

Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

Chapter 2: Exposure and Dosimetry of Inhaled Oxides of Nitrogen

External Review Draft

July 2026

U.S. Environmental Protection Agency

Disclaimer

This document is an external review draft for peer review purposes only. This information is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by the U.S. Environmental Protection Agency. It does not represent and should not be construed to represent any agency determination or policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Document Guide

This Document Guide is intended to orient readers to the organization of the Oxides of Nitrogen Integrated Science Assessment (ISA) in its entirety and to the sub-section of the ISA at hand (indicated in bold). The ISA consists of the Front Matter (list of authors, contributors, reviewers, and acronyms), Executive Summary, Integrated Synthesis, and 14 chapters, which can all be found at <https://www.epa.gov/isa/integrated-science-assessment-isa-oxides-nitrogen-health-criteria>.

Front Matter

Executive Summary

Integrated Synthesis

Chapter 1. Atmospheric Chemistry and Ambient Concentrations

Chapter 2. Exposure and Dosimetry of Inhaled Oxides of Nitrogen

Chapter 3. Respiratory Effects – Short-Term Exposure

Chapter 4. Respiratory Effects – Long-Term Exposure

Chapter 5. Cardiovascular Effects – Short-Term Exposure

Chapter 6. Cardiovascular Effects – Long-Term Exposure

Chapter 7. Reproductive and Developmental Effects

Chapter 8. Metabolic Syndrome and Diabetes

Chapter 9. Nervous System Effects

Chapter 10. Total Mortality – Short-Term Exposure

Chapter 11. Total Mortality – Long-Term Exposure

Chapter 12. Cancer

Chapter 13. Health Effects with Limited Evidence

Chapter 14. Process for Developing the Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

Appendix A. Appendix Tables

Table of Contents

Disclaimer	ii
Document Guide	iii
Table of Contents	iv
List of Tables	vi
List of Figures	vii
Acronyms and Abbreviation	viii
Exposure and Dosimetry of Inhaled Oxides of Nitrogen	1
2.1 Introduction	1
2.2 Sources Contributing to Exposures	3
2.2.1 Concepts Related to Exposures Ambient Air Pollutants	3
2.2.2 Outdoor Sources of Oxides of Nitrogen	6
2.2.3 Indoor Sources of Oxides of Nitrogen and Indoor Dynamics/Chemistry	9
2.3 Exposure Estimation Methods and Exposure Determinants	15
2.3.1 Methods for Exposure Characterization	15
2.3.2 Factors Determining Exposure and Contributing to Exposure Errors	34
2.3.3 Personal-Ambient Relationships for NO ₂	55
2.3.4 Differential Exposures Across Populations	65
2.4 Exposures to Copollutants or Other Stressors	85
2.4.1 NO ₂ and other TRAPs in Near-road Environments	86
2.4.2 Associations of NO ₂ and Copollutant Exposures in Ambient Settings not Specific to Near-road Environments	91
2.4.3 Ambient NO ₂ and Noise	104
2.5 Implications for Epidemiologic Studies	106
2.5.1 Short-term Exposure Studies	107
2.5.2 Long-Term Exposure Studies	112
2.6 Dosimetry of Inhaled Oxides of Nitrogen	116
2.6.1 Introduction	116
2.6.2 Dosimetry of Nitrogen Dioxide	117
2.6.3 Dosimetry of Nitric Oxide	133
2.7 Conclusions	143
2.7.1 Conclusions of Exposure Assessment	143
2.7.2 Dosimetry conclusions	146

2.8 References..... 149

List of Tables

Table 2-1	Nitrogen dioxide and nitrous acid concentrations in indoor air in the presence or absence of indoor combustion sources	10
Table 2-2	Summary of causality determinations by health outcome	12
Table 2-3	Summary of studies using hybrid models and author evaluations	27
Table 2-4	Summary of exposure estimation methods, their typical use in nitrogen dioxide epidemiologic studies, and related errors and uncertainties	30
Table 2-5	Summary of near-road gradient investigations for oxides of nitrogen	40
Table 2-6	Mean ventilation rates (L/min) at different activity levels for different age groups	50
Table 2-7	Meta-analysis results of 32 populations from recent studies examining the relationship between personal nitrogen dioxide exposure measurements and ambient concentrations	57
Table 2-8	Summary of associations between personal oxides of nitrogen exposures and ambient concentrations	58
Table 2-9	Proportion of Children ^a Residing Near Roads Compared to Away From Roads in Major Metropolitan Areas	80
Table 2-10	Correlations between ambient NO ₂ and other pollutants in the near-road environment	89
Table 2-11	Correlations between ambient NO ₂ and PM _{2.5} , PM ₁₀ , O ₃ , SO ₂ , and CO	94
Table 2-12	Correlations between ambient NO ₂ and other traffic-emitted pollutants	100
Table 2-13	Chemical properties of nitrogen dioxide (NO ₂) and nitric oxide (NO) ¹	117
Table 2-14	Small molecular weight antioxidant concentrations in epithelial lining fluid and predicted penetration distances for nitrogen dioxide	127

List of Figures

Figure 2-1	Indoor dynamics of oxides of nitrogen.	14
Figure 2-2	European Study of Cohorts for Air Pollution Effects study areas.	23
Figure 2-3	Diurnal profiles for NO ₂ , NO, and NO _x for two different near-road sites in Atlanta, GA.	37
Figure 2-4	(a) Predicted and observed NO ₂ concentrations for all wind and stability conditions combined and (b) Predicted and observed NO ₂ /NO _x ratios for all wind and stability conditions combined.	38
Figure 2-5	NO ₂ and NO _x concentration measurements relative to Interstate-15 in Las Vegas, NV.	38
Figure 2-5	Distribution of NO _x concentrations in the Dorm Room Inhalation to Vehicle Emissions study.	40
Figure 2-6	Out-of-home and in-home time use: 2019 and 2021 to 2023.	48
Figure 2-7	Travel time by mode: 2019 and 2021 to 2023.	49
Figure 2-8	Two-week integrated paired measurements of NO ₂ and NO _x by city.	54
Figure 2-9	The proximity of children populations to urban roadways in Atlanta (U.S. census data, EPA AQS).	68
Figure 2-10	The proximity of children populations to urban roadways in Boston (U.S. census data, EPA AQS).	69
Figure 2-11	The proximity of children populations to urban roadways in Dallas (U.S. census data, EPA AQS).	70
Figure 2-12	The proximity of children populations to urban roadways in Denver (U.S. census data, EPA AQS).	71
Figure 2-13	The proximity of children populations to urban roadways in Indianapolis (U.S. census data, EPA AQS).	72
Figure 2-14	The proximity of children populations to urban roadways in Los Angeles (U.S. census data, EPA AQS).	73
Figure 2-15	The proximity of children populations to urban roadways in New Orleans (U.S. census data, EPA AQS).	74
Figure 2-16	The proximity of children populations to urban roadways in New York (U.S. census data, EPA AQS).	75
Figure 2-17	The proximity of children populations to urban roadways in Philadelphia (U.S. census data, EPA AQS).	76
Figure 2-18	The proximity of children populations to urban roadways in Phoenix (U.S. census data, EPA AQS).	77
Figure 2-19	The proximity of children populations to urban roadways in San Francisco (U.S. census data, EPA AQS).	78
Figure 2-20	The proximity of children populations to urban roadways in Seattle (U.S. census data, EPA AQS).	79
Figure 2-21	Relative bias in health effect estimates across studies on all criteria pollutants for each exposure measurement error sources examined in the time-series epidemiologic studies; relative bias was calculated as the ratio of the difference in effect estimates and the true effect defined by study authors.	109
Figure 2-22	Relative bias across studies for each exposure measurement error sources examined in the long-term exposure studies.	114

Acronyms and Abbreviation

<i>a</i>	exposure factor	GS	glutathione
<i>a_j</i>	microenvironment's air exchange rate	GSD	geometric standard deviation
AADT	annual average daily traffic	GSH	glutathione
ADMS	Atmospheric Dispersion Modeling System	GSV	Google Street View
AERMOD	American Meteorological Society and EPA Regulatory Model	GWR	Geographically weighted regression
AMF	air mass factor	H ₂ O ₂	hydrogen peroxide
APEX	Air Pollution Exposure	HENGH	Healthy Efficient New Gas Home
AQCD	Air Quality Criteria Documents	HIV	Human immunodeficiency virus
AQS	Air Quality System	HNO ₃	nitric acid
ATUS	American Time Use Survey	HOMEChem	House Observations of Microbial and Environmental Chemistry
avg	average	HONO	nitrous acid
β	beta	HO ₂	hydroperoxyl radical
BC	Black Carbon	HO ₂ NO ₂	Peroxynitric acid
BL	bronchial lavage	hr	hour(s)
<i>C_a</i>	ambient pollutant concentration	IDW	Inverse distance weighting
<i>C_{o,j}</i>	the outdoor concentration	<i>INF_j</i>	infiltration factor of the <i>j</i> th microenvironment
CBSAs	Core-Based Statistical Areas	iNOS	inducible nitric oxide synthase
CH ₄	methane	IQR	Interquartile range
CHAD	Consolidated Human Activity Database	ISA	Integrated Science Assessment
<i>C_j</i>	average pollutant concentration	<i>j</i> th	microenvironment
CMAQ	Community Multiscale Air Quality	<i>k_j</i>	decay rate
CNHS	California New Home Study	L	liter(s)
CO	carbon monoxide	LCSs	low-cost sensors
CTMs	chemical transport modeling	LHEM	London Hybrid Exposure Model
CV	cross-validation	LISTOS	Long Island Sound Tropospheric Ozone Study
Cys	cysteine	LUR	Land use regression
<i>d</i>	square distance	M	male
DNA	Deoxyribonucleic acid	m	milligram
DPPC	dipalmitoyl phosphatidylcholine	M/F	male/female
<i>E_o</i>	Outdoor microenvironmental exposures	m	meter(s)
<i>E_a</i>	ambient pollutant exposure	MESA	Multi-Ethnic Study of Atherosclerosis
<i>E_{o,j}</i>	ambient exposure to NO ₂	MESA-air	Multi-Ethnic Study of Atherosclerosis and Air Pollution study
<i>E_{i,j}</i>	exposure to ambient sources	min	minute(s) or minimum
<i>E_{na}</i>	nonambient exposure	mL	milliliter
<i>E_T</i>	personal exposure	mo	month(s)
EC	elemental carbon	mpp	multiphase process
EGU	Electric Generating Units	MOVES	Motor Vehicle Emissions Simulator
e.g.	exempli gratia (for example)	MVPA	moderate-to-vigorous physical activity
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe	N	Population size
ELF	epithelial lining fluid	N ₂	dinitrogen
ESCAPE	European Study of Cohorts for Air Pollution Effects	NAAQS	National Ambient Air Quality Standard
etc.	et cetera	NASA	National Aeronautics and Space Administration
EPA	Environmental Protection Agency	NDMA	N-nitrosodimethylamine
eNOS	endothelial nitric oxide synthase	NDVI	Normalized Difference Vegetation Index
EVI	Enhanced Vegetation Index	NH ₃	Ammonia
EXPOLIS	Exposure in Polis (or cities)	NEI	National Emissions Inventory
F	female(s)	NHAPS	National Human Activity Pattern Survey
FRM	Federal Reference Method	N ₂ O	nitrous oxide
g	gram(s)	N ₂ O ₄	Dinitrogen tetroxide
GCAS	Geostationary Coastal and Air Pollution Events Airborne Simulator	N ₂ O ₅	dinitrogen pentoxide
GeoTASO	Geostationary Trace Gas and Aerosol Sensor Optimization	NMOR	N nitrosomorpholine
GPS	Global positioning system		

nNOS	neuronal nitric oxide synthase	uEMEP	urban European Monitoring and
NO	nitric oxide		Evaluation Program
NO ₂	nitrogen dioxide	µg	microgram
NO ₃	NITRATE	UH ₂ ⁻	urate
NOS	nitric oxide synthase	UFPs	ultra fine particles
NO _x	NO ₂ + NO	U.K.	United Kingdom
NO _y	oxides of nitrogen	µm	Micrometer
NO _z	nitrogen species	U.S.	United States
NR	Not reported	UV	ultraviolet
NR DRIVE	near-road Dorm Room Inhalation to Vehicle Emissions	VMT	Vehicle Miles Traveled
NR GIT	near-road Georgia Institute of Technology	VOCs	volatile organic compounds
O ₂	oxygen	vs.	versus
O ₃	ozone	WINTER	Wintertime INvestigation of Transport, Emissions, and Reactivity
OH	hydroxyl radical	wk	week(s)
OMI	Ozone Monitoring Instrument	XGB	extreme gradient boosting
ONOO ⁻	peroxynitrite	<i>y_o</i>	all time spent outdoors
ONOOOCO ₂ ⁻	nitrosoperoxylcarbonate	<i>y_{o,j}</i>	the fraction of a day spent in the outdoor microenvironment
OR	odds ratio	<i>y_i</i>	the fraction of time spent indoors
<i>P_j</i>	air pollutant penetration	<i>y_{i,j}</i>	the time spent indoors
PAHs	polycyclic aromatic hydrocarbons	yr	year(s)
PAN	Organic nitrates	ΔNO ₂	reduction in NO ₂
PM	particulate matter		
P.M.	post meridiem		
PM _{2.5}	particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm		
PM ₁₀	particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 µm		
ppb	parts per billion		
ppm	parts per million		
Q	quantile (could be quartile or quintile)		
R	Organic radical		
RAD	Remote Air Data		
r ²	quality assurance		
RLINE	Research Line Source		
RMSE	root mean square error		
RR	relative risk or risk ratio		
RSNO	S-nitrosothiols		
SALSA	Sacramento Area Latino Study on Aging		
SD	standard deviation		
SE	standard error		
SHEDS	Stochastic Human Exposure and Dose Simulation		
SLAMS	State and Local Air Monitoring Stations		
SO ₂	sulfur dioxide		
SPIROMICS	Subpopulations and Intermediate Outcome Measures in COPD Study		
STEM	sources, transport and transformation, extent (concentration), and measurement and modeling		
T	tertile		
<i>t</i>	time		
<i>t_j</i>	time spent in that microenvironment		
TEA	triethanolamine		
TEMPO	Tropospheric Emissions: Monitoring Pollution		
TRAP	traffic-related air pollution		
TROPOMI	Tropospheric Monitoring Instrument		

CHAPTER 2 Exposure and Dosimetry of Inhaled Oxides of Nitrogen

2.1 Introduction

Human exposure to air pollution is governed by contact between individuals and pollutants at specific concentrations for defined time periods, while dosimetry of inhaled pollutants involves their uptake in the respiratory tract and their distribution, metabolism, and elimination. This chapter evaluates inhalation exposure and dosimetry evidence for the oxides of nitrogen. Most of that evidence examines nitrogen dioxide (NO₂), with some studies additionally evaluating nitric oxide (NO) and other oxides of nitrogen.

Because the primary National Ambient Air Quality Standards (NAAQS) are intended to provide public health protection against exposures to ambient air pollution, the focus of this chapter is on the ambient air component of total personal exposure to oxides of nitrogen. Of particular interest is the degree to which measured or modeled exposure surrogates can serve as reliable indicators of personal exposure to oxides of nitrogen of ambient air origin. Common exposure surrogates include NO₂ concentrations in ambient air measured at central site monitors or estimated from satellite data, NO₂ measured by personal monitors, and NO₂ modeled using spatial techniques such as land use regression (LUR), Gaussian dispersion models, or chemical transport models (CTMs). This chapter examines exposure patterns based on such surrogates and evaluates the factors affecting their reliability when used in epidemiologic studies, including errors associated with measurement or modeling approaches, the spatial and temporal variability of ambient NO₂ concentrations, and other factors affecting NO₂ exposures (e.g., proximity to traffic, indoor sources and sinks, and the time people spend indoors and outdoors).

In addition, since studies of indoor NO₂ and other oxides of nitrogen can also inform the understanding of NO₂-related health effects, this chapter evaluates NO₂ indoor air dynamics, including indoor combustion sources (e.g., gas stoves and space heaters), indoor air chemistry, and air exchange with outdoor air. Indoor air studies may also shed light on exposure misclassification, which may result when total human exposure is not disaggregated between various microenvironments.

The key issues described above are assessed based on peer-reviewed publications. Studies included and evaluated in this chapter are relevant to United States (U.S.) exposure scenarios and are consistent with the scope of the STEM statement (i.e., Sources, Transport and transformation, Exposure/extent, and Measurement and modeling) presented in the Integrated Review Plan ([U.S. EPA, 2024](#)). Briefly, studies addressing any one of the following aspects are subject to be evaluated in this chapter.

- Sources (S): Emissions from ambient (e.g., traffic) or non-ambient (e.g., cookstoves) sources of oxides of nitrogen.

- Transport and Transformation (T): Atmospheric and environmental processes of oxides of nitrogen, including the transport of air pollutants at various scales (i.e., national/global, regional, urban, neighborhood, middle, micro scales, and microenvironments), including near-source (e.g., near traffic) transport and transformation, and advances in understanding chemical transformations and deposition from the atmosphere (e.g., photochemical reactions) and microenvironments (e.g., indoor chemistry).
- Exposure/extent (E): Exposure levels of oxides of nitrogen characterized by various surrogates (e.g., ambient concentrations, microenvironmental concentrations, personal exposure) and exposure determinants (i.e., factors which may lead to differential exposures, such as proximity to sources, activity patterns, and socioeconomic status), including characterizing concentrations and spatiotemporal trends of various exposure surrogates and examining populations experiencing elevated exposures or the exposure patterns (e.g., exposure level, duration, and frequency) experienced by populations identified in health studies as being at increased risk of effects.
- Measurement and Modeling (M): Measurement methods (e.g., federal reference and equivalent methods, passive samplers, sensors, and remote sensing) and modeling techniques (e.g., LUR and dispersion models) characterizing ambient air, indoor/microenvironmental air, and personal exposures, including the evaluation of measurement principles and modeling assumptions, examination of potential bias and uncertainties, and comparison of different techniques.

This chapter builds on the major exposure and dosimetry findings and conclusions of the U.S. Environmental Protection Agency's (EPA) 2016 Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (hereafter referred to as the 2016 Oxides of Nitrogen ISA). The 2016 Oxides of Nitrogen ISA evaluated commonly used exposure assessment methods, including central site monitors, passive monitors, LUR, CTM, dispersion models, and microenvironmental models, and errors associated with each method in the context of epidemiologic study designs ([U.S. EPA, 2016](#)). Factors leading to exposure measurement errors were assessed, including temporal activity of epidemiologic study participants, spatial variability of NO₂ concentrations across the study area, infiltration of NO₂ indoors, and instrument accuracy and precision. The 2016 Oxides of Nitrogen ISA also assessed potential chemical and nonchemical confounders, including traffic-related pollutants (e.g., NO, carbon monoxide (CO), elemental carbon (EC), ultrafine particles (UFPs), and benzene), other copollutants [e.g., sulfur dioxide (SO₂), ozone (O₃), particles with an aerodynamic diameter less than 2.5 µm or 10 µm (PM_{2.5} and PM₁₀)], as well as noise. This chapter revisits these key issues in light of the current state of the science related to NO₂ exposures.

Section 2.2 of this chapter briefly reviews the outdoor and indoor sources contributing to oxides of nitrogen exposure as well as key factors affecting human exposure to these pollutants. Section 2.3 discusses exposure estimation approaches, evidence for differential exposures across communities, and evidence for errors associated with exposure estimates. Section 2.4 summarizes the association of oxides of nitrogen exposure and co-exposures with other pollutants or stressors. Section 2.5 evaluates the impacts of exposure measurement errors on epidemiologic findings. Section 2.6 presents dosimetry findings of inhaled oxides of nitrogen. Key findings and conclusions are highlighted in Section 2.7.

2.2 Sources Contributing to Exposures

2.2.1 Concepts Related to Exposures Ambient Air Pollutants

People spend varying amounts of time in different microenvironments, such as residences, workplaces, schools, and vehicle cabins, each characterized by distinct pollutant concentrations. The total personal exposure to a given pollutant is calculated by summing the exposures over all time intervals for all microenvironments an individual encounters. This total personal exposure (E_T) is represented by Equation 2-1:

$$E_T = \sum_j^n C_j t_j$$

Equation 2-1

where C_j is the average pollutant concentration in the j^{th} microenvironment, t_j is the time spent in that microenvironment, and n is the total number of microenvironments encountered ([U.S. EPA, 2008a](#); [Klepeis et al., 2001](#)). This equation emphasizes the importance of considering both microenvironmental pollutant concentrations and time activity patterns when assessing total exposure. In practice, E_T is expressed as time-weighted concentrations across different microenvironments, with the weighting factor being the fraction of time spent in each.

Alternatively, based on the principle of mass balance, an individual's total pollutant exposure can be expressed as the sum of ambient pollutant exposure (E_a) and nonambient exposure (E_{na}) components ([U.S. EPA, 2008a](#); [Wilson and Brauer, 2006](#)):

$$E_T = E_a + E_{na}$$

Equation 2-2

E_a represents exposure derived from outdoor sources, while E_{na} represents exposure from indoor sources. Both can be expressed in terms of microenvironmental concentrations and time spent in each outdoor and indoor microenvironment. This chapter focuses on E_a , the ambient component of personal exposure to oxides of nitrogen, while acknowledging that E_{na} must be considered when evaluating total personal exposures, as nonambient exposures may obscure the true relationship between total personal exposures and ambient air pollutant exposures.

An individual can be exposed to ambient oxides of nitrogen in both outdoor and indoor environments. For outdoor microenvironments, ambient exposure to NO₂ ($E_{o,j}$) is calculated as:

$$E_{o,j} = y_{o,j} \cdot C_{o,j}$$

Equation 2-3

where $y_{o,j}$ is the fraction of a day spent in the outdoor microenvironment and $C_{o,j}$ is the outdoor concentration. For indoor microenvironments, exposure to ambient sources ($E_{i,j}$) is expressed as:

$$E_{i,j} = y_{i,j} INF_j \cdot C_{o,j}$$

Equation 2-4

where INF_j is the infiltration factor of the j^{th} microenvironment, $y_{i,j}$ is the time spent indoors, and $C_{o,j}$ is the outdoor concentration. The infiltration factor is a function of the microenvironment's air exchange rate (a_j), air pollutant penetration (P_j), and decay rate (k_j):

$$INF_j = P_j a_j / (a_j + k_j)$$

Equation 2-5

Thus, indoor exposure to ambient oxides of nitrogen for microenvironment j can be expressed as:

$$E_{i,j} = y_{i,j} \left[\frac{P_j a_j}{a_j + k_j} \right] C_{o,j}$$

Equation 2-6

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 may not be the same as its ambient concentration but the product of the ambient concentration and the infiltration factor (i.e., INF).

In a given microenvironment, the ambient component of a person's microenvironmental exposure to a pollutant is determined by the parameters specified in Equations 2-5 and 2-6, i.e., the ambient concentration, the air exchange rate, the pollutant specific penetration coefficient, the pollutant specific decay rate, and the fraction of time an individual spends in the microenvironment. These parameters in turn are affected by the following interrelated exposure factors ([U.S. EPA, 2008a](#)):

- environmental conditions, such as weather and season;
- microenvironmental conditions, such as 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, and outdoor exercise);
- indoor sinks of a pollutant; and
- individual-specific factors (e.g., age, health, demographics, and socioeconomic status) related to personal activities, proximity to sources, and dwelling conditions.

The total ambient exposure (E_a) can be described as the sum of outdoor pollutant exposure and the ambient component of indoor exposure, summed over j indoor microenvironments ([U.S. EPA, 2008a](#); [Wilson and Brauer, 2006](#); [Wilson et al., 2000](#)):

$$E_a = \sum_{j=1}^n y_{o,j} C_{o,j} + \sum_{j=1}^n y_{i,j} \left[\frac{P_j a_j}{a_j + k_j} \right] C_{o,j}$$

Equation 2-7

Often, measured or modeled ambient or outdoor concentration is used as a surrogate for human exposure, with the assumption that the exposed individual resides in one indoor microenvironment. This simplification reduces time activity data to "time indoors" and "time outdoors." Outdoor microenvironmental exposures (E_o) are expressed simply as the product of the fraction of all time spent outdoors (y_o) and ambient pollutant concentration (C_a): $E_o = y_o C_a$. Furthermore, based on the assumption that the individual occupies only one indoor and one outdoor microenvironment, such as those exposure assessments conducted in residence-based epidemiologic studies, then the infiltration term can be simplified to $y_i [Pa/(a + k)]$, and because $y_o + y_i = 1$. Under these assumptions, the equation for ambient exposure can be simplified to:

$$E_a = \{y_o + y_i [Pa/(a + k)]\} C_a$$

Equation 2-8

where y_o is the fraction of time spent outdoors, y_i is the fraction of time spent indoors, and C_a is the ambient pollutant concentration. An exposure factor (α) can then be defined to express the influence of time weighting and infiltration on pollutant exposure:

$$\alpha = y_o + (1 - y_o)[Pa/(a + k)]$$

Equation 2-9

Finally, an approximate expression for total personal exposure is obtained:

$$E_T = \alpha C_a + E_{na}$$

Equation 2-10

Regarding the associations between E_o and C_a for NO₂, the major interest is the ability of ambient or outdoor NO₂ to serve as a reliable indicator of personal exposure to NO₂ of ambient origin. A key question is what exposure measurement errors are associated with using measured or modeled ambient NO₂ as a surrogate for personal exposure to ambient NO₂ and/or its oxidation products. Exposure measurement errors can result from uncertainties in measurement or modeling, spatial and temporal variability of ambient NO₂ concentrations, and the impact of various exposure factors (e.g., proximity to traffic, the time people spend indoors and outdoors, sociodemographic and socioeconomic factors) on the relationship between ambient concentrations and personal exposures. These factors determine the strength of the association between population exposure to NO₂ of ambient origin and ambient NO₂ concentrations. Further examination of how E_a , α , and C_a are modeled or measured, including how errors and uncertainties in the simplifying assumptions may influence health effect estimates in epidemiologic studies, is necessary to fully understand the implications of using ambient NO₂ concentrations as a proxy for personal exposure.

2.2.2 Outdoor Sources of Oxides of Nitrogen

To understand the ambient component of personal exposures to oxides of nitrogen, it is crucial to characterize the major sources contributing to nitric oxide and nitrogen dioxide (NO_x) emissions to ambient air. By investigating these ambient sources, we gain insights into significant contributors to general population exposures and identify communities facing elevated exposures.

A comprehensive overview of NO_x emissions to the ambient air across the United States is provided in Chapter 1. Notably, key sources of NO_x emissions have been cataloged through the National

Emissions Inventory (NEI), including prominent sectors such as highway vehicles, off-highway engines, utility power plants, non-utility fossil fuel combustion, additional anthropogenic activities, and biogenic events like wildfires. Despite variation in the quality of the information used to develop emissions estimates, the NEI continues to evolve thanks to improvements driven by the EPA along with contributions from states, municipalities, and indigenous groups.

Of particular importance is the finding in Chapter 1 that highway vehicles account for 26% of total NO_x emissions in the United States and remain the dominant source of NO_x emissions in urban areas (see Chapter 1, Section 1.2). This conclusion is drawn from multiple lines of evidence and serves as foundational knowledge when evaluating population exposures (see Section 2.3).

The significance of vehicle emissions as a source of ambient NO₂ has been supported by multiple lines of evidence, including mobile source emission profiles, diurnal variability of NO₂, microscale spatial variability near roads, the relationship between NO₂ concentration and traffic metrics, and the change in NO₂ during natural experiments. These lines of evidence were summarized in the previous ISAs and are supported by recent studies. The 2008 and 2016 Oxides of Nitrogen ISAs [see Section 3.3 in [U.S. EPA \(2016\)](#) and Section 2.2 in [U.S. EPA \(2008a\)](#)] noted the following:

- NO₂ is a useful indicator of traffic pollutants, though its effectiveness as an indicator can vary depending on the presence of other sources (e.g., industrial sources or shipping channels) and local conditions (e.g., traffic counts).
- The diurnal cycle of NO₂ in typical urban areas is driven largely by traffic emissions, with peaks in concentrations occurring during morning and evening rush hour traffic.
- NO₂ concentrations exhibit clear spatial gradients near roadways. However, the NO₂ gradient tends to be less steep compared to other primary traffic pollutants like CO and UFPs. This means that while NO₂ captures many aspects of pollutant gradients from roadways, it may underestimate the magnitude of concentration gradients for some other near-road pollutants.
- Studies have shown positive correlations between NO₂ concentrations and various traffic metrics, such as traffic volume and density.
- Natural experiments, such as road closures or traffic restrictions, have demonstrated that NO₂ concentrations are sensitive to changes in traffic conditions.

Building on this foundation, recent studies have consistently demonstrated a positive relationship between NO₂ concentrations and traffic-related metrics. Higher traffic volumes or counts were generally associated with increased NO₂ concentrations near roadways and in urban areas ([Adza et al., 2022](#); [Kerr et al., 2022](#); [Lovasi et al., 2022](#); [Singh et al., 2022](#); [Heintzelman et al., 2021](#); [Lal et al., 2020](#); [Rossi et al., 2020](#); [Seagram et al., 2019](#); [DeWinter et al., 2018](#); [Liang et al., 2018](#); [Shairsingh et al., 2018](#); [Fuks et al., 2017](#); [Richmond-Bryant et al., 2017b](#); [Hudda et al., 2016](#); [Riley et al., 2016](#); [Sayegh et al., 2016](#); [Gualtieri et al., 2015](#); [Kendrick et al., 2015](#)). For example, [DeWinter et al. \(2018\)](#) reported moderate associations between annual mean NO₂ and annual average daily traffic (AADT), with a coefficient of determination (r^2) of 0.32 from a simple linear regression, and an r^2 of 0.38 when using Fleet-Equivalent AADT, based on data collected from the U.S. national near-road air quality monitoring network from 2014 to 2015.

Similarly, [Lal et al. \(2020\)](#) reported a positive and statistically significant correlation between NO₂ and AADT at near-road sites using the 2017 to 2018 data collected from the same monitoring network. [Kendrick et al. \(2015\)](#) found that in the morning hours, a 100-vehicle increase in a 15-minute period was associated with a 1.2 to 2.5 ppb increase in NO₂. [Liang et al. \(2018\)](#) determined that a 0.28% increase in NO₂ concentrations was associated with every 1,000 traffic count increase.

However, it's important to note that the influence of traffic on NO₂ is not linear. [Richmond-Bryant et al. \(2017b\)](#) found that higher traffic counts were associated with increased turbulence and dispersion. [Seagram et al. \(2019\)](#) noted that while there was some evidence of increasing annual mean NO₂ with AADT and fleet equivalent AADT, the relationships were not always statistically significant. Factors like meteorology and the mix of vehicle types (e.g., heavy-duty vs. light-duty) were also found to play important roles in modulating the relationship between traffic and NO₂ concentrations ([Lal et al., 2020](#); [Richmond-Bryant et al., 2017b](#)).

The COVID-19 pandemic provided a unique opportunity to observe the impact of traffic patterns on NO₂ concentrations across various cities and countries. The reduction in traffic led to substantial decreases in NO₂ concentrations across studied locations. In the 11 major U.S. cities studied by ([Heintzelman et al., 2021](#)), NO₂ reductions ranged from 11% to 65% between January and April 2020 based on near-road monitors. European cities experienced an average reduction in NO₂ of 23.8%, with reductions ranging from approximately 3% to 61% across different cities based on geospatial modeling at a resolution of about 25 km² ([Kerr et al., 2022](#)). In Padova, Italy, NO₂ concentrations dropped by 34% to 40% compared to corresponding days in previous years ([Rossi et al., 2020](#)), whereas Oxford, United Kingdom (U.K.) saw NO₂ reductions of 47.4% at roadside locations and 34.1% at urban background locations during the first lockdown ([Singh et al., 2022](#)). In the Netherlands, observed reductions in NO₂ concentrations were 30% for traffic locations, 26% for urban background locations, and 18% for rural background locations ([Velders et al., 2021](#)).

Some studies provided quantitative relationships between traffic reductions and NO₂ concentrations. For instance, in 11 major cities in the United States, for every 1,000,000 fewer vehicle miles traveled NO₂ decreased by an average of 0.24 ppb ([Heintzelman et al., 2021](#)). In Indianapolis specifically, a 1,876-unit reduction in average truck traffic resulted in a 1.11 ppb decrease in average NO₂ concentrations ([Heintzelman et al., 2021](#)). While the reduction in traffic was a primary driver of decreased NO₂ concentrations, some studies noted additional factors, such as fleet composition and meteorological conditions. The share of diesel passenger vehicles significantly influenced the magnitude of NO₂ reductions, with cities having larger diesel shares experiencing greater reductions. For example, [Kerr et al. \(2022\)](#) found that for every 10% increase in diesel vehicle shares, the reduction in NO₂ (ΔNO_2) increased by 5.3% in European cities. [Velders et al. \(2021\)](#) reported that unusual meteorological conditions during the lockdown also played a role in the observed reductions.

These studies consistently demonstrate that the COVID-19 pandemic lockdowns led to significant reductions in traffic volume across various urban areas, which in turn resulted in substantial decreases in

NO₂ concentrations in ambient air. The magnitude of these reductions varied based on factors such as location, diesel vehicle share, and local meteorological conditions. These findings provide valuable insights into the relationship between traffic patterns and urban air quality.

Other lines of evidence are further assessed in Chapter 1 and other sections in this chapter. Mobile source emission profiles and diurnal variability of NO₂ are presented in Chapter 1. Microscale spatial variation of NO_x in the near-road environment, occurring over distances of a few hundred meters, is briefly discussed in Chapter 1, Section 1.5.3 and is further analyzed in Section 2.3.2. Additionally, in terms of exposure assessment, the contribution of highway vehicles to personal NO_x exposure is determined not only by the near-road gradient of NO_x concentrations but also the activities and locations of individuals. Therefore, maps that illustrate the near-road populations, who are likely to experience elevated levels of exposure, are presented in Section 2.3.4 across the most populated U.S. metropolitan areas and those areas often studied in epidemiologic research.

The other major emission source discussed in Chapter 1 comprises electric generating units (EGUs) and other stationary fuel combustion sources, which account for approximately 25% of NO₂ emissions (see Chapter 1, Section 1.2.5). Human exposure to NO₂ from EGUs is typically localized ([Wang et al., 2023b](#)). However, the impacts of these emissions are not limited to the immediate vicinity of the sources, as the dispersion of NO₂ from elevated stacks is influenced by stack height, meteorological conditions, and local topography. Furthermore, NO₂ emitted from EGUs undergoes dilution and chemical transformation into other oxidized nitrogen species during dispersion. Notably, although EGU emissions often originate in suburban or rural areas, recent urbanization studies consistently indicate that NO₂ concentrations in these regions are lower than in urban areas (see Section 2.3.4.3). However, there is a lack of research specifically addressing localized human exposure to NO₂ originating from EGUs.

2.2.3 Indoor Sources of Oxides of Nitrogen and Indoor Dynamics/Chemistry

Given that the U.S. population spends the majority of their time indoors (see Section 2.3.2.4), oxides of nitrogen from indoor sources can make a substantial contribution to total exposures ([U.S. EPA, 2016](#)). Many studies that rely solely on outdoor measurements and/or do not incorporate time-activity data to estimate indoor exposures may mischaracterize total exposures to oxides of nitrogen. Though the focus of this chapter is exposure to ambient oxides of nitrogen this section evaluates the evidence for NO_x emissions from indoor sources and for the indoor chemistry governing transformation of NO_x to provide information for understanding total exposure and possible co-exposures indoors. Section 2.3.2.5 further explores the relationship of indoor exposure to total personal exposure for oxides of nitrogen.

There are several widespread indoor sources of NO_x emissions in the U.S. indoor sources of NO_x are combustion-based and include gas stoves and heating, oil furnaces, coal and wood burning stoves, kerosene heaters, candle burning, and smoking indoors ([U.S. EPA, 2016](#)). Gas stoves have also been found to emit other gaseous compounds (CO, CH₄, benzene, and formaldehyde) and PM_{2.5}, including

ultrafine particles. These gaseous compounds have been linked to increased usage of gas burners ([Kashtan et al., 2023](#); [Lebel et al., 2022](#); [Singer et al., 2017](#); [Mullen et al., 2015](#)). In particular, PM_{2.5} has been correlated with increases in cooking activity using gas stoves ([Jaffe and Creekmore, 2024](#); [Singer et al., 2017](#); [Wallace et al., 2004](#); [Dennekamp et al., 2001](#)).

The 2016 Oxides of Nitrogen ISA found associations between indoor NO₂, NO_x, or nitrous acid (HONO) concentrations in indoor air and combustion sources ([U.S. EPA, 2016](#)). Table 2-1 below, taken from Table 3-4 of the 2016 Oxides of Nitrogen ISA, summarizes the results of studies that evaluated NO₂ and/or HONO concentrations in indoor air in the presence of various indoor sources ([U.S. EPA, 2016](#)).

Table 2-11 Nitrogen dioxide and nitrous acid concentrations in indoor air in the presence or absence of indoor combustion sources

Study	Combustion Source	Measurement Frequency	NO ₂ (ppb)		HONO (ppb)	
			Peak	24-hr avg	Peak	24-hr avg
Brauer et al. (1990)^a	No source (background)	15 min	29	17	8	5
	Gas range ^a	15 min	157	36	35	13
	Convective space heater ^a	15 min	955	209	106	42
Brauer et al. (1990)^b	No source	15 min	5	1.8	3.5	3.4
	Gas range ^b	15 min	37	8	31	9.6
Brauer et al. (1991)^c	Unknown	15 min	NR	NR	NR	1–12
Spengler et al. (1993)^d	Gas range, stove, furnace	24-hr	NR	60 (24–115)	NR	4.7 (2–8)
Simon and Dasgupta (1995)^e	Kerosene heater	8 min	NR	NR	5–10	NR
Leaderer et al. (1999)^f	No source (summer) ^f	24 hr	NR	NR	NR	0.8 (0.0–2.9)
	Gas stoves (summer) ^f	24 hr	NR	NR	NR	4.0 (0.0–11.3)

Study	Combustion Source	Measurement Frequency	NO ₂ (ppb)		HONO (ppb)	
			Peak	24-hr avg	Peak	24-hr avg
	Kerosene heaters (winter) ^f	24 hr	NR	NR	NR	6.8 (0.2–35.9)
	No source (winter) ^f	24 hr	NR	NR	NR	2.4 (0.1–20.1)
	Gas stoves (winter) ^f	24 hr	NR	NR	NR	5.5 (0.4–20.1)
Khoder (2002) ^g	Gas appliances (summer)	24 hr	NR	39 (20–73)	NR	3.7 (1.3–7.3)
	Gas appliances (winter)	24 hr	NR	65 (27–120)	NR	6.8 (1.6–12.5)
Lee et al. (2002) ^h	Gas range, etc.	6 d	NR	28 (4.3–52.0)	NR	4.6 (0.1–21.1)
Jarvis et al. (2005) ⁱ	Gas hob		NR	12.8	NR	4.1
	Gas oven		NR	12.8	NR	5
Hong et al. (2007) ^j	Gas range	4 min	81.1	NR	9.3	NR
Park et al. (2008) ^k	Gas range	4 min	189.3	19.4	15.2	2.1

List of abbreviations in alphabetical order: avg = average; d = day(s); hr = hour; min= minute(s); NR = not reported.

Note: parentheticals = range

^aLocation: Chicago, IL research home, unvented combustion condition; gas range operation hours: 1-hour (with one burner and 2,320 kcal/hr); convective space heater operation hours: 4-hour (with one burner and 2,785 kcal/hr).

^bLocation: Maryland research home, unvented combustion condition; gas range operation hours: 1-hour (with one burner and 2,320 kcal/hr).

^cLocation: 11 Boston, MA homes (winter).

^dLocation: 10 homes in Albuquerque, NM (winter).

^eLocation: Four different home environments with a small kerosene heater (2,270 kcal/hr).

^fLocation: 58 homes (summer) and 223 homes (winter) in southwest Virginia and Connecticut; 39 inside homes without gas stoves (summer); 19 inside homes with gas stoves (summer); 74 inside kerosene-heater homes (winter); 96 inside homes without kerosene heaters and gas stoves (winter); 52 inside homes without kerosene heaters and with gas stoves (winter).

^gLocation: Four homes in suburban residential areas in Greater Cairo, Egypt.

^hLocation: 119 homes in Southern California (spring).

ⁱLocation: Homes in European community.

^jLocation: Living room of an apartment in Gwangju, Korea (May 2006).

^kLocation: Korean apartment (city and year unspecified, October).

Source: [Park et al. \(2008\)](#) Copyright permission pending.

More recent studies have recorded NO_x concentrations in indoor air that may contribute to greater total exposure of NO_x. Table 2-2 presents study results from the California Healthy Homes Indoor Air Quality Study which measured NO_x and NO₂ inside and outside of 352 homes ([Mullen et al., 2015](#)). This study found that NO_x and NO₂ concentrations were higher in homes that cooked with gas and increased with the frequency of gas cooking. Arithmetic mean NO_x and NO₂ concentrations measured in kitchens were 31% higher (23.2 ppb versus 17.7 ppb) and 13% higher, respectively, than bedrooms. NO_x and NO₂ were higher in homes that used cooktop pilot burners compared to those that did not use pilot

burners. The authors note that overall indoor NO₂ and NO_x concentrations were found to be lower than in past studies, which they attributed to decreases in ambient NO₂ and NO_x, and thus decreased ambient concentrations infiltrating from outdoor air.

Table 2-22 Summary of causality determinations by health outcome

Parameter	No gas appliances (Ref. group)	Only vented gas appliances	Only gas cooking	Gas cooking + vented gas appliances	Compare last two groups
Homes (N)	38	28	144	142	
Mean floor area (m ²) ^a	115	159	148	111	
Median floor area (m ²) ^a	105	163	128	105	
Measured concentrations (ppb)^b					
Bedroom NO _x	20	23	54**	69**	p = 0.03
Kitchen NO _x	18	21	60**	75**	p = 0.09
Bedroom NO ₂	6.7	6	14**	16**	p = 0.01
Kitchen NO ₂	6.5	7.6	18**	22**	p = 0.05
Indoor-attributed (ppb)^{b,c}					
Bedroom NO _x	-0.8	3.2	31**	42**	p = 0.02
Kitchen NO _x	3.9	5.6	38**	53**	p = 0.05
Bedroom NO ₂	1.7	2.6	7.9**	9.6**	p = 0.02
Kitchen NO ₂	1.4	3.2	12.3**	16.9**	p = 0.03
Indoor-attributed and scaled (ppb)^{a,b}					
Bedroom NO _x	-1.2	2.1	32**	35**	
Kitchen NO _x	3.2	4.8 [^]	39**	42**	
Bedroom NO ₂	1.1	2.7 [^]	8.0**	7.7**	
Kitchen NO ₂	1.5	3.0 [^]	12.2**	17.0**	

List of abbreviations in alphabetical order: m = meters; N = population size; NO_x = NO₂ + NO; NO₂ = nitrogen dioxide; ppb = parts per billion. Sample characteristics and median pollutant concentrations (ppb) in homes grouped by the type of gas appliance(s) in the living space.

^aFloor area assigned to each home for purpose of this calculation was the midpoint of the size bin selected by participant during telephone interview. Size bins were 46–70, 70–93, 93–116, 116–139, 139–186, 186–232, 232–279, >279 m².

^bEstimated by subtracting the assigned outdoor NO and 0.4 times the outdoor NO₂ from corresponding kitchen and bedroom measured values, then calculating indoor-attributed NO_x as NO + NO₂.

Symbols indicate statistical discernibility using Kruskal-Wallis test of likelihood that other groups' distributions are drawn from the same distribution as the first group: **p<0.01; *0.01≤p<0.05; ^0.0≤p≤0.15. Last column indicates discernible differences between the last two groups; only shows p≤0.15.

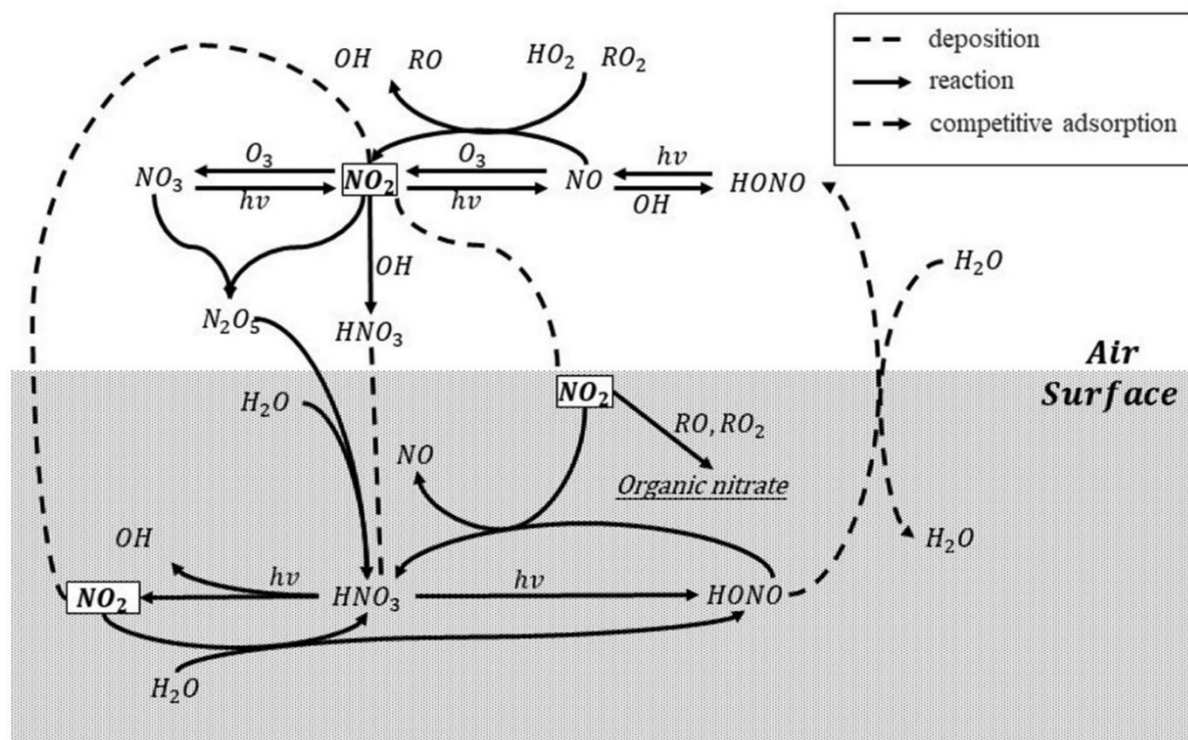
Source: [Mullen et al. \(2015\)](#). Copyright permission pending.

Additional studies have found relationships between natural gas cooking and increases in NO_x concentrations in indoor air. [Lebel et al. \(2022\)](#) found that, in 32 homes, NO_x emissions were linearly related ($r^2 = 0.76$; $p < 0.01$) to amounts of natural gas burned during cooking events. [Singer et al. \(2017\)](#) measured NO, NO_x, and NO₂ concentrations in nine homes during scripted operation of natural gas burners and found that NO_x concentrations rose during cooking events and that 1-hour NO₂ exceeded 100 ppb in four of the nine homes. The HOMEChem study ([Farmer et al., 2019](#)) found increased concentrations of NO₂ and NO during cooking events and a high NO:NO₂ ratio indoors (NO mean: 50 ± 130 ppb; NO₂ mean: 7 ± 27 ppb) relative to outdoor concentrations (NO mean: 1.7 ± 1.4 ppb; NO₂ mean: 5 ± 3 ppb) and background values without cooking.

Indoor combustion can lead to direct emissions of NO and HONO, and conversion of NO to NO₂ can lead to secondary HONO production from heterogeneous reactions involving NO₂ on indoor surfaces. [Park et al. \(2008\)](#) observed HONO to be correlated with both NO (correlation coefficient, $r = 0.64$, $p < 0.001$) and NO₂ ($r = 0.68$, $p < 0.001$) during combustion. They noted that the ratios of HONO to NO₂ concentrations were 4–8% during gas range operations but rose to ~25% after combustion ceased, which underscores the role of surface reactions as the major source of HONO production. In a model of combustion products for oxides of nitrogen during candle and incense burning, [Loupa and Rapsomanikis \(2008\)](#) observed simultaneous NO and HONO production, the latter of which were in agreement with older test chamber results of HONO production during combustion ([De Santis et al., 1996](#)). In a recent review of HONO concentrations by [Liu et al. \(2024\)](#), it was found that average indoor HONO concentrations ranged from 0.13 ppb to 42 ppb depending on the study. In general, residences had higher HONO concentrations than school or office environments. The range for residences was 0.8 ppb to 42 ppb. High concentrations of HONO were found in studies immediately after a combustion source was activated and to peak to around 106 ppb from a background of 5 ppb in one case ([Brauer et al., 1990](#)).

Oxides of nitrogen participate in reactions with other species indoors, deposit within the indoor environment, and move between both outdoor and indoor environments. Figure 2-1 summarizes indoor reactions involving oxides of nitrogen. NO can react with both O₃ and HO₂ to become oxidized to NO₂. O₃ and HO₂ radicals can be generated by indoor O₃ chemistry or volatile organic compounds (VOCs) found in household products. NO₂ also reacts with free radicals to produce PAN. NO₂ removed through surface reactions is known to contribute to NO formation indoors either by surface reduction of NO₂ or by reaction of NO₂ with aqueous HONO on indoor surfaces ([Spicer et al., 1989](#)). [Spicer et al. \(1993\)](#) found that indoor reactive processes for these species took several-hours for NO and HONO, about an hour for NO₂, and less than 30-minutes for HNO₃, when NO₂ and HONO were injected into a test house along with operating two space heaters and a gas range. Deposition velocities for NO₂, HONO, HNO₃, HO₂NO₂, NO₃, and N₂O₅ were reported by [Sarwar et al. \(2002\)](#) to range from $6\text{--}7 \times 10^{-5}$ m/s while NO, PAN, and organic NO₃- species ranged from not detected to 2×10^{-6} m/s. Conversion of NO₂ to HONO occurs through a number of indoor reactions, and the reactions increase with increased relative humidity ([U.S. EPA, 2008a](#)).

Research on indoor HONO production has increased in recent years. [Bartolomei et al. \(2014\)](#) demonstrated the role of irradiance in humidity-driven surface reaction of NO_2 to HONO on paints. Surface reactions of NO and OH radicals may also produce HONO, but the reaction rate is slower than for NO_2 . HONO can also be broken down by photolysis into OH species ([Waring and Wells, 2015](#)). [Wang et al. \(2020\)](#) found that cooking, bleach cleaning, and air conditioning increased concentrations of HONO in homes. [Gandolfo et al. \(2020\)](#) and [Gandolfo et al. \(2015\)](#) found that photocatalytic paint, which has been studied for the photocatalytic reduction of NO_2 indoors as a remediation technology, can contribute to HONO formation and may increase with paint porosity. In a small study looking at HONO production on glass windows, photolytic reactions of NO_2 on glass were also found to produce HONO ([Liu et al., 2020](#)).



Source: [Hu and Zhao \(2020\)](#). Copyright permission pending.

Figure 2-1 Indoor dynamics of oxides of nitrogen.

2.3 Exposure Estimation Methods and Exposure Determinants

2.3.1 Methods for Exposure Characterization

Surrogates for personal exposure to oxides of nitrogen in ambient air are used in various epidemiologic and exposure studies to estimate concentrations that populations are exposed to. Measurement techniques include the use of monitors, personal exposure sampling, and satellites. Modeling techniques include LUR, mechanistic modeling such as CTMs and dispersion models, microenvironmental models and hybrid models which combine various measurement and modeling techniques. The following sections describe these techniques along with recent evidence published since the 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) about the many advancements in exposure characterization, such as improvements in satellite sensing, development of new low-cost sensors (LCSs), and new combinations of measurement and modeling techniques in hybrid models to provide more accurate exposure measurements. Section 2.3.1.3 summarizes the strengths and limitations of these techniques in relation to each other.

