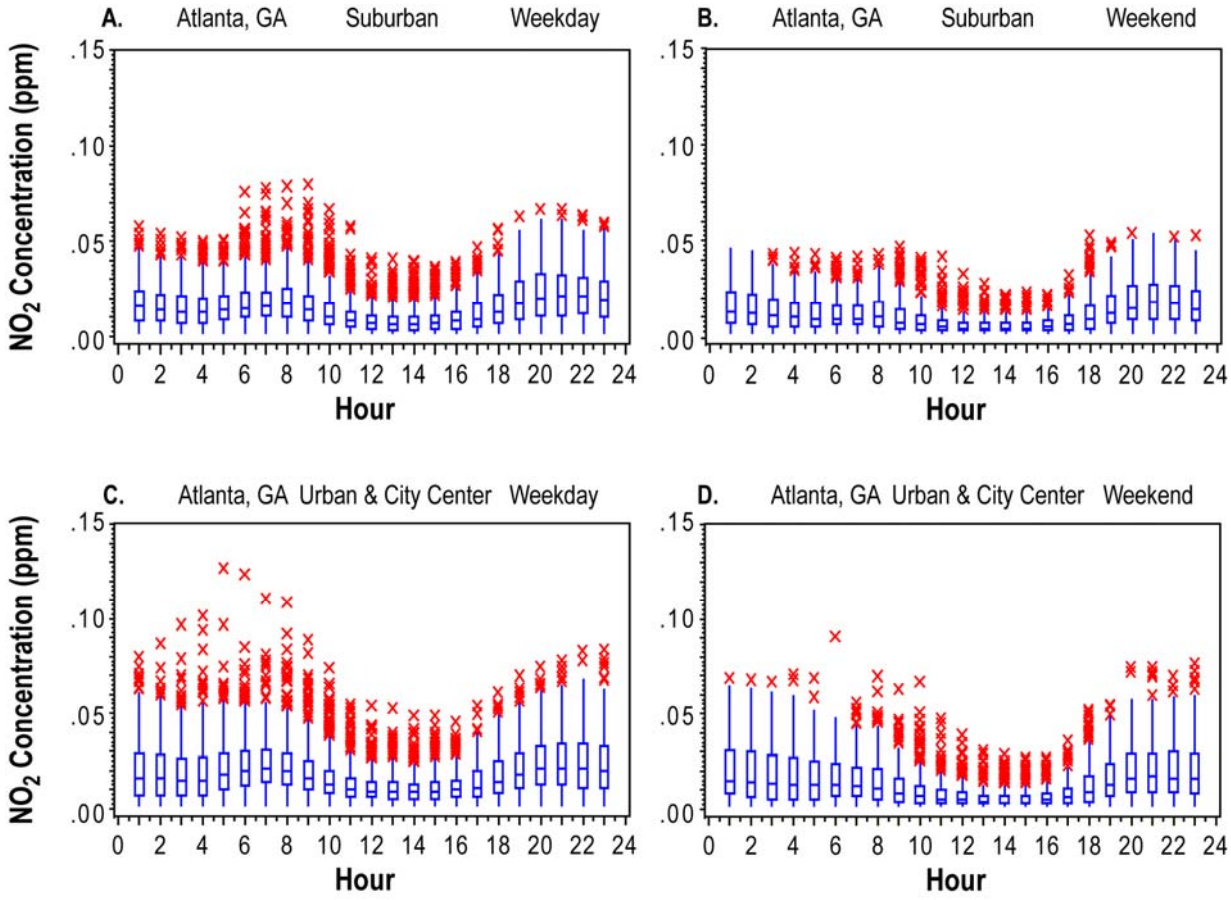



**Figure 2.4-17. Mean hourly $NO_2$ concentrations on weekdays and weekends measured at two sites in Atlanta, GA. A and B refer to a suburban site, and C and D refer to a site classified as urban and city center.**

## 2.4.5. Concentrations of $NO_Z$ Species

Data for concentrations of $NO_Z$ species in urban areas in the U.S. are sparse. The most comprehensive set of data for any $NO_Z$ species was obtained for $HNO_3$ as part of the Children's Health Study for which gas-phase $HNO_3$ was measured at 12 sites in southern California from 1994 through 2001 (Alcorn et al., 2004). Two week avg concentrations ranged from <1 ppb to >10 ppb, with the highest $HNO_3$ concentrations and the highest ratio of $HNO_3/NO_2$ (~0.2) found downwind from central Los Angeles in the San Bernadino during summer, as one would expect for this more oxidized *N* product.

Measurements of HONO in urban areas are very limited; however, data from Stutz et al. (2004) and Wang and Lu (2006) indicate that levels of HONO are <1 ppb even under heavily polluted conditions, with the highest levels found during the night and just after dawn and the lowest values found in the afternoon. However, data collected in the U.K. (AQEG, 2004; Lammel and Cape, 1996) and in the U.S. (Kirchstetter and Harley, 1996) indicate that HONO to $NO_X$ ratios could be of the order of ~5 % in motor vehicle emissions. These results indicate that HONO levels in traffic could be comparable to those of $NO_2$. Several field studies conducted at ground level (Hayden et al., 2003, near Boulder CO; Williams et al., 1987) and aircraft flights (Singh et al., 2007, over eastern North America), have found much higher $NO_Z$ concentrations than $NO_X$ concentrations in relatively unpolluted rural air. Additional information for the concentrations of $NO_Z$ species can be found in Annex section AX3.2.5.

## 2.4.6. Policy-Relevant Background Concentrations of $NO_2$

Background $NO_2$ concentrations used for purposes of informing decisions about NAAQS are referred to as PRB concentrations. PRB concentrations are those that would occur in the U.S. in the absence of anthropogenic emissions in continental North America (defined here as the U.S., Canada, and Mexico). PRB concentrations include contributions from natural sources everywhere in the world and from anthropogenic sources outside these three countries. Background levels defined in this way facilitate separation of pollution levels that can be controlled by U.S. regulations (or through international agreements with neighboring countries) from levels that are generally uncontrollable by the U.S. These levels may also be used in quantitative risk assessments of human health and environmental effects.

Contributors to PRB concentrations include natural emissions of NO, $NO_2$, and reduced nitrogen compounds, as well as their long-range transport from outside North America. Natural sources of $NO_2$ and its precursors include biogenic emissions, wildfires, lightning, and the stratosphere. Biogenic emissions from agricultural activities, such as emissions of NO from fertilized soils, are not considered to be contributing to the formation of PRB concentrations. Discussions of the sources and estimates of emissions are given in Annex section AX2.4.2.

### 2.4.6.1. Analysis of Policy-Relevant Background Contribution

The MOZART-2 global model of tropospheric chemistry (Horowitz et al., 2003) is used to estimate the PRB contribution to $NO_2$ concentration. The model setup for the present-day simulation has been published in a series of papers from a recent model intercomparison (Dentener et al., 2006a; 2006b; Shindell et al., 2006; Stevenson et al., 2006). MOZART-2 is driven by the U.S. National Oceanic and Atmospheric Administration's National Center for Environmental Prediction (NOAA NCEP) meteorological fields using 2001 data and using 2000 emissions from the International Institute for Applied Systems Analysis (IIASA). The model was run at a resolution of 1.9° X 1.9° with 28 sigma levels in the vertical dimension with both gas-phase and aerosol chemistry.

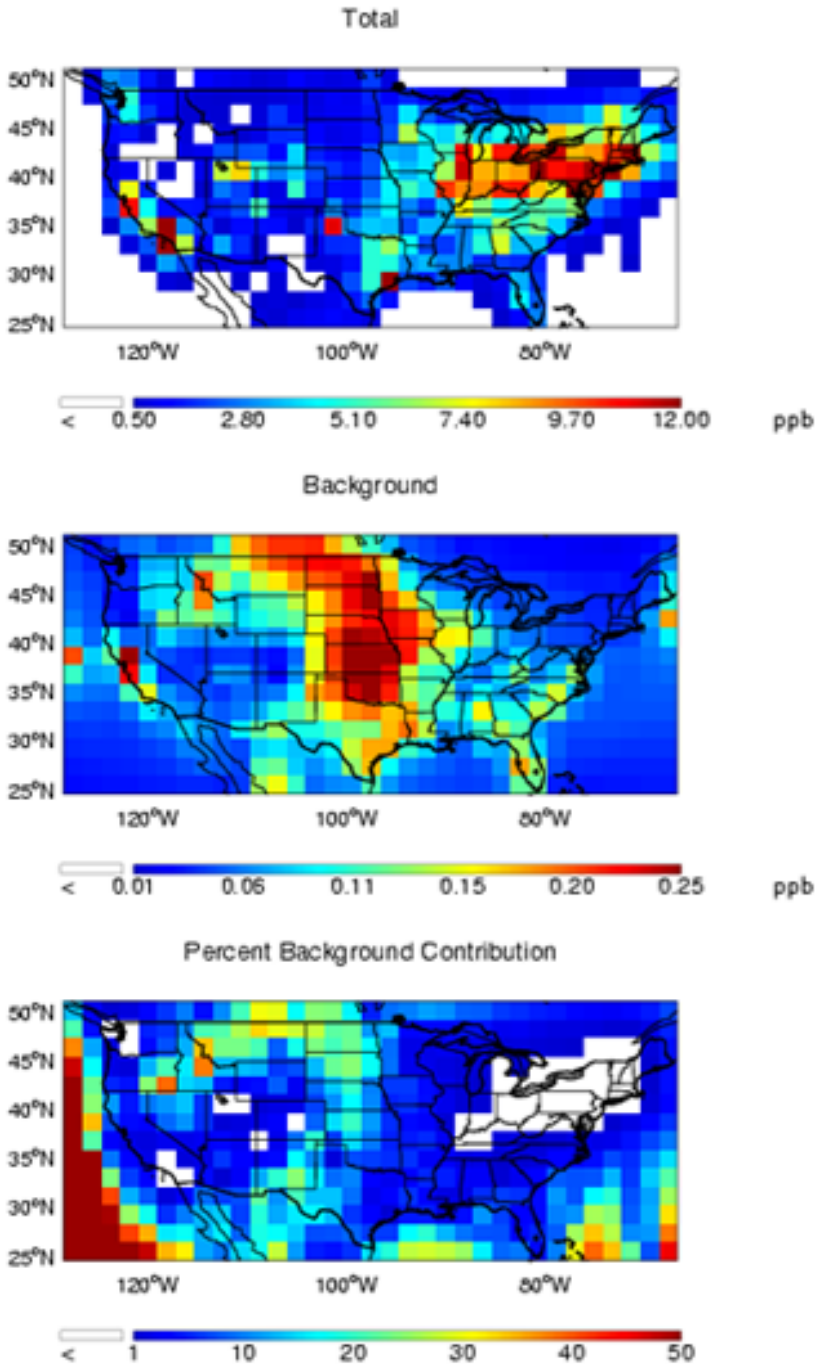



**Figure 2.4-18. Upper panel: Annual mean $NO_2$ concentrations (in ppb) in the U.S. Middle panel: Annual mean PRB concentrations (in ppb) for $NO_2$ in the U.S. These simulations were made using the MOZART-2 global, chemical transport model. The lower panel shows PRB concentrations expressed as a percentage of total $NO_2$ concentrations shown in the upper panel. See text in Annex section AX2.7 for details.**

Figure 2.4-18 shows the annual mean $NO_2$ concentration in surface air in the base case simulation (top panel) and the PRB simulation (middle panel), along with the percentage contribution of the background to the total base case $NO_2$ (bottom panel). Maximum concentrations in the base case simulation occur along the Ohio River Valley and in the Los Angeles basin. While total surface $NO_2$ concentrations are often >5 ppb, PRB is <300 parts per trillion (ppt) over most of the continental U.S. and <100 ppt in the eastern U.S. The distribution of PRB (middle panel of Figure 2.4-18 largely reflects the distribution of soil NO emissions, with some local increases like those in western Montana due to biomass burning. In the northeastern U.S., where present-day $NO_2$ concentrations are highest, PRB contributes <1% to the total. Thus, it appears that PRB levels of $NO_2$ are much smaller than observed levels.

### 2.4.7. Summary of Ambient and Policy-Relevant Background Concentrations of $NO_2$

The annual avg $NO_2$ concentrations of ~15 ppb reported by the regulatory monitoring networks are well below the level of the current NAAQS (0.053 ppm). However, daily maximum 1-h avg concentrations can be greater than 100 ppb in some locations, e.g., areas with heavy traffic. Policy-Relevant Background concentrations of $NO_2$ are much lower than average ambient concentrations and are typically less than 0.1 ppb over most of the U.S., with the highest values found in agricultural areas.

## 2.5. Exposure Issues

### 2.5.1. Introduction

Human exposure to an airborne pollutant consists of contact between the human and the pollutant at a specific concentration for a specified period of time. People spend various amounts of time in different microenvironments characterized by different pollutant concentrations. The integrated exposure of a person to a given pollutant is the sum of the exposures over all time intervals for all microenvironments in which the individual spends time. Figure 2.5-1 represents a composite average of activity patterns across all age groups in the U.S. based on data collected in the National Human Activity Pattern Survey (NHAPS) (Klepeis et al., 2001). The demographic distribution of the respondents was designed to be similar to that of overall U.S. Census data. Different cohorts, e.g., the elderly, young and middle-aged working adults, and children exhibit different activity patterns.[1]

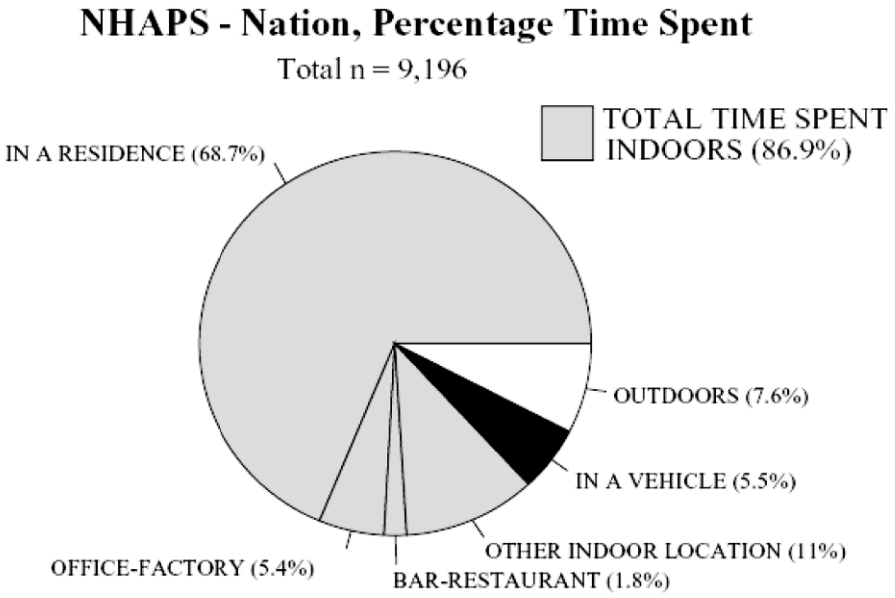
An individual's exposure to a pollutant, such as $NO_2$, can be represented by:

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

where $E_T$ is an individual's total personal exposure for a specific time period, $n$ is the total number of microenvironments encountered, $C_i$ is the average concentration, and $t_i$ is the time spent in the $i$th microenvironment. 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

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

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.




Source: Klepeis et al. (2001)

**Figure 2.5-1. Percentage of time people spend in different environments in the U.S.**

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

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

subject to the constraint,

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

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

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

where $y$ is the fraction of time persons spend outdoors, and α is the ratio of a person's exposure to a pollutant of ambient origin to the pollutant's ambient concentration (or the ambient exposure factor with a

value between 0 and 1). Other symbols have the same definitions in Equation 2.5-2 and 2.5-3. If microenvironmental concentrations are considered, then Equation 2.5-4 can be recast as:

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

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

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

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

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

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

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

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

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

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

addition, exposure to nonambient, microenvironmental sources modifies the relationship between personal exposures and ambient concentrations.

In practice, it is extremely difficult to characterize community exposure by individual personal exposure. Instead, the distribution of personal exposure in a community, or the population exposure, is characterized by extrapolating measurements of personal exposure using various techniques or by stochastic, deterministic, or hybrid exposure modeling approaches such as Air Pollution Exposure (APEX), Simulation of Human Exposure and Dose System (SHEDS), and Modeling Environment for Total Risk for One-Atmosphere (MENTOR) (see Annex section AX3.6 for a description of exposure modeling methods). Variations in community-level personal exposures are determined by cross-community variations in ambient pollutant concentrations and the physical and exposure factors mentioned above. These factors also determine the strength of the association between population exposure to $NO_2$ of ambient origin and ambient $NO_2$ concentrations.

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

## 2.5.2. Personal Sampling of $NO_2$

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

The most widely used passive samplers are Palmes tubes (Palmes et al., 1976), Yanagisawa badges (Yanagisawa and Nishimura, 1982), Ogawa samplers (Ogawa and Company, http://www.ogawausa.com), and radial diffusive samplers (Cocheo et al., 1996). The methodology and application of Palmes tubes and Yanagisawa badges were described in the last $NO_X$ AQCD (U.S. Environmental Protection Agency, 1993). Descriptions of other commercialized samplers are given in Annex section AX3.3. These samplers do not use a pump to bring air into contact with the sampling substrate; rather, they rely on diffusion or small scale turbulence to transport $NO_2$ to a sorbent (Krupa and Legge, 2000). The sorbent can be either physically sorptive (e.g., active carbon) or chemisorptive (e.g., triethanolamine [TEA], KI, sodium arsenite [$NaAsO_2$]); passive samplers for $NO_2$ are chemisorptive, i.e., a reagent coated on a support (e.g., metal mesh, filter) chemically reacts with and captures $NO_2$. The sorbent is extracted and analyzed for one or more reactive derivatives; the mass of $NO_2$ collected is derived from the concentration of the derivative(s) based on the stoichiometry of the reaction. A number of studies indicate that passive samplers have very good precision, generally within 5% (Gair et al., 1991; Gair and Penkett, 1995; Kirby et al., 2001; Plaisance et al., 2004).

$NO_2$ concentrations measured outdoors by Palmes tube passive samplers were a factor of 1.26 higher than those measured by the chemiluminescence method in a study in the UK (Campbell et al., 1994). Campbell et al. proposed that differences could be attributed mainly to wind-driven turbulent mixing in the mouth of the Palmes tube. Deposition driven by turbulence would raise the uptake rate on the tube surface compared to the theoretical value, which is based on molecular diffusion along the length of the tube. Other field evaluation studies showed that the overall avg $NO_2$ concentrations calculated from

diffusion tube measurements were likely to be within ± 10% of chemiluminescent measurement data (Bush et al., 2001) and for Ogawa passive samplers (Mukerjee et al., 2004).

A number of factors could affect the performance of passive samplers. Passive sampler performance has not been extensively studied over a wide range of concentrations, wind velocities, temperatures, and relative humidities (Varshney and Singh, 2003). Variability in environmental conditions (e.g., temperature, wind speed, humidity) can affect the performance of passive samplers because they can cause variations in sampling rates throughout the sampling period. Chemical reactions between $O_3$ and NO occur in the diffusion tube especially at roadsides where NO concentrations are relatively high and when sufficient $O_3$ is present for interconversion between the species resulting in an overestimate of $NO_2$ (Heal et al., 1999). There could also be differential sensitivity to other forms of $NO_Y$, such as HONO, PAN, and $HNO_3$, between the passive samplers and the chemiluminescence analyzers (Gair et al., 1991). However, the kinetics and stoichiometry of interferent compound reactions have not been well established. The lack of specificity of the substrate towards uptake of $NO_2$ could also be an issue, as $SO_2$ can interfere with the uptake of $NO_2$ (Cox, 2003). Another aspect of passive sampler performance is that, compared with ambient chemiluminescence monitors, passive samplers give relatively longer time-averaged concentrations (from days to weeks), with higher detection limits over short sampling periods. Consequently, diffusive samplers including those used for $NO_2$ monitoring provide integrated but not high time-resolution concentration measurements. Hourly fluctuations in $NO_2$ concentrations may be important to the evaluation of exposure-health effects relationships, and continuous monitors, such as the chemiluminescent monitors, remain the only approach for estimating short-term, peak exposures.

## 2.5.3. Spatial Variability in $NO_2$ Concentrations

### 2.5.3.1. Variability of $NO_2$ Concentrations across Ambient Monitoring Sites

Summary statistics for the spatial variability in several urban areas across the U.S. are shown in Table 2.5-1. Data were obtained from EPA's Air Quality System (AQS). These areas were chosen because they are major urban areas with at least five monitors operating from 2003 to 2005. Values in parentheses indicate the number of monitoring sites in that particular city. The second column shows the 3-year mean concentration across all monitors and the range in these means at individual monitor sites. Metrics for characterizing spatial variability include the use of Pearson correlation coefficients (r; column 3), the 90th percentile of the absolute difference in concentrations (column 4), and coefficient of divergence (COD; column 5). The ranges represent results of pairwise monitor comparisons.

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

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

where $X_{ij}$ and $X_{ik}$ represent observed concentrations averaged over some measurement averaging period (hourly, daily, etc.), for measurement period $i$ at site $j$ and site $k$, and $p$ is the number of observations. A COD of 0 indicates there are no differences between concentrations at paired sites (spatial homogeneity), while a COD approaching 1 indicates extreme spatial heterogeneity.

**Table 2.5-1. Spatial variability of $NO_2$ in selected U.S. urban areas.**

| URBAN AREA (# OF MONITORS) | 3-YEAR MEAN CONCENTRATION (RANGE) | PEARSON CORRELATION COEFFICIENT | $90^{TH}$ PERCENTILE DIFFERENCE BETWEEN MONITORS | COEFFICIENT OF DIVERGENCE |
|---|---|---|---|---|
| New York, NY (5) | 29 ppb (25–37) | 0.77–0.90 | 7–19 | 0.08–0.23 |
| Atlanta, GA (5) | 11 ppb (5–16) | 0.22–0.89 | 7–24 | 0.15–0.59 |
| Chicago, IL (7) | 22 ppb (6–30) | -0.05–0.83 | 10–39 | 0.13–0.66 |
| Houston, TX (7) | 13 ppb (7–18) | 0.31–0.80 | 6–20 | 0.13–0.47 |
| Los Angeles, CA (14) | 25 ppb (14–33) | 0.01–0.90 | 8–32 | 0.08–0.51 |
| Riverside, CA (9) | 21 ppb (5–32) | 0.03–0.84 | 10–40 | 0.14–0.70 |

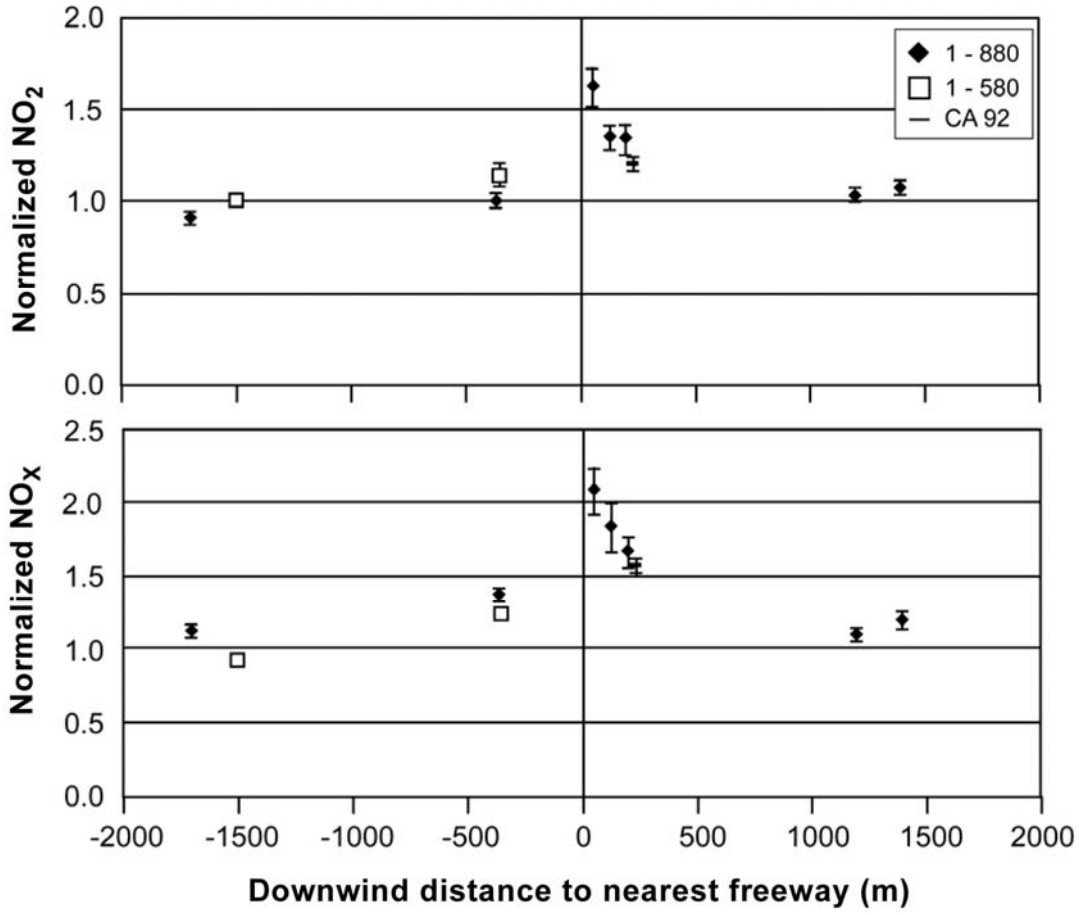
The same statistics shown in Table 2.5-1 have been used to describe the spatial variability of $PM_{2.5}$ (U.S. Environmental Protection Agency, 2004; Pinto et al., 2004) and $O_3$ (U.S. Environmental Protection Agency, 2006a).

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

## 2.5.3.2. Small-Scale Horizontal Variability

Large gradients in $NO_2$ concentrations near roadways have been observed in several studies, and $NO_2$ concentrations have been found to be correlated (or inversely correlated) with distance from roadway, traffic volume, season, road length, open space, and population density (Bignal et al., 2007; Cape et al., 2004; Gauderman et al., 2005; Gilbert et al., 2007; Maruo et al., 2003; Monn et al., 1997; Pleijel et al., 2004; Roorda-Knape et al., 1998; 1999; Singer et al., 2004). A sample gradient is shown in Figure 2.5-2.

Singer et al. (2004) found a strong gradient for concentrations downwind of freeways within the first 230 m. An exponential decay model (e.g., Cape et al., 2004) has been fit to near-road concentration data to estimate $NO_2$ concentration as a function of distance from the roadway. Gilbert et al. (2007) found that associations remained robust when sites within 200 m of roadways were removed from the analysis, indicating that traffic influences concentrations as far as 2000 to 3000 m from roadways. Small-scale spatial variations in $NO_2$ concentrations are more pronounced during spring and summer seasons due to meteorology and increased photochemical activity (Monn, 2001).




Source: Singer et al. (2004).

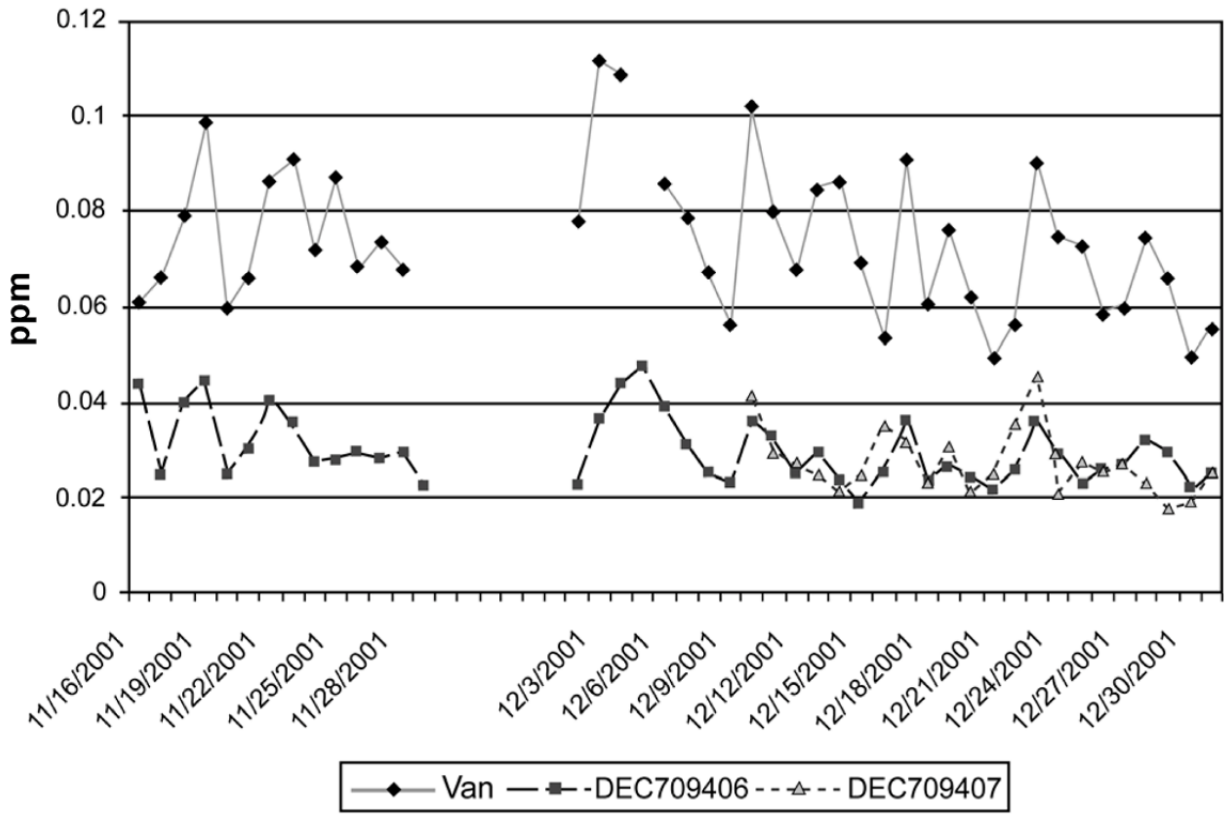
**Figure 2.5-2. $NO_2$ and $NO_X$ concentrations normalized to ambient values, plotted as a function of downwind distance from the freeway. Symbols indicate freeway closest to each monitor.**

Localized effects of roadway sources lead to variability in $NO_2$ concentrations that is not captured by the regulatory monitoring network. This variation affects population-level exposure estimates and adds exposure error to time-series epidemiologic studies relying on ambient concentrations as indicators of exposure. Elevated concentrations near roadways also increase exposure of anyone residing, working, or attending school in the vicinity. As discussed in Chapter 4, these elevated concentrations found near roadways may lead to increased vulnerability among those exposed to high near-roadway concentrations of $NO_2$.

## 2.5.3.3. Small-Scale Vertical Variability

Inlets to instruments for monitoring gas-phase criteria pollutants can be located from 3 to 15 m above ground level (CFR, 2002). Depending on the pollutant, there can be a positive, negative, or no vertical gradient from the surface to the monitor inlet. Positive gradients (i.e., concentrations increase with height) result when pollutants are formed over large areas by atmospheric photochemical reactions (i.e., secondary pollutants such as $O_3$) and destroyed by deposition to the surface or by reaction with

pollutants emitted near the surface. Pollutants that are emitted by sources at or just above ground level show negative vertical gradients. Pollutants with area sources (widely dispersed surface sources) and that have minimal deposition velocities show little or no vertical gradient. Restrepo et al. (2004) compared data for criteria pollutants collected at fixed monitoring sites at 15 m above the surface on a school rooftop to those measured by a van whose inlet was 4 m above the surface at monitoring sites in the South Bronx during two sampling periods in November and December 2001. They found that CO, $SO_2$, and $NO_2$ showed negative vertical gradients, whereas $O_3$ showed a positive vertical gradient and $PM_{2.5}$ showed no significant vertical gradient. As shown in Figure 2.5-3, $NO_2$ mixing ratios obtained at 4 m (mean ~74 ppb) were about a factor of 2.5 higher than at 15 m (mean ~30 ppb). Because tail pipe emissions occur at lower heights, $NO_2$ values could have been much higher nearer to the surface and the underestimation of $NO_2$ values by monitoring at 15 m even larger. Restrepo et al. (2004) noted that the use of the $NO_2$ data obtained by the stationary monitors underestimates human exposures to $NO_2$ in the South Bronx. This situation is not unique to the South Bronx and could arise in other large urban areas in the U.S. with similar settings. This adds another dimension to the exposure assessment, namely, the exposure of pedestrians who spend time walking in these street canyons, and urban residents, who have windows opening onto these canyons. These groups may experience high exposures to near-road concentrations of the same magnitude as exposures that occur on or adjacent to arterial and interstate roadways.




Source: Restrepo et al. (2004).

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

The magnitude of the vertical gradient of $NO_2$ in street canyons depends strongly on the configuration of the buildings forming the canyons and the meteorological conditions; in particular, static stability in the lower planetary boundary layer, local wind direction and speed, and differential solar heating all affect turbulence in street canyons. These meteorological factors also help determine the relative importance of turbulence induced by traffic, in addition to traffic volume and speed. Detailed descriptions of the effects for many of these factors are available only from complex numerical models such as large eddy simulations and very fine grid resolution computational fluid dynamics (CFD) models. A semi-empirical integral model with simplifying assumptions has shown reasonable correlation to measured $NO_2$ concentrations over moderate time scales (1 month) (Berkowicz et al., 2008), while other studies have applied such models to urban neighborhoods to estimate traffic emissions and evaluate the representativeness of air quality monitoring data (Ghenu et al., 2008; Mensink and Cosemans, 2008; Vardoulakis et al., 2005). By constructing simplified geometries, investigators can obtain good agreement between the performance of integral and CFD models; however, generalization and quantitative application of these results to complex urban situations, even at the same location at different times, is difficult due to multi-scale variability in meteorological conditions, traffic composition and flow, building geometry, street dimensions, street canyon aspect ratios, and building packing density (Di Sabatino et al., 2007).

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

## 2.5.4. $NO_2$ On or Near Roads

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

While driving, concentrations for personal exposure in a vehicle cabin could be substantially higher than ambient concentrations measured nearby. Sabin et al. (2005) reported that $NO_2$ concentrations in the cabins of school buses in Los Angeles ranged from 24 to 120 ppb, which were typically factors of 2 to 3 (max, 5) higher than at ambient monitors in the area. Lewné et al. (2006) reported work hour exposures to $NO_2$ for taxi drivers (25.1 ppb), bus drivers (31.4 ppb), and truck drivers (35.6 ppb). These levels were 1.8, 2.7, and 2.8 times the ambient concentrations. Riediker et al. (2003) studied the exposure to $NO_2$ inside patrol cars. The authors found that the mean and maximum $NO_2$ concentrations in a patrol car were 41.7 ppb and 548.5 ppb compared to 30.4 ppb and 69.5 ppb for the ambient sites. These studies indicate that people in traffic can be exposed to much higher levels of $NO_2$ than are measured at ambient

monitoring sites. Due to high peak exposures while driving, total personal exposure could be underestimated if exposures while commuting are not considered, and sometimes exposure in traffic can dominate personal exposure to $NO_2$ (Lee et al., 2000; Son et al., 2004). Variations in traffic-related exposure could be attributed to time spent in traffic, type of vehicle, ventilation in the vehicle, and distance from major roads (Chan et al., 1999; Sabin et al., 2005; Son et al., 2004). Sabin et al. (2005) reported that the intrusion of the vehicle's own exhaust into the passenger cabin is another $NO_2$ source contributing to personal exposure while commuting, but that the fraction of air inside the cabin from a vehicle's own exhaust was small, ranging from 0.02 to 0.28% and increasing with the age of the vehicle (CARB, 2007a,b).

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

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

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

## 2.5.5. Indoor Sources and Sinks of $NO_2$ and Associated Pollutants

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

Penetration of outdoor $NO_2$ and indoor combustion in various forms are the major sources of $NO_2$ to indoor environments, e.g., homes, schools, restaurants, theaters. As might be expected, indoor concentrations of $NO_2$ in the absence of combustion sources are determined by the infiltration of outdoor $NO_2$ (Levy et al., 1998b; Spengler et al., 1994; Weschler et al., 1994). Contributions to indoor $NO_2$ from the reaction of NO in exhaled breath with $O_3$ could potentially be important in certain circumstances (see Annex section AX3.4.2 for sample calculations). Indoor sources of nitrogen oxides have been characterized in several reviews, namely the last $NO_X$ AQCD (U.S. Environmental Protection Agency, 1993); the Review of the Health Risks Associated with Nitrogen Dioxide and Sulfur Dioxide in Indoor Air for Health Canada (Brauer et al., 2002); and the Staff Recommendations for revision of the $NO_2$ standard in California (CARB, 2007a). Mechanisms by which $NO_X$ is produced in the combustion zones of indoor sources were reviewed in the last $NO_X$ AQCD (U.S. Environmental Protection Agency, 1993). It should be noted that indoor sources can affect ambient $NO_2$ levels, particularly in areas in which atmospheric mixing is unlikely, such as in valleys.

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

Many studies have noted the importance of gas cooking appliances as sources of $NO_2$ emissions. Depending on geographical location, season, other sources of $NO_2$, and household characteristics, homes with gas cooking appliances have approximately 50% to over 400% higher $NO_2$ concentrations than homes with electric cooking appliances (Garcia-Algar et al., 2003; Gilbert et al., 2006; Leaderer et al., 1986; Lee et al., 2000; Raw et al., 2004). Gas cooking appliances remain significantly associated with indoor $NO_2$ concentrations after adjusting for several factors that influence exposures, including season, type of community, socioeconomic status, use of extractor fans, household smoking, and type of heating (Garcia Algar et al., 2004; Garrett et al., 1999). Homes with gas appliances with pilot lights emit more $NO_2$, resulting in $NO_2$ concentrations ~10 ppb higher than in homes with gas appliances with electronic ignition (Lee et al., 1998; Spengler et al., 1994).

Secondary heating appliances are additional sources of $NO_2$ in indoor environments, particularly if the appliances are unvented or inadequately vented. As heating costs increase, the use of these secondary heating appliances tends to increase. Gas heaters, particularly when unvented or inadequately vented, produce high levels of indoor $NO_2$ (Kodama et al., 2002). Results summarized by Brauer et al. (2007) indicate that concentrations of $NO_2$ in homes with unvented gas hot water heaters were 10 to 21 ppb higher than in homes with vented heaters, which in turn, had $NO_2$ concentrations 7.5 to 38 ppb higher than homes without gas hot water heaters. On the other hand, mean concentrations of $NO_2$ were all <10 ppb in a study of Canadian homes with vented gas and oil furnaces and electric baseboard heaters (Weichenthal et al., 2007), indicating that these are not likely to be major sources of $NO_2$ to indoor environments.

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

As can be seen from Tables 2.5-2 and 2.5-3, average concentrations while appliances are in operation tend to be much higher than longer-term averages. As Triche et al. (2005) indicated, the 90th percentile concentrations can be substantially greater than the medians, even for 2-week samples. This finding illustrates the high variability of indoor $NO_2$ found among homes, reflecting differences in ventilation of emissions from sources, air exchange rates, the size of rooms, etc. The concentrations for short averaging periods listed in Table 2.5-2 correspond to ~10 to 30 ppb on a 24-h avg basis. As can be seen from inspection of Table 2.5-3, these sources would contribute significantly to the longer-term averages reported if operated daily on a similar schedule. This implies measurements made with long

averaging periods may not capture the nature of the diurnal pattern of indoor concentrations of $NO_2$ in homes with strong indoor sources, a problem that becomes more evident as ambient $NO_2$ levels decrease with more efficient controls on outdoor sources.

**Table 2.5-2. $NO_2$ concentration near indoor sources: minute to hour averages.**

| STUDY | AVERAGE CONCENTRATION (ppb) | PEAK CONCENTRATION (ppb) | COMMENT |
|---|---|---|---|
| Fortmann et al. (2001) | 191 kitchen<br>195 living room<br>184 bedroom | 375 kitchen<br>401 living room<br>421 bedroom | Cooked full meal with gas range for 2 h, 20 min; 7 h TWA. |
| Fortmann et al. (2001) | 400 kitchen<br>living room<br>bedroom | 673 bedroom | Self-cleaning gas range. Avgs are over the entire cycle. |
| Dutton et al. (2001) | 90 (low setting)<br>350 (med setting)<br>360 (high setting) | NR | Natural gas unvented fireplace, 0.5 h TWA in main living area of house (177 $m^3$). |
| Girman et al. (1982) | NR | 1000 | Room concentration with kerosene heater operating for 46 min. |
| Girman et al. (1982) | NR | 1500 | Room concentration with gas heater operating for 10 min. |
| Girman et al. (1982) | 180 to 650 | NR | Calculated steady-state concentration from specific unvented gas space heaters[1] operating in a 1400 $ft^2$ house, 1.0/h for air exchange rate. |

NR=not reported; TWA=time-weighted avg; [1]Unvented appliances are not permitted in many areas, including California.

**Table 2.5-3. $NO_2$ concentration near indoor sources: 24-h to 2 week averages.**

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

The emissions of $NO_2$ from burning biomass fuels indoors have not been characterized as extensively as those from burning gas. A main conclusion from the 1993 $NO_X$ AQCD was that properly vented wood stoves and fireplaces would make only minor contributions to indoor $NO_2$ levels, and several studies have concluded that using wood-burning appliances does not increase indoor $NO_2$ concentrations (Lévesque et al., 2001; Triche et al., 2005).

Other indoor combustion sources of $NO_2$ are candle burning and smoking. In a study of students living in Copenhagen, Sørensen et al. (2005) found that personal exposures to $NO_2$ were significantly associated with time exposed to burning candles in addition to other sources (data not reported). Results of studies relating $NO_2$ concentrations and exposures to environmental tobacco smoke (ETS) have been mixed. Several studies found positive associations between $NO_2$ levels and ETS (e.g., Alm et al., 1998; Cyrys et al., 2000; Farrow et al., 1997; Garcia Algar et al., 2004; Lee et al., 2000; Levy et al., 1998a; Linaker et al., 1996; Monn et al., 1998), whereas others have not (e.g., Hackney et al., 1992; Kawamoto et al., 1993).

### 2.5.5.1. Indoor Air Chemistry

Chemistry in indoor settings can be both a source and a sink for $NO_2$ (Weschler and Shields, 1997). $NO_2$ is produced by reactions of NO with $O_3$ or peroxyl radicals, while $NO_2$ is removed by gas-phase reactions with $O_3$ and assorted free radicals and by surface-promoted hydrolysis and reduction reactions. The concentration of indoor $NO_2$ also affects the decomposition of PAN.

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

At an indoor $O_3$ concentration of 10 ppb and an indoor NO concentration that is significantly smaller than that of $O_3$, the half-life of NO is 2.5 min (using kinetic data contained in Jet Propulsion Laboratory, 2003). This reaction is sufficiently fast to compete with even relatively fast air exchange rates. Hence, the amount of $NO_2$ produced from NO tends to be limited by the amount of $O_3$ available (Weschler et al., 1994).

$NO_2$ reacts with $O_3$ to produce nitrate radicals ($NO_3$). To date, there have been no indoor measurements of the concentration of $NO_3$ radicals in indoor settings. Modeling studies by Nazaroff and Cass (1986), Weschler et al. (1992), Sarwar et al. (2002b), and Carslaw (2007) estimate indoor $NO_3$ radical concentrations in the range of 0.01 to 5 ppt, depending on the indoor levels of $O_3$ and $NO_2$. Once formed, $NO_3$ can oxidize organic compounds by either adding to an unsaturated carbon bond or abstracting a hydrogen atom (Wayne et al., 1991). In certain indoor settings, the $NO_3$ radical may be a more important indoor oxidant than either $O_3$ or the OH radical (Nazaroff and Weschler, 2004; Wayne et al., 1991). Thus, $NO_3$ radicals and the products of $NO_3$ radical chemistry could contribute to uncertainty in $NO_2$ exposure-health outcome studies

Reactions between $NO_2$ and various free radicals can be an indoor source of organo-nitrates, analogous to the chain-terminating reactions observed in photochemical smog (Weschler and Shields, 1997). Additionally, based on laboratory measurements and measurements in outdoor air (Finlayson-Pitts and Pitts, 2000), one would anticipate that $NO_2$, in the presence of trace amounts of $HNO_3$, can react with PAHs sorbed onto indoor surfaces to produce mono- and dinitro-PAHs. $NO_2$ can also be reduced on certain surfaces, forming NO. Spicer et al. (1989) found that as much as 15% of the $NO_2$ removed on various indoor surfaces was reemitted as NO. (Weschler and Shields, 1996) found that the amount of $NO_2$ removed by charcoal filters used in buildings were almost equally matched by the amount of NO subsequently emitted by the same filters.

$NO_2$ can also be converted to HONO by reactions in indoor air. As noted above, HONO occurs in the atmosphere mainly through multiphase processes involving $NO_2$. HONO has been observed to form on surfaces containing partially oxidized aromatic structures (Stemmler et al., 2006) and on soot particles (Ammann et al., 1998). Indoors, surface-to-volume ratios are much larger than they are outdoors, and the surface-mediated hydrolysis of $NO_2$ is a major indoor source of HONO (Brauer et al., 1990; 1993; Febo and Perrino, 1991; Lee et al., 2002; Spengler et al., 1993; Spicer et al., 1993; Wainman et al., 2001). Lee et al. (2002) reported average indoor HONO levels were ~6 times higher than outdoor levels (4.6 versus 0.8 ppb). Indoor HONO concentrations averaged 17% of indoor $NO_2$ concentrations, and the two were strongly correlated. Indoor HONO levels were higher in homes with humidifiers compared to homes without humidifiers (5.9 versus 2.6 ppb). This last observation is consistent with the studies of Brauer et al. (1993) and Wainman et al. (2001), indicating that the production rate of HONO from $NO_2$ surface reactions increases with relative humidity. Spicer et al. (1993) reported that an equilibrium between adsorption of HONO from the gas range (or other indoor combustion sources) and HONO produced by surface reactions determines the relative importance of these processes in producing HONO in indoor air.

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

## 2.5.6. Relationship of Personal Exposure to Ambient Concentrations

### 2.5.6.1. Associations between Personal Exposure and Ambient and Outdoor Concentrations

Results of studies reporting associations between ambient concentrations and personal exposures are shown in Table 2.5-4 for longitudinal correlation coefficients, Table 2.5-5 for pooled correlation coefficients. Results of studies reporting associations between outdoor concentrations and personal exposures are shown in Table 2.5-6. Study designs (longitudinal, daily-averaged, and pooled) used in these studies are summarized in Tables 2.5-4 and 2.5-5.

**Table 2.5-4. Association between personal exposure and ambient concentration (longitudinal correlation coefficients).**

| STUDY | METHODS | MEAN CONCENTRATION | ASSOCIATION VARIABLE | LOCATION | SEASON | $r_p$, $r_s$, or $R^2$ |
|---|---|---|---|---|---|---|
| Linaker et al. (2000)<br>Location: Southampton, Hampshire, UK<br>Time period: Oct 1994 to Dec 1995 | Type: Longitudinal<br>Subjects: 114 asthmatic children, aged 7-12<br>Method: at least 16 consecutive samples (1-wk avgs) for each child (mean duration of follow-up: 32 wks). | Ambient: 6.5 ppb<br>Personal: 8.9 ppb | Personal vs. central (overall measure-ments across children and time)<br>Personal vs. central (subject-wise) | Pooled, urban, no major indoor sources<br>By person | Pooled | Not significant (n=NR)<br>-0.77 to 0.68 and median<br>-0.02 ($r_p$) (n=NR) |
| Kim et al. (2006)<br>Location: Toronto, Canada<br>Time period: Aug 1999 to Nov 2001 | Type: Longitudinal<br>Subjects: 28 adults with coronary artery disease<br>Method: 1 day/wk, 24-h avg, for a max of 10 wks for each person. | Ambient: 24 ppb<br>Personal: 14 ppb | 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)<br>Koutrakis et al. (2005)<br>Location: Baltimore, MD<br>Time period: summer of 1998 and winter of 1999 | Type: Longitudinal<br>Subjects: 56 seniors, schoolchildren, and people with COPD<br>Method: 14 of 56 subjects participated in both sampling seasons; all subjects were monitored for 12 consecutive days (24-h avg samples) in each of the one or two seasons, except children, who were measured for 8 consecutive days during the summer. | Ambient: 20–25 ppb<br>Personal: 10–15 ppb | Personal vs. central (subject-wise) | Urban | Summer<br>Winter | -0.45 to 0.85 ($r_s$) with a median of 0.05* (24 subjects)<br>-0.6 to 0.75 ($r_s$) with a median of 0.05* (45 subjects) |
| Sarnat et al. (2005)<br>Koutrakis et al. (2005)<br>Location: Boston, MA<br>Time period: summer of 1999; winter of 2000 | Type: Longitudinal<br>Subjects: 43 seniors and schoolchildren<br>Method: Similar study design as Sarnat et al. (2001). | Ambient: 21.1–32.6 ppb<br>Personal: 10.6–29.6 ppb | Personal vs. central (subject wise) | Urban | Summer<br>Winter | -0.25 to 0.5 ($r_s$) with a median of 0.3* (n=NR) Slope=0.19 (95% CI, 0.08-0.30)<br>-0.5 to 0.9 ($r_s$) with a median of 0.4* (n=NR) Slope=-0.03 (95% CI, -0.21-0.15) |

* Values were estimated from figures in the original paper. ** NR: Not Reported.