2.3.1.1 Measurements

2.3.1.1.1 Central Site and Near-Road Monitoring

The purpose of this section is to briefly introduce central site and near-road monitors as an exposure surrogate measurement method for NO₂ exposure. More in-depth information about monitoring networks, monitor function, and concentration measurement considerations can be found in Chapter 1, Section 1.4. Discussion of the relationship between ambient NO₂ measurements and personal exposure along with factors that influence this relationship are discussed in Section 2.3.3.

Monitoring of NO₂ concentrations in ambient air is used to compare an area's ambient air to the NAAQS for oxides of nitrogen. Over 80% of NO₂ monitors in the United States are part of the State and Local Area Monitoring (SLAMS) network that reports data to EPA's Air Quality System (AQS). Ambient air pollution monitors can be representative of air pollution concentrations at varying spatial scales, with those not adjacent to a particular source or set of sources being referred to here as "central site" monitors ([U.S. EPA, 2008b](#)). Alternatively, monitors can be placed nearer to sources, in most cases to characterize ambient concentration maxima and/or source impacts, which is the case for NO₂ monitors in the specialized near-road network. Near-road monitors are a subset of the SLAMS network.

Monitored concentrations are also commonly used in epidemiologic studies to estimate exposure. Typically, these concentrations are used either directly as a surrogate measurement for exposures experienced by nearby populations or incorporated into modeling efforts, such as LUR, to estimate

concentrations beyond monitoring sites. How closely a monitoring value represents a local population's true exposure concentration to an ambient pollutant depends on the spatial distribution of the pollutant, activity patterns of the population, and other factors discussed in Section 2.3.2 ([Fuentes, 2009](#)).

Monitoring data can be used in epidemiologic studies examining either short-term or long-term exposures. Typically, monitors report hourly NO₂ data making them useful for capturing temporal variability in studies that focus on time series of short-term exposures as well as in studies that compare long-term average NO₂ concentrations across different geographic areas [see Section 3.2.1.1 of [U.S. EPA \(2016\)](#)]. Any difference between the measured NO₂ concentration and the true exposure would result in exposure error ([Evangelopoulos et al., 2020](#); [U.S. EPA, 2016](#)). The factors that influence exposure error and the relationships between personal exposures and concentrations in ambient air are discussed in detail in Sections 2.3.2 and 2.3.3, respectively.

2.3.1.1.2 Personal, Microenvironmental, and Other Measurements

Personal monitoring of oxides of nitrogen is less commonly used in epidemiologic studies due to cost and implementation challenges that are not present when using fixed-site monitoring data. Typically, personal monitors are used in panel studies that follow small numbers of participants (e.g., tens of participants) for days to weeks at a time. Passive samplers are commonly used for personal or area sampling of NO_x in a badge, tube, or radial manifold. Less commonly, active sampling systems are used to obtain near real-time data, but their use is limited due to their heavy weight, although this is changing with advances in equipment. Passive sampling results are integrated over the time period during which the sorbent material is exposed, and usually spans days to weeks ([U.S. EPA, 2016](#)). Passive samplers may be affected by bias from several sources including positive bias resulting from in-tube production of additional NO₂ from reactions between NO and O₃ that results from the timescale of this reaction (tens of seconds) being much shorter than diffusion within the tube (several-minutes). However, this bias may only be a few percent where O₃ is low in concentration or where NO₂ dominates the NO_x ratio ([Heal et al., 2019](#)). Inflight measurements have not typically been used as exposure surrogates and have been more commonly used to measure atmospheric concentrations over larger regions ([Bourgeois et al., 2022](#)).

The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) also included examples of using passive or miniature active monitors for saturation sampling (i.e., siting monitors over a dense grid). Saturation sampling has been found to improve the capture of spatial and temporal variability of NO₂ concentrations. [Ross et al. \(2013\)](#) used a dense grid of measurements over five boroughs in New York City using 150 monitors over a 790 km² area ([Matte et al., 2013](#)). The authors reported that the dense network of monitors was able to capture more spatial variation of NO₂ and other pollutants than regulatory monitoring alone. [Shmool et al. \(2014\)](#) examined air pollution gradients around Pittsburgh, PA using portable air sampling units at 36 monitoring sites and found that they captured a wider range of concentrations than at regulatory monitoring sites during sampling. New LCSs are also being developed

by various research groups to provide greater spatial resolution for NO_x measurements. LCSs have the advantage of being lower cost than traditional monitoring stations and have the ability to improve spatial and temporal coverage of pollutant concentration data ([Hohenberger et al., 2022](#); [Fattoruso et al., 2020](#); [Bigi et al., 2018](#); [Sousan et al., 2016](#)). However, recent sensor designs need to be validated before they can be used widely. Section 2.3.2.1 discusses instrument error associated with various sensor types and Chapter 1, Section 1.4 discusses monitor instrument error in more detail. [Zuidema et al. \(2021\)](#) studied the performance of a newly built low-cost multipollutant gas sensor monitoring network (54 sensors) as part of a larger epidemiologic study in the Puget Sound region of Washington state. The authors recognized the importance of successful field calibration to ensure accurate results and used field data by co-locating LCSs with state monitor sites for calibration and cross-validation (CV) of NO and NO₂. CV root mean square error (RMSE) and CV r^2 were 2 ppb and 0.97 for NO and 3 ppb and 0.79 for NO₂, respectively, but the authors did acknowledge that individual sensor calibration was complex and unique, and measurements showed some sensor drift over time. A follow-up study by [Zuidema et al. \(In Press\)](#) found that low-cost sensor data helped improve accuracy of a spatiotemporal NO₂ model at residential locations (without LCS: CV-RMSE = 3.8 ppb; r^2 = 0.08; with LCS: CV-RMSE = 2.8 ppb; CV- r^2 = 0.51) but did not provide substantially improved accuracy of low-cost sensors co-located at agency monitor sites.

New LCS designs may also improve temporal resolution of measurements compared to previous personal sampler designs or monitors. As part of the Remote Air Data (RAD) study, [Zuidema et al. \(2021\)](#), LCSs were able to transfer NO and NO₂ concentration information wirelessly every five-minutes. [Downen et al. \(2022\)](#) developed a compact personal NO₂ sensor with 1-minute resolution and sensitivity limit of 15 ppb. Despite difficulties with subject compliance for using the sensors, their small pilot study of 40 chronic asthma participants showed that in-home data could be used to supplement self-reported symptom diaries and patient information to understand exposure. The 1-minute resolution was able to successfully capture spikes in NO₂ exposure that may have been missed using other measurement or modeling methods and link gas stove presence to these higher exposure concentrations.

2.3.1.1.3 Satellite Measurements

Satellite measurements of NO₂ were discussed in the 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) as a measurement technique for atmospheric concentrations of NO₂. Though satellite-derived spatial variability of NO₂ concentrations was consistent with what is known about NO₂ behavior, concentrations less than 100 ppt were not reliable due to satellite retrieval limitations [Appendix 2 of [U.S. EPA \(2016\)](#)]. As discussed at length in Chapter 1, Section 1.4, rapid evolution of satellite remote sensing techniques has occurred in recent years, leading to higher spatial resolutions that can be measured, most notably by the Tropospheric Monitoring Instrument (TROPOMI) system ([Dressel et al., 2022](#)). Previously, the Ozone Monitoring Instrument (OMI) system was used to measure NO₂ ground concentrations but lacked the resolution of the TROPOMI system for NO₂ observations (OMI:

13×24 km; TROPOMI: 3.5×7 km or 3.5×5.5 km) ([Lee et al., 2023](#); [Bechle et al., 2013](#)). In addition, in 2023 the Tropospheric Emissions: Monitoring of Pollution (TEMPO) instrument was launched on a geostationary satellite to capture air pollutant measurements over North America at a ground sample resolution of 2.21×4.97 km. The highest temporal resolution at which OMI and TROPOMI satellite measurements can be performed is daily, making them only useful for epidemiologic studies which use daily or lesser time resolution measurements. It is also important to note that these measurements are once daily measurements and do not represent daily averages. TEMPO can perform hourly measurements. Much more detail on these instruments along with additional systems can be found in Chapter 1, Section 1.4.

TROPOMI has been found to have higher correlation to monitoring measurements than OMI over the continental United States. In [Cooper et al. \(2020\)](#), authors compared OMI and TROPOMI and the use of two different algorithms that infer ground level NO₂ concentrations based on different assumptions regarding vertical mixing in the boundary layer. The authors reported that TROPOMI predicted higher concentrations on average than OMI with a closer correlation to ground measurements (comparison at moderate resolution: TROPOMI $r = 0.71$; OMI $r = 0.64$; comparison at fine resolution: TROPOMI $r = 0.71$; OMI $r = 0.56$). The authors also found that modeled use of both TROPOMI and an updated algorithm, but not TROPOMI alone, indicated that 3 million people across the U.S. live in areas that exceeded the primary annual NO₂ NAAQS set at a level of 53 ppb. In contrast, OMI-inferred concentrations suggested no exceedances of the primary annual NO₂ NAAQS. However, it should be noted that some concentration values found in [Cooper et al. \(2020\)](#) for TROPOMI using the updated algorithm have very high bias [see Figures 3 and 4 of [Cooper et al. \(2020\)](#)] and overpredict concentrations. More on satellite remote sensing methods, including measurements of NO₂ in the atmosphere and associated errors, is discussed in Chapter 1, Section 1.4.

Recently, due to improvements in spatial resolution, remote-based satellite measurements have been used to estimate local (or ground-level) concentrations as exposure estimates in epidemiologic studies. In areas where stationary monitors are sparse, satellite measurements can expand spatial coverage of pollutant concentration predictions ([Huang et al., 2023](#)). Satellites measure column densities of pollutants in the atmosphere and then use scaling factors derived from the vertical distribution of a pollutant in a CTM, and LUR model or land-cover regression data, to convert satellite retrievals to surface concentration values ([Di et al., 2020](#)). Satellite measurements alone are performed at the scale of several kilometers; however, additional data such as from LUR can reduce the spatial scale of overall measurements to several hundred meters, making combined hybrid approaches more useful for epidemiologic studies of urban areas ([Holloway et al., 2021](#)). Satellite measurements are usually used as a starting point for concentration values and then other predictor variables (land use, traffic variables, etc.) for LUR models are incorporated in a stepwise fashion to improve accuracy against ground monitoring values ([Zhang et al., 2021a](#)). It is important to note though that incorporation of local factors such as meteorology or land-use results in the model not being as generalizable to other locations ([Bergen et al., 2013](#)).

Satellite estimates, and other types of models and measurements, can be cross validated against monitor measurements at the surface to understand the reliability of those estimates. CV is a process based in machine learning and statistics that tests a trained model against recent data. For example, a 10-fold CV of satellite-derived data, a type of k-fold CV commonly seen in satellite studies, divides ground measurement data into ten subsets, or “folds”, where the algorithm used to determine ground pollutant concentrations is trained on nine of those folds and is then tested on the last fold. This process is repeated ten times, once for each fold using the other folds as training sets, and an r^2 value is derived. The r^2 values from each one of those folds is then usually averaged to obtain a final r^2 cross-validated value. There are also different types of CV including spatial CV where data is split up by spatial location and leave-one-out CV usually used in smaller datasets, where each individual estimate is left out for validation ([Wang et al., 1999](#)). CV r^2 values indicate that satellite derived estimates are generally reliable, with additional data such as meteorological data improving r^2 values. However, satellite-based models, as seen in [Cooper et al. \(2020\)](#) and [Shetty et al. \(2024\)](#) typically under predict and may more rarely over predict surface NO₂ measurements within the same dataset relative to ground monitoring.

[Dressel et al. \(2022\)](#) reported both 250 m × 250 m airborne NO₂ measurements collected during the 2018 NASA Long Island Sound Tropospheric Ozone Study (LISTOS) and daily TROPOMI tropospheric vertical column densities over the New York City-Newark urbanized area. LISTOS used datasets produced by the Geostationary Coastal and Air Pollution Events Airborne Simulator (GCAS) and the Geostationary Trace gas and Aerosol Sensor Optimization (GeoTASO) instruments, which are differential optical absorption spectroscopy spectrometers (more on this technology is found in Chapter 1, Section 1.4.1.4) that make measurements of backscattered solar radiation and use NO₂ retrieval algorithms similar to TROPOMI. These instruments were flown on NASA aircraft in June 2018 (GeoTASO) and from July to September 2018 (GCAS) following different flight patterns depending on whether regional air pollution was predicted to be elevated. It was found, when comparing the two, that TROPOMI and aircraft NO₂ measurements were highly correlated ($r = 0.82\text{--}0.97$) with slopes of 0.82 ± 0.10 to 1.05 ± 0.07 and 0.76 ± 0.09 to 0.96 ± 0.06 for relative and absolute inequalities, respectively. Satellite measurements are also used as part of hybrid models to provide additional concentration predictions. Another study using TROPOMI and land-use information measured NO₂ concentrations at a 500 m scale in Los Angeles, California. Validation of TROPOMI against 89 monitoring sites showed high correlation (Pearson correlation coefficient $\rho = 0.73$, Spearman $\rho = 0.79$; $p < 0.0001$) ([Lee et al., 2023](#)). Strengths and limitations of satellite estimates as compared to other exposure estimation methods are described in Section 2.3.1.3.

2.3.1.2 Modeling

Studies have also used computational models to estimate NO and NO₂ exposures. These models help estimate spatial variability between monitors and temporal variability over different time scales. Computational models vary in complexity from simple proximity models to much more advanced hybrid

models that incorporate measurement values along with CTMs or other spatiotemporal estimation techniques and statistics ([Jerrett et al., 2005](#)). Some models incorporate land use, urban morphometry and meteorology, and/or localized source emissions ([Goldman et al., 2012](#); [Fernando, 2010](#)). Each method has advantages and limitations, which are discussed in Section 2.3.1.3. Methods commonly used for estimating NO₂ concentrations discussed in this section include statistical interpolation, LUR models, CTMs, dispersion models, and microenvironmental models and are discussed in order of general increasing complexity.

2.3.1.2.1 Statistical Interpolation Methods

Statistical interpolation methods model concentration between monitor measurements over space and time. The most common goal of statistical interpolation methods is to generate estimates of a pollutant between monitor sites. This is done through a variety of geostatistical techniques including kriging, inverse distance weighting (IDW), and splines ([Jerrett et al., 2005](#)). These models decompose the concentration at each study location into a trend and a residual component ([Sampson et al., 2011](#); [Szpiro et al., 2010](#)). These methods may also incorporate other variables such as land use or dispersion modeling to improve estimations. Higher spatial density of monitoring locations generally results in more accurate estimations between monitors ([Niepsch et al., 2022](#); [Jerrett et al., 2005](#)).

The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) describes the results of several studies that use statistical interpolation methods to estimate of NO₂ or NO. [Szpiro et al. \(2010\)](#) developed a statistical interpolation approach as part of the MESA Air Study and used 2005 to 2007 data from 18 AQS monitors to analyze NO₂ concentrations across Los Angeles, resulting in a cross-validated r^2 of 0.67. [Keller et al. \(2015\)](#) used 1999 to 2012 NO₂ and NO_x data from the AQS system, supplemented with results from smaller studies, to spatiotemporally predict these concentrations across six MESA Air Study metropolitan regions using a long-term spatial mean, time trends with spatially varying coefficients, and a spatiotemporal residual. r^2 values were computed from long-term averages which were different by site. r^2 values at home sites were calculated from a small number of observations over a few weeks, whereas r^2 values from fixed sites, collated with AQS monitors in each region, were calculated from long time-series over the 4-year MESA Air sampling period. Cross-validated r^2 values were mostly above 0.45 in all regions, with some indicating high correlation (e.g., 0.98 for NO_x in St. Paul, 0.96 for NO₂ in Baltimore). NO₂ and NO_x showed greater spatial variability than PM_{2.5}. [Lindström et al. \(2013\)](#) replaced Keller's model with dispersion modeling output and found no significant improvement (r^2 within ± 0.04). [Kamboj et al. \(2022\)](#) used kriging and IDW to predict NO₂ across Kota, India and compared values against four monitoring stations. When using CV, 12-month NO₂ concentrations exhibited large errors (~31%) mostly during winters. However, both IDW and kriging showed similar trends for winter, summer, and rainy seasons.

2.3.1.2.2 Land Use Regression Models

LUR models, originally called “regression mapping” models and first introduced in the Small Area Variations in Air Quality and Health Study ([Briggs et al., 1997](#)), distinguish themselves from other types of modeling by fitting a multiple linear regression model of concentration data as a function of land use data. This is then used to estimate concentrations where monitors are not present. LUR models may have bias introduced to them if monitoring values which form the basis of the model have biased measurements (see Chapter 1, Section 1.4.1.1 for discussion on factors which may affect monitor measurements). The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) found that LUR models have been used extensively for estimating spatial distribution of ambient NO₂ or NO concentrations for neighborhood or urban-scale exposure assessment in epidemiologic studies of long-term exposure. [Azmi et al. \(2023\)](#) found that 160 articles (either containing NO_x, NO₂, CO, CO₂, SO₂, O₃ and/or PM data) were published between 2009 and 2021 that used LUR models, with 37 of these conducted within the U.S. Newer models have been developed that incorporate additional microscale data and techniques such as machine learning ([Lu et al., 2021](#); [Wong et al., 2021](#)).

Predictor variables, such as meteorology, traffic, land use, and population density affect the ability of an LUR model to predict concentrations of oxides of nitrogen for a specific city to which the model is applied, and different LUR models incorporate different aspects of these variables ([U.S. EPA, 2016](#)). Because these predictor variables are site-specific, application of the same LUR model to a different location can introduce bias and reduce precision. [Shen et al. \(2024\)](#) attempted to improve European-wide modeling of NO₂ concentrations using modeled AADT values across European roads by collecting observations from six countries during different years (2010 to 2015) and then collecting various urbanization, road-related, and topological variables to model the AADT values for the rest of the roads across Europe. They also performed a five-fold CV ($r^2 = 0.82$) and then compared them against national AADT estimates. They then used this information along with supervised linear regression, geographically weighted regression (GWR), and a random forest model to model European-wide air pollution. The authors reported that inclusion of AADT for every road led to improvement of the NO₂ model for GWR overall by 3% with a larger increase for urban areas of 5%.

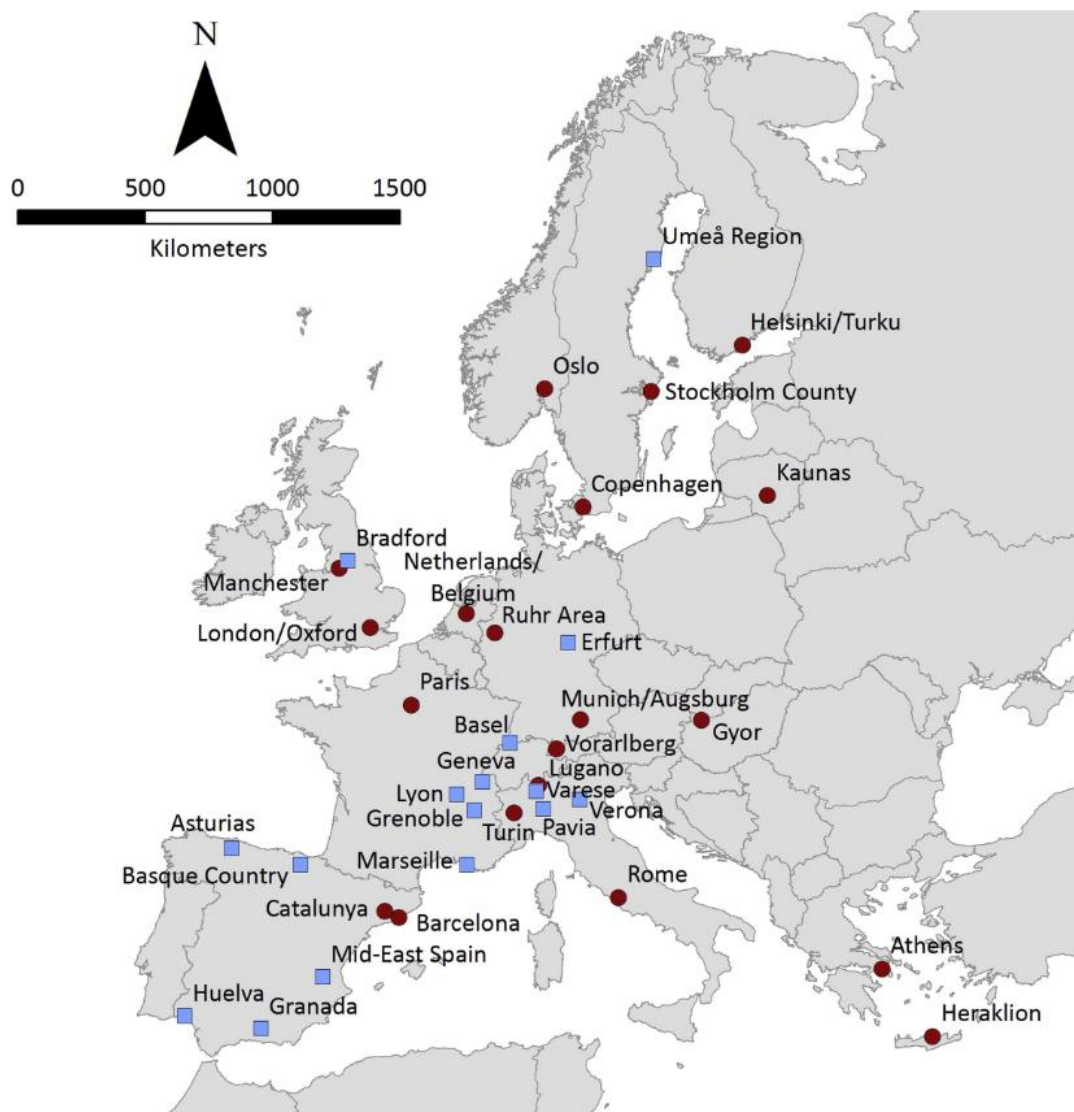
LUR models are usually used for estimating long-term NO₂ exposures (days, weeks, or years). In the short-term, some of the predictor variables such as traffic and meteorology may change rapidly while others such as land use or population density will generally remain static. As a result, depending on the temporal aspects of predictor variables, LUR models do not always account for short-term variability well. Incorporation of seasonality into LUR models has also been investigated, with [Crouse et al. \(2009\)](#) and [Dons et al. \(2014\)](#) finding no significant change in NO₂ spatial variability across seasons for Montreal, Canada, and Antwerp, Belgium, respectively, while [Arain et al. \(2009\)](#) found seasonal changes in spatial patterns of NO₂ concentrations across the Toronto-Hamilton airshed.

There is potential for exposure bias and reduced precision if the solution grid is not finely resolved. LUR models should be applied at the proper spatial scale, which depends on the scale of the

predictor variables, to minimize errors because spatially large LUR models may not effectively capture variability on smaller scales such as differences in exposure between members of different populations. [Chambliss et al. \(2023\)](#) compared 0.01 km² observations of NO₂ concentrations obtained from mobile monitoring in 13 neighborhoods of the San Francisco Bay Area against predictions from national scale models to analyze grid-cell level differences between modeled and observed values. Mobile monitoring was conducted over an 18-month time period from May 2015 to December 2017. The authors reported that extremes of local NO₂ concentrations were not represented by the national model with the national LUR model only capturing a small amount of variation ($r^2 = 0.15$), and a much wider interquartile range for mobile monitoring values. [Denby et al. \(2024\)](#) applied an urban European Monitoring and Evaluation Program (uEMEP) model, which is a downscaling model coupled to the largescale EMEP MSC-W model, to model pollutant concentrations at a resolution of 250 by 250 m² across Europe. The authors reported that the use of the uEMEP model and accounting for sub-grid variability resulted in a population-weighted increase of 31% for NO₂, meaning that the national model likely underpredicted exposure.

A notable example of LUR being used to estimate NO₂ exposures in epidemiology studies comes from the European Study of Cohorts for Air Pollution Effects (ESCAPE) project. ESCAPE investigates the long-term effects of air pollution exposures on health in 13 European nations ([Lipfert, 2016](#); [Beelen et al., 2013](#)). Air pollution estimates were made using passive samplers and LUR modeling. Recent epidemiologic studies have used LUR-derived estimates from ESCAPE to estimate exposure to NO₂ and NO_x ([Li et al., 2023a](#); [Li et al., 2023b](#); [Luo et al., 2022](#); [Klompmaaker et al., 2020](#)). Some epidemiologic studies that use ESCAPE data, including the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE), also use other predictor variables and models to create hybrid model structures, which will be discussed in the hybrid models section below. The original NO₂ and NO_x measurement sampling process and LUR model development process for ESCAPE will be described here to provide background for various studies discussed in later chapters.

ESCAPE used a standardized approach to develop LUR models for each of the 36 study areas (see Figure 2-2 European Study of Cohorts for Air Pollution Effects study areas.). NO_x was measured at 40 to 80 sites per area using Ogawa badges over three 14-day periods representing warm, cold, and intermediate seasons. At each site an average annual NO₂ and NO_x concentration was calculated with a correction for temporal variation retrieved from a centrally located reference site or routine monitoring site for areas with only NO_x measurements. Various predictor variables, including both background variables such as local land use and traffic variables such as traffic density on the nearest major road, were used. Both small-scale and large-scale buffer sizes were used for traffic variables to represent near-source and urban background concentrations, respectively. A workshop was held for those researchers developing LUR models as part of the ESCAPE project to standardize model development procedures. LUR models were developed locally and then centrally evaluated by the ESCAPE exposure working group for final approval.



Note: Circles mark the study areas where both PM and NO_x were measured. Squares indicate the study areas where only NO_x was measured.
Source: [Beelen et al., 2013](#). Copyright permission pending.

Figure 2-2 European Study of Cohorts for Air Pollution Effects study areas.

Predictor variables were evaluated for their contribution to concentration estimates using a stepwise procedure. Univariate regression analyses were conducted for all predictor variables and then all remaining variables were added consecutively and the effect on the overall adjusted r^2 was recorded. The addition of variables was repeated until there were no variables that added more than 1% of the adjusted r^2 of the previous model, and variables with p-values larger than 0.1 were removed from the model at the last step. Various diagnostic tests were applied to the final models including multicollinearity between models (Variance Inflation Factors), influential observations (Cook's D), and heteroscedasticity, normality and spatial autocorrelation (Moran's I) of residuals for assessing the independence assumption. Models were also evaluated for performance using a leave-one-out CV where predicted concentrations were compared against actual concentrations measured at the left-out site. An r^2 , representing overall

level of fit, was then calculated after the CV was repeated N times for the number of sites ([Beelen et al., 2013](#)).

The number of predictor variables ranged from 2 to 7 for both NO₂ and NO_x but varied from site to site as a result of the stepwise procedure used to build the models. The r^2 values for models ranged from 0.55 in Huelva, Spain to 0.92 in Pavia, Italy, and CV r^2 values ranged from 0.31 in Huelva, Italy to 0.87 in several locations (Pavia, Italy; Erfurt, Germany; London, Oxford, U.K.), making CV r^2 only slightly less than model r^2 s. These values are comparable to those found in ([Hoek et al., 2008](#)) for other LUR models and other publications have found similar relative relationships between model r^2 values and leave-one-out CV r^2 values ([Basagaña et al., 2012](#); [Wang et al., 2012](#)). RMSEs were low for different sites relative to the ranges measured for those sites: In Erfurt, Germany, the RMSE was 2 ppb (4.3 $\mu\text{g}/\text{m}^3$), with a range of 8–33 ppb (15.6–61.8 $\mu\text{g}/\text{m}^3$); in Verona, Italy, the RMSE was 17 ppb (32.3 $\mu\text{g}/\text{m}^3$), with a range of 18–151 ppb (33.1–284.4 $\mu\text{g}/\text{m}^3$). The authors note that because the total number of sites was too small to have a completely separate test validation dataset of sufficient size, leave-one-out CV was used to evaluate model performance for ESCAPE. [Basagaña et al. \(2012\)](#) found that r^2 for the LUR model and CV may be inflated, especially if the number of sites were low and possible predictor variables are high. Studies have found that r^2 values are generally lower when using separate validation training sets with fewer sites, discussed above ([Larkin et al., 2017](#); [Basagaña et al., 2012](#)).

Additionally, other researchers have focused on advancing LUR model capabilities through the use of Google Street View (GSV) images. [Qi et al. \(2022\)](#) developed a LUR model that used 4867 NO₂ annual average values across the contiguous United States from national monitors during a 13-year study period, satellite observations, and 336,544 GSV images within 500 m of NO₂ monitors. Though the authors cite several limitations, including an imbalance in image availability over time and space due to different rates at which locations were updated and not all monitors having associated GSV images, the authors reported that random 10-fold cross-validated r^2 values of the model ranged from 0.51 to 0.91 across different scenarios (mean absolute error range: 1.13–2.89 ppb; RMSE range: 1.69–3.83 ppb). The use of OMI satellite NO₂ observations and more GSV images improved all models and incorporated features of the environment extracted using a deep learning model and GSV images also improved CV. Features such as transport vehicles, transport networks, and the built environment were found to have the greatest impact on the model to predict NO₂ concentrations. [Lu et al. \(2021\)](#) also developed a national model for NO₂ that incorporated GSV imagery. The authors evaluated the impact of GSV imagery on prediction of NO₂ concentrations for two different models among many other predictor variables (satellite estimations, local climate zones, traffic, etc.). The authors reported there was limited use of GSV imagery due to images being classified by feature percentage (e.g., tree and awning) and that accounting for greater diversity of microscale features, combining features into appropriate groups (e.g., vegetation), or specifically classifying important sources may improve their usability. In addition, a repository of street-view imagery and recent image-processing techniques may help with classification in future studies.

2.3.1.2.3 Mechanistic Models

Chemical Transport Models

Chapter 1, Section 1.4 reviews information on CTMs and on commonly used models, including the Community Multiscale Air Quality (CMAQ) model. Briefly, CTMs use first principles of chemical transport such as advection, dispersion, diffusion, gas-phase reaction, mixing and mass conservation to determine estimates of NO, NO₂, or NO_x concentrations ([Byun and Schere, 2006](#)). CTMs are driven by emissions inventories for primary species such as NO, NO₂, SO₂, NH₃, VOCs, and primary PM (i.e., PM emitted directly from a source into the atmosphere), and by meteorological fields produced by other numerical prediction models. These models compute interactions between atmospheric pollutants and their transformation products, secondary aerosol production, particle size distributions, and the transport and deposition of pollutants. CTMs provide regional estimates of concentrations and are typically run with surface grid resolutions of 4, 12, or 36 km. CTMs can be run with temporal resolutions as fine as 1-hour but are typically run with longer intervals to maintain a reasonable data file size ([U.S. EPA, 2016](#)). CTMs can be applied in epidemiologic studies of either short- or long-term exposure to NO₂ or NO_x but are more commonly used in long-term exposure studies. Multiple studies have compared CMAQ simulations to remote sensing and ground measurements and found that CMAQ generally overestimates NO_x in populated areas and underestimates NO_x in rural environments ([East et al., 2022](#); [Toro et al., 2021](#); [Choi, 2014](#)) (see Chapter 1, Section 1.4.5). Recent studies have used CTMs as part of hybrid modeling approaches, as discussed in the hybrid models section below and Section 2.3.1.3.

Recent studies have developed advances in CTMs and incorporation of CTMs within hybrid models (described in more detail below) for estimating NO₂ concentrations at finer scales. [Salman et al. \(2024\)](#) developed an emulator of the CMAQ model to simulate surface NO₂ concentrations within 15 urban areas across the continental U.S. Results were similar ($r \geq 0.9$) to CMAQ for hourly NO₂ concentrations, with a simulation rate that was 400 times faster than CMAQ. Work by [Toro et al. \(2021\)](#) found that biases of CMAQ NO_x estimates in the United States have dropped significantly from 2002 to 2016 as a result of updates to the emission inputs and to the CMAQ air quality model itself (see Chapter 1, Section 1.4.5). [Goldberg et al. \(2017\)](#) found improved performance by incorporating CMAQ with OMI NO₂ retrievals, with r^2 values improving from 0.39 to 0.60.

Dispersion Models

Dispersion models, also known as Gaussian plume models, estimate the transport and dispersion of ambient air pollutants emanating from a point or line source by solving for an equation that estimates the spread of the pollutant to follow a Gaussian curve that is a function of distance from the source. Examples of these include the American Meteorological Society and EPA Regulatory Model (AERMOD) and the Atmospheric Dispersion Modeling System (ADMS), which are local plume-dispersion models

that can predict NO₂ and NO_x concentrations across the United States ([Carruthers et al., 2017](#)) (see Chapter 1). The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) and Chapter 1, Section 1.5 contain more detailed descriptions of dispersion models. [Milando and Batterman \(2018\)](#) evaluated the Research Line source model a dispersion model specifically designed for near-road evaluations, for NO_x in Detroit, MI for sensitivity to meteorological, emission, and traffic allocation inputs. Values predicted by the model were compared to five near-road monitoring sites. Different meteorological inputs from National Weather Service stations and AQS-site specific data yielded different results, with site-specific data resulting in the most accurate model predictions. Results suggest that local meteorological inputs should be used in dispersion modeling when possible and highlight the utility of equipping air quality monitoring sites with metrological instrumentation sufficient to obtain parameters for dispersion modeling. In addition, updated alternative emission factors using the 2014 Motor Vehicle Emission Simulator (MOVES) model, as opposed to the 2010 MOVES results, and 2015 input which took into account fleet differences between Detroit and the surrounding three-county area resulted in a better performing model for NO_x. Hourly vehicle volume estimates were also adjusted by temporal allocation factors for month-of-year, day-of-week and hour-of-day adjustments but showed little effect on model performance.

Hybrid Models

Hybrid models refer to models that use a combination of different modeling approaches and sometimes measured values to estimate concentrations of NO₂ and other species where monitors are not present. A common type of hybrid model combines fixed-site measurements with CTMs. The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) also contains descriptions of hybrid microenvironmental models, which use air quality parameter inputs from dispersion models or CTMs rather than monitoring data. Hybrid models may also incorporate different types of data fusion, which refers generally to the integration of data and knowledge from several sources ([Ursino and Takama, 2013](#)). In obtaining air pollution exposure estimates, data fusion refers to how data are combined using modeling and measurement techniques to derive estimates. Common reasons for doing this include increasing spatiotemporal coverage of estimates and constraining modeling results using observed data ([Schneider et al., 2017](#)). An example of a data fusion approach is universal kriging, which combines regression modeling with spatial interpolation, including geographic covariates, to estimate concentrations at different locations ([Wang et al., 2021](#)). [Schneider et al. \(2017\)](#) used this technique to combine low-cost sensor data with dispersion model results to predict NO₂ concentrations in Oslo, Norway.

Since the 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)), many recent studies have been published that use hybrid model approaches. Recent hybrid models incorporate advanced statistical techniques, such as the use of machine learning, and demonstrate many different possible model combinations and data inputs. Their complexity can make the evaluation of hybrid exposure models challenging.

Model users most often cross validate model estimations against stationary monitor values; however, many studies use other methods to evaluate their models including comparing them against passive sampler measurements or reference instruments before deployment. Table 2-3 identifies recent studies that used hybrid models and summarizes how authors evaluated their models for reliability to show the breadth of methods used.

Table 2-33 Summary of studies using hybrid models and author evaluations

Study	Hybrid Model	Author Evaluation
Smith et al. (2016)	LHEM – A combination of time-activity survey data, I/O ratios, and CMAQ outdoor air pollution estimates to estimate exposures across the greater London area in various microenvironments (i.e., in buildings, outdoors, in vehicles, etc.).	Model results were compared against concentrations measured at the residential address. The 2011 LHEM mean annual NO ₂ estimate was 63% lower than when measured only at the residential address. Authors attributed this to time spent indoors (~95%), lower exposures indoors, and duration of travel.
Zhang et al. (2021b)	A combination of the R-LINE dispersion model and LUR to predict 50 m spatial resolution NO ₂ concentrations in the New York tri-state area.	Model performance was evaluated against 32 NO ₂ monitoring sites over 2015–2017. Annual average NO ₂ predicted by the hybrid model and monitors was the same across study years. Out-of-sample coefficient of determination (r^2) and RMSE from a 10-fold CV were 0.75–0.79 and 3.9–4.0 ppb respectively.
Breen et al. (2020)	A combination of an urban-scale air quality model, residential air exchange model, building infiltration model, GPS-based microenvironmental model, and accelerometer-based inhaled ventilation model to predict exposure to NO _x concentrations in central North Carolina.	The model was previously calibrated for PM _{2.5} in Breen et al. (2015) using 591 daily measurements from 31 homes, the same locations in this study, and found median absolute differences for personal exposure to PM _{2.5} to be 1.8 µg/m ³ . The authors did not validate NO _x concentrations against monitors values but state that various components of the model (such as the mechanistic AER ventilation model) can reduce exposure measurement errors.
Weissert et al. (2019)	A combination of a network of eight low-cost monitors along with a microscale LUR model to estimate NO ₂ concentrations along a road in Auckland, New Zealand.	Ten devices were collocated with a reference instrument for 35 d close to a road junction, 3 km from the study area. The last 10 d were used to obtain measurement model coefficients. The RMSE among the NO ₂ test instruments was 2.9 ppb (5.5 µg/m ³). After deployment of the eight test devices, at midday for each site hourly-average values were checked for long-term trends to assess stability over time.

Study	Hybrid Model	Author Evaluation
Hanigan et al. (2017)	A combination of data from fixed-site monitors, chemical transport models, and satellite-based LUR models with data blended using the Bayesian maximum entropy approach to estimate the annual average NO ₂ at the neighborhood scale in Sydney, Australia.	Seasonally adjusted observations from 47 passive samplers were used to validate estimates. Samplers were placed at different locations in the city to capture near-road and within-city variability. RMSE was calculated for the BME model, CTM data inputs and satellite data inputs at 2.6, 3.1, and 2.8 ppb, respectively. All models showed under-prediction at concentrations above 10 ppb.

List of abbreviations in alphabetical order: CMAQ = community Multiscale Air Quality; CTM = chemical transport models; CV = cross validation; GPS = global positioning system; I/O = indoor/outdoor; LHEM = London Hybrid Exposure Model; LUR = land use regression; NO₂ = nitrogen dioxide; NO_x = NO₂ + NO; RMSE = root mean square error.

The ELAPSE project, which aimed to evaluate long-term exposure to low concentrations of various pollutants including NO₂, developed a hybrid-LUR model for Western Europe. This was done because ESCAPE LUR models did not cover the full national study areas of the ELAPSE project, and authors felt that more stable models could be developed based on a large number of training sites ([de Hoogh et al., 2018](#); [Wang et al., 2012](#)). Development of the NO₂ hybrid-LUR model involved incorporating different types of air pollution monitoring data (ESCAPE or AirBASE), satellite derived estimates, chemical transport model estimates and other predictor variables including traffic and land use variables. [de Hoogh et al. \(2016\)](#) found that CTM results improved model predictions over models based only on local and satellite-derived data (7–10% more variation explained than models without satellite or CTM data). In addition, model predictions were slightly improved using AirBASE data over ESCAPE monitoring values. This may likely be in part because AirBASE monitoring was more evenly spread across countries and the number of sites was larger for AirBASE than ESCAPE (2,400 versus 1,436).

[de Hoogh et al. \(2018\)](#) compared ELAPSE hybrid-model results against ESCAPE monitoring datasets. The NO₂ hybrid model was derived from 2010 AirBASE data. In addition, satellite estimates from OMI retrievals, CTM data from MACC-II ENSEMBLE model, and traffic and land use data were incorporated as additional predictor variables. First, separate LUR models were built according to ESCAPE protocol using stepwise linear regression as in [de Hoogh et al. \(2016\)](#), with predictor variables included if they added positively to the r^2 value and had a positive effect on the prediction of NO₂. Then ordinary kriging was applied to residuals and if this was not successful, longitude and latitude were used in the model as additional predictors. Using five hold-out validation models, the authors reported the FULL LUR model explained 58.8% of variation with CTM being the strongest predictor (similar to [de Hoogh et al. \(2016\)](#)) explaining 29% of variation. An independent comparison against all ESCAPE sites (1,396 sites) resulted in $r^2 = 0.49$ and RMSE = 6 ppb (11.47 µg/m³). Comparison against overall ELAPSE sites (780 sites) resulted in $r^2 = 0.46$ and RMSE = 5 ppb (10.28 µg/m³). r^2 and RMSE values varied across cohorts and areas, ranging from 0.07 and 7 ppb (12.74 µg/m³) respectively, for the HUBRO cohort (Oslo) in Norway, to 0.76 and 3 ppb (5.10 µg/m³) respectively, for the EPIC-NL cohort in the Netherlands. The authors reported that the model could not be improved by kriging or geographical coordinates and suggested that the CTM adequately captured large scale variation across Europe. The authors also state

that the moderately high explained variance in hold-out validation and external validation over the entire area suggests that their exposure assessment is robust.

Several publications have used results from ELAPSE model data that also combine data with other models and should be evaluated on a case-by-case basis ([Zhang et al., 2023a](#); [So et al., 2022](#); [Stafoggia et al., 2022](#)). As an example, [Zhang et al. \(2023a\)](#) used ELAPSE model results for 2010 along with annual means of NO₂ estimated at 1 × 1 km resolution using a hybrid model that combined a chemistry transport model, the Danish Eulerian Hemispheric Model and the Urban Background Model, including several domains with different spatial resolutions to calculate intercontinental, regional and local transport of air pollution. Their hybrid model was evaluated against four different public datasets including the Danish air quality monitoring network (dataset 1), a Danish measurement campaign within ESCAPE, a 2011 NO₂ measurement campaign, and a NO₂ measurement campaign at 204 addresses. Results indicated general agreement between model predictions and monitored concentrations, with r² values ranging from 0.45 for Aalborg/Vesterbro to 0.96 for Aarhus/Banegaardsgade in dataset 1.

2.3.1.2.4 Stochastic Models

Microenvironmental Models

Microenvironmental models are typically not used in exposure modeling for epidemiologic studies because of the potential for its stochastic component to add additional measurement error, but they have been used in exposure and risk assessments performed as part of the NAAQS review process ([U.S. EPA, 2016, 2008b](#)). Microenvironmental models use a variety of inputs including pollutant concentrations, human time-activity patterns, population demographics, anthropometric attributes (e.g., height, weight), and other types of data to stochastically predict exposure across various microenvironments. Different microenvironments can contribute to varying levels of exposure. Examples of microenvironmental exposure models include the Air Pollution Exposure (APEX) model, the Stochastic Human Exposure and Dose Simulation (SHEDS) model, and the Exposure in Polis (or cities) (EXPOLIS) model. The APEX model is a population-based inhalation exposure model ([U.S. EPA, 2019a, b](#)). The EPA has used APEX to estimate human exposure to SO₂, O₃, CO, and NO₂ ([2018](#); [U.S. EPA, 2014a, b](#); [2010, 2008b](#)), in support of reviews of the NAAQS. APEX has been used because of its flexible, user-defined physical-based microenvironmental approach and, when combined with extensive activity pattern and population databases, spatially and temporally resolved ambient concentrations, and parameterized distributions that capture variability in other model inputs, can estimate population-based human exposures to air pollutants.

[Dionisio et al. \(2013\)](#) compared estimates of NO_x concentration from a central site monitor and AERMOD with estimates from the APEX and SHEDS models and found that the microenvironmental models captured spatial variability of the concentration distribution well, but temporal variability

produced by the models differed from other concentration estimation methods. [Pattinson et al. \(2016\)](#) used the APEX model to estimate NO_x exposure concentrations for 51 residents living in a 1.5 km² area in South Auckland, New Zealand bisected by a highway. The authors reported that residents were exposed to greater concentrations of NO₂ when positioned 50 m downwind of the highway relative to their actual home location (July 2010 ambient month-long average exposure was 8 ppb or 14.8 µg/m³ greater). In addition, residents experienced slightly more exposure when positioned upwind from the highway (July 2010 ambient month-long average exposure 2 ppb or 3.6 µg/m³ greater) and when positioned 150 m away from the highway in either direction they experienced less overall exposure than either of the 50 m locations.

2.3.1.3 Strengths and Limitations of Exposure Estimation Methods

The choice of exposure assessment approach used in epidemiologic and exposure studies depends on the study design, availability of data, and spatial variability of pollutant concentrations. There are various needs for using different approaches, including expertise required, computing power, and an accurate understanding of local meteorological conditions (e.g., with CTMs). Generally, the use of more complex modeling structures and sources of data requires increased computing power, data input, and expertise ([Jerrett et al., 2005](#)). The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) summarized the epidemiologic applications and errors and uncertainties in exposure estimates associated with each exposure assessment approach. That table is reproduced here as Table 2-4 with updates to reflect more recent information. Errors and uncertainties of hybrid models are not included in Table 2-4 because the wide variety of exposure estimation methods and data fusion techniques used in these models makes it difficult to generalize about their errors and uncertainties; however, some aspects of hybrid model use are discussed near the end of this section. Implications of different modeling and measurement techniques and their associated errors are explored more in Section 2.5.

Table 2-44 Summary of exposure estimation methods, their typical use in nitrogen dioxide epidemiologic studies, and related errors and uncertainties

Method	Epidemiologic Application	Errors and Uncertainties in Exposure Estimates
Central Site Monitors	Short-term community time-series exposure of a population within a city	Correlation between true outdoor concentrations and outdoor measurements typically decreases with increasing distance from the monitor, potentially leading to reduced precision and exposure bias towards the null (see Section 2.3.1.1.1)
	Long-term exposure to compare populations among different cities	Potential for exposure bias and reduced precision if the monitor site does not correspond to the exposed population (see Section 2.3.1.1.1) Positive instrument bias in the central site monitor from other ambient oxidized nitrogen products may lead to exposure bias and reduced precision (see Section 1.4.1.1)

Method	Epidemiologic Application	Errors and Uncertainties in Exposure Estimates
Passive Monitors	Short-term panel (personal monitoring or fixed local site, e.g., residence, school, work)	Positive instrument bias in the passive monitor from other ambient oxidized nitrogen products or internal reaction of NO and O ₃ to produce additional NO ₂ within the passive sampler body may lead to exposure bias and reduced precision (see Section 2.3.1.1.2)
	Long-term exposure characterization or LUR model fit (monitors distributed across a city or at fixed local sites)	Positive instrument bias as described for the short-term panel studies above may add exposure bias and reduced precision when LUR models are fit to passive sampler data (see Section 2.3.1.1.2)
		Potential for exposure bias and reduced precision for monitors sited at fixed locations (see Section 2.3.1.1.2)
Satellite measurements	Short-term and long-term exposure over large areas	Potential for exposure bias and reduced precision due to indirect measurements of NO ₂ concentrations that require a scaling algorithm to predict ground concentrations and AMF error (see Sections 1.4.4 and 2.3.1.1.3) Spatial resolution limitations may reduce precision of estimates and not capture fine-scale pollution variations. Temporal resolution limitations of once a day measurements may reduce precision of short-term exposure studies (see Section 2.3.1.1.3)
LUR	Long-term exposure, usually across a city but sometimes fit among multiple cities	Potential for exposure bias and reduced precision if the solution grid is not finely resolved (see Section 2.3.1.2.2) Potential for bias and reduced precision if the model is incorrectly specified or applied to a location different from where the model was fit (see Section 2.3.1.2.2)
Statistical interpolation methods used in spatiotemporal models (IDW, kriging, splines)	Long-term exposure across a city	Potential for negative bias and reduced precision if sources are not captured or overly smoothed (see Section 2.3.1.2.1)
CTM	Long-term exposure, sometimes within a city but more typically across a larger region	Potential for exposure error and reduced precision when grid cells are too large to capture spatial variability of exposures (see Section 2.3.1.2.3)
Gaussian plume dispersion modeling	Long-term exposure within a city	Potential for bias and reduced precision where the dispersion model does not capture boundary conditions and resulting fluid dynamics well (e.g., in large cities with urban topography affecting dispersion) (see Section 2.3.1.2.3)

List of abbreviations in alphabetical order: AMF = air mass factor; CTM = chemical transport model; IDW = inverse distance weighting; LUR = land use regression; NO = nitric oxide; NO₂ = nitrogen dioxide; O₃ = ozone.

Concentrations measured by central site or near-road monitors are commonly used as surrogates for human exposure in studies of both short- and long-term exposure to NO₂ (see Section 2.3.1.1.1). Monitor measurements are subject to positive bias from instrument error (see Chapter 1, Section 1.4). Correlation between measured central site concentration and concentration at some distant point decreases with distance ([Liu et al., 2018](#); [Richmond-Bryant et al., 2017a](#)). Reduced correlations between measurements at a central site monitor and the true exposure at the location of individuals in an epidemiologic study, caused by human activity and variation in sources over space and time, can lead to

bias towards the null and loss of precision in the exposure estimate for studies of short-term exposure to ambient NO₂ (see Sections 2.3.2.2 and 2.3.2.4). For epidemiologic studies of long-term exposure to NO₂ in ambient air, the difference between the measured concentration and the true exposure would also result in exposure error ([Evangelopoulos et al., 2020](#); [U.S. EPA, 2016](#)).

Passive sampling can be used in studies examining longer term exposures, such as studies using samples that are integrated or averaged over several-weeks or months. The integrated nature of the passive samples limits their application in time-resolved studies of shorter-term exposures. Passive sampling techniques such as Palmes tube measurements are subject to positive instrumentation biases. Additionally, passive monitors left in place for sampling durations of weeks may produce data having errors and uncertainties similar to those associated with using a fixed-site monitor to capture exposures for a population that is dispersed over space and moving in time (see Section 2.3.2.1). Passive monitors used for personal monitoring have the advantage of being able to capture individual variability of exposure for participants in a study but are still limited to longer exposure durations.

Satellite measurements have been used in both short-term and long-term exposure studies to study acute and chronic health effects. Satellite measurements can improve spatial coverage of concentration estimations throughout a region. However, the retrievals made by the satellite, when converted to pollutant concentrations, may be affected by air mass factor (AMF) error (see Chapter 1, Section 1.4) ([Lamsal et al., 2021](#)). In addition, to predict ground concentrations a scaling factor must be applied using a model, such as a CTM or other statistical models including LUR ([Huang et al., 2023](#); [Holloway et al., 2021](#); [U.S. EPA, 2016](#)). The accuracy of these models can affect the ability of satellite concentrations to predict ground concentrations and may usually bias estimates lower, or more rarely higher, than monitor values (see Chapter 1, Section 1.4) ([Cooper et al., 2020](#)). Spatiotemporal resolution limitations may also affect the ability of satellites to accurately predict exposures. OMI and TROPOMI satellites can only take once daily measurements that do not represent daily averages while TEMPO can take measurements once an hour over North America. This makes TEMPO better suited for epidemiologic studies of short-term exposures. Land-use variables are usually incorporated with satellite estimates to improve spatial resolution of estimates (see Section 2.3.1.2).

LUR is often employed to estimate NO₂ concentrations for use in long-term exposure studies. The quality of the exposure metric provided by the model depends on several factors, including spatial resolution of the model, the number of model training sites, the selection of predictor variables, consideration of seasonality, and model validation (see Section 2.3.1.2.2). IDW is also used for exposure estimation between spatially distributed NO₂ concentration measurements. However, if too few monitors are used, then the IDW might not capture the spatial variability of the true exposures (see Section 2.3.1.2.1).