**Table 2.5-5. Association between personal exposure and ambient concentration (pooled correlation coefficients).**

| STUDY | STUDY DESIGN | MEAN CONCENTRATION | ASSOCIATION VARIABLE | LOCATION | SEASON | $r_p$, $r_s$, or $R^2$ |
|---|---|---|---|---|---|---|
| Linn et al. (1996)<br>Location: Southern California<br>Time period: fall, winter, spring, 1992-1994 | Type: Longitudinal<br>Subjects: 269 school children<br>Method: 24-h avg, 1-wk consecutive measurement for each season for each child. | Ambient: 37 ppb<br>Personal: 22 ppb | Personal vs. central | Pooled | Pooled | 0.63 ($r_p$) (n=107) |
| Alm et al. (1998)<br>Location: Helsinki, Finland<br>Time period: winter and spring, 1991 | Type: Longitudinal<br>Subjects: 246 children aged 3-6 yrs old<br>Method: 1-wk averaged sample for each person, 6 consecutive wks in the winter and 7 consecutive wks in the spring. | Ambient: 16.8–26.3 ppb<br>Personal: 9–16.6 ppb | Personal vs. central | Downtown | Spring | 0.64 ($r_p$) p<0.001 (n=NR**) |
| | | | Personal vs. central | Suburban | Spring | 0.78 ($r_p$) p<0.001 (n=NR) |
| | | | Personal vs. central | Downtown | Winter | -0.06 ($r_p$) p >0.05 (n=NR) |
| | | | Personal vs. central | Suburban | Winter | 0.32 ($r_p$) p >0.05 (n=NR) |
| | | | Personal vs. central | Downtown (electric stove home) | Pooled | 0.42 ($r_p$) p<0.01 (n=NR) |
| | | | Personal vs. central | Downtown (gas stove home) | Pooled | 0.16 ($r_p$) p >0.01 (n=NR) |
| | | | Personal vs. central | Suburban (electric stove home) | Pooled | 0.55 ($r_p$) p<0.001 (n=NR) |
| | | | Personal vs. central | Downtown (non-smoking home) | Pooled | 0.47 ($r_p$) p<0.001 (n=NR) |
| | | | Personal vs. central | Downtown (smoking home) | Pooled | 0.23 ($r_p$) p >0.01 (n=NR) |
| | | | Personal vs. central | Suburban (non-smoking home) | Pooled | 0.53 ($r_p$) p<0.001 (n=NR) |
| | | | Personal vs. central | Suburban (smoking home) | Pooled | 0.52 ($r_p$) p<0.001 (n=NR) |
| | | | Personal vs. central | Pooled | Pooled | 0.37 ($R^2$) (n=24) |
| Liard et al. (1999)<br>Location: Paris, France<br>Time period: May-June 1996 | Type: Daily avg/cross-sectional<br>Subjects: 55 adults and 39 children<br>Method: Three 4-day avg measurements for each person, during each measurement session, all subjects measured at same time. | Ambient: 26.3–36.8 ppb<br>Personal: 15.8–26.3 ppb | Adults vs. central | Urban | Summer | 0.41 ($R^2$) p<0.0001 (n=NR) |
| | | | Children vs. central | Urban | Summer | 0.17 ($R^2$) p=0.0004 (n=NR) |

| STUDY | STUDY DESIGN | MEAN CONCENTRATION | ASSOCIATION VARIABLE | LOCATION | SEASON | $r_p$, $r_s$, or $R^2$ |
|---|---|---|---|---|---|---|
| Gauvin et al. (2001)<br>Location: 3 French metropolitan areas<br>Time period: Apr-June 1998 in Grenoble; May-June 1998 in Toulouse; June-Oct 1998 in Paris | Type: Daily avg/cross-sectional<br>Subjects: 73 children<br>Method: one 48-h avg measurement for each child; all children in the same city were measured on the same day. | Ambient: 10.2–25.7 ppb<br>Personal: 13.2–17 ppb | Personal vs. central (Grenoble) | Urban | Pooled | 0.01 ($R^2$) (n=NR) |
| | | | Personal vs. central (Toulouse) | Urban | Pooled | 0.04 ($R^2$) (n=NR) |
| | | | Personal vs. central (Paris) | Urban | Pooled | 0.02 ($R^2$) (n=NR) |
| Piechocki-Minguy et al. (2006)<br>Location: Lille (northern France)<br>Time period: winter 2001 (first campaign); summer 2002 (second campaign) | Type: Pooled<br>Subjects: 13 in 1st campaign, 31 in 2nd<br>Method: two 24-h sampling periods (1on workdays; 1on weekends) for each subject in each campaign; during each sampling period, each subject received 4 samplers to measure personal exposure in 4 different microenvironments (home, other indoor, transport, and outdoors). | Ambient: 15.8–57.9 ppb<br>Personal: 8.9–20.0 ppb | Personal (exposure at home) vs. central | Urban | Pooled | 0.09 ($R^2$) p=0.0101 (n=NR) |
| | | | Personal (exposure at home) vs. central | Urban<br>(electric stove and electric heater home) | Summer | 0.61 ($R^2$) p=0.0001 (n=NR) |
| Sarnat et al. (2006)<br>Location: Steubenville, OH<br>Time period: summer and fall of 2000 | Type: Longitudinal<br>Subjects: 15 senior subjects<br>Method: two consecutive 24-h samples were collected for each subject for each wk, 23 wks total | Ambient: 9.5–11.3 ppb<br>Personal: 9.9–12.1 ppb | 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 2.5-6. Association between personal exposure and outdoor concentration.**

| STUDY | METHODS | ASSOCIATION VARIABLE | LOCATION | SEASON | $r_p$, $r_s$, or $R^2$ |
|---|---|---|---|---|---|
| Krämer et al. (2000)<br>Location: Germany<br>Time period: Mar and Sep 1996 | Subjects: 191 children<br>Method: two 1-wk averaged measurements for each child in each mo. | Personal vs. outdoor | Pooled | Pooled | 0.37 ($r_p$) (n=281) |
| | | Personal vs. outdoor | Urban | Pooled | 0.06 ($r_p$) (n=182) |
| Rojas-Bracho et al. (2002)<br>Location: Santiago, Chile<br>Time period: winters of 1998 and 1999 | Subjects: 20 children<br>Method: five 24-h avg samples for 5 consecutive days for each child. | Personal vs. outdoor | Urban | Winter | 0.27 ($R^2$) (n=87) |

| STUDY | METHODS | ASSOCIATION VARIABLE | LOCATION | SEASON | $r_p$, $r_s$, or $R^2$ |
|---|---|---|---|---|---|
| Raaschou-Nielsen et al. (1997)<br>Location: Copenhagen, Denmark and rural areas<br>Time period: Oct 1994, Apr, May, and June 1995 | Subjects: 204 children<br>Method: two 1-wk avg measurements for each child in each mo. | Personal vs. outdoor | Urban | Pooled | 0.15 ($R^2$) (n=97) |
| | | Personal vs. outdoor | Rural | Pooled | 0.35 ($R^2$) (n=99) |
| Alm et al. (1998)<br>Location: Helsinki, Finland<br>Time period: winter and spring of 1991 | Subjects: 246 children aged 3-6 yrs old<br>Method: 1-wk averaged sample for each person for 6 consecutive wks in the winter and 7 consecutive wks in the spring. | Personal vs. outdoor | Downtown | Winter | 0.46 ($r_p$) (n=NR) |
| | | Personal vs. outdoor | Suburban | Winter | 0.49 ($r_p$) (n=NR) |
| | | Personal vs. outdoor | Downtown | Spring | 0.80 ($r_p$) (n=NR) |
| | | Personal vs. outdoor | Suburban | Spring | 0.82 ($r_p$) (n=NR) |
| | | Personal vs. outdoor | Downtown (electric stove home) | Pooled | 0.55 ($r_p$) (n=NR) |
| | | Personal vs. outdoor | Downtown (gas stove home) | Pooled | 0.59 ($r_p$) (n=NR) |
| | | Personal vs. outdoor | Suburban (electric stove home) | Pooled | 0.63 ($r_p$) (n=NR) |
| | | Personal vs. outdoor | Downtown (non-smoking home) | Pooled | 0.73 ($r_p$) (n=NR) |
| | | Personal vs. outdoor | Downtown (smoking home) | Pooled | 0.51 ($r_p$) (n=NR) |
| | | Personal vs. outdoor | Suburban (non-smoking home) | Pooled | 0.59 ($r_p$) (n=NR) |
| | | Personal vs. outdoor | Suburban (smoking home) | Pooled | 0.46 ($r_p$) (n=NR) |
| | | Personal vs. outdoor | Pooled | Pooled | 0.86 ($R^2$) (n=23) |
| Monn et al.<br>(1998)<br>Location: Geneva, Basel, Lugano, Aarau, Wald, Payerne, Montana, and Davos (SAPALDIA study, Switzerland)<br>Time period: Dec 1993 to Dec 1994 | Subjects: 140 subjects<br>Method: each home was monitored for 3 periods of 1 mo; in the 1st wk of each period, personal, indoor rand outdoor levels were measured, and in the next 3 consecutive wks, only outdoor levels were measured (1-wk averaged measurement). | Personal vs. outdoor | Pooled | Pooled | 0.33 ($R^2$) (n=1,494) |

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

* Values were estimated from figures in the original paper ** NR: Not Reported.

Figures 2.5-4 and 2.5-5 explicitly summarize the correlation coefficients between personal exposures and ambient concentrations for different populations with a forest plot for U.S. studies and European studies, respectively. Correlation coefficients and their 95% confidence intervals (CIs) shown in Figures 2.5-4 and 2.5-5 were transformed from the coefficients in Tables 2.5-4 and 2.5-5 with the consideration of the type of exposure studies. Fisher's Z transform was used, ($Z=0.5\ln[(1+r)/(1-r)]$), where r is the originally reported and Z is the transformed correlation coefficient (Fisher, 1925). The variance of Z is expressed as $1/(n-3)$, where n is the number of observations defined by one of the following three presentations; (1) when the correlation coefficient was based on the average across subjects of personal exposures, n was the number of sampling days, (2) when the partial correlation coefficient was used in the original study, n was the total number of sampling by individual observations minus the sum of three and the number of covariates, and (3) when the mean of individual correlations was used, the standard error was the standard deviation of the correlations divided by the square root of the number of subjects minus one.

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

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

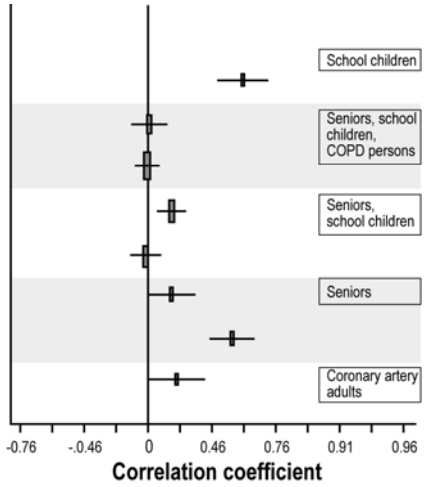



**Figure 2.5-4. Distribution of correlation coefficients (U.S. studies) between personal $NO_2$ exposure and ambient $NO_2$ concentrations based on Fisher's Z transform.**

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

In the context of determining the effects of ambient pollutants on human health, the association between the ambient component of personal exposures and ambient concentrations is more relevant than the association between personal total exposures (ambient component+nonambient component) and ambient concentrations. As described in Equations 2.5-2 and 2.5-4, personal total exposure can be decomposed into two parts; an ambient and a nonambient component. Usually, the ambient component of personal exposure is not directly measurable, but it can be estimated by exposure models, or the personal total exposure can be regarded as the personal exposure of ambient origin if there are no indoor or nonambient sources. Personal exposures were clearly stratified by indoor sources in only four studies among the studies examined for $NO_2$ (Alm et al., 1998; Linaker et al., 2000; Piechocki-Minguy et al., 2006; Sarnat et al., 2006) and only two studies (Alm et al., 1998; Piechocki-Minguy et al., 2006) compared the association between personal total exposures and ambient concentrations and the association between the ambient component of personal exposures and ambient concentrations. A stronger association was observed between the ambient component of personal exposures and the ambient concentrations (Alm et al., 1998; Piechocki-Minguy et al., 2006). It is expected that the association between ambient concentrations and the ambient component of personal exposures would be stronger than the association between ambient concentrations and personal total exposures as long as the ambient and nonambient component of personal total exposure are independent. The correlation coefficients between personal ambient $NO_2$ exposures and ambient $NO_2$ concentrations in different types of exposure studies are relevant to different types of epidemiologic studies.

There are three types of correlations generated from the different study designs as listed in Tables 2.5-4 and 2.5-5: longitudinal, "pooled," and daily-average correlations (U.S. Environmental Protection Agency, 2004).

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

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

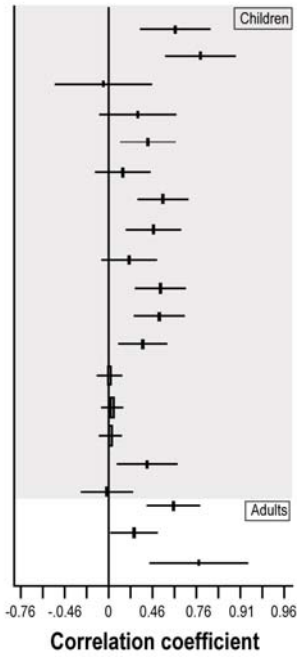



**Figure 2.5-5. Distribution of correlation coefficients (European studies) between personal $NO_2$ exposure and ambient $NO_2$ concentrations based on Fisher's Z transform.**

Longitudinal correlations[1] are calculated when data from a study includes consecutive multiple measurements for each subject (longitudinal study design). Longitudinal correlations describe the temporal relationship between personal $NO_2$ exposure or microenvironment concentration and ambient $NO_2$ concentration for the same subject. The longitudinal correlation coefficient can differ between subjects (i.e. each person may have a different correlation coefficient). The distribution of correlations for each subject across a population could be obtained with this type of data (e.g., Kim et al., 2006; Linaker et al., 2000; Sarnat et al., 2000; 2001; 2005). A longitudinal correlation coefficient between the ambient component of personal exposures and ambient concentrations is relevant to the panel epidemiologic study design. In Table 2.5-4, most longitudinal studies reported the association between personal total exposures and ambient concentrations for each subject; for some subjects the associations were strong and for some subjects the associations were weak. The weak personal and ambient associations do not necessarily mean that ambient concentrations are not a good surrogate for personal exposures, because the weak associations could have resulted from the day-to-day variation in the nonambient component of total personal exposure. The type of correlation analysis can have a substantial effect on the value of the resultant correlation coefficient. Mage et al. (1999) showed that very low correlations between personal exposure and ambient concentrations could be obtained when people with very different nonambient exposures are pooled, even though their individual longitudinal correlations are high.

[1] $$r_{ax_i} = \frac{\sum_j \left(x_{ij} - \overline{x_i}\right)\left(a_j - \overline{a}\right)}{(n-1)s_{x_i} s_a}$$

where "r" is the longitudinal correlation coefficient between personal exposure and ambient concentration, "*a*" represents the ambient concentration, "*x*" represents exposure, "*i*" represents the $i^{th}$ subject, "*j*" represents the $j^{th}$ measurement (with the averaging time ranging from two days to two weeks for $NO_2$ measurement), "*s*" represents the standard deviation, and "*n*" in the longitudinal studies is the number of measurements for each subject. The ambient concentration $a_j$ could be measured by one ambient monitor or the average of several ambient monitors.

Pooled correlations[1] are calculated when a study involves one or only a few measurements per subject and when different subjects are studied on subsequent days. Pooled correlations combine individual-subject/individual-day data for the calculation of correlations. Pooled correlations describe the relationship between daily personal $NO_2$ exposure and daily ambient $NO_2$ concentration across all subjects in the study (e.g., Alm et al., 1998; Gauvin et al., 2001; Liard et al., 1999; Linn et al., 1996; Piechocki-Minguy et al., 2006; Sarnat et al., 2006).

Daily-average correlations[2] are calculated by averaging exposure across subjects for each day. Daily-average correlations then describe the relationship between the daily average exposure and daily ambient $NO_2$ concentration (e.g., EPA, 2004; Gauvin et al., 2001; Liard et al., 1999; Monn, 2001). This type of correlation (i.e. the association between community average exposures (ambient component) and ambient concentrations) is more directly relevant to community time-series and long-term cohort epidemiologic studies, in which ambient concentrations are used as a surrogate for community average exposure to $NO_2$ of ambient origin. However, exposure of the population to $NO_2$ of ambient origin has not been reported in all the studies examined. The following two European studies reported the associations between population total exposures and ambient or outdoor concentrations of $NO_2$. Liard et al. (1999) conducted an exposure study of 55 office workers and 39 children in Paris. Measurements were made during three 4-day-long measurement periods for each group. Apart from occasional lapses, data from the same participants were collected during each period. Liard et al. (1999) correlated the five-panel average personal exposures with ambient monitoring data and derived a longitudinal Spearman correlation coefficient of 1 ($p<0.001$). $R^2$ between ambient monitors and individual personal exposures for adults was 0.41, and for children, $R^2$ was 0.17. Four-day averaging periods were chosen in this study to overcome limitations imposed by the levels of detection of the personal samplers. The results show that passive samplers could be used to measure personal exposures in panel studies over multiday periods and lend some credence to the use of stationary monitors as proxies for personal exposures to ambient $NO_2$. Monn et al. (1998) and Monn (2001) reported personal $NO_2$ exposures obtained in the Study of Air Pollution and Lung Diseases in Adults (SAPALDIA) study (eight study centers in Switzerland). In each study location, personal exposures for $NO_2$ were measured simultaneously for all participants; in addition, residential outdoor concentrations were measured for 1 year (Table 2.5-6). Monn (2001) observed a strong association between the average personal exposures in each study location and corresponding average outdoor concentrations with an $R^2$ of 0.965. As pointed out by the author, in an analysis of individual single exposure and outdoor concentration data, personal versus outdoor $R^2$ was less than 0.3 (Monn et al., 1998). Because spatial heterogeneity in $NO_2$ concentrations likely produces stronger associations between average personal exposures and residential monitors than with central site ambient monitors in urban areas, caution should be exercised in using these data to infer that long-term averaged ambient concentrations are a good surrogate for population exposures in long-term cohort epidemiologic studies.

Not only does the exposure study design determine the meaning of the correlation coefficients in the context of exposure assessment in epidemiologic studies, but it also affects the strength of the association between personal exposures and ambient concentrations. The strength of the association

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

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

[2] $$r_{a\bar{x}} = \frac{\sum_{j}\left(\bar{x_j}-\bar{x}\right)\left(a_j-\bar{a}\right)}{(n-1)s_{\bar{x}_j} s_a},$$

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

between personal exposures and ambient and/or outdoor concentrations for a population is determined by variations in several physical factors: indoor or other local sources, air exchange rate, penetration, and decay rate of $NO_2$ in different microenvironments and the time people spend in different microenvironments with different $NO_2$ concentrations. For different types of correlation coefficients, the components of the variance of these physical factors are different, and therefore the strength of different types of correlation coefficients is different. Longitudinal correlation coefficients reflect the intra-personal variations of these physical factors; pooled correlation coefficient reflect both inter- and intra- personal variations of these physical factors; and for the association between community average exposures and ambient concentrations, inter-personal variations of these physical factors are reduced by averaging personal exposures across a community. Therefore, the strength of the associations between personal exposures and ambient concentrations may not be comparable directly, although these associations are determined by the same set of physical factors (but affected in different ways).

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

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

Local and indoor sources also affect the strength of the association between personal exposures and ambient concentrations. Alm et al. (1998) found that the association between personal exposure and outdoor concentration was stronger than the correlation between personal exposure and central site concentration. However, Kim et al. (2006) found that the association was not improved using the ambient sampler closest to a home. The lack of improvement in the strength of the association by choosing the closest ambient monitor could be in part due to the differences in the small-scale spatial heterogeneity of $NO_2$ in different urban areas, as shown in Table 2.5-1. Higher personal to ambient correlations have been found for subjects living in rural areas and lower correlations for subjects living in urban areas (Alm et al., 1998; Rojas-Bracho et al., 2002). Spengler et al. (1994) also observed that the relationship between personal exposure and outdoor concentration was highest in areas with lower ambient $NO_2$ levels ($R^2$=0.47) and lowest in areas with higher ambient $NO_2$ levels ($R^2$=0.33). This might reflect the highly heterogeneous distribution or the effect of local sources of $NO_2$ in an urban area.

Associations between ambient concentrations and personal exposures for the studies examined for $NO_2$ were not stratified by the presence of indoor sources except in Alm et al. (1998), Sarnat et al. (2006), Linaker et al. (2000) and Piechocki-Minguy et al. (2006). When there is little or no contribution from indoor sources, ambient concentrations primarily determine exposure; however, if there are indoor sources, the importance of outdoor levels in determining personal exposures decreases. The association between ambient or outdoor concentrations and personal exposures strengthens after controlling for indoor sources. Raaschou-Nielsen et al. (1997), Spengler et al. (1994), and Gauvin et al. (2001) reported that $R^2$ values increased by 10 to 40% after controlling for indoor sources, such as gas appliances and ETS (see Tables 2.5-4 through 2.5-6).

The strength of the associations between personal exposures and ambient and outdoor concentrations could also be affected by the quality of the data collected during the exposure studies. There are at least six aspects associated with the quality of the data: method precision, method accuracy

(compared with FRM), percent of data above method detection limits (based on field blanks), completeness of the data collection, sample size, and soundness of the quality assurance/quality control procedures. Unfortunately, not all studies reported the aspects of the data quality issue. Although data imprecisions and inaccuracies are less than 10% in most studies (Section 2.5.2), the fraction of data below the detection limit might be a concern for some studies (see e.g., Sarnat et al., 2000; 2001; 2006). Correlation coefficients would be biased low if data used in their calculation are below detection limits. Sampling interferences (caused by some $NO_Y$ compounds and other gas species) associated with both ambient (see Section 2.3) and personal sampling (see Section 2.5.2) could also affect data quality. Therefore, caution must be exercised when interpreting the results in Tables 2.5-4 and 2.5-5.

In summary, the evidence relating ambient levels to personal exposures is inconsistent. Some of the longitudinal studies examined found that ambient levels of $NO_2$ were reliable proxies of personal exposures to $NO_2$. However, a number of studies did not find significant associations between ambient and personal levels of $NO_2$. The differences in results are related in large measure to differences in study design and in exposure determinants. Measurement artifacts and differences in analytical measurement capabilities could also have contributed to the inconsistent results. Indeed, in a number of the studies examined, the majority of measurements of personal $NO_2$ concentrations were beneath detection limits, and in all studies some personal measurements were beneath detection limits.

## 2.5.6.2. Ambient Contribution to Personal Exposure

Another aspect of the relationship of personal $NO_2$ exposure and ambient $NO_2$ is the contribution of ambient $NO_2$ to personal exposures. The infiltration factor ($F_{inf}$) and alpha (α) are the keys to evaluate personal $NO_2$ exposure of ambient origin. As defined in Equations 2.5-2 through 2.5-5, the $F_{inf}$ of $NO_2$, the physical meaning of which is the fraction of ambient $NO_2$ found in the indoor environment, is determined by the $NO_2$ penetration coefficient ($P$), air exchange rate ($a$), and the $NO_2$ decay rate ($k$). Alpha (α) is a function of $F_{inf}$ and the fraction of time people spend outdoors ($y$), and the physical meaning of α is the ratio of personal ambient exposure concentration to ambient concentration, (i.e., in the absence of exposures to nonambient sources (i.e., when $E_{na}$=0).

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

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

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

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

Steady state models based on equations 2.5-2 through 2.5-5 are typically used to simulate indoor and outdoor concentrations and personal exposures. However, the assumption of steady state could result in missing peak exposures and obscuring the real short-term outdoor contribution to indoor and personal exposure. For example, the $NO_2$ concentrations at locations close to busy streets vary with traffic density, wind direction and speed etc. If steady state is assumed, the real-time indoor/outdoor concentration ratio may indicate either a too low relative importance of indoor sources (if concentrations outdoors are increasing) or a too high relative importance of indoor sources (if concentrations outdoors are decreasing) (Ekberg, 1996). The time dependence of indoor and outdoor sources and meteorological conditions can affect $P$, $k$, and $a$, and thus affect the relationships between indoor and outdoor $NO_2$ concentration and between personal exposure and outdoor $NO_2$ concentrations on short time scales. Thus, relationships among $P$, $k$, and $a$ derived using a steady state model might not be representative of short term values. It should also be pointed out that both $P$ and $k$ are functions of complex physical and chemical processes that occur on indoor surfaces and therefore are associated with indoor-outdoor air exchange, which in turn affects indoor air flows.

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

The random component superposition (RCS) model is an alternative way to calculate $F_{inf}$ or α using observed ambient and personal exposure concentrations (Ott et al., 2000). The RCS statistical model (shown in Equations 2.5-2 through 2.5-5) uses the slope of the regression line of personal concentration on the ambient $NO_2$ concentration to estimate the population averaged attenuation factor and means and distributions of ambient and nonambient contributions to personal $NO_2$ concentrations (the intercept of the regression is the averaged nonambient contribution to personal exposure) (U.S. Environmental Protection Agency, 2004). As shown in Annex Table AX3.5-1a, $F_{inf}$ ranges from 0.4 to 0.7. Similarly, as shown in Annex Table AX3.5-1b, α, calculated by the RCS model, ranges from 0.3 to 0.6.

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

Nerriere et al. (2005) used data from the Genotox ER study in France (Grenoble, Paris, Rouen, and Strasbourg) and reported that factors affecting the differences between personal exposure to ambient $NO_2$ and corresponding ambient monitoring site concentrations were season, city, and land use dependence.

During the winter, city and land use categorization account for 31% of the variation, and during the summer, 54% of the variation can be explained by these factors. When data from the ambient monitoring site were used to represent personal exposures, the largest difference between ambient and personal exposure was found at the "proximity to traffic" site, while the smallest difference was found at the "background" site. When using data from the urban background site, the largest difference was observed at the "industry" site, and the smallest difference was observed at the background site, which reflected the heterogeneous distribution of $NO_2$ in an urban area. During winter, differences between ambient site and personal exposure concentrations were larger than those in the summer.

# 2.5.7. $NO_2$ as a Component and Indicator of Pollutant Mixtures

## 2.5.7.1. Associations between Ambient $NO_2$ and Ambient Copollutants

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

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

As can be seen from Table 2.5-7, $NO_2$ was moderately correlated with $PM_{2.5}$ (range: 0.37 to 0.78) and with CO (0.41 to 0.76) in suburban and urban areas. At some sites (e.g., Riverside, CA) associations between ambient $NO_2$ and ambient CO concentrations (both largely traffic-related pollutants) are much lower, likely as the result of other sources of both CO and $NO_2$ increasing in importance in going from urban environments to more rural and sparsely populated areas. These sources include oxidation of methane ($CH_4$) and other biogenic compounds; residential wood burning and prescribed and wild land fires for CO; and soil emissions, lightning, and residential wood burning and wild land fires for $NO_2$. In urban areas, the ambient $NO_2$-CO correlations vary widely. The strongest correlations are seen between $NO_2$ and elemental carbon (EC). Note that the results of Hochadel et al. (2006) for $PM_{2.5}$ optical absorbance have been interpreted in terms of EC. Brook et al. (2007) also found relatively high correlations between ambient $NO_2$ and combustion-related organics, including the BTEX compounds (benzene, toluene, ethylbenzene, and o-, m-, p-xylene) (r=0.45-0.6) and hopanes (r=0.67-0.8). Correlations between ambient $NO_2$ and ambient $O_3$ are mainly negative, owing to the chemical interaction between the two, with again considerable variability in the observed correlations. Only one study (Sarnat et al., 2001) examined associations between ambient $NO_2$ and ambient $SO_2$ concentrations, and it showed a negative correlation during winter.

Figure 2.5-6 shows seasonal plots of correlations between $NO_2$ and $O_3$ versus correlations between $NO_2$ and CO. As can be seen from the figure, $NO_2$ is positively correlated with CO during all seasons at all sites. However, the sign of the correlation of $NO_2$ with $O_3$ varies with season, ranging from negative during winter to slightly positive during summer. There are at least two main factors contributing to the observed seasonal behavior. $O_3$ and radicals correlated with it tend to be higher during the summer, thereby tending to increase the ratio of $NO_2$ to NO. Nitrogen oxide compounds formed by further oxidation of $NO_X$ are also expected to be correlated with $O_3$ and increased summertime photochemical activity. Because some of these additionally oxidized *N* compounds create a positive artifact in the FRM for $NO_2$, they may also tend to increase the correlation of $NO_2$ with $O_3$ during the warmer months.

**Table 2.5-7. Pearson correlation coefficient between ambient $NO_2$ and ambient copollutants.**

| STUDY | LOCATION | $PM_{2.5}$ | CO | $O_3$ | $SO_2$ |
|---|---|---|---|---|---|
| AQS (2007)* | Los Angeles, CA | 0.49 (u[2])<br>0.56 (s) | 0.59 (u)<br>0.64 (s) | –0.29 (u)<br>–0.11 (s) | NR |
| AQS (2007)* | Riverside, CA | NR | 0.43 (u)<br>0.41 (s)<br>0.15 (r) | 0.045 (u)<br>0.10 (s)<br>–0.31 (r) | NR |
| AQS (2007)* | Chicago, IL | 0.49 (s) | 0.53 (u)<br>0.46 (s) | –0.20 (u) | NR |
| AQS (2007)* | New York, NY | 0.58 (u) | 0.46 (u) | –0.06 (u) | NR |
| Kim et al. (2006) | Toronto, Canada | 0.44 | 0.72 | NR | NR |
| Sarnat et al. (2006) | Steubenville, OH (autumn) | 0.78 (0.70 for sulfate; 0.82 for EC) | NR | NR | NR |
| Sarnat et al. (2006) | Steubenville, OH (summer) | 0.00 (0.1 for sulfate; 0.24 for EC) | NR | NR | NR |
| Connell et al. (2005) | Steubenville, OH | 0.50 | NR | NR | NR |
| Kim et al. (2005) | St. Louis, MO (RAPS) | NR | 0.64[4] | NR | NR |
| Sarnat et al. (2001)[1] | Baltimore, MD (summer) | 0.37 | 0.75 | 0.02 (not significant) | NR |
| Sarnat et al. (2001) | Baltimore, MD (winter) | 0.75 | 0.76 | –0.71 | –0.17 |
| Hochadel et al. (2006) | Ruhr area, Germany | 0.41 (0.93 for EC[3]) | NR | NR | NR |
| Hazenkamp-von Arx et al. (2004) | 21 European cities | 0.75 | NR | NR | NR |
| Cyrys et al. (2003) | Erfurt, Germany | 0.50 | 0.74 | NR | NR |
| Brook et al. (2007) | 10 Canadian cities | 0.54 | NR | NR | NR |
| Mosqueron et al. (2002) | Paris, France | 0.69 | NR | NR | NR |
| Rojas-Bracho et al. (2002) | Santiago, Chile | 0.77 | NR | NR | NR |

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

*Data obtained from EPA's AQS Database, available at http://www.epa.gov/ttn/airs/airsaqs/

## 2.5.7.2. Associations among $NO_2$ and Other Pollutants in Indoor Environments

In addition to $NO_2$, indoor combustion sources such as gas ranges and unvented gas heaters emit other pollutants that are already present in the fuel or are formed during combustion. The major products from the combustion of natural gas are carbon dioxide ($CO_2$), CO, followed by formaldehyde (HCHO), with smaller amounts of other oxidized organic compounds in the gas phase. PM, especially in the ultrafine-size range and HONO are also emitted. The production of pollutants by reactions of $NO_2$ in indoor air was covered in Section 2.5.5.

Dennekamp et al. (2001) measured levels of NO, $NO_2$, and ultrafine particles (UFP) generated by gas and electric cooking ranges in a test laboratory room. They found average levels of NO ranging from ~500 to ~3,000 ppb, with peak (15-min avg) levels ranging from ~1,000 to ~6,000 ppb depending on how many burners (1 to 4) were turned on and for how long (15 min to 2 h). Corresponding levels of $NO_2$ tracked those of NO but were typically factors of 2 to 5 lower. Spicer et al. (1993) compared the measured increase in HONO in a test house resulting from direct emissions of HONO from a gas range and from production by surface reactions of $NO_2$. They found that emissions from the gas range could

account for ~84% of the measured increase in HONO. In a study of homes in southern California, Lee et al. (2002) found that indoor levels of $NO_2$ and HONO were positively associated with the presence of gas ranges.

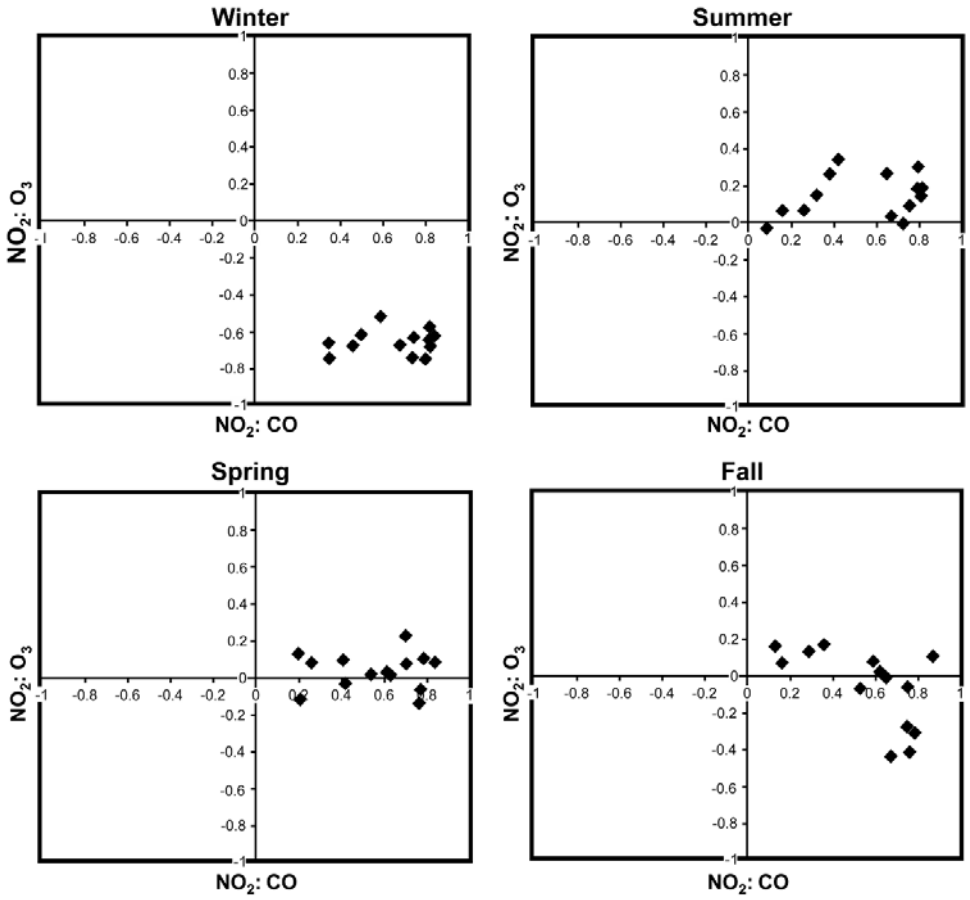



**Figure 2.5-6. Correlations of $NO_2$ to $O_3$ versus correlations of $NO_2$ to CO for Los Angeles, CA (2001-2005).**

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

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

Rogge et al. (1993) found that at least 22% of the fine particle mass emitted by natural gas heaters consists of PAHs, oxy-PAHs, and aza-and thia-arenes. They also identified emissions of speciated alkanes, n-alkanoic acids, polycyclic aromatic ketones, and quinones. However, these accounted for only another ~4% of the emitted fine PM. Although the PM emissions rates were low and not likely to affect

PM levels, the PAH content of natural gas combustion emissions in this study indicates that natural gas combustion could be a substantial source of PAHs in indoor environments

## 2.5.7.3. Personal and Ambient Associations between $NO_2$ and Copollutants

Correlations between ambient concentrations of $NO_2$ and $PM_{2.5}$ (and PM components where available), are summarized in Table 2.5-8. Correlations between personal concentrations of $NO_2$ and ambient copollutants, $PM_{2.5}$, $PM_{10}$, EC, CO, and sulfate are summarized in Table 2.5-9, and correlations between personal $NO_2$ concentrations and personal copollutant concentrations are shown in Table 2.5-10. Most studies examined showed that personal $NO_2$ concentrations were significantly correlated with either ambient or personal level $PM_{2.5}$ or other combustion-generated pollutants, e.g., CO, EC.

**Table 2.5-8. Pearson correlation coefficient between ambient $NO_2$ and personal copollutants.**

| STUDY | LOCATION | $PM_{2.5}$ | SULFATE | EC | UFP |
|---|---|---|---|---|---|
| Sarnat et al. (2006) | Steubenville, OH Fall | 0.71 | 0.52 | 0.70 | — |
| Sarnat et al. (2006) | Steubenville, OH Summer | 0.00 | 0.1 not significant | 0.26 | — |
| Vinzents et al. (2005) | Copenhagen, Denmark | — | — | — | 0.49 ($R^2$) explained by ambient $NO_2$ and ambient temperature |

**Table 2.5-9. Pearson correlation coefficient between personal $NO_2$ and ambient copollutants.**

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

A number of case studies show correlations between ambient $NO_2$ and other pollutants that are associated with traffic. Particulate and gaseous copollutant data were analyzed at 10 sites in the St. Louis Regional Air Pollution Study (RAPS) dataset (1975, 1977) by Kim et al. (2005). This study examined the spatial variability in source contributions to $PM_{2.5}$. Table 2.5-11 shows correlations between $NO_X$ and traffic pollutants measured in ambient air.

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

**Table 2.5-10. Pearson correlation coefficient between personal $NO_2$ and personal copollutants.**

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

**Table 2.5-11. Pearson correlation coefficient between $NO_X$ and traffic-generated pollutants.**

| SPECIES | ALL SITES | WITHOUT UPWIND OR BACKGROUND SITE |
|---|---|---|
| $NO_X$: $PM_{2.5}$ (motor vehicle component) | $0.48<r<0.75$[1] | $0.48<r<0.75$[2] |
| $NO_X$: CO | $0.30<r<0.77$[1] | $0.54<r<0.77$[2] |
| $NO_X$: Pb | $0.42<r<0.76$[1] | $0.48<r<0.76$[2] |
| $NO_X$: Br | $0.55<r<0.73$[1] | $0.58<r<0.73$[2] |
| $NO_2$: EC | 0.93[3] | — |
| $NO_2$: EC | 0.82 autumn, 0.24 summer[4] | — |

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

## 2.5.7.4. $NO_2$ as an Indicator of the Mixture of Traffic Pollutants

In the Restrepo et al. (2004) study, $NO_2$ behaved as if traffic were its main source, since $NO_2$ behaved similarly to CO and $PM_{2.5}$; i.e., their concentrations decreased with height. $O_3$ showed the opposite vertical gradient; i.e., its concentration increased with height.

UFPs have long been associated with motor vehicle traffic (e.g., PM AQCD, 2004). Seaton and Dennekamp (2003) proposed that $NO_2$ may be a surrogate for UFPs, in particular for particle number concentrations. The results from the measurements made at a background site in Aberdeen, Scotland, over the course of 6 months showed very high correlation between the number concentration of particles <100 nm in diameter and $NO_2$. The correlation between $NO_2$ and the particle number concentration (r=0.89) was much higher than that between $NO_2$ and $PM_{2.5}$ (r=0.55) and that between $NO_2$ and $PM_{10}$ (r=0.45). A time-series mortality study (re-analysis by Stölzel et al., 2003; Wichmann et al., 2000) conducted in Erfurt, Germany, measured, and analyzed UFP number and mass concentrations as well as $NO_2$. Unlike Seaton and Dennekamp's data, in this data set, the correlation between $NO_2$ and various number concentration indices were not much stronger than those between $PM_{2.5}$ and number concentration indices

or those between $PM_{10}$ and number concentration indices. For example, the correlation between NC0.01-0.10 (particle number concentration for particle diameter between 10 and 100 nm) and $NO_2$, $PM_{2.5}$, and $PM_{10}$ were 0.66, 0.61, and 0.61, respectively.

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

The composite diurnal variability of $NO_2$ in selected urban areas with multiple sites (New York, NY, Atlanta, GA, Baton Rouge, LA, Chicago, IL, Houston, TX, Riverside, CA, and Los Angeles, CA) is shown in Figure 2.5-7. Figure 2.5-7 shows that lowest hourly median concentrations are typically found at around midday and that highest hourly median concentrations are found either in the early morning or in mid-evening. Median values range by about a factor of two from ~13 ppb to ~25 ppb. However, individual hourly concentrations can be considerably higher than these typical median values, and hourly $NO_2$ concentrations of >0.10 ppm can be found at any time of day. The diurnal pattern in median concentrations shown in Figure 2.5-7 is consistent with that shown in Figures 2.4-5 and 2.4-6 for Atlanta, indicating some commonality in sources across these cities. The pattern in the median concentrations is consistent with traffic as the major source of variability. However, the patterns in the upper end of the concentration distribution differ between cities and the composite, indicating that other sources and meteorological processes affect $NO_2$ levels, causing them to differ from city to city.

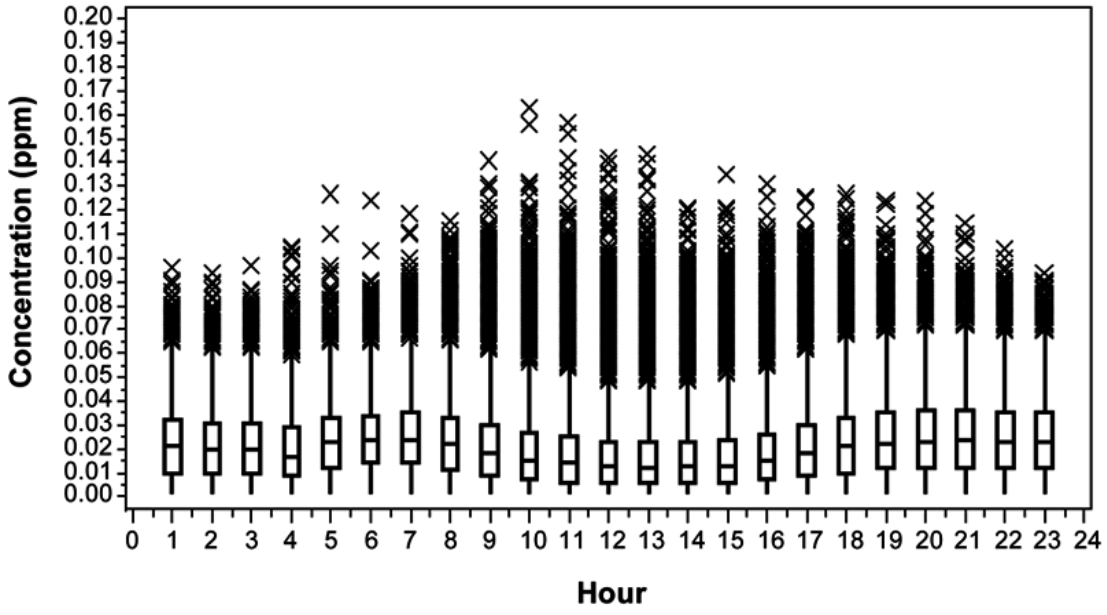



**Figure 2.5-7. Composite, diurnal variability in 1-h avg $NO_2$ in urban areas. Values shown are averages from 2003 through 2005. Boxes define the interquartile range, and the whiskers the 5th and 95th percentile values. "X" denotes individual values above the 95th percentile.**

Information concerning the seasonal variability of ambient $NO_2$ concentrations is given in Annex section AX3.2. $NO_2$ levels are highest during the cooler months of the year and still show positive correlations with CO. Mean $NO_2$ levels are lowest during the summer months, though of course, there can be large positive excursions associated with the development of high-pressure systems. In this regard, $NO_2$ behaves as a primary pollutant, although there is no good reason to suspect strong seasonal variations in its emissions.

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

## 2.5.8. Exposure Error in Epidemiologic Studies

For the purposes of this ISA, the effects of exposure error on epidemiologic study results refers to changes in the point estimate and in the standard error of the calculated health effect estimate, β, that result from using the concentration of an air pollutant as an exposure indicator rather than using the actual personal exposure to the causal factor in the epidemiologic statistical analysis. There are many assumptions made in going from the available experimental measurement of a pollution indicator, to an estimate of the personal exposure, to the causal factor. The importance of these assumptions and their effect on β depend on the type of epidemiologic study. A more detailed discussion of these issues is provided in Annex section AX6.1.

### 2.5.8.1. Community Time-Series Studies

This section applies primarily to studies of the association between short-term $NO_2$ concentrations and short-term measures of mortality or morbidity. With $NO_2$ time-series epidemiologic analysis, the following three exposure issues are of primary concern: (1) the relationship of the experimental measurement of $NO_2$ to the true concentration of $NO_2$; (2) the relationship of day-to-day variations of the concentration of the indicator, as measured at a central monitoring site, with the corresponding variations in the avg concentration of the indicator over the geographic area from which the health measurements are drawn; and (3) the relationship of the community avg concentration of $NO_2$ to the avg personal exposure to ambient $NO_2$. These three issues are described below.

Since there is always some instrumental error in the experimental measurement of $NO_2$ concentration, the correlation of the measured $NO_2$ with the true $NO_2$, on either a 24-h or 1-h basis, will be less than 1. Averaging across multiple unbiased ambient monitors in a region should reduce the instrument measurement error (Sheppard, 2005; Wilson and Brauer, 2006; Zeger et al., 2000). This error component is not expected to have a major effect on personal exposure estimation. It may tend to attenuate the estimate of α (Sheppard, 2005) and is unlikely to greatly affect β, particularly if the instrument error is of the Berkson type. Zeger et al. (2000) showed that instrument error has both Berkson and non-Berkson error components.

The concentration of $NO_2$, measured at any given monitoring site, may not be highly correlated with the avg community concentration. Large spatial variations (expressed as coefficient of divergence (COD) have been observed in some urban areas, as shown in Table 2.5-1. Site-to-site correlations of $NO_2$ concentrations, as shown for several cities in Table 2.5-1 included some very low values, possibly due to

local sources, monitor siting, meteorology, and topography. Low correlations between the ambient concentration and the community avg concentration quantitatively reduce β if the single pollutant model is the true model. Similarly, β will be reduced if there are subareas of the community where the correlation of the subarea avg concentrations with the concentrations measured at the ambient monitoring site is <1. Therefore, if a local source affected a sizable portion of the population, that community might not be suitable for time-series epidemiologic analyses.

Zeger et al. (2000) made a major contribution to the understanding of exposure error by pointing out that for community time-series epidemiology, which analyzes the association between health effects and potential causal factors at the community scale rather than the individual scale, it is the correlation of the daily community avg personal exposure to the ambient concentration, $X_t^A$, with daily community avg concentration, $C_t$, that is important, not the correlation of each individual's exposure $X_{it}^A$ with $C_t$. Thus, the low correlation of $X_{it}^A$ with $C_t$, as frequently found in pooled panel exposure studies, is not relevant to error in community time-series epidemiologic analysis. Unfortunately, few experimental studies provide adequate information to calculate the community avg exposure. Most exposure panel studies measure one or a few subjects on 1 day, and another one or a few subjects on the next day, etc. (i.e., a pooled study design). A few studies have measured one subject for several days and another subject for a different set of several days (i.e., a longitudinal study design). This requires measurement of the personal exposure of every subject on every day along with sufficient information to separate the ambient component of exposure from the measured total personal exposure. Such information was available from one study of combined $PM_{10}$ and showed that the correlation of $X_t^A$ with $C_t$ was much greater than the correlation of $X_{it}^A$ with $C_t$ (U.S. Environmental Protection Agency, 2004). The Research Triangle Park PM Panel Study found similar effects in the relationship of outdoor and personal $PM_{2.5}$ concentrations (Williams et al., 2003). Ott et al. (2000) provided a statistical argument that such an increase in the correlation of the daily avg over the individual values should be expected.

Inter-individual daily variation in $\alpha_{it}$ around the daily community avg $\alpha_t$ tends to produce Berkson error, which will not change the point estimate of β, although it may increase the standard error (Zeger et al., 2000). Overestimation of exposure by substitution of the ambient concentration for the ambient exposure leads to underestimation of the effect estimate proportional to α, or bias toward the null (Sheppard, 2005).

Panel epidemiology refers to time-series studies that follow a relatively small number of subjects for a relatively short time, usually tens of subjects for 5 to 20 days a subject. Thus, neither the averaging of exposure over millions of people, as in community time-series studies, or the averaging of exposure over time periods of years and hundreds or thousands of subjects, as in chronic cohort studies was available. Therefore, exposure errors may be more important than in other types of epidemiology. Panel studies typically examine the association between symptoms or health outcomes and either ambient concentrations or personal exposures. Most panel epidemiology studies of $NO_2$ used ambient concentrations rather than personal exposures. Similar types of exposure error, as discussed for community time series studies apply to panel studies, with some differences depending on whether ambient concentrations or personal exposures are used.

### 2.5.8.2. Long-Term Exposure Studies

For long-term exposure epidemiologic studies, concentrations are integrated over time periods of a year or more, and usually for spatial areas the size of a city, county, or MSA, although integration over smaller areas may be feasible. Health effects are then regressed, in a statistical model, against the avg concentrations in the series of cities (or other areas). In time-series studies, a constant difference between the measured and the true concentration (instrument offset) will not affect β, nor will variations in the daily average α or the daily average nonambient exposure, unless the variations are correlated with the daily variations in concentrations. However, in long-term exposure epidemiologic studies, if instrument measurement errors, long-term average values of α, or long-term averages of nonambient exposure differ

for different cities (or other areas used in the analysis), the city-to-city long-term ambient $NO_2$ concentrations will not be perfectly correlated with the long-term average exposure to either ambient or total $NO_2$. This lack of correlation would be expected to lead to a lowering of the point estimate of β.

## 2.5.9. Summary of Issues in Assessing Exposures to $NO_2$

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

The evidence relating ambient levels to personal exposures is inconsistent. Some of the longitudinal studies examined found that ambient levels of $NO_2$ were reliable proxies of personal exposures to $NO_2$. However, a number of studies did not find significant associations between ambient and personal levels of $NO_2$. The differences in results were related in large measure to differences in study design and in exposure determinants. Measurement artifacts and differences in analytical measurement capabilities could also have contributed to the inconsistent results. Indeed, in a number of the studies examined, the majority of measurements of personal $NO_2$ concentrations were beneath detection limits, and in all studies some personal measurements were beneath detection limits.

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

# 2.6. Dosimetry of Inhaled $NO_X$

This section provides a brief overview of $NO_2$ dosimetry and updates information provided in the 1993 $NO_X$ AQCD. A more extensive discussion of $NO_2$ dosimetry appears in Annex AX4. $NO_2$, classified as a reactive gas, interacts with surfactants, antioxidants, and other compounds in the epithelial lining fluid (ELF). The compounds thought to be responsible for adverse pulmonary effects of inhaled $NO_2$ are the reaction products themselves or the metabolites of these products in the ELF.

Acute $NO_2$ uptake in the lower respiratory tract is thought to be rate-limited by chemical reactions of $NO_2$ with ELF constituents rather than by gas solubility in the ELF (Postlethwait and Bidani, 1990). Postlethwait and Bidani (1994) concluded that the reaction between $NO_2$ and water does not significantly contribute to the absorption of inhaled $NO_2$. Rather, uptake is a first-order process for $NO_2$ concentrations of <10 ppm, is aqueous substrate-dependent, and is saturable. Postlethwait et al. (1991) reported that inhaled $NO_2$ (<10 ppm) does not penetrate the ELF to reach underlying sites and proposed that cytotoxicity may be due to $NO_2$ reactants formed in the ELF. Related to the balance between reaction product formation and removal, it was further hypothesized that cellular responses may be nonlinear with greater responses being possible at low levels of $NO_2$ uptake versus higher levels of uptake.

Glutathione (GSH) and ascorbate are the primary $NO_2$ absorption substrates in rat ELF (Postlethwait et al., 1995). Velsor and Postlethwait (1997) investigated the mechanisms of acute epithelial injury from $NO_2$ exposure. Membrane oxidation was not a simple monotonic function of GSH and ascorbic acid levels. The maximal levels of membrane oxidation were observed at low antioxidant levels versus null or high antioxidant levels. GSH- and ascorbic acid-related membrane oxidation were superoxide- and hydrogen peroxide-dependent, respectively. The authors proposed that increased absorption of $NO_2$ occurred at the higher antioxidant concentrations, but little secondary oxidation of the membrane occurred because the reactive species (e.g., superoxide and hydrogen peroxide) generated during absorption were quenched. A lower rate of $NO_2$ absorption occurred at the low antioxidant concentrations, but oxidants were not quenched and so were available to interact with the cell membrane.

In vitro studies have clearly illustrated the role of antioxidants in mediating $NO_2$ uptake and membrane oxidation; however, the temporal dynamics of biological responses to $NO_2$ that occur in vivo are far more complex. Antioxidant levels vary spatially between lung regions and temporally with $NO_2$ exposure. Kelly et al. (1996a) examined the effect of a four-hour $NO_2$ (2 ppm) exposure on antioxidant levels in bronchial lavage fluid (BLF) and bronchoalveolar lavage fluid (BALF) of 44 healthy nonsmoking adults (19-45 yr, median 24 yrs). The baseline concentrations of uric acid and ascorbic acid were strongly correlated between the BLF and BALF within individuals ($r=0.88$, $p<0.001$; $r=0.78$, $p=0.001$; respectively), whereas the concentrations of GSH in the BLF and BALF were not correlated. At 1.5 h after the $NO_2$ exposure, uric acid and ascorbic acid levels were significantly reduced in both lavage fractions while GSH levels were significantly increased but only in BLF. By 6 h postexposure, ascorbic acid levels had returned to baseline in both lavage fractions, but uric acid had become significantly increased in both lavage fractions and GSH levels remained elevated in BLF. By 24 hours postexposure, all antioxidant levels had returned to baseline. The levels of GSH in BALF did not change from baseline at any time point in response to $NO_2$ exposure. The depletion of uric acid and ascorbic acid, but not GSH has also been observed with ex vivo exposure of human BALF to $NO_2$ (Kelly et al., 1996a; 1996b).

Very little work related to the quantification of $NO_2$ uptake has been reported since the 1993 $NO_X$ AQCD. In both humans and animals, the uptake of $NO_2$ by the upper respiratory tract decreases with increasing ventilation rates. This causes a greater proportion of inhaled $NO_2$ to be delivered to the lower respiratory tract. In humans, the breathing pattern shifts from nasal to oronasal during exercise relative to rest. Since the nasal passages absorb more inhaled $NO_2$ than the mouth, exercise (with respect to the resting state) delivers a disproportionately greater quantity of the inhaled mass to the pulmonary region of the lung, where the $NO_2$ is readily absorbed. Bauer et al. (1986) reported a statistically significant increase in uptake from 72% during rest to 87% during exercise in a group of 15 asthmatic adults. The minute ventilation also increased from 8.1 L/min during rest to 30.4 L/min during exercise. Hence,

exercise increased the dose rate of $NO_2$ by 5-fold in these subjects. Similar results have been reported for beagle dogs where the dose rate of $NO_2$ was 3-fold greater for the dogs during exercise than rest (Kleinman and Mautz, 1991).