CTMs and dispersion models are based on the physics of air flow and contaminant transport. Like central site monitors, CTMs can be used to compare NO₂ concentrations among different cities for long-term exposure studies. However, coarse spatial resolution of CTMs limits their applicability within cities

([Bessagnet et al., 2023](#)). Multiple studies have compared CMAQ simulations to remote sensing and ground measurements and found that CMAQ generally overestimates NO_x in populated areas and underestimates NO_x in rural environments ([Fang and Michalski, 2022](#); [Choi, 2014](#)) (see Chapter 1). Dispersion models are frequently used for within-city NO₂ concentration estimates in long-term exposure studies, but the simplifying assumption of Gaussian dispersion can add error to the concentration estimate if meteorology or topography of the built environment are complex. In addition, an incomplete understanding of the atmospheric chemistry, such as the photo reactivity of NO to form NO₂, in a given region can create error ([Kimbrough et al., 2017](#)). Given this complexity, the direction of exposure error is not predictable. Biases in dispersion model output can occur in either direction and they depend strongly on the specific environment (i.e., topography, meteorology, source representation) being modeled. Correction methods may sometimes be applied to minimize such error for a given location, but the effectiveness of error minimization must be determined on a case-by-case basis ([Briant et al., 2011](#); [Colville et al., 2002](#)).

Studies comparing the effects of using different exposure estimation models on epidemiologic findings are scarce. Recent studies, however, compare the effectiveness of different models in different scenarios on exposure estimations. [Klompmaaker et al. \(2021\)](#) compared the use of hybrid, LUR, and dispersion models on exposure estimations for PM_{2.5}, black carbon (BC), and NO₂ in relation to natural cause (International Classification of Diseases, 10th Revision codes: A00-R99) and cause-specific mortality in the Netherlands. The authors reported that model performance was similar among methods (Pearson correlations ranged from 0.83 for the NO₂ LUR-hybrid comparison to 0.61 for the PM_{2.5} LUR-hybrid comparison), likely due to spatial variability caused by traffic emissions, of which the three models relied on in some form, having a strong impact on exposure estimates. NO₂ models had the strongest correlation (NO₂, LUR-hybrid: 0.83; dispersion model-hybrid: 0.79; dispersion model-LUR: 0.78) among the different model comparisons, likely due to traffic being a strong contributor to NO₂. The hybrid NO₂ model produced higher concentrations than the LUR (which was similar to other publications; [de Hoogh et al. \(2018\)](#)) or dispersion models. The authors were unsure of why there was a difference between model results, but hypothesized that the difference was due to a difference in monitoring sites and limitations in applying models meant for wider Europe to one country. Past research has shown that using an LUR model in a location other than the location in which it was originally fit can impair the ability of that model to predict concentrations because predictor variables used to fit LUR models are site-specific [see Section 3.2.1.1 of [U.S. EPA \(2016\)](#)]. [Yu et al. \(2018\)](#) compared fourteen different methods, including eight observation-based methods, two emissions-based air quality methods, and four hybrid-modeling techniques estimating concentrations of NO₂ in the greater Atlanta region. The authors reported that hybrid data-fusion methods resulted in overall better results than unadjusted outputs from the air quality models. [Huang et al. \(2018\)](#) also found improved capture of temporal and spatial variability of NO₂ and NO_x when using a data-fusion approach that combined observations from ambient monitors and CMAQ outputs.

Generally, model comparison over the same region can be difficult because models may not have the same spatial resolution or account for the same physical phenomena ([U.S. EPA, 2016](#)). However, for sites that have less spatial and temporal variability, simpler models may be sufficient ([Jerrett et al., 2005](#)). Temporal aspects of concentration data are usually more consistent for more stable pollutants like PM_{2.5}, rather than NO₂ ([Yu et al., 2018](#)). Current data also seem to point toward data-fusion methods as generally having better performance than raw model outputs when comparing standalone method results versus data fused results for the same location ([Huang et al., 2018](#); [Yu et al., 2018](#)).

2.3.2 Factors Determining Exposure and Contributing to Exposure Errors

Recent studies examining factors that contribute to differential exposures and exposure errors build on literature that was reviewed in the 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)). Differential exposure refers to different levels of exposure that can occur between groups of people. Exposure measurement error refers to the difference between a true, unknown exposure and an exposure concentration estimated using an exposure surrogate such as an ambient monitor measurement and uncertainty associated with the use of this exposure surrogate ([Richmond-Bryant and Long, 2020](#)). Evaluation of exposure measurement error present in exposure models can be challenging because various contributing factors may exist. These factors can include model misspecification, as discussed previously in Sections 2.3.1.2 and 2.3.1.3, and factors related to measurement accuracy and precision (see Section 2.3.2.1), spatial and temporal variability (see Section 2.3.2.2), infiltration and building ventilation (see Section 2.3.2.3), time-activity patterns (see Section 2.3.2.4), and indoor exposures (see Section 2.3.2.5).

2.3.2.1 Measurement Accuracy and Precision

Instrument error can cause deviation of the measured concentration from the true concentration at a measurement site. Instrument error is discussed in depth in Chapter 1, Section 1.4. This section discusses the impact of measurement accuracy and precision from an exposure perspective. For epidemiologic studies, inter-monitor comparisons have been used to estimate instrument precision. A review by [Richmond-Bryant and Long \(2020\)](#) found only one study [Goldman et al. \(2010\)](#) that investigated the effect of instrument error on epidemiologic bias for NO_x. The authors concluded that while instrument error can positively bias effect estimates, that bias is small and unlikely to impact effect estimates in a meaningful way. The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) also reviewed this study and found that instrument precision error increased with increasing concentration. However, due to specific site conditions such as sampler type, meteorological conditions, or the presence of interferants, instrument error may vary in magnitude or direction and may not always be correlated with concentration. [Goldman et al. \(2010\)](#) also notes that instrument error was found to exhibit some autocorrelation at 1- and 2-day lags, meaning that diurnal variability in relative NO₂ instrument error does not change substantially

day to day and the influence of instrument error would not be expected to change if health data were obtained on a daily basis over a few-days for short-term NO₂ exposure studies.

Bias from instrumentation error may influence exposure estimates in long-term exposure studies in some situations but would likely differ more among different cities than within a single urban area. This is because monitors and other sensors can be influenced by local meteorological conditions such as temperature, wind speed, and relative humidity. Recent LCSs that are more rarely used are also affected by aging and impurity of the electrochemical sensor over time. Past research has also found that NO₂ Federal Reference Methods (FRMs) are subject to positive interference by NO_x oxidation products (see Chapter 1, Section 1.4.1.1) and additional research since the 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) has investigated the contributions by individual compounds.

Personal samplers measuring NO₂, depending on the sorbent material, may be biased due to interference from other species such as HONO, PAN, HNO₃, and high relative humidity ([Centro di Ricerche Ambientali, 2006](#); [Gair et al., 1991](#)). Results from studies reviewed in the 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) found mixed results when bias was investigated for samplers in relation to FRM monitors. [Sather et al. \(2007\)](#) found that Ogawa passive samplers had good agreement (mean absolute difference of 1.2 ppb and $r^2 = 0.95$ for NO₂) with an FRM site over a 4-week field study, and [Buzica et al. \(2008\)](#) found in a laboratory and field evaluation comparison that there was little difference for membrane-closed Palmes diffusion tubes compared with reference methods, but uncertainty increased with decreasing concentration. [Hagenbjork-Gustafsson et al. \(2009\)](#) observed negatively biased (9.1%) NO₂ measurements and positively biased (15%) NO_x concentrations when compared to an FRM when using manufacturer recommended uptake rates to calculate concentration but these biases changed to a positive 2% for NO₂ and disappeared for NO_x when uptake rates were derived in the field. Sampling efficiency using triethanolamine (TEA), often used as a sorbent material in denuders for both active and passive sampling, was found to be sensitive to sampler flow rate ([Vichi and De Santis, 2012](#)), relative humidity ([Poddubny and Yushketova, 2013](#); [Šerevičienė and Paliulis, 2012](#); [Vardoulakis et al., 2009](#)), averaging time ([Vardoulakis et al., 2009](#)), ambient temperature ([Poddubny and Yushketova, 2013](#)), and bias was introduced depending on how TEA was applied to the substrate ([Heal, 2008](#)) [see Section 3.2.1.2 in [U.S. EPA \(2016\)](#)].

Recently, new sensor designs have been researched for their use in supplementing national networks of NO₂ monitors. Though LCSs improve spatial coverage, they have been reported to display inaccuracies with sensor readings that can offset their advantages ([Hohenberger et al., 2022](#); [Castell et al., 2016](#)). Factors such as humidity and temperature can affect sensor readings and may not be able to be mimicked in a laboratory environment before deployment ([Spinelle et al., 2017](#)). [Zuidema et al. \(2021\)](#) studied the performance of a newly built low-cost gas sensor monitoring network as part of a larger epidemiologic study in the Puget Sound region of Washington state. The authors demonstrated that constructing a multiple linear regression model for calibration resulted in improved performance, but not all factors improved accuracy and there were important factors unique to each sensor (e.g., the calibration

intercept term, the effects of relative humidity and temperature on sensor response, and inclusion of other gases in the calibration model such as CO in the case of calibrating NO₂). The mean drift for NO₂ sensors over the deployment time from May 2017 to March 2019 was small with a drift of 1 (with a range of -3 to 5) ppb. However, 66% of NO values were below the detection limit of 15 ppb. The EPA webpage “Evaluation of Emerging Air Sensor Performance” (<https://www.epa.gov/air-sensor-toolbox/evaluation-emerging-air-sensor-performance>) contains a series of different evaluation studies of emerging gas-phase sensors. In addition, Chapter 1, Section 1.4 contains additional information on LCSs.

2.3.2.2 Spatial And Temporal Variability in NO₂

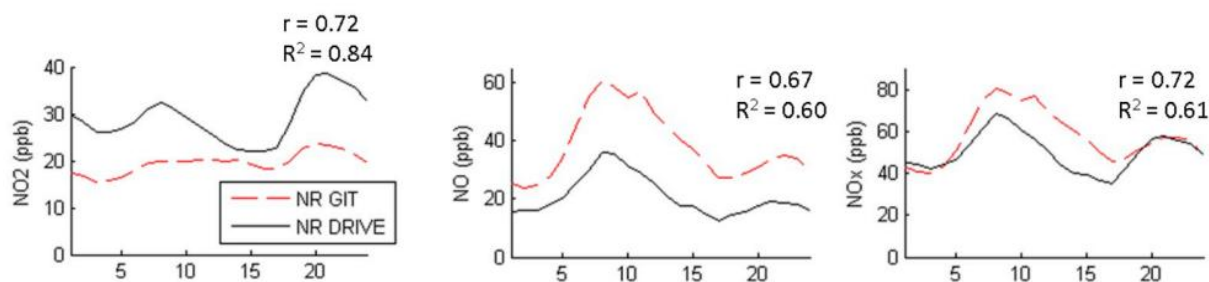
The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) found that spatial variation for oxides of nitrogen at urban and smaller scales is influenced by source location, source strength, meteorology, and natural and urban topography, and that NO_x concentrations can be more variable than other air pollutants such as PM. NO_x has a variety of sources from which it can be directly emitted, including traffic, stationary fuel combustion sources, wildfires, and agricultural burning. More detail on contributors to spatial variability and trends are described in detail in Chapter 1, Section 1.5. Oxides of nitrogen can exhibit both vertical and horizontal small-scale spatial variability, as measured by evaluating divergence between ambient monitoring sites over small urban scales and vertical distances up to 15 meters [see Sections 2.5.3.2 and 2.5.3.3 in [U.S. EPA \(2008a\)](#)].

Chapter 1, Section 1.5.4 discusses the high regional spatial variability of NO₂ concentrations in detail. Central site monitors are often used to assess exposure or act as a basis measurement from which more complex models are built. Error in estimation of concentrations between monitors increases with increasing distance between monitors, resulting in the need for modeling techniques to estimate personal exposure of a population ([Liu et al., 2018](#); [Richmond-Bryant et al., 2017a](#)). Extensions of exposure concentrations by statistical modeling techniques are generally more essential in rural settings, where monitoring locations are more sparsely distributed.

NO_x concentrations vary not only spatially but also temporally. Chapter 1, Section 1.5.5 contains details of concentration trends by season, weekday, and hour. Briefly, NO₂ exhibits strong seasonal variability with higher concentrations in summer and lower concentrations in winter. NO_x concentrations in urban areas have also been found to be lower on weekends than on weekdays, with this trend weakening as a result of lower anthropogenic emissions ([Simon et al., 2024](#); [Stavrou et al., 2020](#)). [Goldberg et al. \(2021\)](#), using TROPOMI satellite data across the continental United States, found agreement with earlier studies that normalized mean NO₂ concentrations were generally lower across cities measured on weekends compared to weekdays ([de Foy et al., 2016](#)).

Ambient NO_x concentrations have been found to follow a daily pattern, peaking during morning and evening rush hours ([U.S. EPA, 2016](#)). [Moutinho et al. \(2020\)](#) further confirmed the temporal relationships of NO₂ and NO that were found in the 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)).

These authors analyzed data from two roadside monitors adjacent to where Interstates 75 and 85 merge in Atlanta. The monitors were set 325 m away from each other to understand temporal changes in NO_x concentrations. Figure 2-3 shows the temporal pattern at the two sites based on average weekday data. Both monitors showed similar diurnal variations, with the greatest NO_x concentrations during morning rush hours when traffic emissions were high and atmospheric mixing was weaker. Concentrations were also higher during evening rush hour. Overall concentrations were different for NO₂ and NO between sites; however, the authors postulated that less dispersion occurred at the near-road (NR) Georgia Institute of Technology (GIT) site due to vegetation which drove different mixing rates with O₃. The NR GIT site had lower NO₂ concentrations and higher NO concentrations than the NR Dorm Room Inhalation to Vehicle Emissions (DRIVE) study site, which was situated about a meter from the west side of a fifteen-lane highway. In some urban and suburban locations, a midday minimum of NO_x concentrations may occur due to lower traffic emissions, higher O₃ concentrations, and a deeper mixed layer that supports enhanced atmospheric mixing ([Squizzato et al., 2018](#)).



List of abbreviations in alphabetical order: NO = nitric oxide; NO₂ = nitrogen dioxide; NO_x = sum of NO and NO₂; NR DRIVE = near-road Dorm Room Inhalation to Vehicle Emissions; NR GIT = near-road sampling location on the Georgia Institute of Technology campus; ppb = parts per billion; r = Spearman's rank correlation for temporal variability in hourly concentrations between the two sites; r² = coefficient of determination between the two sites.

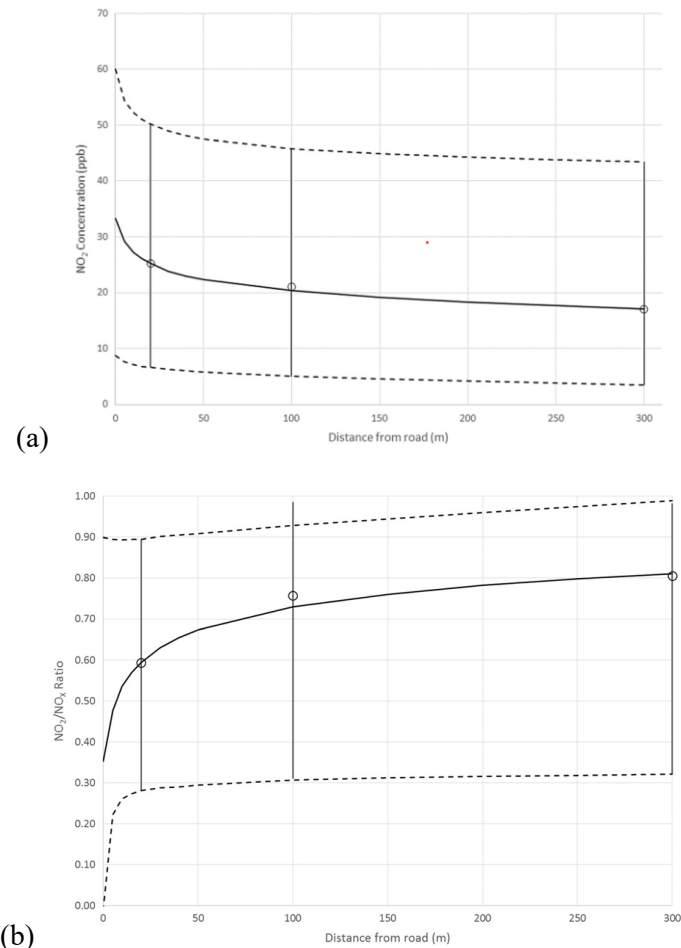
Note: The x-axis represents hours throughout the day from 0 to 24. Diurnal profiles for NO₂, NO, and NO_x for two near-road sites in Atlanta, GA, near the intersection of Interstate-75 and Interstate-85 based on average weekday data.

Source: [Moutinho et al. \(2020\)](#) Copyright permission pending.

Figure 2-3 Diurnal profiles for NO₂, NO, and NO_x for two different near-road sites in Atlanta, GA.

The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) found that near-road concentration gradients caused by mobile source emissions played a large role in urban spatial gradients and have been extensively studied. Several extensive reviews found that elevated NO₂ concentrations typically extend 200 to 500 m from roads with heavy traffic ([HEI, 2010](#); [Karner et al., 2010](#); [Zhou and Levy, 2007](#)). However, the influence of the road on NO₂ concentrations can extend farther, up to several kilometers, but with smaller differences in concentrations ([Gilbert et al., 2007](#); [Gonzales et al., 2005](#)). Past researchers have tried to fit various models to NO₂ concentration data as a function of distance from the road including logarithmic, exponential decay, and shifted power law models ([Zou et al., 2006](#); [Cape et al., 2004](#); [Pleijel et al., 2004](#)). The model fits depend on many different factors in each of these publications, though the impacts of factors such as seasonality and traffic on these gradients is more thoroughly investigated in more recent studies discussed below.

Near-road spatial gradients are a function of wind direction and speed, traffic, and the presence of other chemical species which may interact with NO_x in the atmosphere, including O_3 (Richmond-Bryant et al., 2017a; Richmond-Bryant et al., 2017b). Figure 2-4 displays results of a near-road gradient for NO_2 and NO_x found near Interstate-85 in Las Vegas, NV as part of Richmond-Bryant et al. (2017a). Overall concentrations displayed a negative slope with increasing distance from the road and NO_2/NO_x ratios showed a positive slope as NO was converted to NO_2 as air moved away from the interstate. This section contains additional studies that look at spatiotemporal variability of NO_x around roadways.

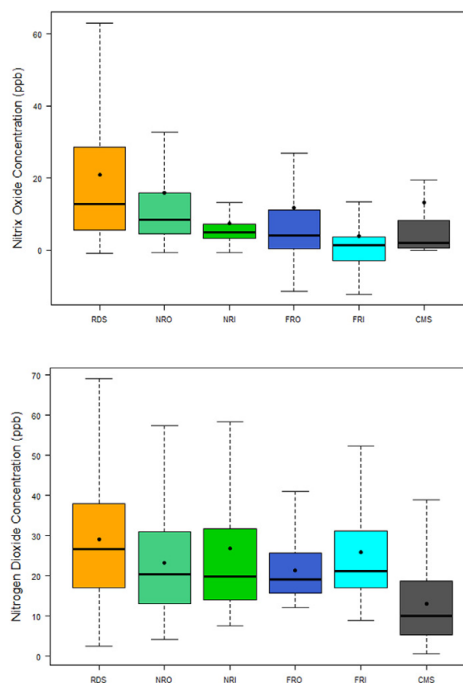


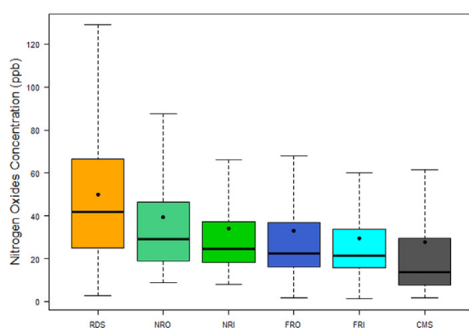
Note: Measured NO_2 and NO_x concentrations at three Las Vegas measurement sites during the study period (December 12, 2008 to January 21, 2010). (a) Predicted and observed NO_2 concentrations for all wind and stability conditions combined, and (b) Predicted and observed NO_2/NO_x ratios for all wind and stability conditions combined. Predicted median (solid), predicted 98th and 2nd percentile (dotted), observed median (circles), and observed 98th and 2nd percentiles (error bars) are shown.

Source: modified from Richmond-Bryant et al. (2017a) Copyright permission pending.

Figure 2-4 (a) Predicted and observed NO_2 concentrations for all wind and stability conditions combined and (b) Predicted and observed NO_2/NO_x ratios for all wind and stability conditions combined. NO_2 and NO_x concentration measurements relative to Interstate-15 in Las Vegas, NV.

As part of the DRIVE study, [Liang et al. \(2018\)](#) investigated the impact on measured NO and NO₂ concentrations of using monitors at different distances (10 m (nearest road site; RDS), 20 m (outside dormitory; NRO), 20 m (inside dormitory; NRI), 1.4 km (outside dormitory; FRO), 1.4 km (inside dormitory; FRI), and a 2.3 km urban background site; CMS) from the intersection of Interstates 75 and 85 on the Georgia Institute of Technology campus, with average annual daily traffic of approximately 350,000 vehicles. The authors treated RDS as an error-prone surrogate of pollutant concentrations at other “true” measurement sites, due to measurement error introduced by the presence of a spatial gradient or other contributions specific to the microenvironment that not accounted for at this measurement site. The authors reported that NO_x concentrations generally decreased farther away from the RDS site with NO having a stronger gradient than NO₂, which the authors attribute to interactions of NO with O₃ (see Figure 2-5). In addition, NO₂ concentrations were found to be generally higher for indoor sites at the same location while NO concentrations were lower. Hourly-resolved spatial gradients were also stronger with higher wind speeds and during times with greater traffic counts (10am–3pm), indicating that exposure measurement error can vary temporally based on these factors. This study further confirms that increasing distance away from a road and differences in daily meteorology and traffic count can lead to changes in NO₂ or NO concentrations and therefore greater spatial measurement error depending on where exposure is measured.





Note: Boxplot presenting the distribution of NO, NO₂, and NO_x concentrations during September 8th, 2014 to January 5th, 2015 at outdoor and indoor sampling locations, ordered in increasing distance from the highway source: (1) RDS: near-highway stationary site [10 m], (2) NRO: near dorm outside [20 m], (3) NRI: near dorm inside [20 m], (4) FRO: far dorm outside [1.4 km], (5) FRI: far dorm inside [1.4 km], and (6) CMS: urban background [2.3 km]. The horizontal line within the box indicates the median, boundaries of the box indicate the 25th- and 75th -percentile, the whiskers are the 5th and 95th percentile, and the “•” marked in the box indicates the mean.
Source: [Liang et al. \(2018\)](#) Copyright permission pending.

Figure 2-5 Distribution of NO_x concentrations in the Dorm Room Inhalation to Vehicle Emissions study.

Near-road concentration gradients generally are impacted by distance from the roadway, traffic volume and composition, and wind speed and direction. These are critical details that must be considered when assessing near-road concentration gradients for exposure considerations. Other factors that influence near-road concentration gradients are temporality, such as seasonality or time of day/week, and meteorology, such as wind speed and direction. A limited number of peer-reviewed studies detail measurements of oxides of nitrogen at two or more distances from a single roadway. Those studies evaluating the concentration gradient are summarized in Table 2-5 and discussed below. In Table 2-5, “near” is defined as the closest monitor to the road, while “far” is defined as the farthest monitor from the roadway.

Table 2-55 Summary of near-road gradient investigations for oxides of nitrogen

Study ID, Location	Traffic Count (vehicles/time)	AT	Time of Year	Oxides of Nitrogen Measured	C _{near} Average (ppb#)	C _{far} Average (ppb#)	Distance From Road (m)
Baldwin et al. (2015) , Detroit, Michigan, U.S.	Range: 25,963–167,800 vehicles/d	5 min	Winter (December 2012)	NO	C _{diff} Average: 14.7*		50 m
				NO _x	C _{diff} Average: 17.1*		150 m
				NO ₂	C _{diff} Average: 5.8*		500 m
Jeong et al. (2022) , Toronto, Canada	Average: 11,000 vehicles/hr	1 min	Winter (February 2017)	NO	23	9	
				NO _x	47	29	10 m
				NO ₂	24	20	150 m
Liang et al. (2018) , Atlanta, Georgia, U.S.		24 hr and 1 hr		NO	20.9	15.7	
				NO _x	NA	NA	

Study ID, Location	Traffic Count (vehicles/time)	AT	Time of Year	Oxides of Nitrogen Measured	C _{near} Average (ppb#)	C _{far} Average (ppb#)	Distance From Road (m)
	Average vehicles/day: Highway: 353,700 Arterial roadway: 6,990		Winter (September 2014 - January 2015)	NO ₂	30.3	14.5	10 m 20 m 1.4 km 2.3 km
Richmond-Bryant et al. (2017a) , Las Vegas, Nevada, U.S.	Average: 206,000 vehicles/d	1 hr	Year-round (December 2008 - January 2010)	NO	NA	NA	20 m
				NO _x	32.56	37.55	100 m ^a 100 m ^b 300 m
				NO ₂	22.01	22.40	
Richmond-Bryant et al. (2017b) , Las Vegas, Nevada, U.S.	Average: 206,000 vehicles/d	1 hr	Year-round (December 2008 - January 2010)	NO	NA	NA	25 m
				NO _x	51.0	31.3	115 m ^a 100 m ^b 300 m
				NO ₂	25.9	19.5	
Saha et al. (2018) , Durham, North Carolina, U.S.	Average: 6,350 vehicles/hr [†]	1 hr	Summer 2015, Winter 2016	NO	NA	NA	10 m ^c 50 m
				NO _x	44 [‡] (50 m) [°]	24 [‡] (220 m) [°]	100 m 150 m 220 m 400 m ^b
				NO ₂	NA	NA	
Zhang et al. (2017) , Houston, Texas, U.S.				NO	NA	NA	0–20 m 20–50 m
				NO _x	25.73 µg/m ³	16.56 µg/m ³	50–100 m 100–150 m 150–200 m 200–250 m 250–300 m 300–350 m 350–400 m 450–500 m
	Not Reported	annual	Year-round (January - December, 2011)	NO ₂	NA	NA	

List of abbreviations in alphabetical order: AT = averaging time; NO = nitric oxide; NO_x = NO₂ + NO; NO₂ = nitrogen dioxide.

[†]Calculated average based on seasonality averages in vehicles/hour.

[#]All concentrations reported in ppb unless otherwise noted.

^{*}Only C_{diff} (C_{far} – C_{near}) reported.

[‡]Figure 2 extracted using WebPlotDigitizer, averaged across morning, afternoon, and season.

^adownwind.

^bupwind.

^cfixed trailer.

[°][Saha et al. \(2018\)](#) used 50 m as the beginning of the near-road gradient, and 400 m as an upwind, background monitor.

Oxides of nitrogen concentrations are generally observed to decrease with increasing distance from a major roadway. Studies detailed herein described gradients moving away from major roadways, such as highways, in urban settings. Multiple studies ([Jeong et al., 2022](#); [Liang et al., 2018](#); [Richmond-Bryant et al., 2017a](#); [Richmond-Bryant et al., 2017b](#); [Baldwin et al., 2015](#)) attempted to fit this concentration decrease with a mathematical model. Both logit ([Richmond-Bryant et al., 2017a](#)) and exponential ([Jeong et al., 2022](#); [Saha et al., 2018](#) 2018, 4775391; [Zhang et al., 2017](#); [Baldwin et al., 2015](#)). The concentration gradient varies by pollutant. NO₂ gradients tend to be less steep compared to primary pollutants like BC and UFPs. For example, [Baldwin et al. \(2015\)](#) found that NO₂ decreased by

50% within 89–129 m downwind of a road, while BC and UFPs decreased by 50% within 14–20 m. [Liang et al. \(2018\)](#) observed that NO₂ concentrations did not exhibit as strong a spatial gradient compared to other primarily emitted pollutants, with moderately homogeneous levels from roadside to far-road sites in Atlanta. These gradients were modified temporarily based on factors such as traffic patterns, wind speed, thermally-driven turbulence, and time of day. Factors such as temperature also affect NO_x emissions, and cold temperatures can lead to elevated NO_x concentrations ([Jeong et al., 2022](#); [Zhang et al., 2017](#)). NO_x concentrations decreased by 40% from 20 to 500 m from the roadside, with average concentrations attenuating slower than PM_{2.5} for the first 200 m, and then faster after 200 m ([Liang et al., 2018](#)). Gradients were modeled for distances from 10 m to 220 m ([Saha et al., 2018](#)), 20 to 300 m ([Richmond-Bryant et al., 2017a](#)), 50 to 500 m ([Baldwin et al., 2015](#)) from the major roadways. NO_x was observed to attenuate slower than PM_{2.5} within the first 200 m of the road, but then faster than PM_{2.5} outside the 200 m buffer ([Zhang et al., 2017](#)). As compared to studies from Detroit ([Baldwin et al., 2015](#)) and central North Carolina ([Saha et al., 2018](#)), lower concentration attenuation rates were observed in Houston within the first 200 m ([Zhang et al., 2017](#)). Concentration attenuation was accelerated when monitoring sites were downwind from the highway, and was affected by seasonality, with steeper gradients observed with cooler temperatures. Some studies indicate that the steepest concentration declines occur within the first 20 m of a roadway for certain species, such as NO ([Liang et al., 2018](#)), though distances up to 350 m are typically required to reach background for oxides of nitrogen in general ([Saha et al., 2018](#); [Baldwin et al., 2015](#)).

Both wind speed and wind direction impact near-road gradient concentrations for oxides of nitrogen. Wind direction was seemingly more impactful, as downwind concentrations dissipated by nearly 9% for NO₂ and 17% for NO per 200 m from the roadway ([Liang et al., 2018](#)), and NO and NO_x concentrations decreased by half when downwind by about 130 m from the roadway and to background (upwind) concentrations by 350 m ([Baldwin et al., 2015](#)). In contrast, wind speed had a smaller impact on the spatial decay gradient, with increasing wind speed resulting in 2.87% and 1% decreases in outdoor NO and NO₂ concentrations, respectively, per 200 m ([Liang et al., 2018](#)). Concentrations are typically higher downwind and under low wind speed conditions. Gradients are steeper under stable atmospheric conditions with less vertical mixing. Statistically significant concentration decreases of 67% were observed for NO as wind speed increased from <3 m/s to >5 m/s by [Baldwin et al. \(2015\)](#), though wind speed was not found to be significant when investigated in other studies. In the case of [Richmond-Bryant et al. \(2017a\)](#), concentrations of oxides of nitrogen were only measured by this study when monitors were downwind from the major roadway. When measured from 10 to 150 m downwind of a roadway, 1-minute NO, NO₂, and NO_x concentrations decreased by 61%, 20%, and 61%, respectively. These decreases in NO, NO₂, and NO_x were larger than the differences observed between the same distances during upwind conditions (no change, 1 ppb, and 1 ppb, respectively) or those observed under stagnant air conditions (-6 ppb, -2 ppb, and -8 ppb, respectively) ([Jeong et al., 2022](#)).

As discussed earlier in this section, traffic volume and composition are known variables that impact the concentration of oxides of nitrogen, as NO₂ concentration has often been used as a surrogate

for traffic-related exposure. Traffic within the papers detailed herein was reported as either traffic volume, traffic composition, or traffic counts, each having a slightly different definition. Other metrics of traffic, such as density and load, were not investigated in these near-road gradient studies. Higher traffic, especially heavy-duty vehicles, leads to greater emissions and steeper gradients. Generally, however, near-road NO concentrations are typically much higher than near-road NO₂ concentrations, and most NO_x emissions are associated with highway vehicle emissions (see Chapter 1, Section 1.2). Traffic counts, reported as AADT, were found to be a significant factor for NO₂ concentration decreases per 200 m from the roadway ([Liang et al., 2018](#)), though traffic volume, rather than counts, was more commonly cited as a significant factor by other publications. Fleet mix, or the traffic composition, was also impactful, as diesel vehicles are associated with emissions of oxides of nitrogen ([U.S. EPA, 2016](#)). Traffic composition and volume, which vary temporally, can be impactful, as different times of the day are usually accompanied by different wind conditions. For example, during the evening rush hour, 3–8 pm, when more thermally-driven turbulence and dispersion occurs due to increased traffic, weaker correlations were found between NO₂ measured at the roadside and at other sites ([Liang et al., 2018](#)). Though most of the studies summarized herein were investigating emissions on highways ([Liang et al., 2018](#); [Saha et al., 2018](#); [Richmond-Bryant et al., 2017a](#); [Zhang et al., 2017](#); [Baldwin et al., 2015](#)), local land surface arterial roadways were also investigated ([Liang et al., 2018](#); [Richmond-Bryant et al., 2017a](#); [Baldwin et al., 2015](#)). AADT values ranged greatly across and within studies, from 6,990 to 353,700 ([Jeong et al., 2022](#); [Liang et al., 2018](#); [Saha et al., 2018](#); [Richmond-Bryant et al., 2017a](#); [Zhang et al., 2017](#); [Baldwin et al., 2015](#)). The percentage of heavy-duty vehicles ranged from 6% ([Saha et al., 2018](#)) to 10% ([Richmond-Bryant et al., 2017a](#)), while diesel vehicles were reported to range from 1.6 to 12.0% per day ([Baldwin et al., 2015](#)).

Generally, those studies with higher AADT values or hourly vehicle counts were associated with more urban areas ([Liang, Atlanta GA](#); [Richmond-Bryant, Las Vegas, NV](#); [Baldwin, Detroit, MI](#); [Jeong, Toronto, Canada](#)), while lower values were found in suburban areas such as [Durham, NC](#) ([Saha et al., 2018](#)). NO₂ was observed to have some dependence on AADT ([Saha et al., 2018](#); [Zhang et al., 2017](#); [Baldwin et al., 2015](#)), though this dependence was also found to depend on seasonality ([Saha et al., 2018](#); [Zhang et al., 2017](#)), fleet mix ([Richmond-Bryant et al., 2017a](#); [Zhang et al., 2017](#); [Baldwin et al., 2015](#)), wind speed and direction ([Baldwin et al., 2015](#)), and speed of traffic ([Baldwin et al., 2015](#)). The interrelated nature of these variables is further demonstrated by [Kendrick et al. \(2015\)](#) which found that in the morning hours, a 100-vehicle increase in a 15-minute period was associated with a 1.2–2.5 ppb increase in NO₂, depending on the season. Variation in traffic volume was responsible for only 1.9% of the NO₂ variation in a Las Vegas study and 4.7% of the NO_x variation ([Richmond-Bryant et al., 2017a](#)). Traffic volume was more important when data were constrained to only those measurements captured while downwind, accounting for 6.8% of the variance for NO₂ and 16.5% for NO_x ([Richmond-Bryant et al., 2017b](#)). The AADT in this study was approximately 106,000 vehicles per day, with 10% of that traffic being heavy-duty trucks ([Richmond-Bryant et al., 2017b](#)). Generally, as traffic increased, NO_x concentrations near the roadway increased. Traffic varies throughout the day and week, which must be considered in the context of diurnal and annual temperature variations as well.

Diurnal variation of traffic and temperature can affect near-road gradient concentrations of oxides of nitrogen. Regarding variations in temperature over time, five of the gradient papers reported the impact of temperature and/or season on concentration gradients of oxides of nitrogen moving away from roadways ([Liang et al., 2018](#); [Saha et al., 2018](#) [Richmond-Bryant, 2018, 414386](#); [Richmond-Bryant et al., 2017a](#); [Zhang et al., 2017](#)). Three of these studies were conducted in the southern part of the United States, where winter seasonal temperatures are milder than other parts of the country ([Liang et al., 2018](#); [Saha et al., 2018](#); [Zhang et al., 2017](#)). Decay rates from the road were influenced by seasonal differences between summer and winter, though concentrations still decreased with increasing distance from the roadway. NO_x, along with BC and PM_{2.5}, decayed faster in the summer than in the winter. Average, seasonal hourly NO_x concentrations were highest in winter and lowest in spring ([Zhang et al., 2017](#)). Similarly, one study found that the relative humidity increased the concentration of both NO and NO₂ by 0.05% per 200 m from the roadside, while temperature decreases the concentration of NO and NO₂ by 1–2% per 200 m away from the roadside, per 10° F increase ([Liang et al., 2018](#)). Diurnal and seasonal variations in traffic patterns were observed, as detailed by [Saha et al. \(2018\)](#), where average vehicles per hour reported in Durham, North Carolina ranged from 6,900 vehicles per hour in the summer and 5,800 vehicles per hour in the winter ([Saha et al., 2018](#)). Higher concentrations of NO_x were observed during lower temperatures, across studies ([Saha et al., 2018](#) [2017, 4171247](#); [Richmond-Bryant et al., 2017a](#)). Decreases in NO_x were observed as temperature increased by [Jeong et al. \(2022\)](#) from -15°C to 10°C on weekdays, during morning rush hour, in downwind conditions. Using a logit equation to model the gradient in Las Vegas, NV, [Richmond-Bryant et al. \(2017b\)](#) found that time of the day contributed to 15.8% of the variance for NO_x, but only 3.3% for NO₂. However, time of day contributed more when constrained to only datapoints captured when monitors were downwind: 18.9% for NO_x and 5.8% for NO₂. Temperature, however, did not change concentrations considerably for NO_x and NO₂ when considering all data or constraining data to downwind datapoints only (NO₂: 3.0%, 2.7% when downwind; NO_x 1.2%, 2.8% when downwind) ([Jeong et al., 2022](#)). For further impacts of oxides of nitrogen due to photolysis and sunlight, both related to some of these diurnal variations, see Sections 1.3.1, and 1.5.5 for more information.

In addition to temporal variations due to temperature, the concentration of oxides of nitrogen also varied across the week and within each day based on traffic patterns. The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) found that NO₂ concentrations near and far away from roads are influenced by season and time of day. Roadway gradients were observed between weekend and weekday for both NO and NO₂, though greater differences were observed for NO (12.46% decreases on weekday, and 15.01% on weekends, per 200 m from roadway) ([Liang et al., 2018](#)). One study by [Liang et al. \(2018\)](#) found that hourly NO₂ concentrations were higher 10–15 m from the road than 80–100 m regardless of location, season, or time of day, and that near-road influence was higher during the day in warmer months and smallest at night in winter NO₂ concentrations were observed to increase during morning rush hour, gradually decrease from late morning to mid-afternoon, and then increase again during evening rush hour and nighttime, but the near-roadway gradient was found to be largest in the afternoon hours ([Polidori and Fine, 2012](#)). Another study detailed that, when measured at 200 m from the roadside, NO and NO₂

concentrations were found to vary with time of day with the greatest concentration decrease for NO (17.12%) during mid-day and for NO₂ (8.68%) during mid-day ([Jeong et al., 2022](#)). Further, [Richmond-Bryant et al. \(2017a\)](#) found steeper NO₂ gradients in the morning and late afternoon compared to overnight in Las Vegas. [Jeong et al. \(2022\)](#) reported that downwind NO_x and UFP concentrations increased by a factor of 2 and 3, respectively; as ambient temperature decreased from -5°C to -15°C near Highway 401 in Toronto as compared to those values measured while temperatures were between 5°C and 15°C. As temperature, wind movement, traffic volume, and fleet composition vary throughout the day, these factors may account for some of the differences observed based on the temporality of measurement ([Jeong et al., 2022](#)).

NO_x concentrations can also vary in different microenvironments, including during travel. In a Montreal study, the PTV Visum platform (a transportation planning software) was used to simulate traffic flow validated against traffic counts at several major intersections, and emission factors were determined using the Motor Vehicle Emission Simulator model. Based on analysis of four different land-use clusters, it was found that although the differences between mean NO_x emissions and mean home neighborhood NO₂ concentrations between clusters were small, individuals who generated higher NO_x emissions from travel lived in neighborhoods with lower NO₂ concentrations. Between 20% and 45% of individuals were estimated to experience exposure to NO₂ that was largely different (average mean concentrations $\pm 20\%$ of the mean at-home concentration) than at-home concentrations ([Shekarrizfard et al., 2016a](#)). [Xu et al. \(2017\)](#) studied spatial differences in exposure to NO, NO₂, and NO_x during 14-days of scripted activities in Chicago at 1-minute intervals. Grouping all microenvironments among three different microenvironment categories, it was found that median NO_x concentrations were highest among all transportation microenvironments (26 ppb), versus indoor (21 ppb) and outdoor (17 ppb) environments. Dividing up the data between all indoor, outdoor, and transportation environments, residential environments had the highest median NO_x concentrations. In the transportation category, the highest NO_x concentrations were found on regional trains, presumably due to NO concentrations from diesel locomotives.

2.3.2.3 Infiltration and Building Ventilation

The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) found that building infiltration and ventilation can vary for indoor spaces depending on the opening and closing of windows, building envelope tightness, and the presence of mechanical ventilation ([U.S. EPA, 2016](#)). These factors that influence infiltration and building ventilation can change by season. [Meng et al. \(2012a\)](#) found seasonal differences, with slopes of 0.24 ± 0.04 for total personal exposure, E_T , versus the concentration measured at a central site monitor, $C_{a,csn}$, and of 0.13 ± 0.06 for exposure to pollutants of ambient origin, E_a , versus $C_{a,csn}$ for summer measurements. For winter measurements, associations were lower (E_T vs. $C_{a,csn}$: slope = 0.08 ± 0.05 ; E_a vs. $C_{a,csn}$: slope = 0.07 ± 0.07). It was found that high air exchange rate (>1.3 air changes per hour), no central air conditioning, use of window fans, and the presence of old carpeting influenced

exposure in summer, but not in winter. [Mölter et al. \(2012\)](#) used the INDAIR model, which accounts for infiltration based on home ventilation characteristics and indoor sources, and found that in the absence of indoor sources the NO₂ model was very sensitive to air exchange rate.

Given that people spend most of their time indoors (see Section 2.3.2.4), differences in infiltration by different microenvironments may have impacts on exposure differences between groups of people. A recent review by [Hu and Zhao \(2020\)](#) found that infiltration factors for NO₂, which represent the contribution of outdoor environment to indoor NO₂ without influence from indoor sources, ranged from 0.30±0.08 in a school environment with natural ventilation to 1.02±0.13 (i.e. ~100% penetration from the outdoors indicating a very open building envelope) in a different school environment during summer with natural ventilation. [Hudda et al. \(2020\)](#) continuously measured both outdoor and indoor NO_x concentrations for a residence 1.3 km from the eastern end of runway 9/27 at Logan International Airport in Boston. NO₂, NO, and NO_x concentrations were all higher at the residence when it was downwind of the airport and flight trajectories indicating that NO_x concentrations were likely infiltrating the building. There were also lower NO but higher NO₂ concentrations than at regulatory sites, indicating an aged plume from aircraft emissions. [Hazlehurst et al. \(2018\)](#) found through a 2-week monitoring campaign measuring 128 people as a subset of the MESA Air cohort that incorporation of infiltrated indoor and measured in-vehicle NO₂ produced an estimated exposure average of 5.6 ppb lower than relying solely on outdoor concentrations.

Recent studies have found that mechanical ventilation, especially related to gas stove cooking, can influence indoor NO_x concentrations. [Singer et al. \(2020\)](#) compared homes between the Healthy Efficient New Gas Home (HENGH) study, where mechanical ventilation was required as a result of California's 2008 Title 24 standards, and homes in the California New Home Study (CNHS), without mechanical ventilation. The study found slightly higher NO₂ concentrations in HENGH homes (N = 66, median: 4.5 ppb) than in CNHS homes (N = 29, median: 1.6 ppb). It is important to note that measured adjacent outdoor NO₂ concentrations were higher for HENGH homes than CNHS homes (median values: 3.6 ppb vs. 1.5 ppb; 10th–90th percentile range: 0.1–11 ppb vs. 1.4–1.7 ppb). In a related study, [Zhao et al. \(2021\)](#) found that NO₂ concentrations on average were significantly (p<0.1) higher in 23 smaller apartments than in 70 larger houses with similar cooking frequencies (p<0.1), all equipped with mechanical ventilation. Besides the use of mechanical ventilation, factors that may have contributed to this difference include higher NO₂ outdoor concentrations around apartments and smaller indoor volume of apartments. A further analysis, treating 10 apartments and 37 houses as well-mixed steady state volumes with inputs from both cooking events and infiltration from outdoors, found that apartments had a mean NO₂ concentration of 14.0 ppb (range: 4.8–32.4 ppb) and houses had a mean of 4.8 ppb (range: 0–16.3 ppb). Typically, higher indoor concentrations of NO_x species produced by combustion sources result in I/O values greater than 1, meaning that I/O ratios alone do not indicate the level of building infiltration or ventilation. [Zhao et al. \(2021\)](#) also found that mean NO₂ I/O ratios across 22 apartments and approximately 37 houses that used gas cooking were 18.8/10.1 and 7.1/6.1, respectively.

NO_x from ambient air may also infiltrate into vehicles. The ratio of indoor to outdoor NO_x concentrations depends on several factors including vehicle tightness and ventilation rate and mode of ventilation ([Souza et al., 2024](#); [Leavey et al., 2017](#)). Studies show that outdoor NO_x concentrations are generally higher or sometimes equal to in-cabin concentrations when ambient measurements are made immediately outside of the vehicle ([Matthaïos et al., 2020](#); [Patton et al., 2016](#)). However, an outside measurement far away from the vehicle may not represent concentration levels that infiltrate into the vehicle and in-cabin measurements may be higher than those of the reference measurement. [Patton et al. \(2016\)](#) evaluated a scripted drive protocol where, from 2007 to 2014, participants were driven around the area of the New Jersey turnpike for 190-days. Integrated results of NO₂ showed that full rides had a median in-cabin NO₂ concentration that was 2.4 times higher (20.6 vs. 8 ppb) than hourly ambient measurements measured at the NJ DEP Rutgers University site (AQS Code 34-023-0011).

The use of filtration devices in both indoor and in-vehicle scenarios has shown reductions in exposure to NO₂. [Kang et al. \(2022\)](#) retrofitted 40 homes in Chicago with three different types of residential mechanical ventilation systems (continuous exhaust, intermittently powered central-fan-integrated-supply or continuous balanced system with an energy recovery ventilator). Mean reductions in I/O ratios across all systems for NO₂ was 10% ($p = 0.008$). [Matthaïos et al. \(2023\)](#) replaced used car filters with new standard pollen and new activated carbon filters for ten vehicles of different make and model (petrol, diesel, hybrid, electric and cabin size volume ranged from 1.26 to 2.72 m³) in Birmingham, U.K. to study the impact on in-cabin NO₂ concentrations. The new activated carbon filters resulted in a significant reduction in NO₂ concentrations, with mean in-vehicle NO₂ concentrations across all measurements during mechanical ventilation of 9.2 µg/m³ (SD: 8.6 µg/m³) (4.9 ppb; SD: 4.6 ppb) and 50.8 µg/m³ (SD: 32.7 µg/m³) (27.0 ppb SD: 17.4 ppb) for new activated carbon filters and new pollen filters, respectively. There was a linear correlation ($r^2 = 0.93$) between the newness of an activated carbon filter measured in months and its ability to reduce NO₂ in-cabin concentrations. [Mallach et al. \(2023\)](#) studied in-cabin NO₂ concentrations for 48 adults exposed to traffic-related air pollution (TRAP) with or without cabin air filtration using an electrostatic cabin air filter. The authors reported that in-cabin filtration did not reduce exposures to NO₂. The differences in the results of these two studies may be due to the type of air filter. Activated carbon air filters are more likely to capture gaseous components while electrostatic air filters are more efficient for large particle capture rather than gaseous components.

2.3.2.4 Time-Activity Patterns

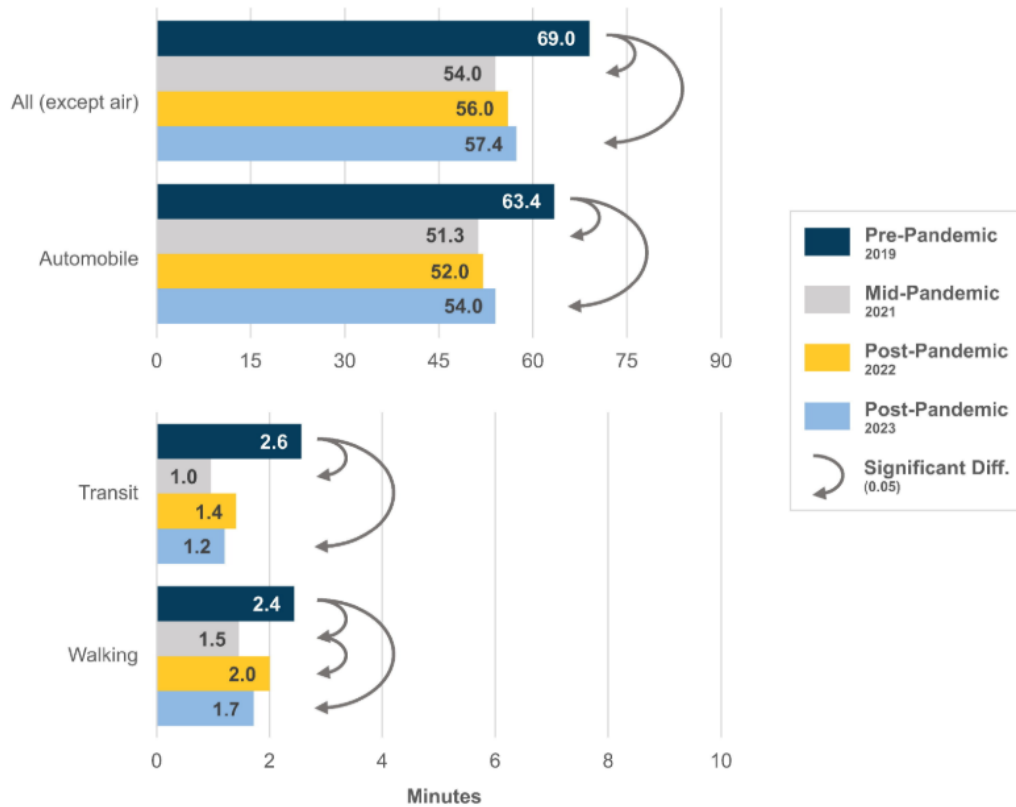
Activity patterns can affect the accuracy and precision of personal exposure estimates when using monitoring or modeling techniques. Data from the Consolidated Human Activity Database (CHAD) and National Human Activity Pattern Survey (NHAPS) show that the U.S. population spends most of its time inside and moves between work, school, or other indoor places on a daily basis ([Mccurdy and Graham, 2003](#); [Klepeis et al., 2001](#)). In addition, seasonal and diurnal patterns predict that people spend more time inside at night and during winter months than in other seasons ([Kornartit et al., 2010](#)). A recent study by

[Morris et al. \(2024\)](#) used data from the American Time Use Survey (ATUS) and the Census Bureau's Current Population Survey to sample 34,018 people in the U.S. over the age of 17. Figure 2-6 and Figure 2-7 show that they found that the COVID-19 pandemic resulted in more time in the home and less time traveling overall. Thus, since 2020 it has become increasingly important to consider the in-home environment when evaluating total exposure for NO₂.



Source: [Morris et al. \(2024\)](#). Copyright permission pending.

Figure 2-6 Out-of-home and in-home time use: 2019 and 2021 to 2023.



Note changing scale of minutes.

Source: [Morris et al. \(2024\)](#). Copyright permission pending.

Figure 2-7 Travel time by mode: 2019 and 2021 to 2023.

Past time-activity data from (NHAPS has shown that time spent doing different activities can vary by age, with school-age (5–17-years old) children spending more time outdoors engaged in physical activity than those of working age (18-64-years old) ([U.S. EPA, 2016](#); [Klepeis et al., 1996](#)). [Wu et al. \(2011\)](#), in a longitudinal analysis of Californians, found that there was a larger proportion of children than adults that reported spending over 30-minutes performing moderate or vigorous outdoor physical activity and that children were more likely than adults to participate in vigorous activity or aerobic exercise both indoors and outdoors.

Recent data has shown that COVID-19 likely had an impact on the amount of time children spent doing physical activity and time spent inside versus outside. [Burkart et al. \(2022\)](#) used wrist bound fitness trackers to track the activity of 231 children aged 7-12 years over 6-weeks during the spring and summer from 2018 to 2020. They found that the COVID-19 pandemic decreased daily-minutes of light physical activity (light PA) and moderate-to-vigorous physical activity (MVPA) and increased sedentary behavior (Spring 2018: Light PA 488.8±84.0; MVPA 78.7±31.1; Sedentary 313.8±95.6; Spring 2020: Light PA 394.4±109.4; MVPA: 60.5±33.3; Sedentary: 465.9±145.1). [Singh et al. \(2024\)](#) used wearable sensors on 94 children aged 5-17 in Durham, NC, with obesity to track their steps, finding that average daily step

count decreased by 1,655 steps from March 15, 2020 to March 31, 2021. [Dahl et al. \(2024\)](#) found by using data of 11,743 children from the 2021 National Survey of Children’s Health that 36.9%, 34.3%, and 28.8% of children 3–5-years old spent less than 1-hour, 2-hours, and more than 3-hours, respectively, playing outdoors on weekdays. Additionally, they found that 23.7%, 27%, and 49.3% spent less than 1-hour, 2-hours, and more than 3-hours, respectively, playing outdoors on weekend days.

Given that these studies did not use data collected after the COVID-19 pandemic, it is unclear if these trends in activity levels stayed the same for U.S. children post-pandemic. However, ATUS 2023 data [U.S. BLS \(2023\)](#) of annual averages found that participants 15-19-years of age spent more average hours per day participating in sports, exercise, and recreation activities (0.63) versus those older than 20-years of age (0.29; averaged across age groups from 20–24 to over 75-years of age). [Morris et al. \(2024\)](#) found a drop in out-of-home exercise and sports from 2019 to 2022 among those over 17-years of age with an increase in indoor exercise and sports but this rebounded in 2023 and there was no longer a significant difference.

Exertion levels have been shown to affect ventilation rates among different age groups, with a dramatic increase in ventilation rates with exercise intensity (see Table 2-6). Most of the age-related variability is seen for moderate and high intensity activities, except for individuals under 1-year. For moderate intensity, ventilation rate increases with age through childhood and adulthood until age 61, after which a moderate decrease is observed. Ventilation rate is most variable for high intensity activities. Children aged 1 to <11-years have ventilation rates of approximately 40 L/ per minute, while children aged 11+ years and adults have ventilation rates of approximately 50 L/ per minute. The peak is observed for the 51 to <61-year age group, at 53 L/ per minute, with lower ventilation rates for older adults. A dramatic increase in ventilation rate also occurs as exercise intensity increases. For children and adults <31-years, high intensity activities result in nearly double the ventilation rate for moderate activity, which itself is nearly double the rate for light activity. Children tend to have a greater oral breathing contribution than adults, and they breathe at higher minute ventilations relative to their lung volumes. Both of these factors tend to increase dose normalized to lung surface area. Those who exert themselves outside through increased physical activity may experience higher rates of mean exposure or more frequent high-exposure episodes ([U.S. EPA, 2016](#)).

Table 2-66 Mean ventilation rates (L/min) at different activity levels for different age groups

Age Group (yr)	Sleep or Nap	Sedentary/Passive	Light Intensity	Moderate Intensity	High Intensity
Birth to <1	3.0	3.1	7.6	14.0	26.0
1 to <2	4.5	4.7	12.0	21.0	38.0
2 to <3	4.6	4.8	12.0	21.0	39.0

Age Group (yr)	Sleep or Nap	Sedentary/Passive	Light Intensity	Moderate Intensity	High Intensity
3 to <6	4.3	4.5	11.0	21.0	37.0
6 to <11	4.5	4.8	11.0	22.0	42.0
11 to <16	5.0	5.4	13.0	25.0	49.0
16 to <21	4.9	5.3	12.0	26.0	49.0
21 to <31	4.3	4.2	12.0	26.0	50.0
31 to <41	4.6	4.3	12.0	27.0	49.0
41 to <51	5.0	4.8	13.0	28.0	52.0
51 to <61	5.2	5.0	13.0	29.0	53.0
61 to <71	5.2	4.9	12.0	26.0	47.0
71 to <81	5.3	5.0	12.0	25.0	47.0
81+	5.2	4.9	12.0	25.0	48.0

List of abbreviations in alphabetical order: yr = year

Source: Data from Exposure Factors Handbook ([U.S. EPA, 2011](#)).

Though it is difficult to extend results from specific geographic locations to the entire United States population because of differences in spatiotemporal concentrations and time-activities by region, several studies summarize recent research on time-activity patterns and their relationship to personal exposure levels. [Hoek et al.](#) explored epidemiologic studies that reported correlations between exposures estimated or measured outside of the home and those incorporating time-activity data for nine studies that looked at NO₂ exposures. They found that there was generally high correlation between these measurements, indicating that integrating time-activity data had little effect on changes in overall exposure measurements as compared to just using residential exposure measurements. Other studies have only found small differences between using residential exposure and time-activity integrated measurements. A study of children of eight-years of age living in Utrecht, Netherlands, with data taken from the Dutch Prevention and Incidence of Asthma and Mite Allergy prospective birth cohort study, estimated NO_x concentrations using different exposure assessment methodologies. These included measuring (1) residential exposure as a point estimate; (2) residential exposure as an average air pollution level within 20m around the front door; (3) time-weighted activity exposure using an estimated school address; and (4) time-activity weighted exposure using an actual school address. Mean levels and variation were relatively similar between residential exposure approaches and time-weighted activity pattern approaches ([Ntarladima et al., 2021](#)). A U.K. study that combined United Kingdom Census data on workplace population densities and a 1-km spatiotemporal resolution atmospheric chemistry transport model found an estimated 0.3 µg/m³ (0.2 ppb) increase in population-weighted average annual exposure to NO₂ across the U.K. when workplace location was taken into account ([Reis et al., 2018](#)). A Montreal, Canada study compared residential exposures versus exposures when daily transport was included for

approximately 66,000 homes and 157,000 individuals undertaking a total of 355,000 daily trips. An origin-destination survey from 2008 was used to assign traffic flow, average speed, and vehicle composition on every road segment. While 89.6% of individuals had higher exposures during transport than at home, only 31% of those individuals had their exposure increase by more than 10% ([Shekarrizfard et al., 2016b](#)).

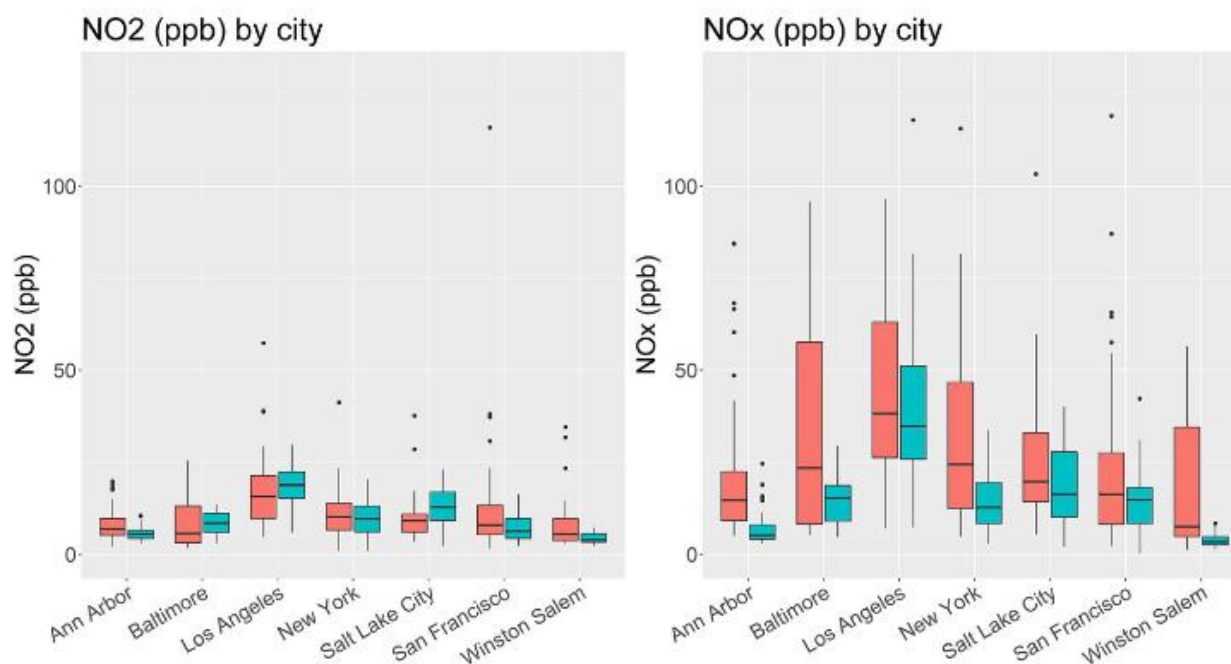
In addition, a study done in Netanya, Israel, found little change in exposure from including time-activity information. A high spatial resolution (500 m × 500 m) dispersion model was used to predict personal exposure to NO₂ concentrations over five-daily activity periods for a representative sample of 168,000 adults. The authors used various exposure scenarios to explore the implications of exposure misclassification by incorporating daily mobility and variability of temporal concentration. When they compared the different exposure scenarios, inclusion of temporal variability resulted in little difference in daily personal exposure levels (<1 ppb). The inclusion of daily mobility estimations resulted in a larger difference in estimated exposures (i.e., up to 4 ppb) and showed that the inclusion of mobility information resulted in much wider distributions of exposure concentrations between participants. Notably, the authors did not have individual trajectory data, but relied on general behavior patterns, such as assuming being at a work location from 8:00 am to 5:00 pm ([Shafran-Nathan et al., 2018](#)). A 2016 study by the same group looking at a large cohort of children and adults found that, because schoolchildren had shorter commutes than adults, residence-only estimates for children were more closely related to estimates that included time-activity patterns ([Shafran-Nathan et al., 2016](#)).

Though overall exposure may not change, personal measurements incorporating time-activity may be able to capture wider variability between participants ([Physick et al., 2011](#)). [Gao et al. \(2023\)](#) used passive wearable wristbands and detailed participant survey data to measure personal exposures to NO₂ for 25 schoolchildren over a 5-day period in Springfield, Massachusetts. They developed an LUR model to estimate exposures outside of participants' residential addresses and along home-to-school commuting routes. They also used a time-weighted average approach to estimate exposures based on LUR estimates. These exposure estimates incorporated time-activity patterns of participants and LUR-derived estimates in children's microenvironments (homes, schools, and commute paths). Estimated infiltration rates of 0.71 and 0.79 for school and home, respectively, and outdoor LUR estimates at those locations were used to predict indoor concentrations. The LUR-derived NO₂ exposure estimates displayed normal distributions with 34.8±4.8, 38.6±3.4, and 28.7±2.5 ppb mean values for outdoor values at homes, outdoor values along commute paths, and time-weighted averages, respectively. Personal wristband measurements displayed wide variability, with a mean of 30.5 ppb and range from 17.1 to 55.5 ppb. The authors concluded that, for this scenario, home-based measurements alone would overestimate exposure. The wide variability of the wristband measurements was attributed by the authors to the ability of the wristbands to absorb NO₂ from indoor sources. Indoor sources of NO₂ likely differed between participants. This has implications for the use of LUR approaches in epidemiologic studies, where other forms of personal measurements, such as absorbent wristbands, may capture variability between participants better.

2.3.2.5 Indoor NO₂

As discussed above, indoor NO_x concentrations can affect total exposure levels. The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) found that though there is wide variability in correlations between indoor and ambient concentrations, personal NO₂ exposure concentrations tend to be more highly correlated with indoor concentrations. Total exposure may be higher than just exposure to ambient NO_x concentrations if a population or individual is exposed to NO_x from combustion-based indoor sources. The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) and Section 2.2.3 of this document found strong associations in published literature between indoor combustion sources and indoor NO₂ and NO_x concentrations. [Kashtan et al. \(2024\)](#) used indoor modeling validated against NO₂ measurements from 18 test residences with gas stove usage. The authors estimated, by extrapolating using published housing characteristic and resident use patterns, that U.S. median gas and propane stove use increases long-term NO₂ exposure by 4.0 ppb (95% CI:2.4, 6.1). In contrast, in the absence of these indoor sources, large amounts of time spent indoors may result in lower exposures to ambient NO_x due to limited penetration of NO_x to indoor spaces.

The 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)) found wide variability in indoor NO₂ concentrations across studies. This is a result of the various indoor sources (combustion sources, infiltration, etc.) and sinks (deposition, indoor chemistry, ventilation) described above that can vary greatly between different indoor spaces. [Zusman et al. \(2021\)](#) further highlighted the great variability in indoor NO_x concentrations, as part of the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) and performed two-week integrated paired indoor-outdoor measurements of NO₂ and NO_x at 216 homes around 12 different clinical centers around the U.S. Measurements for Ann Arbor, San Francisco, and Salt Lake City collected during two different campaigns to look at seasonal differences (winter and summer in Ann Arbor and Salt Lake City; fall and spring in San Francisco) (see Figure 2-8). More than half (53%) of NO₂ measurements were higher indoors than outdoors, though average outdoor NO₂ concentrations in ambient air were higher than indoor concentrations in Baltimore, Los Angeles and Salt Lake City. For NO_x, 72% of measurements were higher indoors than outdoors, and average indoor concentrations were higher than average outdoor concentrations in all cities examined.



Note: Indoor and outdoor concentrations grouped by city. Indoor concentrations can be found on the left side and outdoor concentrations are found on the right side for each city.

Source: [Zusman et al. \(2021\)](#) Copyright permission pending.

Figure 2-8 Two-week integrated paired measurements of NO₂ and NO_x by city.

Temporal variability of NO₂ in indoor spaces can be high, making single measurements poor predictors of long-term indoor NO₂ concentrations ([Topp et al., 2004](#)). Temporal patterns of NO_x are determined not only by indoor sources but also infiltration from outdoor concentrations. A study in Kocaeli, Turkey done by [Bozkurt et al. \(2015\)](#) found that indoor concentrations of office environments increased in the morning and then decreased midday, similar to outdoor environments suggesting outside influence. They also found that concentrations of NO₂ in home environments increased in the morning largely as a result of cooking activities. [Zusman et al. \(2021\)](#) had similar findings with NO_x concentrations correlated with gas stove usage and frequency of cooking, and the use of mechanical ventilation reduced indoor concentrations of NO₂ and NO_x in model results.

A study by [Downen et al. \(2022\)](#), which used a newly developed compact personal NO₂ sensor with 1-minute resolution and sensitivity limit of 15 ppb to measure personal concentrations of 40 chronic asthma participants, found that indoor concentrations likely had an impact on overall hospital admissions. More than half of the patients (17 out of 30 successful deployments) experienced at least one-hour each day with NO₂ exposure above 21 ppb. This was higher in the group with gas stoves (Mann-Whitney U = 27, p ≤ 0.001). A more recent review by [Hu and Zhao \(2020\)](#) found that published I/O ratios varied significantly across several countries (median values ranged from 0.06 (Ireland) to 1.64 (Serbia); U.S. values ranged from 0.50 to 7.71), with these ratios being higher for residential spaces than offices or schools, likely due to the increased presence of indoor NO_x-emitting combustion sources in homes. As a

result, the generalizability of indoor NO_x exposures across different indoor spaces and time is challenging.

[Kim et al. \(2017\)](#) compared different estimation methods of personal exposure to NO₂ in Seoul, South Korea for 177 children with atopic dermatitis and 70 adults with asthma. Overall, incorporation of indoor concentrations and time-activity data (scenario AQ2) resulted in lower exposure estimates versus using values from the daily average of nearby monitors (scenario AQ1) (AQ1: 33.6±13.8 ppb vs. AQ2: 20.7±17.6 ppb for atopic dermatitis participants; AQ1: 35.0±13.5 ppb vs. AQ2: 23.7±17.7 ppb for asthma participants). Children with atopic dermatitis and asthmatic adults spent, on average, 93.0% and 88.1% of their days inside, respectively.

2.3.3 Personal-Ambient Relationships for NO₂

Numerous epidemiologic studies presented in Chapters 3 through 13 have reported adverse health impacts associated with ambient NO₂ concentrations. Generally, one underlying assumption in these epidemiologic studies relying on ambient NO₂ measurements or estimates is that ambient NO₂ is an appropriate surrogate for personal exposure to NO₂ of ambient origin. As such, it is crucial to understand the relationships between ambient NO₂ concentrations and personal NO₂ exposures of ambient origin. However, exposure to ambient NO₂ is not directly measurable. Instead, as described in Sections 2.2 and 2.3.1, personal total exposure (ambient component + nonambient component) is directly measured in most studies, and personal total exposure can be regarded as the personal exposure of ambient origin only if there are no nonambient sources.

The 2008 and 2016 Oxides of Nitrogen ISAs document a wide range of correlations between personal total exposure to NO₂ and ambient NO₂ [see Section 3.4.2 in the 2016 Oxides of Nitrogen ([U.S. EPA, 2016](#)), and Section 2.5.6 in the 2008 oxides of nitrogen ([U.S. EPA, 2008a](#))], with some studies finding associations between personal and central site monitors and other studies finding no association. The previous oxides of nitrogen ISAs identified several factors that influence the strength of these associations. These factors include

- proximity and strength of sources of ambient and nonambient NO_x,
- spatiotemporal variability of NO₂ concentrations,
- indoor or other local sources,
- air exchange rate, penetration, decay rate of NO₂ in different microenvironments,
- season,
- the time people spend in different microenvironments with different NO₂ concentrations, and
- study design.

Consistent with the studies documented in previous oxides of nitrogen ISAs, emerging evidence generally confirms low (typically $\rho < 0.4$) to moderate (typically $0.4 < \rho < 0.7$) correlations between personal total exposures to NO₂ and ambient NO₂ concentrations. However, a low correlation between personal NO₂ exposure and ambient NO₂ concentrations does not necessarily mean ambient NO₂ is inadequate to serve as a surrogate for the ambient component of personal exposure. The strength of a correlation coefficient can be largely impacted by the design of an exposure study ([Meng et al., 2012b](#); [U.S. EPA, 2008a](#)). Generally, three types of correlation coefficients are reported in the literature: pooled, longitudinal, and daily-average correlations. Correlation coefficients from older and more recent studies are described below and summarized in Table 2-7 and Table 2-8, respectively.

Pooled correlations are calculated when a study involves one or only a few measurements per subject and when different subjects are studied on subsequent days, so individual-subject/individual-day data are combined for the calculation of correlations. Pooled correlations describe the relationship between daily personal NO₂ exposures and daily ambient NO₂ concentrations across all subjects in the study. Most of the recent correlation coefficients in Table 2-8 belong to this category ([Gao et al., 2023](#); [Zhang et al., 2023b](#); [Frampton et al., 2022](#); [Languille et al., 2022](#); [Van Ryswyk et al., 2022](#); [Ha et al., 2020](#); [Rich et al., 2020](#); [Sarnat et al., 2018](#); [Xu et al., 2017](#); [Hart et al., 2015](#); [Ouidir et al., 2015](#); [Weichenthal et al., 2015](#); [Helen et al., 2013](#)). [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.

Longitudinal correlations are calculated when a study includes consecutive multiple measurements for each subject (i.e., a longitudinal study design). Longitudinal correlations describe the temporal relationships between personal NO₂ exposures or microenvironment concentrations and ambient NO₂ concentrations 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. A longitudinal correlation coefficient between the ambient component of personal exposures and ambient concentrations is particularly relevant to the panel epidemiologic study design. Recent studies in Table 2-8 reported longitudinal associations between personal total exposures and ambient concentrations for each subject ([Zhang et al., 2023b](#); [Languille et al., 2022](#)). For some subjects, associations were strong whereas for other subjects associations were weak (see Table 2-8). No further analyses or details were reported in these studies to interpret inter-personal variations in personal-ambient associations. Weak associations in some individuals could have resulted from day-to-day variation in the nonambient component of total personal exposures. The type of correlation analysis can have a substantial effect on the value of the resultant correlation coefficient.

Daily average correlations are calculated by averaging exposures across subjects for each day. Daily average correlations then describe the relationships between daily average exposures and daily ambient NO₂ concentrations. Compared to other metrics, this type of correlation is more directly relevant

to the exposure estimation approaches used in community time-series and long-term cohort epidemiologic studies, in which ambient concentrations are used as a surrogate for community average exposures to NO₂ of ambient origin. While few exposure studies report daily average correlations, when reported they often indicate stronger relationships between ambient and personal NO₂ than other correlation metrics ([Meng et al., 2012b](#)).

[Meng et al. \(2012b\)](#) conducted a random effects meta-analysis and meta-regression of 32 populations from recent studies that reported correlations between personal total exposure to NO₂ and NO₂ concentrations in ambient air measured at central monitoring sites. Among these correlation coefficients, 17 were reported as pooled correlation coefficients, 8 were from longitudinal panel analyses, and 7 were from daily average analyses. The meta-analysis results are shown in Table 2-7. The meta-analysis and meta-regression results reported by ([Meng et al., 2012b](#)) highlight the differences among the three types of correlation coefficients. Overall, the analyses found that personal NO₂ exposure is significantly correlated with NO₂ concentrations in ambient air, regardless of study design (i.e., pooled data across days, longitudinal panel, or daily average). However, the strength of the correlation is influenced by factors such as study design, season, meteorological conditions, non-ambient sources, and personal activities. Studies reporting daily average analyses showed the strongest correlations. [Meng et al. \(2012b\)](#) also noted that measurements below the detection limit could potentially reduce the correlations, which would otherwise be expected to be higher.

Table 2-77 Meta-analysis results of 32 populations from recent studies examining the relationship between personal nitrogen dioxide exposure measurements and ambient concentrations

Study Design	Based on Original Studies		Corrected for Publication Bias	
	Correlation	CLL ^a and CLU ^b	Correlation	CLL and CLU
Pooled (N = 17)^c	0.42	0.23 and 0.57	0.37	0.18 and 0.53
Longitudinal panel (N = 8)	0.16	0.02 and 0.30	0.16	0.02 and 0.30
Daily average (N = 7)	0.72	0.44 and 0.87	0.45	0.07 and 0.72

^aCLL: Lower bound of the 95% confidence limit.

^bCLU: Upper bound of the 95% confidence limit.

^cN: Number of populations.

Source: [Meng et al. \(2012b\)](#).

Results from more recent studies reporting associations between concentrations in ambient air and personal exposures are shown in Table 2-8. The number of recent studies examining this subject matter is limited, and most of the studies present pooled correlations, with recent studies presenting longitudinal correlations and none presenting daily average correlations.

Table 2-88 Summary of associations between personal oxides of nitrogen exposures and ambient concentrations

Study ID	Study Design	Ambient Con. (ppb)	Personal Con. (ppb)	Personal-Ambient correlation	Personal-Ambient Slope
Frampton et al. (2022); Rich et al. (2020)	Location: Rochester, NY Population: Thirty-two healthy volunteers, 55 to 70 yr of age; Multicenter Ozone Study of oldEr Subjects (MOSES) Study period: July 2012 - April 2015 Measurement: AQS monitors for ambient, and Ogawa passive badge (72-hr average) for personal exposure	6.48±3.39 (based on 87 measurements)	10.04±9.77 (based on 93 measurements)	$r_p = 0.04$	
Frampton et al. (2022); Rich et al. (2020)	Location: Chapel Hill, NC Population: Twenty-nine healthy volunteers, 55 to 70 yr of age; Multicenter Ozone Study of oldEr Subjects (MOSES) Study period: July 2012–April 2015 Measurement: AQS monitors for ambient, and Ogawa passive badge (72-hr average) for personal exposure	6.15±3.41 (based on 63 measurements)	4.00±5.85 (based on 85 measurements)	$r_p = 0.00$	

Study ID	Study Design	Ambient Con. (ppb)	Personal Con. (ppb)	Personal-Ambient correlation	Personal-Ambient Slope
Frampton et al. (2022); Rich et al. (2020)	Location: San Francisco, CA Population: Twenty-six healthy volunteers, 55 to 70 yr of age; Multicenter Ozone Study of oldEr Subjects (MOSES) Study period: July 2012–April 2015 Measurement: AQS monitors for ambient, and Ogawa passive badge (72-hr average) for personal exposure	10.88±8.34 (based on 73 measurements)	14.44±10.98 (based on 73 measurements)	$r_p = 0.04$	
Ha et al. (2020)	Location: Birmingham, AL; Chicago, IL Population: Pregnant women with and without asthma in the Breathe—Well-Being, Environment, Lifestyle, and Lung Function Study Study period: 2015–2018 Measurement: AQS monitors for ambient (nearest monitors to home address and GPS positions), and Cairpol CairClip real-time sensors (2–4 d) for personal exposure	16.3 (range: 4–35.8) (based on the nearest AQS monitors to home address for 40 participants) 16.5 (range: 3–35) (based on the nearest AQS monitors to GPS positions for 24 participants)	5.1 (range: 0–27.4) (based on personal exposure measurements for 39 participants)	$r_p = -0.25$ (based on the nearest AQS monitors to home address) $r_p = -0.27$ (based on the nearest AQS monitors to GPS positions)	
Xu et al. (2017)	Location: Chicago, IL Population: Two researchers Study period: March – May 2016 Measurement: AQS monitors for ambient, and real-time UV absorbance monitor for personal exposure in a 14-d scripted study	NO ₂ : 19 (Estimated from Table 2 and Figure 9 of the publication) NO: 6 (Estimated from Table 2 and Figure 9 of the publication) NO _x : 24 (Estimated from Table 2 and Figure 9 of the publication)	NO ₂ : 11 (Estimated from Table 2 of the publication) NO: 17 (Estimated from Table 2 of the publication) NO _x : 27 (Estimated from Table 2 of the publication)	$r^2 = 0.04$ for NO ₂ (based on 72 hourly averages) $r^2 = 0.009$ for NO (based on 72 hourly averages) $r^2 = 0.004$ for NO _x (based on 72 hourly averages)	0.10 for NO ₂ (based on 72 hourly averages) -0.28 for NO (based on 72 hourly averages) 0.09 for NO _x (based on 72 hourly averages)

Study ID	Study Design	Ambient Con. (ppb)	Personal Con. (ppb)	Personal-Ambient correlation	Personal-Ambient Slope
Sarnat et al. (2018)	Location: Atlanta, GA Population: College students Study period: September 2014–January 2015 Measurement: AQS central and roadside monitors for ambient, and Ogawa badge (48-hrs average) to measure exposure for 54 colleague students (2 wk per participant)	Central Site (SEARCH network): 13.01±9.82 (based on 2654 measurements) Roadside Site: 29.09±15.55 (based on 2666 measurements) Roadside Site (EPD): 19.46±8.57 (based on 2798 measurements)	14.7 (range: 6.9–28.8) (based on 45 measurements of participants living in near-road dorms) 17.5 (range: 2.2–43.5) (based on 58 measurements of participants living in far-away-from-road dorms)	$r^2 = 0.57$ (based on the regression of 103 personal measurements on near-road ambient measurements at Roadside Site)	(0.03 [95% CI:-0.15, 0.20]) (based on the regression of 103 personal measurements on near-road ambient measurements at Roadside Site)
Gao et al. (2023)	Location: Springfield, MA Population: Twenty-five children (aged 12–13 years) Study period: January – February, and April 2018 Measurement: Ogawa badge (4-d average) saturation sampling at 40 locations for ambient, and Ogawa badge (5-d average) for personal exposure	31.8 (range: 14.3–49.9) (based on ambient saturation sampling at 40 locations)	30.5 (range: 17.1–55.5) (based on exposure measurement of 25 participants)	$r_s = 0.16$	
Languille et al. (2022)	Location: Paris, France Population: General public Study period: June 2018 – March 2019 Measurement: Paris ambient monitoring stations for ambient, and real-time Cairsen sensors on 37 participants (2 wk per person) for personal exposure	Not reported	Spring: 9±10 (based on exposure measurement of 16 participants) Fall: 9±12 (based on exposure measurement of 15 participants) Winter: 6±19 (based on exposure measurement of 6 participants)	Spring: $r_p = 0.14–0.26$ (pooled, based on hourly averages); $r_p = 0.05–0.51$ (longitudinal, based on hourly averages) Fall: $r_p = 0.06–0.10$ (pooled, based on hourly averages); $r_p = -0.18–0.64$ (longitudinal, based on hourly averages) Winter: $r_p = 0.15–0.23$ (pooled, based on hourly averages);	

Study ID	Study Design	Ambient Con. (ppb)	Personal Con. (ppb)	Personal-Ambient correlation	Personal-Ambient Slope
				$r_p = -0.15-0.53$ (longitudinal, based on hourly averages) Spring: $r_p = 0.26-0.30$ (pooled, based on daily averages); $r_p = -0.49-1.00$ (longitudinal, based on daily averages) Fall: $r_p = 0.02-0.17$ (pooled, based on daily averages); $r_p = -0.83-0.93$ (longitudinal, based on daily averages) Winter: $r_p = 0.40-0.41$ (pooled, based on daily averages); $r_p = -0.20-0.69$ (longitudinal, based on daily averages)	
Hart et al. (2015)	Location: Utrecht, the Netherlands Population: Netherlands Cohort Study on Diet and Cancer (validation study) Study period: November 2004 and July 2005 Measurement: Ogawa badge (48-hr average) at central urban background site and outdoor measurements for ambient, Ogawa badge (48-hr average) up to five times from 47 adult nonsmoking participants for personal exposure	17 ± 4 (reported as $32.0 \pm 8.4 \mu\text{g}/\text{m}^3$, based on 209 measurements)	14 ± 6 (reported as $26.9 \pm 11.3 \mu\text{g}/\text{m}^3$, based on 209 measurements)	$r_p = 0.04$	

Study ID	Study Design	Ambient Con. (ppb)	Personal Con. (ppb)	Personal-Ambient correlation	Personal-Ambient Slope
Ouidir et al. (2015)	Location: Grenoble, France Population: SEPAGES-Feasibility cohort, pregnant women Study period: July 2012–July 2013 Measurement: Monitor nearest to participant's home address for ambient, Passam tube passive sampler (7-d average) for personal exposure	12±4 (reported as 23.3±8.0 µg/m³)	Overall: 14±2 (reported as 26.7±4.1 µg/m³, based on measurement of 10 participants) Subgroup with gas stove at home: 15±2 (reported as 28.6±3.0 µg/m³, based on measurement of 7 participants) Subgroup without gas stove at home: 12±1 (reported as 22.3±2.6 µg/m³, based on measurement of 3 participants)	$r_s = 0.07$ (based on exposure measurements for the overall group, i.e., n = 10)	
Van Ryswyk et al. (2022)	Location: Windsor, Canada Population: Children with asthma (ages 10–13 years) Study period: January–March 2006 and July–August 2006 Measurement: Ogawa badge (24-hr average) outside participant's home for ambient, Ogawa badge (24-hr average) for personal exposure	Winter 21.0±4.8 (based on measurements outside 17 participants' homes with 5 measurements per participant) Summer 12.8±5.4 (based on measurements outside 25 participants' homes with 5 measurements per participant)	Winter 12.6±4.5 (based on measurement of 17 participants with 5 measurements per participant) Summer 8.0±3.3 (based on measurement of 25 participants with 5 measurements per participant)	Winter: $r_p = -0.09$ Summer: $r_p = 0.22$	
Weichenthal et al. (2015)	Location: Windsor, Canada Population: Forty-seven children forty-eight adults Study period: 2005–2006	Adults, Summer 15.3±5.6 (based on 223 measurements) Adults, Winter 24.2±10.2 (based on 239 measurements) Children, Summer 15.3±4.6 (based on 228 measurements) Children, Winter 20.9±6.2 (based on 232 measurements)	Adults, Summer 10.5±8.2 (based on 208 measurements) Adults, Winter 10.6±10.7 (based on 225 measurements) Children, Summer 7.3±4.1 (based on 215 measurements) Children, Winter 13.0±7.7 (based on 227 measurements)	Adults, Summer $r_p = 0.007$ Adults, Winter $r_p = 0.08$ Children, Summer $r_p = 0.007$ Children, Winter $r_p = 0.00$	Adults, Summer 0.12 Adults, Winter 0.30 Children, Summer 0.072 Children, Winter 0.0029

Study ID	Study Design	Ambient Con. (ppb)	Personal Con. (ppb)	Personal-Ambient correlation	Personal-Ambient Slope
	Measurement: Canadian National Air Pollution Surveillance monitors for ambient, Ogawa badge with 5 consecutive daily measurements for each participant for personal exposure				
Helen et al. (2013)	Location: Trujillo, Peru Population: One hundred Pregnant women Study period: 2004–2005 Measurement: Palmes Tubes (48-hr average) on the roof of the city hall for ambient, Palmes Tubes (48-hr average) for personal exposure	7.9±5.1	10.4±8.8		-0.06 (p = 0.27)
Zhang et al. (2023b)	Location: Beijing and Baoding, China Population: Seven office workers in each city Study period: August, October, and December 2019 Measurement: Air quality monitors nearest to residence or workplace for ambient, Ogawa badge (24-hr average, 10–30 measurements per participant) for personal exposure	Not reported	NO ₂ Summer 8±7 (reported as 15.4±12.8 µg/m ³ , based on 81 measurements) Fall 25±15 (reported as 46.2±27.3 µg/m ³ , based on 89 measurements) Winter 40±23 (reported as 74.7±44.0 µg/m ³ , based on 89 measurements) NO Summer 19±20 (reported as 23.0±24.0 µg/m ³ , based on 14 measurements) Fall 48±38 (reported as 58.8±46.7 µg/m ³ , based on 79 measurements)	r _p = 0.01–0.45 for NO ₂ (longitudinal for each participant)	0.011 for NO ₂ 0.020 for NO

Study ID	Study Design	Ambient Con. (ppb)	Personal Con. (ppb)	Personal-Ambient correlation	Personal-Ambient Slope
			Winter 150±117 (reported as 184±143 µg/m ³ , based on 81 measurements)		

List of abbreviations in alphabetical order: AQS = Air Quality System; CA = California; GA = Georgia; GPS = global positioning system; MA = Massachusetts; NC = North Carolina; NO = nitric oxide; NO_x = NO₂ + NO; NY = New York; NO₂ = nitrogen dioxide; UV = ultraviolet.

Studies in Table 2-8 indicate that home ventilation is an important factor in modifying personal-ambient relationships. If other factors are similar (e.g., indoor sources), the strongest associations would be anticipated for subjects spending time indoors with open windows. Consistent with this hypothesis, [Van Ryswyk et al. \(2022\)](#) reported a stronger personal-ambient/outdoor association in Windsor, Canada, during the summertime ($r = 0.22$) compared with winter ($r = -0.09$), while personal-indoor associations remain the same for summer ($r = 0.75$) and winter ($r = 0.75$). A similar pattern was reported for children by [Weichenthal et al. \(2015\)](#) in another exposure assessment conducted in Windsor. [Hu et al. \(2020\)](#) characterized personal exposure to ambient NO₂ across 31 provinces in China. The authors reported a higher ambient exposure factor (i.e., α in Equation 2-10) during summer (0.49–0.65) than winter (0.28–0.58), reflecting differential air exchange rates in different seasons.

Studies included in Table 2-8 additionally indicate that the presence of local and indoor sources affects the strength of the association between personal exposures and ambient concentrations. A few studies consistently illustrate that indoor sources of NO₂ can add noise to the ambient NO₂ exposure signal. ([Ha et al., 2020](#)) reported the association between personal exposures to NO₂ and indoor NO₂, as well as the association between personal NO₂ exposures and ambient NO₂ measured by ambient monitoring network, for pregnant women enrolled in the Breathe—Well-Being, Environment, Lifestyle, and Lung Function Study. Personal exposures were positively associated with indoor-monitor measurements ($r = 0.76$) and no significant personal-ambient associations were detected, indicating the importance of indoor source contribution to total personal exposures. [Xu et al. \(2017\)](#) conducted a scripted exposure assessment in Chicago with real-time NO and NO₂ instruments. Researchers detected the highest NO_x concentrations in transportation microenvironments (i.e., in personal vehicles or public transit, median = 26 ppb), followed by indoor environments (median = 21 ppb), and lowest concentrations in the outdoor environments (median = 17 ppb), highlighting contributions of transportation microenvironments to total personal exposure. The study did not find a significant association between personal total exposures and ambient concentrations ($r = 0.09, 0.2$, and 0.06 for NO, NO₂, and NO_x, respectively). [Gao et al. \(2023\)](#) found no significant association between personal NO₂ exposure and ambient NO₂ concentration, attributing this to indoor sources such as gas stoves. These indoor sources elevated the mean indoor air NO₂ concentration to 54.5 ppb, compared with the mean outdoor concentration of 32.0 ppb.

The impact of personal activities on personal exposure to NO₂ has long been recognized (see Section 2.3.2). For example, [Hazlehurst et al. \(2018\)](#) reported the impact of time-activity patterns on

personal exposures for 128 participants in a Multi-Ethnic Study of Atherosclerosis and Air Pollution study (MESA-air) in Los Angeles and Winston-Salem. High in-vehicle contributions (21–56%) to personal NO₂ exposures were identified for participants spending 1.3-h or more in traffic, compared with the average in-vehicle contribution (18–40%), indicating the importance of considering personal activity patterns when conducting exposure assessments. If data from heavy commuters and light commuters are combined when analyzing the personal-ambient association of NO₂ exposures, the true relationship may be obscured. Similarly, using a random forest model, [Gao et al. \(2023\)](#) found that commute time was the primary factor influencing school children’s total personal exposure to NO₂ in Springfield, Massachusetts.

Since the release of the 2016 Oxides of Nitrogen ISA, a limited number of studies have reported on personal-ambient associations, largely supporting the conclusions drawn in the 2008 and 2016 Oxides of Nitrogen ISAs: Despite varying strengths of these associations, ambient NO₂ continues to be used in epidemiologic studies as an important surrogate for personal exposure to NO₂ of ambient origin. The low to moderate correlations observed in recent studies reinforce that personal-ambient associations can be influenced by numerous factors, including nonambient sources, seasonal variations, ventilation, and individual activities. While daily-average study designs remain the most relevant for common epidemiologic studies and demonstrate the strongest personal-ambient associations, no recent studies fall into this category. Recent research consistently shows stronger associations during warm seasons compared to cold seasons, aligning with previous findings. Furthermore, these studies consistently illustrate that indoor sources of NO₂ can obscure personal-ambient associations, a conclusion that is consistent with evidence assessed in previous oxides of nitrogen ISAs. In addition, personal-residential outdoor associations could be stronger than personal-ambient associations if individuals spend most of their time at home, highlighting the impacts of personal activities and proximity to monitors on these relationships.

2.3.4 Differential Exposures Across Populations

The level of human exposure to ambient NO₂ is influenced by a complex interplay of factors. The 2016 Oxides of Nitrogen ISA concluded that:

- Urban areas generally experience higher ambient NO₂ concentrations compared to suburban areas, potentially exposing large populations to elevated concentrations, underscoring the significant public health impact of NO₂-related health effects among urban residents; and
- Proximity to roads is a crucial determinant of personal NO₂ exposure, and the higher road density in urban areas and proximity to major roads may result in increased exposure for urban residents.

Recent studies have expanded upon these physical factors, while also exploring differential NO₂ exposure across populations with varying socioeconomic status, demographics, and neighborhood characteristics. This section briefly summarizes the physical factors and population characteristics that

can contribute to differential oxides of nitrogen exposures across populations, including proximity to roads; demographic and economic factors; and neighborhood characteristics.

2.3.4.1 Proximity to Road

The proximity to high-traffic roadways is a critical determinant of NO₂ and NO_x exposure. As elucidated in Chapter 1, Section 1.2, highway vehicular emissions constitute a significant source of NO_x, accounting for 26% of total NO_x emissions according to the 2020 National Emission Inventory. Through the process of rapid titration, NO undergoes conversion to NO₂ (see Chapter 1, Section 1.3). Moreover, Section 2.3.2 provides evidence of concentration gradients for both NO₂ and NO_x in near-road environments, characterized by a steep decline within the initial 150-300 meters from the roadway. This spatial distribution pattern strongly suggests that populations residing in close proximity to a primary road are subject to elevated exposures of NO₂ and NO_x.

Given that urban areas are characterized by higher road density and population density, proximity to roads impacts a large number of people in these environments. [Antonczak et al. \(2023\)](#) found that 24% of the U.S. population lived within 500 m of roads with $\geq 25,000$ AADT in 2020.

To better understand the characteristics of populations living in close proximity to traffic, demographic data were collected at the census block group level from the U.S. Census using the Integrated Public Use Microdata Series National Historic Geographic Information System (<https://www.nhgis.org/>). This approach enables a granular analysis of population distribution and composition in relation to traffic exposure. Given findings in this ISA that the evidence from health studies is adequate to conclude children are at increased risk for respiratory effects from both short-term (see Chapter 3, Section 3.10.2.1.1) and long-term (see Chapter 4, Section 4.10.1.1.1) NO₂ exposures, this section evaluates the proportion of children in U.S. metropolitan areas who live near major roads.

The analysis includes the 12 most-populated U.S. metropolitan areas (see Figure 2-9 through Figure 2-20). These metropolitan areas were selected based on their populations exceeding one million residents, their geographic diversity across the United States, and their relevance to the communities examined in U.S. epidemiologic studies discussed in Chapters 3-13. The near-road environment was defined using the U.S. Census primary road shapefile. Census block groups were considered 'near road' if any portion of the block group was within 150 meters of the primary road. Of the 54,334 block groups in the 12 selected most-populated metropolitan areas, 11,576 qualified as near-road block groups. Additionally, census blocks were measured from their center to the nearest primary road, with blocks having a distance of less than 300 meters considered 'centroid near road'. A total of 3,187 of the block groups in the 12 cities qualified as 'near road' from the center point.

This analysis found that 4.25% of the population in the selected statistical areas live within 150 meters of a U.S. Census-defined primary road, while 10.05% live within 300 meters. Of the 77.3 million

people within the 12 selected Core-Based Statistical Areas (CBSAs), 16.9 million lived in a census block considered 'near road.' The percentage of the population considered 'near road' varied among the CBSAs, ranging from 19% in Philadelphia, PA to 31% in Dallas-Fort Worth, TX. Among the total population of 77.3 million, 18.8 million are children; within the 'near road' population of 16.9 million, 4 million are children.

Atlanta Core Based Statistical Area

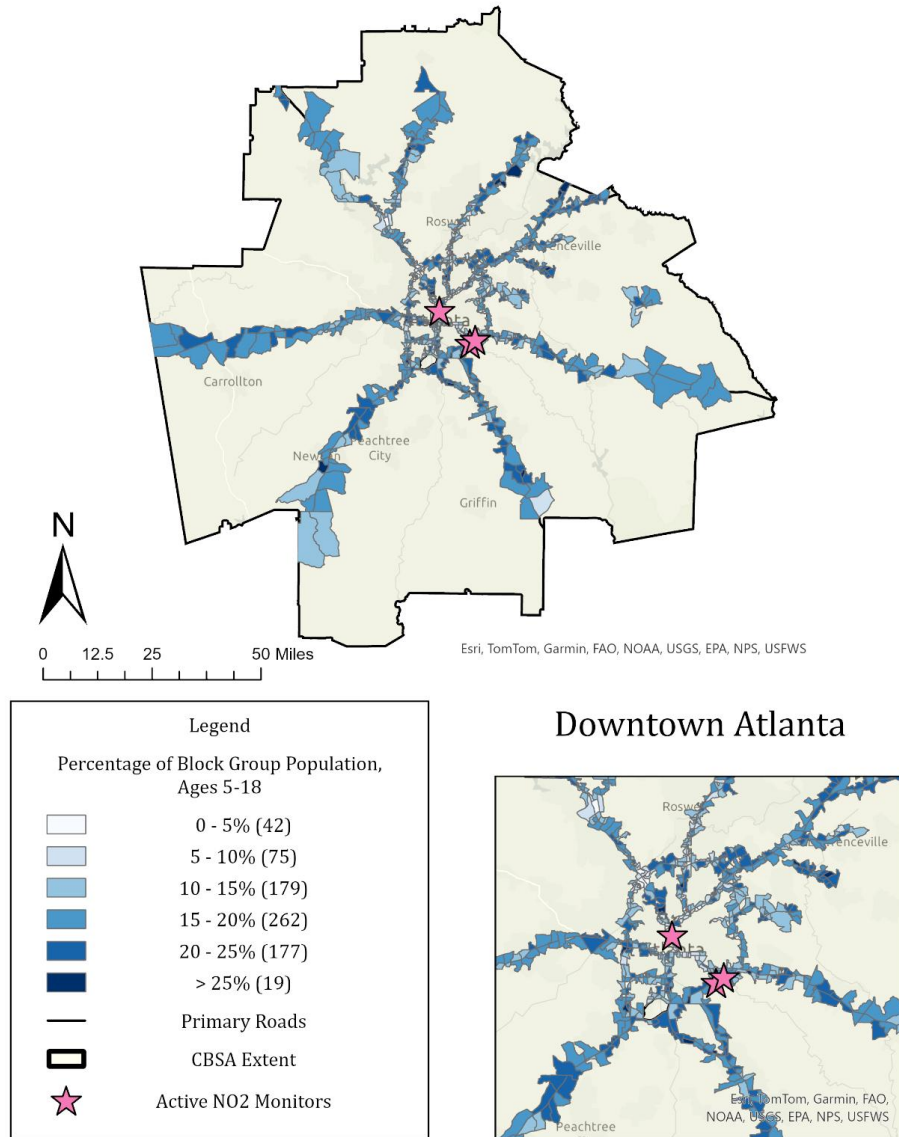


Figure 2-9 The proximity of children populations to urban roadways in Atlanta ([U.S. census data](#), [EPA AQS](#)).

Boston Core Based Statistical Area

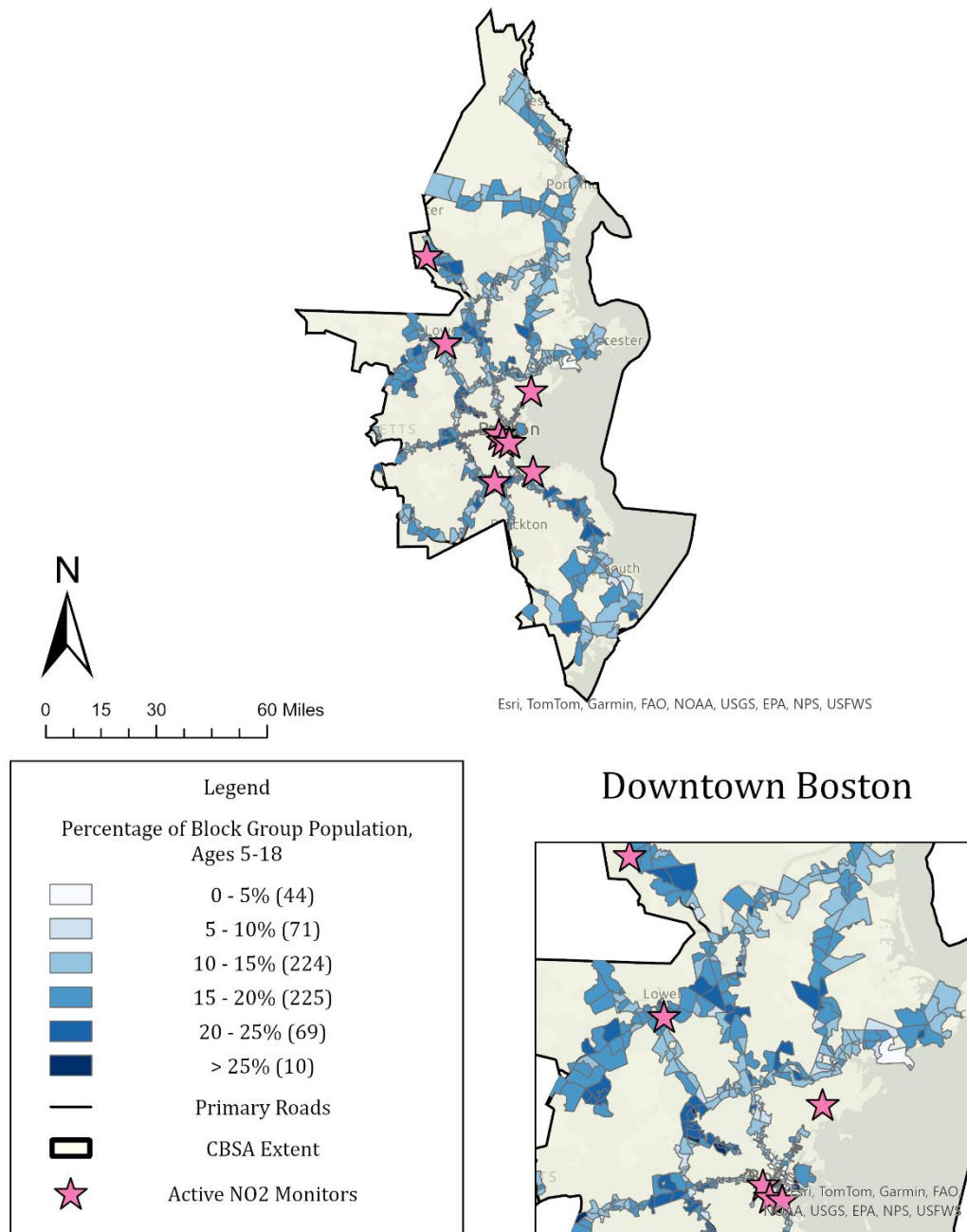


Figure 2-10 The proximity of children populations to urban roadways in Boston ([U.S. census data](#), [EPA AQS](#)).

Dallas Core Based Statistical Area

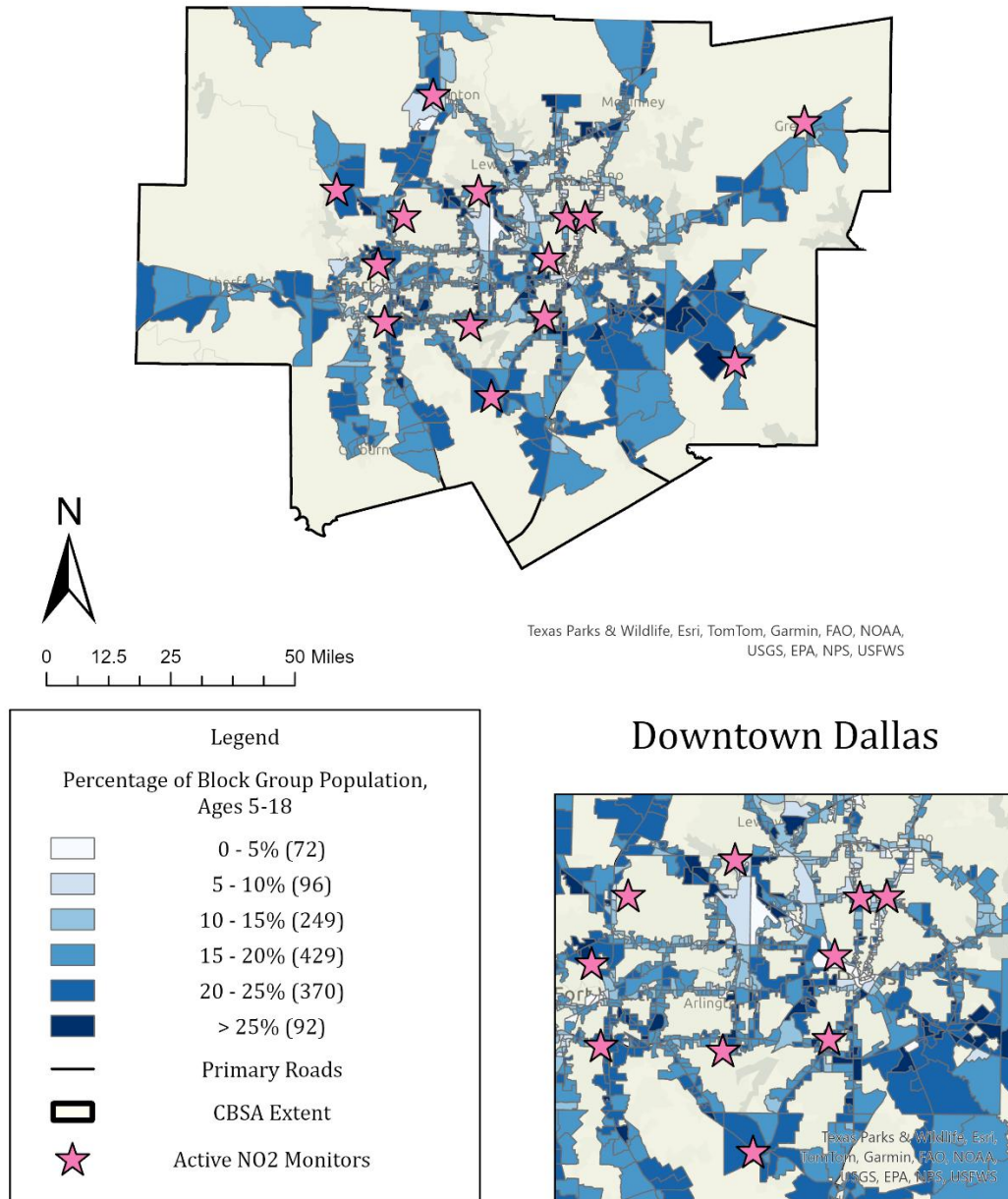


Figure 2-11 The proximity of children populations to urban roadways in Dallas ([U.S. census data](#), [EPA AQS](#)).