Modeling studies also predict that the net $NO_2$ dose ($NO_2$ flux to air-liquid interface) is relatively constant from the trachea to the terminal bronchioles and then rapidly decreases in the pulmonary region. The pattern of net $NO_2$ dose rate or uptake rate is expected to be similar between species and unaffected by age in humans. The predicted tissue dose and dose rate of $NO_2$ ($NO_2$ flux to liquid-tissue interface) is low in the trachea, increases to a maximum in the terminal bronchioles and the first generation of the pulmonary region, and then decreases rapidly with distal progression. The site of maximal $NO_2$ tissue dose is predicted to be fairly similar between species, ranging from the first generation of respiratory bronchioles in humans to the alveolar ducts in rats. The production of toxic $NO_2$ reactants in the ELF and the movement of these reactants to the tissues have not been modeled. Contrary to what recent in vitro studies have shown (Kelly et al., 1996a), modeling studies have generally considered $NO_2$ reactions in the ELF to be protective. The complex interactions between antioxidants, spatial differences in antioxidants between lung regions, temporal changes in antioxidant levels in response to $NO_2$ exposure, and species differences in antioxidant defenses are poorly understood. Thus, the current dosimetry models are inadequate to put response data collected from animals and humans on a comparative footing with each other and with the exposure conditions in the epidemiologic studies.

# Chapter 3. Integrated Health Effects

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

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

The epidemiologic studies contain important information on potential associations between health effects and exposures of human populations to ambient levels of $NO_2$, and they help to identify susceptible subgroups and associated risk factors. However, the associations derived for specific air pollutants and health outcomes in epidemiologic studies may be confounded by copollutants and/or meteorological conditions and can be influenced by model specifications in the analytical methods. Extensive discussion of issues related to confounding effects among air pollutants in epidemiologic studies is provided in the 2004 PM AQCD and so is not repeated in detail here. Briefly, though, the use of multipollutant regression models has been the approach most commonly used to control for potential copollutant confounders.

One specific concern has been that a given pollutant may act as a surrogate for other unmeasured or poorly measured pollutants or pollutant mixtures. Specifically, traffic is a nearly ubiquitous source of combustion pollutant mixtures that include $NO_2$ and can be an important contributor to $NO_2$ levels in near-road locations. This complicates efforts to disentangle specific $NO_2$-related health effects as distinct from those effects of the whole traffic-generated combustion mix. These multipollutant models use terms for measured variables as important tools for estimating an effect in multisource epidemiologic studies. Both single- and multipollutant models that include $NO_2$ were considered and examined for robustness of results.

Model specification and model selection also are factors to consider in the interpretation of the epidemiologic evidence. Epidemiologic studies investigated the association between various measures of $NO_2$ (e.g., multiple lags, different exposure metrics) and various health outcomes using different model specifications (for further discussion, see the 2006 $O_3$ AQCD [U.S. Environmental Protection Agency, 2006a]).

Human clinical studies conducted in controlled exposure chambers use fixed concentrations of air pollutants under carefully regulated environmental conditions and subject activity levels to minimize possible confounding of the health associations by other factors. Additionally, sensitive experimental techniques can be used to measure health effects (and markers of injury) that are not evaluated in epidemiologic studies, e.g. airway hyperresponsiveness. These studies provide important information on effects, concentration-response relationships, biological plausibility of associations observed between $NO_2$ exposure and health outcomes in epidemiologic studies, and insights into sensitive subpopulations. While human clinical studies provide a direct quantitative assessment of the $NO_2$ exposure-health response relationship, such studies have a number of limitations. First, it is requisite that subjects be either healthy individuals or individuals whose level of illness does not preclude them from participating in the study. Therefore, the results of human clinical studies may underestimate the health effects of exposure to

certain sensitive subpopulations. Second, studies of controlled exposure to $NO_2$ typically have used concentrations that are higher than those normally present in ambient air. Third, human clinical studies normally are conducted on a relatively small number of subjects, which reduces the power of the study to detect significant differences in the health outcomes of interest and exposures to varying concentrations of $NO_2$ and clean air.

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

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

# 3.1. Respiratory Morbidity Related to Short-Term Exposure

## 3.1.1. Lung Host Defenses and Immunity

Lung host defenses are sensitive to $NO_2$ exposure, with numerous measures of such effects observed at concentrations of <1 ppm. The following discussion focuses on studies published since the 1993 AQCD and conducted at near-ambient exposure concentrations; as needed, it refers to studies described in the 1993 AQCD. A major concern has been the potential for $NO_2$ exposure to enhance susceptibility to, or the severity of illness resulting from, respiratory infections and asthma, especially in children. Potential mechanisms of lung host defense impairment (Chauhan and Johnston, 2003), include "direct effects on the upper and lower airway by ciliary dyskinesis (Carson et al., 1993), epithelial damage (Devalia et al., 1993a), increases in pro-inflammatory mediators and cytokines (Devalia et al., 1993b), rises in IgE concentration (Siegel et al., 1997), and interaction with allergens (Tunnicliffe et al., 1994), or indirectly through impairment of bronchial immunity (Sandström et al., 1992a)." Table 3.1-1 provides more details and summarizes a range of proposed mechanisms by which exposure to $NO_2$ in conjunction with viral infections may exacerbate upper and lower airway symptoms (Chauhan et al., 1998).

Several epidemiologic studies investigated the relationship between $NO_2$ exposure and effects related to viral infection. Personal exposure to $NO_2$ and the severity of virus-induced asthma (Chauhan et al., 2003), including risk of airflow obstruction (Linaker et al., 2000) was studied in a group of 114 asthmatic children in England. Children were supplied with Palmes diffusion tubes, which they attached to their clothing during the day and placed in their bedroom at night. Tubes were changed every week for the duration of the 13-month study period. Nasal aspirates were obtained and analyzed for a variety of respiratory illness-causing viruses. The authors observed that exposure to $NO_2$ levels of greater than 14 $\mu g/m^3$ (7.4 ppb) in the week preceding any viral infection was associated with increases in the four-point symptom severity score (score increase of 0.6 [95% CI: 0.01, 1.18]) in the week immediately after the infection. Associations also were observed for the respiratory syncytial virus (RSV) alone (score increase

of 2.1 [95% CI: 0.52, 3.81]). A significant reduction in peak expiratory flow (PEF) was associated with exposure greater than 14 $\mu g/m^3$ (7.3 ppb) (by 12 L/min [95% CI: -23.6, -0.80]) (Chauhan et al., 2003). Exploration of the relationship between PEF and $NO_2$ showed that the risk of a PEF episode (as diagnosed by a clinician's review of each child's PEF data) beginning within a week of an upper respiratory infection was significantly associated with exposure to $NO_2$ greater than 28 $\mu g/m^3$ (14.9 ppb) (relative risk [RR]=1.9 [95% CI: 1.1, 3.4]) (Linaker et al., 2000). Thus, high personal $NO_2$ exposure in the week before an upper respiratory infection was associated with either increased severity of lower respiratory tract symptoms or reduction of PEF for all virus types together and for two of the common respiratory viruses, C-picornavirus and RSV, individually.

**Table 3.1-1. Proposed mechanisms whereby $NO_2$ and respiratory virus infections may exacerbate upper and lower airway symptoms.**

| | PROPOSED MECHANISMS |
|---|---|
| ***Upper Airway*** | |
| Epithelium | ↓ Ciliary beat frequency |
| | ↑ Epithelial permeability |
| ***Lower Airway*** | |
| Epithelium | (as in upper airway) |
| Cytokines | ↓ Epithelial-derived IL-8, GM-CSF, TNF-α |
| | ↑ Macrophage-derived IL-1b, IL-6, IL-8, TNF-α |
| Inflammatory cells | ↑ Mast cell tryptase |
| | ↑ Neutrophils |
| | ↑ Total lymphocytes |
| | ↑ NK lymphocytes |
| | ↓ T-helper/T-cytotoxic cell ratio |
| Inflammatory mediators | ↑ Free radicals, proteases, TXA2, TXB2, LTB4 |
| Allergens | ↑ Penetrance due to ciliostasis |
| | ↓ PD20-$FEV_1$ |
| | ↑ Antigen-specific IgE |
| | ↑ Epithelial permeability |
| ***Peripheral Blood*** | |
| | ↓ B and NK lymphocytes |
| | ↓ Total lymphocytes |

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

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

to examine the effects of in vivo $NO_2$ exposure on the function of alveolar macrophages (AMs) obtained by bronchoalveolar lavage (BAL), including the susceptibility of these cells to viral infection in vitro. Two studies since 1993 involved 2.0-ppm $NO_2$ exposures for 4 or 6 h with intermittent exercise and found no effect on AM inactivation of influenza virus either immediately or 18 h after exposure (Azadniv et al., 1998; Devlin et al., 1999). However, Devlin et al. (1999) found ex vivo AM phagocytic capacity reduced following a 4-h exposure of healthy volunteers to 2 ppm $NO_2$, indicating a reduced ability to clear inhaled bacteria or other infectious agents. Frampton et al. (2002) examined $NO_2$ effects on viral infectivity of airway epithelial cells. Subjects were exposed to air, or 0.6- or 1.5-ppm $NO_2$, for 3 h, and bronchoscopy was performed 3.5 h after exposure. Epithelial cells were harvested from the airway by brushing and then challenged in vitro with influenza virus and RSV. $NO_2$ exposure did not alter viral infectivity, but appeared to enhance epithelial cell injury in response to infection with RSV ($p=0.024$). Similar results were reported with influenza virus. These findings indicate that prior exposure to $NO_2$ may increase the susceptibility of the respiratory epithelium to injury by subsequent viral challenge.

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

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

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

Animal studies provide clearer evidence that host defense system components such as mucociliary transport and AMs (see Annex Table AX4.3) are targets for inhaled $NO_2$. Animal studies further show that $NO_2$ can impair the respiratory host defense system sufficiently to render the host more susceptible to respiratory infections (See Annex Table AX4.6).

Exposure of guinea pigs to 3- or 9-ppm $NO_2$ 6 h/day, 6 days/week for 2 weeks resulted in concentration-dependent decreases in ciliary activity of 12 and 30% of control values, respectively

(Ohashi et al., 1994). These concentration-dependent decreases were accompanied by a concentration-dependent increase in eosinophil accumulation on the epithelium and submucosal connective tissue layer of the nasal mucosa. For foreign agents such as some bacteria and viruses that deposit below the mucociliary region in the gas-exchange region of the lung, AMs primarily provide host defenses by acting to remove or kill viable particles, remove nonviable particles, and process and present antigens to lymphocytes for antibody production. AMs are one of the sensitive targets for $NO_2$, as evidenced by in vivo animal exposures and in vitro studies (see Annex Table AX4.3 for details of studies related to each of these morphological or functional parameters in exposed animals).

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

### Summary of Short-Term Exposure on Lung Host Defenses and Immunity

Impaired host-defense systems and increased risk of susceptibility to both viral and bacterial infections have been observed in epidemiologic, human clinical, and animal toxicological studies. A study by Chauhan et al. (2003) produced evidence that increased personal exposures to $NO_2$ worsened virus-associated lower respiratory tract symptoms in children with asthma. The limited evidence from human clinical studies indicates that $NO_2$ may increase susceptibility to injury by subsequent viral challenge at exposures as low as 0.6 ppm for 3 h (Frampton et al., 2002). Toxicological studies have shown that lung host defenses are sensitive to $NO_2$ exposure, with several measures of such effects observed at concentrations of less than 1 ppm. Together, the epidemiologic and experimental evidence show coherence for effects of $NO_2$ exposure on host defense or immune system effects. This group of outcomes also provides biological plausibility for other respiratory effects described subsequently, such as respiratory symptoms or ED visits for respiratory diseases.

## 3.1.2. Airway Inflammation

Epidemiologic studies have examined biological markers for inflammation (exhaled NO and inflammatory nasal lavage [NAL] markers) and lung damage (urinary Clara cell protein CC16). Several studies have been conducted in cohorts of children. Steerenberg et al. (2001) studied 126 schoolchildren from urban and suburban communities in the Netherlands. Sampling of exhaled air and NAL fluid was performed seven times, once per week over the course of 2 months. On average, the ambient $NO_2$ concentrations were 1.5 times higher, and ambient NO concentrations were 7.8 times higher, in the urban compared to the suburban community. Compared to children in the suburban community, urban children had significantly greater levels of inflammatory NAL markers (interleukin [IL]-8, urea, uric acid, albumin) but not greater levels of exhaled NO. However, within the urban group, a statistically significant

concentration-response relationship for exhaled NO was observed. Exhaled NO increased by 6.4 to 8.8 ppb per 20-ppb increase in $NO_2$ lagged by 1 or 3 days. Another study by Steerenberg et al. (2003) of 119 schoolchildren in the Netherlands found associations between ambient $NO_2$ and level of exhaled NO, but quantitative regression results were not given. The authors concluded from their data that an established, ongoing inflammatory response to pollen was not exacerbated by subsequent exposure to high levels of air pollution or pollen.

In one recent U.S. study, Delfino et al. (2006) evaluated the relationship between personal and ambient levels of fine PM ($PM_{2.5}$), elemental carbon (EC), organic carbon (OC), and $NO_2$ and fractional exhaled NO (FeNO), a biomarker of airway inflammation, in a panel of 45 schoolchildren with persistent asthma living in two southern California communities (Riverside and Whittier). FeNO was higher in subjects with poorly controlled asthma. Positive associations were found for FeNO with several air pollutants, including $NO_2$, with evidence from multipollutant approaches indicating that traffic-related sources of air pollutants underlie the findings. The authors concluded that the "association of FeNO with personal and ambient $NO_2$ was largely independent of personal and ambient EC and OC fractions of $PM_{2.5}$ in two-pollutant models", indicating that both ambient and personal $NO_2$ represent other causal pollutant components not sufficiently captured by ambient EC or OC in the study regions." While the effect was small ($\leq$ 2.5 ppb FeNO), making it difficult to determine if it is clinically relevant, the findings support that air pollutant exposure increases inflammation in children with asthma.

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

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

Annex Table AX5.2-1 summarizes the key clinical studies of $NO_2$ exposure in healthy subjects published since 1993, with a few key studies included prior to that date. Figure 3.1-1 illustrates the concentration-response relationship between $NO_2$ exposure and inflammatory responses in healthy subjects.

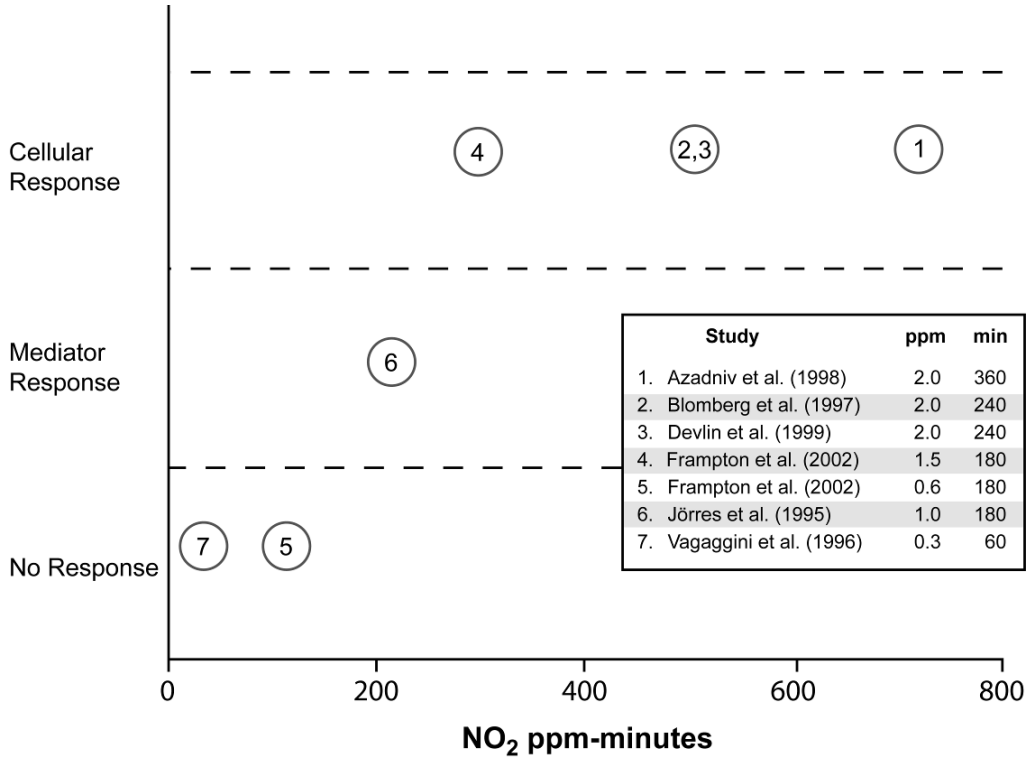



**Figure 3.1-1. Studies of airway inflammatory responses in relation to the total exposure to $NO_2$, expressed as ppm-minutes. All of the studies involved intermittent exercise, and no attempt was made to adjust the exposure metric for varying intensity and duration of exercise. Studies that did not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

Healthy volunteers exposed to 2.0-ppm $NO_2$ for 6 h with intermittent exercise showed a slight increase in the percentage of PMNs obtained in BAL fluid 18 h after exposure (air, 2.2 ± 0.3%; $NO_2$, 3.1 ± 0.4%) (Azadniv et al., 1998). Gavras et al. (1994) studied a separate group of subjects exposed using the same protocol but assessed immediately after exposure. In this case, no effects were found in AM phenotype or expression of the cell adhesion molecule CD11b or receptors for IgG. Blomberg et al. (1997) reported that 4-h exposures to 2.0-ppm $NO_2$ resulted in an increase in IL-8 and PMNs in the proximal airway of healthy subjects, although no changes were seen in bronchial biopsies. This group also studied the effects of repeated 4-h exposures to 2-ppm $NO_2$ on 4 consecutive days, with BAL, bronchial biopsies, and BAL fluid antioxidant levels assessed 1.5-h after the last exposure (Blomberg et al., 1999). The bronchial wash fraction of BAL fluid showed a 2-fold increase in PMNs and a 1.5-fold increase in myeloperoxidase, indicating persistent mild airway inflammation with repeated $NO_2$ exposure. Devlin et al. (1999) exposed 8 healthy nonsmokers to 2.0-ppm $NO_2$ for 4-h with intermittent exercise. BAL performed the following morning showed a 3.1-fold increase in PMNs recovered in the bronchial fraction, indicating small airway inflammation. These investigators also observed a reduction in AM phagocytosis and superoxide production, indicating possible adverse effects on host defense.

Pathmanathan et al. (2003) conducted four repeated daily exposures of healthy subjects to 4-ppm $NO_2$ or air for 4 h, with intermittent exercise. Exposures were randomized and separated by 3 weeks. Bronchoscopy and bronchial biopsies were performed 1-h after the last exposure. Immunohistochemistry of the respiratory epithelium showed increased expression of IL-5, IL-10, and IL-13, as well as intercellular adhesion molecule-1 (ICAM-1). These interleukins are upregulated in Th2 inflammatory

responses, which are characteristic of allergic inflammation. The findings show that repeated $NO_2$ exposures may drive the airway inflammatory response toward a Th2 or allergic-type response. Unfortunately, the report provided no data on inflammatory cell responses in the epithelium or on the cells or cytokines in BAL fluid. Thus, the findings cannot be considered conclusive regarding allergic inflammation. Furthermore, the exposure concentrations of 4 ppm are considerably higher than ambient outdoor concentrations.

Recent studies provide evidence for airway inflammatory effects at concentrations of <2.0 ppm. Frampton et al. (2002) examined $NO_2$ concentration responses in 21 healthy nonsmokers. Subjects were exposed to air or 0.6- or 1.5-ppm $NO_2$ for 3 h, with intermittent exercise, with exposures separated by at least 3 weeks. BAL was performed 3.5-h after exposure. PMN numbers in the bronchial lavage fraction increased slightly (<3-fold) but significantly ($p=0.0003$) after exposure to 1.5-ppm $NO_2$; no increase was evident at 0.6-ppm $NO_2$. Lymphocyte numbers increased in the bronchial lavage fraction after 0.6-ppm $NO_2$, but not 1.5 ppm. CD4+T lymphocyte numbers increased in the alveolar lavage fraction, and lymphocytes decreased in blood. These findings indicate a lymphocytic airway inflammatory response to 0.6-ppm $NO_2$, which changes to a mild neutrophilic response at 1.5-ppm $NO_2$. Solomon et al. (2000) also showed increased PMNs in the bronchial fraction of BAL 18 h after the third consecutive day of exposure to 2.0 ppm $NO_2$ for 4 h with intermittent exercise. Jörres et al. (1995) found that 3-h exposures to 1-ppm $NO_2$ with intermittent exercise altered levels of eicosanoids, but not inflammatory cells, in BAL fluid collected 1-h after exposure. Eicosanoids are chemical mediators of the inflammatory response; their increase in BAL fluid reported in this study indicates inflammation. The absence of an increase in PMN numbers may reflect the timing of bronchoscopy (1 h after exposure). The peak influx of PMNs may occur several hours after exposure, as it does following $NO_2$ exposure.

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

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

It has been reported that protein content changes in BAL fluid can be dependent on dietary antioxidant status. $NO_2$ exposure increases the protein content of BAL fluid in vitamin C-deficient guinea pigs at $NO_2$ levels of as low as 1880 $\mu g/m^3$ (1.0 ppm) after a 72-h exposure, but a 1-week exposure to 752 $\mu g/m^3$ (0.4 ppm) did not increase protein levels (Selgrade et al., 1981). However, Sherwin and Carlson (1973) found increased protein content of BAL fluid from vitamin C-deficient guinea pigs exposed to 752-$\mu g/m^3$ (0.4 ppm) $NO_2$ for 1 week. Differences in exposure techniques, protein measurement methods, and/or degree of vitamin C deficiencies may explain the difference between the two studies. Hatch et al. (1986) found that the $NO_2$-induced increase in BAL protein in vitamin C-deficient guinea pigs was accompanied by an increase in lung content of nonprotein sulfhydryls and ascorbic acid and a decrease in vitamin E content. The increased susceptibility to $NO_2$ was observed when lung vitamin C was reduced (by diet) to levels <50% normal.

Studies in rats and mice published since the 1993 $NO_X$ AQCD have investigated the ability of $NO_2$ to induce protein level changes consistent with inflammation. Overall, these more recent studies (included

in Annex Table AX4.4), such as Müller et al. (1994) and Pagani et al. (1994), propose that markers of inflammation measured in BAL fluid such as total protein content and content of markers of cell membrane permeability (e.g., lactate dehydrogenase increase only at or above 5-ppm exposure.

### Summary of Short-Term Exposure on Airway Inflammation

Overall, short-term exposure to $NO_2$ has been found to increase airway inflammation in human clinical and animal toxicological studies with exposure concentrations that are higher than ambient levels. Human clinical studies provide evidence for increased airway inflammation at $NO_2$ concentrations of <2.0 ppm; the onset of inflammatory responses in healthy subjects appears to be between 100 and 200 ppm-min, i.e., 1 ppm for 2 to 3 h. Increases in biological markers of inflammation were not observed consistently in healthy animals at levels of less than 5 ppm; however, increased susceptibility to NO concentrations of as low as 0.4 ppm was observed when lung vitamin C was reduced (by diet) to levels <50% of normal. The few available epidemiologic studies point to an association between ambient $NO_2$ concentrations and inflammatory response in the airways of children, though the associations were inconsistent in the adult populations examined.

## 3.1.3. Airway Hyperresponsiveness

Inhaled pollutants such as $NO_2$ may have direct effects on lung function or they may enhance the inherent responsiveness of the airway to challenge by bronchoconstricting agents. Asthmatics are generally more sensitive to nonspecific bronchoconstricting agents than nonasthmatics, and airway challenge testing is used diagnostically in asthmatics. There is a wide range of airway responsiveness in healthy people, and responsiveness is influenced by many factors, including medications, cigarette smoke, air pollutants, respiratory infections, occupational exposures, and respiratory irritants. Several drugs and other stimuli that cause bronchoconstriction have been used in challenge testing, including the cholinergic drugs methacholine and carbachol, as well as histamine, hypertonic saline, cold air, and $SO_2$. Challenge with "specific" allergens is also considered in asthmatics. In asthmatics, there is strong relationship between the degree of nonspecific airway hyperresponsiveness and the intensity of the early airway response to allergens (Cockcroft and Davis 2006). Standards for airway challenge testing have been developed for the clinical laboratory (American Thoracic Society, 2000a). Variations in methods for administering the bronchoconstricting agents may substantially affect the results (Cockcroft et al., 2005).

Airway hyperresponsiveness appears to have two components: fixed and variable (Cockcroft and Davis 2006). Presumably, exposure to air pollutants such as an $NO_2$ or $O_3$ could affect the variable component, although long-term, repeated exposure to air pollutants may also contribute to the fixed component. The mechanisms for these two components appear to differ. There is convincing evidence that the fixed component reflects airway remodeling, due to the chronic, long-term effects of airway inflammation (Cockcroft and Davis 2006). The variable component is thought to reflect airway inflammation. It is linked to the late response to allergen challenge in asthmatics, during which an influx of eosinophils and other inflammatory cells, in response to the allergen, reduces lung function and airway caliber. The variable component is episodic and generally responds to bronchodilators and anti-inflammatory agents, while the fixed component is less reversible and does not respond to anti-inflammatory agents.

The degree of airway hyperresponsiveness is related to the severity of asthma (Juniper et al. 1981; Murray et al. 1981). Airway responsiveness improves when asthma is treated with bronchodilators and anti-inflammatory drugs (Newhouse and Dolovich 1986), and the severity of the airway hyperresponsiveness predicts the lung function response to inhaled steroids (Kerstjens et al. 1993). Increased airway responsiveness is linked with airway inflammation and airway remodeling (Chetta et al. 1996), increased risk for exacerbations (Van Schayck et al. 1991), reduced lung function (Xuan et al. 2000), and increased adverse respiratory symptoms (Murray et al. 1981). In adults with asthma, more

severe airway responsiveness is predictive of a more rapid loss of lung function during follow-up (Van Schayck et al. 1991). Increases in airway responsiveness in children may have important implications. For instance, airway hyperresponsiveness is a risk factor for asthma development (Postma and Boezen 2004). Airway hyperresponsiveness in children is also predictive of a reduced rate of growth in lung function and associated with a subsequent decline in the forced expiratory volume in 1 s/forced vital capacity ($FEV_1$/FVC) ratio, a measure of airway obstruction (Xuan et al. 2000).

What is the clinical impact of transient increases in the variable component of airway responsiveness following exposure to $NO_2$ or other pollutants? In healthy adults without asthma or airway hyperresponsiveness, there is likely little or no clinical impact of transient small increases in airway responsiveness following low-level inhalation exposures. Acute inhalation exposures to very high concentrations of respiratory irritants, however, can cause persistent asthma-like airway disease and hyperresponsiveness, a condition known as the reactive airway dysfunction syndrome, or RADS (Bardana Jr. 1999). In asthmatics, transient changes in nonspecific airway responsiveness in response to inhaled pollutants may have clinical consequences. A variety of environmental challenges can transiently increase airway responsiveness and worsen asthma control, such as allergen exposures (Brusasco et al. 1990), viral infections (Cheung et al. 1995; Fraenkel et al. 1995), cigarette smoke (Tashkin et al. 1993), $O_3$ (Kehrl et al. 1999), and other respiratory irritants (Kinsella et al. 1991). An exposure that worsens airway responsiveness to one agent in asthmatic subjects may enhance airway responsiveness to other challenge agents. Transient increases in airway responsiveness following $NO_2$ or other pollutant exposures have the potential to increase symptoms and worsen asthma control, even if the pollutant exposure does not cause acute decrements in lung function.

## 3.1.3.1. Allergen Responsiveness

### Asthmatic Individuals

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

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

The potential for $NO_2$ exposure to enhance responsiveness to allergen challenge in asthmatics deserves special mention. Several recent studies, summarized in Annex Table AX5.3-2, have addressed the question of whether low-level exposures to $NO_2$, both at rest and with exercise, enhance the response to specific allergen challenge in mild asthmatics. These recent studies involving allergen challenge show that $NO_2$ may enhance the sensitivity to allergen-induced decrements in lung function and increase the allergen-induced airway inflammatory response. Figure 3.1-2 categorizes the allergen challenge studies as

"positive," i.e., showing evidence for increased responses to allergen in association with $NO_2$ exposure that reach statistical significance, or "negative" for responses that are null or not statistically significant, with the exposure metric expressed as ppm-min. In comparing Figure 3.1-2 with Figure 3.1-1, the enhancement of allergic responses in asthmatics occurs at exposure levels more than an order of magnitude lower than those associated with airway inflammation in healthy subjects. The dosimetry difference is even greater when considering that the allergen challenge studies generally were performed at rest, while the airway inflammation studies in healthy subjects were performed with intermittent exercise.

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

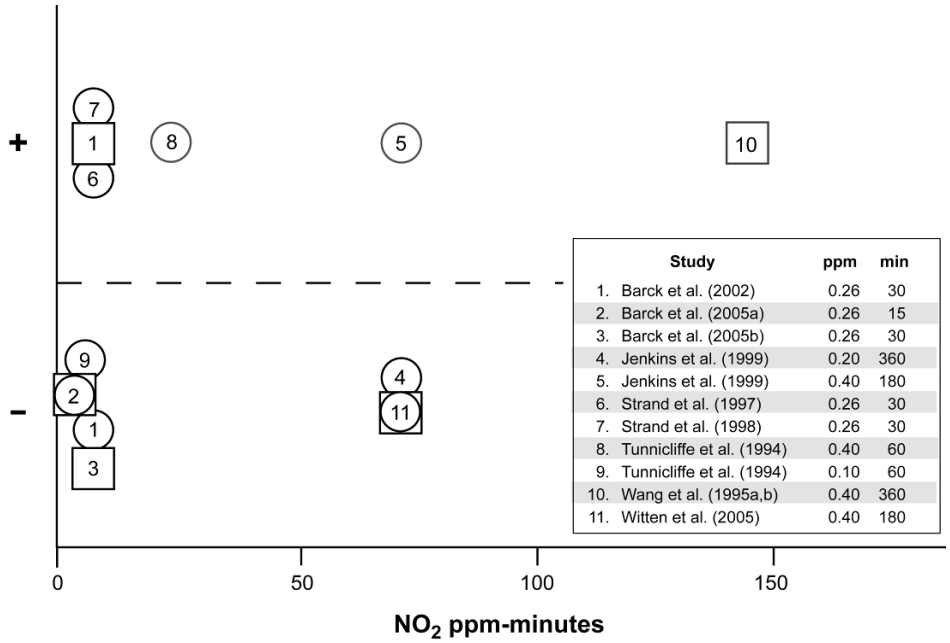



**Figure 3.1-2. Airway responsiveness to allergen challenge in asthmatic subjects following a single exposure to $NO_2$. Responsiveness was assessed using spirometric (circles) and inflammatory (squares) endpoints. On the vertical axis, positive and negative indicate studies finding statistically significant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

A series of studies from the Karolinska Institute in Sweden have explored airway responses to allergen challenge in asthmatics. Strand et al. (1997) demonstrated that single 30-min exposures to 0.26 ppm $NO_2$ increased the late phase response to allergen challenge 4 h after exposure. In a separate study (Strand et al., 1998), four daily repeated exposures to 0.26 ppm $NO_2$ for 30 min increased both the early and late phase responses to allergen. Barck et al. (2002) used the same exposure and challenge protocol as used in the earlier Strand et al. (1997) studies (0.26 ppm for 30 min, with allergen challenge 4-h after exposure) and performed BAL 19-h after the allergen challenge to determine $NO_2$ effects on the

allergen-induced inflammatory response. $NO_2$ followed by allergen caused increases in the BAL recovery of PMN and eosinophil cationic protein (ECP), with reduced volume of BAL fluid and reduced cell viability, compared with air followed by allergen. ECP is released by degranulating eosinophils, is toxic to respiratory epithelial cells, and is thought to play a role in the pathogenesis of airway injury in asthma. These findings indicate that $NO_2$ exposure enhanced the airway inflammatory response to allergen. Subsequently, Barck et al. (2005a) exposed 18 mild asthmatics to air or $NO_2$ for 15 min on day 1, followed by two 15-min exposures separated by 1-h on day 2, with allergen challenge after exposures on both days 1 and 2. Sputum was induced before exposure on day 1 and after exposures (morning of day 3). $NO_2$+allergen, compared to air+allergen, treatment resulted in increased levels of ECP in both sputum and blood and increased myeloperoxidase levels in blood. A separate study examined $NO_2$ effects on nasal responses to nasal allergen challenge (Barck et al., 2005b). Single 30-min exposures to 0.26 ppm $NO_2$ did not enhance nasal allergen responses. All exposures in the Karolinska Institute studies (Barck et al., 2002, 2005a; (Strand et al., 1997; 1998) used subjects at rest. These studies utilized an adequate number of subjects, included air control exposures, randomized exposure order, and separated exposures by at least 2 weeks. Together, they indicate that quite brief exposures to 0.26-ppm $NO_2$ can cause effects in allergen responsiveness in asthmatics.

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

Several studies have been conducted using longer $NO_2$ exposures. Wang et al. (1995a,b, 1999) found that more intense (0.4 ppm) and prolonged (6 h) $NO_2$ exposures enhanced allergen responsiveness in the nasal mucosa in subjects with allergic rhinitis. Jenkins et al. (1999) examined $FEV_1$ decrements and airway responsiveness to allergen in a group of mild, atopic asthmatics. The subjects were exposed for 3 h to 0.4 ppm $NO_2$, 0.2 ppm $O_3$, and 0.4 ppm $NO_2$+0.2 ppm $O_3$. The subjects were also exposed for 6 h to produce exposure concentrations that would provide identical doses to the 3-h protocols (i.e., equivalent in concentration times duration of exposure [C X T]). Significant increases in airway responsiveness to allergen occurred following all the 3-h exposures, but not following the 6-h exposures. However, Witten et al. (2005) did not find enhanced airway inflammation or a reduction in allergen provocative dose that produces a 20% decrease in $FEV_1$ ($PD20\text{-}FEV_1$) with allergen challenge in 15 asthmatic subjects allergic to house dust mite allergen who were exposed to air and 0.4 ppm $NO_2$ for 3-h with intermittent exercise. Allergen challenge was performed immediately after exposure, and sputum induction was performed 6 and 26 h after the allergen challenge. There was no overall effect of $NO_2$ on allergen responsiveness, although 3 subjects required a much smaller concentration of allergen after $NO_2$ than after air exposure and were deemed to be $NO_2$ "responders." $NO_2$ exposure was surprisingly associated with a reduction in sputum eosinophils, with no increase in allergen-induced neutrophilic inflammation.

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

Lastly, one study examined the effects on allergen responsiveness of exposure to traffic exhaust in a tunnel (Svartengren et al., 2000). Twenty mild asthmatics sat in a stationary vehicle within a busy tunnel for 30 min. Allergen challenge was performed 4 h later. The control exposure was in a hotel room in a suburban area with low air pollution levels. Exposures were separated by 4 weeks and the order was randomized. Median $NO_2$ levels in the vehicle were 313 $\mu g/m^3$ (range, 203 to 462), or 0.166 ppm, (range, 0.106 to 0.242). $PM_{10}$ levels were 170 $\mu g/m^3$ (range, 103 to 613), and $PM_{2.5}$ levels were 95 $\mu g/m^3$ (range, 61 to 128). Median $NO_2$ levels outside the hotel were 11 $\mu g/m^3$ or 0.006 ppm. Subjects in the tunnel experienced increased cough, and also reported awareness of noise and odors. More importantly, there was a greater allergen-induced increase in specific airway resistance after the tunnel exposure than after

the control exposure (44% versus 31% respectively). Thoracic gas volume also was increased to a greater degree after the tunnel exposure, demonstrating increased gas trapping within the lung. These findings were most pronounced in the subjects exposed to the highest levels of $NO_2$. This study proposes that exposure to traffic exhaust, and particularly the $NO_2$ component, increases allergen responsiveness in asthmatics, and the results fit well with the findings in studies of clinical exposures of $NO_2$ (Barck et al., 2002, 2005a). However, it was not possible to blind the exposures, and the control exposure (hotel room, presumably quiet and relaxed) was not well matched to the experimental exposure (vehicle, noisy, odorous). It remains possible that factors other than $NO_2$ contributed to, or were responsible for, the observed differences in allergen responsiveness. These recent studies involving allergen challenge show that $NO_2$ may enhance the sensitivity to allergen-induced decrements in lung function and increase the allergen-induced airway inflammatory response. Enhancement of allergic responses in asthmatics occurs at exposure levels of more than an order of magnitude lower than those associated with airway inflammation in healthy subjects. The dosimetry difference is even greater when considering that the allergen challenge studies generally were performed at rest, while the airway inflammation studies in healthy subjects were performed with intermittent exercise. Enhancement of allergen responses has been found at exposures as low as 8 ppm-min, i.e., 0.26 ppm for 30 min. The exposure-response characteristics of $NO_2$ effects on allergen responses, as well as the effects of exercise, relationship to the severity of asthma, the role of asthma medications, and other clinical factors are not fully understood.

### Toxicological Studies

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

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

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

To determine the effect of $NO_2$ on allergenic airway responses in sensitized animals, Hubbard et al. (2002) exposed ovalbumin (OVA)-sensitized mice to $NO_2$ (0.7 or 5 ppm, 2 h/day for 3 days) or air. While the air-exposed mice developed lower airway inflammation (increased total BAL cellularity and increased eosinophil levels), the $NO_2$-exposed mice had significantly lower levels of eosinophils for both $NO_2$ concentrations, with the greatest effect seen at the lower $NO_2$ concentration. These results were confirmed in a subsequent experiment (0.7 ppm $NO_2$ for 3 or 10 days) showing significant reductions in BAL cellularity and eosinophil levels for both time points. In a similar study (Proust et al., 2002), mice were sensitized and challenged with OVA and then exposed to $NO_2$ (5 or 20 ppm, 3 h). The 20 ppm $NO_2$ exposure resulted in a significant increase in bronchopulmonary hyperreactivity 24 h after exposure, as

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

## 3.1.3.2. Nonspecific Responsiveness

### Healthy Individuals

Several observations indicate that $NO_2$ exposures in the range of 1.5 to 2.0 ppm cause small but significant increases in airway responsiveness in healthy subjects. Mohsenin (1988) found that a 1-h exposure to 2 ppm $NO_2$ increased responsiveness to methacholine, as measured by changes in specific airway conductance, without directly affecting lung function. Furthermore, pretreatment with ascorbic acid prevented the $NO_2$-induced increase in airway responsiveness (Mohsenin, 1987a). A mild increase in responsiveness to carbachol was observed following a 3-h exposure to 1.5 ppm $NO_2$, but not to intermittent peaks of 2.0 ppm (Frampton et al., 1991). Thus, the lower threshold concentration of $NO_2$ for causing increases in nonspecific airway responsiveness in healthy subjects appears to be in the 1- to 2-ppm range.

### Asthmatic Individuals

The 1993 $NO_X$ AQCD reported results that showed $NO_2$ might enhance subsequent responsiveness to challenge at relatively low $NO_2$ concentrations within the range of 0.2 to 0.3 ppm. From the studies for which individual data were readily available, the number of subjects whose airway responsiveness increased and whose airway responsiveness decreased is listed in Table 3.1-2. Table 3.1-2 reproduces airway responsiveness data for asthmatics that was previously provided in Table 15-9 of the 1993 $NO_X$ AQCD. In the 19 studies included in this table, asthmatics were exposed to $NO_2$ concentrations ranging from 0.1 to 1.0 ppm. The vast majority (17 of 19) of these studies utilized nonspecific challenge agents. Tabulation of data from this table provides information regarding the direction of the change (i.e., increase or decrease) in airway responsiveness following $NO_2$ exposure. Some of the disparate findings of these studies are discussed below.

**Table 3.1-2. Changes in airway responsiveness associated with $NO_2$ exposure.**

| STUDY | N | $NO_2$ (ppm) | EXP (min) | CHAL-LENGE TYPE | END POINT | TIME POST EXP (min) | EXER | CHANGE IN AHR | | AVERAGE PD ± SD | | NOTES |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | INC | DEC | AIR | $NO_2$ | |
| Ahmed et al. (1983b) | 20 | 0.1 | 60 | CARB | sGAW | — | N | 13 | 7 | 6.0 | 2.7 | |
| Ahmed et al. (1983a) | 19 | 0.1 | 60 | RAG | sGAW | — | N | 10 | 8 | 9.0 ± 25 | 3.4 ± 4.6 | |
| Hazucha et al. (1983) | 15 | 0.1 | 60 | METH | sRaw | 20 | N | 6 | 7 | 1.9 ± 0.4 | 2.0 ± 1.0 | |
| Orehek et al. (1976) | 20 | 0.1 | 60 | CARB | sRaw | 0 | N | 14 | 3 | 0.6 | 0.4 | |
| Rasmussen et al. (1990) | 20 | 0.1 | 120 | METH | $FEV_1$ | 0 | Y | — | — | ($AIR-NO_2$=0.00) | | |
| Orehek et al. (1981) | 7 | 0.11 | 60 | GRASS | sRaw | 0 | N | — | — | 1.2 ± 0.3 | 1.3 ± 0.3 | 4 allergic 3 asth-matic |
| Bylin et al. (1988) | 20 | 0.14 | 30 | HIST | sRaw | 25 | N | 14 | 6 | — | — | |
| Roger et al. (1990) | 19 | 0.15 | 80 | METH | sRaw | 60 | Y | 10 | 7 | 3.3 ± 0.7 | 3.1 ± 0.7 | |
| Kleinman et al. (1983) | 31 | 0.20 | 120 | METH | $FEV_1$ | 0 | Y | 20 | 7 | 8.6 ± 16 | 3.0 ± 6.2 | |
| Rasmussen et al. (1990) | 20 | 0.20 | 120 | METH | $FEV_1$ | 0 | Y | — | — | ($AIR-NO_2$=0.02) | | |
| Jörres and Magnussen (1990) | 14 | 0.25 | 30 | $SO_2$ | sRaw | 27 | N | 11 | 2 | 47 ± 5.1 | 37.7 ± 3.5 | |
| Jörres and Magnussen (1991) | 11 | 0.25 | 30 | METH | sRaw | 60 | Y | 7 | 4 | 0.4 ± 1.6 | 0.4 ± 1.6 | |
| Bylin et al. (1988) | 20 | 0.27 | 30 | HIST | sRaw | 25 | N | 14 | 6 | — | — | |
| Avol et al. (1988) | 37 | 0.30 | 120 | COLD | $FEV_1$ | 60 | Y | 11 | 16 | -8.4 ± 11 | -10.7 ± 12 | Delta $FEV_1$ |
| Avol et al. (1989) | 34 | 0.30 | 30 | COLD | $FEV_1$ | 60 | Y | 12 | 21 | -5.3 ± 12 | -4.7 ± 13 | Delta $FEV_1$ |
| Bauer et al. (1986a) | 12 | 0.30 | 30 | COLD | $FEV_1$ | 60 | Y | 9 | 3 | 0.8 ± 0.4 | 0.5 ± 0.3 | PD10RHE |
| Linn et al. (1986) | 21 | 0.30 | 120 | COLD | $FEV_1$ | 0 | Y | | | -11.4 | -12.1 | Delta $FEV_1$ |
| Morrow and Utell (1989) | 20 | 0.30 | 225 | CARB | sGaw | — | Y | — | — | — | — | |
| Roger et al. (1990) | 19 | 0.30 | 80 | METH | sRaw | 60 | Y | 8 | 9 | 3.3 ± 0.7 | 3.3 ± 0.8 | |
| Rubinstein et al. (1990) | 9 | 0.30 | 30 | $SO_2$ | sRaw | 60 | Y | 4 | 5 | 1.3 ± 0.7 | 1.3 ± 0.8 | |
| Bylin et al. (1985) | 8 | 0.48 | 20 | HIST | sRaw | 20 | N | 5 | — | — | — | |
| Mohsenin (1987b) | 10 | 0.50 | 60 | METH | sGaw | 0 | N | 7 | 2 | 9.2 ± 1.5 | 4.6 ± 8.0 | |
| Bylin et al. (1988) | 20 | 0.53 | 30 | HIST | sRaw | 25 | N | 12 | 7 | — | — | |
| Avol et al. (1988) | 37 | 0.60 | 120 | COLD | $FEV_1$ | 60 | Y | 13 | 16 | -8.4 ± 11 | -10.4 ± 14 | Delta $FEV_1$ |
| Roger et al. (1990) | 19 | 0.60 | 80 | METH | sRaw | 60 | Y | 11 | 8 | 3.3 ± 0.7 | 3.7 ± 1.1 | |
| Rasmussen et al. (1990) | 20 | 0.80 | 120 | METH | $FEV_1$ | 0 | Y | — | — | ($AIR-NO_2$=-0.06) | | |
| Linn et al. (1986) | 21 | 1.00 | 120 | COLD | $FEV_1$ | 0 | Y | — | — | -11.4 | -11.2 | Delta $FEV_1$ |

AHR: Airway Hyperresponsiveness
CARB: Carbachol
COLD: Cold-dry air
GRASS: Grass pollen
HIST: Histamine
METH: Methacholine
RAG: Ragweed
PD: Provocative dose
PD10RHE=Respiratory heat exchange (loss) for 10% drop in $FEV_1$

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

The effects of $NO_2$ exposure on $SO_2$-induced bronchoconstriction also have been examined, but with inconsistent results. Jörres and Magnussen (1990) found an increase in airway responsiveness to $SO_2$ in asthmatic subjects following exposure to 0.25-ppm $NO_2$ for 30 min at rest; yet Rubenstein et al. (1990) found no change in responsiveness to $SO_2$ inhalation following exposure of asthmatics to 0.30-ppm $NO_2$ for 30 min with 20 min of exercise.

The varied results of these studies have not been satisfactorily explained. It is evident that a wide range of responses occurs among asthmatics exposed to $NO_2$. This variation may in part reflect differences in individual subjects and exposure protocols: mouthpiece versus chamber, obstructed versus non-obstructed asthmatics, rest versus exercise, and varying use of medication(s) among subjects. Indeed, via meta-analysis, Folinsbee (1992) found that airway responsiveness was greater in asthmatics exposed to $NO_2$ at rest than during exercise. Following $NO_2$ exposures between 0.2 and 0.3 ppm $NO_2$, only 52% of subjects exposed with exercise had increased responsiveness, whereas 76% of subjects had increased responsiveness in protocols using resting exposures. The factors that predispose some asthmatics to $NO_2$ responsiveness is still not understood. Studies have typically involved volunteers with mild asthma; data are lacking from more severely affected asthmatics, who may be more susceptible.

Table 3.1-3 provides a meta-analysis of the non-specific airway responsiveness data in Table 3.1-2. In terms of the fraction of asthmatics affected and statistical significance for the indicated exposure concentration ranges, the data in Table 3.1-3 are similar to those provided in Table 15-10 of the 1993 $NO_X$ AQCD and by Folinsbee (1992). Table 3.1-3 differs from the prior analysis in that a study using specific responses to ragweed was excluded (Ahmed et al., 1983a), a recent study using nonspecific responses to histamine was included (Strand et al., 1996), and an additional concentration range of 0.1 ppm was considered. Overall, analysis of these data for 355 asthmatics indicates that short-term exposures to $NO_2$ at outdoor ambient concentrations (<0.3 ppm) are linked to nonspecific airway hyperresponsiveness in people with mild asthma.

**Table 3.1-3. Fraction of $NO_2$-exposed asthmatics with increased non-specific airway hyperresponsiveness.**

| $NO_2$ ppm | ALL EXPOSURES | EXPOSURE WITH EXERCISE | EXPOSURE AT REST |
|---|---|---|---|
| 0.1 | 0.66 (50)[B] | — | 0.66 (50)[B] |
| 0.1 - 0.15 | 0.66 (87)[C] | 0.59 (17) | 0.67 (70)[C] |
| 0.2 - 0.3 | 0.58 (187)[B] | 0.52 (136) | 0.75 (51)[C] |
| >0.3 | 0.59 (81) | 0.49 (48) | 0.73 (33)[B] |
| 0.1 - 0.6 | 0.60 (355)[C] | 0.52 (201) | 0.71 (154)[C] |

Note: Values represent the fraction of asthmatics (out of the total number of individuals in parentheses) having an increase in airway responsiveness following $NO_2$ exposure versus air. Analysis is for 355 asthmatics in Table 3.1-2 with the exclusion of the Ahmed et al. (1983a) data for the specific airway responsiveness of 18 asthmatics to ragweed and the addition of responses of 18 asthmatics (13 with increased responsiveness to histamine) 30 minutes after exposure to 0.26 ppm $NO_2$ for 30 minutes during rest from Strand et al. (1996). [B] $p \leq 0.05$ two-tailed sign test. [C] $p \leq 0.01$ two-tailed sign test.

### Toxicological Studies

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

Kobayashi and Miura (1995) studied the concentration- and time-dependency of airway hyperresponsiveness to inhaled histamine aerosol in guinea pigs exposed subchronically to $NO_2$. In one experiment, guinea pigs were exposed by inhalation to 0, 0.06, 0.5, or 4.0 ppm $NO_2$, 24 h/day for 6 or 12 weeks. Immediately following the last exposure, airway responsiveness was assessed by measurement of specific airway resistance as a function of increasing concentrations of histamine aerosol. Animals exposed to 4 ppm $NO_2$ for 6 weeks exhibited increased airway response to inhaled histamine aerosol; airway response at 12 weeks was not determined. No effects were observed at the lower exposure levels. In another experiment conducted in this study (Kobayashi and Miura, 1995), guinea pigs were exposed by inhalation to 0, 1.0, 2.0, or 4.0 ppm $NO_2$, 24 h/day for 6 or 12 weeks, and the airway hyperresponsiveness was determined. Increased hyperresponsiveness to inhaled histamine was observed in animals exposed to 4 ppm for 6 weeks, 2 ppm for 6 and 12 weeks, and 1 ppm for 12 weeks only. The results also showed that at 1 or 2 ppm $NO_2$, airway hyperresponsiveness developed to a higher degree with the passage of time. Higher concentrations of $NO_2$ were found to induce airway hyperresponsiveness faster compared to lower concentrations. When the specific airway resistance was compared to values determined 1 week prior to initiation of the $NO_2$ exposure, values were increased in the 2.0 and 4.0 ppm animals at 12 weeks only. Specific airway resistance was also increased to a higher degree with the passage of time.

## 3.1.3.3. Summary of Short-Term Exposure on Airway Responsiveness

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

Exposure to $NO_2$ also has been found to enhance the inherent responsiveness of airway to subsequent nonspecific challenges in human clinical studies. In general, small but significant increases in nonspecific airway responsiveness were observed in the range of 1.5 to 2.0 ppm for 3 h in healthy adults and between 0.2 and 0.3 ppm $NO_2$ for 30 min for asthmatics, but a wide range of responses were observed, particularly among asthmatics. Subchronic $NO_2$ exposure (6 to 12 weeks) of animals also increases responsiveness to nonspecific challenges at 1 to 4 ppm $NO_2$.

Results from human studies were inconsistent; some, reported increased responsiveness following $NO_2$ exposure. A variety of factors could contribute to this apparent inconsistency. For instance, responsiveness has been observed to be greater following resting than exercising exposures to $NO_2$, despite the greater $NO_2$ exposure to the respiratory tract during exercise. In addition, the methods for administering the bronchoconstricting challenge agents and degree of sensitization to specific allergen also are recognized to affect responsiveness (Cockcroft et al., 2005; Cockcroft and Davis, 2006).

## 3.1.4. Effects of Short-Term Exposure on Respiratory Symptoms

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

### 3.1.4.1. Indoor and Personal Exposure and Respiratory Outcomes

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

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

One intervention study provided strong evidence of a detrimental effect of exposure to indoor levels of $NO_2$. Pilotto et al. (2004) conducted a randomized intervention study of respiratory symptoms of asthmatic children in Australia before and after selective replacement of unflued gas heaters in schools. In the study, 18 schools using unflued gas heaters were randomly allocated to have an electric heater (n=4) or a flued gas heater (n=4) installed or to retain their original heaters (n=10). Changes to the heating systems were disguised as routine maintenance to prevent bias in reporting of symptoms. Children were eligible for the study if they had physician-diagnosed asthma and no unflued heater in their home. For the 114 children enrolled, symptoms were recorded daily and reported in biweekly telephone interviews during 12 weeks in the winter. Passive diffusion badges were used to measure $NO_2$ exposure in classrooms (6 h/day) and in the children's homes. Schools in the intervention group (with new heaters) averaged overall means (standard devision [SD]) of 15.5 (6.6) ppb $NO_2$, while control schools (with unflued heaters) averaged 47.0 (26.8) ppb. Exposure to $NO_2$ in the children's homes was quite variable but with similar mean levels. Indoor levels at homes for the intervention group were 13.7 (19.3) ppb and 14.6 (21.5) ppb for the control group. Children attending intervention schools had significant reductions in several symptoms (see Table 3.1-4): difficulty breathing during the day (RR=0.41 [95% CI: 0.07, 0.98]) and at night (RR=0.32 [95% CI: 0.14, 0.69]); chest tightness during the day (RR=0.45 [95% CI: 0.25, 0.81]) and at night (RR=0.59 [95% CI: 0.28, 1.29]); and asthma attacks during the day (RR=0.39 [95% CI: 0.17, 0.93]).