Denver Core Based Statistical Area

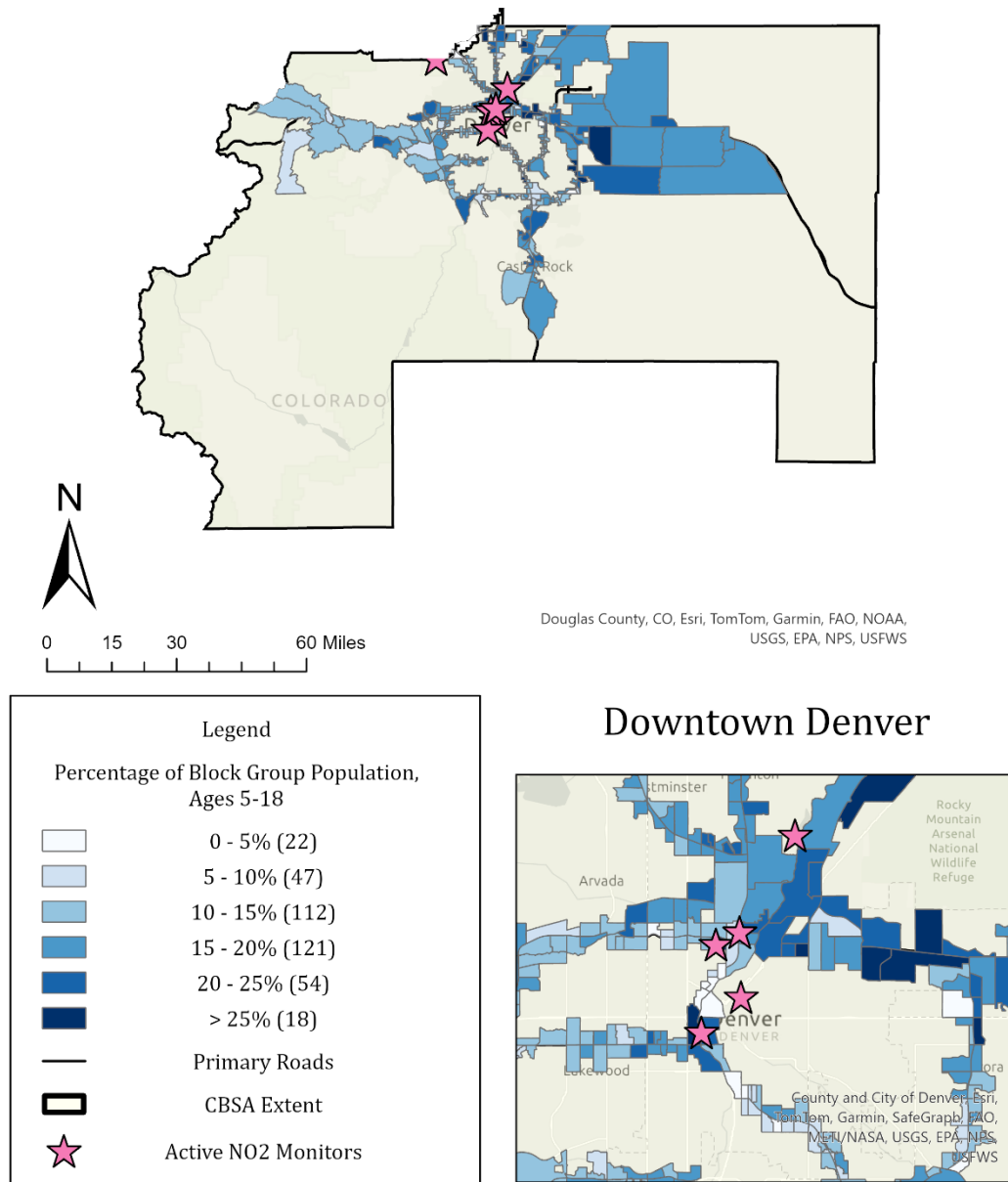


Figure 2-12 The proximity of children populations to urban roadways in Denver ([U.S. census data](#), [EPA AQS](#)).

Indianapolis Core Based Statistical Area

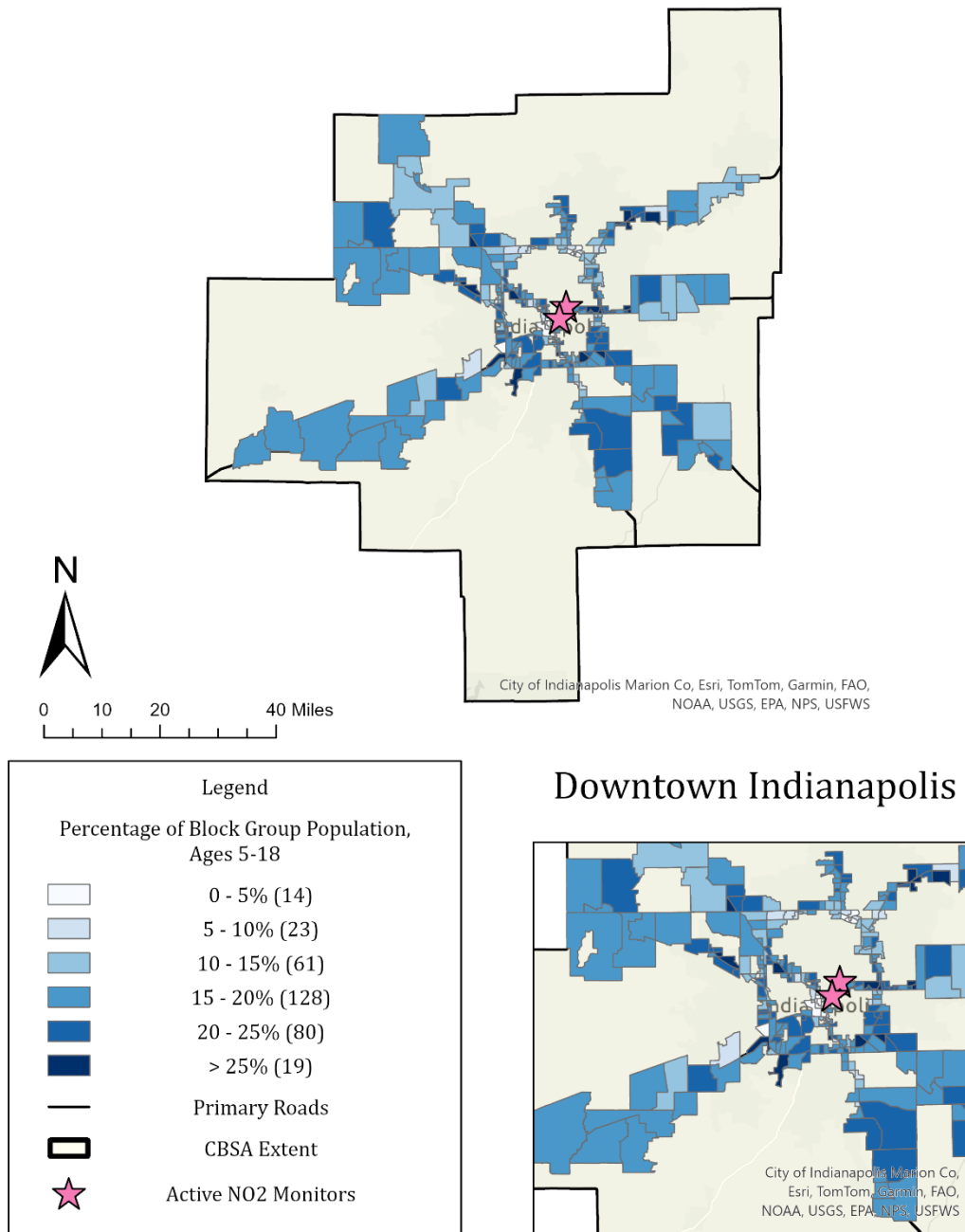


Figure 2-13 **The proximity of children populations to urban roadways in Indianapolis**
([U.S. census data](#), [EPA AQS](#)).

Los Angeles Core Based Statistical Area

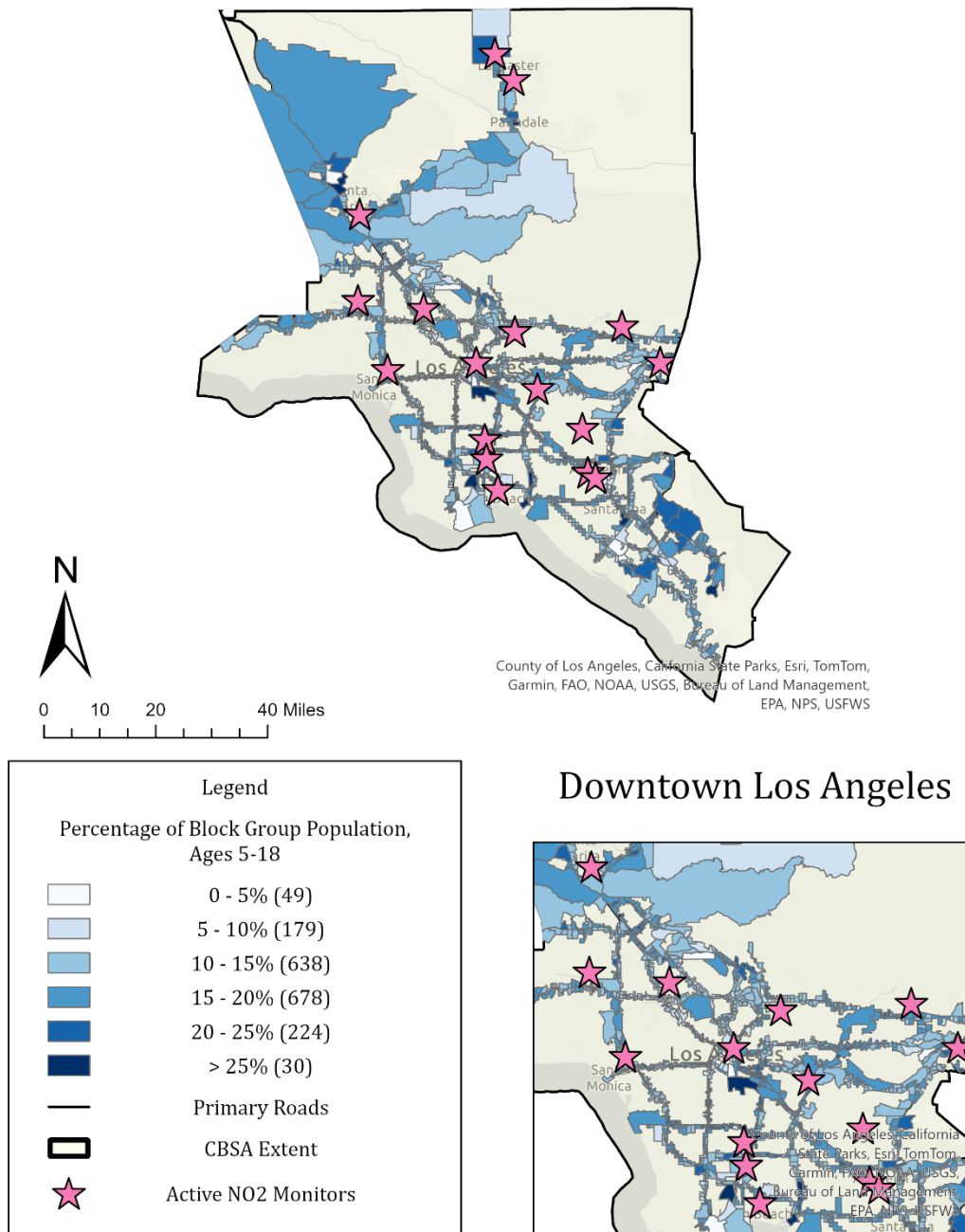


Figure 2-14 The proximity of children populations to urban roadways in Los Angeles ([U.S. census data](#), [EPA AQS](#)).

New Orleans Core Based Statistical Area

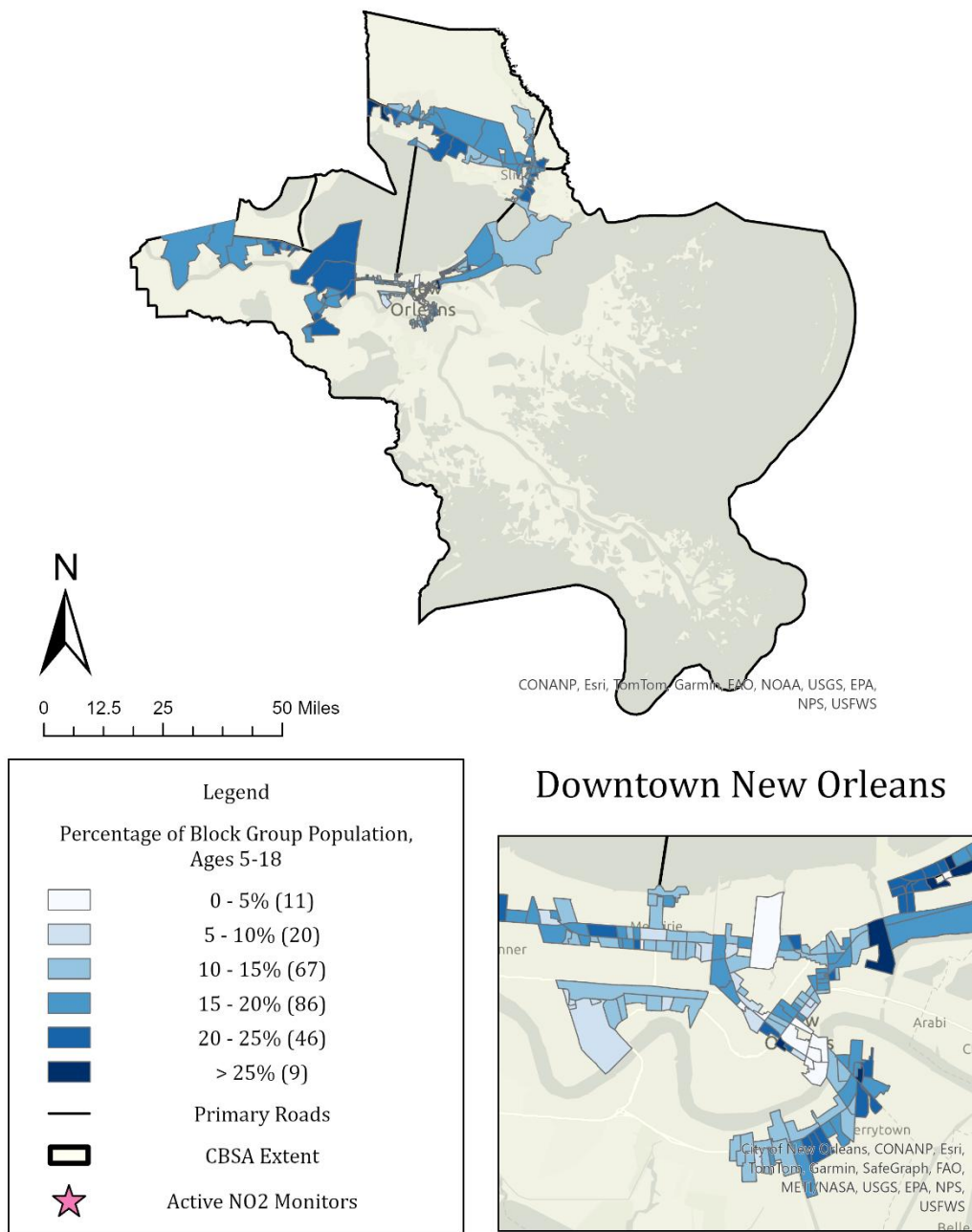
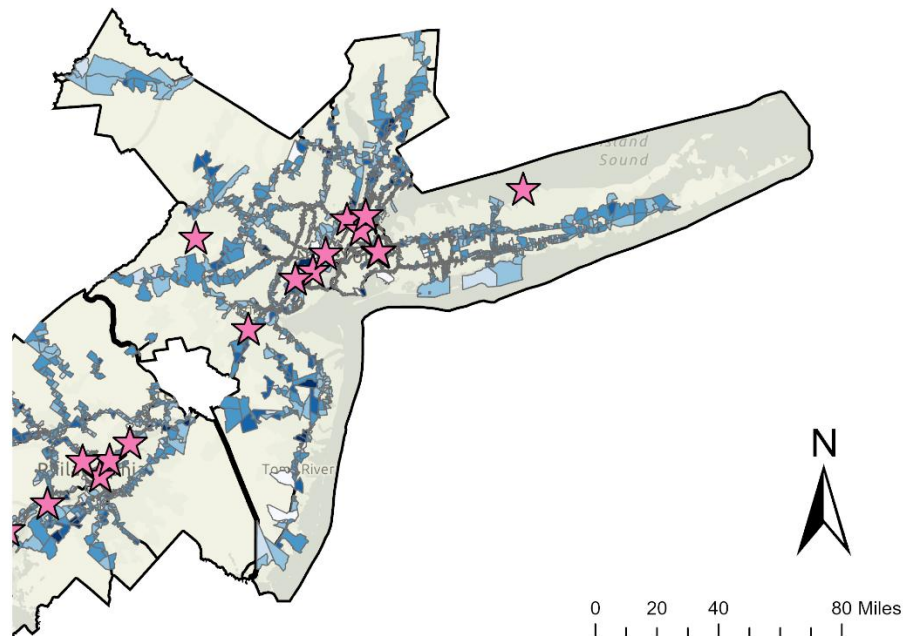
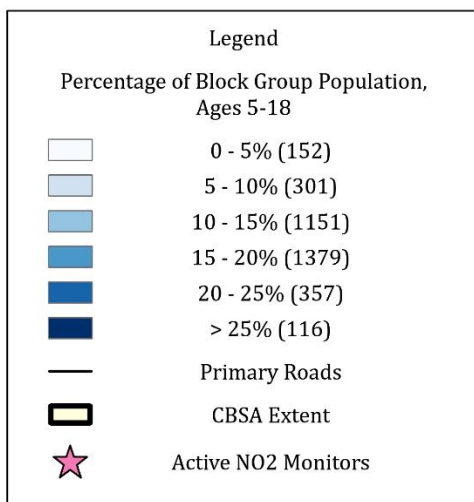


Figure 2-15 The proximity of children populations to urban roadways in New Orleans ([U.S. census data](#), [EPA AQS](#)).

New York City Core Based Statistical Area



Esri, TomTom, Garmin, FAO, NOAA, USGS, EPA, NPS, USFWS



Downtown New York City

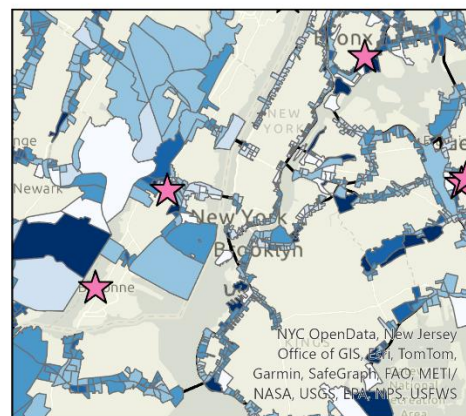


Figure 2-16 The proximity of children populations to urban roadways in New York ([U.S. census data](#), [EPA AQS](#)).

Philadelphia Core Based Statistical Area

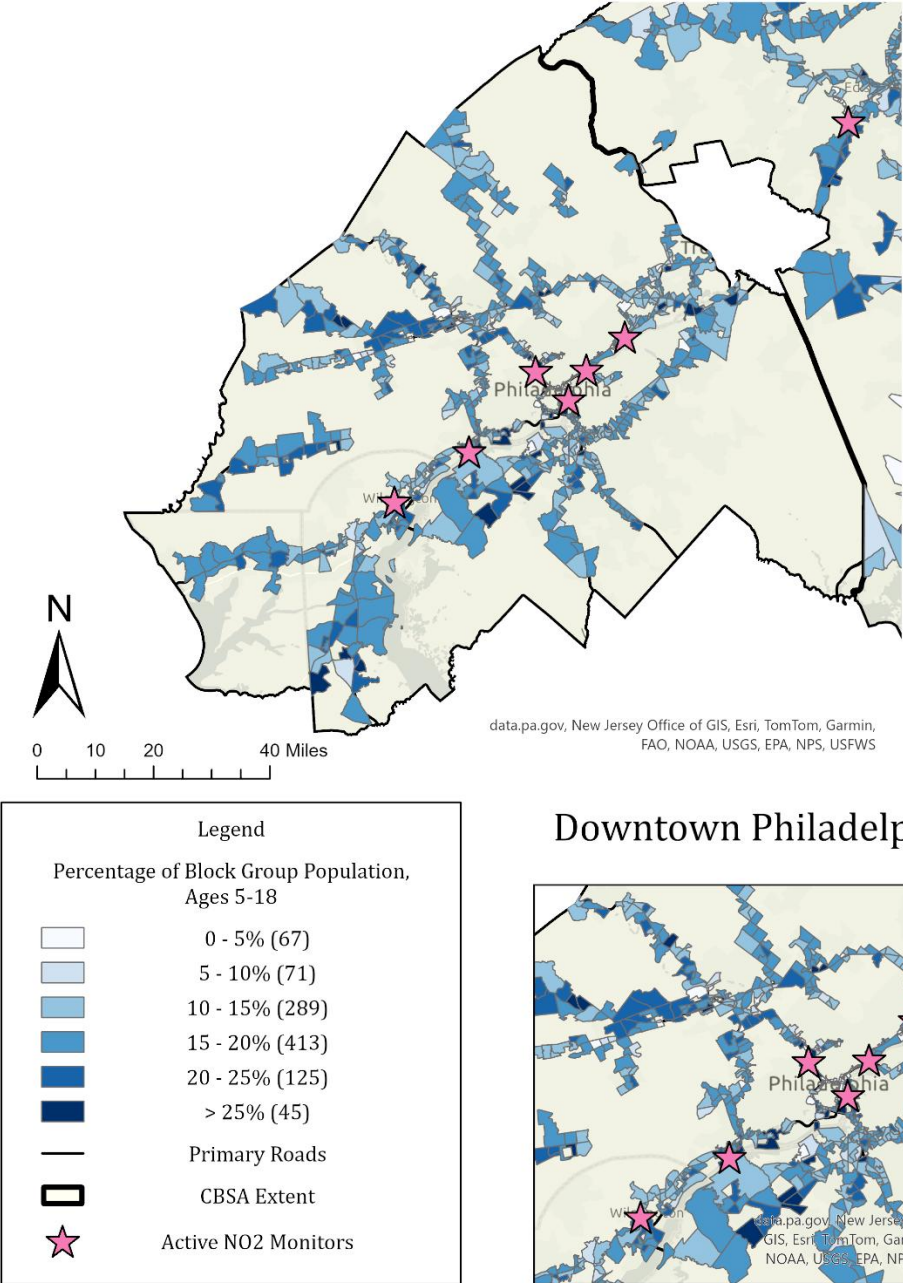


Figure 2-17 The proximity of children populations to urban roadways in Philadelphia ([U.S. census data](#), [EPA AQS](#)).

Phoenix Core Based Statistical Area

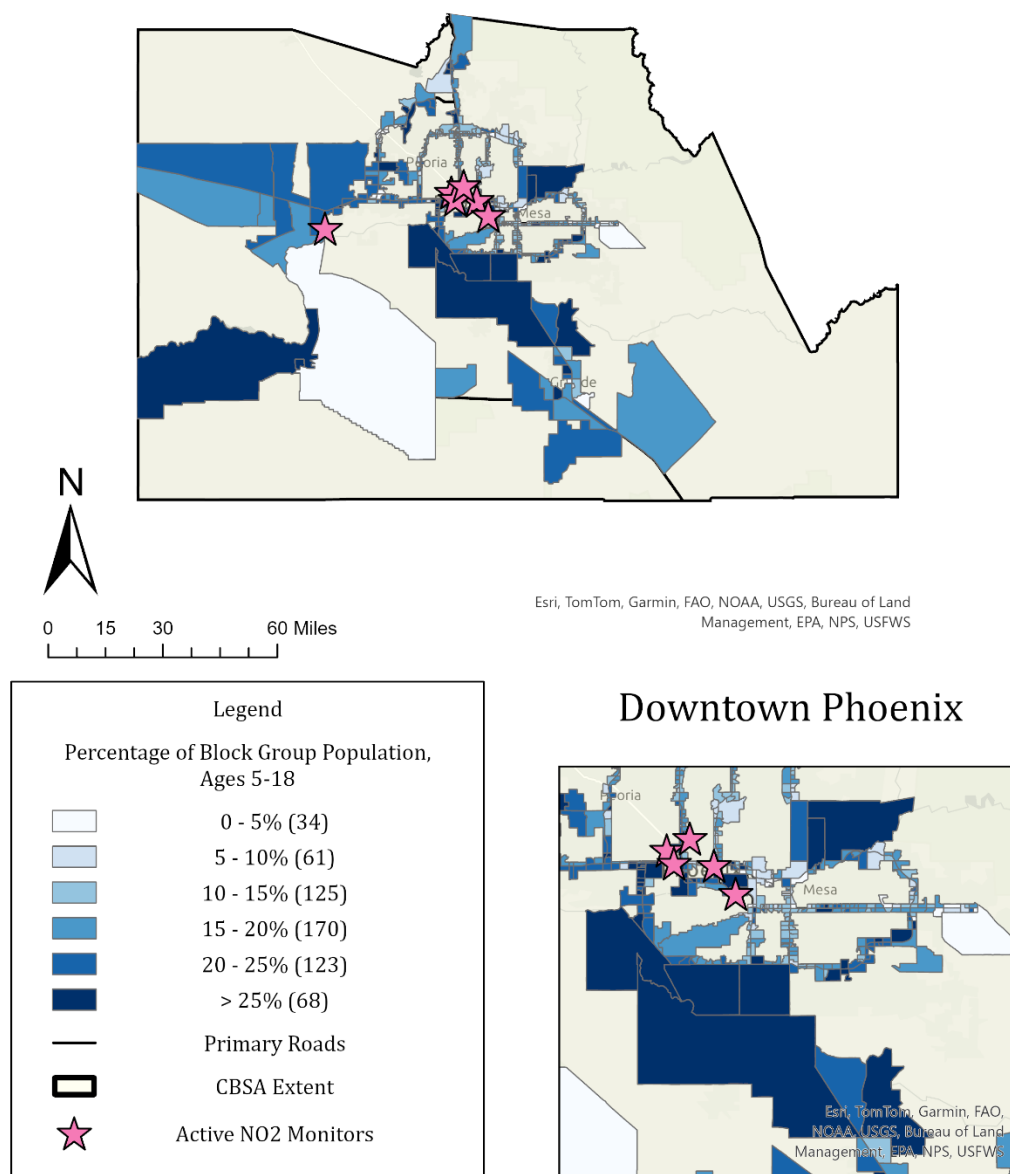


Figure 2-18 The proximity of children populations to urban roadways in Phoenix ([U.S. census data](#), [EPA AQS](#)).

San Francisco Core Based Statistical Area

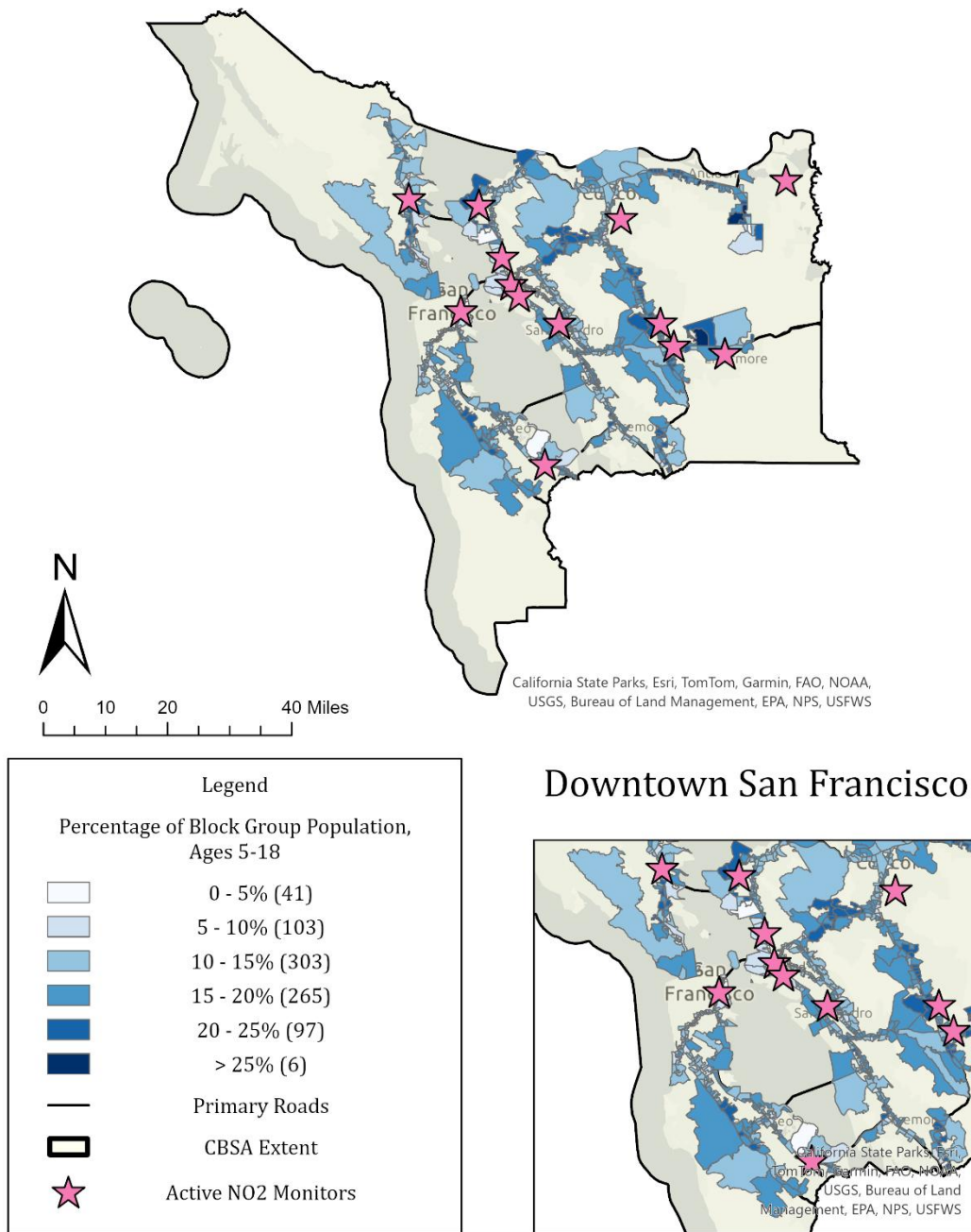


Figure 2-19 The proximity of children populations to urban roadways in San Francisco ([U.S. census data](#), [EPA AQS](#)).

Seattle Core Based Statistical Area

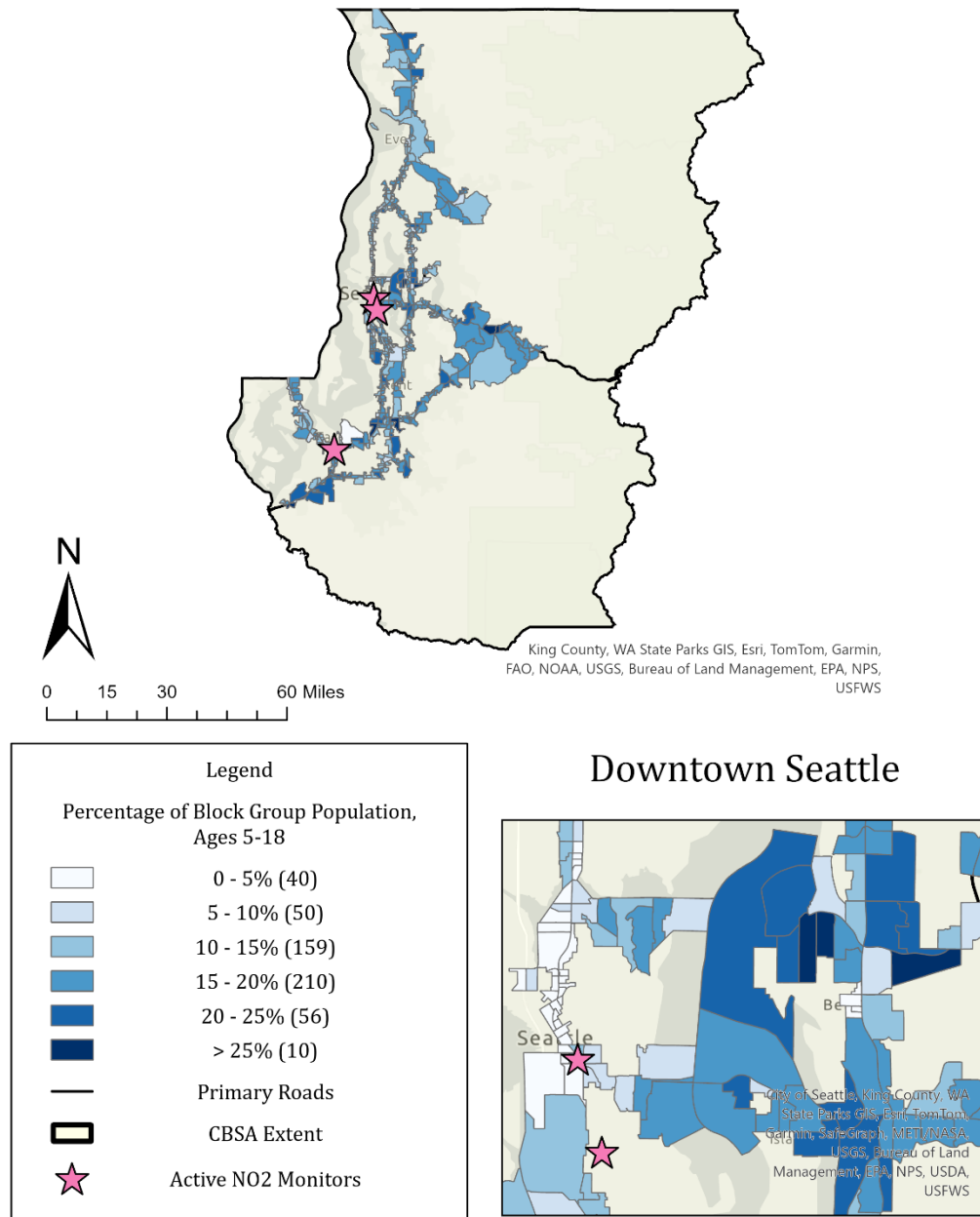


Figure 2-20 The proximity of children populations to urban roadways in Seattle ([U.S. census data](#), [EPA AQS](#)).

Table 2-9 presents the percentage of children in various age groups across 12 major U.S. metropolitan areas, comparing populations living near roads with those living away from roads.

Table 2-99 Proportion of Children^a Residing Near Roads Compared to Away From Roads in Major Metropolitan Areas

CBSA	Population Near Road Status	Total Population	Under 5	5–9	10–14	15–17	18–19	0–19
Atlanta, GA	Away	4,819,784	5.63%	6.49%	7.34%	4.49%	2.73%	26.67%
	Near	1,160,858	5.91%	6.12%	6.41%	3.73%	3.02%	25.19%
Boston, MA	Away	3,783,931	4.96%	5.24%	5.64%	3.54%	2.75%	22.13%
	Near	972,083	4.74%	5.18%	5.68%	3.59%	2.51%	21.69%
Dallas, TX	Away	5,218,133	6.23%	7.06%	7.77%	4.67%	2.88%	28.61%
	Near	2,345,294	6.31%	6.66%	7.12%	4.16%	2.75%	26.99%
Denver, CO	Away	2,347,365	5.54%	6.05%	6.64%	4.00%	2.28%	24.52%
	Near	578,805	5.59%	5.95%	6.31%	3.68%	2.28%	23.82%
Indianapolis, IN	Away	1,557,667	6.17%	6.90%	7.28%	4.30%	2.47%	27.13%
	Near	495,333	6.47%	6.77%	6.99%	4.01%	2.58%	26.82%
Los Angeles, CA	Away	10,238,110	5.00%	5.62%	6.27%	3.84%	2.68%	23.40%
	Near	2,881,151	4.95%	5.47%	6.11%	3.72%	2.81%	23.05%
New Orleans, LA	Away	952,956	5.74%	6.06%	6.52%	3.76%	2.41%	24.50%
	Near	298,694	5.79%	6.19%	6.66%	3.82%	2.48%	24.94%
New York, NY	Away	16,024,057	5.43%	5.74%	6.09%	3.74%	2.48%	23.48%
	Near	3,976,687	5.23%	5.56%	5.90%	3.68%	2.57%	22.94%
Philadelphia, PA	Away	5,015,608	5.30%	5.89%	6.31%	3.80%	2.80%	24.11%
	Near	1,147,338	5.25%	5.75%	6.21%	3.77%	2.37%	23.35%
Phoenix, AZ	Away	3,903,221	5.72%	6.52%	7.18%	4.26%	2.79%	26.47%

CBSA	Population Near Road Status	Total Population	Under 5	5–9	10–14	15–17	18–19	0–19
	Near	918,826	5.88%	6.37%	6.71%	3.90%	2.65%	25.51%
San Francisco, CA	Away	3,370,049	4.93%	5.30%	5.66%	3.39%	2.37%	21.65%
	Near	1,309,629	5.18%	5.49%	5.81%	3.45%	2.08%	22.01%
Seattle, WA	Away	3,212,473	5.67%	6.07%	6.18%	3.55%	2.36%	23.83%
	Near	782,822	5.86%	5.83%	5.73%	3.25%	2.10%	22.77%

*Children are defined by the U.S. Environmental Protection Agency (EPA) as encompassing a sequence of life stages from conception through 21 -years of age ([U.S. EPA, 2021](#)). The analysis focuses on individuals younger than 18-years (census data group ages 18 and 19 together, precluding their separate consideration). This focus on individuals younger than 18-years aligns with the assessment of respiratory effects presented in Chapter 3, Section 3.10.2.1.1 for short-term exposures and Chapter 4, Section 4.10.1.1.1 for long-term exposures.

As noted above, among the 16.9 million people living near a primary road in the 12 most-populated U.S. metropolitan areas, 4 million are children. Notably, across all age groups and metropolitan areas, the percentage of children in near-road populations is very similar to the percentage of children in populations away from primary roads, with differences typically less than 1%. When considering the aggregate percentage of children under 19-years, or within the 5–19-year age range, only New Orleans and San Francisco demonstrate slightly higher percentages in near-road areas.

Taken together, this analysis indicates that the total population of children living near primary roads in the United States is substantial, with similar percentages of near-road and away-from-road populations being comprised of children across major metropolitan areas. Given near-road gradients of traffic-related pollutants, children living near major roads are likely exposed to higher concentrations of NO₂ and other oxides of nitrogen than those living farther away from roads (see Section 2.3.2.2). These higher exposure concentrations, together with the higher risk of NO₂-associated asthma development and asthma exacerbation in children, suggest that children living near major roads are a particularly important population to evaluate when considering the public health protection provided against exposures to NO₂ and other oxides of nitrogen.

2.3.4.2 Sociodemographic and socioeconomic Factors

Compared to children, the evidence is not adequate to indicate that particular racial, ethnic, or economic groups are at higher risk than the general population from oxides of nitrogen exposures (See Chapters 3 through 13 in this ISA). However, it is useful to understand the degree to which these groups may be exposed to higher concentrations of NO₂ and other oxides of nitrogen. The sections below discuss the evidence for differential exposures based on income and demographics.

2.3.4.2.1 Income

Recent studies examining differential NO₂ exposures across income groups in the United States suggest that lower-income populations generally experience higher NO₂ exposures. However, analyses in student populations demonstrate that the relationship between income and NO₂ exposure is complex and can vary across study designs and locations.

Recent U.S. studies show that lower-income populations face higher NO₂ exposure levels. [Bramble et al. \(2023\)](#) found in the Greater Seattle Area that the lowest income group ($\leq \$20,000$) experienced an average NO₂ concentration of 13.9 ppb over 2019 to 2020, 46% higher than the overall population average of 8.7 ppb. In contrast, the highest income groups ($> \$90,000$) had exposures of 7.6 ppb, 13% below the population average. Similar trends were observed in other recent U.S. studies [Fabisiak et al. \(2020\)](#) [Willis et al. \(2023\)](#). [Willis et al. \(2023\)](#) additionally observed the persistence of differential exposures over time. Overall, annual-average NO₂ concentrations decreased substantially over the 20-year period from 1996 to 2016 for all income groups, i.e., from 15.6 ± 4.8 ppb to 7.2 ± 2.7 ppb for low-income neighborhoods, from 14.5 ± 4.8 ppb to 5.8 ± 2.5 ppb for middle-income neighborhoods, and from 14.1 ± 4.3 ppb to 5.3 ± 2.1 ppb for high-income neighborhoods. However, the relative difference between low and high-income neighborhoods actually increased from 11% in 1996 to 36% in 2016.

Research focusing on school environments in the United States presents a more complicated picture. For example, [Bechle et al. \(2023\)](#), [Matthaios et al. \(2022\)](#), and [Cheeseman et al. \(2022\)](#) found that lower income students experienced higher NO₂ concentrations at schools. However, [Chakraborty \(2022\)](#) reported a reverse U-shaped relationship between the percentage of children below the poverty level and NO₂ exposure in Texas school districts (i.e., lower levels of NO₂ exposure were found in school districts with both relatively small and large percentages of children below the poverty level), and [Chakraborty and Aun \(2023\)](#) found that a pattern of higher NO₂ exposure in schools with more students eligible for free/reduced lunches was reversed in models controlling for factors like racial/ethnic composition and urban/rural location.

2.3.4.2.2 Demographics

Differential NO₂ exposures across racial and ethnic groups have been consistently observed in the United States, both at national and local/state levels. These observed differential exposures persist across different geographical scales, time periods, and measurement methods.

At the national level in the United States, [Wang et al. \(2023b\)](#) found that Asian-dominant communities experienced the highest exposure levels (29.65 ± 7.63 ppb), with concentrations 70% higher than low-income white communities (17.11 ± 7.84 ppb) and 40% higher than high-income white communities (21.89 ± 8.17 ppb). Hispanic-dominant (26.62 ± 9.66 ppb) and Black-dominant (24.51 ± 8.90 ppb) block groups also experienced higher NO₂ concentrations compared to white-dominant census block groups. [Kerr et al. \(2023\)](#) corroborated these findings, showing that non-Hispanic white populations experienced NO₂ concentrations that were 5–15% lower than the overall average, whereas

Asian, Hispanic, and Black populations were exposed to levels that were 15–50% higher – ranging from 15% higher for Black populations to 50% higher for Asian populations. Proximity to road could be a factor contributing to these differential exposures.

Studies focusing on public school students at the national level also revealed notable differential NO₂ exposures. [Bechle et al. \(2023\)](#) found that minority students (i.e., defined as all students except for non-Hispanic white students) experienced an annual average of 3.6 ppb (39%) higher NO₂ concentrations at school locations and 3.8 ppb (37%) higher levels at home locations compared to non-Hispanic white students in 2006. [Cheeseman et al. \(2022\)](#) reported that Hispanic students had the highest median annual average exposure (9.9 ppb), followed by Asian or Asian/Pacific Islander (9.7 ppb), and Black or African American students (9.2 ppb), while white students had the lowest median exposure (7.7 ppb) for the contiguous United States in 2017 to 2019.

These national-level findings are mirrored in local and state-level studies. In the Greater Seattle Area, [Bramble et al. \(2023\)](#) found that Black residents experienced the highest NO₂ exposures at 9.4 ppb between 2019 and 2020, 9.3% higher than non-Hispanic white residents. Similar patterns were observed in the San Francisco Bay Area by ([Chambliss et al., 2021](#)), where Black and Hispanic/Latino populations had median annual average exposures up to 13% higher than the total-population median between 2015 and 2017. Studies in Texas ([Willis et al., 2023](#)) and Allegheny County, Pennsylvania ([Fabisiak et al., 2020](#)) also demonstrated differential NO₂ exposures between minority and white populations, where census tracts having over 30% non-white minority population and/or over 20% of residents below the poverty line, were 18.5 times more likely to be in the highest quartile of annual NO₂ exposure (median 6.8 ppb, and range 6.1–10.5 ppb) compared to the lowest quartile (median 3.0 ppb, and range 1.6–3.7 ppb) in 2011 and 2012.

The magnitude of these exposure differences varies depending on the study and methodology. In the United States, [Wang et al. \(2023b\)](#) reported the largest long-term (17-year annual averages) difference of about 9 ppb between low-income white and Asian populations, while [Kerr et al. \(2023\)](#) found exposure differences in 2019 between Asian and non-Hispanic white ranging from about 25% based on AQS monitors to 60% based on TROPOMI satellite data. For school children in the U.S., the differences were 3.6 ppb–3.8 ppb between minority and non-hispanic white students ([Bechle et al., 2023](#)), and 2.2 ppb between Hispanics and white students ([Cheeseman et al., 2022](#)).

The spatial resolution of data used could impact the observed exposure differences among racial/ethnic groups. [Clark et al. \(2022\)](#) found that differential exposures are often underestimated based on state and county-level data compared with those using tract and finer scales, highlighting the importance of high-resolution data in accurately assessing NO₂ exposure disparities.

It is also important to note that current studies suggest that differentials between racial and ethnic groups persist while overall NO₂ concentrations have generally decreased over time for all groups. [Willis et al. \(2023\)](#) observed that the relative difference in NO₂ exposure between non-Hispanic Black and non-

Hispanic white pregnant women in Texas grew from 13.3% in 1996 (15.3 ppb vs. 13.5 ppb) to 28% in 2016 (6.7 ppb vs. 5.2 ppb), despite overall decreases in absolute NO₂ concentrations.

Consistent with the broader body of evidence on sociodemographic factors and NO₂ exposures, a few recent studies have found associations between historical property values and present-day exposure differences in NO₂. A national study of 202 U.S. cities revealed that population-weighted mean NO₂ concentrations in 2010 were 6.0 ppb (56%) higher in areas often characterized by older housing, lower incomes, and higher proportions of non-white residents (16.8 ppb) compared to areas with higher property values and greater wealth (10.8 ppb) ([Lane et al., 2022](#)). Similar findings were observed in individual cities with the magnitude of concentration differences varying according to property value categories. For example, an analysis of 2019 NO₂ concentrations across neighborhoods in the Greater Seattle Area found that neighborhoods with historically lower property values had NO₂ concentrations 28% higher than those in more affluent neighborhoods ([Bramble et al., 2023](#)). In Denver, Colorado, a study using high-resolution satellite data from 2019 found that communities with lower historical property values experienced TROPOMI NO₂ columns 13% higher than those in wealthier districts ([Bradley et al., 2024](#)).

2.3.4.3 Neighborhood Characteristics

2.3.4.3.1 Urbanization

Recent studies have consistently demonstrated that urbanization plays a crucial role in determining NO₂ concentrations. [Cheeseman et al. \(2022\)](#) found that urban schools in the United States had median NO₂ concentrations (modeled annual average within 1 km of schools) of 10–12 ppb between 2017 and 2019, in contrast to the 6–8 ppb observed within 1 km at schools in suburban, town, and rural areas. Similarly, [Bechle et al. \(2023\)](#) examined NO₂ exposures for nearly 48 million public school students across the contiguous United States, using modeled annual average outdoor NO₂ concentrations for 2006. They found that urban schools, likely characterized by higher road density, had NO₂ concentrations of 12.9 ppb, nearly double the 6.7 ppb found in non-urban areas.

This urban-rural divide was corroborated by studies conducted in the EU. [Stucki et al. \(2023\)](#) in Sweden showed that annual-average NO₂ concentrations over a 20-year period were about 2 ppb higher in urban areas than in suburban and rural areas. Similarly, [van den Brekel et al. \(2024\)](#) observed approximately 3 ppb higher NO₂ concentrations (2019 annual average) in highly urbanized areas of the Netherlands compared to rural areas. [Samoli et al. \(2019\)](#) reported that in European metropolitan areas, the highest quartile of population density was associated with a 48.7% increase in the 2010 annual average NO₂ concentrations compared to the lowest quartile.

2.3.4.3.2 Vegetation Coverage

Recent studies have examined the impact of the proportion of land covered by vegetation or water bodies on NO₂ concentrations in both the United States and European Union. These studies reveal a consistent inverse relationship between ambient NO₂ concentrations and vegetation or water coverage.

In the United States, [Werder et al. \(2024\)](#) examined the relationship between annual average NO₂ concentrations and vegetation density across Alabama, Florida, Louisiana, Mississippi, and Texas between 2011 and 2013 during the Gulf Long-term Follow-up Study. The authors reported a negative Pearson correlation coefficient of -0.3 between NO₂ concentrations and the Enhanced Vegetation Index (EVI), which quantifies vegetation abundance.

In the Netherlands, [Klompmaaker et al. \(2019\)](#) found a moderate negative correlation ($\rho = -0.49$) between the Normalized Difference Vegetation Index (NDVI) in a 300 m buffer around a study participant's house and NO₂ concentrations. In Spain, negative correlations between NO₂ and vegetation measures (NDVI: $\rho = -0.57$, percentage vegetation cover: $\rho = -0.59$) were reported ([Nieuwenhuijsen et al., 2018](#)). A Danish study found that NO₂ concentrations were positively correlated with the lack of vegetation, with a Spearman correlation coefficient of 0.40, indicating that areas with higher vegetation coverage tend to have less NO₂ exposures ([Sørensen et al., 2022a](#)). Across multiple European cities, [Robinson et al. \(2018\)](#) observed negative correlations between NDVI scores within 300 m of a residential address and NO₂ concentrations, ranging from -0.35 in Kaunas to -0.76 in Valencia. [Moitra et al. \(2022\)](#) found that greater distances to vegetation or water bodies were associated with higher NO₂ concentrations ($\rho = 0.20$) in Barcelona, Spain.

Although the strength of the inverse relationship between NO₂ concentrations and vegetation coverage varies across different urban areas, the consistent inverse relationship suggests that people living in communities with less vegetation may experience elevated ambient NO₂ exposures.

2.4 Exposures to Copollutants or Other Stressors

Multipollutant models have been employed in a number of air pollution epidemiologic studies to identify the independent health effects of NO₂. In those epidemiologic studies, confounders are controlled for in the statistical model or in the study design. In this context, a confounder is associated with both NO₂ exposure and the health effect(s) examined. Therefore, it is important to understand the association between NO₂ and other copollutants or stressors. NO₂ is correlated with other air pollutants or stressors because they are emitted from the same sources (e.g., motor vehicles), participate in the same physicochemical processes (e.g., transport or atmospheric chemistry) in the atmosphere, or are otherwise present in the same locations. This section examines how NO₂ is associated with other air pollutants or stressors (e.g., the lack of green space) in the context of human exposure to ambient NO₂. Specifically, the spatial and temporal correlations of NO₂ and other copollutants or stressors are assessed. The information in this section contributes to our understanding of the independent effects of NO₂ associated with a health effect in an epidemiologic study.