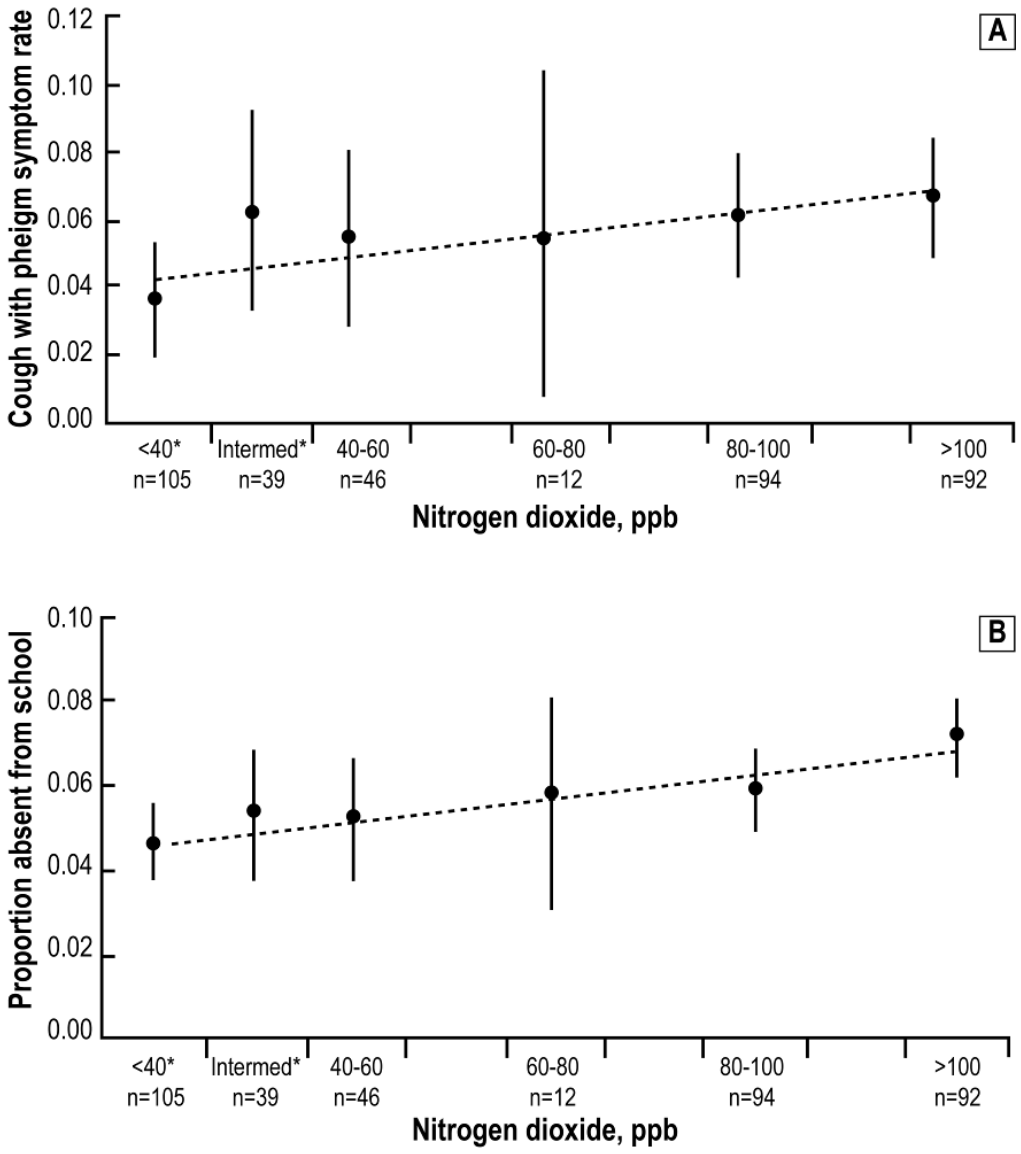
Samet and Bell (2004) stated that Pilotto et al. (2004) provided persuasive evidence of an association between exposure to $NO_2$ from classroom heaters and the respiratory health of children with asthma; further, the intervention study design alleviated some potential limitations of observational studies.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

**Table 3.1-4. Mean rates (SD) per 100 days at risk and unadjusted rate ratio (RR) for symptoms/activities over 12 weeks during the winter heating period.**

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

Note: Following adjustment for hay fever and parental education at baseline, results remained substantially unchanged except that difficulty breathing during the day assumed borderline significance (RR=0.46: 95% CI: 0.19, 1.08), while the reduction in asthma attacks during the night reached statistical significance (RR=0.33; 95% CI: 0.13, 0.84).
Source: Adapted from Pilotto et al. (2004).

In an earlier study of the health effects of unflued gas heaters on wintertime respiratory symptoms of 388 Australian schoolchildren, Pilotto et al. (1997a) measured $NO_2$ in 41 classrooms in 8 schools. Half used unflued gas heaters; half used electric heat. Although similar methods were used to measure $NO_2$ levels (passive diffusion badge monitors exposed for 6 h at a time), there were three major differences between this study and the Pilotto et al. (2004) study: (1) the 1997 study was not a randomized trial, (2) enrollment in the 1997 study was not restricted to asthmatic children, and (3) enrollment in the 1997 study was not restricted to children from homes without unflued gas heaters. In Pilotto et al. (1997a), only children from nonsmoking homes were enrolled, and a subset of children (n=121) living in homes with unflued gas heaters were given badges to be used at home. Parents recorded symptoms daily. Children were classified into low- and high-exposure groups based on measured exposure at school, measured exposure at home (if their homes had unflued gas heaters), or their reported use of electric heat. Maximum hourly concentrations in these classrooms recorded during 2 weeks were highly correlated with their corresponding 6 h concentrations (r=0.85). Hourly peaks of $NO_2$ on the order of $\geq$ 80 ppb were associated with 6 h average levels of approximately $\geq$ 40 ppb. The authors inferred that children in classrooms with unflued gas heaters that had 6-h average levels of $\geq$ 40 ppb were experiencing approximately 4 fold or higher 1-h peaks of exposure than the $NO_2$ levels experienced by children who had no gas exposure (6-h average levels of 20 ppb). The importance of this study was that it examined the effect of repeated peaks over time as have been used in the toxicological infectivity studies (e.g., Miller et al., 1987) that were noted earlier in Section 3.1.1.




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

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

Pilotto et al. (1997a) reported that during the winter heating season, children in the high-exposure category ($NO_2$>40 ppb) had higher rates of sore throat, colds, and absenteeism than all other children. In models adjusted for personal risk factors including asthma, allergies, and geographic area, classroom $NO_2$ level and school absence were significantly associated (odds ratio [OR]=1.92 [95% CI: 1.13, 3.25]). Increased likelihood of individual respiratory symptoms was not significantly associated with classroom $NO_2$ level (e.g., cough with phlegm adjusted OR=1.28 [95% CI: 0.76, 2.15]). Exposure-response relation-

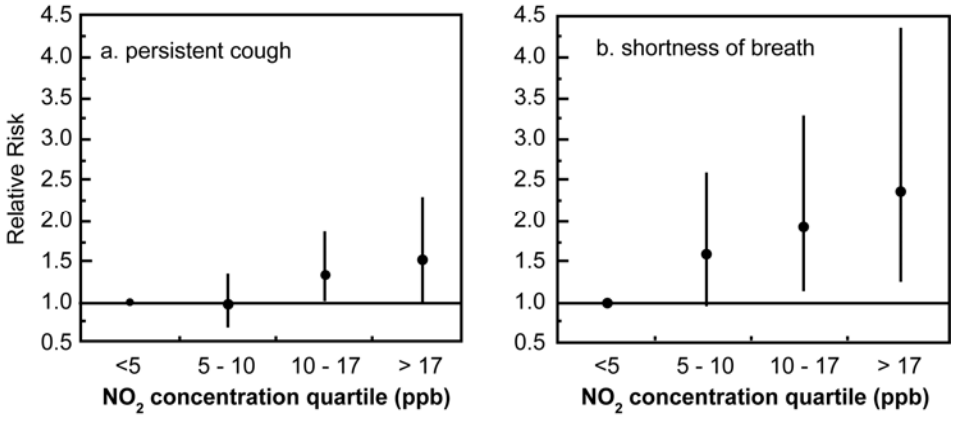
ships are illustrated in Figure 3.1-3 for symptom rates for cough with phlegm and proportion of children absent from school. Statistically significant positive exposure-response trends were found for mean rates for cough with phlegm ($p=0.04$, adjusted for confounders) and proportion of children absent from school ($p=0.002$) using mixed models allowing for correlation between children within classrooms. Pilotto et al. (1997b) noted that this study "provides evidence that short-term exposure to the peak levels of $NO_2$ produced by unflued gas appliances affects respiratory health and that the significant dose-response relationship seen with increasing $NO_2$ exposure strengthens the evidence for a cause-effect relationship."

In a cross-sectional survey of 344 children in Australia, Ponsonby et al. (1997b) used passive gas samplers to measure personal exposure to $NO_2$. Personal badges were pinned to a child's clothing at the end of each school day and removed when the child arrived at school the next day. School exposures were measured with passive samplers placed in each child's classroom. Sampling took place over two consecutive days. Mean (SD) personal exposure was 10.4 (11.1) ppb and mean total $NO_2$ exposure (personal plus schoolroom) was 10.1 (8.6) ppb. Of the health outcomes measured (recent wheeze, asthma ever, lung function measured when $NO_2$ sampling stopped), only the $FEV_1$/FVC ratio following cold air challenge was significantly associated with $NO_2$ levels measured with the personal badges (-0.12 [95% CI: -0.23, -0.01]) per 1 ppb increase in personal exposure). In Finland, Mukala et al. (1999; 2000) studied 162 preschool-age children. Mukala et al. (2000) used passive monitors exposed for 1-week periods over the course of 13 weeks both indoors and outdoors and on the clothing of preschool children attending eight day care centers in Helsinki. The only significant association between personal $NO_2$ measurements and symptoms was for cough during the winter (RR=1.86 [95% CI: 1.15, 3.02] for $NO_2$ at level above 27.5 $\mu g/m^3$ [14.5 ppb]). Similar results were obtained when data were analyzed unstratified by season, but including a factor for season (RR=1.52 [95% CI: 1.00, 2.31] for $NO_2$ at levels above 27.5 $\mu g/m^3$ [14.5 ppb], Mukala et al., 1999).

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

Results from a recent analysis of a subset of 469 asthmatic children enrolled in the National Cooperative Inner City Asthma Study (NCICAS) (Kattan et al., 2007) where household measurements of $NO_2$ levels were also available, are consistent with those described above for Belanger et al. (2006). The median level of indoor $NO_2$, measured with Palmes tubes left for 7 days, was 29.8 ppb, with median level in homes with gas stoves (31.4 ppb) significantly higher than levels in homes with electric stoves (15.9 ppb). Associations between exposure to high levels of $NO_2$ and symptoms in the previous 2 weeks or peak flow of <80% predicted were examined with models that adjusted for study site, gender, medication use, household smoking, and socioeconomic status (SES) variables and were stratified by season or by atopic status. Among the subset of 76 children without positive skin tests, the adjusted risk ratio (95% CI) for asthma symptoms was 1.75 (95% CI: 1.10, 2.78) for those with higher $NO_2$ exposure. Among the

317 children with $NO_2$ measured in the cold season, the risk ratio for a peak flow measurement of <80% predicted was 1.46 (95% CI: 1.07, 1.97). One limitation of the study is that the "high" $NO_2$ level was defined vaguely as approaching the NAAQS level of 0.052 ppm (annual average) (52 ppb).




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

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

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

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

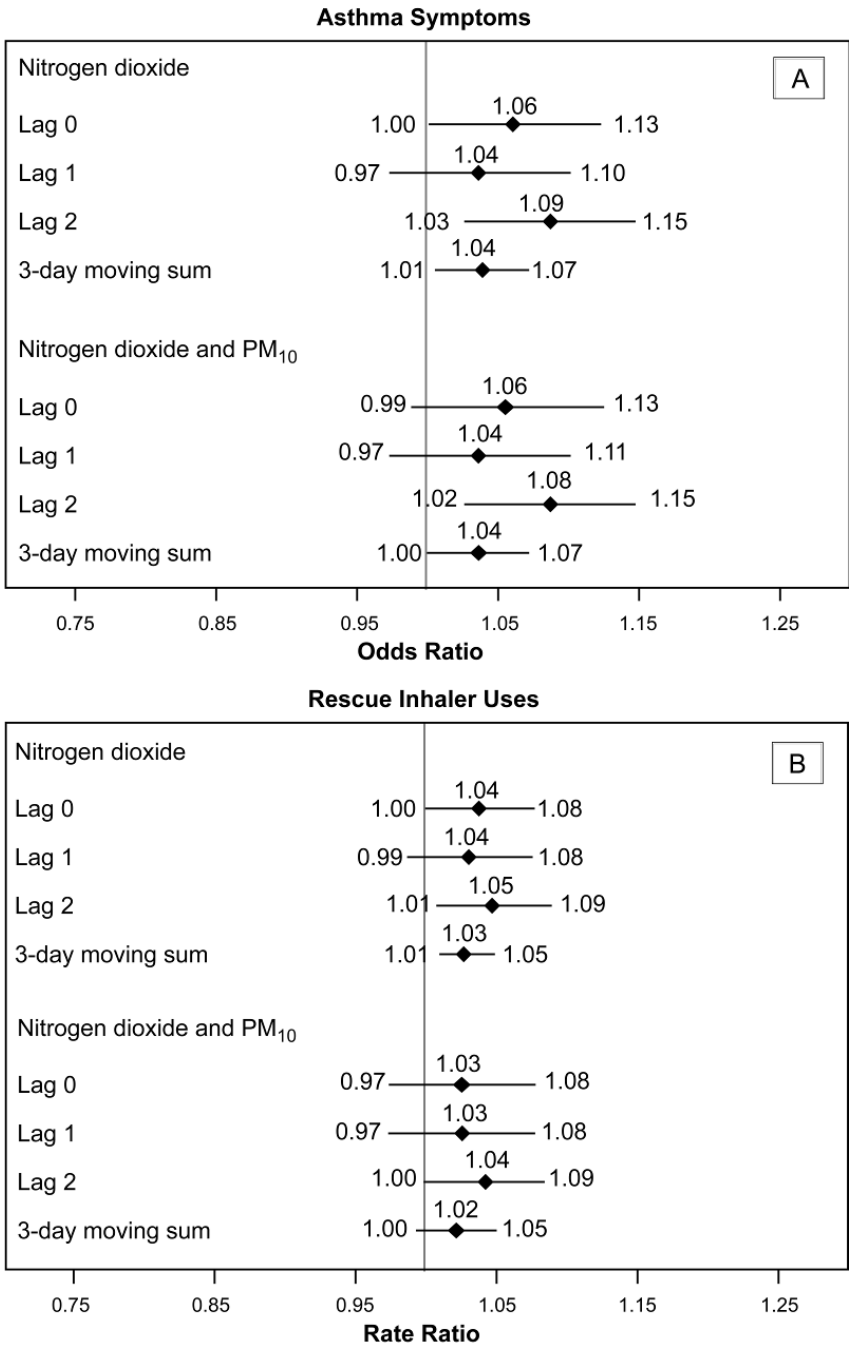
### 3.1.4.2. Ambient $NO_2$ Exposure and Respiratory Symptoms

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

The report from the Six Cities study includes 1,844 schoolchildren, followed for 1 year (Schwartz et al., 1994). Symptoms (in 13 categories, analyzed as cough, lower or upper respiratory symptoms), were recorded daily. Cities included Watertown, MA, Baltimore, MD, Kingston-Harriman, TN, Steubenville, OH, Topeka, KS, and Portage, WI. In Mortimer et al. (2002), 864 asthmatic children from the eight NCICAS cities (New York City, NY [two sites: Bronx and East Harlem], Baltimore, MD, Washington, DC, Cleveland, OH, Detroit, MI, St Louis, MO, and Chicago, IL) were followed daily for four 2-week periods over the course of 9 months. Morning and evening asthma symptoms (analyzed as none versus any) and peak flow were recorded. Schildcrout et al. (2006) reported on 990 asthmatic children living within 50 miles of one of 31 $NO_2$ monitors located in eight North American cities, seven of which included data for $NO_2$ (Boston, MA, Baltimore, MD, Toronto, ON, St. Louis, MO, Denver, CO, Albuquerque, NM, and San Diego, CA). Symptoms (analyzed as none versus any per day) and rescue medication use (analyzed as number of uses per day) were recorded daily such that each subject had an approximate average of 2 months of data. All three studies found significant associations between ambient $NO_2$ concentrations and risk of respiratory symptoms in children (Schwartz et al., 1994), and in particular, asthmatic children (Mortimer et al., 2002; Schildcrout et al., 2006).

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

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




Source: Schildcrout et al. (2006).

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

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

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

Another Australian study includes a large number of children (n=263) at risk for developing allergy who were followed for 5 years (Rodriguez et al., 2007). Daily air pollutant concentrations, including those for $NO_2$, were averaged over 10 monitoring sites in the Perth metropolitan region. Mean level of 24-h $NO_2$ for the 8-year study period was 7 ppb (range 0-24 ppb). Significant associations were found between same-day level of $NO_2$ (both 1- and 24-h avg) and cough (OR 1.0005 [95% CI: 1.0000, 1.0011]) per 20-ppb increase in 24-h avg $NO_2$). No multipollutant models were presented. Boezen et al. (1999) reported associations between ambient $NO_2$ exposure and lower respiratory symptoms among children (n=121) with bronchial hyperreactivity and elevated total IgE in urban and rural areas of the Netherlands. These effects were seen for all lags examined (lag 0-, 1-, 2-, and 5-day mean), with the strongest association for the 5-day mean (OR=1.75 [95% CI: 1.37, 2.22]) for each 20 ppb increase). Significant associations between lower respiratory symptoms and ambient exposures were seen in single-pollutant models with $PM_{10}$, black smoke, and $SO_2$. No multipollutant models were reported.

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

Among the studies discussed above, odds ratios and 95% CI for associations with asthma symptoms in children are presented in Figure 3.1-6. The figure shows the several lag periods presented in each study. In the figure, the area of the square denoting the odds ratio represents the relative weight of that estimate based on the width of the 95% CI. When combined in a random effect meta-analysis[1], the

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

combined OR for asthma symptoms was 1.14 (95% CI: 1.05, 1.24) and the test for heterogeneity had a p value of 0.055. The results of multipollutant analyses for the three U.S. multicity studies are presented in Figure 3.1-7. Associations with $NO_2$ were generally robust to adjustment for copollutants, as stated previously. Odds ratios were often unchanged with the addition of copollutants, though reductions in magnitude are apparent in certain models, such as with adjustment for $SO_2$ in the Six Cities study results (Schwartz et al., 1994).

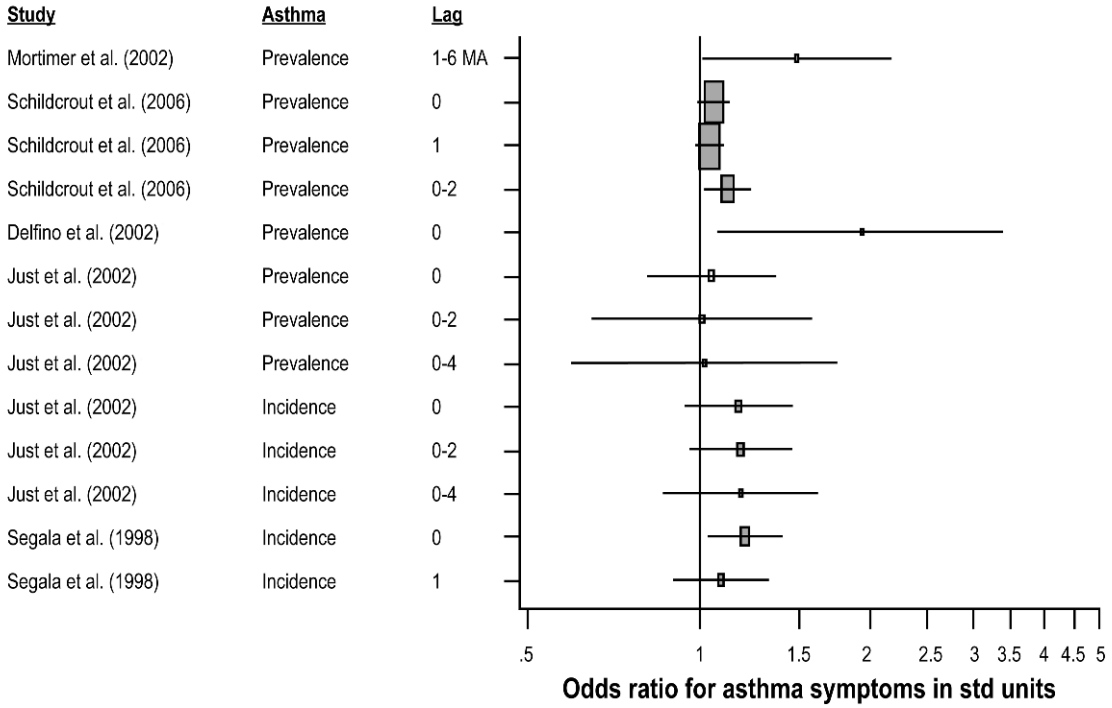



**Figure 3.1-6. Odds ratios (95% CI) for associations between asthma symptoms in children and 24-h average $NO_2$ concentrations (per 20 ppb). The size of the box of the central estimate represents the relative weight of that estimate based on the width of the 95% CI.**

## 3.1.4.3. Summary of Short-Term Exposure on Respiratory Symptoms

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

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

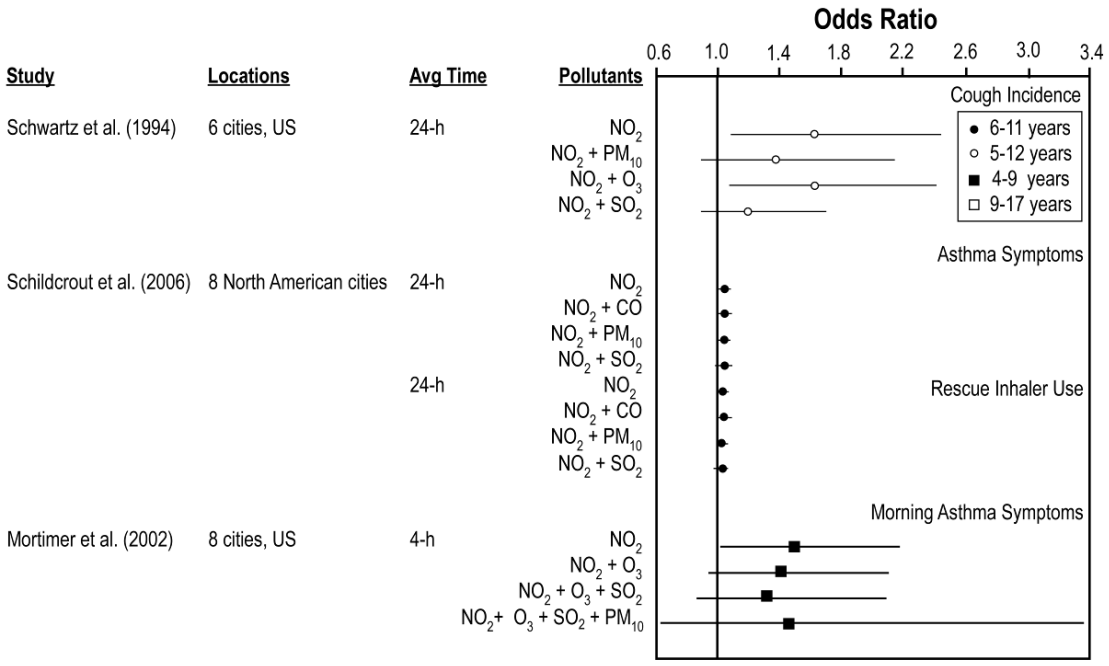



**Figure 3.1-7. Odds ratios and 95% CI for associations between asthma symptoms and 24-h average $NO_2$ concentrations (per 20 ppb) from multipollutant models.**

# 3.1.5. Effects of Short-Term Exposure on Lung Function

## 3.1.5.1. Epidemiologic Studies of Lung Function

### Spirometry in Children

Reliable measurement of lung function in children presents special challenges. The method that produces the most accurate results is spirometry, which requires special equipment and trained examiners. Of the short-term exposure studies reviewed here that did use spirometry (Hoek and Brunekreef, 1994; Linn et al., 1996; Timonen et al., 2002; Moshammer et al., 2006), all conducted repeated lung function measurements in schoolchildren. All found significant associations between small decrements in lung function and increases in ambient $NO_2$ levels. Hoek and Brunekreef (1994) enrolled 1,079 children in the Netherlands to examine the effects of low-level winter air pollution on FVC, $FEV_1$, maximal midexpiratory flow (MMEF), and PEF. A significant effect was found only for the PEF measure: the mean (over all subjects) slope (SE) was a reduction of 52 mL/s (95% CI: 21, 83) for a 20-ppb increase in the previous day's $NO_2$. The authors do not present mean values for lung function measurements, so it is not possible to calculate what percentage of PEF this decrement represents. Linn et al. (1996) examined 269 Los Angeles-area schoolchildren and short-term air pollution exposures. The authors found statistically significant associations between previous-day 24-h avg $NO_2$ concentrations and FVC the next morning (mean decline of 8 mL [95% CI: 2, 14] per 20-ppb increase in $NO_2$) and current-day 24-h avg $NO_2$ concentrations and morning to evening changes in $FEV_1$ (mean decline of 8 mL [95% CI: 2, 14] per 20-ppb increase in $NO_2$). Timonen et al. (2002) enrolled 33 Finnish children with chronic respiratory

symptoms to study the effects of exercise-induced lung function changes and ambient air pollution. No significant effects were observed for lung function changes due to exercise, but significant associations were observed for level of $NO_2$ lagged by 2 days and baseline FVC (mean decline of 21 mL [95% CI: -29, -12] for 20 ppb $NO_2$) and $FEV_1$ (mean decline of 20 mL [95% CI: -26, -13] for 20 ppb $NO_2$). An Austrian study enrolled 163 healthy children for repeated lung function testing (11 to 12 tests during the school year) (Moshammer et al., 2006). A central site monitor adjacent to the school was used to calculate 8-h avg (midnight. to 8 a.m.) PM and $NO_2$ concentrations. The median 8-h avg $NO_2$ concentration was 17.5 $\mu g/m^3$ (9.2 ppb). In both single pollutant and multipollutant models including $PM_{2.5}$, the authors found each 20-ppb increase in $NO_2$ level produced reductions in lung function of around 4% for $FEV_1$, FVC, forced expiratory volume in 0.5 s ($FEV_{0.5}$), maximal expiratory flow at 50% ($MEF_{50}$), and maximal expiratory flow at 25% ($MEF_{25}$). $PM_{2.5}$ was not significantly associated with lung function decrements in the multipollutant model.

### Peak Flow Meter Measurements in Children

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

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

### Lung Function in Adults

Spirometry was used in a large cross-sectional study in Switzerland (Schindler et al., 2001). A subset of 3,912 lifetime nonsmoking adults participated in the spirometric lung function measurements in the SAPALDIA study (Study of Air Pollution and Lung Diseases in Adults). Significant inverse relationships were found between increases in $NO_2$ and decreases in FVC (by 2.74% [95% CI: 0.83, 4.62]) and $FEV_1$ (by 2.52% [95% CI: 0.49, 4.55]) for a 20-ppb increase in $NO_2$ on the same day as the examination. Forced expiratory flow at 25 to 75% of FVC ($FEF_{25-75}$) was found to decrease by 6.73% (95% CI: 0.038, 13.31) for each 20-ppb increase in average $NO_2$ concentration over the previous 4 days. One study (Lagorio et al., 2006) of COPD patients found significant inverse relationships for $FEV_1$ in both COPD and asthmatic patients. Another study of COPD subjects (Silkoff et al., 2005) observed no adverse effects of ambient air pollution on lung function for the first winter; however, in the second

winter, a significant decrease in morning PEF associated with same day and previous day $NO_2$ level was seen (quantitative results not provided). In a study of 60 asthmatic adults in London, decreases in two lung function measures, $FEV_1$ and $FEF_{25-75}$, and increased FeNO were reported with increased $NO_2$ exposure while walking along a roadway with heavy traffic; associations were also reported with $PM_{2.5}$, UFP, and EC (McCreanor et al., 2007).

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

## 3.1.5.2. Clinical Studies of Lung Function

### Healthy Adults

Studies examining responses of healthy volunteers to acute exposure to $NO_2$ have generally failed to show alterations in lung mechanics such as airway resistance (Hackney et al., 1978); Kerr et al., 1979; Linn et al., 1985a; Mohsenin, 1987a, 1988; Frampton et al., 1991; Kim et al., 1991; (Morrow et al., 1992) Rasmussen et al., 1992; Vagaggini et al., 1996; (Azadniv et al., 1998; Devlin et al., 1999). Exposures ranging from 75 min to 5 h at concentrations of up to 4.0 ppm $NO_2$ did not alter pulmonary function. Bylin et al. (1985) found increased airway resistance after a 20-min exposure to 0.25 ppm $NO_2$ and decreased airway resistance after a 20-min exposure to 0.5 ppm $NO_2$, but no change in airway responsiveness to aerosolized histamine challenge in the same subjects. These effects have not been confirmed in other laboratories.

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

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

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

### Patients with COPD

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

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

As noted in the previous section, Gong et al. (2005) exposed 6 elderly healthy adults and 18 COPD patients to four separate atmospheres: (a) air, (b) 0.4 ppm $NO_2$, (c) ~200 $\mu g/m^3$ CAPs, or (d) CAPs+$NO_2$. Nitrogen dioxide can become absorbed to particles (Kalberer et al., 1999). This could act as a mechanism to increase $NO_X$ delivery to the peripheral lung. However, $NO_2$+CAPs did not produce greater respiratory effects than for CAPs alone in either healthy or the COPD patients. As noted above, there were also no significant effects of $NO_2$ alone in group of subjects.

### Patients with Asthma

Kleinman et al. (1983) evaluated the response of lightly exercising asthmatic subjects to inhalation of 0.2 ppm $NO_2$ for 2 h, during which resting minute ventilation doubled. Forced expiratory flows and airway resistance were not altered by the $NO_2$ exposure. Bauer et al. (1986) studied the effects of mouthpiece exposure to 0.3 ppm $NO_2$ for 30 min (20 min at rest followed by 10 min of exercise at ~40 L/min) in 15 asthmatics. At this level, $NO_2$ inhalation produced significant decrements in forced expiratory flow rates after exercise, but not at rest. Jörres and Magnussen (1991) found no effects on lung function in 11 patients with mild asthma exposed to 0.25 ppm $NO_2$ for 30 min, including 10 min of exercise. However, small reductions in $FEV_1$ were observed following 1 ppm $NO_2$ exposure for 3 h with intermittent exercise in 12 mild asthmatics. Koenig et al. (1994) found no pulmonary function effects of exposure to 0.3 ppm $NO_2$ in combination with 0.12-ppm $O_3$, with or without sulfuric acid ($H_2SO_4$) (70 $\mu g/m^3$) or $HNO_3$ (0.05 ppm), in 22 adolescents with mild asthma. However, 6 additional subjects dropped out of the study citing uncomfortable respiratory symptoms.

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

## 3.1.5.3. Summary of Short-Term Exposure on Lung Function

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

Clinical studies have not provided compelling evidence of $NO_2$ effects on pulmonary function. Acute exposures of young, healthy volunteers to $NO_2$ at levels of as high as 4.0 ppm did not alter lung function as measured by spirometry or airway resistance. The small number of studies of COPD patients prevented any conclusions about effects on pulmonary function. The Morrow et al. (1992) study, performed in Rochester, NY, indicated restrictive type effects of 0.3 ppm $NO_2$ exposure for 4 h. However, three other studies, performed in southern California at similar exposure concentrations, found no effects. The contrasting findings in these studies may, in part, reflect the difference in duration of exposure or the differing levels of background ambient air pollution to which the subjects were exposed chronically; as there were much lower background levels in Rochester, NY than in southern California. For asthmatics, the effects of $NO_2$ on pulmonary function have also been inconsistent at exposure concentrations of less than 1 ppm $NO_2$. Overall, clinical studies have failed to show effects of $NO_2$ on pulmonary function at exposure concentrations relevant to ambient exposures. However, the range of findings in COPD and asthmatic patients may reflect that some individuals within such groups may be particularly more susceptible to $NO_2$ effects than others.

## 3.1.6. Hospital Admissions and ED Visits

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

### 3.1.6.1. All Respiratory Outcomes

Overall, the majority of studies that have examined all respiratory outcomes as a single group have focused on hospital admission data. The results from the hospitalization and ED visit studies, for all ages and stratified by age group are presented in Figures 3.1-8 and 3.1-9. More details are provided in Annex Tables AX6.3-3, AX6.3-4, and AX6.3-5. These studies report generally positive associations between ambient $NO_2$ levels and ED visits and hospitalizations for all respiratory causes when participants of all ages are considered in the analyses. Stronger and more consistent associations were observed among children and older adults (65+ years) compared to adults (<65 years), with an interquartile range (IQR) of 1 to 13% excess risk estimated per 20 ppb incremental change in 24-h avg $NO_2$ or 30 ppb incremental change in 1-h max $NO_2$.

Peel et al. (2005) examined ED visits for all respiratory causes among all ages in relation to ambient $NO_2$ concentrations in Atlanta, GA during the period of 1993 to 2000. They found a 2.4% (95% CI: 0.9, 4.1) increase in respiratory ED visits associated with a 30-ppb increase in 1-h max $NO_2$ concentrations. Tolbert et al. (2007) recently reanalyzed these data with 4 additional years of data and found similar results (2.0% increase, 95% CI: 0.5, 3.3). Results of a copollutant model with CO and $NO_2$ were presented in a figure and indicated that $NO_2$ was a stronger predictor of respiratory disease than CO, though no quantitative results for copollutant models were presented.

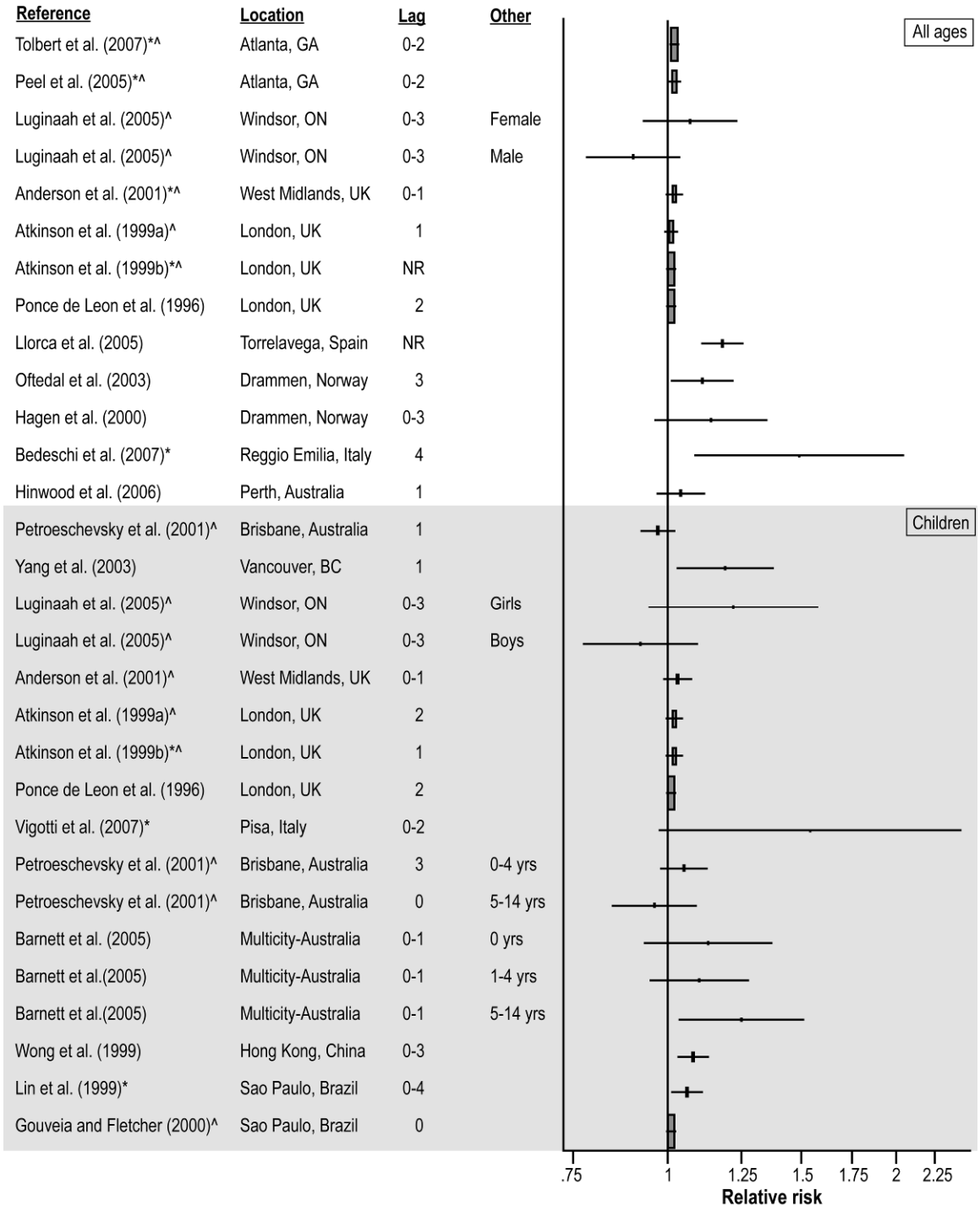



**Figure 3.1-8. Relative risks (95% CI) for hospital admissions or ED visits for all respiratory disease stratified by all ages or children. Results from studies using 24-h average standardized to a 20-ppb increase, results from studies using 1-h max standardized to a 30-ppb increase (* indicates ED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

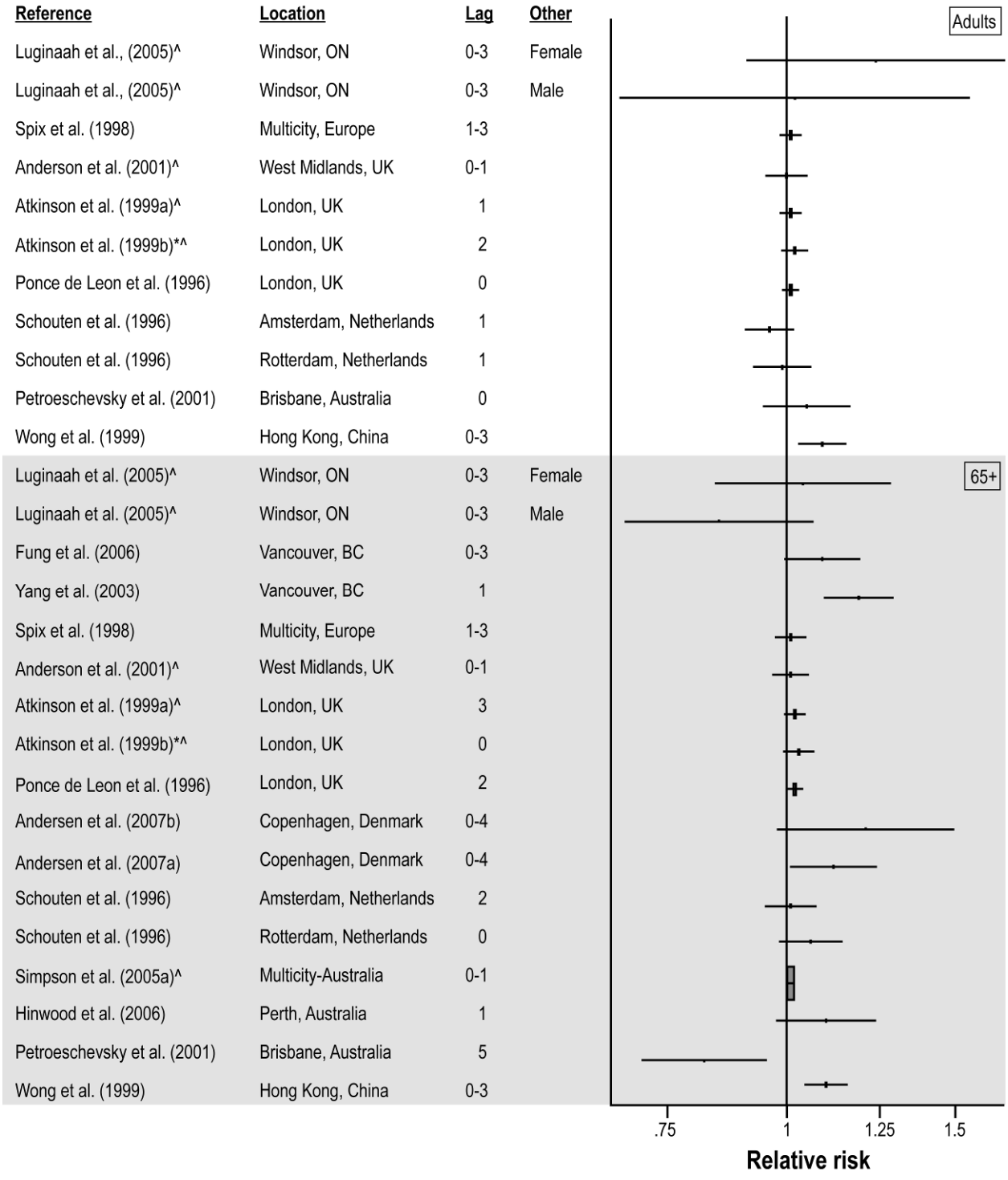



**Figure 3.1-9. Relative Risks (95% CI) for hospital admissions or ED visits for all respiratory disease stratified by adults or older adults (≥ 65 years). Results from studies using 24-h average standardized to a 20-ppb increase, results from studies using 1-h max standardized to a 30-ppb increase (*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

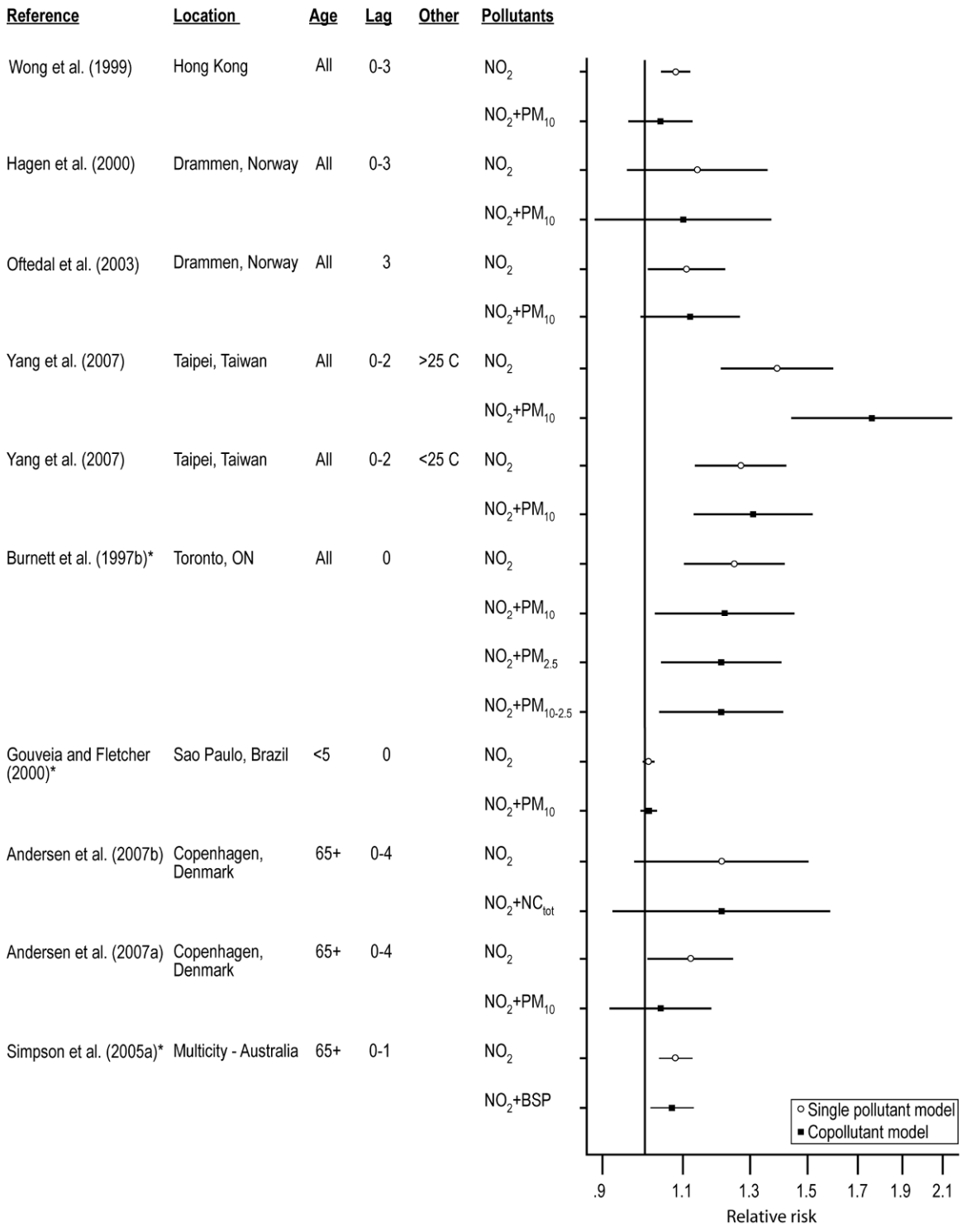



**Figure 3.1-10. Relative risks (95% CI) for hospital admissions or emergency department visits for all respiratory causes, standardized from two-pollutant models adjusted for particle concentration. (* indicates 1-h peak avg times, all others are 24-h avg; effect estimates from studies using 1-h peak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

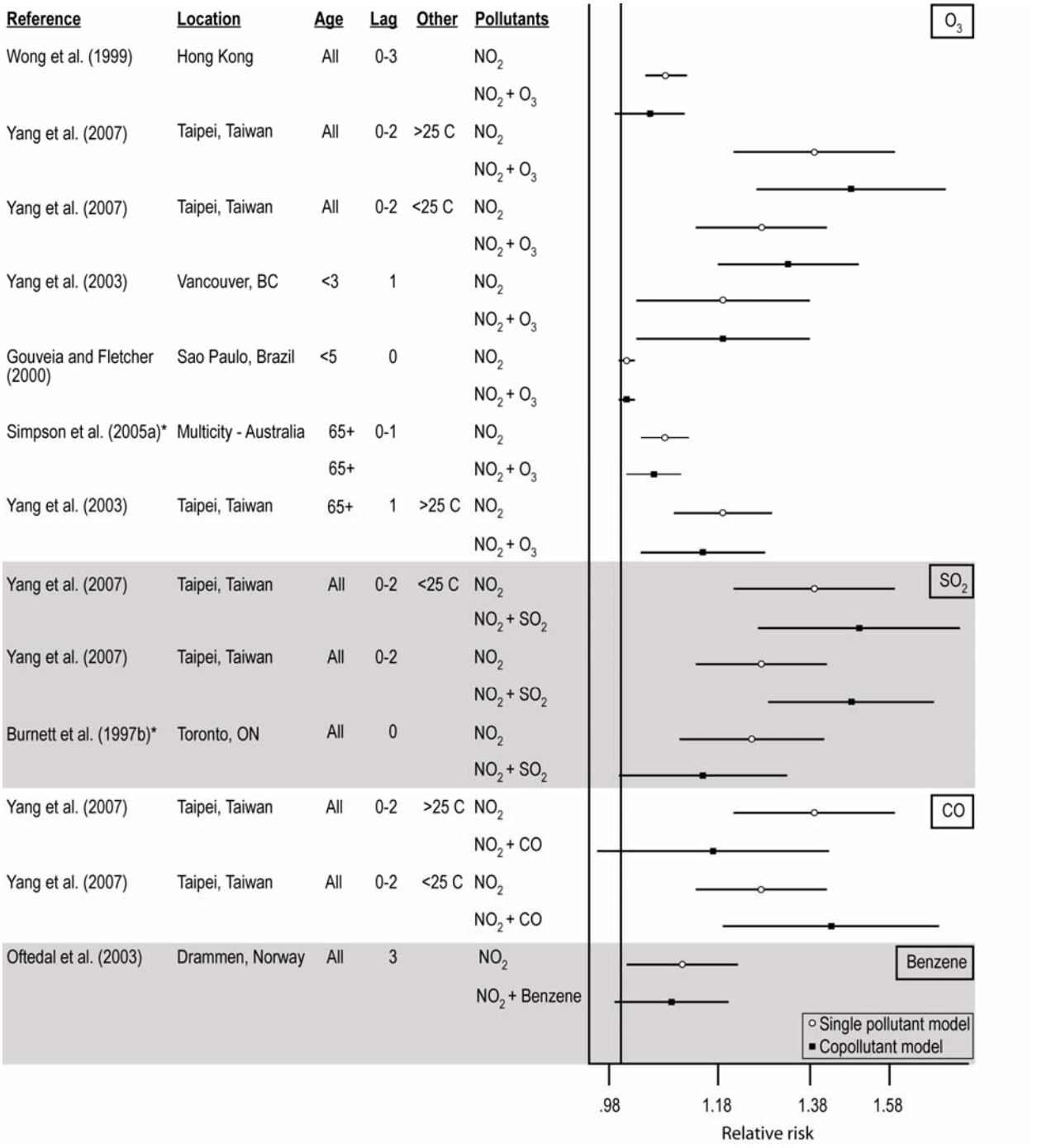



**Figure 3.1-11. Relative risks (95% CI) for hospital admissions or emergency department visits for all respiratory causes, standardized from two-pollutant models adjusted for gaseous pollutant concentration. (* indicates 1-h peak averaging times, all others are 24-h average; effect estimates from studies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

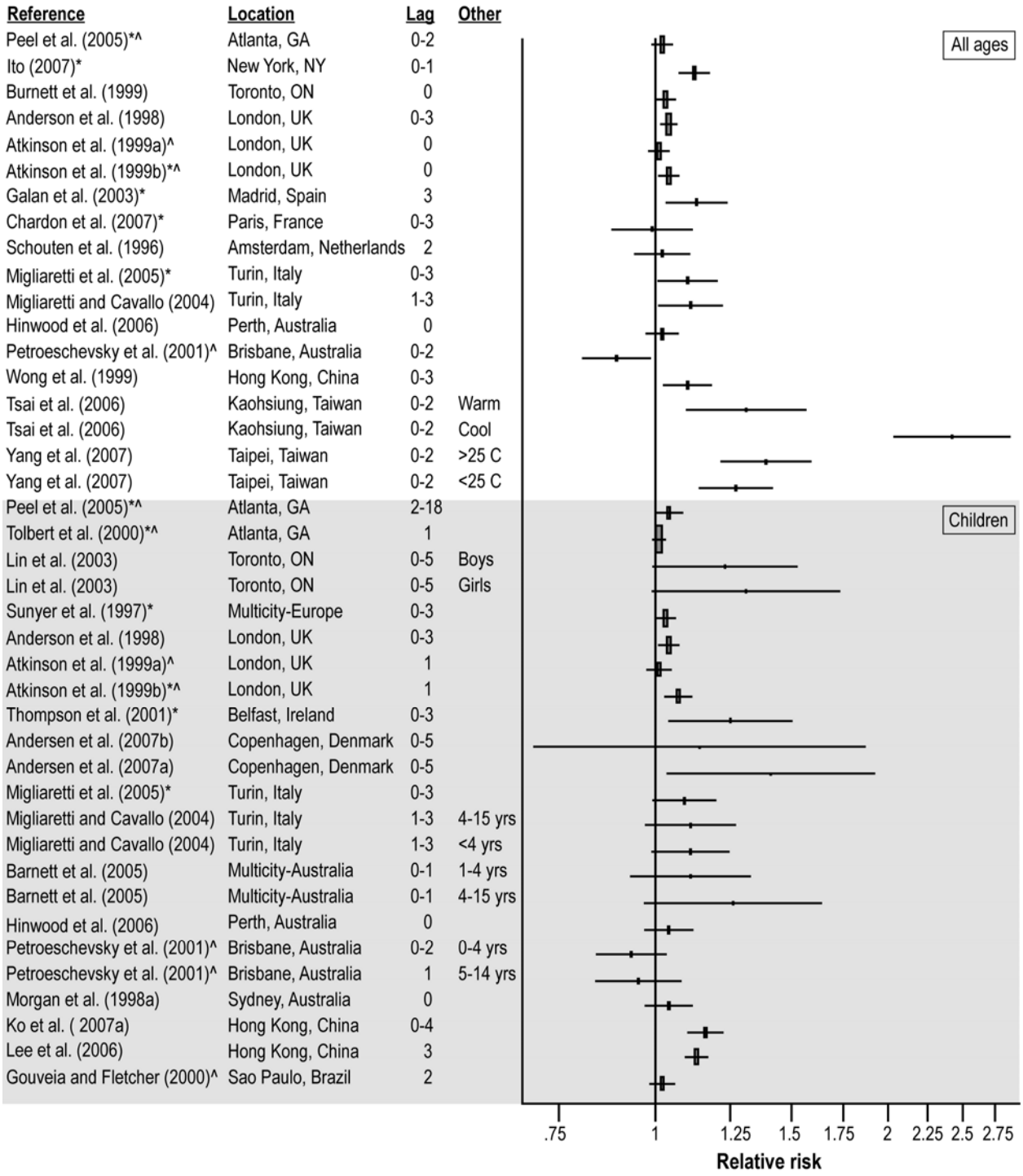



**Figure 3.1-12. Relative Risks (95% CI) for hospital admissions or emergency department visits for asthma stratified by all ages or children. Results from studies using 24-h average standardized to a 20-ppb increase, results from studies using 1-h max standardized to a 30-ppb increase (* indicates ED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

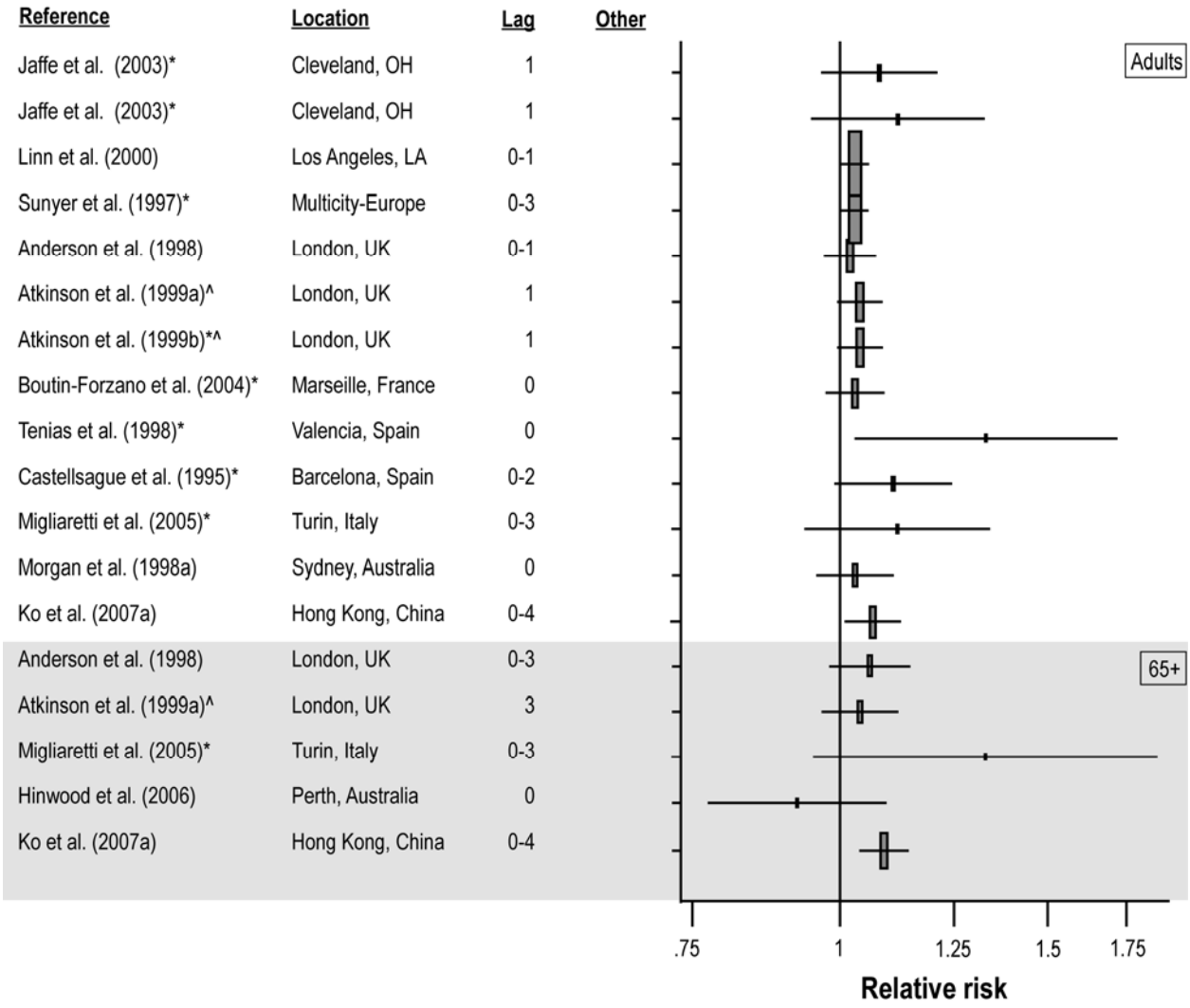



**Figure 3.1-13. Relative risks (95% CI) for hospital admissions or emergency department visits for asthma stratified by adults and older adults (≥ 65 years). Results from studies using 24-h average standardized to a 20-ppb increase, results from studies using 1-h max standardized to a 30-ppb increase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

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

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

Two Canadian studies compared multiple statistical methods for data analysis in studies of hospitalizations for all respiratory outcomes. In Vancouver, Fung et al. (2006) used time-series analysis, the method of Dewanji and Moolgavkar (2000), and case-crossover analyses to examine the association of ambient $NO_2$ concentrations with all respiratory hospitalizations for adults aged 65 years and older. All three methods showed similar results, with positive associations between incremental changes in $NO_2$ of 5.43 ppb (IQR) from a mean concentration of 16.83 ppb. Using a time-series analysis, Fung et al. (2006) reported a percent increase (standardized to 20 ppb) of 6.8% ([95% CI: 1.1%, 13.1%] lag 0), while the case-crossover analysis showed a significant change in the percent increase of 10.7% ([95% CI: 3.7%, 15.5%] lag 0). The Dewanji and Moolgavkar (2000) model did not produce a statistically significant association between $NO_2$ and hospitalization for an increase of 20 ppb, though the central estimate remained positive (percent increase=4.5% [95% CI: -1.1%, 10.3%] lag 0)]. In the second of these two studies, Luginaah et al. (2005) used two approaches that included both time-series and case-crossover analyses segregated by sex. They noted a positive trend between an incremental change in 24-h avg $NO_2$ of 20 ppb and respiratory admissions. Though associations for females in each of the age groups examined were positive, the authors found only one statistically significant association in females aged 0 to 14 years that identified an increased percent of hospitalization of 24.1% using the case-crossover analysis (24.1% [95% CI: 0.3%, 53.8%] lag 2). The results of the time-series analyses from the Luginaah et al. (2005) and Fung et al. (2006) studies are presented in Figures 3.1-8 and 3.1-9, respectively.