This section assesses (1) the correlation between NO₂ and other traffic-related pollutants in proximity to roadways, (2) the temporal and spatial correlations of NO₂ with criteria or hazardous air pollutants, and (3) the correlations of NO₂ with noise and the lack of green/blue space, as emerging nonchemical stressors are considered in NO₂ epidemiologic studies. Each sub-section starts with presenting major findings in the 2016 Oxides of Nitrogen ISA followed by assessing recent studies published since the publication of the last ISA.

2.4.1 NO₂ and other TRAPs in Near-road Environments

As presented in Section 2.3.4, a substantial proportion of the United States population resides in close proximity to roadways. The near-road environment serves as a crucial interface between vehicular emissions and human exposure, characterized by complex interplay of emission (i.e., traffic-related air pollutants), atmospheric dynamics (e.g., dispersion), and chemical reactions (e.g., NO titration). Consequently, the near-road environment exhibits unique pollutant interactions and multipollutant exposure patterns, distinguishing it from other urban microenvironments. Previous oxides of nitrogen ISAs assessed correlations between NO₂ and other traffic-related pollutants near roads [see Chapter 3, Sections 3.3.1 and 3.4.4 in [U.S. EPA \(2016\)](#) and Chapter 2, Section 2.5 in [U.S. EPA \(2008a\)](#)]. These previous assessments made the following observations:

- NO₂ concentrations generally correlate well with other traffic-related pollutants (e.g., benzene, toluene, ethylbenzene, xylenes, or BTEX) in urban areas. This evidence is particularly strong in short-term exposure studies and more limited in long-term exposure studies.
- NO₂ concentrations exhibit clear spatial gradients near roadways, making it a useful indicator of traffic pollution. However, the NO₂ gradient tends to be shallower compared to other primary traffic pollutants like CO and UFPs. This means that while NO₂ captures many aspects of pollutant gradients from roadways, it may underestimate the magnitude of concentration gradients for some other near-road pollutants.
- The correlations between NO₂ and other traffic pollutants like CO, NO, and EC have led to the development of an Integrated Mobile Source Indicator for traffic-related air pollution.

Emerging mobile monitoring technology has been applied in recent studies to quantify real-time on-road or near-road concentrations of NO₂, BC, and particle counts ([Alexeeff et al., 2022](#); [Blanco et al., 2022](#); [Brantley et al., 2019](#); [Apte et al., 2017](#)). These studies further examine the complex associations between NO₂ and other pollutants in near-road environments and associated influencing factors.

The near-road behavior of NO₂ is influenced by direct emissions from vehicles and its secondary formation through the rapid reaction of NO with O₃ (see Chapter 1, Section 1.2). Hence, NO₂ dynamics are governed by a combination of dispersion and chemical kinetics. In contrast, NO_x is more sensitive to mechanical dispersion driven by wind speed and turbulence ([Richmond-Bryant et al., 2017b](#)). As a result, NO_x exhibits near-road gradients similar to those of other primary emissions, such as BC ([Liang et al.,](#)

[2018](#); [Saha et al., 2018](#)). For instance, [Saha et al. \(2018\)](#) measured the decay of NO_x and BC adjacent to Interstate 40 near Durham, North Carolina, during the summer of 2015 and winter of 2016. Measurements were taken at multiple distances (10, 50, 100, 150, and 220 m from the highway), with a background site located 400 m upwind. The study observed exponential decays for both NO_x and BC: concentrations halved at 50 m during summer and at 150 m during winter, reaching near-background levels by 200–300 m. Similarly, [Liang et al. \(2018\)](#) reported comparable decay patterns for NO_x, BC, and carbon monoxide (CO) in Atlanta, Georgia, based on data collected at six monitoring sites near a 16-lane highway.

The near-road behaviors of NO_x, BC, and CO result in moderate (typically $0.4 < \rho < 0.7$) to strong (typically $\rho > 0.7$) correlations among these pollutants. For example, [Rattigan et al. \(2020\)](#) analyzed data from two near-road sites in Rochester and Queens, New York, located 12 m and 30 m from major highways, respectively. NO_x was strongly correlated with BC (Spearman correlation coefficient, $r_s = 0.75\text{--}0.86$ in Rochester and $0.84\text{--}0.91$ in Queens), ultrafine particles (UFP; $r_s = 0.62\text{--}0.87$ in Rochester and $0.66\text{--}0.79$ in Queens), and CO ($r_s = 0.63\text{--}0.81$ in Rochester and $0.79\text{--}0.88$ in Queens). In comparison, NO₂ exhibited slightly lower correlations with these pollutants: $r_s = 0.68\text{--}0.84$ in Rochester and $0.71\text{--}0.82$ in Queens for BC; $r_s = 0.53\text{--}0.78$ in Rochester and $0.38\text{--}0.65$ in Queens for UFP; and $r_s = 0.60\text{--}0.74$ in Rochester and $0.78\text{--}0.82$ in Queens for CO. The slight reduction in correlations between NO₂ and other pollutants compared to NO_x reflect the dual role of NO₂ as both a primary and secondary pollutant.

Although NO₂ is correlated with primary traffic emissions such as BC and CO, its decay is generally less steep compared to these pollutants ([Jeong et al., 2022](#); [Liang et al., 2018](#)). For instance, [Jeong et al. \(2022\)](#) reported a 38% decrease in NO₂ concentrations between 10 m and 150 m from Highway 401 in Toronto, Canada, compared to steeper reductions of 75% for UFP and 50% for BC. Similarly, [Baldwin et al. \(2015\)](#) found that NO₂ concentrations decreased by 50% within 89–129 m downwind, whereas BC and UFP showed much sharper reductions within 14–20 m. According to [Liang et al. \(2018\)](#), BC concentrations often approached background concentrations within 20–50 m of highways, and CO gradients were especially pronounced during periods of high traffic volume.

Overall, studies consistently report moderate to strong correlations between NO₂ and other traffic-related air pollutants (TRAPs) ([Alexeeff et al., 2022](#); [Blanco et al., 2022](#); [Blanco-Alegre et al., 2020](#); [Miller et al., 2020](#); [Rattigan et al., 2020](#); [Brantley et al., 2019](#); [Apte et al., 2017](#); [Patton et al., 2016](#)). However, the strength of these correlations varies across studies. For instance, [Blanco et al. \(2022\)](#) reported a strong correlation ($\rho = 0.92$) between NO₂ and BC in Seattle, whereas [Brantley et al. \(2019\)](#) observed a moderate correlation ($\rho = 0.6$) between these pollutants in Atlanta.

Several factors influence the association between NO₂ and other TRAPs, including road and fleet conditions ([Tessum et al., 2018](#); [Baldwin et al., 2015](#); [Mukerjee et al., 2015](#); [Dickerson et al., In Press](#)), meteorological conditions ([Jeong et al., 2022](#); [Liang et al., 2018](#); [Richmond-Bryant et al., 2017b](#); [Baldwin et al., 2015](#)), and site characteristics ([Moutinho et al., 2020](#)). [Dickerson et al.](#) documented the impact of traffic lights on pollutant concentrations near a diesel truck route in Baltimore. The presence of traffic

lights caused turbo lag in diesel trucks, resulting in elevated BC ($2.08 \mu\text{g}/\text{m}^3$ vs. $0.67 \mu\text{g}/\text{m}^3$) but lower NO_2 (4.9 ± 2.3 ppb vs. 6.3 ± 2.1 ppb) compared to a nearby road without traffic lights.

Seasonal factors also play a notable role. In particular, O_3 concentrations strongly influence NO_2 gradients, as higher O_3 concentrations enhance the conversion of NO to NO_2 , amplifying NO_2 gradients while shrinking the near-road zone of elevated NO_2 ([Gantt et al., 2021](#); [Richmond-Bryant et al., 2017b](#)). Downwind conditions further intensify TRAP correlations, according to [Gantt et al. \(2021\)](#).

[Moutinho et al. \(2020\)](#) found that a vegetation barrier near a monitoring site trapped CO emissions and inhibited NO_2 formation by limiting O_3 mixing, whereas an open layout enhanced dispersion.

Distinct spatial variability away from road has also been reported. [Ducret-Stich et al. \(2013\)](#) observed that correlations between NO_2 and other TRAPs (e.g., elemental carbon and particle number concentrations) were stronger near highways ($r_s = 0.73$ for EC and 0.83 for particle number concentration) but diminished with increasing distance ($r_s \leq 0.35$ for EC and ≤ 0.56 for particle number concentration). This finding suggests that epidemiologic studies assessing NO_2 health impacts may yield more pronounced insights when participants are located farther from roadways, where TRAP correlations are weaker.

Compared to NO_2 , $\text{PM}_{2.5}$ exhibits less spatial variability in the near-road environment. [Baldwin et al. \(2015\)](#) reported smaller near-road elevations in $\text{PM}_{2.5}$ compared to NO_2 in Detroit, with minimal variability near the highway ([Liang et al., 2018](#); [Dickerson et al., In Press](#)). Consequently, correlations between NO_2 and $\text{PM}_{2.5}$ are typically weak ($\rho < 0.5$; see Table 2-10).

Although O_3 is not conventionally classified as a TRAP, it interacts significantly with NO_x in near-road environments (see Chapter 1). O_3 correlations with NO_2 are seasonally dependent, often stronger in summer due to heightened photochemical activity. Higher O_3 concentrations are typically observed in summer afternoons, whereas background O_3 concentrations drop sharply in late afternoons due to NO scavenging from vehicles emissions ([Saha et al., 2018](#); [Richmond-Bryant et al., 2017a](#)).

Table 2-1010 Correlations between ambient NO₂ and other pollutants in the near-road environment

Study	City	Year	Season	Averaging time	Correlation Type	PM _{2.5}	PM ₁₀	O ₃	CO	UFP	BC/EC
Apte et al. (2017)	Oakland	2015–2016	All	1 Hertz	Pearson						0.5
Alexeeff et al. (2022)	Oakland; San Francisco, San Jose, San Mateo, Livermore, Sunnyvale, Redwood City, Mountain view, Sebastopol, Fremont	2015–2017	All	1 Hertz	Pearson						0.29
Brantley et al. (2019)	Atlanta	May, 2012	Summer	Real time	Pearson						0.6
Patton et al. (2016)	NJ Turnpike	2007–2014	All	about 1 hr	Pearson	0.42			0.22		0.37
Rangel et al. (2022)	El Paso	2017	Fall	1 hr	Spearman	0.31–0.73	0.25–0.67	-0.8– -0.6			
Rattigan et al. (2020)	Rochester	2016–2018	Spring	24 hr	Spearman				0.71	0.59	0.78
			Summer	24 hr	Spearman				0.6	0.53	0.84
			Fall	24 hr	Spearman				0.74	0.78	0.79
			Winter	24 hr	Spearman				0.72	0.66	0.68
	NYC	2017–2018	Spring	24 hr	Spearman				82	0.65	0.82
			Summer	24 hr	Spearman				0.78	0.53	0.8
			Fall	24 hr	Spearman				0.81	0.59	0.71

Study	City	Year	Season	Averaging time	Correlation Type	PM _{2.5}	PM ₁₀	O ₃	CO	UFP	BC/EC
			Winter	24 hr	Spearman				0.82	0.38	0.77
Blanco et al. (2022)	Seattle	2019–2020	All	Annual average based on real-time measurements	Pearson	0.67					0.92

List of abbreviations in alphabetical order: hr = hour; s = seconds.

2.4.2 Associations of NO₂ and Copollutant Exposures in Ambient Settings not Specific to Near-road Environments

Regarding the ambient environments beyond near-road settings, the previous ISAs for oxides of nitrogen also evaluated temporal correlations among copollutants and how these relationships may vary spatially. Key aspects covered in the 2016 Oxides of Nitrogen ISA [see Sections 3.3.1 and 3.4.4 in [U.S. EPA, \(2016\)](#)] include:

- Many studies assessed in the 2016 Oxides of Nitrogen ISA were short-term exposure studies that reported Pearson or Spearman correlations between ambient NO₂ concentrations and those of criteria pollutants, primarily focusing on traffic-related sources such as PM_{2.5}, CO, and PM₁₀.
- A limited number of studies explored correlations between NO₂ concentrations and other traffic-related pollutants, including EC, UFP, and VOCs.
- Strong temporal correlations were typically observed between NO₂ concentrations and primary traffic-related pollutants, such as benzene, CO, EC, and PNC.
- Both the 2008 and 2016 Oxides of Nitrogen ISAs reported that NO₂ concentrations generally exhibited correlations with a Pearson ρ greater than 0.5 with criteria pollutants and traffic-related pollutants. For short-term studies, NO₂ consistently shows correlations above 0.5 with BC, EC, CO, PNC, and UFP, with most of these correlations being stronger in near-road environments. In the more limited long-term studies, the correlations between NO₂ and other pollutants remain above 0.5 for EC, OC, and PNC in near-road studies.
- Few studies reported long-term correlations between NO₂ and traffic-related pollutants, and correlations derived from LUR studies were not included in the 2016 Oxides of Nitrogen ISA.

Since the release of the 2016 Oxides of Nitrogen ISA, advancements have been made in understanding the correlations between NO₂ and copollutants, especially in long-term studies utilizing geospatial modeling. This section will assess temporal copollutant correlations and how relationships among copollutants may change spatially across urban areas, using studies conducted in ambient environments not specific to near-road settings.

Temporal copollutant correlations are computed from the time series of concentrations for two or more different pollutants. These correlations are informative for epidemiologic studies of short-term NO₂ exposure when the sampling interval is 1-month or less for each copollutant. For long-term NO₂ exposure studies, temporal correlations are relevant when sampling intervals range from months to years. Spatial relationships are evaluated by comparing the differences in spatial variation across different pollutants. In addition, findings from long-term correlations based on LUR results will be discussed, given their extensive use in epidemiologic studies. The following sections will review copollutant exposures that can potentially confound the relationship between health effects and NO₂ exposure across different temporal and spatial resolutions.

Correlations between NO₂ concentrations and concentrations of criteria air pollutants are summarized in Table 2-11, broken into short- and long-term exposure studies. The most abundant data available is on the correlation between NO₂ and PM_{2.5}, CO, and O₃, which is consistent with the 2016 Oxides of Nitrogen ISA. Moderate to strong correlations were reported between ambient NO₂ and PM_{2.5}, and between ambient NO₂ and CO (see Table 2-11). NO₂ is consistently negatively correlated with O₃ except in one study conducted in Florida ([El-Sayed et al., 2021](#)), which shows a positive correlation between O₃ and NO₂, presumably due to increased photochemical activities in the study area, resulting in enhanced O₃ formation. Higher O₃ concentrations increase the ratio of NO₂ concentration to NO concentration due to enhanced oxidation, thereby resulting in a stronger correspondence between NO₂ concentration and O₃ concentration during the summer.

Interestingly, [El-Sayed et al. \(2021\)](#) compared the correlations among NO₂, PM_{2.5}, PM₁₀, SO₂, O₃, and CO measured during the COVID-19 pandemic lockdown (February to April 2020) with those observed during the same months over the preceding five-years in Jacksonville, Orlando, Tampa, and Miami, Florida. The correlation patterns differ before and during the COVID-19 pandemic. For example, in Miami, the correlations between NO₂ and PM_{2.5}, O₃, SO₂, and CO were 0.19, 0.58, 0.36, and 0.39, respectively, during the pandemic, while the same correlations were 0.52, 0.27, 0.24, and 0.29 before the pandemic, indicating a change in chemical mixtures in the atmosphere before and during the pandemic.

Table 2-12 summarizes the correlations between ambient NO₂ concentrations and air toxics or other air pollutants used as markers of traffic emission. Black carbon and PAHs show the most robust correlations with NO₂ across studies. In Fresno, [Mann et al. \(2021\)](#) reported moderate to strong Pearson correlations between NO₂ and BC/EC, ranging from 0.76 (24-hour average) to 0.56 (annual average), with even higher values for PAHs containing 4–6 aromatic rings ($\rho = 0.84\text{--}0.5$). These findings align with European studies, such as [Andersen et al. \(2017\)](#), where annual BC/EC-NO₂ correlations reached 0.9 in Sweden and 0.93 in Italy.

CO exhibits variable correlations depending on urban characteristics. [Frampton et al. \(2022\)](#) documented a remarkably high 24-hour Pearson correlation of 0.93 in San Francisco, likely reflecting dense traffic and topographic trapping of pollutants. However, correlations were 0.59–0.6 in Chapel Hill and Rochester, suggesting localized emission profiles and dispersion conditions moderate this relationship. Likewise, UFP correlations with NO₂ are less consistent, highlighting UFP's high spatiotemporal variability.

[Rattigan et al. \(2020\)](#) reported seasonal correlations between NO₂ and UFP, CO, BC/EC, NO, NO_x in New York City (NYC) and Rochester, using the monitoring data collected between 2016 to 2018 for Rochester and 2017 to 2018 for NYC. There was no significant seasonal contrast for these correlations in either city, and NO₂ demonstrated strong correlations with NO, NO_x, CO, and BC, and moderate correlations with UFP. No other seasonal patterns of the correlation can be identified due to the limited number of studies examining this effect. The 2016 Oxides of Nitrogen ISA concluded that studies show

stronger correlations of NO₂ concentration with PM_{2.5} and PM₁₀ concentrations during cooler seasons compared with warmer seasons.

A limited number of studies reported the correlation between NO₂ and VOCs, including BTEX ([Blanco et al., 2022](#); [Brantley et al., 2019](#); [Miller et al., 2019](#)). The majority of the correlations are within the range of 0.5–0.7, which is generally consistent with the studies assessed in the 2016 Oxides of Nitrogen ISA.

Similar to what was reported in the 2016 Oxides of Nitrogen ISA, long-term exposure studies that evaluate copollutant correlations are lacking, especially for measurement-based studies. However, exposure modeling has been adopted in a large number of long-term epidemiologic studies. As stated in Section 2.3.1, these studies employed LUR models or CTM/dispersion models to estimate individual exposures, using estimated residential outdoor concentration as a surrogate. A few large-scale Canadian- or European-based studies reported correlations between NO₂ and other air pollutants, computed from LUR or CTM/dispersion models ([Sørensen et al., 2022b](#); [So et al., 2020](#); [Andersen et al., 2017](#); [Stieb et al., 2016](#)). These studies focus on PM_{2.5}, PM₁₀, and BC (reported as PM absorbance). Moderate correlations between NO₂ and PM_{2.5} ($\rho = 0.4$ – 0.8) and stronger correlations between NO₂ and BC ($\rho = 0.7$ – 0.9) have been identified in these modeling-based long-term studies.

Regarding the spatial associations between NO₂ and other pollutants, ([Dionisio et al., 2013](#)) observed that the spatial variation of the studied pollutants, quantified by the coefficient of variation across Atlanta, GA, exhibited a decreasing trend: NO_x (0.88)>CO (0.58)>EC (0.50)> PM_{2.5} (0.13)>O₃ (0.07)>SO₄²⁻(0.05). Furthermore, ([Goldman et al., 2012](#)) and ([Ivy et al., 2008](#)) demonstrated that NO₂ and NO_x concentrations, along with CO, SO₂, and EC concentrations, displayed notably steeper spatial correlograms compared to O₃, PM₁₀, PM_{2.5}, SO₄²⁻, NO₃⁻, NH₄⁺, and OC concentrations. These findings, which highlight the difference in spatial variability between NO₂ concentration and copollutants, suggest a reduced likelihood of copollutant confounding occurring as a spatial confounder.

The general findings of the correlation between NO₂ and copollutants are consistent with previous ISAs for short-term studies. For long-term studies, copollutant correlations calculated with LUR or other exposure models demonstrate a moderate to strong correlations primarily with PM_{2.5} and BC. In addition, limited information suggests a change in the correlations between NO₂ and other air pollutants during the COVID-19 pandemic.

Table 2-1111 Correlations between ambient NO₂ and PM_{2.5}, PM₁₀, O₃, SO₂, and CO

Study	City	Year	Season	Spatial Scale	Averaging time	Correlation Type	PM _{2.5}	PM ₁₀	O ₃	SO ₂	CO
El-Sayed et al. (2021)	Jacksonville	Feb–April, 2020	Spring - covid lockdown	Ambient	24 hr	Pearson			0.14	0.09	0.19
		Feb–April, 2015–2019	Spring	Ambient	24 hr	Pearson	0.46		0.37	0.14	
	Orlando	Feb–April, 2020	Spring - covid lockdown	Ambient	24 hr	Pearson					0.4
		Feb–April, 2015–2019	Spring	Ambient	24 hr	Pearson	0.42		0.43	0.42	0.23
	Tampa	Feb–April, 2020	Spring - covid lockdown	Ambient	24 hr	Pearson	0.3		0.51	0.46	
		Feb–April, 2015–2019	Spring	Ambient	24 hr	Pearson	0.47		0.55		
	Miami	Feb–April, 2020	Spring - covid lockdown	Ambient	24 hr	Pearson	0.19		0.58	0.36	0.39
		Feb–April, 2015–2019	Spring	Ambient	24 hr	Pearson	0.52		0.27	0.24	0.29
Mann et al. (2021)	Fresno	2002–2017	All	Residential address	24 hr	Not reported	0.77				
Trees et al. (2024)	New York State	2008–2010		Census track centroid	24 hr	Not reported	0.86 (NO _x)	0.89 (NO _x)	-0.75 (NO _x)	0.55 (NO _x)	0.97 (NO _x)
Hsu et al. (2023)	Boston, Massachusetts; ACCESS cohort	2001–2008		Residential address	24 hr	Spearman			from -0.31 to -0.22		
Frampton et al. (2022)	San Francisco	2012–2015		Ambient	72 hr	Pearson	0.55		-0.66		0.93
	Chapel Hill	2012–2016		Ambient	72 hr	Pearson	0.17		0.01	0.06	0.59
	Rochester	2012–2017		Ambient	72 hr	Pearson	0.44		-0.36	0.3	0.6

Study	City	Year	Season	Spatial Scale	Averaging time	Correlation Type	PM _{2.5}	PM ₁₀	O ₃	SO ₂	CO
Mann et al. (2021)	Fresno	2002–2017	All	Residential address	1 wk	Not reported	0.84				
Krajewski et al. (2023)	North Carolina Birth Cohort	2003–2015		PM _{2.5} and NO ₂ – 1 km x 1 km based on hybrid spatial modeling O ₃ - census track based on downscaler modeling	Weekly critical windows	Pearson	0.183–0.185		from -0.147 to -0.109		
Mann et al. (2021)	Fresno	2002–2017	All	Residential address	1 mo	Not reported	0.83				
Sun et al. (2022)	Southern California	2007–2018		Residential address	1 mo	Pearson	0.61	0.31	-0.36		
Cassidy-Bushrow et al. (2020)	Detroit	Sep 2008 and June 2009	All	Residential address	1 mo	Pearson	0.52	0.09			
Jiao et al. (2023)	Southern California	2008–2018		Residential address	1 mo	Pearson	0.61	0.28	-0.39		
Sun et al. (2023)	Southern California	2008–2016		Residential address	1 mo	Pearson	0.64	0.3	-0.33		
Wesselink et al. (2023)	North American preconception cohort, U.S.	2012–2019		Residential address	menstrual cycle	Spearman	0.31		-0.38		
Wesselink et al. (2023)	North American preconception cohort, Canada	2012–2019		Residential address	menstrual cycle	Spearman	0.4		-0.3		

Study	City	Year	Season	Spatial Scale	Averaging time	Correlation Type	PM _{2.5}	PM ₁₀	O ₃	SO ₂	CO
Krajewski et al. (2023)	North Carolina Birth Cohort	2003–2015		PM _{2.5} and NO ₂ – 1 km x 1 km based on hybrid spatial modeling O ₃ - census track based on downscaler modeling	Trimesters	Pearson	0.169–0.174		from -0.25 to -0.21		
Mann et al. (2021)	Fresno	2002–2017	All	Residential address	3 mo	Not reported	0.86				
Mann et al. (2021)	Fresno	2002–2017	All	Residential address	6 mo	Not reported	0.74				
Stieb et al. (2016)	Canada			Postal code	9 mo	Spearman	0.61				
Krajewski et al. (2023)	North Carolina Birth Cohort	2003–2015		PM _{2.5} and NO ₂ – 1 km x 1 km based on hybrid spatial modeling O ₃ - census track based on downscaler modeling	Overall pregnancy	Pearson	0.46		0.026		
Mann et al. (2021)	Fresno	2002–2017	All	Residential address	1-yr average	Not reported	0.29				
Andersen et al. (2017)	EPIC-Turin, Italy	2008–2011		Residential address	1-yr average	Pearson	0.71	0.71			
	HUBRO, Norway			Residential address	1-yr average	Pearson	0.41	0.37			
	CEANS, Sweden			Residential address	1-yr average	Pearson	0.67	0.55			
	DCH, Denmark			Residential address	1-yr average	Pearson	0.56	0.71			

Study	City	Year	Season	Spatial Scale	Averaging time	Correlation Type	PM _{2.5}	PM ₁₀	O ₃	SO ₂	CO
	EPIC-NL, Netherlands			Residential address	1-yr average	Pearson	0.37	0.80			
	EPIC-Oxford, U.K.			Residential address	1-yr average	Pearson	0.86	0.51			
	VHM&PP, Austria			Residential address	1-yr average	Pearson	0.46	0.60			
Werder et al. (2024)	Gulf Study participants	2011–2013		Residential address	1-yr average	Pearson	0.1				
Wei et al. (2024)	Health Cost and Utilization Project, 14 States, U.S.	2000–2016		Zip code	1-yr average	Not reported			-0.065		
Wang et al. (2023a)	U.S., six cities in MESA air	2010–2012		Residential address	1-yr average	Not reported	0.71				
Berneron et al. (In Press)	San Diego County, California	2014–2017		Zip code level based on IDW	1-yr average	Pearson	0.8				
Bennett et al. (2023)	ARIC cohort from Minneapolis suburbs, MN; Jackson, MS; Forsyth County, NC; and Washington County, MD	2002–2011		Residential address	1-yr average	Pearson	0.71		24 hr averages: -0.64 8-hr averages: -0.12		0.82
Wesselink et al. (2023)	North American preconception cohort, U.S.	2012–2019		Residential address	1-yr average	Spearman	0.41		-0.45		

Study	City	Year	Season	Spatial Scale	Averaging time	Correlation Type	PM _{2.5}	PM ₁₀	O ₃	SO ₂	CO
Wesselink et al. (2023)	North American preconception cohort, Canada	2012–2019		Residential address	1-yr average	Spearman	0.54		-0.2		
Nobile et al. (2023)	Rome, Italy	2011–2019		Residential address	1-yr average	Pearson	0.79				
Liu et al. (2023)	nationwide Medicare beneficiaries	2001–2016		Zip code	3-yr average	Not reported	0.38		0.24 (May–Oct)		
So et al. (2020)	Demark	1990–2013		Residential address	3-yr average	Pearson	0.54				
Sørensen et al. (2022b)	Demark	1995–2017		Residential address	5-yr average	Spearman	0.8				
Brauer et al. (2019)	MAPLE study, Canada	2001–2016		PM _{2.5} at 1 km ² , NO ₂ at 100 m ² , and O ₃ at 10- or 21-km ² based on satellite and geospatial modeling	1-yr average	Not reported	0.553				
Brauer et al. (2019)	MAPLE study, Canada	2001–2016		PM _{2.5} at 1 km ² , NO ₂ at 100 m ² , and O ₃ at 10- or 21-km ² based on satellite and geospatial modeling	3-yr average	Not reported	0.582				

Study	City	Year	Season	Spatial Scale	Averaging time	Correlation Type	PM _{2.5}	PM ₁₀	O ₃	SO ₂	CO
Brauer et al. (2019)	MAPLE study, Canada	2001–2016		PM _{2.5} at 1 km ² , NO ₂ at 100 m ² , and O ₃ at 10- or 21-km ² based on satellite and geospatial modeling	8-yr average	Not reported	0.624				
Brauer et al. (2019)	MAPLE study, Canada	2001–2016		PM _{2.5} at 10 km ² , NO ₂ at 100 m ² , and O ₃ at 10- or 21-km ² based on satellite and geospatial modeling	3-yr moving average	Not reported	0.492		0.168		

List of abbreviations in alphabetical order: avg = average; CO = carbon monoxide; d = day(s); hr = hour(s); km² = kilometers squared ; m² = meters squared; MD = Maryland; MN = Minnesota; MS = Mississippi; NC = North Carolina; NO₂ = nitrogen dioxide; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 µm; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm; O₃ = ozone; SO₂ = sulfur dioxide; U.K. = United Kingdom; U.S. = United States; yr = year.

Table 2-1212 Correlations between ambient NO₂ and other traffic-emitted pollutants

Study	City	Year	Season	Spatial Scale	Averaging time	Correlation Type	UFP	CO	BC/EC	PAH
El-Sayed et al. (2021)	Jacksonville	Feb–April, 2020	Spring - covid lockdown	Ambient	24 hr	Pearson		0.19		
	Orlando	Feb–April, 2020	Spring - covid lockdown	Ambient	24 hr	Pearson		0.4		
		Feb–April, 2015–2019	Spring	Ambient	24 hr	Pearson		0.23		
	Miami	Feb–April, 2020	Spring - covid lockdown	Ambient	24 hr	Pearson		0.39		
		Feb–April, 2015–2019	Spring	Ambient	24 hr	Pearson		0.29		
Mann et al. (2021)	Fresno	2002–2017	All	Residential address	24 hr	Not reported			0.76	0.84 (PAHs with 4,5,6 rings)
Frampton et al. (2022)	San Francisco	2012–2015		Ambient	72 hr	Pearson		0.93		
	Chapel Hill	2012–2016		Ambient	72 hr	Pearson		0.59		
	Rochester	2012–2017		Ambient	72 hr	Pearson		0.6		

Study	City	Year	Season	Spatial Scale	Averaging time	Correlation Type	UFP	CO	BC/EC	PAH
Miller et al. (2019)	Detroit	May–June, 2009	Summer	Urban	14 d	Pearson				0.26 (total PAHs)
	Windsor	May–June, 2009	Summer	Urban	14 d	Pearson				0.4 (total PAHs)
Mann et al. (2021)	Fresno	2002–2017	All	Residential address	1 wk	Not reported			0.8	0.91 (PAHs with 4,5,6 rings)
Mann et al. (2021)	Fresno	2002–2017	All	Residential address	1 mo	Not reported			0.76	0.92 (PAHs with 4,5,6 rings)
Sun et al. (2023)	Southern California	2008–2016		Residential address	1 mo	Pearson			0.67	
Jiao et al. (2023)	Southern California	2008–2018		Residential address	1 mo	Pearson			0.62	
Sun et al. (2022)	Southern California	2007–2018		Residential address	1 mo	Pearson			0.62	
Hsu et al. (2023)	Boston, Massachusetts; ACCESS cohort	2001–2008		Residential address	3 mo	Spearman			0.53–0.57	
Mann et al. (2021)	Fresno	2002–2017	All	Residential address	3 mo	Not reported			0.78	0.94 (PAHs with 4,5,6 rings)

Study	City	Year	Season	Spatial Scale	Averaging time	Correlation Type	UFP	CO	BC/EC	PAH
Mann et al. (2021)	Fresno	2002–2017	All	Residential address	6 mo	Not reported			0.67	0.9 (PAHs with 4,5,6 rings)
Mann et al. (2021)	Fresno	2002–2017	All	Residential address	1 yr	Not reported			0.56	0.5 (PAHs with 4,5,6 rings)
Andersen et al. (2017)	EPIC-Umeå, Sweden	2008–2011		Residential address	1 yr	Pearson				
	HUBRO, Norway			Residential address	1 yr	Pearson			0.75	
	CEANS, Sweden			Residential address	1 yr	Pearson			0.9	
	DCH, Denmark			Residential address	1 yr	Pearson			0.7	
	EPIC-NL, Netherlands			Residential address	1 yr	Pearson			0.77	
	EPIC-Oxford, U.K.			Residential address	1 yr	Pearson			0.74	
	VHM&PP, Austria			Residential address	1 yr	Pearson			0.68	

Study	City	Year	Season	Spatial Scale	Averaging time	Correlation Type	UFP	CO	BC/EC	PAH
	EPIC-Turin, Italy			Residential address	1 yr	Pearson			0.93	
Wei et al. (2024)	U.S., 14 States	2000–2016		Zip code	1 yr	Not reported			0.725	
Wang et al. (2023a)	U.S., six cities in MESA air	2010–2012 NO ₂ 2007–2008 (PM constituents)		Residential address	1 yr	Not reported			0.83	
Bennett et al. (2023)	ARIC cohort from Minneapolis suburbs, MN; Jackson, MS; Forsyth County, NC; and Washington County, MD	2002–2011		Residential address	1 yr	Pearson			0.87	
Nobile et al. (2023)	Rome, Italy	2011–2019		Residential address	1 yr	Pearson	0.35		0.91	
Sørensen et al. (2022b)	Demark	1995–2017		Residential address	5 yr	Spearman	0.92		0.92	

List of abbreviations in alphabetical order: BC/EC = black carbon/elemental carbon; CO = carbon monoxide; d = day(s); hr = hour(s); mo = month(s); MD = Maryland; MN = Minnesota; MS = Mississippi; NC = North Carolina; NO₂ = nitrogen dioxide; PAH = polycyclic aromatic hydrocarbons; PM = particulate matter; UFP = ultrafine particles; U.K. = United Kingdom; U.S. = United States; wk = week (s); yr = year.

2.4.3 Ambient NO₂ and Noise

The 2016 Oxides of Nitrogen ISA assessed the correlations between traffic-related noise and NO₂ concentrations in ambient air. For short-term exposure studies, there was more evidence to consider the relationship between traffic-related noise and NO₂. These studies demonstrated moderate correlations between NO₂ concentrations in ambient air and noise levels, suggesting potential for confounding, especially when noise is decomposed by frequency. The relationship between noise and NO₂ or NO concentrations in ambient air was determined to be influenced by distance from road, noise frequency, fleet mix, and time of day. Long-term exposure studies were lacking to evaluate the association between NO₂ concentrations in ambient air and traffic-related noise. Since the release of the 2016 Oxides of Nitrogen ISA, more European-based long-term epidemiologic studies have been conducted, considering traffic-related noise as a potential confounder.

Emerging evidence related to the association between NO₂ concentrations in ambient air and traffic-related noise exposures is primarily from long-term exposure studies, presumably due to the improvement of spatial and temporal resolution of both NO₂ and noise modeling, allowing for more refined exposure assessments for both. A couple of these studies were U.S.-based, and the rest were European-based.

[Yu et al. \(2020\)](#) reported the correlation between NO₂ exposure and traffic-related noise for the cohort of the Sacramento Area Latino Study on Aging (SALSA) from 1998 to 2007. Noise exposure levels were calculated using the SoundPLAN software package, estimating annual average 24-hour noise levels at participants' baseline residential addresses. NO_x exposure was estimated using the CALINE4 line dispersion model based on participants' baseline residential addresses and 2002 traffic data. The annual average traffic-generated NO_x concentrations were moderately correlated with annual average residential-address noise levels, with a Pearson correlation coefficient of 0.41.

Another U.S.-based study was the Southern California Children's Health Study ([Franklin and Fruin, 2017](#)), which examined correlations between annual average NO_x concentrations and traffic noise for approximately 1,400 children in eight Greater Los Angeles communities: Anaheim, Glendora, Long Beach, Mira Loma, Riverside, Santa Barbara, San Dimas, and Upland. The CALINE4 line source dispersion model was used to estimate annual average NO_x concentrations from freeway and non-freeway roads, while traffic noise was assessed using the U.S. Federal Highway Administration's traffic noise model. A Pearson correlation coefficient of 0.53 was found between freeway NO_x and noise, and 0.33 for non-freeway NO_x and noise. A consistent pattern ($\rho = 0.53\text{--}0.65$) was observed across seven of the eight communities for freeway NO_x and noise, with Long Beach being the exception ($\rho = 0.13$).

Long-term exposure to NO₂ and traffic noise have been examined in multiple European-based cohort studies, including the Danish National Birth Cohort ([Pedersen et al., 2019](#)), Danish Nurse Cohort ([Cole-Hunter et al., 2022](#)), the Danish Diet, Cancer and Health study ([Roswall et al., 2017](#)), The European ESCAPE study cohorts ([Fuks et al., 2017](#)), the German 1000BRAINS cohort ([Lucht et al., 2022](#)), the

German longitudinal HNR cohort ([Ohlwein et al., 2019](#)), the Dutch Public Health Monitor national health survey ([Klompmaaker et al., 2019](#)), the Dutch PIAMA study ([Bloemsma et al., 2022](#)), the Spain Breathe Project ([Foraster et al., 2022](#)), the Spain INMA (Childhood and Environment) study ([Fernandez-Somoano et al., 2015](#)), the Swiss SAPALDIA study ([Eze et al., 2020](#)), the Swiss National Cohort ([Vienneau et al., 2023](#)), the UK Biobank ([Yang et al., 2023](#)), and a U.K. birth cohort in London ([Smith et al., 2020](#)).

These studies usually estimate annual average concentrations for both NO₂ and noise levels, typically modeled at the residential address level. Moderate correlation coefficients were consistently reported across these cohorts. Correlation coefficients ranged from 0.39 to 0.65 for the Danish cohorts ([Cole-Hunter et al., 2022](#); [Sørensen et al., 2022a](#); [Pedersen et al., 2019](#); [Roswall et al., 2017](#); [Hjortebjerg et al., 2016](#)), 0.30–0.37 for the German cohorts ([Lucht et al., 2022](#); [Ohlwein et al., 2019](#)), 0.23–0.51 for the Dutch cohorts ([Bloemsma et al., 2022](#); [Klompmaaker et al., 2019](#)), 0.40–0.41 for the Swiss cohorts ([Vienneau et al., 2023](#); [Eze et al., 2020](#)), and 0.41–0.46 for the U.K. cohorts ([Yang et al., 2023](#); [Smith et al., 2020](#)). The correlation range in the EU-based cohorts is similar to the scale of the correlation coefficients reported in the United States. In addition, these studies reported comparable correlation coefficients between noise and BC or PM_{2.5} absorbance.

These findings underscore the importance of considering traffic-related noise as a potential confounder in epidemiologic studies examining health impacts due to long-term exposures to ambient NO₂.

The association between noise frequency and oxides of nitrogen has been examined in recent studies, with varying results depending on the location, time period, and methodologies employed. A study conducted in NYC in August 2009 ([Ross et al., 2011](#)) analyzed second-resolution data over six 24-hour periods. The researchers found no correlation between unweighted noise of all frequencies and NO₂ concentration (Spearman $\rho = -0.01$), but observed a moderate correlation with NO concentration (Spearman $\rho = 0.43$). Notably, medium frequency noise exhibited stronger correlations with both NO₂ ($\rho = 0.22$) and NO ($\rho = 0.57$). During nighttime, high frequency noise demonstrated strong correlations with both NO₂ ($\rho = 0.83$) and NO ($\rho = 0.73$) concentrations.

A more recent study conducted in Long Beach, California in 2021 ([Fallah-Shorshani et al., 2024](#)) provided further insights into the relationship between NO₂ and traffic noise near a major highway. This research utilized simultaneous NO₂ and noise measurements taken at 1-minute intervals over an extended 28-day period. Employing advanced modeling techniques, particularly extreme gradient boosting (XGB), the researchers identified a strong correlation between NO₂ and specific noise frequencies. The XGB model achieved a high correlation ($\rho = 0.87$) for NO₂ prediction, with the most significant noise frequencies for predicting NO₂ being 40 Hz, 500 Hz, and 800 Hz. The prominence of the 40 Hz frequency suggests that lower frequency noise, typically associated with engine activity, serves as a reliable predictor of NO₂ concentrations. Despite these findings, the evidence linking traffic noise frequency, fleet mix, and NO_x concentrations remains limited. Given the evolving nature of vehicle fleets in recent years, further research is warranted to elucidate the complex relationships between these variables.

2.5 Implications for Epidemiologic Studies

Many air pollution epidemiologic studies use measured or modeled pollutant concentrations as surrogates for pollutant exposures. The use of such surrogates introduces exposure error, which refers to the bias and uncertainty associated with using concentration metrics to represent the actual exposure of an individual or population. [Richmond-Bryant and Long \(2020\)](#) described the sources of exposure measurement error as follows:

- **Instrument Error:** Happens when the concentration reported by a monitor differs from the true concentration due to measurement interference or other artifacts.
- **Time-Activity Error:** Arises when variations in exposure concentration over time are not captured, typically because exposure is measured or modeled at a single point rather than integrated over time and across locations.
- **Nonambient Source:** Occurs when nonambient exposures (e.g., due to indoor sources) obscure the contribution of ambient air pollutants to the total exposure.
- **Spatial Error:** Occurs when there is a deviation between the true exposure concentration at an individual's location and the concentration measured or modeled at a receptor location.
- **Model Misspecification:** Results from the omission of important prediction variables in models used to estimate exposure concentrations, leading to inaccuracies in exposure estimates.

These errors have been analyzed in detail in Chapter 1 and Section 2.3.2 of this chapter. These errors can be modeled as classical error and Berkson error ([Samoli and Butland, 2017](#)). Classical error is characterized by exposure estimates that are scattered around the true personal exposure and are independent of the level of the estimated exposure. In an epidemiologic study classical error can lead to bias in effect estimates, typically resulting in a negative bias where the true effect is underestimated. In contrast, Berkson error is defined as error scattered around the measured exposure surrogate (e.g., ambient concentration) and is independent of the true exposure. This error can also affect the precision of the effect estimate by inflating or reducing the standard error (SE). Without the presence of confounders, Berkson error does not bias health effect estimates, but it can lead to bias (generally toward null) in the presence of confounders ([Wei et al., 2022](#)). Exposure assessment methods in air pollution epidemiologic studies could introduce a combination of classical and Berkson errors, resulting in bias and increased imprecision in effect estimates ([Richmond-Bryant and Long, 2020](#)).

Exposure measurement errors could also be described as classical-like or Berkson-like errors when using models to represent exposures in lieu of measurements ([Szpiro et al., 2011](#)). As stated in the 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)), Berkson-like and classical-like errors share some characteristics with Berkson and classical errors, respectively, but with differences. Specifically, Berkson-like errors occur when the modeled exposure does not capture all of the variability in the true exposure. Berkson-like errors increase the variability around the health effect estimate in a manner similar to pure Berkson error, but Berkson-like errors are spatially correlated and not independent of predicted exposures, unlike pure Berkson errors. Hence, Berkson-like error can lead to bias of the health effect

estimate in either direction ([Szpiro and Paciorek, 2013](#)). Classical-like errors can add variability to predicted exposures and can bias health effect estimates in a manner similar to pure classical errors, but they differ from pure classical errors in that the variability in estimated exposures is also not independent across space.

Exposure measurement errors can impact the interpretation of findings in epidemiologic studies. When exposure measurement errors negatively bias effect estimates, a true effect may be larger than the observed effect and that true effect may not be detected. On the other hand, when exposure measurement errors positively bias effect estimates, the true health effect deviates away from null, which can potentially lead to an incorrect conclusion that a health effect association exists when the true effect estimate is not different from the null. Therefore, it is important to assess the impact of exposure measurement error on the findings of epidemiologic studies.

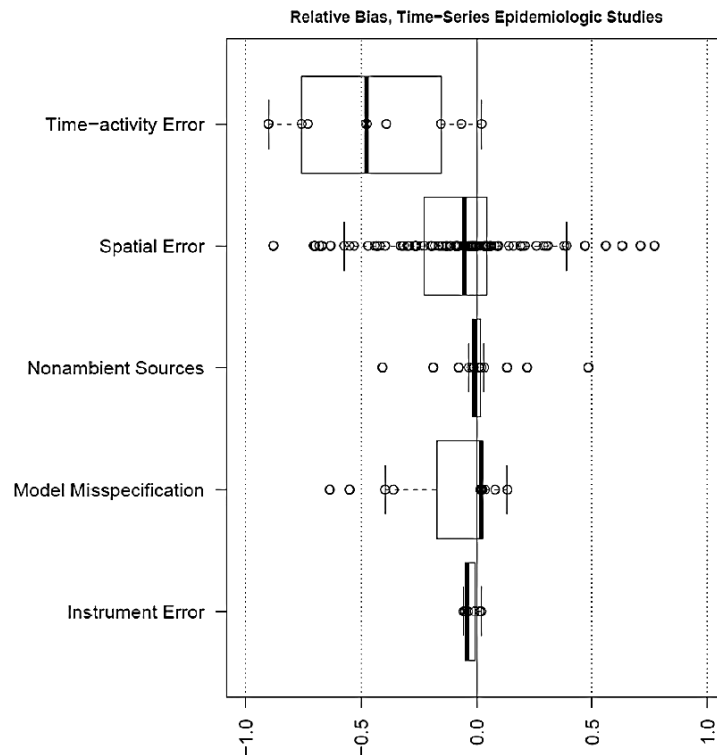
The following sub-sections further examine the implications of exposure measurement errors for epidemiologic studies evaluating short-term and long-term exposures. For each sub-section, major findings in the 2016 Oxides of Nitrogen ISA are summarized first, followed by describing the advancement of knowledge since the last ISA.

2.5.1 Short-term Exposure Studies

For epidemiologic studies examining short-term exposures, the 2016 Oxides of Nitrogen ISA assessed the impacts of exposure measurement error on community time-series studies and panel studies. Most community time-series studies used central site monitors to estimate human exposure to NO₂ in ambient air. Uncertainty associated with using central site measurements of NO₂ concentrations to represent personal exposure arise due to the difference between the temporal variability of the true exposure and the temporal variability of the central site exposure estimate. A critical component of exposure measurement error in time-series studies is the spatial representativeness of central site monitors, i.e., central site monitors might not capture the spatial variability of the concentration field. Nonambient contributions and differential infiltration of NO₂ can also add error or uncertainty to a health effect estimate. Instrument precision and accuracy are not thought to have a substantial influence on health effect estimates in time-series studies. Most simulation studies demonstrated exposure errors may widen the confidence intervals of the health effect estimate and bias the estimate towards the null [see Section 3.4.5 in the 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#))]. Given that, the 2016 Oxides of Nitrogen ISA concluded that reported health effect estimates in time-series studies of NO₂ exposure are potentially lower than true health effect estimates or that the reported confidence intervals around those health effect estimates are wider than the true confidence intervals. For panel studies, the 2016 Oxides of Nitrogen ISA did not reach conclusions about the magnitude and direction of error in the health effect estimates related to exposure error, due to the limited evidence available to evaluate the influence of exposure measurement error in these studies.

Since the release of the 2016 Oxides of Nitrogen ISA, exposure measurement and modeling techniques have advanced (see Section 2.3.1). A number of studies have further evaluated and quantified the impact of exposure error from different sources on epidemiologic studies examining short-term exposures ([Richmond-Bryant and Long, 2020](#)). Recent studies have evaluated the choice and goodness-of-fit of exposure models ([Butland et al., 2020](#); [Alexeeff et al., 2015](#)) and the potential deviation of predicted exposures from true exposures ([Butland et al., 2019](#)). In addition, since copollutant epidemiologic models have been widely used, a number of simulation studies have addressed the impacts of exposure measurement error in the context of copollutant models in time-series studies ([Evangelopoulos et al., 2021](#); [Evangelopoulos et al., 2020](#); [Dionisio et al., 2016b](#); [Dionisio et al., 2014](#)). Simulation studies have also been conducted to understand the impact of exposure measurement errors on panel studies ([Ponzi et al., 2020](#); [Deffner et al., 2018](#); [Liang et al., 2018](#)).

[Richmond-Bryant and Long \(2020\)](#) analyzed peer-reviewed studies which assessed the exposure measurement errors from different sources, i.e., instrument error, time-activity error, errors due to exposures to nonambient sources, spatial error, and errors due to model misspecifications. [Richmond-Bryant and Long \(2020\)](#) calculated relative bias of effect estimates (i.e., the ratio of the difference in effect estimates and the true effect) for exposure measurement error from each source across time-series epidemiologic studies across all criteria pollutants (see Figure 2-21): -0.03 ± 0.03 (mean $\pm$ standard deviation) for instrument error, -0.09 ± 0.24 for model misspecification error, 0.01 ± 0.16 for nonambient sources, -0.48 ± 0.34 for time-activity error, and -0.08 ± 0.28 for spatial error. [Richmond-Bryant and Long \(2020\)](#) found that the impacts of instrument error and nonambient source errors were near-zero, but time-activity error generally biased the effect estimates in time-series studies toward the null and increased the standard error around effect estimates. In most cases, spatial error also negatively biased effect estimates in time-series studies. However, positive bias might occur when the exposure estimates and the variance of error correlated with each other. The aforementioned general observations across criteria pollutants align with NO₂-specific findings. While the impact of NO₂ instrument error was found to be negligible (ranging from -0.043 to -0.05), time-activity error (-0.9 in a single study) and spatial error (-0.09 ± 0.32) demonstrated more substantial impacts on effect size estimates.



Source: [Richmond-Bryant and Long \(2020\)](#). Copyright permission pending.

Figure 2-21 Relative bias in health effect estimates across studies on all criteria pollutants for each exposure measurement error sources examined in the time-series epidemiologic studies; relative bias was calculated as the ratio of the difference in effect estimates and the true effect defined by study authors.

The past decade witnessed the advancement of exposure modeling approaches (e.g., air quality and exposure models) and their applications in epidemiologic studies. [Ebelt et al. \(2023\)](#) compared various NO₂ exposure assessment methods for their impact on health effect estimates in a time-series study of emergency department visits (2009 to 2013) in Atlanta, Georgia. The study area covered 192 residential ZIP codes within the 20-county Atlanta metropolitan statistical area. Eight different NO₂ exposure assessment methods were evaluated, ranging from central monitor measurements to modeling approaches, including CMAQ and LUR, all estimating daily NO₂ concentrations for the 2009 to 2013 period. At the central ZIP code where the central site monitor is located, most non-central monitor methods to estimate NO₂ concentrations were highly correlated with central monitor values ($\rho > 0.97$ for IDW, Kriging, and CMAQ-Kriging; $\rho > 0.80$ for SA), while CMAQ values showed the lowest correlation ($\rho = 0.47\text{--}0.79$). For cardiovascular ED visits, the central monitor showed a positive association (relative risk (RR): 1.010 [95% CI: 0.999, 1.021] per 10 ppb increase in NO₂). Non-central monitor metrics largely reproduced this association, with full spatial IDW and Kriging reporting stronger associations (RR: 1.016 and 1.020, respectively). Interestingly, CMAQ, CMAQ-data fusion, and LUR reported weaker or null associations when using full spatial data. For respiratory ED visits, the central monitor reported no

association (RR: 0.996 [95% CI: 0.989, 1.002] per 10 ppb increase). However, full spatial IDW and Kriging reported strong positive associations (RR: 1.018 and 1.026, respectively). CMAQ, CMAQ-data fusion, and LUR also reported positive associations, contrary to the central monitor results. These findings suggest that NO₂ concentrations used as a surrogate for exposure based on routinely-collected monitoring data were generally moderately correlated with NO₂ concentrations that use more sophisticated modeling approaches in Atlanta. However, the inconsistent health effects associations in models using AQS, CMAQ, and LUR-based techniques to estimate NO₂ highlight the need for cautious interpretation and thorough data characterization when using these complex modeling approaches in health studies.