European studies on associations with respiratory hospitalizations were conducted in London, Paris, and in Drammen, Norway (Ponce de Leon et al., 1996; Dab et al., 1996; Oftedal et al., 2003). Ponce de Leon et al. (1996) found significant positive relative risks for all ages and for children (0 to 14 year olds), but not for adults (15 to 64 years). Dab et al. (1996) determined that there was no statistically significant association between admissions for all respiratory causes combined based on an incremental change of 52.35 ppb, though the estimates were positive. Oftedal et al. (2003) reported that the relative rate of hospitalizations for all respiratory disease increased based on an increment of 20 ppb $NO_2$ (RR=1.111 [95% CI: 1.031, 1.19.9] lag 3 days). Other studies also found positive outcomes (Andersen et al., 2007a,b; Atkinson et al., 1999a,b; Bedeschi et al., 2007; Burnett et al., 2001; Farchi et al., 2006; Hinwood et al., 2006; Lin et al., 1999; Llorca et al., 2005; Pantazopoulou et al., 1995; Vigotti et al., 2007; Wong et al., 1999; Yang et al., 2003). Several studies presented null results (Anderson et al., 2001; Gouveia and Fletcher, 2000a; Hagen et al., 2001; Schouten et al., 1996). Finally, a number of studies were considered that did not quantitatively estimate the association of $NO_2$ concentration on all respiratory disease hospital admissions, ED visits or clinic visits (Atkinson et al., 2001; Buchdahl et al., 1996; Burnett et al., 1997a; Chen et al., 2005; Fung et al., 2007; Linares et al., 2006; Pantazopoulou et al., 1995; Prescott et al., 1998; Villeneuve et al., 2006). These studies are included in Annex Tables AX6.3-3, AX6.3-4, and AX6.3-5.

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

### 3.1.6.2. Asthma

Studies of ED visits and hospitalizations provide suggestive evidence of an association between ambient $NO_2$ levels and ED visits and hospitalizations for asthma among children and adults. Figures 3.1-12 and 3.1-13 show the relative risks (and 95% confidence limits) of hospitalizations and visits to the ED for asthma associated with daily $NO_2$ concentrations, for all ages and stratified by age. Larger effect estimates were generally observed for children compared to adults and older adults (65+ years), with an IQR of 1 to 25% excess risk estimated per 20 ppb incremental change in 24-h avg $NO_2$ or 30 ppb incremental change in 1-h max $NO_2$. The few studies that examined the association of asthma and $NO_2$ levels among older adults (65+ years) generally reported positive central estimates, though none of these was statistically significant. When subjects of all ages were examined, the results of ED visits and hospitalizations were overwhelmingly positive, especially when the 24-h averaging time was used. The epidemiologic studies of ED and clinic visits and hospital admissions for asthma are summarized in Annex Tables AX6.3-3, AX6.3-4, and AX6.3-5.

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

In New York City, NY, Ito et al. (2007) examined numbers of ED visits for asthma in relation to pollution levels from 1999 to 2002. $NO_2$ was generally the most significant (and largest in effect size per the same distributional increment) predictor of asthma ED visits among $PM_{2.5}$, $O_3$, $SO_2$, and CO (percent increase=12% [95% CI: 7%, 15%] per 20 ppb increase). Further, $NO_2$'s risk estimates were most robust to the addition of other pollutants in the model, and the addition of $NO_2$ reduced other pollutant's risk estimates most consistently. A study conducted in (NY Dept of Health, 2006) found a 6% (95% CI: 1, 10) excess risk in asthma hospital admissions per 20-ppb increase in 24-h avg $NO_2$ for Bronx residents, but a null association for the residents of Manhattan.

Jaffe et al. (2003) examined the effects of ambient pollutants during the summer months (June through August) on the daily number of ED visits for asthma among Medicaid recipients aged 5 to 34 years from 1991 to 1996 in Cincinnati and Cleveland. The percent change in ED visits for asthma as the primary diagnosis per 20-ppb increase in 24-h avg $NO_2$ concentration was 12% (95% CI: -2, 28) in Cincinnati and 8% (95% CI: -2, 16.6) in Cleveland, with an overall percent increase in ED visits of 6% (95% CI: -2, 14).

Barnett et al. (2005) examined specific respiratory disease outcomes and did not find associations between incremental changes in $NO_2$ concentration and respiratory admissions for asthma among children 1 to 4 years old. The largest association found in this study was a 25.7% increase in asthma admissions in the 5- to 14-year age group related to a 20-ppb increase in 24-h $NO_2$, with evidence of a seasonal impact that resulted in larger increases in admissions during the warm season. When the same groups were examined for the effect of a 30-ppb change in the 1-h max concentration of $NO_2$, there were no significant associations between $NO_2$ and hospitalizations for asthma.

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

asthma admissions in both sexes. Differences in the results of these two studies might be attributed to differences in the study designs or differences in subject population sizes.

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

Studies of ED visits and hospitalizations for asthma have been reported in London, U.K. (Atkinson et al., 1999a,b; Hajat et al., 1999); Belfast, Ireland (Thompson et al., 2001); Valencia, Barcelona, and Madrid, Spain (Tenías et al., 1998; Galán et al., 2003; Castellsague et al., 1995); Turin, Italy (Migliaretti and Cavallo, 2004; Migliaretti et al., 2005); Marseille and Paris, France (Boutin-Forzano et al., 2004; Dab et al., 1996); Amsterdam and Rotterdam, the Netherlands (Schouten et al., 1996), and Melbourne, Brisbane, and Perth, Australia (Erbas et al., 2005; Hinwood et al., 2006). Sunyer et al. (1997) have described a meta-analysis of several cities under the umbrella of the Air Pollution on Health: a European Approach (APHEA) protocol (Katsouyanni et al., 1996). Additional studies report a positive association between $NO_2$ concentration and hospital admissions or ED visits (Andersen et al., 2007a; Anderson et al., 1998; Arbex et al., 2007; Burnett et al., 1999; Kim et al., 2007; Ko et al., 2007; Lee et al., 2006; Linn et al., 2000; Tsai et al. 2006; Wong et al., 2001; Yang et al., 2007). Several studies have reported null or negative associations (Andersen et al., 2007b; Anderson et al., 1998; Chardon et al., 2007; Gouveia and Fletcher 2000a; Petroeschevsky et al., 2001; Spix et al., 1998; Tanaka et al., 1998; Tolbert et al., 2000).

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

Finally, there were a number of studies that were considered but did quantitatively estimate the association of $NO_2$ concentration on asthma hospital admissions or ED or clinic visits (Atkinson et al., 2001; Bates et al., 1990; Chew et al., 1999; Garty et al., 1998; Kesten et al., 1995; Lipsett et al., 1997; Magas et al., 2007; Neidell, 2004; Pönkä, 1991; Pönkä and Vitanen 1996; Rossi et al., 1993; Stieb et al., 1996; Sun et al., 2006; Tobias et al., 1999). These studies are included in Annex Tables AX6.3-3, AX6.3-4, and AX6.3-5.

### 3.1.6.3. COPD

Relatively few studies have examined the association of ED visits and hospitalizations for COPD and ambient $NO_2$ levels. The epidemiologic studies of ED and clinic visits and hospital admissions for COPD are summarized in Annex Tables AX6.3-3, AX6.3-4, and AX6.3-5. Studies examining COPD outcomes have focused on hospital admission data, including multicity studies in the U.S. (Moolgavkar, 2000, 2003), Europe (Anderson et al., 1997) and Australia (Simpson et al., 2005a), and single-city studies in the U.S. (Peel et al., 2005), Canada (Yang et al., 2005), Europe (Anderson et al., 2001; Atkinson et al., 1999a; Dab et al., 1996; Tenias et al., 2002), Australia (Morgan et al., 1998a; Hinwood et al., 2006), and Asia (Lee et al., 2007; Yang and Chen, 2007).In a time-series study in Vancouver, an area with low pollution concentrations (24-h mean $NO_2$ of 17.03 ppb), Yang et al. (2005) reported associations between $NO_2$ and hospital admissions for COPD in patients ≥ 65 years for both the lag 1 day (RR=1.19; 95% CI: 1.04, 1.37) and 7-day extended lag period (RR=1.46 [95% CI: 1.15, 1.94]). Additional studies found weaker, though statistically significant positive associations with ambient levels of $NO_2$ and COPD (Moolgavkar, 2003; Anderson et al., 1997; Simpson et al., 2005a). A time-series analysis in Sydney, Australia, examined respiratory outcomes in children and adults but did not show an association between changes in $NO_2$ (24-h average) for increased hospital admissions among COPD patients ≥ 65 years (Morgan et al., 1998a). Similarly, a study in Paris, France, of COPD and related obstructive respiratory disease found that $NO_2$ was not statistically significantly associated with increased hospital admissions (Dab et al., 1996).

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

ED visits or hospital admissions for respiratory diseases include upper respiratory infections (URIs), pneumonia, bronchitis, allergic rhinitis, and lower respiratory disease (LRD). The reviewed epidemiologic studies of clinic and ED visits and hospital admissions for these respiratory diseases are summarized in Annex Tables AX6.3-3, AX6.3-4, and AX6.3-5. Though some of these studies reported positive and statistically significant results (Atkinson et al., 1999a; Burnett et al., 1997b, 1999; Farchi et al., 2006; Gouveia and Fletcher, 2000a; Hwang and Chan, 2002; Ilabaca et al., 1999; Lin et al., 2005; Peel et al., 2005; Simpson et al., 2005a), others reported null or negative associations (Barnett et al., 2005; Chardon et al., 2007; Hinwood et al., 2006; Karr et al., 2006; Lin et al., 1999; Pönkä and Virtanen, 1994; Zanobetti and Schwartz, 2006). Finally, there are two studies that were considered but that did not quantitatively estimate the association of $NO_2$ concentration on all respiratory disease hospital admissions or ED and clinical visits (Bates et al., 1990; Linares et al., 2006). These studies are included in Annex Tables AX6.3-3, AX6.3-4, and AX6.3-5.

### 3.1.6.5. Summary of Short-Term Exposure on Respiratory ED Visits and Hospitalizations

In summary, many studies have observed positive associations between ambient $NO_2$ concentrations and ED visits and hospitalizations for all respiratory diseases and asthma. These associations are particularly consistent among children and older adults (65+ years) for hospital admissions for all respiratory diseases. For asthma hospitalization, the effect estimates were largest when children and subjects of all ages were included in the analysis. Results from copollutant models indicated that the effect of $NO_2$ on ED visits and hospitalizations for all respiratory causes and asthma were generally robust and independent of the effects of ambient particles or gaseous copollutants. In preceding sections, exposure to $NO_2$ has been found to result in host defense and immune system changes, airway inflammation, and airway responsiveness. While not providing specific mechanistic data linking exposure to ambient $NO_2$ and respiratory hospitalization or ED visits for asthma, these findings provide plausibility and coherence for such a relationship.

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

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

The main body of evidence for an association between respiratory morbidity and $NO_X$ exposure comes from epidemiologic studies. In addition, clinical and animal toxicological studies provide some supporting data. Taken together, the findings of epidemiologic, human clinical, and animal toxicological studies provided evidence that is sufficient to infer a likely causal relationship for respiratory effects with short-term $NO_2$ exposure. The body of evidence from epidemiologic studies has grown substantially since the 1993 AQCD and provided scientific evidence that short-term exposure to $NO_2$ is associated with a broad range of respiratory morbidity effects, including altered lung host defense, inflammation, airway hyperresponsiveness, respiratory symptoms, lung function decrements, and ED visits and hospital admissions for respiratory diseases. New evidence came from large longitudinal studies, panel studies, and time-series studies. $NO_2$ exposure was associated with aggravation of asthma effects that include symptoms, medication use, and lung function. Effects of $NO_2$ on asthma were most evident with

cumulative lag of 2 to 6 days, rather than same-day levels of $NO_2$. Time-series studies also demonstrated a relationship in children between hospital admissions or ED visits for asthma and $NO_2$ exposure. In many of these studies, there were high correlations between ambient measures of $NO_2$ and CO and PM; however, the effect estimates for $NO_2$ were robust after the inclusion of CO and PM in multipollutant models. Recent epidemiologic studies provided somewhat inconsistent evidence on short-term exposure to $NO_2$ and inflammatory responses in the airways, as well as for associations with lung function decrements. The epidemiologic evidence for these effects can be characterized as consistent, in that associations are reported in studies conducted in numerous locations with a variety of methodological approaches. While the individual risk estimates were small in magnitude, and thus not considered strong individually, the body of epidemiologic evidence had strength in that fairly precise and robust risk estimates were reported from multicity studies.

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

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

Human clinical studies provided evidence for airway hyperresponsiveness i.e., a heightened bronchoconstrictive response to a challenge agent, following short-term exposure to $NO_2$. In acute exacerbations of asthma, bronchial smooth muscle contraction (bronchoconstriction) occurs quickly to narrow the airways in response to exposure to various stimuli including allergens or irritants. Bronchoconstriction is the dominant physiological event leading to clinical symptoms and interference with airflow (National Heart, Lung, and Blood Institute, 2007). Recent studies involving allergen challenge in asthmatics showed that $NO_2$ may enhance the sensitivity to allergen-induced decrements in lung function and affect allergen-induced inflammatory responses following exposures as low as 0.26 ppm $NO_2$ for 30 min during rest. Nonspecific responsiveness also was increased following 30-min exposures of resting asthmatic subjects to 0.2- to 0.3-ppm $NO_2$ and following 1-h exposures to 0.1-ppm $NO_2$.

The few recent epidemiologic studies reported associations between ambient $NO_2$ exposure and airway inflammation. These studies were indicative of effects in children, but offered more limited evidence for effects in adults. Human clinical studies provided consistent evidence for airway inflammation at a $NO_2$ concentration of 2.0 ppm (one study found airway inflammation at a concentration of 1.5 ppm); the onset of inflammatory responses in healthy subjects appeared to be between 100 and 200 ppm-min, i.e., 1 ppm for 2 to 3 h. Biological markers of inflammation were reported in antioxidant-

deficient laboratory animals with exposures to 0.4 ppm $NO_2$, though healthy animals did not respond until exposed to much higher levels, i.e., 5 ppm $NO_2$. The biochemical effects observed in the respiratory tract following exposure to $NO_2$ included chemical alteration of lipids, amino acids, proteins, enzymes, and changes in oxidant/antioxidant homeostasis, with membrane polyunsaturated fatty acids and thiol groups as the main biochemical targets for $NO_2$ exposure. However, the biological implications of such alterations are unclear. Potential mechanisms for effects on the respiratory system included membrane damage from increases in reactive oxygen species, lipid and protein pertubations, and recruitment of inflammatory cells from epithelial cell injury by reactive oxygen species.

In evaluating the potential relationships between short-term exposure to $NO_2$ and respiratory effects, it is important to note the interrelationships between $NO_2$ and other pollutants, and the potential for $NO_2$ to serve as a marker for a pollutant mixture, particularly traffic-related pollution. As outlined in the preface to this ISA, this included consideration of potential pathways, such as the direct causal pathway for effects, mediation of effects, the pollutant acting as a surrogate for a pollutant mixture, or confounding between pollutants. As observed above, associations with $NO_2$ were often robust to adjustment for traffic-related pollutants (e.g., PM and CO), even in locations where the correlations between pollutants were substantial. The epidemiologic evidence has thus been found to be consistent and coherent for respiratory symptoms and respiratory hospitalization and ED visits. In addition, toxicological and clinical studies reported effects of exposure to gaseous $NO_2$, as discussed previously, for outcomes related to lung host defense and immune system changes. The experimental studies indicated that $NO_2$ is solely responsible for the effects reported. The findings of direct effects of $NO_2$ in toxicological or human clinical studies, in combination with robust associations reported in epidemiologic studies, supported a conclusion that $NO_2$ is independently responsible for some respiratory effects. There was little available evidence to evaluate the potential for $NO_2$ effects to be modified by other pollutants or exposures; further, clinical and epidemiologic study findings did not appear to support that coexposure with another pollutant is required to observe $NO_2$-related effects.

The evidence summarized here supports the conclusion that there is a likely causal relationship between short-term exposure to $NO_2$ and effects on the respiratory system. However, the challenge remains in considering the potential for $NO_2$ to serve as an indicator for a mixture of combustion-related pollutants. Most studies examined showed that personal $NO_2$ exposures were significantly correlated either with ambient or personal level $PM_{2.5}$, or other combustion-generated products (e.g., CO and EC). As discussed in Chapter 2, ambient $NO_2$ measurements can provide a valid estimate of personal exposure to ambient $NO_2$ as used in most epidemiology studies. Although the evidence indicated that $NO_2$ exposure is independently associated with some respiratory health effects, there remains the possibility that $NO_2$ also serves as a marker for combustion-related emissions, particularly from traffic, for some health outcomes. Although this complicates efforts to disentangle specific $NO_2$-related health effects, the evidence indicates that $NO_2$ associations generally remain robust in multipollutant models and supports a direct effect of short-term $NO_2$ exposure on respiratory morbidity at current ambient concentrations.

# 3.2. Cardiovascular Effects Related to Short-Term Exposure

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

## 3.2.1. Heart Rate Variability

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

the autonomic nervous system and lead to an imbalance of cardiac autonomic control characterized by sympathetic activation unopposed by parasympathetic control (Liao et al., 2004; Brook et al., 2004). Such an imbalance of cardiac autonomic control may predispose susceptible people to greater risk of ventricular arrhythmias and consequent cardiac deaths (Liao et al., 2004; Brook et al., 2004). Findings from studies of ambient $NO_2$ and HRV were mixed with some studies reporting an adverse effect (reduction in variability) (Liao et al., 2004; Chan et al., 2005; Wheeler et al., 2006), while other studies reported no significant change (Luttman-Gibson et al., 2006; Holguin et al., 2003; Schwartz et al. 2005). In some studies reporting reductions in HRV, reductions for PM were similar to those observed for $NO_2$ (Liao et al., 2004; Wheeler et al. 2006). See Annex Table AX6.3-10 for a detailed discussion of HRV studies.

## 3.2.2. Arrhythmias Recorded on Implanted Defibrillators

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

## 3.2.3. Repolarization Changes

In addition to the role played by the autonomic nervous system in arrhythmogenic conditions, myocardial vulnerability and repolarization abnormalities are believed to be key factors contributing to the mechanism of such diseases. Henneberger et al. (2005) reported that $NO_2$ and NO were not associated with repolarization abnormalities.

## 3.2.4. Markers of Cardiovascular Disease Risk

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

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

A few human clinical studies which indicated effects of $NO_2$ exposure on cardiac output, blood pressure, and circulating red blood cells at concentrations of less than 2.0 ppm (Drechsler-Parks, 1995;

Linn et al., 1985a; Posin et al., 1978; (Frampton et al., 2002) require confirmation. Drechsler-Parks (1995) observed a lower mean stroke volume for $NO_2$+$O_3$ than for air and speculated that chemical interactions between $O_3$ and $NO_2$ at the level of the epithelial lining fluid led to the production of nitrite, leading to vasodilatation, with reduced cardiac preload and cardiac output. Linn et al. (1985a) reported small but statistically significant reductions in blood pressure after exposure to 4 ppm $NO_2$ for 75 min, a finding consistent with systemic vasodilatation in response to the exposure; this finding has not been repeated. Frampton et al. (2002) reported a concentration-related reduction in hematocrit and hemoglobin in both males and females, among health subjects exposed to $NO_2$, confirming the findings of an earlier study conducted by Posin et al. (1978). See Annex AX5 for a detailed discussion of these studies.

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

## 3.2.5. Toxicology of Inhaled Nitric Oxide

Nitric oxide is used in humans therapeutically as a pulmonary vasodilator, and has shown little evidence for adverse respiratory effects. The literature on therapeutic uses of nitric oxide provides the strongest evidence for its lack of toxicity. Infants and adults with acute respiratory failure and refractory hypoxemia, as well as pulmonary hypertension, are sometimes considered candidates for inhaled NO. Inhaled NO acts as a selective pulmonary vasodilator, causing vascular smooth muscle relaxation and increased perfusion in ventilated lung regions. Beneficial effects in patients with respiratory failure include reduced pulmonary artery pressures and improved ventilation-perfusion matching. Nitric oxide is used clinically at concentrations ranging from 5 ppm to as high as 80 ppm. There has been little or no toxicity reported, even when used in premature infants with respiratory failure. In a recently published multicenter study (Kinsella et al., 2006), 793 premature infants with respiratory failure were randomized to therapy with inhaled NO or air. NO therapy was associated with a reduced risk of brain injury, and in a reduced risk of bronchopulmonary dysplasia, a chronic lung condition resulting from lung injury in infancy, in infants weighing at least 1000 gm. NO can cause methemoglobinemia, and this was seen transiently in only 2 infants. NO can inhibit activation of blood leukocytes and platelets (Gianetti et al. 2002); however there was no evidence for increased susceptibility to infection or bleeding. One of the concerns about NO therapy is the potential for NO to be oxidized to $NO_2$, so administration systems are designed to avoid this.

## 3.2.6. Hospital Admissions and ED Visits for CVD

Cases of CVD are typically identified using ICD codes, which were recorded on hospital discharge records in these studies. However, counts of hospital or ED admissions were used in some studies. Studies of ED visits may include cases that are less severe than those included in hospital admission

studies. Hospital admission studies are distinguished from ED visit studies in Annex Tables AX6.3-6 through AX6.3-9. Many studies grouped all CVD diagnoses (ICD9 codes 390–459), evaluating cardiac diseases (ICD9 codes 390–429), and cerebrovascular disease (ICD9 430–448) together. Other studies evaluated cardiac and cerebrovascular diseases separately or further distinguished ischemic heart disease (IHD: ICD9 410–414), myocardial infarction (MI: ICD9 410), congestive heart failure (CHF: ICD9 428), cardiac arrhythmia (ICD9 427), angina pectoris (ICD9 413), or stroke (ICD9 430-438).

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

## 3.2.7. Cardiac Disease

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

Most investigators reporting results from multipollutant models observed diminished effect estimates for $NO_2$ and hospital admissions or ED visits for CVDs. In two U.S. studies conducted in Los Angeles, investigators indicated that their analyses were unable to distinguish the effects of $NO_2$ from PM, CO, and other traffic pollutants (Linn et al., 2000; Mann et al., 2002). In both studies, CO was more highly correlated with $NO_2$ than PM. In an Atlanta study, Metzger et al. (2004) and Tolbert et al. (2007) also observed a diminished effect of $NO_2$ on visits for CVD when CO was modeled with $NO_2$, while the effect of CO remained robust. Tolbert et al. (2007) discussed the limitations of multipollutant models and concluded that these models might help researchers identify the strongest predictor of disease, but might not isolate the independent effect of each pollutant. $NO_2$ was not robust to adjustment for other pollutants in several non-U.S. studies (Jalaludin et al., 2006; Ballester et al., 2006; Simpson et al., 2005a; Poloniecki et al., 1997; Barnett et al., 2006; Llorca et al., 2005). However, in other studies, investigators reported that the effect of $NO_2$ was robust in multipollutant models (Von Klot et al., 2005; Yang et al., 2004b; Chang et al., 2005; Morgan et al., 1998a; Burnett et al., 1997a, 1999). See Annex section AX6.2.1.6 for a detailed description of results from multipollutant models.

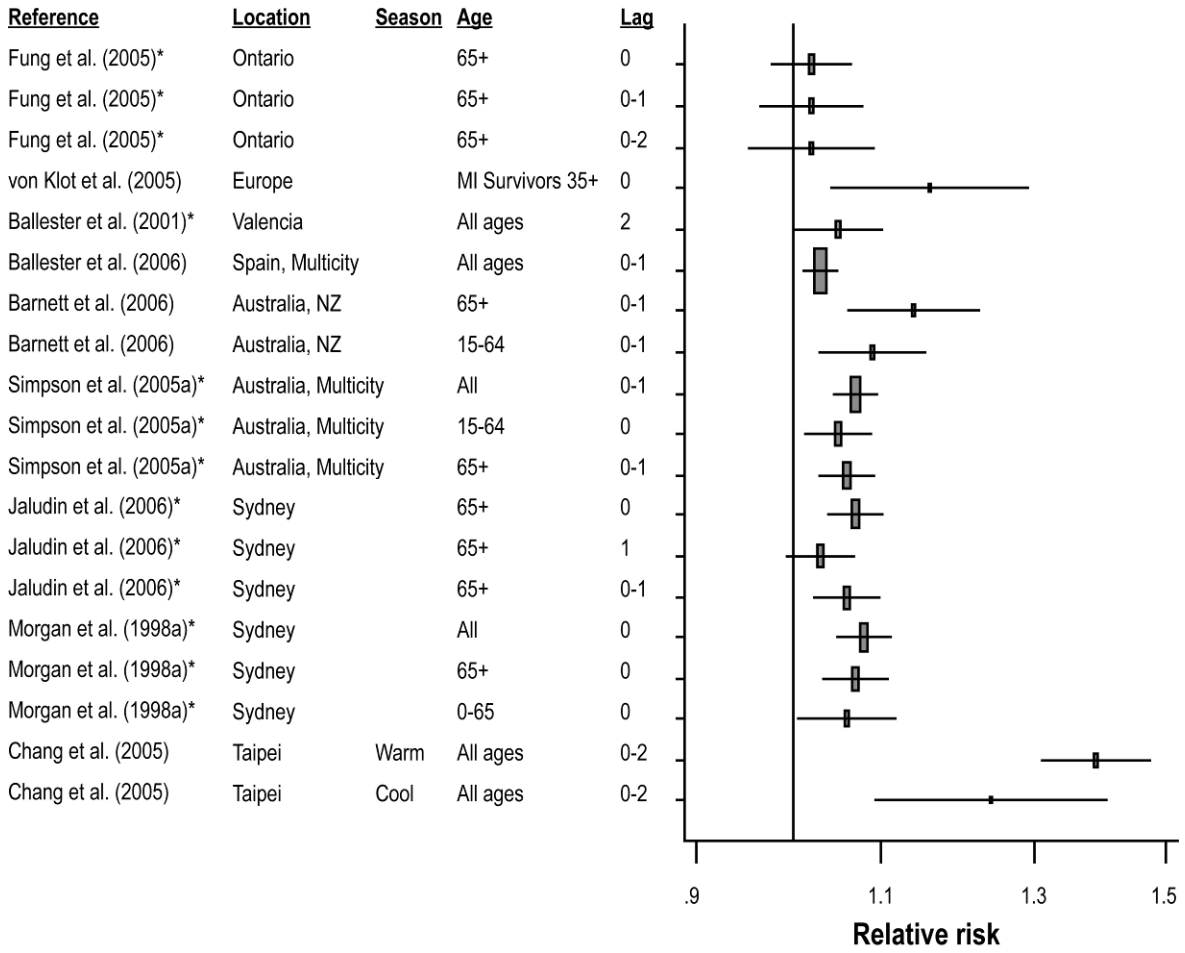



**Figure 3.2-1. Relative risks (95% CI) for associations of 24-h $NO_2$ (per 20 ppb) and daily 1-h max* $NO_2$ (per 30 ppb) with hospitalizations or emergency department visits for cardiac diseases. Primary author and year of publication, city, stratification variable(s), and lag are listed. Results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

## 3.2.8. Hospital Admissions for Stroke and Cerebrovascular Disease

Studies of the association between all cerebrovascular disease and ambient $NO_2$ concentration are summarized in Figure 3.2-2. Results from these studies were generally inconsistent. Metzger et al. (2004) reported a significant increase in cerebrovascular disease emergency visits in Atlanta. However, Peel et al. (2007) did not find associations between cerebrovascular disease visits and $NO_2$ concentrations among those with hypertension and diabetes in the same city. The daily 1-h max $NO_2$ level in Atlanta during the study period ranged from 26 to 45.9 ppb (Metzger et al., 2004; Peel et al., 2007). Ballester et al. (2001) reported a relatively large increased risk in cerebrovascular admissions in the Spanish city of Valencia at lag 4, while Poloniecki et al. (1997) and Pönkä and Virtanen (1996) did not observe associations in London and Helsinki. Two Asian studies report positive but nonsignificant associations of cerebrovascular disease with 24-h avg $NO_2$ (Chan et al., 2006; Wong et al., 1999). The 24-h avg $NO_2$ levels reported for Taipei and Hong Kong were approximately 30 ppb and 27 ppb, respectively (Chan et al., 2006; Wong et al., 1999).

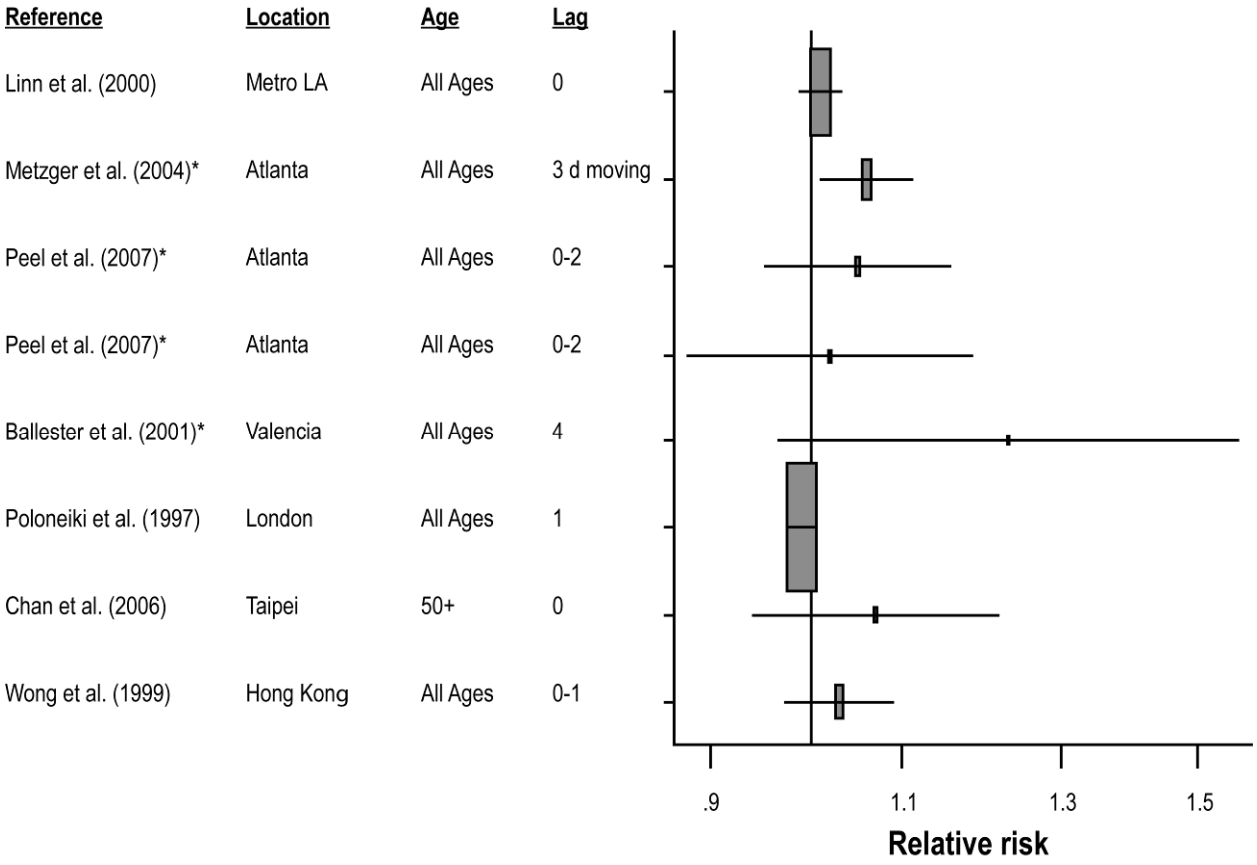



**Figure 3.2-2. Relative risks (95% CI) for associations of 24-h $NO_2$ (per 20 ppb) and daily 1-h max $NO_2$* (per 30 ppb) with hospitalizations for all cerebrovascular disease. Primary author and year of publication, city, stratification variable(s), and lag are listed. Results for lags 0 or 1 are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

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

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

Several investigators presented estimates for the association of $NO_2$ with cerebrovascular outcomes from multipollutant models. The association of $NO_2$ with stroke was not robust to adjustment for CO in a

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

## Summary of Cardiovascular Effects Related to Short-Term Exposure

The available evidence on the effect of short-term exposure to $NO_2$ on cardiovascular health effects was inadequate to infer the presence or absence of a causal relationship at this time. Evidence from epidemiologic studies of HRV, repolarization changes, and cardiac rhythm disorders among heart patients with implanted cardioverter defibrilators are inconsistent. In most studies, observed associations with PM were similar or stronger than associations with $NO_2$. Generally positive associations between ambient $NO_2$ concentrations and hospital admissions or ED visits for CVD have been reported in single-pollutant models; however, most of the effect estimates were diminished in multipollutant models also containing CO and PM indices. Mechanistic evidence of a role for $NO_2$ in the development of CVDs from studies of biomarkers of inflammation, cell adhesion, coagulation, and thrombosis was lacking. Furthermore, the effects of $NO_2$ on various hematological parameters in animals are inconsistent and, thus, provide little biological plausibility for effects of $NO_2$ on the cardiovascular system. However, there was limited evidence from human clinical studies which showed a reduction in hemoglobin with $NO_2$ exposure at concentrations of 1.0 to 2.0 ppm (with 3 h exposures) that requires confirmation.

# 3.3. Mortality Related to Short-Term Exposure

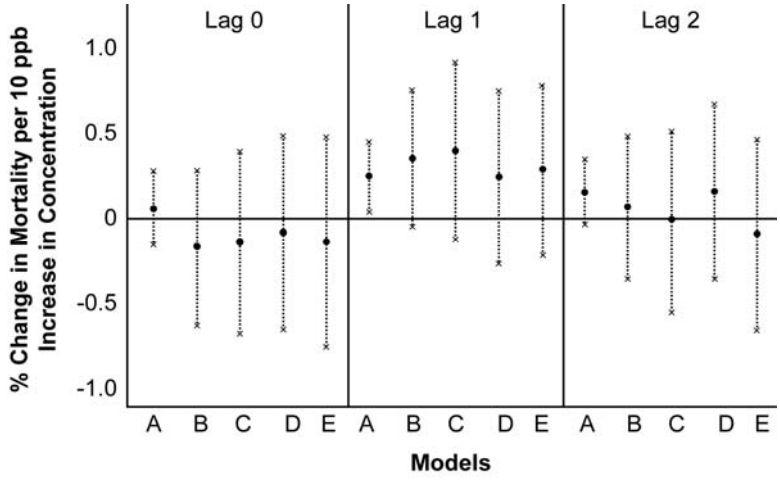
There was no epidemiologic study reviewed in the 1993 AQCD that examined the mortality effects of ambient $NO_2$. Since the 1993 AQCD, a number of studies, mostly using time-series analyses, reported short-term mortality risk estimates for $NO_2$ (see Annex Table AX6.3-19). However, since most of these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

## 3.3.1. Multicity Studies and Meta-Analyses

In reviewing the range of mortality risk estimates, multicity studies provided the most useful information because they analyzed multiple cities data in a consistent method, avoiding potential publication bias. Risk estimates from multicity studies usually are reported for consistent lag days, further reducing potential bias caused by choosing the "best" lag in individual studies. There have been several multicity studies from the U.S., Canada, and Europe. Meta-analysis studies also provided useful information on describing heterogeneity of risk estimates across studies, but unlike multicity studies, the heterogeneity of risk estimates seen in meta-analysis may also reflect the variation in analytical approaches across studies. Thus, we focused our review mainly on the results from multicity studies, and effect estimates from these studies were summarized. Discussion focused on the studies that were not affected by generalized additive models (GAMs) with convergence issues (Dominici et al., 2002; Ramsay et al., 2003) unless otherwise noted when the studies raised relevant issues.

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

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




Source: Dominici et al. (2003).

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

### 3.3.1.2. Canadian Multicity Studies

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

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

the 3-day moving average (i.e., average of 0-, 1-, and 2-day lags), and for $O_3$, it was the 2-day moving average. Of the single-day lag estimates for $NO_2$,

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

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

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

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

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

Samoli et al. (2006) analyzed 29 APHEA2 cities to estimate $NO_2$ associations for total, cardiovascular, and respiratory deaths. The average of lags 0-1 days was chosen a priori to avoid potential bias with the "best" lag approach. In addition, the association of total mortality with $NO_2$ over 6 days (lags 0-5) were summarized over all cities using a cubic polynomial distributed lag model. Results from this model showed multiday effects, with the strongest association shown at lag 1 day, which was consistent with the results from NMMAPS and Canadian multicity studies. The risk estimates for total, cardiovascular, and respiratory causes were comparable. In the two-pollutant models with black smoke, $PM_{10}$, $SO_2$, and $O_3$, the risk estimates for total and cardiovascular mortality were not affected. The second-stage analysis examined possible effect modifiers. For total and cardiovascular mortality, the geographical area (defined as western, southern, and central eastern European cities) was the most important effect modifier (estimates were lower in eastern cities), followed by smoking prevalence ($NO_2$ risk estimates were higher in cities with a lower prevalence of smoking). The authors concluded that the

results showed effects of $NO_2$ on mortality, but that the role of $NO_2$ as a surrogate of other unmeasured pollutants could not be completely ruled out.

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

### 3.3.1.4. The Netherlands Study

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

### 3.3.1.5. Other Multicity Studies

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

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

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

sensitive to the addition of nephelometer readings in the two-pollutant models for total mortality, but the nephelometer risk estimate was greatly reduced in the model with $NO_2$.

### 3.3.1.6. Meta-Analyses of $NO_2$ Mortality Studies

Stieb et al. (2002) reviewed time-series mortality studies published between 1985 and 2000, and conducted a meta-analysis to estimate combined effects for each of $PM_{10}$, CO, $NO_2$, $O_3$, and $SO_2$. Since many of the studies reviewed in that analysis were affected by the GAM convergence issue, Stieb et al. (2003) updated the estimates by separating the GAM versus non-GAM studies and by single- versus multipollutant models. There were more GAM estimates than non-GAM estimates for all the pollutants except $SO_2$. For $NO_2$, there were 11 estimates from single-pollutant models and only 3 estimates from multipollutant models. The lags and multiday averaging used in these estimates varied. The combined estimate for total mortality was 0.8% (95% CI: 0.2, 1.5) per 20-ppb increase in the daily average $NO_2$ from the single-pollutant models and 0.4% (95% CI: -0.2, 1.1) per 20-ppb increase in the 24-h average from the multipollutant models. Note that, although the estimate from the multipollutant models was smaller than that from the single-pollutant models, the number of the studies for the multipollutant models was small (3), also, the data extraction procedure of this meta-analysis for the multipollutant models was to extract from each study the multipollutant model that resulted in the greatest reduction in risk estimate compared with that observed in single-pollutant models. It should be noted that all the multicity studies whose combined estimates have been discussed above were published after this meta-analysis.

## 3.3.2. Summary of Mortality Related to Short-Term Exposure

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

In the short-term exposure studies, the range of $NO_2$ total mortality risk estimates is 0.5 to 3.6% per 20-ppb increase in the 24-h average $NO_2$ or 30-ppb increase in daily 1-h max (Figure 3.3-2). The use of various lag periods, averaging days, and distributed lags did not appear to alter the estimates substantially. The heterogeneity of estimates in these studies may be due to several factors, including the differences in (1) model specification, (2) $NO_2$ levels, and (3) effect modifying factors. Interestingly, the Canadian 12-city study showed combined risk estimates (average of 0-1 day or single 1-day lag) about 4 times larger than that for the U.S. estimate, despite the fact that the range of Canadian $NO_2$ concentrations (10 to 26 ppb) was somewhat lower than that for the U.S. data (9 to 39 ppb for the 10%-trimmed data). In fact, the NMMAPS estimate is the smallest among the multicity studies, a pattern appearing in $PM_{10}$ mortality risk estimates (U.S. Environmental Protection Agency, 2004). Thus, it is possible that this may be due to the difference in model specifications.

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

multipollutant results generally indicated a lack of confounding, it was difficult to attribute the observed excess mortality risk estimates to $NO_2$ alone.

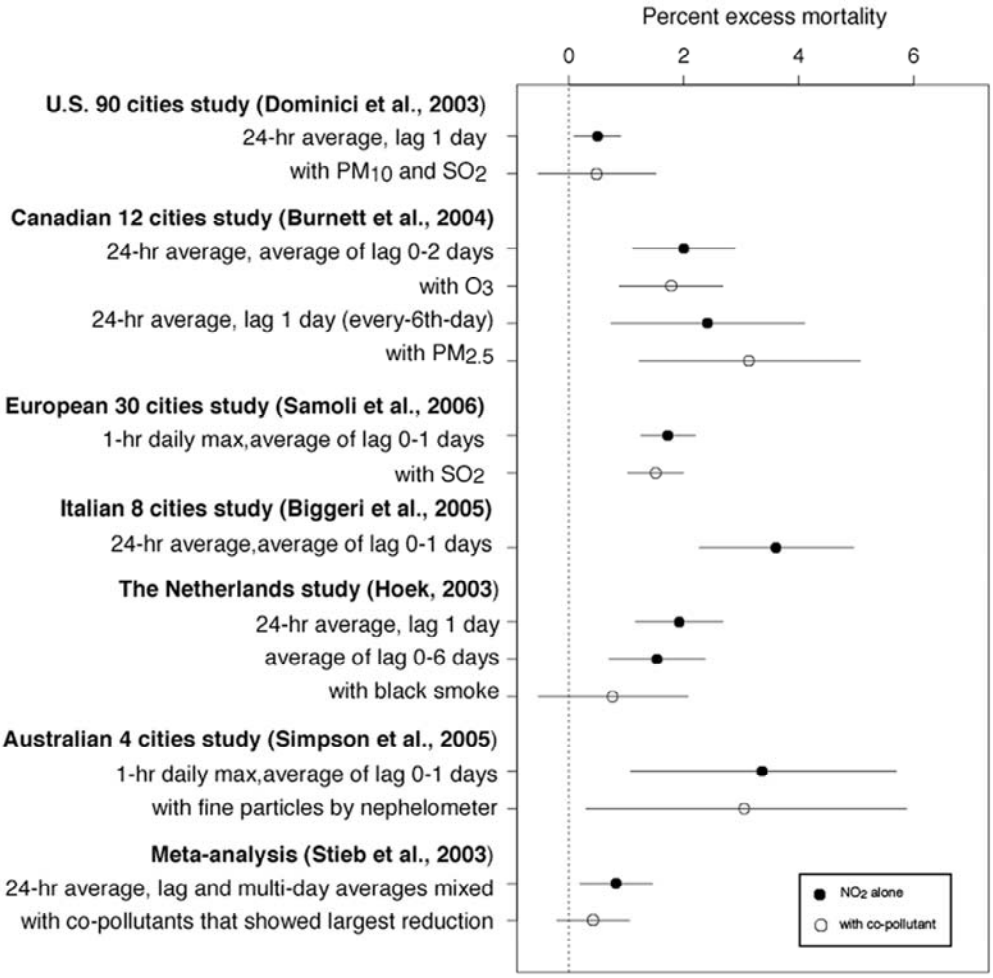



**Figure 3.3-2. Combined $NO_2$ mortality risk estimates from multicity and meta-analysis studies. Risk estimates are computed per 20-ppb increase for 24-h average or 30-ppb increase for 1-h daily max $NO_2$ concentrations. For multipollutant models, results from the models that resulted in the greatest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

While the multicity studies examining the relationship between short-term $NO_2$ exposure and mortality observed statistically significant associations for total, cardiovascular, and respiratory causes, the issue of surrogacy of the role of $NO_2$ and possible interactions with PM and other pollutants remained unresolved. As reviewed in earlier sections, human clinical studies, by necessity, were restricted to acute, fully reversible functional and/or symptomatic responses in healthy or mildly asthmatic subjects. A number of animal studies (described in Section 3.1.3) have shown biochemical, lung host defense, permeability, and inflammation effects with acute exposures and may provide weak biological plausibility for mortality in susceptible individuals. A 5 ppm $NO_2$ exposure for 24 h in rats caused increases in blood and lung total GSH and a similar exposure resulted in impairment of alveolar surface tension of surfactant

phospholipids due to altered fatty acid content. A fairly large body of literature described the effects of $NO_2$ on lung host defenses at low exposures. However, most of these effects were seen only with subchronic or chronic exposure and, therefore, do not correlate well with the short lag times evidenced in the epidemiologic studies. The results from several large U.S. and European multicity studies and a meta-analysis study observed positive associations between ambient $NO_2$ concentrations and risk of all-cause (nonaccidental) mortality, with effect estimates ranging from 0.5 to 3.6% excess risk in mortality per standardized increment (Section 3.3.2, Figure 3.3-2). In general, the $NO_2$ effect estimates were robust to adjustment for copollutants. Both cardiovascular and respiratory mortality have been associated with increased $NO_2$ concentrations in epidemiologic studies (Figure 3.3-3); however, similar associations were observed for other pollutants, including PM and $SO_2$. The range of mortality excess risk estimates was generally smaller than that for other pollutants such as PM.

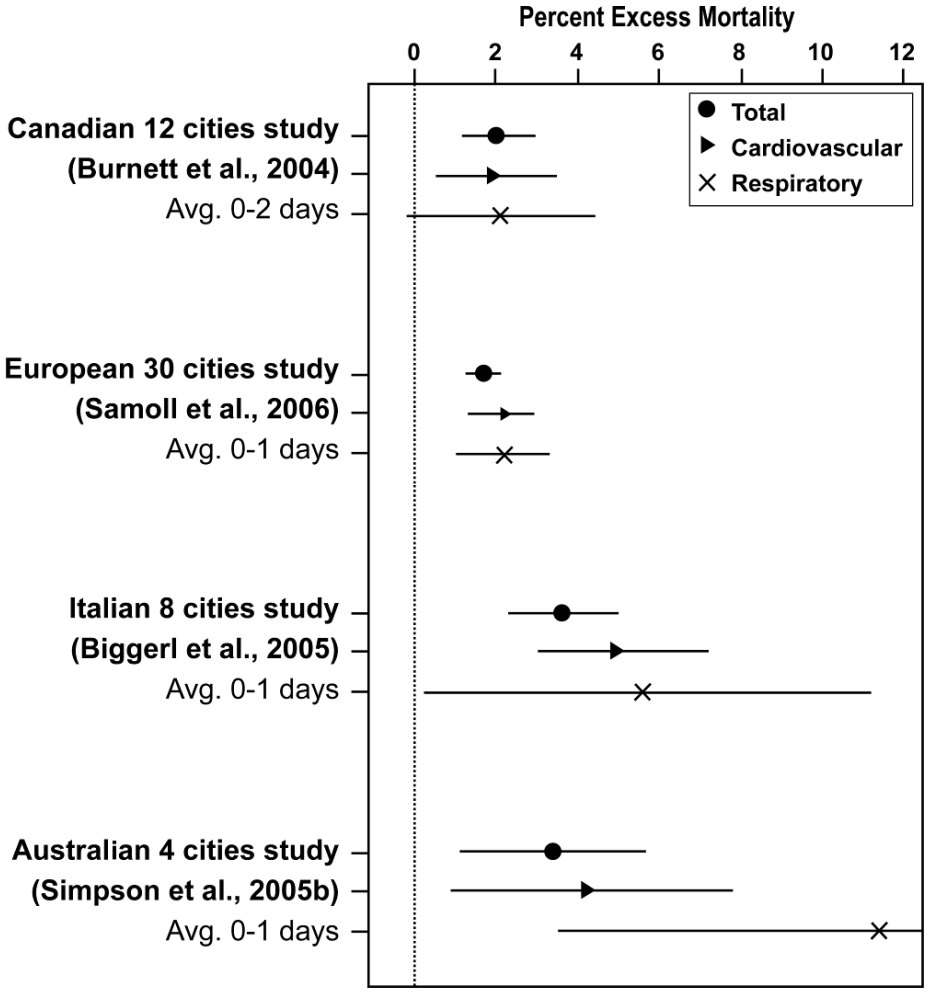



**Figure 3.3-3. Combined $NO_2$ mortality risk estimates for broad cause-specific categories from multicity studies. Risk estimates are computed per 20-ppb increase for 24-h avg or 30-ppb increase for 1-h daily max $NO_2$ concentrations.**

# 3.4. Respiratory Effects Related to Long-Term Exposure

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

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

## 3.4.1. Lung Function Growth

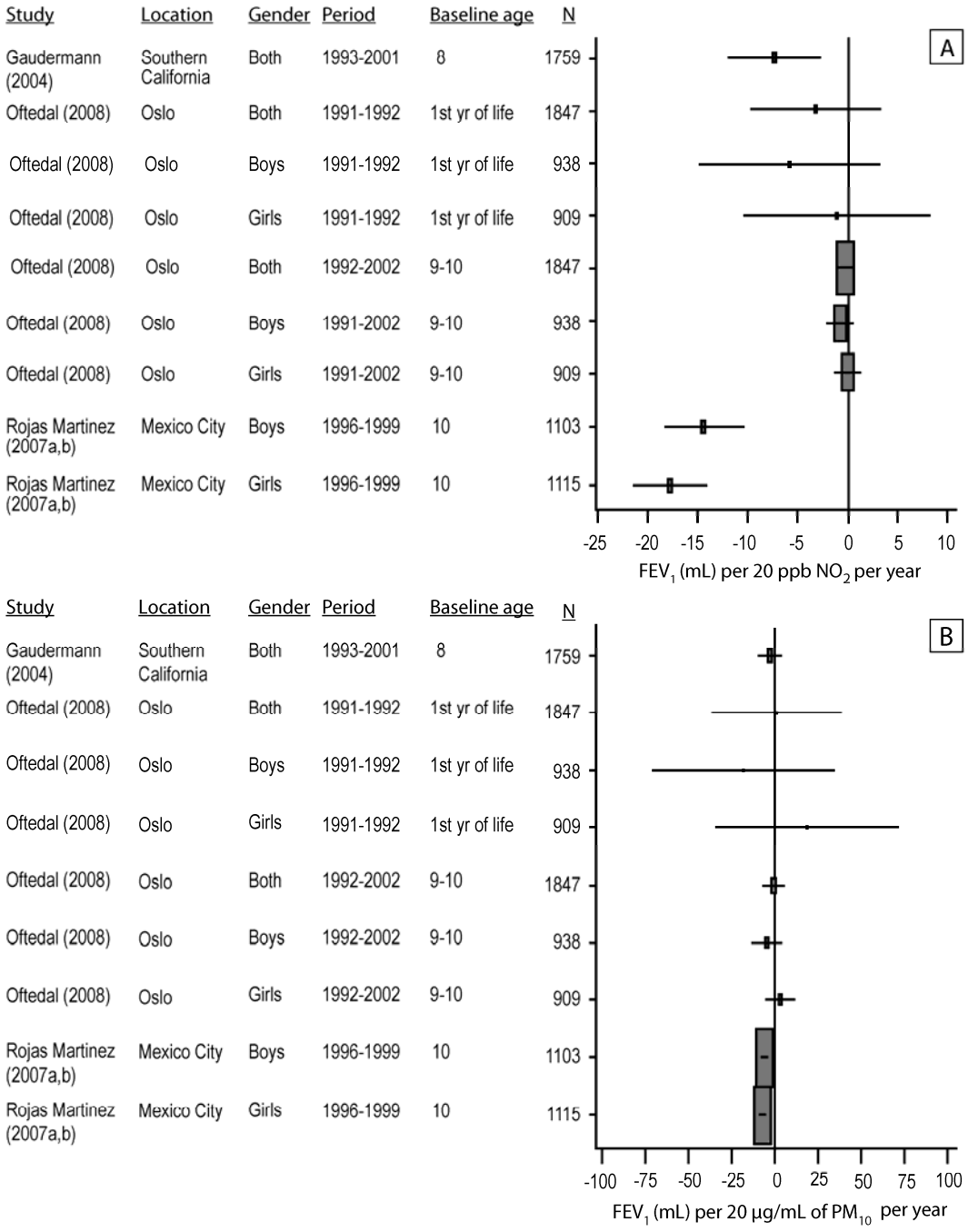
Studies of lung function demonstrate some of the strongest effects of long-term exposure to $NO_2$. Recent cohort studies have examined the effect of long-term exposure to $NO_2$ in both children and adults (see Annex Table AX6.3-15). Forest plots of the results for $FEV_1$ and FVC from three major children's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

The Children's Health Study (CHS) in southern California was a longitudinal cohort study designed to investigate the effect of chronic exposure to several air contaminates (including $NO_2$) on respiratory health in children. Twelve California communities were selected based on historical data indicating different levels of specific pollutants. In each community, monitoring sites were set up to measure hourly $O_3$, $NO_2$, and $PM_{10}$ and 2-week averages of $PM_{2.5}$, and acid vapor. Children in grades 4, 7, and 10 were recruited though local schools. The study followed children for 10 years, with annual questionnaires and lung function measurement. The study had several important characteristics: it was prospective and exposure and outcome data were collected in a consistent manner over the duration of the study, and confounding by SES was controlled in the models by selecting communities similar in demographic characteristics at the outset.

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

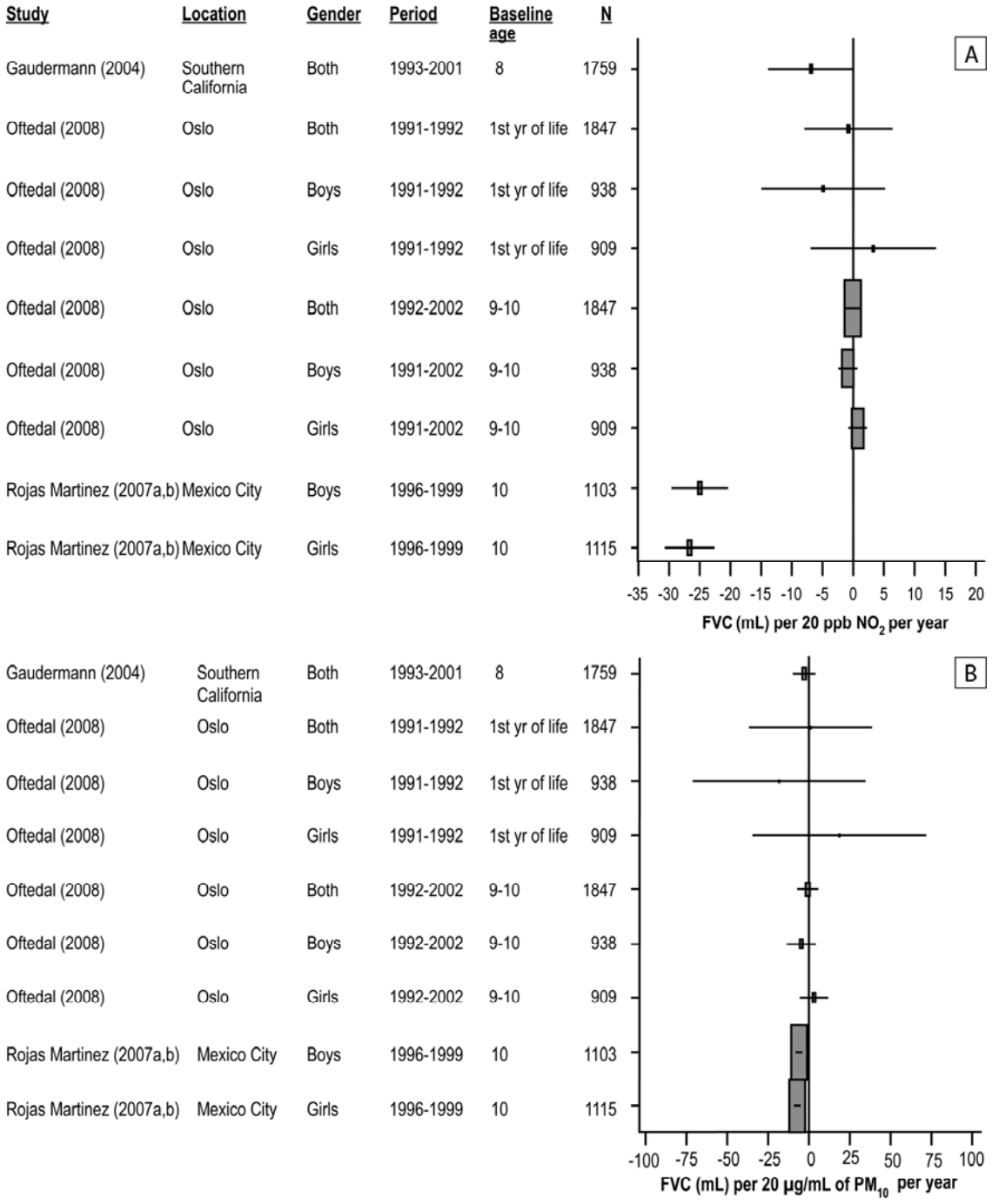
In 2004, Gauderman et al. reported results for an 8-year follow up of the children enrolled in grade 4 (n=1,759). Exposure to $NO_2$ was significantly associated with deficits in lung growth over the 8-year period. The difference in FVC for children exposed to the lowest versus the highest levels of $NO_2$ (34.6 ppb) was -95.0 mL (95% CI: -189.4 to -0.6). For $FEV_1$, the difference was -101.4 mL (95% CI: -165.5 to -38.4), and for MMEF, -221.0 mL/s (95% CI: -377.6, -44.4). Results were similar for boys and girls and among children without a history of asthma. These deficits in growth of lung function resulted in clinically significant differences in $FEV_1$ at age 18. In addition, the $NO_2$ concentration associated with deficits in lung function growth was 34.6 ppb (range of means across communities: 4.4-39.0 ppb), a level below the current standard. Similar results were reported for acid vapor (resulting primarily from photochemical conversions of $NO_X$ to $HNO_3$). These results are depicted in Figure 3.4-3. The authors

concluded that the effects of $NO_2$ could not be distinguished from the effects of particles ($PM_{2.5}$ and $PM_{10}$) as $NO_2$ was strongly correlated with these contaminants (0.79, and 0.67, respectively).



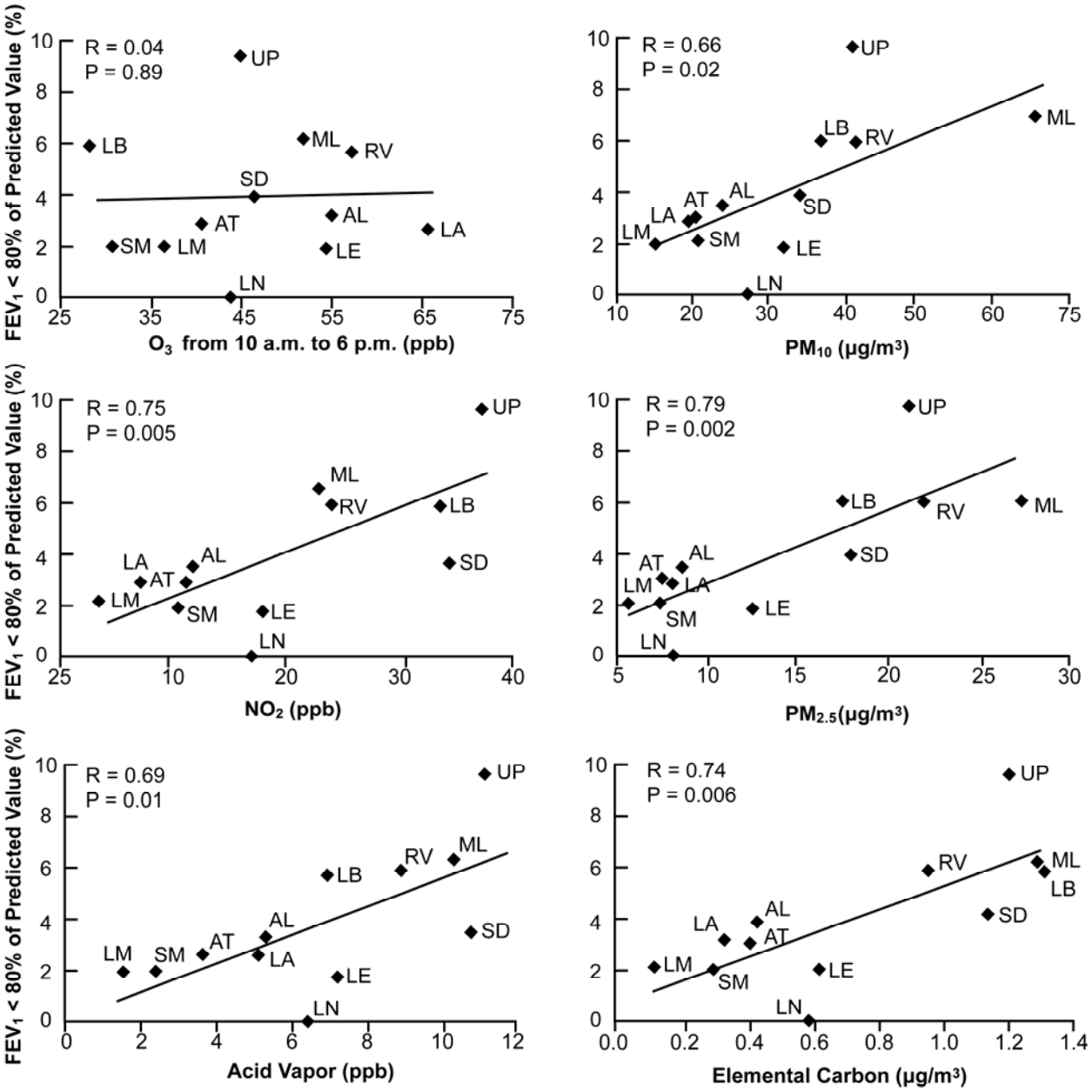

Source: Gauderman et al. (2004); Oftedal et al. (2008), Rojas-Martinez et al. (2007a,b).

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




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

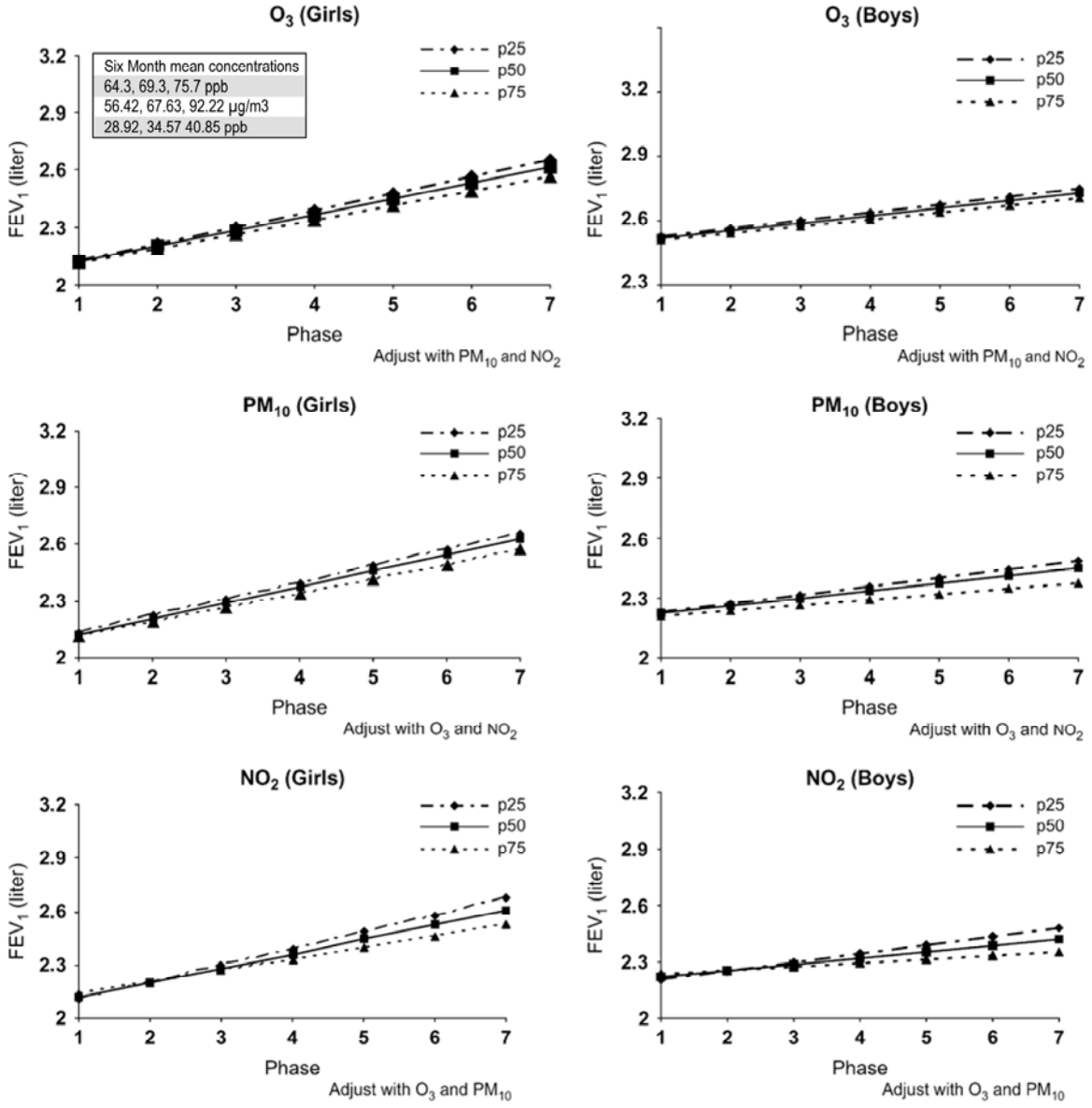
**Figure 3.4-2. Decrements in FVC associated with a 20-ppb increase in $NO_2$ (A) and a 20-µg/m$^3$ increase in $PM_{10}$ (B) in children, standardized per year of follow-up. Results from three major children's long-term cohort studies are presented.**




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

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

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




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

**Figure 3.4-4. Estimated annual growth in $FEV_1$, of $O_3$, $PM_{10}$, and $NO_2$ in girls and boys. Mexico City, 1996 to 1999 (multipollutant models). Adjusted for age, body mass index, height, height by age, weekday time spent in outdoor activities, environmental tobacco smoke exposure, pervious-day mean air pollutant concentration, and study phase of every six months.**

More recently, Gauderman et al. (2007) has reported results of an 8-year follow-up on 3,677 children who participated in the CHS. Children living <500 m from a freeway (n=440) had significant deficits in lung function growth over the 8-year follow-up compared to children who lived at least 1500 m from a freeway. The difference in FVC was -63 mL (-131 to 5); the difference in $FEV_1$ -81 mL (-143 to -18); and the difference in MMEF -127 mL/s (-243 to -11). This study did not attempt to measure specific pollutants near freeways or to estimate exposure to specific pollutants for study subjects. Thus, while the

study presented important findings with respect to traffic pollution and respiratory health in children, it did not provide evidence that $NO_2$ was responsible for these deficits in lung function growth.

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

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

Another cohort study in Oslo, Norway, examined short- and long-term $NO_2$ and other pollutant exposure effects on lung function (PEF, forced expiratory flow at 25% of forced vital capacity [$FEF_{25}$], forced expiratory flow at 50% of forced vital capacity [$FEF_{50}$]) in 2,307 nine- and ten-year-old children (Oftedal et al., 2008). The EPISODE dispersion model (Slordal et al., 2003) was used for the exposure estimate and evaluation concluded that the modeled $NO_2$ and PM levels represent the long- and short-term exposure reasonably well. An incremental change equal to the IQR of lifetime exposure to $NO_2$, $PM_{10}$, and $PM_{2.5}$ was associated with changes in adjusted peak flow of -79 mL/s (95% CI: -128,-31), -66 mL/s (95% CI: -110, -23), and -58 mL/s (95% CI: -94, -21), respectively. Examining short- and long-term $NO_2$ exposures simultaneously yielded only the long-term effects. Adjusting for a contextual socioeconomic factor diminished the association. The association between long-term exposure to $NO_2$ and decreased PEF was comparable to that found in the CHS, but associations with forced volumes were considerably weaker.

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

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

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

Goss et al. (2004) examined the relationship of ambient pollutants on individuals with cystic fibrosis using the Cystic Fibrosis Foundation National Patient Registry in 1999 and 2000. Exposure was assessed by linking air pollution values from the Aerometric Information Retrieval System with the patient's home ZIP code. Associations were reported between PM and exacerbations or lung function changes, but no clear associations were found for $O_3$, $SO_2$, $NO_2$, or CO. The odds of patients with cystic fibrosis having two or more pulmonary exacerbations per 10-ppb $NO_2$ was 0.98 (95% CI: 0.91, 1.01) for the year 2000.

A number of epidemiologic studies examined the effects of long-term exposure to $NO_2$ and observed associations with decrements in lung function and partially irreversible decrements in lung function growth. Decreases in $FEV_1$ ranged from 1 to 17.5 per 20 ppb increase in annual $NO_2$ concentration. Results from the Southern California Children's Health Study indicated that decrements were similar for boys compared to girls, and among children who did not have a history of asthma (Gauderman et al., 2004). The mean $NO_2$ concentrations in these studies range from 21.5 to 34.6 ppb; thus, all have been conducted in areas where mean $NO_2$ levels are below the level of the NAAQS. The epidemiologic studies of long-term exposure to $NO_2$, however, may be confounded by other ambient copollutants. In particular, similar associations have also been found for PM and proximity to traffic (<500 m). The results of the CHS study support an association between decreased lung function growth and a mixture of traffic-related pollutants, but as observed by the authors, it is difficult to distinguish effects for $NO_2$ and other individual pollutants within these mixtures (Gauderman et al., 2004).

## 3.4.2. Asthma Prevalence and Incidence

Several publications from the CHS in southern California reported results on the associations of $NO_2$ exposure with asthma prevalence and incidence. Gauderman et al. (2005) conducted a study of children randomly selected from the CHS with exposure measured at children's homes. Although only 208 were enrolled, exposure to $NO_2$ was strongly associated with both lifetime history of asthma and asthma medications use. Gauderman et al. (2005) measured ambient $NO_2$ with Palmes tubes attached to the subjects' homes at the roofline eaves, signposts, or rain gutters at an approximate height of 2 m above the ground. Samplers were deployed for 2-week periods in both summer and fall. Traffic-related pollutants were characterized by three metrics: (1) proximity of home to freeway, (2) average number of vehicles within 150 meters, and (3) model-based estimates. Yearly average $NO_2$ levels within the 10 communities ranged from 12.9 to 51.5 ppb. The average $NO_2$ concentration measured at home was associated with asthma prevalence (OR=8.33 [95% CI: 1.15, 59.87] per 20-ppb increase) with similar results by season and when taking into account several potential confounders. In each community studied, $NO_2$ was more strongly correlated with estimates of freeway-related pollution than with non-freeway-related pollution. In a related CHS study, McConnell et al. (2006) studied the relationship of proximity to major roads and asthma and also found a positive relationship.

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

Millstein et al. (2004) studied the effects of ambient air pollutants on asthma medication use and wheezing among 2,034 fourth-grade schoolchildren from the CHS. Included in the pollutants examined were $NO_2$ and $HNO_3$. They observed that monthly average pollutant levels produced primarily by photochemistry (i.e., $HNO_3$, acetic acid), but not $NO_2$, were indicative of a positive association with asthma medication use among children with asthma—especially among children who spent more than the

calculated median time outdoors. The March-August OR for $HNO_3$ (IQR 1.64 ppb) was 1.62 (95% CI: 0.94, 2.80) and for $NO_2$ (IQR 5.74 ppb), 0.96 (95% CI: 0.68, 1.37).

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

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

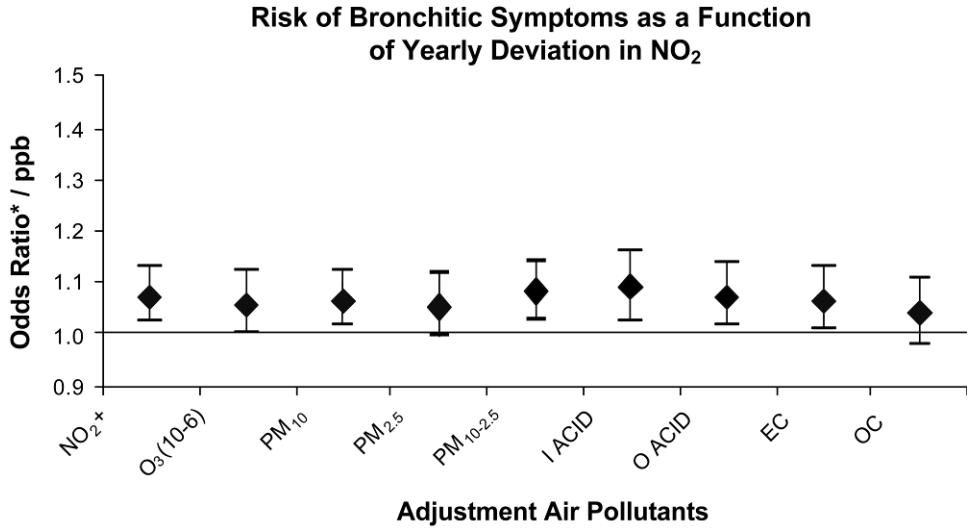
Other studies (see Annex Table AX6.3-16) also have investigated asthma prevalence and incidence in children associated with $NO_2$ exposure. Although several of these studies have reported positive associations, the large number of comparisons made and the limited number of positive results do not support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

Overall, results from the available epidemiologic evidence investigating the association between long-term exposure to $NO_2$ and increases in asthma prevalence and incidence are inconsistent. Two major cohort studies, the Children's Health Study in southern California (Gauderman et al., 2005) and a birth cohort study in the Netherlands (Brauer et al., 2007) observed significant associations; however, several other studies did not find consistent associations between long-term $NO_2$ exposure and asthma outcomes.

## 3.4.3. Respiratory Symptoms

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

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




Source: McConnell et al. (2003).

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

In the Netherlands (Brauer et al., 2002), the same protocol was used to estimate $NO_2$ exposure in a birth cohort of 3,730 infants. However, these study subjects lived in many different communities from rural areas to large cities in northern, central, and western parts of the Netherlands. Forty sites were selected to represent different exposures and measurements were taken as in the Gehring et al. (2002) study. In this study, ear, nose, and throat infections (OR=1.16 [95% CI: 1.00, 1.34]) and physician-diagnosed flu (OR=1.11 [95% CI: 1.00, 1.23]) were marginally significant. The association of $NO_2$ with dry cough at night observed in the German study could not be replicated, nor was $NO_2$ associated with asthma, wheeze, bronchitis, or eczema.

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

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

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

## 3.4.4. Respiratory Morphology

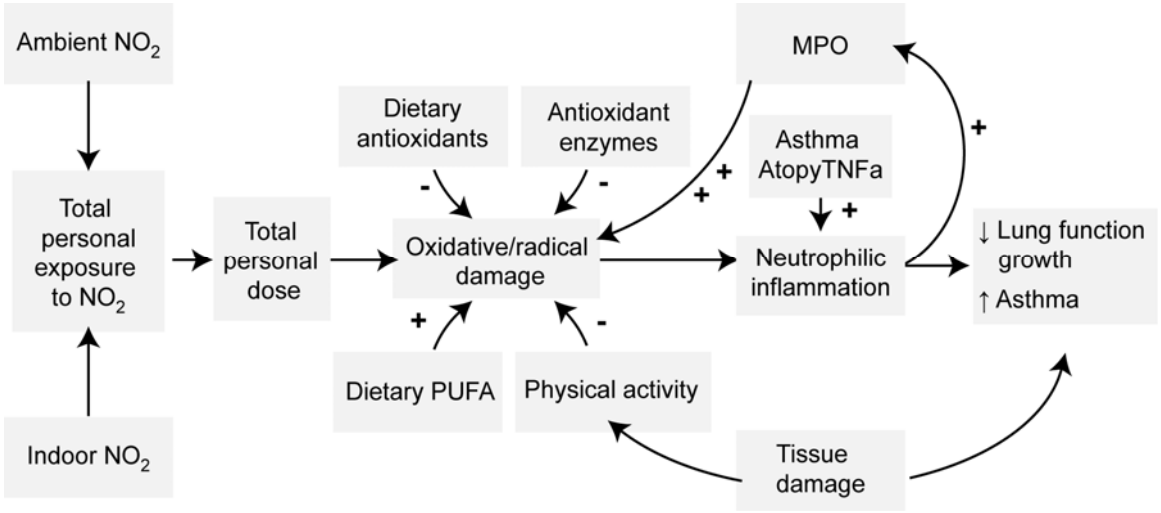
Animal toxicology studies demonstrated morphological changes to the respiratory tract from exposure to $NO_2$ that may provide further biological plausibility for the decrements in lung function growth observed in epidemiologic studies discussed above. Several investigators have studied the temporal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

## 3.4.5. Summary of Respiratory Effects Related to Long-Term Exposure

Overall, the epidemiologic and experimental evidence was suggestive but not sufficient to infer a causal relationship between long-term $NO_2$ exposure and respiratory morbidity. The available database evaluating the relationship between respiratory illness in children associated with long-term exposures to $NO_2$ has increased. Three recent studies in large cohorts in three countries have examined this relationship. The California-based CHS, examining $NO_2$ exposure in children over an 8-year period, demonstrated deficits in lung function growth (Gauderman et al., 2004). This has been observed also in Mexico City, Mexico (Rojas-Martinez et al., 2007a,b), and in Oslo, Norway (Oftedal et al., 2008), with decrements ranging from 1 to 17.5 ml per 20- ppb increase in annual $NO_2$ concentration.

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

Models and/or mechanisms of action for decrements in lung function growth and other respiratory effects from long-term exposure to air pollution are not clearly established. Figure 3.4-6 was adapted from an earlier model discussed by Gilliland et al. (1999), reflective of efforts of the CHS research. Gilliland et al. (1999) proposed that respiratory effects in children from exposure to gaseous and particulate air pollutants result from chronically increased oxidative stress, alterations in immune regulation, and repeated pathologic inflammatory responses that overcome lung defenses to disrupt the normal regulatory and repair processes. Rojas-Martinez et al. (2007a,b) noted that oxidative stress resulting from increased exposure to oxidized compounds ($O_3$, $NO_2$, and particle components) has been identified as a major feature underlying the toxic effects of air pollutants (Kelly et al., 2003; Saxon and Diaz-Sanchez, 2005; Cross et al., 2002). They further noted that the resulting increased expression of enhanced proinflammatory cytokines leads to enhanced inflammatory response (Saxon and Diaz-Sanchez, 2005) and potential chronic lung damage. If this results in permanent loss, it is not clear whether repeated versus average exposure is the major factor. Current data and the nonlinear pattern of childhood lung function growth (Pérez-Padilla et al., 2003) were noted by Rojas-Martinez et al. (2007a,b) as limitations on estimating the impact on lung function attained in early adulthood.




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

**Figure 3.4-6. Biological pathways of long-term $NO_2$ exposure on morbidity.**
**MPO=myeloperoxidase; PUFA=polyunsaturated fatty acids; TNF-α=tumor necrosis factor-alpha.**

Other important biochemical mechanisms examined in animals may provide biological plausibility for the chronic effects of $NO_2$ observed in epidemiologic studies. The main biochemical targets of $NO_2$ exposure appear to be antioxidants, membrane polyunsaturated fatty acids, and thiol groups. Reactions of $NO_2$ with these species in the extracellular lining fluid of the lung leads to the formation of nitrite ($NO_2^-$) and hydrogen ($H^+$) ions. $NO_2$ effects include changes in oxidant/antioxidant homeostasis and chemical alterations of lipids and proteins. Lipid peroxidation has been observed at $NO_2$ exposures as low as 0.04 ppm for 9 months and at exposures of 1.2 ppm for 1 week, indicating lower effect thresholds with longer durations of exposure. Other studies showed decreases in formation of key arachidonic acid metabolites in AMs following $NO_2$ exposures of 0.5 ppm. $NO_2$ has been shown to increase collagen synthesis rates at concentrations as low as 0.5 ppm. This could indicate increased total lung collagen, which is associated with pulmonary fibrosis, or increased collagen turnover, which is associated with remodeling of lung connective tissue. Morphological effects following chronic $NO_2$ exposures have been

identified in animal studies that link to these increases in collagen synthesis and may provide plausibility for the deficits in lung function growth described in epidemiologic studies.

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

In regard to asthma prevalence incidence associated with $NO_2$ long-term exposure, the results are inconsistent. In two major cohort studies, the CHS in southern California and a birth cohort study in the Netherlands, significant associations were reported; however, several other studies did not find consistent associations between long-term $NO_2$ exposure and asthma prevalence.

# 3.5. Other Morbidity Effects Related to Long-Term Exposure

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

## 3.5.1. Cancer Incidence

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

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

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

What is particularly striking in these two studies is the similarity in the estimate of effect. Despite the fact that these two studies were conducted by different investigators, in different countries, using different study designs and different methods for modeling exposure, the odds ratios and CI for exposure per 10 $\mu g/m^3$ (5.2 ppb) and above 30 $\mu g/m^3$ (15.7 ppb) are virtually identical. It is possible that $NO_2$ may

be acting as an indicator of traffic-related carcinogens, and thus the observed increased cancer incidence may be related to exposure of these carcinogens, such as PAHs.

### 3.5.1.1. Animal and In Vitro Carcinogenicity and Genotoxicity Studies

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

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

$NO_2$ has been shown to be positive when tested for genotoxicity in in vitro assays. $NO_2$ is mutagenic in bacteria and in plants. In cell cultures, three studies showed chromosomal aberrations, sister chromatid exchanges (SCEs), and DNA single-strand breaks. However, a fourth study (Isomura et al., 1984) concluded that NO, but not $NO_2$, was mutagenic in hamster cells (see Annex Tables AX4.11, 4.12, and 4.13).

### 3.5.1.2. Toxicological Studies of Coexposure with Known Carcinogens

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

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

damage induced by $NO_2$ and/or $SO_2$ may have resulted in increased cellular permeability of the DEPcCBP particles into the cells.

### 3.5.1.3. Studies in Animals with Spontaneously High Tumor Rates

The frequency and incidence of spontaneously occurring pulmonary adenomas was increased in strain A/J mice (with spontaneously high tumor rates) after exposure to 10-ppm $NO_2$ for 6 h/day, 5 days/week for 6 months (Adkins et al., 1986). These small, but statistically significant, increases were only detectable when the control response from nine groups (n=400) were pooled. Exposure to 1 and 5 ppm $NO_2$ had no effect. In contrast, Richters and Damji (1990) found that an intermittent exposure to 0.25 ppm $NO_2$ for up to 26 weeks decreased the progression of a spontaneous T cell lymphoma in AKR/cum mice and increased survival rates. The investigators attributed this effect to an $NO_2$-induced decrease in the proliferation of T lymphocyte subpopulation in the spleen (especially T-helper/inducer CD+ lymphocytes) that produces growth factors for the lymphoma. A study by Wagner et al. (1965) showed that $NO_2$ may accelerate the production of tumors in CAF1/Jax mice (a strain that has spontaneously high pulmonary tumor rates) after continuous exposure to 5 ppm $NO_2$. After 12 months of exposure, 7/10 mice in the exposed group had tumors, compared to 4/10 in the controls. No differences in tumor production were observed after 14 and 16 months of exposure. A statistical evaluation of the data was not presented.

### 3.5.1.4. Facilitation of Metastases

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

### 3.5.1.5. Production of *N*-Nitroso Compounds and other Nitro Derivatives

Because of evidence that $NO_2$ could produce $NO_2^-$ and $NO_3^-$ in the blood and the fact that $NO_2^-$ is known to react with amines to produce animal carcinogens (nitrosamines), the possibility that $NO_2$ could produce cancer via nitrosamine formation has been investigated. Iqbal et al. (1980) were the first to demonstrate a linear time- and concentration-dependent relationship between the amount of *N*-nitrosomorpholine (NMOR, an animal carcinogen) found in whole-mouse homogenates after the mice were gavaged with 2 mg of morpholine (an exogenous amine that is rapidly nitrosated) and exposure to 15 to 50 ppm $NO_2$ for between 1 and 4 h. In a follow-up study at more environmentally relevant exposures, Iqbal et al. (1981) used dimethylamine (DMA), an amine that is slowly nitrosated to dimethylnitrosamine (DMN). They reported a concentration-related increase in biosynthesis of DMN at $NO_2$ concentrations of as low as 0.1 ppm; however, the rate was significantly greater at concentrations above 10 ppm $NO_2$. Increased length of exposure also increased DMN formation between 0.5 and 2 h, but synthesis of DMN was less after 3 or 4 h of exposure than after 0.5 h.

Mirvish et al. (1981) concluded that the results of Iqbal et al. (1980) were technically flawed, but they found that in vivo exposure to $NO_2$ could produce a nitrosating agent (NSA) that would nitrosate morpholine only when morpholine was added in vitro. Further experiments showed that the NSA was localized in the skin (Mirvish et al., 1983) and that mouse skin cholesterol was a likely NSA (Mirvish

et al., 1986). It has also been reported that only very lipid-soluble amines, which can penetrate the skin, would be available to the NSA. Compounds such as morpholine, which are not lipid-soluble, could only react with $NO_2$ when painted directly on the skin (Mirvish et al., 1988). Iqbal (1984), responded to the Mirvish et al. (1981) criticisms, verifing their earlier (Iqbal et al., 1980) studies.

The relative contribution of $NO_2^-$ from $NO_2$ compared with other $NO_2^-$ sources such as food, tobacco, and nitrate-reducing oral bacteria is uncertain. Nitrosamines have not been detected in tissues of animals exposed by inhalation to $NO_2$ unless precursors to nitrosamines and/or inhibitors of nitrosamine metabolism are coadministered. Rubenchik et al. (1995) could not detect *N*-nitrosodimethylamine (NDMA) in tissues of mice exposed to 7.5- to 8.5-mg/$m^3$ $NO_2$ for 1 h. NDMA was found in tissues, however, if mice were simultaneously given oral doses of amidopyrine and 4-methylpyrazole, an inhibitor of NDMA metabolism. Nevertheless, the main source of $NO_2^-$ in the body is endogenously formed, and food is also a contributing source of nitrite (from nitrate conversion).

## 3.5.1.6. Summary of Cancer Incidence Related to Long-Term Exposure

In summary, two epidemiologic studies conducted in Europe showed an association between long-term $NO_2$ exposure, used as an indicator of traffic exposure, and incidence of cancer (Nyberg et al., 2000; Nafstad et al., 2003); however, the animal toxicological studies have provided no clear evidence that $NO_2$ directly acts as a carcinogen, though it does appear to act as a tumor promoter at the site of contact (Section 3.5.1). There are no in vivo studies that support that $NO_2$ causes teratogenesis or malignant tumors. Only very high exposure studies, i.e., levels not relevant to ambient $NO_2$ levels, demonstrated increased chromosomal aberrations and mutations in in vitro studies. A more likely pathway for $NO_2$ involvement in cancer induction is through secondary formation of nitro-PAHs, as nitro-PAHs are known to be more mutagenic than their parent compounds. The evidence for a causal relationship between $NO_2$ and increased cancer risk is inadequate to infer the presence or absence of a causal relationship at this time.

The information presented in this section is relevant to potential mechanisms by which exposure to products formed by reaction of gaseous nitrogen oxides with organic compounds can be carcinogenic. As discussed previously in Section 2.2, nitro-PAHs and other nitrated organic compounds can be produced through reactions of $NO_2$ or NO with organic compounds in the atmosphere. Nitro-PAHs are largely found on particles, and they can also be including in direct emissions of particles, such as diesel exhaust particles. Effects of particulate nitrogen compounds have been considered in previous reviews of the PM NAAQS. In addition, it is possible that the products of $NO_2$ ($NO_2^-$ and $NO_3^-$) could produce carcinogens (e.g., *N*-nitrosomorpholine) through exposure from an environmentally occurring precursor compound (e.g., morpholine) within the body. The studies demonstrated that this is a possible mechanism; however, it should be pointed out that (1) that these studies used only a single precursor compound whereas humans would be exposed to multiple precursor compounds thus producing an array of nitrosamines and other nitrated compounds, (2) the level of nitrosamines per se produced in this fashion would be small compared to the nitrosamines that come from cigarette smoke, smoked meats, and other food sources and from the atmospheric transformation of products in the ambient air, and (3) a wide array of nitrated products are produced in the ambient air with a number of these products known to be carcinogens and/or mutagens.

### Cardiovascular Effects

One epidemiologic study examined the association of cardiovascular effects with long-term exposure to $NO_2$. Miller et al. (2007) studied 65,893 postmenopausal women between the ages of 50 and 79 years without previous CVD in 36 U.S. metropolitan areas from 1994 to 1998. They examined the association between one or more fatal or nonfatal cardiovascular events and the women's exposure to air pollutants. Subject's exposures to air pollution were estimated by assigning the annual mean levels of air

pollutants in 2000 measured at the monitor nearest the residence based on its five-digit ZIP Code centroid, which resulted in a more spatially resolved exposure estimate. A total of 1,816 women had one or more fatal or nonfatal cardiovascular events, including 261 deaths from cardiovascular causes. The main focus of the study was $PM_{2.5}$, but the overall CVD events (but not results for death events only) using all the copollutants ($PM_{10}$, $PM_{10}$-2.5, $SO_2$, $NO_2$, CO, and $O_3$) in both single- and multipollutant models were presented. The results for the models only including subjects with non-missing exposure data (n=28,402 subjects resulting in 879 CVD events) are described here. In the single-pollutant model results, $PM_{2.5}$ showed the strongest associations with the CVD events by far among the pollutants, followed by $SO_2$. $NO_2$ did not show any association with the overall CVD events (heart rate [HR]=0.98 [95% CI: 0.89, 1.08] per 10-ppb increase in the annual average). In the multipollutant model, which included all the pollutants, the association of $PM_{2.5}$ and $SO_2$ with overall CVD events became even stronger. $NO_2$ became negatively associated with the overall CVD events (HR=0.82 [95% CI: 0.70, 0.95]). Correlations among these pollutants were not described; therefore, it was not possible to estimate the extent of confounding among these pollutants in these associations, but it is clear that $PM_{2.5}$ was the best predictor of the CVD events.

Limited toxicology data exist on the effect of $NO_2$ on the heart. Alterations in vagal responses have been shown to occur in rats exposed to 10 ppm $NO_2$ for 24 h; however, exposure to 0.4 ppm $NO_2$ for 4 weeks revealed no change (Tsubone and Suzuki, 1984). $NO_2$-induced effects on cardiac performance were indicated by a significant reduction in the pressure of oxygen in arterial blood ($PaO_2$) in rats exposed to 4.0 ppm $NO_2$ for 3 months. When exposure was decreased to 0.4-ppm $NO_2$ over the same exposure period, $PaO_2$ was not affected (Suzuki et al., 1981). In addition, a reduction in HR has been reported in mice exposed to both 1.2 and 4.0 ppm $NO_2$ for 1 month (Suzuki et al., 1984). Whether these effects were the direct result of $NO_2$ exposure or secondary responses to lung edema and changes in blood hemoglobin content was 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 in response to a 24-week exposure of 0.16 ppm $NO_2$.No effects on hematocrit and hemoglobin have been reported in squirrel monkeys exposed to 1.0 ppm $NO_2$ for 16 months (Fenters et al., 1973) or in dogs exposed to ≤ 5.0 ppm $NO_2$ for 18 months (Wagner et al., 1965). There were, however, polycythemia and an increased ratio of PMNs to lymphocytes in rats exposed to 2.0 and 1.0 ppm $NO_2$ for 14 months (Furiosi et al., 1973).

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

## 3.5.2. Reproductive and Developmental Effects

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

While most studies analyzed average $NO_2$ exposure for the whole pregnancy, many also considered exposure during specific trimesters or other time periods. Fetal growth, for example, is much more variable during the third trimester. Thus, studies of fetal growth might anticipate that exposure during the third trimester would have the greatest likelihood of an association, as is true for the effect of maternal smoking during pregnancy. However, growth can also be affected through placentation, which occurs in

the first trimester. Similarly, preterm delivery might be expected to be related to exposure early in pregnancy affecting placentation, or through acute effects occurring just before delivery.

Of three studies conducted in the U.S., one (Bell et al., 2007) reported a significant decrease in birthweight associated with exposure to $NO_2$ among mothers in Connecticut and Massachusetts. The two studies conducted in California did not find associations between $NO_2$ exposure and any adverse birth outcome (Ritz et al., 2000; Salam et al., 2005). Differences in these studies that may have contributed to the differences in results included the following: sample size, exposure assessment methods, average $NO_2$ concentration, and different pollution mixtures. The results reported by Bell et al. (2007) had the largest sample size and, therefore, greater power to assess small increases in risk. The two California studies reported higher mean concentrations of NO, but also strong correlations of $NO_2$ exposure with PM mass and CO.

Annex Table AX6.3-12 lists seven studies that investigated the relationship of ambient $NO_2$ exposure with birth weight. Since low birth weight may result from either inadequate growth in utero or delivery before the usual 40 weeks of gestation, three of the authors only considered low birth weight (<2500 g [5 lbs, 8 oz]) in full-term deliveries (>37 weeks); the other four controlled for gestational age in the analysis. When correlations with other pollutants were reported in these studies, they ranged from 0.5 to 0.8. All of these studies reported strong effects for other pollutants.

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

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

Three studies (see Annex Table AX6.3-14) specifically investigated fetal growth by comparing birth weight for gestational age with national standards. Two of these studies reported associations between small for gestational age and $NO_2$ exposure. Mannes et al. (2005) determined increased risk for exposure in trimesters 2 and 3, while Liu et al. (2003) reported risks associated only with $NO_2$ exposure in the first month of pregnancy. In all three studies, $NO_2$ exposure was correlated with CO exposure (r=0.69, 0.57, 0.72 in the three studies) (Salam et al., 2005; Mannes et al., 2004; Liu et al., 2003).

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

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

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

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

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

### 3.5.2.1. Summary of Reproductive and Developmental Effects Related to Long-Term Exposure

In summary, the epidemiologic evidence did not consistently report associations between $NO_2$ exposure and intrauterine growth retardation; however, some evidence is accumulating for effects on preterm delivery. Similarly, scant animal evidence supported a weak association between $NO_2$ exposure and adverse birth outcomes and provided little mechanistic information or biological plausibility for an association between long-term $NO_2$ exposure and reproductive or developmental effects.

## 3.5.3. Summary of Other Morbidity Effects Related to Long-Term Exposure

Epidemiologic and toxicological studies evaluating limited evidence of cancer incidence, cardiovascular effects, and reproductive and developmental effects linked to long-term $NO_2$ exposure were presented. The epidemiologic studies report some associations between long-term $NO_2$ exposure on

adverse birth outcomes and cancer incidence; however, $NO_2$ is specifically used as an indicator of traffic exposure in the studies of cancer incidence. Animal studies did not provide mechanistic information to support these observational findings. Some toxicological studies demonstrated an effect of $NO_2$ exposure on cardiovascular endpoints. However, whether these effects are the direct result of $NO_2$ exposure or secondary responses to lung edema and changes in blood hemoglobin content are not known. Similar findings were reported in the epidemiologic literature for short-term exposures only. Thus, while some individual associations may be reported for these effects, the findings are inconsistent and there is no evidence supporting coherence or plausibility in the data. Overall, these data are inadequate to infer the presence or absence of a causal relationship.

# 3.6. Mortality Related to Long-Term Exposure

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

## 3.6.1. U.S. Studies on Mortality Related to Long-Term Exposure

Dockery et al. (1993) conducted a prospective cohort study to examine the effects of air pollution, focusing on PM components, in six U.S. cities, which were chosen based on the levels of air pollution (with Portage, WI being the least polluted and Steubenville, OH, the most polluted). In this study, a 14-to-16-year mortality follow-up of 8,111 adults in the six cities was conducted. Fine particles were the strongest predictor of mortality; $NO_2$ was not analyzed in this study. Krewski et al. (2000) conducted a sensitivity analysis of the Harvard Six Cities study and examined associations between gaseous pollutants (i.e., $O_3$, $NO_2$, $SO_2$, CO) and mortality. $NO_2$ showed risk estimates similar to those for $PM_{2.5}$ per "low to high" range increment with total (1.15 [95% CI: 1.04, 1.27] per 10-ppb increase), cardiopulmonary (1.17 [95% CI: 1.02, 1.34]), and lung cancer (1.09 [95% CI: 0.76, 1.57]) deaths; however, in this dataset $NO_2$ was highly correlated with $PM_{2.5}$ (r=0.78), $SO_4^{2-}$ (r=0.78), and $SO_2$ (r=0.84).