Similar to measurement (e.g., AQS monitors), all models contain errors (see Section 2.3.1). [Butland et al. \(2020\)](#) conducted a simulation study to compare the performance of different air pollution models, including LUR, dispersion, and hybrid model (LUR and dispersion), in estimating exposure variables for epidemiologic analyses of air pollution and health. The simulation utilized a sample of 1,000 small geographical areas within London, U.K. Researchers simulated all-cause mortality and cardiovascular hospital admissions using "true" pollution data (a simulated dataset) with predefined effect parameters for short and long-term exposure in a multilevel Poisson model. The study compared four air pollution modeling approaches: LUR, dispersion models, hybrid models combining LUR with dispersion output as a spline, and generalized additive models integrating splines from both LUR and dispersion outputs. The researchers observed that the choice of exposure model can significantly impact health effect (i.e., all-cause mortality) association in epidemiologic studies. For example, short-term exposure-related health effects associated with NO₂ exposure can be biased from -38% for LUR to 6.6% for hybrid model, depending on which exposure models are used. Combining both LUR and dispersion predictions of NO₂ concentrations in a generalized additive model minimized bias (6.6%) in the association between health effects and estimated exposure to NO₂. This study demonstrates that the choice of exposure model is crucial in estimating the health effects of air pollution.

Exposure model evaluation has been further examined by ([Alexeeff et al., 2015](#)). Although the simulation study was for PM_{2.5}, the general principle applies to NO₂ exposures. In the simulation study, [Alexeeff et al. \(2015\)](#) tested how the goodness of fit of a kriging and LUR model impacts the short-term health effect estimates. [Alexeeff et al. \(2015\)](#) observed that LUR models generally performed better than a kriging model. Poor LUR model out-of-sample r^2 (i.e., reflecting model predictability) generally led to large biases towards the null in health effect estimates; however, the simulation also demonstrated that a high r^2 does not necessarily reduce the bias. Therefore, caution needs to be exercised for choosing exposure models based on model r^2 . As recommended by ([Dionisio et al., 2016a](#)), clear rationales are needed for selecting exposure metrics in an epidemiologic study, and the selection should not be solely based on statistical criteria.

Unsound model choice could lead to the deviation of estimated exposure from true exposure. [Butland et al. \(2019\)](#) conducted a single pollutant simulation study to characterize the impact of imperfect

NO₂ exposure estimates on the association with daily mortality in a time-series study. [Butland et al. \(2019\)](#) found health effect estimates were generally biased towards the null (-0.8 to -65.1%). However, under conditions of high correlation between modelled and “true” exposure (Pearson correlation coefficient = 0.9) and a small ratio of their variances (ratio = 0.5, i.e., modeled exposures have a lower variance than “true” exposures), the bias could deviate away from null (2.1–27.2%).

Additional realistic simulations were conducted for multipollutant time-series epidemiologic studies ([Evangelopoulos et al., 2021](#); [Evangelopoulos et al., 2020](#); [Dionisio et al., 2016b](#); [Dionisio et al., 2014](#)). Building on the work of ([Dionisio et al., 2014](#)), which was evaluated in the 2016 Oxides of Nitrogen ISA, [Dionisio et al. \(2016b\)](#) conducted a simulation study to quantify the impact of correlated measurement errors in time-series studies using ED visits for respiratory disease as an example in Atlanta. Substantial attenuation of RRs was observed for NO_x, decreasing from 1.05 (true RR) to 1.01, due to spatial error and population error. [Evangelopoulos et al. \(2021\)](#) observed “effect transferability” (i.e., “effect estimate is overestimated for the pollutant estimated with more error to the one estimated with less error”) in a copollutant time-series model containing NO₂ and PM_{2.5}. Effect transferability is due to the relative larger variability of errors (i.e., the variation of the errors) for NO₂ compared with PM_{2.5}, and results in underestimates of health impacts of NO₂. Interestingly, the sum of single pollutant model effect estimates was found closer to the summed true associations than those from multipollutant models ([Evangelopoulos et al., 2021](#)).

The impacts of exposure error on panel epidemiologic study results have also been evaluated through simulation ([Ponzi et al., 2020](#); [Deffner et al., 2018](#); [Liang et al., 2018](#)). [Deffner et al. \(2018\)](#) investigated the impact of a mixture of Berkson and classical errors on health effect estimates in the context of ultrafine particle measurements, although the insights from this study could apply to NO₂ panel studies when using real-time sensor measurements.

[Deffner et al. \(2018\)](#) reported that Berkson error does not cause bias in effect estimates but increases their variance, with attenuation factors close to 1 (i.e., no attenuation or bias). Classical error typically causes attenuation of effect estimates, biasing them towards 0, with attenuation factors ranging from 0.65 to 0.95. A mixture of classical and Berkson error causes attenuation similar to classical error alone, but to a different extent, with attenuation factors ranging from 0.75 to 0.97, depending on the proportion of each error type.

[Deffner et al. \(2018\)](#) also examined the impacts of autocorrelation on both classical and Berkson errors. Autocorrelated Berkson error does not cause bias but further increases estimate variance. Autocorrelated classical error generally inflates attenuation compared to uncorrelated error. For a mixture of autocorrelated classical and Berkson errors, the attenuation factor becomes more complex, with bias strongly dependent on both error magnitudes and autocorrelation coefficients. Across all error types, autocorrelation increased variability in attenuation factor estimates.

[Deffner et al. \(2018\)](#) illustrated the concepts stated above using the Augsburg Umweltstudie data on ultrafine particle exposure, and observed that the complex error structure had only a slight impact on effect estimates. The results indicate that complex measurement error structures may not always significantly impact effect estimates in environmental epidemiologic studies.

[Liang et al. \(2018\)](#) simulated bias observed when using near-road monitoring network as a surrogate of exposure for students living in dorms ranging from 20 m to 1.4 km from a highway in Atlanta. Bias toward null (i.e., $\beta = -0.401$ to -0.195 ; vs. “true” $\beta = -0.41$ which was defined by the author based on effect estimates in a previous study) was observed for the reduction of FEV₁ due to exposures to NO₂ measured at the near-road network. Similar effect attenuation was also observed by ([Ponzi et al., 2020](#)) in a panel study, linking NO₂ exposures omics outcomes in a panel study.

In summary, since the publication of the 2016 Oxides of Nitrogen ISA, significant advancements have been made in modeling approaches to estimate ambient NO₂ concentrations (see Section 2.3.1). Technically, models that more accurately capture the spatial and temporal variability of NO₂ can enhance exposure assessment and mitigate exposure measurement error in epidemiologic studies. Therefore, this improvement is crucial, as reliance solely on ambient monitoring data may introduce bias toward the null, potentially obscuring true associations between NO₂ exposure and health outcomes.

Nevertheless, the selection of an appropriate modeling approach remains critically important. High goodness-of-fit statistics and cross-validated r^2 values do not guarantee improved exposure estimates unless the model structure is well-justified and its applicability to the specific study context is clearly established. Furthermore, in multipollutant models, exposure measurement error can differ substantially across pollutants, complicating the interpretation of effect estimates. Pollutants with greater exposure measurement error, such as NO₂ compared with PM_{2.5}, may have attenuated effect sizes, making associations more difficult to detect. Therefore, the identification of robust associations between NO₂ and adverse health outcomes in such analyses strengthens the evidence that there is a positive association between NO₂ exposure and negative health effects.

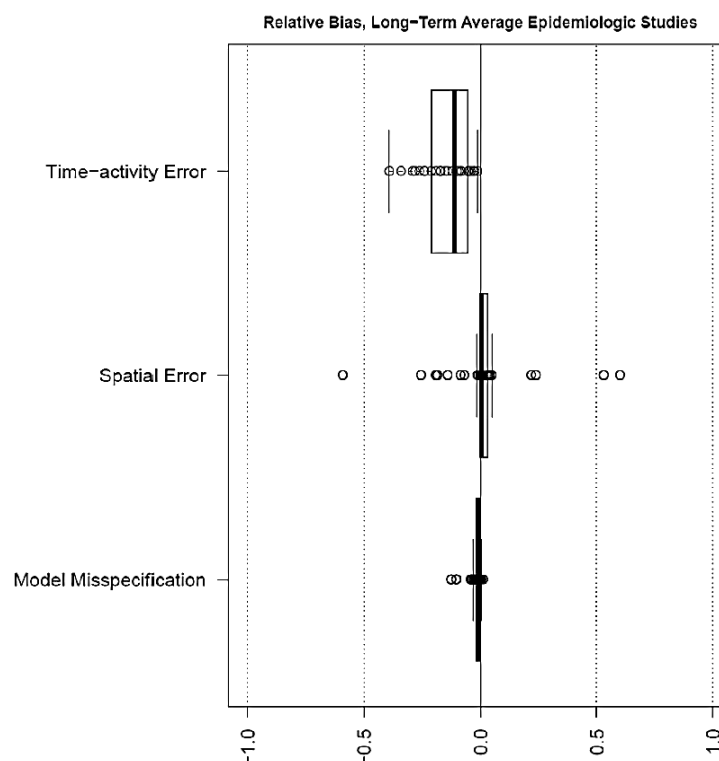
2.5.2 Long-Term Exposure Studies

Regarding long-term exposure epidemiologic studies, the 2016 Oxides of Nitrogen ISA identified uncertainties associated with using central site measurements of NO₂ concentrations in ambient air to represent personal exposure, due to the differential distributions of concentrations measured at a central site monitor and the distribution of true exposures. At the time when the 2016 Oxides of Nitrogen ISA was released, NO₂ concentrations in ambient air measured at central site monitors were often used to represent exposures when human health cohorts were compared among cities, though exposure models, including LUR models, CTMs, dispersion models, spatial smoothing models, and spatiotemporal models, had started gaining significant traction and widespread application in epidemiologic studies of long-term exposures. The 2016 Oxides of Nitrogen ISA concluded that (1) the influence of spatial exposure error on

health effect estimates varies with the particular study parameters, such as model selection and location; (2) nonambient contributions to the total personal exposure estimates would be expected to widen the confidence interval around the health effect estimates by adding noise to the exposure signal; (3) instrumentation bias could be anticipated to influence health effect estimates from epidemiologic studies of long-term NO₂ exposures in some situations due to the interference of NO_y, and (4) not accounting for time activity patterns of study participants adds uncertainty to exposure estimates obtained via spatial modeling such as LUR. Overall, the magnitude and direction of bias and the size of confidence intervals depend on differences between the distribution of true exposures and the distribution of concentrations estimated by the exposure assignment method.

Since the release of the 2016 Oxides of Nitrogen ISA, the impacts of exposure measurement errors from various sources on long-term health effect estimates have been further assessed and quantified ([Richmond-Bryant and Long, 2020](#)). The choice of exposure models and errors associated with models have been further evaluated for their impacts on health effects estimates ([Butland et al., 2020](#); [Samoli et al., 2020](#); [Butland et al., 2019](#); [Vlaanderen et al., 2019](#); [Fallah-Shorshani et al., 2018](#); [Alexeeff et al., 2016](#); [Smith et al., 2016](#); [Alexeeff et al., 2015](#); [Ragettli et al., 2014](#)).

[Richmond-Bryant and Long \(2020\)](#) analyzed long-term exposure studies that evaluate exposure error impacts on health outcomes. [Richmond-Bryant and Long \(2020\)](#) found most spatial errors did not bias the effect estimate. For long-term exposure studies reviewed, large uncertainties were observed when exposure concentrations were modeled with low spatial and temporal resolution for a spatially variable pollutant, such as NO₂. Figure 2-22 illustrates the relative bias (mean±standard deviation) on effect size estimates in long-term exposure studies across criteria pollutants, attributable to time-activity error (-0.14±0.10), spatial error (0.01±0.18), and model misclassification error (-0.01±0.01). These general relative bias estimates, which scale across criteria pollutants, are consistent with NO₂-specific effects: time-activity error (-0.14±0.10), spatial error (-0.03±0.12), and model misclassification error (-0.04±0.05).



Source: [Richmond-Bryant and Long \(2020\)](#). Copyright permission pending.

Figure 2-22 Relative bias across studies for each exposure measurement error sources examined in the long-term exposure studies.

LUR models, which are frequently used for modeling NO_x concentration surfaces, have been further evaluated for their impacts on long-term health effect estimates ([Vlaanderen et al., 2019](#); [Alexeeff et al., 2016](#); [Alexeeff et al., 2015](#)). [Alexeeff et al. \(2015\)](#) conducted a simulation study to evaluate kriging and LUR as tools to estimate exposure in epidemiologic studies examining long-term exposures. [Alexeeff et al. \(2015\)](#) concluded that LUR models performed better in studies of long-term exposures (compared to short-term exposures), although they slightly biased health effect estimates away from null – estimated $\beta = 1.013\text{--}1.050$ vs. true $\beta = 1.001$ for continuous endpoints, and estimated odds ratio = 2.072–2.111 vs. true odds ratio = 2.028. Consistent with the short-term simulation studies mentioned above, the authors warned that a high LUR model r^2 does not guarantee an unbiased effect estimates, even though r^2 is a helpful tool in assessing LUR model performance. [Alexeeff et al. \(2016\)](#) stated that a mis-specified LUR model, e.g., a LUR model omitting certain spatial covariates, could cause serious bias in health effect estimates, up to 20.3% toward null. The simulation conducted by [Alexeeff et al. \(2016\)](#) was for PM_{2.5} but the same principle should apply to NO₂, which is more spatially varying than PM_{2.5} and missing a spatial predictor could cause less reliable LUR results. [Vlaanderen et al. \(2019\)](#) identified positional error, which is a form of spatial error, as another aspect of applying LUR model in long-term exposure studies. Positional error refers to the differential precision of the geographical data used for LUR development and application. Less precise geographical data could attenuate health effect estimates toward null.

The benefit of using hybrid models for health effect estimates has been illustrated by [Butland et al. \(2020\)](#), who conducted a simulation study to estimate all-cause mortality and cardiovascular hospital admissions due to exposures to NO₂ estimated with LUR models, CMT/dispersion models, and the hybrid models including both LUR and CMT/dispersion models. Using a LUR model alone caused -98% to -68% bias for long-term exposure health effect estimates, and using dispersion models alone caused -52% to 0.5% bias. In contrast, hybrid models reduced the bias range to -28% to 11%.

In long-term health effect studies, residential outdoor concentrations have been used as an exposure surrogate for personal exposure to NO₂ in ambient air. The utilization of residential outdoor concentrations may mitigate systematic biases in longitudinal exposure studies that arise from the employment of monitoring stations geographically distant from exposed populations. However, this approach may potentially introduce errors due to the absence of data pertaining to individual activity patterns. [Ragettli et al. \(2014\)](#) investigated the sufficiency of using residential home outdoor concentration alone as the exposure surrogate, by comparing and considering (1) residential outdoor concentration, (2) work location or school outdoor concentrations, and (3) concentrations related to commute. [Ragettli et al. \(2014\)](#) observed a 12% bias toward null for health estimates if work or school outdoor concentrations are not considered. Another 4% bias emerged for individuals commuting between cities. The study highlights the importance of considering people's time-activity pattern in NO₂ exposure assessment.

Consistent with the aforementioned findings, studies conducted in Southern California, the Netherlands, and other locations have reported a bias towards null when time-activity patterns of study participants were not considered, although the magnitude of this bias was generally small ([Letellier et al., 2022](#); [Ntarladima et al., 2021](#); [McConnell et al., 2010](#)). [Letellier et al. \(2022\)](#) observed that the relative risk for metabolic syndrome decreased from (RR: 1.17 [95% CI: 1.07, 1.28]) when accounting for personal activity to (RR: 0.92 [95% CI: 0.84, 1.02]) when using only residence address concentrations. Similarly, [McConnell et al. \(2010\)](#) reported a slight reduction in the hazard ratio from (HR: 1.34 [95% CI: 1.07, 1.68]) when considering activity patterns to (HR: 1.32 [95% CI: 1.08, 1.61]) when using only home address data. [Ntarladima et al. \(2021\)](#) found that the decrease in FEV1 associated with per IQR increase in NO₂ concentrations changed marginally from (-1.5% [95% CI: -2.7, -0.3]) when considering both residential and non-residential exposures to (-1.4% [95% CI: -2.5, -0.2]) when considering residential outdoor exposure only.

[Smith et al. \(2016\)](#) also highlighted the role of time-activity pattern in NO₂ exposure assessment. Compared with modeled personal exposure to NO₂ of ambient origin, residential outdoor concentration is a more reliable surrogate ($\rho = 0.86$) for people staying home all day but is a less reliable indicator ($\rho = 0.39$) for people who walk or bike on the road. Similar conclusions were drawn by ([Fallah-Shorshani et al., 2018](#)) in Canada. In a single pollutant simulations study, [Butland et al. \(2019\)](#) suggested that exposure measurement errors are critically important for both NO₂ and PM_{2.5} and concluded that bias from

multipollutant measurement error can be severe, and in opposite directions or simultaneously positive or negative.

Both short-term and long-term exposure health studies are subject to exposure measurement errors which arise from instrument error, time-activity error, errors due to exposures to nonambient sources, spatial error, and errors due to model misspecifications. In reality, these errors have a combination of classical and Berkson components, which might bias health effect estimates and increase standard errors of health effect estimates, although it is noteworthy that Berkson error typically does not produce bias and classical error often results in errors toward the null. These errors appear not only in measurement studies but also in modeling studies. The severity of bias depends on (1) the true exposure variance relative to the error variance, (2) variance and covariance of true exposures and estimated exposure, and (3) the portion of classical- vs. Berkson errors in exposure estimates. Simulation studies conducted for both short-term and long-term health effect studies generally indicate that (1) exposure measurement error biases the health effect estimates toward the null in a majority of situations, although positive bias cannot be ruled out for both short-term and long-term exposure studies, and (2) improved exposure estimates reduce bias in health effect estimates but improved exposure estimates should not be judged solely based on statistical criteria but should be based on clear rationales for the purpose. It is of critical importance to recognize that bias towards the null implies that the true health effect would be larger than what the epidemiologic model indicates. Consequently, the observed health impacts could be important to consider even in the presence of this type of error.

2.6 Dosimetry of Inhaled Oxides of Nitrogen

2.6.1 Introduction

This section provides an overview of NO₂ and NO (the sum of which is NO_x) dosimetry. The dosimetry of other NO_y components beyond NO_x such as oxidized forms of N-containing molecules (e.g., nitric acid [HNO₃] and nitrous acid [NNO₂ or HONO]) are discussed only in terms of their formation as reaction products of NO_x following absorption in the respiratory tract. The NO₂ dosimetry discussion is largely unchanged since the 2016 Oxides of Nitrogen ISA ([U.S. EPA, 2016](#)), whereas the NO dosimetry discussion is largely new to this ISA. Attention is given to properties of inhaled NO₂ and NO that affect their absorption, distribution, metabolism, and elimination. Particular attention has been given to endogenous production of NO due to its numerous biological functions in the respiratory tract. Within dosimetry subsections, all values are expressed as mean±standard deviation unless otherwise stated.

The basic chemical properties of NO₂ and NO are provided in Table 2-13 and discussed in Sections 2.6.2 and 2.6.3. The biological chemistry of NO₂, NO, and other related species (e.g., nitrite, peroxyxynitrite, s-nitrosothiols) are reviewed by [Fukuto et al. \(2012\)](#). NO₂ is a radical species and a highly reactive oxidant gas. When inhaled, NO₂ forms oxidation and nitration products, which initiate numerous

responses at the cellular, tissue, and whole organ level of the respiratory system. NO is a radical species and a gas that is more selective in its reactivity than NO₂. Once inhaled, NO rapidly crosses the alveolar capillary barrier into the vascular compartment and readily binds to hemoglobin. Subsequent reactions with hemoglobin lead to the generation of circulating nitrate (NO₃⁻), nitrite (NO₂⁻), and methemoglobin.

Table 2-1313 Chemical properties of nitrogen dioxide (NO₂) and nitric oxide (NO)¹

NO ₂	NO
Radical species	Radical species
Somewhat hydrophobic	Very hydrophobic
Very reactive	Selectively reactive
Less diffusible	More diffusible
Reactions with: (1) unsaturated fatty acids (2) thiols (3) low molecular weight antioxidants	Radical-radical reactions with: (1) superoxide to form peroxynitrite (2) thiol radicals to form S nitrosothiols (3) organic peroxy radicals
Reacts with amino acids, proteins, and lipids to form nitrated species	Reacts with free radicals, heme-containing proteins, transition metals, and oxygen
Initiates radical reactions and lipid peroxidation, i.e., oxidative deterioration of lipids	Quenches free radical reactions and inhibits oxidation of lipids
Metabolites include nitrite and nitrate	Metabolites include nitrite and nitrate

List of abbreviations in alphabetical: NO = nitric oxide; NO₂ = nitrogen dioxide.

¹(Jomova et al., 2024; Radi, 2013; Hummel et al., 2006; Kirsch et al., 2002; Beckman and Koenol, 1996)

2.6.2 Dosimetry of Nitrogen Dioxide

NO₂ is a highly reactive gas that occurs as a radical (often indicated as •NO₂ in the literature due to its free radical nature) and a resonance structure wherein the unpaired electron is more localized to the nitrogen atom than either of the oxygen atoms (Kirsch et al., 2002). Once inhaled, NO₂ first encounters the aqueous phase of the epithelial lining fluid (ELF), which is a contiguous but biologically complex aqueous fluid layer that covers all of the respiratory tract surfaces (Bastacky et al., 1995). The ELF composition shows appreciable heterogeneity with respect to anatomic site and species. The ELF of alveolar surfaces and conducting airway surfaces has a monomolecular layer of surface active lipids (Bernhard et al., 2004; Hohlfeld, 2002; Mercer et al., 1994), largely fully saturated, which reduces surface tension and may provide a resistive barrier to the interfacial transfer of NO₂ (see Section 2.6.2.1). Upon dissolution into the ELF, NO₂ is converted from a gas to a nonelectrolyte solute, and thus becomes subject to partitioning and reaction/diffusion. Thus, the ELF represents the initial barrier between NO₂ contained within the respiratory tract gas phase and the underlying epithelia (Postlethwait and Bidani, 1990). NO₂ chemically interacts with antioxidants, unsaturated lipids, and other compounds in the ELF. It preferentially reacts with one electron donors (e.g., small molecular weight antioxidants, protein thiols, etc.), undergoes radical-radical addition reactions, may abstract allylic hydrogen atoms from polyunsaturated fatty acids, and through a complex series of reactions, can add to unsaturated fatty acids

to generate nitrolipids ([Bonacci et al., 2012](#); [Rudolph et al., 2010](#); [O'Donnell et al., 1999](#)). The compounds thought responsible, in large part, for the health effects of inhaled NO₂ are the reaction products themselves or the metabolites of these products in the ELF ([Adgent et al., 2012](#); [Velsor et al., 2003](#); [Velsor and Postlethwait, 1997](#); [Postlethwait and Bidani, 1994](#)).

2.6.2.1 Absorption of Nitrogen Dioxide

At the time of the 1993 Oxides of Nitrogen AQCD ([U.S. EPA, 1993](#)), it was thought that inhaled NO₂ probably reacted with the water molecules in the ELF to form HNO₂ and HNO₃. Some limited data suggested that the absorption of NO₂ was linked to reactive substrates in the ELF and subsequent nitrite (NO₂⁻) production. By the time of the 2008 Oxides of Nitrogen ISA ([U.S. EPA, 2008a](#)), chemical reactions between NO₂ and ELF substrates were more readily recognized as governing NO₂ absorption in the respiratory tract. The primary product of the chemical reactions of NO₂ in the respiratory tract is nitrite, which in the presence of red blood cells oxidized to nitrate.

2.6.2.1.1 Determinants of Nitrogen Dioxide Absorption in the Respiratory Tract

The absorption of inhaled NO₂ into the ELF is governed by a process termed “reactive absorption” that involves dissolution followed by chemical reaction with reactive substrates in the ELF ([Postlethwait and Bidani, 1990](#)), as well as reactions within the interfacial region. Due to the limited aqueous solubility of NO₂ and thus the rapid saturation of the aqueous phase interfacial thin film ([Bidani and Postlethwait, 1998](#)), the net flux of NO₂ into reactant-free water is constrained by the relatively slow direct reaction of NO₂ with water compared with its radical reactions with biological substrates. Rapid reactions with ELF substrates provide the net driving force for NO₂ mass transfer from the intra-pulmonary gas phase into the ELF ([Bidani and Postlethwait, 1998](#); [Postlethwait and Bidani, 1994](#); [Postlethwait et al., 1991a](#); [Postlethwait and Bidani, 1990](#)). Concentrations of “free” solute NO₂ are likely negligible due to reaction-mediated removal. Empirical evidence suggests that acute NO₂ uptake in the lower respiratory tract is rate governed by chemical reactions of NO₂ with ELF constituents (other than water) rather than by gas solubility in the ELF ([Postlethwait and Bidani, 1994, 1990](#)). Absorption increases with increasing temperature, an indication of chemical reaction rather than aqueous solubility since gas solubility decreases with increasing temperature ([Postlethwait and Bidani, 1990](#)).

[Postlethwait et al. \(1991b\)](#) proposed that inhaled NO₂ (≤10 ppm) did not penetrate the ELF to reach underlying sites and suggested that cytotoxicity likely was initiated by products formed during NO₂ reactions with ELF constituents. Subsequently, the reactive absorption of NO₂ was examined in a number of studies that sought to identify the substrates that predominantly drive NO₂ reactive absorption and to quantify the mass transfer kinetics of NO₂ in the respiratory tract. Uptake was observed to be first-order with respect to NO₂ at concentrations less than 10 ppm, to be aqueous substrate dependent, and to be

saturable, meaning that the absolute amount of NO₂ uptake would reach a maximum value even if reactive substrate concentrations were in significant excess ([Postlethwait et al., 1991a, b](#)).

The absorption of inhaled NO₂ is thought to be coupled with either radical-mediated hydrogen abstraction to form HNO₂ ([Postlethwait and Bidani, 1994, 1989](#)) or electron transfer from ELF anionic species that directly reduces NO₂ to nitrite ([Adgent et al., 2012](#)). Both mechanisms produce an organic radical from the initial ELF substrate. At physiologic pH, any formed HNO₂ subsequently dissociates to hydrogen ion (H⁺) and nitrite. The concentration of the resulting nitrite is likely insufficient to alter physiological function because basal nitrite levels may not change appreciably in either the respiratory tract or the circulation due to ambient NO₂ exposure. This is, in part, because nitrite will diffuse into the underlying epithelial cells and vascular space where, in the presence of red blood cells, it is oxidized to nitrate [([Postlethwait and Bidani, 1989](#); [Postlethwait and Mustafa, 1981](#)); Section 2.6.2.4]. Consequently, effects are probably attributable to the organic radical secondary oxidants formed ([Adgent et al., 2012](#); [Velsor et al., 2003](#); [Velsor and Postlethwait, 1997](#)) and/or to the proton load, although the ELF buffering capacity is anticipated to compensate for environmentally relevant exposure-related proton generation.

[Postlethwait et al. \(1995\)](#) investigated the preferred absorption substrates for NO₂ in the ELF lavaged from male Sprague-Dawley rats. A linear association was found between the first-order rate constant for NO₂ absorption and the relative concentration of the BAL fluid constituents. This suggests that concentration of the reactive substrates in the ELF, in part, determines the rate of NO₂ absorption. The absorption due to specific ELF constituents was also examined in chemically pure solutions. The most active hydrophilic substrates for NO₂ absorption were albumin, reduced cysteine, glutathione, ascorbate, and urate. Unsaturated fatty acids (such as oleic, linoleic, and linolenic; i.e., omega-9, omega-6, and omega-3, respectively) were also identified as active absorption substrates and thought to account for up to 20% of NO₂ absorption. Vitamins A and E exhibited the greatest reactivity of the substrates that were examined. The ELF of rodents and some non-human primates contains significantly less urate than the ELF of humans due to differences in nitrogenous waste metabolism. The authors concluded that ascorbate and glutathione were the primary NO₂ absorption substrates in rat ELF, whereas low concentrations of urate, vitamin A, and vitamin E were thought to preclude them from being appreciable substrates. [Postlethwait et al. \(1995\)](#) also found that the pulmonary surfactant component, dipalmitoyl phosphatidylcholine (DPPC), was relatively unreactive towards NO₂, and subsequent studies documented that compressed monomolecular interfacial films of DPPC inhibit NO₂ absorption in vitro ([Connor et al., 2001](#)). Determining whether surface active phospholipids (which comprise surfactant) inhibit NO₂ mass transfer in vivo remains an area of uncertainty since any manipulations that disrupt the surface tension-lowering actions of a surfactant will likely have numerous pathophysiologic consequences.

2.6.2.1.2 Reactions of Nitrogen Dioxide with Water and Solutes

At the time of the 1993 Oxides of Nitrogen AQCD ([U.S. EPA, 1993](#)), it was thought that inhaled NO₂ likely reacted with the water molecules in the ELF to form HNO₂ and HNO₃. Studies demonstrated that it is not NO₂ but instead the NO₂ dimer, dinitrogen tetroxide (N₂O₄), that reacts with water to yield NO₂⁻ and nitrate [NO₃⁻; ([Finlayson-Pitts et al., 2003](#); [Schwartz and White, 1983](#); [England and Corcoran, 1974](#))]. In aqueous solutions, NO₂ rapidly reacts with many solutes (e.g., ascorbate and urate), particularly those that are easily oxidized. At environmentally relevant concentrations of NO₂ (e.g., around 100 ppb), the direct reactions of NO₂ with dissolved substrates are important, at equilibrium, as demonstrated by very little N₂O₄ compared to NO₂. For example, using the difference in Gibbs energies for the formation of gaseous NO₂ and N₂O₄ ([Chase, 1998](#)), one can calculate that at equilibrium, when the concentration of NO₂ is 1,000 and 100 ppb, there are 1.48×10⁵ and 1.48×10⁶, respectively, molecules of NO₂ for each molecule of N₂O₄. That is, at environmental exposure levels there are approximately 1.5 million NO₂ molecules for each N₂O₄ molecule. At these concentrations, it is far more likely for NO₂ (compared to N₂O₄) to enter the aqueous milieu of the ELF. Ensuing reactions of NO₂ with dissolved reactive substrates are more likely than reaction with a second NO₂ molecule (to form N₂O₄). During uptake by pure water, all reactions occur via N₂O₄ regardless of the concentration of NO₂. However, in the presence of dissolved reactive substrates (as expected in ELF) and at low, environmentally relevant concentrations of NO₂, this process (i.e., reactions occurring via N₂O₄) is unlikely, and instead uptake occurs via direct reactions of NO₂ with reactive substrates. Reactive uptake of NO₂ in the ELF most likely entails direct reactions of NO₂ with small molecular weight antioxidants like glutathione (GSH), ascorbate, or urate.

2.6.2.1.3 Epithelial Lining Fluid Reactions with Nitrogen Dioxide

Small molecular weight antioxidants vary appreciably among species. Due to the lack of urate oxidase, humans, non-human primates, and select other species have increased levels of urate. Conversely, urate concentrations in rodents are low compared to humans. Such differences need to be recognized when considering preferential reactive absorption substrates and the profile of products formed via reaction with NO₂. Glutathione and ascorbate are the primary NO₂-absorption substrates in rat ELF with nearly a 1-to-1 stoichiometric yield of NO₂ uptake to nitrite formation, suggesting that one-electron reduction of NO₂ is a predominant reaction pathway that also yields the corresponding organic radical ([Postlethwait et al., 1995](#)).

Beyond cell-specific differential susceptibility and the airway lumen concentration of NO₂, site-specific injury depends on the rate of bioactive reaction product formation relative to the extent of quenching (detoxification) of these products within the ELF. [Velsor and Postlethwait \(1997\)](#) investigated the mechanisms of acute cellular injury from NO₂ exposure (7.5–10 ppm for 20 to 30 minutes for most experiments). In an in vitro test system using red blood cells, the maximal levels of membrane oxidation occurred at low antioxidant levels versus the complete absence of antioxidants or high antioxidant levels.

In the absence of antioxidants (reduced glutathione and/or ascorbate), there was minimal NO₂ absorption and minimal indication of membrane (lipid) oxidation relative to an air control exposure. At low concentrations of antioxidants, absorption of NO₂ led to membrane oxidation by superoxide (O₂^{•-}) and hydrogen peroxide (H₂O₂). The authors proposed that although increased absorption of NO₂ occurred at the higher antioxidant concentrations, little membrane oxidation occurred because the reactive species (i.e., O₂^{•-} and H₂O₂) generated during NO₂ absorption were quenched. A lower rate of NO₂ absorption occurred at low antioxidant concentrations, but the reactive oxidant species were not quenched and so were available to interact with the cell membrane. Further in vitro analyses also suggested that exposure-related responses may not be strictly linear with respect to the inhaled NO₂ dose (concentration and/or time) because NO₂ absorption and biologic target oxidation exhibited a bell-shaped function with respect to the initial antioxidant concentration ([Adgent et al., 2012](#); [Velsor et al., 2003](#)). Because the ELF varies throughout the respiratory tract, the heterogeneous distribution of epithelial injury observed following NO₂ exposures [see Section 13.2.2.4 of [U.S. EPA \(1993\)](#)]¹ may be explained, in part, by the ELF-dependent effects on local NO₂ uptake and product formation.

More recently, [Li et al. \(2024\)](#) investigated oxidative stress in pulmonary surfactant extracted from porcine lungs following exposures of up to 4-hours to 38,200 µg/m³ NO₂ (20 ppm) or 4,000 µg/m³ O₃ (2 ppm). Pulmonary surfactant is composed of phospholipid components, predominantly DPPC as well as surfactant proteins. With exposure of pulmonary surfactant to NO₂, reactive oxygen species (O₂^{•-}; H₂O₂; and hydroxyl radicals, •OH) and malondialdehyde (an end product of lipid peroxidation) increased linearly with exposure time. The effect of antioxidants (ascorbic acid, citric acid monohydrate, uric acid, and reduced glutathione) on oxidative product formation in the pulmonary surfactant following 60-minute exposures was examined for antioxidants individually at concentrations of 0, 100, 200, 300, and 400 µM. Like the results of [Velsor and Postlethwait \(1997\)](#), following NO₂ exposure [Li et al. \(2024\)](#) observed an increase in oxidative products (O₂^{•-}, H₂O₂, and •OH) with an increase in ascorbic acid from 0 to 100 µM and a decline in these oxidative products with further increases of ascorbic acid from 200 to 400 µM. All the oxidative products from NO₂ exposure showed a significant negative correlation with the concentrations from 0 to 400 µM of citric acid monohydrate and uric acid. Interestingly, the oxidative products from NO₂ exposure were positively correlated with the concentration of reduced glutathione. The authors concluded that O₂^{•-} is created by the reaction of NO₂ with antioxidants (primarily ascorbic acid and reduced glutathione). Subsequently, O₂^{•-} forms H₂O₂, and •OH through reactions with antioxidants and radical reactions. The reaction of •OH with unsaturated lipids leads to lipid peroxidation (as indicated by malondialdehyde increases) and further oxidative product formation. Despite the order of

¹The junction of the conducting airways with the gas exchange area (i.e., the centriacinar region) is the most sensitive region to NO₂-induced injury. The affected cell types are the ciliated cells of the bronchiolar epithelium and the Type 1 cells of the alveolar epithelium. In proximal alveoli, but not more distal alveoli, exposure to NO₂ can result in necrosis and sloughing of Type 1 alveolar epithelial cells followed by proliferation of, and replacement by, Type 2 alveolar epithelial cells. Ciliated cells located in terminal or respiratory bronchioles (this anatomical region does not occur in rats) lose some or all cilia or become necrotic and are shed from the epithelium.

magnitude difference in the NO₂ and O₃ exposure concentrations, O₃ exposure caused greater formation of reactive oxygen species and malondialdehyde.

While the above dose-response relationships have been documented in vitro, in vivo validation has not yet been well investigated due to the complexities in reproducibly modulating in situ ELF compositions. Importantly, such in vitro results are difficult to directly extrapolate to the in vivo situation, as precise rates of NO₂ uptake, and thus product formation, are a function of many factors including gas-phase NO₂ concentration, aqueous substrate concentrations, surface area, gas flow, and pH of the ELF ([Adgent et al., 2012](#); [Bidani and Postlethwait, 1998](#)). However, an in vivo study of healthy male albino mice (five weeks old) suggested that a low dose of ascorbate (25 mg/kg) may exacerbate inflammatory responses in terminal bronchial tissues following NO₂ exposure (20 ppm; four hour/day, 10 days); whereas at a higher dose of ascorbate (100 mg/kg), NO₂-exposed mice tissues were similar to tissues from filter air-exposed controls ([Zhang et al., 2010](#)). These in vivo responses seem parallel to those observed in vitro.

Antioxidant levels also vary spatially between lung regions and temporally with NO₂ exposure. While in vitro studies have clearly illustrated the role of antioxidants in mediating NO₂ uptake and membrane oxidation, the temporal dynamics of biological responses to NO₂ that occur in vivo are far more complex. Given the rapid reactions of inhaled NO₂ with various biological substrates, the short half-life of some primary and secondary reaction products as well as the continuous turnover of the ELF, specific chemical species do not likely persist at any given anatomic locale for an appreciable period of time. [Kelly et al. \(1996a\)](#) examined the effect of a 4-hour NO₂ (2,000 ppb) exposure on antioxidant levels in bronchial lavage (BL) fluid and BAL fluid of 44 healthy nonsmoking adults (19–45 years, median 24 years). The baseline concentrations of urate and ascorbate were strongly correlated between the BL fluid and BAL fluid within individuals ($r = 0.88$, $p < 0.001$; $r = 0.78$, $p = 0.001$; respectively); whereas the concentrations of glutathione in the BL fluid and BAL fluid were not correlated. At 1.5 hours after the NO₂ exposure, urate and ascorbate were significantly reduced in both lavage fractions, while glutathione levels were significantly increased but only in BL fluid. By 6-hours post-exposure, ascorbate levels had returned to baseline in both lavage fractions, but urate had become significantly increased in both lavage fractions and glutathione levels remained elevated in BL fluid. By 24-hours post-exposure, all antioxidant levels had returned to baseline. The levels of glutathione in BAL fluid did not change from baseline at any time point in response to NO₂ exposure.

The partial depletion of urate and ascorbate, but not glutathione, has also been observed with ex vivo exposure of human BAL fluid to NO₂. [Kelly et al. \(1996b\)](#) collected BAL fluid from male lung cancer patients ($n = 16$) and exposed the BAL fluid ex vivo at 37°C to NO₂ (50, 150, 400, 1,000 or 2,000 ppb; four hours) or O₃ (50 to 1,000 ppb; four hours). In a separate experiment, [Kelly and Tetley \(1997\)](#) also collected BAL fluid from lung cancer patients ($n = 12$; 54 ± 16 years) and exposed the BAL fluid ex vivo to NO₂ (50, 150, 400, or 1,000 ppb; four hours). Both studies found that NO₂ depletes urate and ascorbate linearly as a function of time with a slope that increases with increasing airborne NO₂

concentration, but only slightly lowers glutathione levels in a manner independent of the airborne NO₂ concentration. [Kelly et al. \(1996b\)](#) noted a differential consumption of the antioxidants, with urate loss being greater than that of ascorbate, which was lost at a much greater rate than glutathione. [Kelly and Tetley \(1997\)](#) found that the rates of urate and ascorbate consumption were correlated with their initial concentrations in the BAL fluid, such that higher initial antioxidant concentrations were associated with a greater rate of antioxidant depletion. Illustrating the complex interaction of antioxidants, these studies also suggest that glutathione oxidized by NO₂ may be again reduced by urate and/or ascorbate.

Human and animal results stemming from samples obtained after exposure should be viewed with appropriate caution. As detailed below, secondary reactions within the ELF, sample handling, and importantly, the temporal sequence of exposure relative to sample acquisition may all confound data interpretation. Because the ELF is a dynamic compartment, samples obtained after exposure (>30 minutes) may not reflect biochemical conditions present during exposure. This is a critical point, because while there is some value in quantifying the net short-term effects on ELF composition due to exposure, the biological consequences of exposure are largely a function of the ELF conditions during exposure, which initiate a cascade of events leading to alterations in cell signaling, cell injury, inflammation, and so forth. Thus, measurements of ELF components should be interpreted in the context of ELF turnover time, clearance of “stable” reaction products, and species generated and/or regenerated because of secondary redox reactions. Reported measurements may reflect net effects on individual antioxidants but lend limited insights into the initial reactions of NO₂ within the ELF, and by extension, into what bioactive products may be formed and how differences in ELF constituent profiles govern biological outcomes. A clear example is evident in the work of [Ford et al. \(2002\)](#), who characterized the reaction of the GSH radical (GS•) with urate (UH₂⁻) at a pH (6.0), below the recognized ELF pH (~6.8 to 7.0). NO₂ more readily reacts with glutathione than urate, producing GS• and NO₂⁻. However, the subsequent reaction GS• + UH₂⁻ → GSH + UH•⁻ has a rate constant of $\sim 3 \times 10^7 \text{ M}^{-1} \text{ sec}^{-1}$, which could translate to an initial NO₂ reaction with glutathione followed by reduction of the thiyl radical by urate. This could result in an apparent, but potentially inaccurate, conclusion of direct loss of urate during subsequent analyses. Consequently, an understanding of the precise and preferential substrates is needed to discern the genesis of species differences and the products formed that account for NO₂ exposure-related cellular perturbations.

Given the above considerations, variability in antioxidant concentrations and reactions among species may affect NO₂ dose and health outcomes. Guinea pigs and mice have a lower basal activity of glutathione transferase and glutathione peroxidase and lower α-tocopherol levels in the lung compared to rats ([Ichinose et al., 1988](#); [Sagai et al., 1987](#)). Human nasal lavage fluid has a high proportion of urate and low levels of ascorbate; whereas mice, rats, and guinea pigs have high levels of ascorbate and undetectable levels of urate. Glutathione is not detected in the nasal lavage fluid of most of these species, except monkeys. Guinea pigs and rats have a higher antioxidant-to-protein ratio in nasal lavage fluid and BAL fluid than humans ([Hatch, 1992](#)). The BAL fluid profile differs from that of the nasal lavage fluid. Humans have a higher proportion of glutathione and less ascorbate in their BAL fluid compared to guinea

pigs and rats ([Slade et al., 1993](#); [Hatch, 1992](#)). Rats have the highest antioxidant-to-protein mass ratio in their BAL fluid ([Slade et al., 1993](#)). Antioxidant defenses also vary with age ([Servais et al., 2005](#)) and exposure history ([Duan et al., 1996](#)). In the case of another reactive gas, O₃, some studies have found that differences in antioxidant levels among species and lung regions did not appear to be the primary factor affecting O₃-induced tissue injury ([Duan et al., 1996](#); [Duan et al., 1993](#)). However, close correlations have been observed between site-specific O₃ dose and the degree of epithelial injury, as well as the depletion of reduced glutathione in monkeys ([Plopper et al., 1998](#)). For both NO₂ and O₃, differences in reactive substrates among species and regions of the respiratory tract are recognized, but the importance of these differences in relation to tissue injury is not fully understood.

2.6.2.1.4 Reaction/Diffusion of Nitrogen Dioxide in the Epithelial Lining Fluid, Potential for Penetration to Underlying Cells

Because the uptake of NO₂ from inhaled air into the ELF is governed by reactive absorption (see Section 2.6.2.1.3), it may be postulated that rapid ELF reactions prevent NO₂ from reaching underlying respiratory tract tissues.² To evaluate this supposition, consideration must be given to the time required for NO₂ to diffuse through some thickness of the ELF versus the rate of NO₂ reactions with substrates in that ELF.

The ELF varies in composition and thickness with distal progression into the lung. The ELF of most of the tracheobronchial region may generally be described as consisting of two layers: an upper mucus layer and a periciliary layer, which surrounds the cilia ([Button et al., 2012](#); [Widdicombe, 2002](#); [Widdicombe and Widdicombe, 1995](#); [Van As, 1977](#)). The length of motile human cilia is about 7 µm in the distal nasal airways, trachea, and bronchi and around 5 µm in the bronchioles ([Yaghi et al., 2012](#); [Song et al., 2009](#); [Clary-Meinesz et al., 1997](#); [Widdicombe and Widdicombe, 1995](#)). In the healthy lung, the thickness of the periciliary layer is roughly the length of the cilia ([Song et al., 2009](#); [Widdicombe and Widdicombe, 1995](#)). This periciliary layer forms a continuous liquid lining over the tracheobronchial airways; whereas the upper mucus layer is discontinuous and diminishes or is absent in smaller bronchioles ([Widdicombe, 2002](#); [Van As, 1977](#)). The periciliary layer may be the only ELF layer (i.e., there is little to no overlaying mucus) in the ciliated airways of infants and healthy adults who are unaffected by pathology related to disease, infection, or other stimuli ([Bhaskar et al., 1985](#)).

The ELF covering the alveolar surface is considerably thinner than the periciliary layer found in the tracheobronchial region. The alveolar ELF consists of two layers: an upper surfactant layer and a subphase fluid ([Ng et al., 2004](#)). [Bastacky et al. \(1995\)](#) conducted a low-temperature scanning electron microscopy analysis of rapidly frozen samples (9 animals; 9,339 measurements) of rat lungs inflated to

²Some studies ([Chiu et al., 2024](#); [Nathanael and Wille, 2023](#); [Nathanael et al., 2022](#)) suggest that exogenous NO₂ and O₃ can react during inhalation to form highly reactive nitrate radicals that can rapidly react with amino acids and fatty acids. However, these studies are considered of questionable biological relevance since reactions were investigated in solvents of acetonitrile or 6M nitric acid with a pH<1.

approximately 80% total lung capacity. The alveolar ELF was found to be continuous, but of varied depth. Three distinct ELF areas were described: (1) a thin layer [0.1 μm median depth, geometric standard deviation (GSD) ~ 2.16]³ over relatively flat areas and comprising 80% of the alveolar surface, (2) a slightly thinner layer (0.08 μm , GSD ~ 1.79) over protruding features and accounting for 10% of the surface, and (3) a thick layer (0.66 μm , GSD ~ 2.18) occurring at alveolar junctions and accounting for 10% of the surface. Based on these distributions of thicknesses, 10% of the alveolar region is covered by an ELF layer of 0.04 μm or less. Presuming that these depths would also occur in humans at 80% total lung capacity and assuming isotropic expansion and contraction, depths should be expected to be 20–40% greater during normal tidal breathing (rest and light exercise) when the lung is inflated to between 50% and 60% total lung capacity averaged across the respiratory cycle. During tidal breathing, a median ELF depth of 0.12–0.14 μm would be expected over 80% of the alveolar surface with 10% of the alveolar surface having a median depth of around 0.05 μm or less. Considering the entire distribution of depths during tidal breathing, about 30, 60, and 90% of the alveolar surface would be estimated to have a lining layer thickness of less than or equal to 0.1, 0.2, and 0.5 μm , respectively.

The root mean square distance (d) that NO_2 can diffuse in some time (t) is given by the Einstein-Smoluchowski equation:

$$d = \sqrt{2Dt}$$

Equation 2-11

where D is the molecular diffusion coefficient of NO_2 . A D value for NO_2 in water at 25°C of $1.4 \times 10^{-9} \text{ m}^2/\text{second}$ has been reported and will be used in the calculations ([Ford et al., 2002](#)). In the lung, the D for NO_2 would be increased by temperature and decreased by the higher viscosity of the ELF compared to water.

The time available for diffusion can be estimated based on the half-time for reactions between NO_2 and reactive substrates, assuming pseudo first-order kinetics apply. This half-time (τ) has the form:

$$\tau = \frac{\ln(2)}{\sum_i^n k_i c_i}$$

Equation 2-12

³Although the authors stated that the distributions appeared to be log-normal, they did not report the geometric standard deviation (GSD) for the three distinct areas they described. The GSD values were calculated from 25, 50, and 75th percentiles of the distributions.

where $\sum_i^n k_i c_i$ is the summation of the products of the second-order rate constants (k_i) and substrate concentrations (c_i) for the primary reactive substances in the ELF.

Substituting τ for t in Equation 2-11 yields:

$$d = \sqrt{\frac{2D \ln(2)}{\sum_i^n k_i c_i}}$$

Equation 2-13

and approximates the distance NO_2 may diffuse before it chemically reacts with ELF constituent molecules (e.g., antioxidants, proteins, lipids). A similar approach of comparing the half-time in Equation 2-12 to the time for diffusion through the ELF or other phase boundaries such as a membrane bilayer (see Equation 2-11 and solve for t) was originally applied by [Pryor \(1992\)](#) and later by [Ford et al. \(2002\)](#).

In considering the classes of ELF biomolecules that react with NO_2 , one may focus on the water-soluble, small molecular weight antioxidants (e.g., ascorbate, urate, glutathione), which exist in the ELF in high concentrations and are very reactive toward NO_2 and consequently have large $k_i c_i$ terms. Lipids, on the other hand, would not be expected to considerably decrease the transit time of NO_2 because only those lipids containing fatty acids with two or more double bonds have significant reactivity towards NO_2 , and the lipids in the ELF are highly saturated.

The reaction rate constants of $3.5 \times 10^7 \text{ M}^{-1} \text{ sec}^{-1}$, $2 \times 10^7 \text{ M}^{-1} \text{ sec}^{-1}$, and $2 \times 10^7 \text{ M}^{-1} \text{ sec}^{-1}$ were assumed for the small molecular weight antioxidants ascorbate, urate, and glutathione, respectively ([Ford et al., 2002](#)). These rates were determined in solution using the pulse radiolysis fast kinetics technique. The kinetics of ascorbate and urate were directly monitored, while in the case of glutathione, ABTS²⁻ [2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)] was used to produce the intense chromophore ABTS^{•-} (note, here and elsewhere the superscript [•] designates a radical species) from its reaction with the glutathionyl radical.

Species and anatomical loci must be considered when selecting appropriate concentrations of reactive ELF biomolecules. Table 2-14 illustrates the small molecular weight antioxidant composition differences between human and rat bronchoalveolar ELF and the differences between human nasal and bronchoalveolar ELF ([Squadrito et al., 2010](#); [van der Vliet et al., 1999](#)). Predicted by Equation 2-13 and shown in Table 2-14, NO_2 is predicted to penetrate 0.2 to 0.6 μm into the ELF and would not likely reach airway tissues in the bronchi or bronchioles. Even extending the time for diffusion to 5τ , NO_2 would only be predicted to penetrate 0.5 to 1.3 μm into the ELF, which does not approach the 5 μm depth expected in the ciliated airways. However, minimal NO_2 diffusion through the ELF in the bronchi and bronchioles does not preclude the potential for NO_2 reactions with cilia or potential importance of reaction products reaching the underlying tissues in these regions.

Table 2-1414 Small molecular weight antioxidant concentrations in epithelial lining fluid and predicted penetration distances for nitrogen dioxide

Species—Site	Ascorbate	Urate	Glutathione	$\sum_i^n k_i c_i$ (sec ⁻¹)	ELF Penetration Distance μm	ELF Thickness μm
Substrate Concentration, c_i (μM)^a						
Human—nasal	28±19	225±105	<0.5	5.5×10^3	0.6	7 ^c
Human— bronchoalveolar	40±18	207±167	109±64	7.7×10^3	0.5	5–7 ^{c,d} <0.1–0.5 ^e
Rat—bronchoalveolar	1,004±325	81±27	43±15	3.8×10^4	0.2	5–7 ^{c,d} <0.1–0.5 ^e
Rate Constant, k_i (M⁻¹ sec⁻¹)^b						
	3.5×10^7	2×10^7	2×10^7			

List of abbreviations in alphabetical order: ELF = epithelial lining fluid.

^aSubstrate concentrations from [van der Vliet et al. \(1999\)](#) for human and [Squadrito et al. \(2010\)](#) for rat.

^bReaction rate constants from [Ford et al. \(2002\)](#).

^cBased on length of cilia.

^dTracheobronchial airways.

^eAlveolar airways.