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

Lipfert et al. (2000a) conducted an analysis of a national cohort of ~70,000 male U.S. military veterans who were diagnosed as hypertensive in the mid 1970s and were followed up for about 21 years (up to 1996). This cohort was 35% black and 81% had been smokers at one time. Thus, unlike other cohort studies described in this section, this hypertensive cohort with a very high smoking rate is not representative of the U.S. population. Total suspended particulates (TSP), $PM_{10}$, CO, $O_3$, $NO_2$, $SO_2$, $SO_4^2$, $PM_{2.5}$, and $PM_{10}$-2.5 were considered. The county of residence at the time of entry to the study was used

to estimate exposures. Four exposure periods (1960-1974, 1975-1981, 1982-1988, and 1989-1996) were defined, and deaths during each of the three most recent exposure periods were considered. Lipfert et al. (2000a) noted that the pollution risk estimates were sensitive to the regression model specification, exposure periods, and the inclusion of ecological and individual variables. The authors reported that indications of concurrent mortality risks were found for $NO_2$ (the estimate was not given with confidence bands) and peak $O_3$. Their subsequent analysis (Lipfert et al., 2003) reported that the air pollution-mortality associations were not sensitive to the adjustment for blood pressure. Lipfert et al. (2006a) also examined associations between traffic density and mortality in the same cohort, whose follow-up period was extended to 2001. They reported that traffic density was a better predictor of mortality than the ambient air pollution variables, with the possible exception of $O_3$. The log-transformed traffic density variable was moderately correlated with $NO_2$ (r=0.48) and $PM_{2.5}$ (r=0.50) in this data set. For the 1989 to 1996 data period (the period that generally showed the strongest associations with exposure variables among the four periods), the estimated mortality relative risk for $NO_2$ was 1.025 (95% CI: 0.983, 1.068) per 10-ppb increase in a single-pollutant model. The two-pollutant model with the traffic density variable reduced $NO_2$ risk estimates to 0.996 (95% CI: 0.954, 1.040). Interestingly, as the investigators pointed out, the risk estimates due to traffic density did not vary appreciably across these four periods. They speculated that other environmental factors such as particles from tire, traffic noise, spatial gradients in socioeconomic status might have been involved. Lipfert et al. (2006b) further extended analysis of the veteran's cohort data to include one year of the EPA's Speciation Trends Network (STN) data, which collected chemical components of $PM_{2.5}$. As in the previous Lipfert et al. (2006a) study, traffic density was the most important predictor of mortality, but associations were also seen for EC, vanadium, $NO_3$–, and nickel. $NO_2$, $O_3$, and $PM_{10}$ also showed positive but weaker associations. The risk estimate for $NO_2$ was 1.043 (95% CI: 0.967, 1.125) per 10-ppb increase in a single-pollutant model. Multipollutant model results were not presented for $NO_2$ in this updated analysis. The results from the series of studies by Lipfert et al. are indicative of a traffic-related air pollution effect on mortality, but the study population (hypertensive with very high smoking rate) was not representative of the general U.S. population.

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

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

averaging in the ACS study and county-level averaging in the veterans' study. Traffic density and other pollutants that showed mortality associations in the veterans study, including EC and $NO_2$, were more localized pollutants; therefore, using county-level aggregation, rather than MSA-level, may have resulted in smaller exposure misclassification.

## 3.6.2. European Studies on Mortality Related to Long-Term Exposure

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

Hoek et al. (2002) investigated a random sample of 5,000 subjects from the Netherlands Cohort Study on Diet and Cancer (NLCS) ages 55 to 69 from 1986 to 1994. Long-term exposure to traffic-related air pollutants (black smoke and $NO_2$) was estimated using 1986 home addresses. Exposure was estimated with the measured regional and urban background concentration and an indicator variable for living near major roads. Cardiopulmonary mortality was associated with living near a major road (RR=1.95 [95% CI: 1.09, 3.52]) and less strongly with the estimated air pollution levels (e.g., for $NO_2$, RR=1.32 [95% CI: 0.88, 1.98] per 10-ppb increase). The risk estimate for living near a major road was 1.41 (95% CI: 0.94, 2.12) for total mortality. For estimated $NO_2$ (incorporating both background and local impact), the RR was 1.15 (95% CI: 0.60, 2.23) per 10-ppb increase). Because the $NO_2$ exposure estimates were modeled, interpretation of their risk estimates was not straightforward. However, these results did support that $NO_2$, as a marker of traffic-related air pollution, was associated with these mortality outcomes.

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

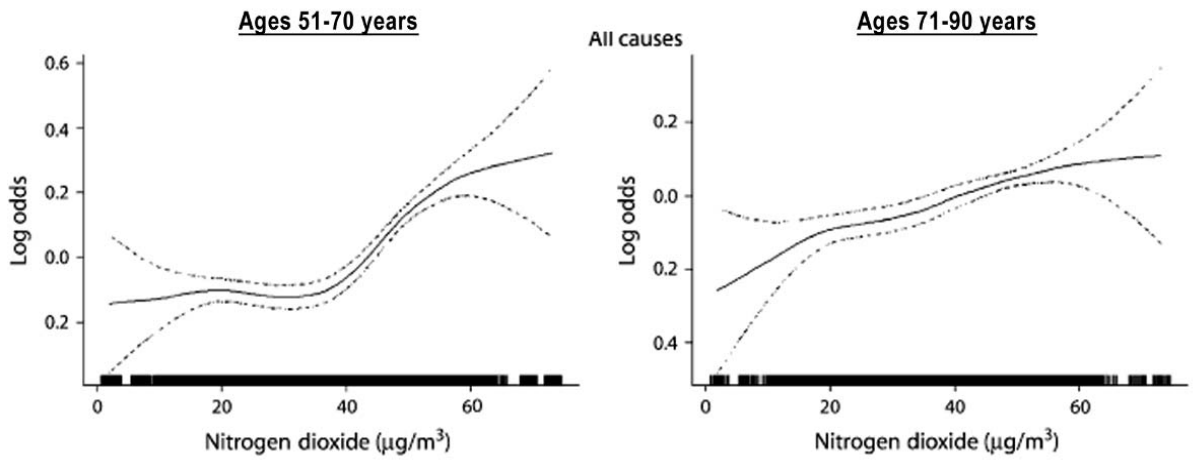
Nafstad et al. (2004) investigated the association between mortality and long-term air pollution exposure in a cohort of 16,209 Norwegian men followed from 1972/1973 through 1998. PM was not considered in this study because measurement methods changed during the study period. $NO_X$, rather than $NO_2$, was used. Exposure estimates for $NO_X$ and $SO_2$ were constructed using models based on subjects' addresses and emission data for industry, heating, and traffic measured concentrations. Addresses linked to 50 of the busiest streets were given an additional exposure based on estimates of annual average daily traffic. The adjusted risk estimate for total mortality was 1.16 [95% CI: 1.12, 1.22] for a 10-ppb increase in the estimated exposure to $NO_X$. Corresponding mortality risk estimates for respiratory causes other than lung cancer was 1.16 (95% CI: 1.06, 1.26); for lung cancer, 1.11 (95% CI: 1.03, 1.19); and for ischemic heart diseases, 1.08 (95% CI: 1.03, 1.12). $SO_2$ did not show similar associations. The risk estimates presented for categorical levels of these pollutants showed mostly monotonic exposure-response relationships for $NO_X$. These results are indicative of the effects of traffic-related air pollution on long-term mortality, but $NO_X$ likely represented the combined effects of that source, possibly including PM, which could not be analyzed in this study. A case-control study of 1,043 men aged 40 to 75 with lung cancer and 2,364 controls in Stockholm County (Nyberg et al., 2000) reported similar results to this

study. They mapped residence addresses to a GIS database indicating 4,300 traffic-related line sources and 500 point sources of $NO_2$ exposure. Exposure was derived from a model validated by comparison to actual measurements of $NO_2$ at six sites. Exposure to 10 ppb $NO_2$ was associated with an OR of 1.20 (95% CI: 0.94 1.49). Exposure to the 90th percentile (≥ 29.26 μg/$m^3$ 915.5 ppb]) of $NO_2$ was associated with an OR of 1.44 (95% CI: 1.05, 1.99).

Gehring et al. (2006) investigated the relationship between long-term exposure to air pollution originating from traffic and industrial sources, and total and cause-specific mortality in a cohort of women living in North Rhine-Westphalia, Germany. The area includes the Ruhr region, one of Europe's largest industrial areas. Approximately 4,800 women (age 50 to 59 years) were followed for vital status and migration. Exposure to air pollution was estimated by GIS models using the distance to major roads, $NO_2$, and $PM_{10}$ (estimated from 0.71 X TSP, based on available $PM_{10}$ and TSP data in the area) concentrations from air monitoring station data. Cardiopulmonary mortality was associated with living within a 50-m radius of a major road (RR=1.70 [95% CI: 1.02, 2.81]) and $NO_2$ (RR=1.72 [95% CI: 1.28, 2.29] per 10-ppb increase in annual average). Exposure to $NO_2$ was also associated with all-cause mortality (1.21 [95% CI: 1.03, 1.42] per 10 ppb increase). $NO_2$ was generally more strongly associated with mortality than the indicator for living near a major road (within versus beyond a 50-m radius) or $PM_{10}$.

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

Most of the European cohort studies estimated an individual subject's exposure based on spatial modeling using emission and concentration data. These studies may have provided more accurate exposure estimates than the community-level air pollution estimates typically used in the U.S. studies. However, because they generally involved modeling with such information as traffic volume and other emission estimates in addition to monitored concentrations, additional uncertainties may have been introduced. Thus, validity and comparability of various methods may need to be examined. In addition, because the relationship between the concentration measured at the community monitors and the health effects was ultimately of interest in this ISA, interpreting the risk estimates based on individual-level exposures will require an additional step to translate the difference. Finally, a more accurate exposure estimate does not solve the problem of the surrogate role that $NO_2$ may play. Most of these studies did acknowledge this issue and generally treated $NO_2$ as a surrogate marker, but the extent of such surrogacy and confounding with other traffic- or combustion-related pollutant was not clear at this point. In the Hoek et al. study (2002), the indicator of living near a major road was a better predictor of mortality than the estimated $NO_2$ exposures. In the Gehring et al. (2006) study, the estimated $NO_2$ exposure was a better predictor of total and cardiopulmonary mortality than the indicator of living near a major road. Comparing the results for the indicators of living near a major road and the estimated $NO_2$ or $NO_X$ exposures is not straightforward, but it is possible that, depending on the presence of other combustion sources (e.g., the North Rhine-Westphalia area included highly industrial areas), $NO_2$ may represent more than traffic-related pollution.




Source: Næss et al. (2007).

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

## 3.6.3. Summary of Mortality Related to Long-Term Exposure

Figure 3.6-2 summarizes the $NO_2$ relative risk estimates for total mortality from the studies reviewed in the previous sections. The relative risk estimates are grouped by those that used community- or ecologic-level exposure estimates and those that used individual-level exposure estimates, but because of the small number of studies listed, no systematic pattern could be elucidated. The relative risk estimates for total mortality ranged from 1.0 to 1.28 per 10-ppb increase in annual or longer averages of $NO_2$.

Potential confounding by copollutants needs to be considered in the interpretation of the $NO_2$ risk estimates. Not all of the studies presented correlations between $NO_2$ and other pollutants, but those that did indicated generally moderate to high correlations. For example, in the Harvard Six Cities study (Krewski et al, 2000), the French study (Filleul et al., 2005), and the German study (Gehring et al., 2006), the correlation between $NO_2$ and PM indices ranged from 0.72 to 0.8. The high correlations between $NO_2$ and PM indicated possible confounding between these pollutants. Further, the results from the Netherlands study (Hoek et al., 2002), that living near major roads was more strongly associated with mortality than $NO_2$, supported a possible surrogate role of $NO_2$ as a marker of traffic-related pollution. However, this does not preclude the possibility of $NO_2$ playing a role in interactions among the traffic-related pollutants. Essentially no information was available on the possible effect modification of apparent $NO_2$-mortalty associations.

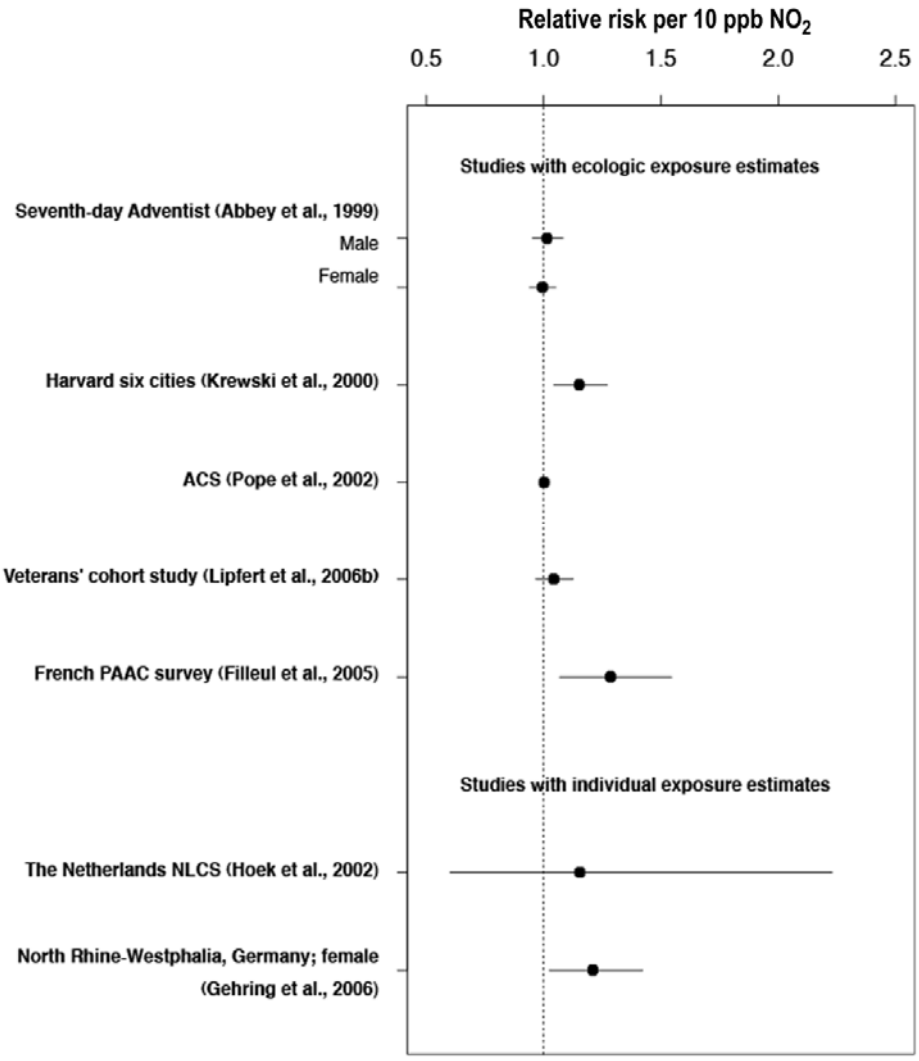



**Figure 3.6-2. Total mortality relative risk estimates from long-term studies. The original estimate for the Norwegian study was estimated for $NO_X$. Conversion of $NO_2$=0.35 X $NO_X$ was used.**

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

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

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

# Chapter 4. Public Health Impact

This chapter discusses several issues relating to the broader public health impact of exposure to $NO_X$. First, concepts related to defining adverse health effects are discussed. Second, the concentration-response relationship for $NO_2$ and evidence for thresholds (the concentration of $NO_2$ that must be exceeded to elicit a health response) are discussed, with consideration of the limited evidence available to assess individual and population threshold values for health effects. The next section identifies characteristics of subpopulations that may experience increased risks from $NO_2$ exposures, through either enhanced susceptibility (i.e., as a result of an intrinsic condition such as pre-existing disease, genetic factors, age) and/or differential vulnerability associated with increased exposure (e.g. residing close to roadways). In the final section the size of the potentially susceptible and vulnerable populations in the U.S. is discussed.

## 4.1. Defining Adverse Health Effects

A recent American Thoracic Society (ATS) statement (ATS, 2000b) updated the guidance for defining adverse respiratory health effects published 15 years earlier (ATS, 1985), taking into account new investigative approaches used to identify the effects of air pollution and reflecting concern for impacts of air pollution on specific susceptible groups. In the 2000 update, there was an increased focus on quality-of-life measures as indicators of adversity and a more specific consideration of population risk. An increased risk to the entire population was identified as adverse, even though it may not increase the risk of any identifiable individual to an unacceptable level (ATS, 2000b). For example, a population of asthmatics could have a distribution of lung function such that no individual demonstrates impairment. Exposure to air pollution could adversely shift the distribution,without demonstrable clinical effects. This distribution shift would be considered adverse because individuals would have diminished reserve function, putting them at increased risk if affected by another agent or as a result of aging.

The 2006 Ozone AQCD (U.S. Environmental Protection Agency, 2006a) provided information useful in helping to define adverse health effects associated with ambient $O_3$ exposure by describing the gradation of severity of respiratory effects. The definitions that relate to responses in impaired persons are presented in Table 4.1-1. The severity of effects described in the table is valid and reasonable in the context of the new ATS (2000b) statement, and can be applied to $NO_2$ exposure.

As assessed in detail in Chapter 3, Section 3.1, exposures to a range of $NO_2$ concentrations have been reported to be associated with increased severity of health effects, such as respiratory symptoms, ED visits and hospital admission for respiratory causes. The adverse effects associated with $NO_2$ exposure are anticipated to lead to a shift in the population distribution of reserve capacity for exposed individuals, and/or increase the proportion of severe responses across a broad spectrum of respiratory outcomes. These adverse outcomes have the potential to impair the quality of life among those affected.

**Table 4.1-1. Gradation of individual responses to short-term $NO_2$ exposure in persons with impaired respiratory systems.**

| SYMPTOMATIC RESPONSE | NORMAL | MILD | MODERATE | SEVERE |
|---|---|---|---|---|
| Wheeze | None | With otherwise normal breathing | With shortness of breath | Persistent with shortness of breath |
| Cough | Infrequent Cough | Cough with deep breath | Frequent spontaneous cough | Persistent uncontrollable cough |
| Chest pain | None | Discomfort just noticeable on exercise or deep breath | Marked discomfort on exercise or deep breath | Severe discomfort on exercise or deep breath |
| Duration of response | None | <4 h | 4 – 24 h | >24 h |
| **FUNCTIONAL RESPONSE** | **NONE** | **SMALL** | **MODERATE** | **LARGE** |
| $FEV_1$ change | Decrements of <3% | Decrements of 3 -10% | Decrements of 10-20% | Decrements of ≥ 20% |
| Bronchial responsiveness | Within normal range | Increases of <100% | Increases of 100-300% | Increases of >300% |
| Specific airway resistance (sRaw) | Within normal range (± 20%) | sRaw increased <100% | sRaw increased 100-200% or up to 15 cm $H_2O \cdot s$ | sRaw increased >200% or more than 15 cm $H_2O \cdot s$ |
| Duration of response | None | <4 h | 4 – 24 h | >24 h |
| **IMPACT OF RESPONSES** | **NORMAL** | **MILD** | **MODERATE** | **SEVERE** |
| Interference with normal activity | None | Few persons choose to limit activity | Many persons choose to limit activity | Most persons choose to limit activity |
| Medical treatment | No change | Normal medication as needed | Increased frequency of medication use or additional medication | Physician or emergency department visit |

An increase in bronchial responsiveness of 100% is equivalent to a 50% decrease in provocative dose that produces a 20% decrease in $FEV_1$ (PD20) or provocative dose that produces a 100% increase in sRaw (PD100). Source: This table is adapted from the 2006 $O_3$ AQCD (Table 8-3, page 8-68) (U.S. Environmental Protection Agency, 2006a).

# 4.2. Concentration-Response Functions and Potential Thresholds

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

Human clinical studies typically provide individual-level response data in relation to different levels of $NO_2$. The percentage of individuals showing responses across a range of $NO_2$ exposures, the interindividual variability in response and the concentration at which an individual begins to respond can often be determined based on these studies. The previous assessment concluded that human clinical studies provided evidence that some asthmatics are more susceptible to the effects of $NO_2$ but a concentration-response relationship was not evident (U.S. Environmental Protection Agency, 1993). Findings from recent human clinical studies do not provide evidence that would change the previous conclusion (see Chapter 3). Inconsistencies in clinical findings could be due to a sensitive subpopulation

not well represented in human clinical studies or peculiarities in protocols necessary to elicit a response. Such peculiarities might include an unanticipated time course for a response not well captured in human clinical studies or other factors that influence a response that may not be measured in all human clinical studies (i.e., prior allergen sensitization by allergen or infectious agent).

Epidemiologic studies evaluate population-level responses, rather than individual responses. Low data density in the lower concentration range, response measurement error, exposure measurement error, and a shallow slope are some of the factors that complicated the ability to determine the shape of the concentration-response curve. A sigmoidal or S-shaped curve with a shallow slope may approximate linearity over a wide range of concentrations, making it difficult to characterize the exact nature of the concentration-response relationship. Biological characteristics that tend to linerarize concentration-response relationships include inter-individual variability, additivity of $NO_2^-$ induced effects to a naturally occurring background of disease, and additivity to effects induced by other pollutant exposures.

Epidemiologic studies are generally consistent with a linear or log linear relationship between ambient $NO_2$ concentration and the health outcome; however the shape of the $NO_2$ concentration-response relationship has only been explored in several studies. To examine the shape of the concentration-response relationship between $NO_2$ and daily physician consultations for asthma and lower respiratory disease in children, Hajat et al. (1999) used bubble plots to examine residuals of significant models plotted against moving averages of $NO_2$ concentration. They noted a weak trend for asthma and 0-1 day moving average lag of $NO_2$ and proposed that effects are weaker at lower concentrations and stronger at higher concentrations than predicted by the linear model. These departures were in accord with the shape of the sigmoidal dose-response model below the median effective dosage.

Several studies of ED visits or hospitalizations for cardiac or respiratory disease examined the shape of the concentration-response curve. Burnett et al. (1997a) used the locally estimated smoothing splines (LOESS) to describe the concentration-response for respiratory and cardiac hospitalizations for the summers of 1992-94 in Toronto. Both graphs showed a smaller slope at lower concentrations, but a chi-square test detected no significant difference between the LOESS and a linear effect. In another study of respiratory hospitalizations in 16 Canadian cities, Burnett et al. (1997b) were unsuccessful in identifying the shape of the concentration-response function, i.e. a linear effect was not significant nor did inclusion of a quadratic term improve the fit of the model. In another study of hospitalizations for CHF in 10 Canadian cities, Burnett et al. (1997c) found that a logarithmic concentration-response model, which has a steeper slope at lower concentrations, provided the best fit for the data compared to the other forms of the model examined. In a study among Medicaid-enrolled asthmatics in two urban cities in Ohio, Jaffe et al. (2003) found that when a concentration-response relationship was examined by quintile of $NO_2$ concentration, no consistent pattern was found. Tenías et al. (1998) also reported no consistent pattern in their study of the association between ambient $NO_2$ and ED visits in Valencia's Hospital Clìnic Universitari from 1994 to 1995. Castellsague et al. (1995) found a small but significant association of $NO_2$ and ED visits due to asthma in Barcelona. Specifically, the adjusted risk estimates of asthma visits for each quartile of $NO_2$ showed increased risks in each quartile for the summer months, but not the winter months. Together these studies indicate some disagreement in the trend of the concentration-response curve below 50 ppb 24 h $NO_2$.

Samoli et al. (2003) examined the relationship between mortality and $NO_2$ in a subset of 9 European cities out of 30 APHEA cities. The cities were selected to have overlapping $NO_2$ ranges to improve the detection of nonlinearity. They found the linear assumption to be adequate for these cities. Kim et al. (2004b) investigated non-linearity in relationships between air pollutants and mortality in Seoul, Korea, by analyzing data using a log-linear Generalized Additive Model (GAM; linear model), a cubic natural spline model (nonlinear model), and a B-mode splined model (threshold model). They did not detect a nonlinear association for $NO_2$ with mortality.

In conclusion, of the epidemiology studies that attempted to look at the shape of the concentration-response below 50 ppb, one indicated that effects were weaker at lower levels (Hajat et al. 1999), and one showed a steeper log-linear relationship at lower doses (Burnett et al. 1997c). The remainder found that a

linear function best described the data (Burnett et al. 1997a,b; Jaffe et al. 2003; Tenias et al., 1998; Castellsague et al., 1995). These results do not provide adequate evidence to suggest that nonlinear departures exist along any part of this range of $NO_2$ exposure concentrations. Evidence from human clinical studies has not helped to clarify understanding of the concentration-response function of $NO_2$ (see chapter 3).

# 4.3. Susceptible and Vulnerable Populations

The NAAQS are intended to provide an adequate margin of safety for both general populations and sensitive subpopulations, or those subgroups potentially at increased risk for ambient air pollution health effects. The term susceptibility generally encompasses innate or acquired factors that make individuals more likely to experience effects with exposure to pollutants. Genetic or developmental factors can lead to innate susceptibility, while acquired susceptibility may result from age, disease, or personal risk factors such as smoking, diet, or exercise. In addition, new attention has been paid to the concept of some population groups having increased vulnerability to pollution-related effects due to extrinsic factors including socioeconomic status (e.g., reduced access to health care) or particularly elevated exposure levels. Potentially susceptible and/or vulnerable groups comprise a large fraction of the U.S. population. Given the likely heterogeneity of individual responses to air pollution, the severity of health effects experienced by a susceptible subgroup may be much greater than that experienced by the population at large (Zanobetti et al., 2000).

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

## 4.3.1. Preexisting Disease as a Potential Risk Factor

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

### 4.3.1.1. Asthmatics

Evidence from epidemiologic studies shows an association between $NO_2$ exposure and children's hospital admissions, ED visits, and calls to doctors for asthma. This evidence came from large longitudinal studies, panel studies, and time-series studies. $NO_2$ exposure was associated with aggravation of asthma effects that include symptoms, medication use, and lung function. Effects of $NO_2$ on asthma were most evident with a cumulative lag of 2 to 6 days, rather than same-day levels of $NO_2$. Time-series studies also demonstrated a relationship in children between hospital admissions or ED visits for asthma

and $NO_2$ exposure, even after adjusting for copollutants such as PM and CO. Important evidence was also available from epidemiologic studies of indoor $NO_2$ exposures. A number of recent studies showed associations with wheeze, chest tightness, and length of symptoms (Belanger et al., 2006); respiratory symptom rates (Nitschke et al., 2006); school absences (Pilotto et al., 1997a); respiratory symptoms, likelihood of chest tightness, and asthma attacks (Smith et al., 2000); and severity of virus-induced asthma (Chauhan et al., 2003). However, several studies (Mukala et al., 1999, 2000; (Farrow et al., 1997) evaluating younger children found no association between indoor $NO_2$ and respiratory symptoms.

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

Toxicological studies provided biological plausibility that asthmatics are likely susceptible to the effects of $NO_2$ exposure. Numerous animal studies provide evidence that $NO_2$ can produce inflammation and lung permeability changes. These studies provided evidence for several mechanisms by which $NO_2$ exposure can induce effects, including reduced mucociliary clearance, and alveolar macrophage function such as depressed phagocytic activity and altered humoral- and cell-mediated immunity. Chauhan et al. (2003) reviewed potential mechanisms by which $NO_2$ exacerbates asthma in the presence of viral infections. These mechanisms included "direct effects on the upper and lower airway by ciliary dyskinesis, epithelial damage, increases in pro-inflammatory mediators and cytokines, rises in IgE concentration, and interactions with allergens, or indirectly through impairment of bronchial immunity." These are all mechanisms that can provide biological plausibility for the $NO_2$ effects in asthmatic children observed in epidemiologic studies. However, it must be noted that the experimental animal studies that looked at effects on markers of inflammation, such as BAL fluid levels of total protein and lactate dehydrogenase and recruitment or proliferation of leukocytes, occured only at exposure levels of $\geq$ 5 ppm. Studies conducted at these higher exposure concentrations may elicit mechanisms of action and effects that do not occur at near-ambient levels of $NO_2$.

### 4.3.1.2. Cardiopulmonary Disease and Diabetes

While less evidence was available for these conditions, preexisting cardiovascular-related conditions may lead to heightened susceptibility to the effects of $NO_2$ exposure. Recent epidemiologic studies reported that persons with preexisting conditions may be at increased risk for adverse cardiac health events associated with ambient $NO_2$ concentrations (Peel et al., 2007; Mann et al., 2002; D'Ippoliti et al., 2003; von Klot et al., 2005). Peel et al. (2007) reported evidence of effect modification by comorbid hypertension and diabetes on the association between ED visits for arrhythmia and $NO_2$ exposure. In another study, a statistically significant positive relationship was reported between $NO_2$ concentrations and hospitalizations for IHD among those with prior diagnoses of CHF and arrhythmia (Mann et al., 2002). However, Mann et al. (2002) noted the vulnerability in the secondary CHF group could be due to increased prevalence of MI as the primary diagnosis in this group. In addition, these authors stated they were unable to distinguish the effects of $NO_2$ from other traffic pollutants (Mann et al., 2002). Von Klot et al. (2005) reported cardiac readmission among MI survivors was associated with $NO_2$ and this association was robust to adjustment for $PM_{10}$. Modification of the association between $NO_2$ and MI by conduction disorders but not diabetes or hypertension was observed by D'Ippoliti et al. (2003).

Park et al. (2005b) examined the relationship of $NO_2$ and HRV among those with IHD, hypertension and diabetes but did not find an association.

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

## 4.3.2. Age as a Potential Risk Factor

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

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

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

In elderly populations, associations between $NO_2$ and hospitalizations or ED visits for CVD, including stroke, have been observed in several studies (Anderson et al., 2007a; Atkinson et al., 1999b; Jalaludin et al., 2006; Hinwood et al., 2005; Wong et al., 1999; Barnett et al., 2006; Zanobetti and Schwartz, 2006; Simpson et al., 2005a; Wellenius et al., 2005b; Morgan et al., 1998a; Morris et al., 1995). However, some results were inconsistent across cities (Morris et al., 1995), and investigators could not distinguish the effect of $NO_2$ from the effect of other traffic-related pollutants such as PM and CO (Simpson et al., 2005a; Barnett et al., 2006; Morgan et al., 1998b; Jalaludin et al., 2006; Zanobetti and Schwartz, 2006).

Several mortality studies investigated age-related differences in $NO_2$ effects. Among the studies that observed positive associations between $NO_2$ and mortality, a comparison of all-age– or ≤ 64-years-of-age–group $NO_2$-mortality risk estimates to that of the ≥ 65-years-of-age group indicated that, in general, the elderly population was more susceptible to $NO_2$ effects (Biggeri et al., 2005; Burnett et al.,

2004). One study (Simpson et al., 2005a) found no difference in increases in CVD mortality associated with $NO_2$ concentrations between all ages and those participants of ≥ 65 years of age.

## 4.3.3. Gender as a Potential Risk Factor

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

## 4.3.4. Genetic Factors for Oxidant and Inflammatory Damage

A consensus now exists among epidemiologists that genetic factors related to health outcomes and ambient pollutant exposures merit serious consideration (Kauffmann et al., 2004; Gilliland et al., 1999; ATS 2000b). Interindividual variation in human responses to air pollutants may indicate that that some subpopulations are at increased risk of detrimental effects from pollutant exposure, and it has become clear that genetic background is an important susceptibility factor (Kleeberger, 2005). Several criteria must be satisfied in selecting and establishing useful links between polymorphisms in candidate genes and adverse respiratory effects. First, the product of the candidate gene must be instrumentally involved in the pathogenesis of the adverse effect of interest, often a complex trait with many determinants. Second, polymorphisms in the gene must produce a functional change in either the protein product or in the level of expression of the protein. Third, in epidemiologic studies, the issue of confounding by other environmental exposures must be carefully considered. In general, work has focused on genes involved in oxidant and inflammation damage.

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

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

## 4.3.5. Other Potentially Susceptible Populations

Although data specific to $NO_2$ exposures was lacking for many of the susceptibility factors listed below, several potentially susceptible groups deserve specific mention in this document. These include individuals in a chronic pro-inflammatory state (e.g., diabetics), obesity, and children born prematurely or with low birth weight.

Factors that may influence susceptibility or vulnerability are:

### Susceptibility Factors

- Age, Gender
- Adverse birth outcomes: e.g., preterm birth, low birth weight, growth restriction, birth defects
- Race/ethnicity
- Genetic factors
- Pre-existing disease, e.g., diabetes
- Obesity
- Respiratory diseases, e.g., asthma, COPD
- Cardiovascular diseases

### Vulnerability Factors

- Socioeconomic status
- Education level
- Air conditioning Use
- Proximity to Roadways
- Geographic Location (West vs. East)
- Level of Exercise
- Work Environment (e.g., outdoor workers)

Chronic inflammation appears to enhance susceptibility for air pollution-related cardiovascular events in older individuals and persons with diabetes, coronary artery disease, obesity, and past myocardial infarctions (Bateson and Schwartz 2004, Goldberg et al., 2001; Zanobetti and Schwartz, 2002; Peel et al. 2007). Dubowsky et al. (2006) reported that individuals with conditions associated with both chronic inflammation and increased cardiac risk were more vulnerable to the short-term pro-inflammatory effects of air pollution. This included individuals with diabetes; obesity; and concurrent diabetes, obesity and hypertension. Zanobetti and Schwartz (2001) reported more than twice the risk for hospital admissions for heart disease in persons with diabetes than in persons without diabetes associated with exposure to ambient air pollution, indicating that persons with diabetes are an important at-risk group. Data from the Third National Health and Nutrition Examination Survey indicated that 5.1% of the U.S. population older than 20 years of age has diagnosed diabetes and an additional 2.7% has undiagnosed diabetes (Harris et al., 1998). Moreover, another study found that subjects with impaired glucose tolerance without type II diabetes also had reduced HRV (Schwartz, 2001). This may indicate that the at-risk population may be even larger.

Mortimer et al. (2000) reported that among asthmatic children, birth characteristics continue to be associated with increased susceptibility to air pollution later in life, demonstrating that air pollution-induced asthma symptoms were more severe in children born prematurely or of low birth weight. Specifically, the authors revealed asthmatic children born more than three weeks prematurely or weighing less than 2,500 grams (5.5 pounds) had a six-fold decrease in breathing capacity associated with air pollution compared to full-weight, full-term children. The low birth weight and premature children also reported a five-fold greater incidence of symptoms like wheezing, coughing and tightness in the chest.

## 4.3.6. Increased Vulnerability Associated with Increased Exposure

Certain groups may experience relatively high exposure to $NO_2$, thus forming a potentially vulnerable population. Many studies found that indoor, personal, and outdoor $NO_2$ levels are strongly

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

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

Many recent studies examined modification by SES indicators on the association between mortality and PM (O'Neill et al., 2003; Martins et al., 2004; Jerrett et al., 2004; Finkelstein et al., 2003; Romieu et al., 2004a) or other indices such as traffic density, distance to roadway or a general air pollution index (Ponce et al., 2005; Woodruff et al., 2003; Finkelstein et al., 2004). SES modification of $NO_2$ associations has been examined in fewer studies. For example, in a study conducted in Seoul, Korea, community-level SES indicators modified the association of air pollution with ED visits for asthma; of the five criteria air pollutants evaluated, $NO_2$ showed the strongest association in lower SES districts compared to high SES districts (Kim et al., 2007.) In addition, Clougherty et al. (2007) evaluated exposure to violence (a chronic stressor) as a modifier of the effect of traffic-related air pollutants, including $NO_2$, on childhood asthma. The authors reported an elevated risk of asthma with a 4.3-ppb increase in $NO_2$ exposure solely among children with above-median exposure to violence in their neighborhoods.

# 4.4. At-Risk Susceptible Population Estimates

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

There are approximately 2.5 million deaths from all causes per year in the U.S. population, with about 100,000 deaths from chronic lower respiratory diseases (Kochanek et al., 2004) and 4,000 from

asthma (NCHS, 2006c). For respiratory health diseases, there are nearly 4 million hospital discharges per year (DeFrances et al., 2005), 14 million ED visits (McCaig and Burt, 2005), 112 million ambulatory care visits (Woodwell and Cherry, 2004), and an estimated 700 million restricted-activity days per year due to respiratory conditions (Adams et al., 1999). Of the total number of visits for respiratory disease, 1.8 million annual ED visits were reported for asthma, including more than 750,000 visits by children. In addition, nearly 500,000 annual hospitalizations for asthma were reported (NCHS, 2006c).

Centers for Disease Control and Prevention (CDC) analyses have shown that the burden of asthma has increased over the past two decades (NCHS, 2006c). In 2005, approximately 22.2 million people (7.7% of the population) had asthma. The incidence was higher among children (8.9% of children) compared to adults (7.2%) (Note: 2004 data is shown in Table 4.4-1, with a prevalence of 6.7%). In addition, prevalence and severity is higher among certain ethnic or racial groups such as Puerto Ricans, American Indians, Alaskan Natives, and African Americans. The asthma hospitalization rate for black persons was 240% higher than for white persons. Puerto Ricans were reported to have the highest asthma death rate (360% higher than non-Hispanic white persons) and non-Hispanic black persons had an asthma death rate that was 200% higher than non-Hispanic white persons. Furthermore, a higher prevalence of asthma among persons of lower SES and an excess burden of asthma hospitalizations and mortality in minority and inner-city communities have been observed in several studies (Wright and Subramanian, 2007). Gender and age are also determinants of prevalence and severity: adult females had a 40% higher prevalence than adult males; and boys, a 30% higher prevalence than girls. Overall, females had a hospitalization rate about 35% higher than males.

**Table 4.4-1. Prevalence of selected respiratory disorders by age group and by geographic region in the U.S.(2004 [U.S. Adults] and 2005 [U.S. Children] National Health Interview Survey).**

| CHRONIC CONDITION/DISEASE ADULTS (18+ YEARS) | AGE (YEARS) | | | | | | REGION | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ALL ADULTS | | 18-44 | 45-64 | 65-74 | 75+ | NORTH-EAST | MID-WEST | SOUTH | WEST |
| | CASES ($\times 10^6$) | % | % | % | % | % | % | % | % | % |
| Asthma | 14.4 | 6.7 | 6.4 | 7.0 | 7.5 | 6.6 | 6.8 | 6.8 | 6.0 | 7.5 |
| COPD: Chronic Bronchitis | 8.6 | 4.2 | 3.2 | 4.9 | 6.1 | 6.3 | 4.0 | 4.7 | 4.4 | 3.5 |
| COPD: Emphysema | 3.5 | 1.7 | 0.3 | 2 | 4.9 | 6.0 | 1.5 | 1.7 | 2.0 | 1.1 |
| **CHRONIC CONDITION/DISEASE CHILDREN (<18 YEARS)** | **ALL CHILDREN** | | **0-4** | **5-11** | **12-17** | | **NORTH-EAST** | **MID-WEST** | **SOUTH** | **WEST** |
| | CASES ($\times 10^6$) | % | % | % | % | | % | % | % | % |
| Respiratory Conditions | 6.5 | 8.9 | 6.8 | 9.9 | 9.6 | | 10.1 | 8.5 | 9.3 | 7.9 |

Source: National Center for Health Statistics (2006a,b)

In addition, population groups based on age group also comprise substantial segments of the population that may be potentially at risk for $NO_2$-related health impacts. Based on U.S. census data from 2000, about 72.3 million (26%) of the U.S. population are under 18 years of age, 18.3 million (7.4%) are under 5 years of age, and 35 million (12%) are 65 years of age or older. Hence, large proportions of the U.S. population are in age groups that are likely to have increased susceptibility and vulnerability for health effects from ambient $NO_2$ exposure.

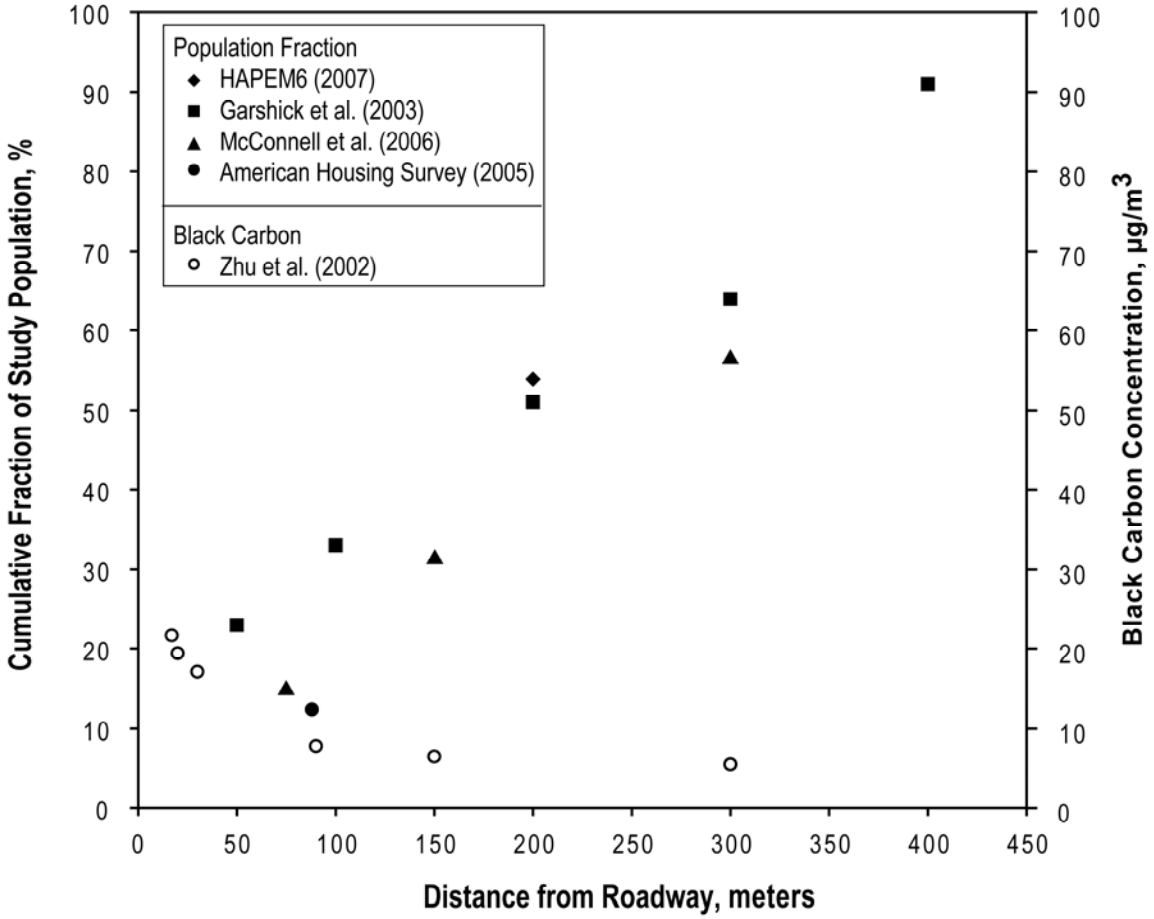



**Figure 4.4-1. Fraction of the study populations living within a specified distance from roadways. For comparison, concentrations of the traffic pollutant black carbon are plotted as a function of distance from the roadway.**

Based on data from the American Housing Survey, approximately 36 million persons live within 300 feet (~90 meters) of a four-lane highway, railroad, or airport and 12.6% of U.S. housing units are located within this distance (U.S. Census Bureau, 2006). Furthermore, several exposure studies offer insight into differential exposures to $NO_2$ from traffic in childhood. In California, 2.3% of schools, grades K–12, with a total enrollment of more than 150,000 students were located within ~500 feet (150 m) of high-traffic roads, and a higher proportion of nonwhite and economically disadvantaged students attended schools within close proximity to these high-traffic roadways (Green et al., 2004). Similar findings were reported for Detroit schoolchildren (Wu and Batterman, 2006). Figure 4.4-1 shows the proportion of study populations in Boston, MA (Garshick et al. 2003) and Los Angeles, CA (McConnell et al. 2006), the entire U.S. (American Housing Survey, 2005), and from population exposure models (HAPEM6, 2007) living within a certain distance from major roadways. It also presents results of air quality measurements showing the decrease in concentration of black carbon, a traffic-related pollutant, with increasing distance from the roadway. The considerable size of the population groups at risk indicate that exposure to ambient $NO_2$ could have an impact on public health in the U.S.

# 4.5. Summary of Public Health Issues

In the few studies that specifically examined concentration-response relationships between $NO_2$ and health outcomes, there was little evidence of an effect threshold. However, various factors, such as interindividual variation in response, additivity to background of effect and/or exposure, and measurement error tend to linearize the concentration-response relationship and obscure any population-level thresholds that might exist.

Persons with preexisting respiratory disease, children, and older adults may be more susceptible to the effects of $NO_2$ exposure. Individuals in sensitive groups may be affected by lower levels of $NO_2$ than the general population or experience a greater impact with the same level of exposure. A number of factors may increase susceptibility to the effects of $NO_2$. Studies generally reported a positive excess risk for asthmatics, and there was emerging evidence that CVD may cause persons to be more susceptible, though it is difficult to distinguish the effect of $NO_2$ from other traffic pollutants. Children and older adults (65+ years) may be more susceptible than adults, possibly due to physiological changes occurring among these age groups.

In addition to intrinsically susceptible groups, a portion of the population may be at increased vulnerability due to higher exposures, generally people living and working near roadways. A considerable fraction of the population resides, works, or attends school near major roadways. Of this population, those with physiological susceptibility will have even greater risks of health effects related to $NO_2$.

# Chapter 5. Summary and Conclusions

## 5.1. Introduction

The Integrated Plan for the Primary NAAQS for $NO_2$ (U.S. Environmental Protection Agency, 2007) presents a series of policy-relevant questions to structure this assessment of the scientific evidence (Section 1.1). This ISA focuses on evaluating recent scientific evidence while incorporating information from the last review to best inform consideration of these policy-relevant questions. The purpose of this ISA is to form the scientific basis for regulatory decision making as it pertains to retaining or revising the current primary NAAQS for $NO_2$ (0.053 ppm, annual average). The previous chapters present the most policy-relevant science. This chapter first summarizes key findings and then draws conclusions about health effects associated with exposure to $NO_X$. These conclusions are based on explicit guidelines (Section 1.3) derived from the Hill aspects (Hill, 1965) and modeled after other pertinent frameworks.

The framework for evaluation of evidence regarding causality is described in Chapter 1. The framework and language draw from similar efforts across the Federal government and the wider scientific community, especially from the recent NAS Institute of Medicine document, *Improving the Presumptive Disability Decision-Making Process for Veterans* (Institute of Medicine, 2007). A five-level hierarchy is used to be consistent with the Guidelines for Carcinogen Risk Assessment (U.S. Environmental Protection Agency, 2005). Conclusions concerning causality of association were placed into one of five categories with regard to weight of the evidence based on the framework. The five descriptors are:

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

This integrative discussion begins with some key conclusions from the atmospheric sciences that are relevant to the interpretation of the health evidence and provide important underpinnings for potential quantitative assessments, including information about ambient concentrations and monitoring, and estimation of policy-relevant background. Consideration of exposure measurement error and exposure assessment issues is an essential component of this review, and provides an overview of the findings that inform the evaluation of the health evidence. Conclusions regarding causality for different categories of health outcomes are presented. Highlights of findings that support these conclusions are presented. The key findings from atmospheric science, exposure assessment, and health effects, including animal toxicological, human clinical and epidemiologic studies are integrated with regard to levels at which effects are observed, the time period (or averaging time) over which these effects are observed, and $NO_2$ serving as the indicator for the oxides of nitrogen NAAQS, and presented in Section 5.4.

# 5.2. Key Source to Exposure Findings

## 5.2.1. Atmospheric Science and Ambient Concentrations

An understanding of atmospheric processes affecting a given pollutant is crucial for understanding the causal chain linking $NO_X$ sources to health effects. $NO_2$ plays a key role in the formation of $O_3$ and photochemical smog. $NO_2$ is an oxidant and reacts to form other photochemical oxidants, including organic nitrates like the PANs and inorganic acids like $HNO_3$. $NO_2$ also reacts with toxic compounds such as PAHs to form nitro-PAHs, which can be more toxic than either reactant alone.

Major anthropogenic sources of $NO_X$ include motor vehicles, power plants, and fossil fuel combustion in general. $NO_X$ also is emitted by burning biomass fuels. Natural $NO_X$ sources include wildfires, microbial activity in soils, and lightning. $NO_X$ is emitted by all of the above sources mainly as NO. Atmospheric reactions oxidize NO to $NO_2$. Thus, most $NO_2$ in the atmosphere is the result of the oxidation of primary NO. As noted in Chapter 2, NO and $NO_2$ interconvert rapidly in the atmosphere, and so it is often convenient to refer to their sum ($NO_X$) instead of to them individually. The definition of nitrogen oxides contains a number of *N*-containing compounds formed by the oxidation of $NO_2$ as described in Chapter 2. Aspects of the atmospheric chemistry of $NO_X$ most relevant for interpreting the human exposure and health evidence are:

- The current method of determining ambient $NO_X$ and then reporting $NO_2$ concentrations by subtraction of NO is subject to positive interference by $NO_X$ oxidation products, chiefly $HNO_3$, and PAN as well as other oxidized *N*-containing compounds. Measurements of these oxidation products in urban areas are sparse.
- Products are expected to peak in the afternoon because of the continued oxidation to $NO_2$ emitted during the morning rush hours and during conditions conducive to photochemistry in areas well downwind of sources, particularly during summer.
- Within urban cores, where many of the ambient monitors are sited close to strong $NO_X$ sources such as motor vehicles on busy streets (i.e., where $NO_2$ concentrations are highest), the positive artifacts due to $NO_2$ oxidation products are much smaller on a relative basis, generally <10%. Conversely, the positive artifacts are larger in locations more distant from local $NO_X$ sources (i.e. where $NO_2$ concentrations are lowest) and could exceed 50%. Therefore, variable, positive artifacts associated with measuring $NO_2$ using the FRM severely hamper its ability to serve as an accurate and precise indicator of $NO_2$ concentrations at the typical ambient levels generally encountered outside of urban cores. The result of these positive artifacts when using ambient monitoring data in health outcome studies depends on whether or not the $NO_2$ oxidation products exert the same effect as $NO_2$ on the health endpoint being considered.
- Because the dominant urban source is typically on-road vehicle emissions, ambient $NO_2$ generally behaves with the temporal and spatial variability of other traffic-generated pollutants.
- The **annual average $NO_2$ concentrations of ~15 ppb reported by the regulatory monitoring networks are well below the level of the current NAAQS (0.053 ppm)**. However, daily max 1-h avg concentrations can be greater than 100 ppb in some locations, e.g., areas with heavy traffic.
- **Policy-relevant background concentrations of $NO_2$ are much lower than average ambient concentrations and are typically less than 0.1 ppb over most of the U.S.**, with the highest values found in agricultural areas.

## 5.2.2. Exposure Assessment

Personal exposure to ambient and outdoor $NO_2$ is affected by many factors that influence the contribution of ambient $NO_2$ to personal exposures. Personal activity patterns determine when, where, and how people are exposed to $NO_2$. The variations of these physical and exposure factors determine the strength of the association between personal exposure and ambient concentrations in both longitudinal and cross-sectional studies. The observed strength of the association between personal exposures and ambient concentrations are not only affected by the variation in physical parameters (e.g., penetration coefficient (P), mass transfer coefficient (k), air exchange rate (a), and indoor sources) but also affected by data quality and study design. The collective variability in all of the above parameters, in general, contributes to exposure error in air pollution-health outcome studies. **The errors and uncertainties associated with the use of ambient $NO_2$ concentrations as a surrogate for personal exposure to ambient $NO_2$ generally tend to reduce rather than increase effect estimates, and therefore are not expected to change the principal conclusions from $NO_2$ epidemiologic studies.**

The association between the ambient component of personal exposures and ambient concentrations is most relevant to the interpretation of epidemiologic evidence, but this type of correlation coefficient is not generally reported. Therefore, the weak association between personal total exposures and ambient concentrations in some longitudinal studies might not reflect the true association between the ambient component of personal exposures and ambient concentrations. A number of studies found that personal $NO_2$ exposure was associated with ambient $NO_2$ exposure, but the strength of the association ranged from poor to good. Key findings related to assessing $NO_2$ exposures are listed below.

- **$NO_2$ concentrations are highly spatially and temporally variable** in urban areas. Intersite correlations for $NO_2$ concentrations range from slightly negative to highly positive in examined cities. The range of spatial variation in $NO_2$ concentrations is similar to that for $O_3$, but larger than that of fine particulate matter ($PM_{2.5}$). Differences between 24-h avg concentrations at individual paired sites in a MSA can be larger than the annual means at these sites.
- Elevated and rooftop $NO_2$ measurements, particularly in inner cities, likely underestimate concentrations and hence personal exposures occurring at lower elevations, closer to motor vehicle emissions. Pedestrians that spend time walking in street canyons and residents that have windows opening onto these canyons can therefore experience exposures to high near-road concentrations that may equal or exceed those on roads in transit.
- Co-located samples showed that passive $NO_2$ samplers generally correlate well with FRM ambient samplers, and the concentration differences are generally within 10%. However, personal passive samplers and the ambient samplers were both subject to measurement artifacts.
- In the absence of indoor sources, indoor $NO_2$ levels are about one-half those found outdoors. In the presence of indoor sources, particularly unvented combustion sources, $NO_2$ levels can be much higher than reported ambient concentrations.
- Alpha ($\alpha$), the ratio of personal exposure to $NO_2$ of ambient origin to the ambient $NO_2$ concentration, ranged from ~0.3 to ~0.6 in studies where it was determined.
- Indoor exposures to $NO_2$ are accompanied by exposures to other products of indoor combustion and to products of indoor $NO_2$ chemistry, such as HONO.
- The **evidence relating ambient levels to personal exposures was inconsistent**. Some of the longitudinal studies examined found that ambient levels of $NO_2$ were reliable proxies of personal exposures to $NO_2$. However, a number of studies did not find significant associations between ambient and personal levels of $NO_2$. The differences in results were related in large measure to differences in study design and in exposure determinants. Measurement artifacts and differences in analytical measurement capabilities could also have contributed to the inconsistent results.

Indeed, in a number of the studies examined, the majority of measurements of personal $NO_2$ concentrations were beneath detection limits, and in all studies some personal measurements were beneath detection limits.

- In two European studies, community averages of personal total exposures were highly correlated with either ambient or outdoor microenvironment concentrations. However, because of limitations in these studies, caution should be exercised in using these results to determine whether ambient concentrations of $NO_2$ can be used as surrogates for long-term community average exposures in epidemiologic studies.

# 5.3. Key Health Effects Findings

## 5.3.1. Findings from the Previous Review

The 1993 $NO_X$ AQCD concluded that there were two key health effects of greatest concern at ambient or near-ambient concentrations of $NO_2$:

- Increases in airway hyperresponsiveness of asthmatic individuals after short-term exposures.
- Increased respiratory illness among children associated with longer-term exposures to $NO_2$.

Evidence also was found for increased risk of emphysema, but this appeared to be of major concern only with exposures to levels of $NO_2$ that were much higher than current ambient levels of $NO_2$ (U.S. Environmental Protection Agency, 1993). Qualitative evidence regarding airway hyperresponsiveness and lung function changes was drawn from human clinical and animal toxicological studies; these did not elucidate a concentration-response relationship. Epidemiologic studies reported increased respiratory symptoms with increased indoor $NO_2$ exposures. Animal toxicological findings of lung host defense system changes with $NO_2$ exposure provided a biologically plausible basis for these results. Subpopulations considered potentially more susceptible to the effects of $NO_2$ exposure included persons with preexisting respiratory disease, children, and the elderly. In the 1993 AQCD, the epidemiologic evidence for respiratory health effects was limited, and no studies had considered effects such as hospital admissions, ED visits, or mortality.

## 5.3.2. New Health Effects Findings

Evidence published since the last review generally has confirmed and extended the conclusions articulated in the 1993 AQCD. The epidemiologic evidence has grown substantially, including new field or panel studies on respiratory health outcomes, intervention studies, numerous time-series epidemiologic studies of effects such as hospital admissions, and a substantial number of studies evaluating mortality risk with short-term $NO_2$ exposures. As noted above, no epidemiologic studies were available in 1993 that assessed relationships between nitrogen oxides and outcomes such as hospital admissions, ED visits, or mortality; in contrast, dozens of epidemiologic studies on such outcomes are now included in this evaluation. Several recent studies also have reported findings from prospective cohort studies on respiratory health effects with long-term $NO_2$ exposure. In addition, recent evidence characterizing the responses of susceptible and vulnerable populations has been reported since 1993, particularly concerning children, asthmatics, and those living or working near roadways. While not as marked as the growth in the epidemiologic literature, a number of recent toxicological and human clinical studies provide further insights into relationships between $NO_2$ exposure and health effects.

These new findings allow us to draw several overall conclusions concerning the health effects of $NO_2$ exposures. These conclusions are integrated across disciplines at the organ-system level (e.g.,

respiratory and cardiovascular morbidity, cardiopulmonary mortality). Integration at this level is generally more meaningful than reporting on separate health effects, which themselves may be serious, but individually do not fully characterize impacts on health. The conclusions of this ISA are summarized in Table 5.3-1, along with those of the previous review. Following the table is more discussion of evidence that supports these conclusions, organized by exposure duration and specific health effect.

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**Table 5.3-1. Summary of evidence from epidemiologic, human clinical, and animal toxicological studies on the health effects associated with short- and long-term exposure to $NO_2$.**

| HEALTH OUTCOME | CONCLUSION FROM PREVIOUS NAAQS REVIEW | CONCLUSION FROM 2008 ISA |
|---|---|---|
| ***SHORT-TERM EXPOSURE TO $NO_2$*** | | |
| **Respiratory Morbidity** | **No Overall Conclusion** | **"sufficient to infer a likely causal relationship"** |
| Lung Host Defense | Human clinical studies suggest $NO_2$ effects; Animal toxicological studies indicate that alveolar macrophages and humoral and cell-mediated immune systems are affected and show that exposure can impair the respiratory host defense system resulting in susceptibility to infection. | Impaired host-defense systems and increased risk of susceptibility to both viral and bacterial infections after $NO_2$ exposures have been observed in epidemiologic, human clinical, and animal toxicological studies. |
| Airway Inflammation | No Studies | Human clinical studies report effects of $NO_2$ (1-2 ppm) on airway inflammation in healthy humans. Animal toxicological studies and limited available epidemiologic studies on children support these findings. |
| Airway Hyperresponsiveness | An increase in responsiveness to bronchoconstrictors was found in asthmatics and healthy individuals exposed to $NO_2$ at rest. | Human clinical studies of allergen and nonspecific bronchial challenges in asthmatics observed increased airway hyperresponsiveness at near ambient concentrations (0.1-0.3 ppm). Increased responsiveness to nonspecific challenges was also observed in animals at higher $NO_2$ levels (e.g., 0.5 ppm). |
| Respiratory Symptoms | Children living in homes with gas stoves are at increased risk for developing respiratory diseases and illnesses compared to children living in homes without gas stoves. | Epidemiologic studies provide consistent evidence of an association of respiratory effects with indoor and personal $NO_2$ exposures in children. Multicity studies provide further support for associations between ambient $NO_2$ concentrations (means of 7-70 ppb) and respiratory symptoms in asthmatic children. |
| Lung Function | Lung function changes in asthmatics reported at low (0.2 to 0.5 ppm), but not higher (up to 4 ppm), $NO_2$ concentrations. No convincing evidence of lung function decrements in healthy individuals below 1.0 ppm. | The association between ambient $NO_2$ concentrations and lung function in epidemiologic studies were generally inconsistent. Recent clinical evidence generally confirms prior findings. |
| ED Visits / Hospital Admissions | No Studies | Positive and generally robust associations observed between ambient $NO_2$ levels (means of 3-50 ppb) and increased ED visits and hospital admissions for respiratory causes, especially asthma. |
| **Cardiovascular Morbidity** | **No Studies** | **"inadequate to infer the presence or absence of a causal relationship"** |
| Cardiovascular Effects | No Studies | Evidence from epidemiologic studies of heart rate variability, repolarization changes, and cardiac rhythm disorders among heart patients with ischemic cardiac disease are inconsistent. |
| ED Visits / Hospital Admissions | No Studies | Generally positive associations between ambient $NO_2$ concentrations and hospital admissions or ED visits for cardiovascular disease; however, the effects were not robust to adjustment for copollutants. |
| **Mortality** | **No Studies** | **"suggestive but not sufficient to infer a causal relationship"** |
| All Cause and Cardiopulmonary Mortality | No Studies | Positive and generally robust associations between ambient $NO_2$ concentrations and risk of nonaccidental and cardiopulmonary mortality. |

| HEALTH OUTCOME | CONCLUSION FROM PREVIOUS NAAQS REVIEW | CONCLUSION FROM 2008 ISA |
|---|---|---|
| ***LONG-TERM EXPOSURE TO $NO_2$*** | | |
| **Respiratory Morbidity** | **No Overall Conclusion** | **"suggestive but not sufficient to infer a causal relationship"** |
| Respiratory Effects | $NO_2$ can cause emphysema (meeting the human definition criteria) in animals at high concentrations of $NO_2$. | Epidemiologic studies observed decrements in lung function growth associated with long-term exposure to $NO_2$. |
| **Other Morbidity** | **No Studies** | **"inadequate to infer the presence or absence of a causal relationship"** |
| Cancer | No Studies | Limited epidemiologic studies observed an association between long-term $NO_2$ exposure and cancer; animal toxicological studies have not provided clear evidence that $NO_2$ acts as a carcinogen. |
| Cardiovascular Effects | No Studies | Very limited epidemiologic and toxicological evidence does not suggest that long-term exposure to $NO_2$ has cardiovascular effects. |
| Birth Outcomes | No Studies | The epidemiologic evidence for an association between long-term exposure to $NO_2$ and birth outcomes is generally inconsistent, with limited support from animal toxicological studies. |
| **Mortality** | **No Studies** | **"inadequate to infer the presence or absence of a causal relationship"** |
| All Cause and Cardiopulmonary Mortality | No Studies | The results of epidemiologic studies examining the association between long-term exposure to $NO_2$ and mortality were generally inconsistent. |

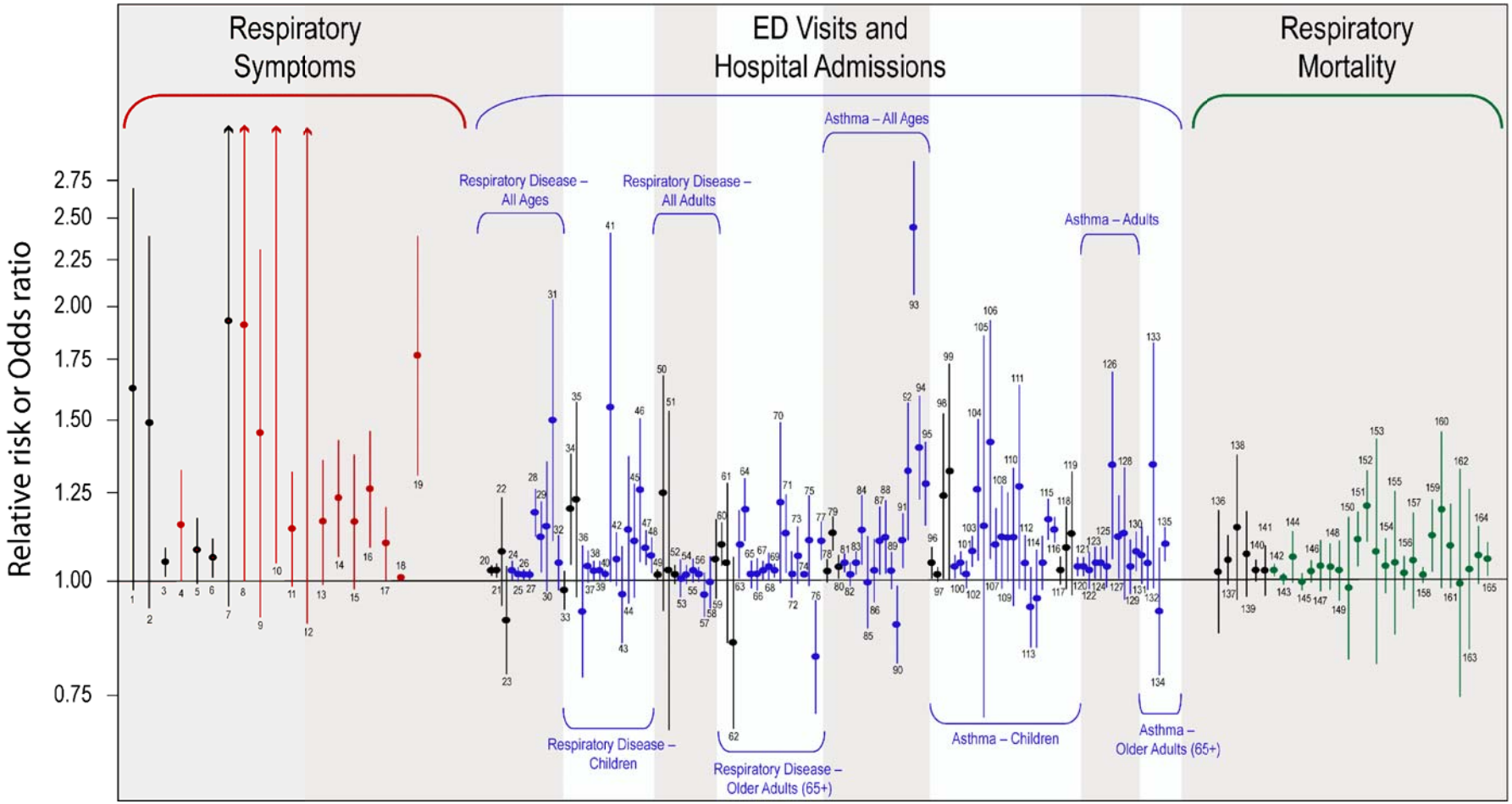
## 5.3.2.1. Respiratory Effects Related to Short-Term Exposure

Taken together, recent studies provided scientific evidence that $NO_2$ is associated with a range of respiratory effects and provide evidence **sufficient to infer a likely causal relationship between short-term $NO_2$ exposure and adverse effects on the respiratory system**. The greatest weight of evidence comes predominantly from the large body of recent epidemiologic evidence, with supportive evidence from human and animal experimental studies. The main body of evidence pertaining to causality for respiratory health outcomes is shown in Figure 5.3-1. The epidemiologic studies generally show positive associations between $NO_2$ and respiratory symptoms and hospitalization or ED visits, with a number being statistically significant, particularly the more precise effect estimates. There also is a pattern of positive associations with respiratory mortality, though most are not statistically significant. A number of the epidemiologic studies have been conducted in locations where the ambient $NO_2$ levels are well below the level of the NAAQS of 0.053 ppm (53 ppb) (annual average). The mean ambient concentrations, associated with the health outcomes reported in Figure 5.3-1 are in the range of 3 to 70 ppb for 24 h avg, with maximum ambient concentrations as high as 100 to 300 ppb.

The epidemiologic evidence for respiratory effects can be characterized as consistent, in that associations are reported in studies conducted in numerous locations with a variety of methodological approaches. The findings are coherent in the sense that the studies report associations with respiratory health outcomes that are logically linked together.

**Figure 5.3-1. Summary of epidemiologic studies examining short-term exposures to ambient $NO_2$ and respiratory outcomes.**

**Effect estimates for studies conducted in the U.S. or Canada are presented in black. Circles represent effect estimates. Lines represent 95% CI. Legend to figure on following page.**



## Legend to Figure 5.3-1.

### Respiratory Symptoms

1 Schwartz et al. (1994) Cough
2 Mortimer et al. (2002) Asthma symptoms
3 Schildcrout et al. (2006) Asthma symptoms
4 Pino et al. (2004) Wheezy bronchitis
5 Ostro et al. (2001) Wheeze
6 Ostro et al. (2001) Cough
7 Delfino et al. (2002) Asthma symptoms
8 Segala et al. (1998) Asthma symptoms
9 Segala et al. 1998 Cough
10 Just et al. (2002) Cough
11 Jalaludin et al. (2004) Cough
12 Segala et al. (2004) Cough
13 von Klot et al. (2002) Wheeze
14 von Klot et al. (2002) Phlegm
15 von Klot et al. (2002) Cough
16 von Klot et al. (2002) Breathing problems
17 Ward et al (2002) Cough
18 Rodriguez et al. (2007) Cough
19 Boezen et al. (1999) LRS

### Respiratory Disease – All Ages

20 Tolbert et al. (2007)
21 Peel et al. (2005)
22 Luginaah et al. (2005)
23 Luginaah et al. (2005)
24 Anderson et al. (2001)
25 Atkinson et al., (1999a)
26 Atkinson et al., (1999b)
27 Ponce de Leon et al. (1996)
28 Llorca et al. (2005)
29 Oftedal et al. (2003)
30 Hagen et al. (2000)
31 Bedeschi et al. (2007)
32 Hinwood et al., (2006)
33 Petroeschevsky et al. (2001)

### Respiratory Disease – Children

34 Yang et al. (2003)
35 Luginaah et al. (2005)
36 Luginaah et al. (2005)
37 Anderson et al. (2001)
38 Atkinson et al. (1999a)
39 Atkinson et al. (1999b)
40 Ponce de Leon et al. (1996)
41 Vigotti et al. (2007)
42 Petroeschevsky et al. (2001)
43 Petroeschevsky et al. (2001)
44 Barnett et al. (2005)
45 Barnett et al. (2005)
46 Barnett et al. (2005)
47 Wong et al. (1999)
48 Lin et al. (1999)
49 Gouveia and Fletcher (2000a)

### Respiratory Disease – Adults

50 Luginaah et al. (2005)
51 Luginaah et al. (2005)
52 Spix et al. (1998)
53 Anderson et al. (2001)
54 Atkinson et al. (1999a)
55 Atkinson et al. (1999b)
56 Ponce de Leon et al. (1996)
57 Schouten et al. (1996)
58 Schouten et al. (1996)
59 Petroeschevsky et al. (2001)
60 Wong et al. (1999)

### Respiratory Disease – Older Adults (65+)

61 Luginaah et al. (2005)
62 Luginaah et al. (2005)
63 Fung et al. (2006)
64 Yang et al. (2003)
65 Spix et al. (1998)
66 Anderson et al. (2001)
67 Atkinson et al. (1999a)
68 Atkinson et al. (1999b)
69 Ponce de Leon et al. (1996)
70 Andersen et al. (2007b)
71 Andersen et al. (2007a)
72 Schouten et al. (1996)
73 Schouten et al. (1996)
74 Simpson et al. (2005a)
75 Hinwood et al. (2006)
76 Petroeschevsky et al. (2001)
77 Wong et al. (1999)

### Asthma – All Ages

78 Peel et al. (2005)
79 Ito et al. (2007)*
80 Burnett et al. (1999)
81 Anderson et al. (1998)
82 Atkinson et al. (1999a)
83 Atkinson et al. (1999b)
84 Galan et al. (2003)
85 Chardon et al. (2007)
86 Schouten et al. (1996)
87 Migliaretti et al. (2005)
88 Migliaretti and Cavallo (2004)
89 Hinwood et al. (2006)
90 Petroeschevsky et al. (2001)
91 Wong et al., (1999)
92 Tsai et al. (2006)
93 Tsai et al. (2006)
94 Yang et al. (2007)
95 Yang et al. (2007)

### Asthma – Children

96 Peel et al. (2005)
97 Tolbert et al. (2000)
98 Lin et al. (2003)
99 Lin et al. (2003)
100 Sunyer et al. (1997)
101 Anderson et al. (1998)
102 Atkinson et al. (1999a)
103 Atkinson et al. (1999b)
104 Thompson et al. (2001)
105 Andersen et al. (2007b)
106 Andersen et al. (2007a)
107 Migliaretti et al. (2005)
108 Migliaretti and Cavallo (2004)
109 Migliaretti and Cavallo (2004)
110 Barnett et al. (2005)
111 Barnett et al. (2005)
112 Hinwood et al. (2006)
113 Petroeschevsky et al. (2001)
114 Petroeschevsky et al. (2001)
115 Morgan et al. (1998a)
116 Ko et al. (2007)
117 Lee et al. (2006)
118 Gouveia and Fletcher (2000a)
119 Jaffe et al. (2003)
120 Jaffe et al. (2003)
121 Linn et al. (2000)

### Asthma – Adults

122 Sunyer et al. (1997)
123 Anderson et al. (1998)
124 Atkinson et al. (1999a)
125 Atkinson et al. (1999b)
126 Boutin-Forzano et al. (2004)
127 Tenias et al. (1998)
128 Castellsague et al. (1995)
129 Migliaretti et al. (2005)
130 Morgan et al. (1998a)
131 Ko et al. (2007)
132 Anderson et al. (1998)
133 Atkinson et al. (1999a)
134 Migliaretti et al. (2005)
135 Hinwood et al. (2006)
136 Ko et al. (2007)

### Respiratory Mortality

137 Ostro et al. (2000)
138 Fairley (1999); (Reanalysis 2003)
139 Gamble (1998)
140 Gwynn et al. (2000)
141 Burnett et al. (2004)
142 Villeneuve et al. (2003)
143 Samoli et al. (2006)
144 Zmirou et al. (1998)
145 Biggeri et al. (2005)
146 Anderson et al. (1996)
147 Bremner et al. (1999)
148 Anderson et al. (2001)
149 Le Tertre et al. (2002)
150 Dab et al. (1996)
151 Zmirou et al. (1996)
152 Hoek et al. (2000); (Reanalysis, Hoek (2003)
153 Hoek et al. (2000); (Reanalysis, Hoek (2003)
154 Saez et al. (2002)
155 Garcia-Aymerich et al. (2000)
156 Saez et al. (1999)
157 Sunyer et al. (1996)
158 Borja-Aburto et al. (1998)
159 Gouveia and Fletcher (2000b)
160 Simpson et al. (2005a,b)
161 Simpson et al. (2000)
162 Tsai et al. (2003)
163 Yang et al. (2004b)
164 Wong et al. (2001)
165 Wong et al. (2002)

Animal toxicologic and human clinical studies have been conducted within the range of maximum ambient concentrations observed in epidemiologic studies (100 to 300 ppb) and provide some supporting evidence for the effects observed in the epidemiologic studies. Generally, exposure durations used in human clinical studies are more similar to peak exposures than 24-h avg exposures. Tables 5.3-2 and 5.3-3 summarize the health endpoints that have been linked with $NO_2$ exposure in human clinical and animal toxicologic studies, respectively, along with the lower range of doses or concentrations with which these effects have been reported. To put the concentration information in perspective, average and maximum ambient concentrations from earlier years in the United States and elsewhere were substantially greater than current levels; yet in the 3-year period 2003–2005, 1-h excursions in the United States have been observed in the range of 100 to 200 ppb (see Chapter 2). The human and animal findings underlying this causal judgment are summarized below.

**Table 5.3-2. Key studies and effects of exposure to $NO_2$ from clinical studies.**

| STUDY | $NO_2$ (ppm) | EXPOSURE DURATION (h) | OBSERVED EFFECTS |
|---|---|---|---|
| Folinsbee (1992) | 0.1-0.3 | 0.5-2.0 | Meta-analysis showed increased airway responsiveness following $NO_2$ exposure in asthmatics. Large variability in protocols and responses. Most studies used nonspecific airway challenges. Airway responsiveness tended to be greater for resting (mean 45 min) than exercising (mean 102 min) exposure conditions. |
| Barck et al. (2002, 2005a)<br>Strand et al. (1996; 1997; 1998) | 0.26 | 0.5 | Asthmatics exposed to $NO_2$ during rest experienced enhanced sensitivity to bronchial challenge-induced decrements in lung function and increased allergen-induced airway inflammatory response. Inflammatory response to allergen observed in the absence of allergen-induced lung function response. No $NO_2$-induced change in lung function. |
| Gong et al. (2005)<br>Morrow et al. (1992)<br>Vagaggini et al. (1996) | 0.3-0.4 | 2-4 | Inconsistent effects on FVC and $FEV_1$ in COPD patients with mild exercise. |
| Azadniv et al. (1998)<br>Blomberg et al. (1997; 1999)<br>Devlin et al. (1999)<br>Frampton et al. (2002)<br>Jörres et al. (1995) | 1.0-2.0 | 2-6 | Increased inflammatory response and airway responsiveness to nonspecific challenge in healthy adults exposed during intermittent exercise. Effects on lung function and symptoms in healthy subjects not detected by most investigators. Small decrements in $FEV_1$ reported for asthmatics. |
| Beil and Ulmer (1976)<br>Nieding et al. (1979)<br>Nieding and Wagner (1977)<br>Nieding et al. (1980) | ≥ 2.0 | 1-3 | Lung function changes (e.g., increased airway resistance) in healthy subjects. Effects not found by others at 2-4 ppm. |

## Lung Host Defenses and Immunity

**Impaired host-defense systems and increased risk of susceptibility to both viral and bacterial infections after $NO_2$ exposures were observed in epidemiologic, human clinical, and animal toxicological studies** (Section 3.1.2). A recent epidemiologic study (Chauhan et al., 2003) provided evidence that increased personal exposure to $NO_2$ worsened virus-associated symptoms and decreased lung function in children with asthma. The limited evidence from human clinical studies indicated that **$NO_2$ increases susceptibility to injury by subsequent viral challenge** (Frampton et al., 2002). Animal toxicological studies have shown that lung host defenses are sensitive to $NO_2$ exposure, with several measures of such effects observed at concentrations of less than 1 ppm. The epidemiologic and

experimental evidence indicated coherence for effects of $NO_2$ exposure on host defense (i.e., immune system effects). This group of outcomes also provided plausibility and potential mechanistic support for other respiratory effects described subsequently, such as respiratory symptoms or increased ED visits for respiratory diseases.

**Table 5.3-3. Summary of toxicological effects in rats from $NO_2$ exposure.**

| STUDY | $NO_2$ (ppm) | EXPOSURE DURATION | OBSERVED EFFECTS |
|---|---|---|---|
| Kumae and Arakawa (2006) | 0.2 | From conception to 12 wks post delivery | Increase in BALF lymphocytes (indicative of inflammation) |
| Kumae and Arakawa (2006) | 0.5 | Weanling period (from 5 wks old to 12 wks) | Suppression of ROS (indicative of lung host defense impairment) |
| Robison et al. (1993) | 0.5 | 0.5-10 days | Depressed activation of arachidonic acid metabolism and superoxide production (indicative of lung host defense impairment) |
| Mercer et al. (1995) | 0.5 spikes of 1.5 | 9 wks | Increase in the number of fenestrae in the lungs (morphological effects) |
| Barth et al. (1994) | 0.8 | 1 or 3 days | Increase in bronchiolar epithelial proliferation (morphological effects) |

Note: Lowest-observed-effect level based on category BALF=Bronchoalveolar lavage fluid ROS=Reactive oxygen species

## Airway Inflammation

Together, the findings of human and animal studies provided some evidence for airway inflammation with $NO_2$ exposure, particularly in the more sensitive subgroups such as children or asthmatics. The few epidemiologic studies that considered inflammation showed an association between ambient $NO_2$ concentrations and inflammatory response in the airways in children. The associations were inconsistent in the adult populations examined (Section 3.1.3). Effects of $NO_2$ on airway inflammation have been observed in human clinical and animal toxicological studies at higher than ambient levels (0.4-5 ppm). **Human clinical studies shows that airway inflammation is increased at $NO_2$ concentrations of <2.0 ppm; the onset of inflammatory responses in healthy subjects appears to be between 100 and 200 ppm-min, i.e., 1 ppm for 2 to 3 h** (Figure 3.1-1). Increases in biological markers of inflammation were not observed consistently in healthy animals at levels of less than 5 ppm; however, increased susceptibility to $NO_2$ concentrations of as low as 0.4 ppm was observed when lung vitamin C was reduced (by diet) to levels that were <50% of normal. These data provided some evidence for biological plausibility and one potential mechanism for other respiratory effects, such as exacerbation of asthma symptoms or increased ED visits for asthma.

## Airway Hyperresponsiveness

The evidence from human and animal experimental studies provided some evidence for increased airway responsiveness to specific allergen challenges following $NO_2$ exposure (Section 3.1.4.1). Recent human clinical studies involving allergen challenge in asthmatics reported that **$NO_2$ exposure may enhance the sensitivity to allergen-induced decrements in lung function and increase the allergen-induced airway inflammatory response at exposures as low as 0.26 ppm $NO_2$ for 30 min** (Figure 3.1-2). Increased immune-mediated pulmonary inflammation also was observed in rats exposed to house dust mite allergen following exposure to 5 ppm $NO_2$ for 3 h. Exposure to $NO_2$ also has been found to enhance the inherent responsiveness of the airway to subsequent nonspecific challenges in human clinical studies (Section 3.1.4.2). In general, small but significant **increases in nonspecific airway hyperresponsiveness**

**were observed in the range of 1.5 to 2.0 ppm for 3 h exposures in healthy adults and between 0.2 and 0.3 ppm $NO_2$ for 30 -min exposures and at 0.1 ppm $NO_2$ for 60-min exposures in asthmatics**. Subchronic exposures (6 to 12 weeks) of animals to $NO_2$ also increased responsiveness to nonspecific challenges at exposures of 1 to 4 ppm.

### Respiratory Symptoms

Consistent evidence has been observed for an association of respiratory effects with indoor and personal $NO_2$ exposures in children at ambient concentration levels (Section 3.1.5.1). In particular, the Pilotto et al. (2004) intervention study provided evidence of improvement in respiratory symptoms with reduced $NO_2$ exposure in asthmatic children. This study linked respiratory effects with exposure to $NO_2$ from an indoor combustion source,(i.e., unflued gas heaters), thus, increased confidence that $NO_2$ is not solely a marker for an ambient air pollution mixture in observed associations with $NO_2$ from outdoor sources (in particular traffic emissions) that has infiltrated indoors. The epidemiologic studies using community ambient monitors also found associations between ambient $NO_2$ concentration and respiratory symptoms (Section 3.1.4.2, see Figure 3.1-6). The results of recent multicity studies (Schildcrout et al., 2006; Mortimer et al., 2002) provided further support for associations between respiratory symptoms and medication use in asthmatic children. **Positive associations were observed in cities where the median range was 18 to 26 ($90^{th}$ percentiles: 34 to 37) ppb for a 24-h avg (Schildcrout et al., 2006) and the mean $NO_2$ level was 32 (range: 7 to 96) ppb for a 4-h avg (Mortimer et al., 2002).** These concentrations were within the range of 24-h avg concentrations observed in recent years. In the results of multipollutant models, $NO_2$ associations in these multicity studies were generally robust to adjustment for copollutants including $O_3$, CO, and $PM_{10}$ (Figure 3.1-7).

Most human clinical studies do not report or observe respiratory symptoms with $NO_2$ exposure, and animal toxicological studies do not measure effects that would be considered symptoms. The experimental evidence on immune system effects and airway inflammation discussed previously, however, provide some plausibility and coherence for the observed respiratory symptoms in epidemiologic studies.

### Lung Function

Recent epidemiologic studies that examined the association between ambient $NO_2$ concentrations and lung function in children and adults generally produced inconsistent results (Section 3.1.5.1). **Human clinical studies generally did not find direct effects of $NO_2$ on lung function in healthy adults at levels as high as 4.0 ppm** (Section 3.1.5.2). For asthmatics, the direct effects of $NO_2$ on lung function also have been inconsistent at exposure concentrations of less than 1 ppm $NO_2$.

### Respiratory ED Visits and Hospitalizations

Epidemiologic evidence exists for **positive associations of short-term ambient $NO_2$ concentrations below the current NAAQS level with increased numbers of ED visits and hospital admissions for respiratory causes, especially asthma** (Section 3.1.7). A number of studies were conducted in locations where mean 24-h concentrations were in the range of 3 to 50 (maxima: 28 to 82) ppb (Figure 5.3-1). These associations are particularly consistent among children and older adults (65+ years) when all respiratory outcomes are analyzed together (Figures 3.1-8 and 3.1-9), and among children and subjects of all ages for asthma admissions (Figures 3.1-12 and 3.1-13). When examined with copollutant models, associations of $NO_2$ with respiratory ED visits and hospital admissions were generally robust and independent of the effects of copollutants (Figures 3.1-10 and 3.1-11). In preceding sections, mechanistic evidence was described related to host defense and immune system changes, airway

inflammation, and airway responsiveness that provide plausibility and coherence for these observed effects.

### 5.3.2.2. Cardiovascular Effects Related to Short-Term Exposure

The available evidence on the effects of short-term exposure to $NO_2$ on cardiovascular health effects is **inadequate to infer the presence or absence of a causal relationship** at this time. Evidence from epidemiologic studies of heart rate variability (HRV), repolarization changes, and cardiac rhythm disorders among heart patients with ischemic cardiac disease was inconsistent (Section 3.2.1). In most studies, associations with PM were found to be similar or stronger than associations with $NO_2$. The mean 24-h concentrations generally were in the range of 9 to 39 ppb (Annex Table AX6.3-6). Generally positive associations between ambient $NO_2$ concentrations and hospital admissions or ED visits for cardiovascular disease have been reported in single-pollutant models where mean 24-h concentrations generally were in the range of 20 to 40 ppb (Section 3.2.2); however, most of these effect estimates were diminished in multipollutant models that also contained CO and PM. Mechanistic evidence of a role for $NO_2$ in the development of cardiovascular diseases from studies of biomarkers of inflammation, cell adhesion, coagulation, and thrombosis is lacking (Section 3.2.1.4; Seaton and Dennekamp, 2003). Furthermore, the effects of $NO_2$ on various hematological parameters in animals are inconsistent and, thus, provide little biological plausibility for effects of $NO_2$ on the cardiovascular system. However, evidence from two human clinical studies was indicative of a reduction in hemoglobin with $NO_2$ exposure at concentrations between 1.0 and 2.0 ppm (with 3 h exposures).

### 5.3.2.3. Mortality Related to Short-Term Exposure

The epidemiologic evidence is **suggestive but not sufficient to infer a causal relationship** of short-term exposure to $NO_2$ with all cause and cardiopulmonary-related mortality. Results from several large U.S. and European multicity studies and a meta-analysis study indicated positive associations between ambient $NO_2$ concentrations and the risk of all-cause (nonaccidental) mortality, with effect estimates ranging from 0.5 to 3.6% excess risk in mortality per standardized increment[1] (Section 3.3.1, Figure 3.3-2). In general, the $NO_2$ effect estimates were robust to adjustment for copollutants. Both cardiovascular and respiratory mortality were associated with increased $NO_2$ concentrations in epidemiologic studies (Figure 3.3-3); however, similar associations were observed for other pollutants, including PM and $SO_2$. The range of risk estimates for excess mortality was generally smaller than that for other pollutants such as PM. While $NO_2$ exposure, alone or in conjunction with other pollutants, may contribute to increased mortality, evaluation of the specificity of this effect was difficult. Clinical studies showing hematologic effects and animal toxicological studies showing biochemical, lung host defense, permeability, and inflammation changes with short-term exposures to $NO_2$ provide limited evidence of plausible pathways by which risks of morbidity and, potentially, mortality may be increased, but no coherent picture is evident at this time.

### 5.3.2.4. Respiratory Morbidity Related to Long-Term Exposure

The epidemiologic and toxicological evidence examining the effect of long-term exposure to $NO_2$ on respiratory morbidity is **suggestive but not sufficient to infer a causal relationship** at this time. A number of epidemiologic studies examined the effects of long-term exposure to $NO_2$ and reported positive associations with decrements in lung function and partially irreversible decrements in lung function

[1]Excess risk estimates are standardized to a 20-ppb incremental change in daily 24-h avg $NO_2$ or a 30-ppb incremental change in daily 1-h max $NO_2$.

growth (Section 3.4.1, Figures 3.4-1 and 3.4-2). Results from the Southern California Children's Health Study indicated that decrements were similar for boys and girls and among children who had no history of asthma (Gauderman et al., 2004). The mean $NO_2$ concentrations in these studies range from 21.5 to 34.6 ppb. Similar associations have also been found for PM, $O_3$, and proximity to traffic (<500 m), though these studies did not report the results of copollutant models. The high correlation among traffic-related pollutants made it difficult to accurately estimate the independent effects in these long-term exposure studies. Results from the available epidemiologic evidence investigating the association between long-term exposure to $NO_2$ and increases in asthma prevalence and incidence were suggestive (Section 3.4.2). Two major cohort studies, the Children's Health Study in southern California (Gauderman et al., 2005) and a birth cohort study in the Netherlands (Brauer et al., 2007) observed significant associations; however, several other studies did not find consistent associations between long-term $NO_2$ exposure and asthma outcomes. Epidemiologic studies conducted in both the U.S. and Europe also have produced inconsistent results regarding an association between long-term exposure to $NO_2$ and respiratory symptoms (Section 3.4.3). While some positive associations were noted, a large number of symptom outcomes were examined and the results across specific outcomes were inconsistent. Animal toxicological studies demonstrated that $NO_2$ exposure resulted in morphological changes in the centriacinar region of the lung and in bronchiolar epithelial proliferation (Section 3.4.4), which may provide some biological plausibility for the observed epidemiologic associations between long-term exposure to $NO_2$ and respiratory morbidity. Susceptibility to these morphologic effects was found to be influenced by many factors, such as age, compromised lung function, and acute infections.

### 5.3.2.5. Other Morbidity Related to Long-Term Exposure

The available epidemiologic and toxicological evidence was **inadequate to infer the presence or absence of a causal relationship** for carcinogenic, cardiovascular, and reproductive and developmental effects related to long-term $NO_2$ exposure. Two epidemiologic studies conducted in Europe showed an association between long-term $NO_2$ exposure and increased incidence of cancer (Nyberg et al., 2000; Nafstad et al., 2003). However, the animal toxicological studies provided no clear evidence that $NO_2$ acts as a carcinogen, though it does appear to act as a tumor promoter at the site of contact (Section 3.5.1). There were no in vivo studies supporting the hypothesis that $NO_2$ causes teratogenesis or malignant tumors. A more likely pathway for $NO_2$ involvement in cancer induction is through secondary formation of nitro-PAHs, as nitro-PAHs are known to be more mutagenic than the parent compounds. The very limited epidemiologic and toxicological evidence does not indicate that long-term exposure to $NO_2$ has cardiovascular effects (Section 3.5.2). The U.S. Women's Health Initiative study (Miller et al., 2007) did not find any associations between long-term $NO_2$ exposure and cardiovascular events. The toxicological studies found some effects of $NO_2$ on cardiac performance and heart rate, but only at exposure levels of above 4 ppm. The epidemiologic evidence was not consistent for associations between $NO_2$ exposure and growth retardation; however, some evidence is accumulating for effects on preterm delivery (Section 3.5.3). Similarly, scant animal evidence supports a weak association between $NO_2$ exposure and adverse birth outcomes and provides little mechanistic information or biological plausibility for the epidemiologic findings.

### 5.3.2.6. Mortality Related to Long-Term Exposure

The epidemiologic evidence was **inadequate to infer the presence or absence of a causal relationship** between long-term exposure to $NO_2$ and mortality. In the U.S. and European cohort studies examining the relationship between long-term exposure to $NO_2$ and mortality, results were generally inconsistent (Section 3.6, Figure 3.6-2). Further, when associations were noted, they were not specific to

$NO_2$, but also implicated PM and other traffic indicators. The relatively high correlations reported between $NO_2$ and PM indices (r ~0.8) make it difficult to interpret these associations.

### 5.3.2.7. Exposure Indices

The available $NO_2$ indices used to indicate short-term ambient $NO_2$ exposure are daily 1-h max; 24-h avg; and 2-week avg $NO_2$ concentrations. New data on short-term exposures have been published since the 1993 $NO_X$ AQCD. Some studies examined only one index, and these studies form an evidence base for that individual index. A few studies used both 1-h and 24-h data and, thus, allow a comparison of these averaging periods. These included studies of respiratory symptoms, ED visits for asthma, hospital admissions for asthma, and mortality. **Comparisons of effect estimates for asthma ED visits for the 1-h and 24-h time periods showed that the effect estimates are not different**. Experimental studies in both animals and humans provided evidence that short-term $NO_2$ exposure (i.e., <1 h to 2–3 h) can result in respiratory effects such as increased airway responsiveness or inflammation, thereby increasing the potential for exacerbation of asthma. These findings generally supported epidemiologic evidence on short-term exposures, but did not provide evidence that distinguishes effects for one short-term averaging period from another. Differences between daily 1-h max and 24-h avg exposures estimates are unlikely to be well characterized by the limited monitoring data available. Though an array of studies that examined short-term (24-h avg and 1-h maximum) $NO_2$ exposures and respiratory morbidity consistently produced positive associations, it is not possible to discern whether these effects are attributable to average daily (or multiday) concentrations (24-h avg) or high, peak exposures (1-h max).

### 5.3.2.8. Susceptible and Vulnerable Populations

Based on both short- and long-term studies of an array of respiratory health effects data, **persons with preexisting pulmonary conditions are likely at greater risk from ambient $NO_2$ exposures than the general public**, with the most extensive evidence available for asthmatics as a potentially susceptible group. In addition, studies indicated that upper respiratory viral infections can trigger susceptibility to the effects of exposure to $NO_2$. There was supporting evidence of age-related differences in susceptibility to $NO_2$ health effects such that the elderly population (>65 years of age) appeared to be at increased risk of mortality and hospitalizations, and that children (<18 years of age) experienced other potentially adverse respiratory health outcomes with increased $NO_2$ exposure. People with occupations that require them to be in or close to traffic or roadways (i.e., bus and taxi drivers, highway patrol officers) may have enhanced exposure to $NO_2$ compared to the general population, possibly increasing their vulnerability. A considerable portion of the population resides and/or attends school near major roadways, increasing their exposure to $NO_2$ and other traffic pollutants. Otherwise susceptible individuals (schoolchildren, older adults) in this subpopulation may be at increased risk. Recent studies have evaluated the effect of socioeconomic status (SES) on susceptibility to the effects of $NO_2$ exposure; however, to date, these studies are too few in number to draw conclusions. Though data are just emerging (Romieu et al., 2006; Islam et al., 2007), it is believed that a genetic component could be important in characterizing the association between $NO_2$ exposure and adverse health effects.

### 5.3.2.9. Concentration-Response Relationships and Thresholds

The conclusions pertaining to respiratory health presented in this ISA are based on numerous studies, including panel and field, intervention, and multipollutant studies that control for the effects of other pollutants, and studies conducted in areas where the whole distribution of ambient 24-h avg $NO_2$ concentrations was below the current NAAQS level of 0.053 ppm (annual average). In some cases the mean exposure in positive epidemiologic studies are <10 ppb; the policy-relevant background

concentration is <0.01 ppb. In studies that have examined concentration-response relationships between $NO_2$ and health outcomes, the concentration-response relationship appears linear within the observed range of data, including at levels below the current standard. There is **little evidence of any effect threshold** (Section 4.2). Factors that made it difficult to identify any threshold that may exist included: interindividual variation; additivity of pollutant-induced effects to the naturally occurring background disease processes; additivity to health effects due to other environmental insults having a mode of action similar to that of $NO_2$; exposure error; and response measurement error. Low data density in the lower concentration range as a result of limited monitoring is a particular problem in terms of measurement error. Additionally, if the concentration-response relationship was shallow, identification of any threshold that may exist will be more difficult to discern.

# 5.4. Conclusions

New evidence confirms previous findings in the 1993 AQCD that short-term $NO_2$ exposure is associated with increased airway responsiveness, often accompanied by respiratory symptoms, particularly in children and asthmatics. This ISA concludes that the strongest evidence for an association between $NO_2$ exposure and adverse human health effects comes from epidemiologic studies of respiratory symptoms and ED visits and hospital admissions. These new findings were based on numerous studies, including panel and field studies, multipollutant studies that control for the effects of other pollutants, and studies conducted in areas where the whole distribution of ambient 24-h avg $NO_2$ concentrations was below the current NAAQS level of 0.053 ppm (53 ppb) (annual average). The effect estimates from the U.S. and Canadian studies generally indicate a 2-20% increase in risks for ED visits and hospital admissions. Risks associated with respiratory symptoms generally were higher. The studies providing this evidence (summarized in Table 5.4-1) were identified based on criteria for selecting epidemiologic studies for inclusion in the ISA (Annex Section AX1.3.2 and Annex Figure AX1.3-1). They include U.S. and Canadian studies conducted at or near ambient concentrations, which were well-designed, properly implemented, and thoroughly described. All of the U.S. and Canadian studies included in Figure 5.3-1 are included in Table 5.4-1. Evidence from human clinical studies, especially for airway hyperresponsiveness in asthmatic individuals, was generally supportive of the epidemiologic evidence (see Table 5.3-2).

These conclusions were supported by some evidence from toxicological and human clinical studies. These data sets formed a plausible, consistent, and coherent description of a relationship between $NO_2$ exposures and an array of adverse health effects that range from the onset of respiratory symptoms to hospital admission. Though an array of studies that examined short-term (24-h avg and 1-h max) $NO_2$ exposures and respiratory morbidity consistently produced positive associations, it is not possible to discern whether these effects are attributable to average daily (or multiday) concentrations (24-h avg) or high, peak exposures (1-h max). While the evidence supported a direct effect of short-term $NO_2$ exposure on respiratory morbidity, the available evidence was inadequate to infer the presence or absence of a causal relationship for morbidity and mortality effects related to long-term $NO_2$ exposure. Further, the health evidence was inadequate to infer the presence or absence of a causal relationship for carcinogenic, cardiovascular, and reproductive and developmental effects, or for premature mortality, related to long-term $NO_2$ exposure.

The available evidence on the effects of short-term exposure to $NO_2$ for cardiovascular health effects is inadequate to infer the presence or absence of a causal relationship at this time. Though there is no human clinical or animal toxicological evidence, the epidemiologic evidence is suggestive but not sufficient to infer a causal relationship of short-term exposure to $NO_2$ with nonaccidental and cardiopulmonary-related mortality.

It is difficult to determine from these new studies the extent to which $NO_2$ is independently associated with respiratory effects or if $NO_2$ is a marker for the effects of another traffic-related pollutant or mix of

pollutants (see Section 5.2.2 for more details on exposure issues). On-road vehicle exhaust emissions are a nearly ubiquitous source of combustion pollutant mixtures that include $NO_2$ and can be an important contributor to $NO_2$ levels in near-road locations. Although this complicates the efforts to disentangle specific $NO_2$-related health effects, the evidence summarized in this assessment indicates that $NO_2$ associations generally remain robust in multipollutant models and supports a direct effect of short-term $NO_2$ exposure on respiratory morbidity at ambient concentrations below the current NAAQS level. The robustness of epidemiologic findings to adjustment for copollutants, coupled with data from animal and human experimental studies, support a determination that the relationship between $NO_2$ and respiratory morbidity is likely causal, while still recognizing the relationship between $NO_2$ and other traffic related pollutants. In addition, an intervention study by Pilotto et al. (2004) found that exposure to $NO_2$ from an indoor combustion source is associated with respiratory effects; in this study $NO_2$ effects would not be confounded by other motor vehicle emission pollutants, though potential confounding by other pollutants from gas stove emissions, such as UFP, could occur.

Human clinical and toxicological study findings also provide support for independent effects of $NO_2$ on respiratory health. Limited evidence from human clinical studies indicated that $NO_2$ may increase susceptibility to injury by subsequent viral challenge; toxicological studies show that lung host defenses are sensitive to $NO_2$ exposure. The epidemiologic and experimental evidence together show coherence for effects of $NO_2$ exposure on host defense or immune system effects providing plausibility and mechanistic support for respiratory symptoms and ED visits for respiratory disease. Additionally, short-term exposure to $NO_2$ shows increased airway inflammation in human clinical and animal toxicological studies but at exposure concentrations higher than ambient levels. Human and animal experimental studies provide support for increased airways responsiveness to specific and nonspecific challenge following $NO_2$ exposure. Transient increases in airway responsiveness following $NO_2$ exposure have the potential to increase symptoms and worsen asthma control.

Identification of a concentration-response relationship is an additional uncertainty that must be considered when describing the association of $NO_2$ and adverse health effects. In studies that have examined concentration-response relationships between $NO_2$ and health outcomes specifically, there was little evidence of an effect threshold. Because ambient levels of $NO_2$ are low in many of the epidemiologic study sites, the concentration-response relationship may be shallow, making it difficult to identify any threshold.

**Table 5.4-1. Ambient $NO_2$ concentrations and selected effect estimates from studies of respiratory symptoms, ED visits and hospital admissions in the U.S. and Canada.Complete results and study details in Annex Tables AX6.3-2 through AX6.3-5.**

| STUDY | POPULATION | AVG TIME | MEAN (SD) | RANGE | STANDARDIZED[a] % EXCESS RISK (95% CI) |
|---|---|---|---|---|---|
| ***Respiratory Symptoms*** | | | | | |
| Schwartz et al. (1994) | 6 cities, U.S. | 24-h avg | 13 ppb (NR) | Max: 44 | 61.3% (8.2, 143.4) Cough Incidence |
| Mortimer et al. (2002) | 8 urban areas, U.S. | 4-h avg | 32 ppb (NR) | –7, 96 | 48% (2, 116) Morning Asthma Symptoms |
| Schildcrout et al. (2006) | 8 North American Cities | 24-h avg | 17-26 ppb (NR) | NR | 4.0% (1.0, 7.0) Asthma Symptoms |
| Ostro et al. (2001) | LA and Pasadena, CA | 1-h max | 68-80 ppb (NR) | 20, 220 | 7.0% (1.0, 13.8) Cough Onset |
| Delfino et al. (2002) | Alpine, CA | 1-h max | 24 ppb (10) | 8, 53 | 34.6% (-17.9, 122.1) Asthma Symptoms |
| Delfino et al. (2003) | East LA County, CA | 1-h max | 7.2 ppb (2.1) | 3, 14 | 120% (-46, 2,038) Asthma Symp. Scores >1 |
| Linn et al. (1996) | Los Angeles, CA | 24-h avg | 33 ppb (22) | 1, 96 | -18.2% (-47.3, 27.1) Morning Symptom Score |
| ***Emergency Department Visits – All Respiratory*** | | | | | |
| Peel et al. (2005) | Atlanta, GA | 1-h max | 45.9 ppb (17.3) | Max: 256 | 2.4% (0.9, 4.1) |
| Tolbert et al. (2007) | Atlanta, GA | 1-h max | 43.2 ppb (NR) | 1.0-181 | 2% (0.5, 3.3) |
| ***Emergency Department Visits – Asthma*** | | | | | |
| Jaffe et al. (2003) | 2 cities, OH, (Clev, Cinc) | 24-h avg | Cinc:50 ppb (15)<br>Clev:48 ppb (15) | NR | 6.1% (-2.0, 14.0) |
| Ito et al. (2007) | New York, NY | 24-h avg | 31.1 ppb (8.7) | NR | 12% (7, 16) |
| New York State Department of Health (2006) | Bronx and Manhattan, NY | 24-h avg | 34 ppb (NR) | NR | 6% (1, 10) Bronx. -3% (-18, 14) Manhattan |
| Peel et al. (2005) | Atlanta, GA | 1-h max | 45.9 ppb (17.3) | NR | 2.1% (-0.4, 4.5) All Ages. 4.1% (0.8, 7.6) 2-18 yrs |
| Tolbert et al. (2000) | Atlanta, GA | 1-h max | 81.7 ppb (53.8) | 5.4, 306 | 0.7% (-0.8, 2.3) |
| ***Hospital Admissions – All Respiratory*** | | | | | |
| Burnett et al. (1997a) | 16 Canadian Cities | 1-h max | 35.5 ppb (16.5) | NR | -0.3% (-2.4, 1.8) adjusted for CO, $O_3$, $SO_2$, CoH |
| Yang et al. (2003) | Vancouver, BC | 24-h avg | 18.7 ppb (5.7) | NR | 19.1% (7.4, 36.3)<3 yrs. 19.1% (11.2, 36.3) >65 yrs |
| Fung et al. (2006) | Vancouver, BC | 24-h avg | 16.8 ppb (4.3) | 7.2, 33.9 | 9.1% (1.5, 17.2) |
| Burnett et al. (2001) | Toronto, ON | 1-h max | 44.1 ppb (NR) | Max: 146 | 13.3% (5.3, 22.0) |
| Luginaah et al. (2005) | Windsor, ON, | 1-h max | 38.9 ppb (12.3) | NR | 6.7% (-5.4, 20.4) female. -10.3% (-20.3, 1.1) male |
| ***Hospital Admissions – Asthma*** | | | | | |
| Linn et al. (2000) | Los Angeles, CA | 24-h avg | 3.4 ppb (1.3) | NR | 2.8% ± 1.0% |
| Lin et al. (2004) | Vancouver, BC | 24-h avg | 18.7 ppb (5.6) | 4.3, 5.4 | 45.3% (12.7, 88.3) Boys. 23.0% (-11.7, 70.2) Girls |
| Lin et al. (2003) | Toronto, ON | 24-h avg | 25.2 ppb (9.04) | 3.0, 82.0 | 18.9% (1.8, 39.3) Boys. 17.0% (-5.4, 41.4) Girls |
| Burnett et al. (1999) | Toronto, ON | 24-h avg | 25.2 ppb (9.1) | NR | 2.60% (0, 5) |

Note: Several U.S. and Canadian studies were excluded from Figure 5.3-1 and this table because they were either GAM-impacted (Cassino et al., 1999; Gwynn et al. 2000; Norris et al. 1999; Stieb et al. 2000) or did not present sufficient quantitative risk estimates (Lipsett et al., 1997; Sinclair and Tolsma 2004).
[a]24-h avg effect estimates standardized to 20 ppb increment; 1-h max effect estimates standardized to 30 ppb increment.

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