In the alveolar region, the ELF is sufficiently thin (≤ 0.2 μm over 60% of the alveolar surface) for NO₂ to diffuse through. There are some important differences between the ELF of the alveolar region and the ELF of the tracheobronchial airways. In studies modeling NO₂ and O₃ uptake, a first-order rate constant has been assumed for the alveolar ELF, which is 60-times slower than that of the tracheobronchial ELF ([Miller et al., 1985](#); [Miller et al., 1982](#)). The slower reaction rate in the alveolar ELF would increase the estimated potential diffusion distance to nearly 4 μm, well beyond the depth of the alveolar ELF. Additionally, the presence of DPPC, a principle component of pulmonary surfactant, has been shown in vitro to reduce the uptake of NO₂ and O₃ by inhibiting their ability to reach and react with the underlying subphase fluid containing ascorbate, glutathione, and uric acid ([Connor et al., 2004](#); [Connor et al., 2001](#)). The physical properties of the interfacial saturated phospholipids may act to reduce the diffusivity of NO₂. Both the DPPC and the overall slower reaction rate in the alveolar ELF would increase diffusive resistance and increase the back diffusion of NO₂ from the surfactant into the gas phase. Nonetheless, the time for NO₂ diffusion through a 0.2 μm alveolar ELF is over two orders of magnitude faster than the NO₂ reaction rate half-time in the alveolar ELF. Thus, of the inhaled NO₂ reaching the alveolar region and diffusing into the ELF, an appreciable amount of NO₂ may reasonably be expected to diffuse through the ELF to reach underlying tissues over much of the alveolar surface. Reaction rates in these underlying tissues are expected to exceed those in the alveolar and tracheobronchial ELF and would more rapidly consume NO₂ ([Pryor, 1992](#); [Miller et al., 1985](#)).

2.6.2.2 Regional and Total Respiratory Absorption of Nitrogen Dioxide

An absorption fraction or fractional uptake of NO₂ was reported by a few studies which were discussed in Section 13.2.1.3 (Dosimetry of Nitrogen Dioxide) of the 1993 Oxides of Nitrogen AQCD ([U.S. EPA, 1993](#)). As recent studies are not available, the results of a few of these studies are briefly summarized here.

2.6.2.2.1 Experimental Studies of Nitrogen Dioxide Uptake

Upper Respiratory Tract Absorption

The nasal uptake (i.e., $1 - \text{exhaled NO}_2 \text{ concentration} / \text{inhaled NO}_2 \text{ concentration}$) of NO₂ has been experimentally measured in dogs, rabbits, and rats under conditions of unidirectional flow. [Yokoyama \(1968\)](#) reported $42.1 \pm 14.9\%$ uptake of NO₂ in the isolated nasal passages of two dogs (3.5 L/minute) and three rabbits (0.75 L/minute) exposed to between 4 and 41 ppm NO₂. Uptake did not appear to depend on the exposure concentration and was relatively constant over a 10- to 15-minute period. [Cavanagh and Morris \(1987\)](#) measured 28 and 25% uptake of NO₂ (40 ppm) in the noses of four naive and four previously exposed rats (0.10 L/minute; 4-hours; 40 ppm), respectively, and uptake was constant over the 24-minute period it was monitored.

[Kleinman and Mautz \(1991\)](#) measured NO₂ uptake in the upper airways during inhalation of six tracheostomized dogs exposed to 1 or 5 ppm NO₂. Uptake in the nasal passages was significantly greater at 1 ppm than at 5 ppm, although the magnitude of this difference was not reported. The mean uptake of NO₂ (1 ppm) in the nasal passages decreased from 80 to 70% as the ventilation rate increased from about 3 to 7 L/minute. During oral breathing, uptake was not dependent on concentration. The mean oral uptake of NO₂ (1 and 5 ppm) decreased from 60 to 30% as the ventilation rate increased from 3 to 7 L/minute. Although nasal uptake tended to be greater than oral uptake, the difference was not statistically significant. The tendency for greater nasal than oral uptake on NO₂ is consistent with that observed for O₃ as described in Chapter 5 of the 2013 ISA for Ozone and related photochemical oxidants ([U.S. EPA, 2013](#)).

Overall, NO₂ fractional absorption (uptake efficiency) in the upper respiratory tract is greater in the nasal passage than in the oral passage and decreases with increasing ventilation rates. As a result, a greater proportion of inhaled NO₂ is delivered to the lower respiratory tract at higher ventilation rates associated with exercise. In humans, exercise causes a shift in the breathing pattern from nasal to oronasal relative to rest. Because the nasal passages scrub gas-phase NO₂ more efficiently than the mouth and because uptake efficiency decreases with increasing flow, exercise delivers a disproportionately greater quantity of the inhaled mass to the lower respiratory tract, where the NO₂ is readily absorbed.

Lower Respiratory Tract Absorption

[Postlethwait and Mustafa \(1989\)](#) investigated the effect of exposure concentration and breathing frequency on the uptake of NO₂ in isolated perfused rat lungs. To evaluate the effect of exposure concentration, the lungs were exposed to NO₂ (4 to 20 ppm) while ventilated at 50 breaths/minute with a tidal volume (V_T) of 2.0 mL. To examine the effect of breathing frequency, the lungs were exposed to NO₂ (5 ppm) while ventilated at 30–90 breaths/minute with a V_T of 1.5 mL. All exposures were for 90-minutes. The uptake of NO₂ ranged from 59 to 72% with an average of 65% and was not affected by exposure concentration or breathing frequency. A combined regression analysis showed a linear relationship between NO₂ dose to the lungs and total inhaled dose. [Postlethwait and Mustafa \(1989\)](#) observed 59% NO₂ uptake in lungs ventilated at 30 breaths/minute with a V_T of 1.5 mL. [Postlethwait and Bidani \(1990\)](#) reported 67% NO₂ uptake in perfused and unperfused rat lungs ventilated at 48 breaths/minute with a V_T of 2.0 mL (FRC = 4 mL; 37°C) while exposed for 60 minutes (37°C) to 20 ppm NO₂. In another study, 73% uptake of NO₂ was reported for rat lungs ventilated at 50 breaths/minute with a V_T of 2.3 mL ([Postlethwait et al., 1992](#)).

In addition to measuring uptake in the upper respiratory tract, [Kleinman and Mautz \(1991\)](#) also measured NO₂ uptake in the lower respiratory tract of tracheostomized dogs. In general, about 90% NO₂ uptake in the lung was independent of ventilation rates from 3 to 16 L/minute.

Total Respiratory Tract Absorption

[Bauer et al. \(1986\)](#) measured the uptake of NO₂ (300 ppb) in 15 adults with asthma exposed for 30-minutes (20-minutes at rest, then 10 minutes exercising on a bicycle ergometer) via a mouthpiece during rest and exercise. There was a statistically significant increase in uptake from 72% during rest to 87% during exercise. The minute ventilation also increased from 8.1 L/minute during rest to 30.4 L/minute during exercise. Hence, exercise increased the NO₂ dose rate by 4.5 times in these individuals. In an earlier study by [Wagner \(1970\)](#), seven healthy adults inhaled a NO₂/NO mixture containing 0.3 to 7.2 ppm NO₂ for brief (but unspecified) periods. The average NO₂ uptake during 4.1 ppm and 7.2 ppm exposures was 82% during normal respiration (V_T, 0.4 L) and 92% during maximal respiration (V_T, 2 to 4 L). [Kleinman and Mautz \(1991\)](#) also measured the total respiratory tract uptake of NO₂ (5 ppm) in non-tracheostomized female beagle dogs standing at rest or exercising on a treadmill. The dogs breathed through a small face mask. Total respiratory tract uptake of NO₂ was 78% during rest and increased to 94% during exercise. This increase in uptake may largely be due to the increase in V_T from 0.18 L during rest to 0.27 L during exercise. Coupled with an increase in minute ventilation from 3.8 L/minute during rest to 10.5 L/minute during exercise, the dose rate of NO₂ was 3.3 times greater for the dogs during exercise than rest.

2.6.2.2.2 Dosimetry Models of Nitrogen Dioxide Uptake

Few theoretical studies have investigated NO₂ dosimetry [see Section 13.2.1.2 of [U.S. EPA \(1993\)](#)]. The original seminal NO₂ dosimetry model of [Miller et al. \(1982\)](#) was developed before much of the above information (see Section 2.6.2.1) regarding NO₂ reaction/diffusion within the ELF had been obtained. Section 2.6.2.1.3 discussed differences among species in ELF constitutions that NO₂ reacts with. However, accounting for such differences is beyond the scope of even more recent NO₂ modeling studies that also did not account for NO₂ reactions in differing ELF compositions among species [e.g., [Tsujino et al. \(2005\)](#)]. The production of NO₂ reaction products in the ELF and the movement of the reaction products to the tissues have not been modeled. The complex interactions among antioxidants, spatial differences in antioxidants across respiratory tract regions, temporal changes in ELF constituent levels in response to NO₂ exposure, and species differences in antioxidant defenses need to be considered in the next generation of dosimetric models. Current NO₂ dosimetry models are inadequate to put response data collected from animals and humans on a comparative footing with each other and with exposure conditions in epidemiologic studies.

2.6.2.3 Endogenous Generation, Metabolism, Distribution, and Elimination of Nitrogen Dioxide

NO₂ can be produced endogenously by various processes. First, the acidification of nitrite (specifically, $2\text{H}^+ + 2\text{NO}_2^- \rightarrow 2\text{HNO}_2 \rightarrow \text{H}_2\text{O} + \text{N}_2\text{O}_3 \rightarrow \text{NO} + \text{NO}_2 + \text{H}_2\text{O}$) (as can transpire in phagolysosomes) can produce NO₂ ([Kirsch et al., 2002](#)). Second, NO₂ can be produced by the decomposition of peroxynitrite (ONOO⁻) and/or the nitrosoperoxycarbonate (ONOOCO₂⁻) anion (specifically, $\text{ONOO}^- + \text{CO}_2 \rightarrow \text{ONOOCO}_2^- \rightarrow \text{CO}_3^{\bullet-} + \text{NO}_2$) ([Namba et al., 2022](#); [Kirsch et al., 2002](#)), and by the action of peroxidases when using nitrite and H₂O₂ as substrates ([Mishra et al., 2023](#)). Alternatively, the protonated form of ONOO⁻, peroxynitrous acid (ONOOH), can decompose at 28% efficiency to •OH and NO₂ with 72% to nitrate + H⁺ ([Namba et al., 2022](#); [Radi, 2013](#); [Kirsch et al., 2002](#)). Nitrated proteins form when tyrosine residues are first oxidized to a tyrosyl radical intermediately followed by radical–radical addition of NO₂ to irreversibly form 3-nitrotyrosine ([Mishra et al., 2023](#); [Namba et al., 2022](#); [Radi, 2013](#)). Since NO₂ is the terminal nitrating agent, the presence of nitrated proteins provides solid evidence for the endogenous production of NO₂. Computational models suggest that inhaled fine particulate matter (i.e., PM_{2.5}) and exogenous NO₂ can act synergistically to elevate nitrotyrosine and peroxynitrite levels in the ELF ([Lelieveld et al., 2024](#); [Mishra et al., 2023](#)). The modeled reactions of PM_{2.5} accounted for superoxide production, transition metals catalyzing formation of hydroxyl radicals through reactions of iron with H₂O₂ or organic peroxides.

Endogenous NO₂ is expected to increase with dietary consumption of nitrite and nitrate (the latter of which occurs in substantial concentrations in some leafy vegetables like spinach), as well as during immune responses and inflammation. There is no known antioxidant enzymatic process for the decomposition of NO₂, probably because NO₂ undergoes spontaneous reactions with small molecular

weight antioxidants, such as glutathione and ascorbate, which result in formation of nitrite and antioxidant radicals. These reactions are so fast that they only allow NO₂ to diffuse small distances in the submicron range before reacting (Table 2-14). NO₂ is slightly hydrophobic ([Squadrito and Postlethwait, 2009](#)) and faces no significant physical barriers to prevent it from readily traversing biological membranes. But due to its high reactivity, NO₂ is unlikely to become systemically distributed; therefore, its endogenous, steady-state levels in distant tissues are unlikely to be affected by inhaled NO₂.

Regarding the lung, understanding the balance between endogenous products and those derived from inhaled ambient NO₂ is a complex and challenging issue. Because inhaled NO₂ predominantly undergoes univalent reduction to nitrite during reactive absorption, changes in nitrite concentrations can be used as a surrogate for initial considerations of how inhaled NO₂ compares with that produced endogenously. For example, rat lung ELF contains low (μM to nM) levels of nitrite, with nitrate being substantially more prevalent. Due to salivary and gut microflora nitrate reductase activity and to reactions of nitrite, especially with heme proteins to yield nitrate, there is a constant cyclic flux between nitrite and nitrate, with nitrate being the primary excretion product in urine. In a rat, there would be a net accumulation of approximately 0.3 μmol of nitrite, assuming for simplicity a gas phase concentration of 200 ppb NO₂, a minute ventilation of 150 mL/minute, an exposure time of 4-hours, quantitative conversion of NO₂ to nitrite, 100% uptake efficiency, an ELF volume of 150 μL, and no ELF clearance [even though nitrite has been shown to diffuse out of the ELF quickly ([Postlethwait and Bidani, 1989](#))]. If the NO₂-derived nitrite were evenly distributed throughout the ELF pool, this would equate to an additional 2 mM concentration of nitrite. However, in vitro studies using isolated lungs have not reported increases of this magnitude consequent to 10–20 ppm NO₂ exposures, well above ambient concentrations, demonstrating that the ELF is a dynamic compartment and that small molecular weight reaction products (though charged) move readily from the respiratory tract surface to the vascular space.

[Floyd et al. \(2020\)](#) exposed healthy adults (10F, 2M; 26±4-years) for 90-minutes to 276.3±38.5 ppb NO₂ (copollutants not measured) from domestic gas cooker versus a control exposure 27.6±2.8 ppb without the cooker in operation. Plasma nitrite increased in association with the NO₂ exposure. During the period between 15 and 90 minutes of exposure, plasma nitrite levels were significantly (p<0.001) greater with NO₂ exposure (175 nM) compared to control (150 nM). Both systolic and diastolic blood pressure were decreased in a temporal fashion similar to the increases in plasma nitrite. This study suggests that inhaled NO₂ can acutely affect plasma nitrite levels. Thus, while inhaled NO₂ itself is not distributed systemically, its reaction products, nitrite and nitrate are found in the blood after acute NO₂ inhalation.

Although inhaled NO₂ may acutely increase plasma nitrite, the magnitude of that change should be considered in the context of biologically normal variations as caused by exercise. Following a maximal graded exercise test, nitrite levels are significantly increased by 39% (about 42 nM) in individuals (n = 41, 53.5±1.1-years) without peripheral vascular disease ([Allen et al., 2009](#)). The 42 nM increase in

plasma nitrite (an NO metabolite) which likely reflects increased in NO production for vasodilation exceeded the 25 nM increase in nitrite levels observed with a 90-minute inhalation of 276 ppb NO₂.

Both nitrite and nitrate levels are very diet dependent, and diet represents the primary source for both ions. The uptake of inhaled NO₂ may potentially increase levels of nitrite and/or other reaction products beyond levels endogenously occurring in the respiratory tract. Although environmental exposures at current ambient NO₂ concentrations would likely have a minimal effect on the overall balance of nitrite and nitrate outside the respiratory tract, recent human evidence demonstrates that high concentrations of inhaled NO₂ (200–300 ppb) can acutely increase human plasma nitrite levels comparable to those occurring with exercise. As discussed above, reaction of nitrite with a hydrogen ion (i.e., acidification of nitrite) is the first step in the production of endogenous NO₂. Thus, while inhaled NO₂ itself is not systemically distributed, its reaction products (namely nitrite) are systemically distributed and could contribute to endogenous NO₂ production outside the lungs.

2.6.2.4 Metabolism, Distribution, and Elimination of Products Derived from Inhaled Nitrogen Dioxide

As stated in Section 2.6.2.1.2, NO₂ absorption may generate some HNO₂, which subsequently dissociates to H⁺ and nitrite. Nitrite enters the underlying epithelial cells and subsequently the blood. In the presence of red blood cells and/or heme proteins, nitrite is oxidized to nitrate ([Postlethwait and Mustafa, 1981](#)). Nitrate is the primary stable oxide of nitrogen product, and it is subsequently excreted in the urine. Nitrate can also be converted to nitrite by bacterial reduction in saliva, the gastrointestinal tract, and the urinary bladder.

There has been concern that inhaled NO₂ may lead to the production of N-nitrosamines, many of which are carcinogenic because inhaled NO₂ can contribute to blood levels of nitrite and nitrate. Nitrite has been found to react with secondary amines to form N-nitrosamines. However, nitrosamines are not detected in tissues of animals exposed by inhalation to NO₂ 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 4 to 4.5 ppm NO₂ for 1-hour. However, NDMA was found in tissues when mice were simultaneously given oral doses of amidopyrine and 4-methylpyrazole, an inhibitor of NDMA metabolism. [Van Stee et al. \(1983\)](#) reported N-nitrosomorpholine (NMOR) production in mice gavaged with 1 g of morpholine/kg body weight per day and then exposed (five to six hours daily for five days) to 16.5–20.5 ppm NO₂. NMOR is a nitrosamine and potent animal carcinogen. The single site containing the greatest amount of NMOR was the gastrointestinal tract, as would be expected due to the pH-dependent facilitation of N-nitrosation chemistry. Later, [Van Stee et al. \(1995\)](#) exposed mice to approximately 20 ppm ¹⁵NO₂ and 1 g/kg morpholine simultaneously. N-nitrosomorpholine was found in the body of the exposed mice. Of the NMOR in the body, 98.4% was labeled with ¹⁵N which was derived from the inhaled ¹⁵NO₂, and 1.6% was derived presumably from endogenous sources.

Inhaled NO₂ may also be involved in the production of mutagenic (and carcinogenic) nitro derivatives of other coexposed compounds, such as polycyclic aromatic hydrocarbons (PAHs), via nitration reactions. [Miyanihi et al. \(1996\)](#) co-exposed rats, mice, guinea pigs, and hamsters to 20 ppm NO₂ and various PAHs (pyrene, fluoranthene, fluorene, anthracene, or chrysene). Nitro derivatives of these PAHs, which were found to be highly mutagenic in the Ames/*S. typhimurium* assay, were excreted in the urine of these animals. Specifically, the nitrated metabolites of pyrene (1-nitro-6/8-hydroxypyrene and 1-nitro-3-hydroxypyrene) was detected in the urine. Further studies indicated that these metabolites are nitrated by an ionic reaction in vivo after the hydroxylation of pyrene in the liver.

Endogenous NO₂ production and the cyclic inter-conversion of nitrite and nitrate may provide the precursors that drive formation of nitrosamine and other nitro derivatives. However, because NO₂ in ambient air contributes only modest amounts of nitrite/nitrate relative to dietary intake, any substantial contribution to systemic formation of nitrosamines and other nitro derivatives is not likely. The relative importance of inhaled NO₂ in formation of N-nitrosamines or other nitro derivatives has yet to be demonstrated.

2.6.3 Dosimetry of Nitric Oxide

NO gas in the luminal space of respiratory tract airways may be present due to: (1) inhalation of ambient NO and (2) transport from its endogenous production within pulmonary tissues, airspace surface inflammatory cells, and the blood. There are two clinical measurements involving NO: (1) diffusing capacity of inhaled NO and (2) exhaled NO concentration. The diffusing capacity of NO is related to NO absorption in the alveolar region (see Section 2.6.3.1). Exhaled NO concentration is related to NO production in the conducting airways (see Section 2.6.3.2). The net uptake of NO within the gas exchange region depends on the balance between intrapulmonary gas phase concentration and the inhaled ambient NO concentration. With endogenous NO production and consumption by chemical reactions, the uptake of inhaled exogenous NO is difficult to quantify and model (see Section 2.6.3.3). Both endogenous NO and inhaled NO can act as a pulmonary vasodilator that can reduce pulmonary hypertension, increase blood oxygenation, induce bronchodilation, and have antibacterial effects (see Section 2.6.3.4).

2.6.3.1 Absorption of Nitric Oxide

The absorption of inhaled NO proceeds similarly to oxygen and CO. [Roughton and Forster \(1957\)](#) described the total resistance to gas transfer from the lung (1/D_L) to the blood as the sum of a resistances in series:

$$1/D_L = 1/D_m + 1/\theta V_c$$

Equation 2-14

where: $1/D_m$ is the resistance to passive diffusion from the alveolar gas to the red blood cell membrane, and $1/\theta V_c$ is the transfer resistance of blood. The reciprocal of resistances is conductance or the ease of transfer. D_L is overall gas transfer [or inhaled gas diffusing capacity], D_m is alveolar-capillary membrane conductance [or the ease of inhaled gas diffusive transfer across the membrane], θ is the blood conductance for NO, and V_c is pulmonary capillary volume. For the case of NO gas transfer, D_L is replaced by notation of D_{NO} . The reaction rate of NO (θ_{NO}) is finite, but for clinical purposes it has been regarded as “operationally” infinite ([Hughes, 2013](#)). Considering the gas reaction rates for CO and NO, both are reaction and diffusion limited. With a reaction rate of ~250 faster than CO, NO is mainly diffusion limited, whereas CO is mainly reaction rate limited ([Hughes, 2013](#)).

[Borland et al. \(2014\)](#) suggested that last term in Eq. 2-14 represents the primary resistance to NO uptake and may be divided into diffusive resistances associated with plasma, the red cell membrane, red cell interior; and the NO reaction rate with hemoglobin as expressed in Eq. 2-15:

$$1/\theta V_c = 1/D_{plasma} + 1/D_{red\ cell\ membrane} + 1/D_{red\ cell\ interior} + 1/D_{reaction}$$

Equation 2-15

Due to the rapid reaction rate of NO with oxyhemoglobin (half-time, 4.6×10^{-4} to 3.7×10^{-3} - seconds), the NO reaction rate resistance is effectively zero ([Borland et al., 2014](#)). In series of experiments altering extracellular fluid resistance based on Fick’s law, the authors observed no effect of NO concentration in fluid, fluid viscosity, or red cell size (effecting the surface area for diffusion) on D_{NO} . However, D_{NO} was decreased by the addition of nitrite, which led to an increase in methemoglobin and a decrease in oxyhemoglobin. Within the red cell, the authors suggested that outer layers of hemoglobin were likely converted to methemoglobin, increasing the diffusive resistance inside the cell for NO reaction with oxyhemoglobin. The authors therefore concluded that the primary site of resistance in the blood compartment to NO uptake resides within the red cell interior. In a subsequent study, [Borland and Patel \(2024\)](#) concluded that NO uptake is limited by a boundary layer ($\leq 1\ \mu m$ between the capillary wall and red cell membrane) and pseudo first-order chemical reaction in the outer molecular layers of red cells. The authors also concluded that although some experimental studies suggest that the red cell membrane permeability limits NO transport into cells, there was no evidence to support the in vivo occurrence of red cell membrane resistance to NO transport.

While NO exists as a radical species, it is much less reactive than many other radical species. However, it selectively participates in radical–radical reactions such as with superoxide radical anions [$O_2^{\bullet-}$, which produces peroxynitrite ($ONOO^-$)], thiyl radicals [e.g., cysteine ($Cys^\bullet$), glutathione ($GS^\bullet$), which produce S-nitrosothiols ($RSNO$)], and organic peroxy radicals ([Madej et al., 2008](#); [Goldstein et al., 2004](#)). In addition, NO reacts with heme-containing proteins such as hemoglobin ([Pacher et al., 2007](#)).

Although the radical-based reactions generally occur at near diffusion-controlled rates, the prevalence of non-NO radical species at any given time is low. Thus, in terms of the overall uptake and tissue diffusion of NO within the lung, interception due to reactions is not expected to consume appreciable amounts of the total NO involved in mass transfer from the alveolar to the vascular space.

In both males ($n = 121$, 33 ± 11 -years) and females ($n = 81$, 29 ± 10 -years) stratified from superior/excellent to poor/very poor cardiorespiratory fitness, the diffusing capacity of NO was shown to increase with aerobic fitness ([Lippai et al., 1999](#)). The authors performed a stepwise multiple linear regression, which included independent variables age, age², body mass, height, sex, alveolar volume, and D_{NO} . Only D_{NO} was a significant predictor ($r^2 = 0.65$, $p < 0.001$) of peak oxygen consumption (a measure of aerobic fitness). The authors speculated that the effect of intensive fitness training on D_{NO} may reflect larger pulmonary capillary blood volume due to pulmonary angiogenesis and/or increased permeability at the level of the alveolar–capillary membrane.

2.6.3.2 Endogenous Generation of Nitric Oxide

Endogenous NO production is derived primarily from the catalytic activities of three major isoforms of nitric oxide synthase (NOS): endothelial (eNOS), inducible (iNOS), and neuronal (nNOS) ([Förstermann and Sessa, 2012](#); [Jiao et al., 2011](#)).

Estimates of nitrite and/or nitrate stemming from NO production via NOS suggest that endogenous NO production, even during inflammatory states, is modest compared to dietary intake; although, under specific conditions, plasma levels have been shown to transiently increase due to nondietary, endogenous biological activities. Additionally, endogenously generated NO may also occur from the acidification of nitrite in the presence of electron donors, such as within phagolysosomes, by dissociation of RSNO, and by complex interactions within red blood cells that likely lead to the release of NO ([Weitzberg et al., 2010](#)). In combination, these processes result in the appearance of NO within the intra-pulmonary gas phase, the concentration of which can be measured in expired breath.

2.6.3.2.1 Nitric Oxide Production and Exhalation

Endogenous NO production is derived primarily from the catalytic activities of the several isoforms of NOS ([Förstermann and Sessa, 2012](#)). Measured at the mouth, exhaled NO is derived from both the alveolar region and the ciliated airways of tracheobronchial region. In healthy nonsmoking individuals (2F, 5M; 46 ± 18 -years), NO production rates of 80 ± 50 and 190 ± 70 nL/minute were estimated for the ciliated airways and alveolar region, respectively ([Pietropaoli et al., 1999](#)). During a rapid exhalation, most exhaled NO derives from the alveolar region, and the contribution of exhaled NO from the ciliated airways increases with decreasing expiratory flow ([Jörres, 2000](#); [Pietropaoli et al., 1999](#)). For the clinical use of exhaled NO (eNO), a low mean exhalation flow rate of 50 mL/second ($\pm 10\%$) during

the time of the NO plateau generation is recommended ([ATS/ERS, 2005](#)). The low flow of 50 mL/second during the NO plateau provides a measure of NO being produced by the ciliated airways (i.e., the tracheobronchial or conducting airways).

Reported eNO from the lower respiratory tract span a broad range (~5 to >300 ppb), with nasal/sinus concentrations generally accepted as being greater than that measured from the lower respiratory tract. Sinus levels of NO exceed nasal NO by 1–2 orders of magnitude ([Lundberg et al., 1995](#)). Levels of eNO are affected by a variety of factors including disease state, diet, sex (or height), species, smoking history, and environmental exposures ([ATS/ERS, 2005](#); [Dweik et al., 2011](#)). Regarding disease state, eNO is increased with airway inflammation and acute infection. eNO is decreased in patients with cystic fibrosis (despite chronic infections), Human immunodeficiency virus infection, and pulmonary hypertension. In patients with asthma, after withdrawal from inhaled corticosteroids treatment, eNO increases in parallel to other markers of airway inflammation ([ATS/ERS, 2005](#)). Induction of iNOS in proximal or distal airways of asthmatics increases levels of NO in exhaled breath as high to as 20–50 ppb ([Alving et al., 1993](#); [Hamid et al., 1993](#)). Although eNO from the lower respiratory tract is increased by asthma, nasal NO is unaffected by asthma ([ATS/ERS, 2005](#); [Dweik et al., 2011](#)). Aerobic fitness may also affect eNO. Compared to healthy controls (3M, 7F; mean age 41-years), marathoners (10M; mean age 29-years) and runners (9M, 1F; mean age 31-years) showed statistically ($p \leq 0.015$) greater eNO and alveolar NO concentrations ([Thornadtsson et al., 2017](#)). However, effects of age and sex on these findings cannot be ruled out. Compared to the control group, production of NO in the conducting airways also tended to be increased in runners and was statistically ($p = 0.04$) increased in marathoners.

For the general U.S. population, results of the 2007 to 2011 National Health and Nutrition Examination Survey show a geometric mean eNO of 9.7 ppb in children ($n = 1,855$; 6–11 years of age; 10% with current asthma) and 13.3 ppb in teenagers and adults [$n = 11,420$; 12–80 years of age; 8% with current asthma ([See and Christiani, 2013](#)). In healthy, never-smokers [558 males (M), 573 females (F); 25–75 years of age], [Olin et al. \(2007\)](#) reported a geometric mean eNO of 16.6 ppb (95% reference interval, 6 to 47 ppb). The eNO levels increased with age and height of the individuals but did not depend on sex. In healthy children (23 M, 28 F; 1–5 years of age), a geometric mean eNO of 7 ppb [95% CI: 3, 12] has been reported ([van der Heijden et al., 2014](#)). The eNO levels in these children were unrelated to age, height, weight, or sex. The NO production rate (or NO output rate in nL/minute) is the product of eNO (ppb or nL/L) and sample flow (L/minute) ([ATS/ERS, 2005](#)). These eNO levels in ppb correspond to NO output rates of about 40–50 nL/minute from the lower respiratory tract of healthy adults and about 20–30 nL/minute for healthy children.

[Kharitonov et al. \(2005\)](#) reported nasal NO concentrations of 750 ppb (95% CI: 700, 810) in children [$n = 20$; 10 ± 3 years] and 900 ppb (95% CI: 870, 930) in adults ($n = 29$; 38 ± 11 years of age). Another study of healthy adults ($n = 10$; 18–35 years of age) found a nasal NO concentration of 670 ppb ([Sawyer et al., 2007](#)). Higher NO concentrations ($9,100 \pm 3,800$ ppb; $n = 5$) have been reported for the paranasal sinuses of healthy adults ([Lundberg et al., 1995](#)). Of the paranasal sinus regions, the ethmoid

sinuses (anterior and posterior), rather than the larger maxillary sinuses, appear to contribute the most NO to the nasal airway ([Spector et al., 2023](#)). Very little convective flow reaches the sinuses. Computational fluid dynamics modeling shows that diffusive transport is the mechanism for NO movement from the sinuses to the nasal airway where convective transport dominates ([Spector et al., 2023](#)). Mucosal inflammation can act to stimulate NO production while mucosal swelling may act to slow the diffusive transport of NO from the sinuses. However, asthma and current rhinitis do not appear to affect nasal NO concentrations ([Alexanderson et al., 2012](#); [Kharitonov et al., 2005](#)). Nasal NO is reduced by exercise ([ATS/ERS, 2005](#)). The nasal NO production rate (nL/minute) is the product of nasal NO concentration (ppb or nL/L) and sample flow (L/minute) ([Sawyer et al., 2007](#)). The nasal NO concentrations reported by [Kharitonov et al. \(2005\)](#) correspond to NO production rates of about 300 nL/minute for the nasal airways of adults with or without asthma and 230 nL/minute for children with or without asthma. Nasal NO output rates of healthy non-human primates are in the range of 200 to 450 nL/minute ([ATS/ERS, 2005](#)). With a NO output of 730 nL/minute, a large contribution to nasal NO appears to derive from the paranasal sinuses.

Smokers are recognized as having decreased eNO. A study of asymptomatic smokers (2F, 10M; 36±7-years) and age-matched healthy nonsmokers (10F, 12M; 36±13-years) showed that the decrease in eNO was due to a decreased rate of NO production in the conducting airways (smokers, 22±11 nL/minute; nonsmokers, 70±37 nL/minute), whereas NO production in the alveolar region (smokers, 203±104 nL/minute, mean±SD; nonsmokers, 209±74 nL/minute) was not reduced ([Pietropaoli et al., 2007](#)). For this study, with predominately males in the asymptomatic smoker group, a possible influence of sex cannot be ruled out. Another study ([Islam et al., 2017](#)) reported that NOS activity in smokers (40M; 30–40 years of age) was only 41% ($p<0.05$) of that in non-smokers (40M; 30–40 years of age). Supplementation with garlic for three-months increased the smokers' NOS activity by 2.2-times. Interestingly, the smokers' lung function (namely, forced expiratory volume in one-second, FEV₁), which was originally significantly ($p<0.01$) decreased by 16% relative to nonsmokers, showed significant ($p<0.01$) improvement with a 13% increase relative to their baseline FEV₁. Endogenous NO is known to affect mucus clearance and act as a bronchodilator (see Section 2.6.3.4).

2.6.3.2.2 Endogenous versus Inhaled Nitric Oxide Concentrations

Ambient concentrations of NO₂ and NO should be considered in relation to the NO concentrations generated endogenously. As discussed in more detail in Chapter 1, Section 1.5, median daily maximum one-hour NO₂ averages across most of the United States are generally between 10 and 20 ppb (see Chapter 1, Table 1-4). Ninety-ninth percentile daily maximum one-hour NO₂ averages are less than 55 ppb with maximum one-hour averages typically being about 100 ppb or less in the United States. [Matthaios et al. \(2020\)](#) measured NO₂ and NO concentrations inside and outside of four vehicles under differing vehicle ventilation preferences (e.g., open windows) in Birmingham, U.K. Outside the vehicle in an urban area, the median one-minute average concentrations were 63 ppb for NO₂ and 192 ppb for NO.

By comparison, in a sub-urban area, the median one-minute average concentrations were 31 ppb for NO₂ and 110 ppb for NO. As will be discussed in this section, these ambient concentrations are generally in the range of the NO concentrations occurring endogenously in some portions of the respiratory tract.

Using NO production rates based on [Kharitonov et al. \(2005\)](#), the nasal passages may contribute, on average, about 20 ppb NO to the lower respiratory tract during resting breathing in healthy children ($V_T = 333$ mL, 1.58 sec inspiration) and adults ($V_T = 625$ mL, 2.5 sec inspiration). Considering the rates reported by [Pietropaoli et al. \(1999\)](#), NO production in the ciliated airways and alveolar region may contribute another 18 ppb of NO to the alveolar concentration at the end of a breath. That is, at the end of inspiration, there may be close to 40 ppb NO in the alveolar region due the endogenous production in the respiratory tract. However, as discussed in Section 2.6.3.1, much of this NO whether endogenous or exogenous will be rapidly absorbed.

The primary product of NO in the vasculature is nitrite, which in the presence of red blood cells is oxidized to nitrate. Systemic nitrite and nitrate levels are highly dependent on diet (especially leafy vegetables like spinach) and not likely affected by ambient NO exposures. It is not known whether periods of high ambient NO exposure could alter endogenous NO production within the respiratory tract or alter pathways affected by endogenous NO.

2.6.3.3 Regional and Total Uptake of Nitric Oxide

2.6.3.3.1 Experimental Studies of Nitric Oxide Uptake

With endogenous production, the uptake of inhaled exogenous NO is difficult to quantify. In five healthy, non-smoking volunteers rebreathing from a bag at rest on a mouthpiece, [Geigel et al. \(1999\)](#) measured inhaled NO (exogenous NO) and exhaled NO (exogenous + endogenous NO). Nasal suction (8.4±4.6 lpm) was applied to avoid contamination from high nasopharynx NO concentrations on lower respiratory tract samples. The NO entered one nostril at about 3 ppb and exited the other nostril at 73±60 ppb (a nasal generation rate of 440±200 nL/minute). On average, for the lower respiratory tract, 1% more NO was exhaled than inhaled. For three volunteers that inhaled low NO concentrations (2–6 ppb), 2–5% more NO was exhaled than inhaled. For two volunteers that inhaled slightly higher NO concentrations (13 to 17 ppb), they exhaled 1 to 3% less NO than they inhaled, i.e., they absorbed NO from the environment.

2.6.3.3.2 Dosimetry Models of Nitric Oxide

There are a several models of NO transport and exchange (NO absorption and NO production) in the human respiratory tract. The models were developed to understand physiological influences on

clinical measurements of eNO and D_{NO}. These models have primarily focused on exhaled NO (eNO described in Section 2.6.3.2.1). The earliest and simplest of these used a two-compartment lung model (alveolar and tracheobronchial regions) to predict eNO as a function of expiratory flow ([George et al., 2004](#); [Jörres, 2000](#); [Tsoukias and George, 1998](#)). In general, the contribution of eNO from the ciliated airways increases with decreasing expiratory flow. As a step beyond these two-compartment models, [Karamaoun et al. \(2016\)](#) included a symmetric branching structure of the tracheobronchial airways. [Buess et al. \(2020\)](#) further extended eNO modeling to an asymmetric lung morphology to represent respiratory disease (e.g., chronic obstructive pulmonary disease). [Tsoukias et al. \(2000b\)](#) modeled effects of alveolar volume and regional time-constants on D_{NO}. [Tsoukias et al. \(2000a\)](#) subsequently measured D_{NO} in seven healthy nonsmoking men (28.4±3.8-years of age) and fitted model parameters to the observed D_{NO}. They reported that the healthy lung filled, in part, sequentially ($k = 0.51 \pm 0.35$; where $k = 0$ for uniform and $k = 1$ for completely nonsequential). While these latter D_{NO} modeling studies may be of importance for estimates of alveolar particle trapping and deposition, they do not provide information on NO reaction product formation or NO tissue doses in a manner that informs an understanding of respiratory effects due to inhaled NO. Accordingly, these models are not further discussed.

2.6.3.4 Biologic Function of Nitric Oxide

NO is involved in intracellular signaling in virtually every cell and tissue. In general, low levels of endogenous NO play important roles in cellular homeostasis, while higher levels are important in cellular adaptation and still higher levels are cytotoxic. Here the focus is primarily on NO function within the respiratory tract. Within the respiratory tract, NO is a pulmonary vasodilator that can reduce pulmonary hypertension, increase blood oxygenation, induce bronchodilation, and have antibacterial effects.

2.6.3.4.1 Endogenous Nitric Oxide

Endogenous NO is formed in the respiratory tract at high levels and affects host defense. NO produced by nasal airways plays a role in sinus host defense through bacteriostatic activity ([Lundberg et al., 1995](#)). In addition, macrophage and inflammatory neutrophils contain iNOS and may upregulate NO synthesis as part of their antimicrobial response ([Anderson et al., 2011](#); [Hill et al., 2010](#); [Nathan, 1992](#)). Another effect of endogenous NO on host defense is modulation of ciliary beat frequency ([Jain et al., 1993](#)). Specifically, NO derived from more distal airways was found to increase ciliary beat frequency. In the mouse trachea, NO (produced by nNOS), controls both the direction of mucus flow and ciliary beat frequency ([Mikhailik et al., 2021](#)). The action of nNOS on the beat frequency is mediated by guanylate cyclase. Nasal NO is decreased in individuals with ciliary dyskinesia, also known as immotile ciliary syndrome, and in patients with cystic fibrosis ([ATS/ERS, 2005](#)).

NO produced by nasal airways increases blood oxygenation in humans through effects on pulmonary vascular tone and blood flow in the lower respiratory tract. In six of eight healthy individuals, a comparison of nasal and oral breathing demonstrated that nasal airway NO enhanced transcutaneous oxygen tension by 10% ([Lundberg et al., 1996](#)). In six of six intubated patients undergoing long-term mechanical ventilation, nasal airway NO increased arterial oxygenation by 18%. Similarly, during oral ventilation, a 20% increase in arterial oxygenation was seen when 100 ppm NO was delivered to patients. Because NO has a high affinity for heme-bound iron, many of its actions are related to its interactions with heme proteins ([Hill et al., 2010](#)). For example, activation of the heme protein, guanylate cyclase, is responsible for smooth muscle relaxation and vasodilation of pulmonary and systemic vessels. Additionally, endogenous NO has been shown to act as a bronchodilator ([Belvisi et al., 1992](#)). Nitrated (or nitro) fatty acids have a direct relaxing effect on smooth muscle, perhaps even on airway smooth muscle ([Que et al., 2009](#); [Lima et al., 2005](#)). In addition, RSNOs are known to be bronchodilators ([Que et al., 2009](#)).

Endogenous NO is also associated with endothelial function and vasodilation outside the respiratory tract. Nitrite, the primary product of NO in the vasculature, has been found to protect against ischemia-reperfusion injury in the heart and other organs ([Weitzberg and Lundberg, 2013](#)). Both systolic and diastolic blood pressure have been shown to acutely decrease in temporal alignment with increases in plasma nitrite [Floyd et al. \(2020\)](#). [Allen et al. \(2009\)](#) reported baseline nitrite levels of 94 ± 13 nM in individuals without vascular disease ($n = 41$, 53.5 ± 1.1 -years), 79 ± 9 nM in diabetics ($n = 11$, 61.2 ± 1.7 -years), and 112 ± 20 nM in individuals with diagnosed peripheral arterial disease ($n = 29$, 67.2 ± 2.2 -years). These differences in plasma nitrite were not statistically different among group. Nitrate levels in these same groups were 14 ± 2 μ M, 41 ± 5 μ M, and 26 ± 4 μ M, respectively. The nitrate level in the diabetics was significantly greater than observed in the individuals without vascular disease. Following a maximal graded exercise test, [Allen et al. \(2009\)](#) reported nitrite levels significantly increased by 39% in individuals without vascular disease, were not significantly affected in the diabetics (16% decrease), and were significantly decreased by 44% in the group with peripheral arterial disease. Nitrate levels were not significantly affected by exercise in any group. The authors concluded that their results support reduced endothelial health and reduced NO production in response to exercise tests in diabetics and those with peripheral arterial disease. In the individuals without peripheral vascular disease, the increase in plasma nitrite reflects a natural increase in NO (which degrades to nitrite) production for vasodilation during exercise.

While both eNOS and iNOS contribute to NO production in the lung, the relatively low levels of NO produced by eNOS are thought to be more important in metabolic homeostasis ([Ahmad et al., 2011](#)). Some evidence points to a role of iNOS-derived NO in the pathogenesis of asthma because it has been correlated with inflammation, epithelial injury, and clinical exacerbations of asthma ([Anderson et al., 2011](#)). Furthermore, iNOS was upregulated to a greater extent in the distal airways than in more proximal airways of asthmatics. This is of interest because asthma is a disease of the small airways. Signaling functions of NO may be altered in the presence of acute inflammation ([Hill et al., 2010](#)), which is

characterized by enhanced levels of superoxide. Relative to control, ovalbumin sensitized rats showed statistically significant increases in serum oxidant levels (nitrite, nitrate, and malondialdehyde) and decreases levels of antioxidants (catalase, superoxide dismutase, and thiol) ([Shakeri et al., 2023](#)). In sensitized rats treated with an anti-inflammatory (allium cepa or dexamethasone), there was a significant reduction nitrite and nitrate levels relative to the sensitized rats. All markers of lung injury (interstitial inflammation, fibrosis, emphysema, epithelial damage) tended to be reduced by anti-inflammatory treatment compared to sensitized rats. Superoxide dismutase levels rebounded in anti-inflammatory treated rats relative sensitized rats but remained reduced relative to control animals. Superoxide reacts with NO to form peroxynitrite, which has been shown in animal models to play a role in the pathogenesis of allergic airway disease.

Endogenous NO has known pro-oxidant and antioxidant effects. As an antioxidant, NO reacts with free radicals and inhibits lipid oxidation ([Hummel et al., 2006](#); [Beckman and Koenol, 1996](#)). Oxidative stress results from excess oxidant production (reactive oxygen species and reactive nitrogen species) relative to elimination by antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase ([Jomova et al., 2024](#)). At high NO concentrations, NO out competes superoxide dismutase to react with superoxide radicals to form peroxynitrite ([Jomova et al., 2024](#); [Beckman and Koenol, 1996](#)). Peroxynitrite modifies proteins by oxidation or nitration of tyrosine, tryptophan, methionine, and other amino acid residues ([Radi, 2013](#)). In short, reactive oxygen species and reactive nitrogen species may cause damage to all biomolecules, including proteins, Deoxyribonucleic acid (DNA), and membrane lipids. It has been suggested that iNOS, activated by proinflammatory cytokines, may play an important role in the pathophysiology of heart failure ([Ishibashi et al., 2008](#)). Computational models suggest that inhaled fine particulate matter (i.e., PM_{2.5}) and inhaled NO₂ can act synergistically to elevate nitrotyrosine and peroxynitrite levels in the ELF ([Mishra et al., 2023](#)) and that elevated endogenous NO production caused by some inflammatory disorders can further exacerbate oxidative stress ([Lelieveld et al., 2024](#)). Possibly indicating systemic oxidative stress, recent evidence suggests that elevated total serum NO_x (nitrite + nitrate) levels are a risk factor for all-cause mortality and heart failure ([Namba et al., 2022](#)).

2.6.3.4.2 Exogenous Inhaled Nitric Oxide as a Therapeutic

Inhaled NO is a pulmonary vasodilator that can reduce pulmonary hypertension, increase blood oxygenation, induce bronchodilation, and have antibacterial effects. These properties have led to its use in the clinical setting. Therapeutic treatments may involve very high inhaled NO concentrations relative to ambient NO and endogenous NO concentrations. Some therapeutic NO studies are discussed here to highlight its biological activity in the respiratory tract.

Inhaled NO rapidly reacts with soluble guanylate cyclase in the pulmonary arterial smooth muscle. NO decreases pulmonary vascular pressure and relaxes the pulmonary vascular smooth muscle

through increased formation of the second-messenger cyclic guanylyl monophosphate ([Hill et al., 2010](#)). At the same time, inhaled NO rapidly diffuses into the circulation and reacts with red blood cell hemoglobin to form nitrosylhemoglobin, which is subsequently oxidized to methemoglobin and nitrate ([Beckman and Koenol, 1996](#)). Redox reactions of NO and transition metals, such as iron and copper, facilitate S-nitrosylation of protein and nonprotein thiols. Binding of NO to iron- and copper-containing proteins in the mitochondria may play an important role in mitochondrial respiration. NO also rapidly reacts with superoxide, an oxygen-derived radical species, to produce the potent oxidant peroxynitrite ([Hill et al., 2010](#)). Peroxynitrite subsequently reacts with CO₂ to form the nitrosoperoxylcarbonate anion, followed by decomposition to carbonate radical and NO₂.

Both animal and human studies of inhaled NO have demonstrated reductions of pulmonary hypertension. Inhaled NO has the potential for selective pulmonary vasodilation. Inhaled NO (1, 5, 20, and 80 ppm) selectively dilated pulmonary blood vessels, improved ventilation-perfusion mismatch, and reduced hypoxemia-induced pulmonary vascular resistance in a pig model ([Lovich et al., 2011](#)). An inhibition of endogenous NO formation in infants impedes the pulmonary vasodilation normally induced by breathing. The systematic review by [Barrington et al. \(2017\)](#) found that inhalation of 20 ppm NO was an effective treatment for infants less than one-month of age with hypoxic respiratory failure. However, due to inconsistencies in the methods of the studies reviewed, definitive conclusions related to effects on pulmonary hypertension could not be reached.

Following delivery of 160 ppm NO (30 min, twice daily) to COVID-19 patients (13F, 16M; median age 50-years), decreased respiratory rate ($p < 0.05$) in tachypneic patients and increased systemic oxygenation ($p < 0.05$) in hypoxemic patients ([Safaei Fakhr et al., 2021](#)) was observed. It was speculated that improved oxygenation was due to improved ventilation to perfusion matching, due to selective pulmonary vasodilation by NO in lung regions more readily ventilated. Prior to NO delivery, median [interquartile range] methemoglobin was 0.5% [0.2-0.8%] with a maximum of 2.3%. After 15-minutes of NO inhalation, methemoglobin was 1.8% [1.4-2.2%] with a maximum of 4.7%. Five-minutes after treatment, methemoglobin was 1.6% [1.2-2.0%] with a maximum of 3.5%. By comparison, in healthy volunteers (3F, 2M; median age 32-years) with no history of cardiovascular or lung disease inhaled 164.8±10.74 ppm NO (contaminated with 0.7±0.13 ppm NO₂) for 15-minutes ([Gianni et al., 2020](#)) increased methemoglobin concentrations from 1.05±0.58 to 2.26±0.47%.⁴ The decrease in methemoglobin observed by [Safaei Fakhr et al. \(2021\)](#) after NO inhalation suggests normal red cell methemoglobin reductase activity in the COVID-19 patients. Increases in serum creatinine level were not observed during the first 4-days of hospitalization after the initiation of NO treatments, suggesting no adverse kidney effects. No other adverse effects were observed.

⁴Relative to oxyhemoglobin, methemoglobin has a greater binding efficiency to oxygen and ineffectively releases oxygen in tissues. Normal methemoglobin levels are <2.0%. Methemoglobin is converted to hemoglobin by methemoglobin reductase.

Human and especially animal studies have shown inhaled NO to relax smooth muscle and dilate airways subsequent to bronchoconstriction from bronchial challenge with nonspecific agents. In five anesthetized dogs ([Brown et al., 1994](#)), histamine and methacholine were applied to decreased airway lumen area to 60–63% of baseline. The airway area went from 60% during histamine infusion to 85, 102, and 111% of baseline after sequential 10-minute doses of 100, 200, and 400 ppm NO, respectively ($p < 0.01$). Airway area went from 63% during methacholine infusion to 67, 75, and 75% of baseline after sequential 10-minute doses of 100, 200, and 400 ppm NO, respectively ($p < 0.01$). After inducing bronchoconstriction with methacholine in healthy men ($n = 7$), inhalation of 80 ppm NO partially reversed the bronchoconstriction (23% increase in airway conductance; $p < 0.05$), indicating some bronchodilator effects of NO ([Sanna et al., 1994](#)). However, inhalation of 80 ppm NO had no effect on baseline airway tone in these same individuals. A partial reversal of methacholine induced reductions in FEV₁ has also been demonstrated in mild asthmatics ([Kacmarek et al., 1996](#)).

Largely affecting their morbidity and mortality, patients with cystic fibrosis are prone to repeated bouts of microbial infections of the lung. [Deppisch et al. \(2016\)](#) conducted a clinical trial of cystic fibrosis patients (2 F, 6 M; 34.6 ± 7.5 -year) who inhaled 160 ppm NO for 30-minutes, three times per day, for two 5-day periods separated by a weekend without NO inhalations. The NO inhalations showed both anti-bacterial and anti-fungal effects. Colony forming units of all bacteria were reduced from over 25×10^6 pre-NO to about 6×10^3 post-NO ($p = 0.0008$) and for all fungi from 400×10^3 pre-NO to 400 post-treatment ($p = 0.0019$). Improvements in lung function were also observed with percent predicted forced vital capacity increasing from 63.3 to 75.6% ($p = 0.012$) and percent predicted forced expiratory volume in 1-second increasing from 49.9 to 58.7% (0.012). A case study of a 16-year-old female hospitalized due a dramatic decrease in lung function associated with a bacterial lung infection reported similar improvements in lung function, reduction in colony forming units, and improvement of other infection related symptoms (e.g., fever) following forty-six 30–60-minute inhalations of 160 ppm NO over a 28-day period ([Bartley et al., 2020](#)).

2.7 Conclusions

2.7.1 Conclusions of Exposure Assessment

This chapter presents the current state of the science for assessment of human exposure to NO₂ and other oxides of nitrogen in ambient air. It builds upon the 2016 Oxides of Nitrogen ISA [U.S. EPA \(2016\)](#), providing an updated summary of evidence for the sources of NO_x exposures, methods for estimating exposures, exposures to copollutants and other stressors, and implications for epidemiologic studies. Drawing from the evidence, this chapter reaches conclusions on three issues related to oxides of nitrogen exposures, i.e., (1) errors associated with exposure surrogates and the impacts of those errors on

health effects estimates in epidemiologic studies, (2) factors affecting differential exposures, and (3) NO₂ in a multipollutant (multi-stressor) environment.

Various approaches are used as surrogates for personal exposure to oxides of nitrogen in ambient air, primarily NO₂. These approaches include measurements (e.g., central site monitors, passive monitors, [low-cost] sensors, remote sensing) and complex modeling techniques (e.g., LUR, dispersion models, CTMs, hybrid models) that are intended to capture spatial and temporal patterns of exposure to ambient NO₂. Each surrogate has strengths and limitations and may be influenced by different types of exposure error i.e., instrument error, time-activity error, contributions from nonambient sources to total exposure, spatial error, and model misspecification. For example, one of the most important sources of exposure error is spatial misalignment, which can occur when the time-activity patterns of study participants are not factored into the study design or when the location where NO₂ exposure is estimated does not coincide with the residential, school, or work location of interest. In addition, spatial variability of human exposure can add uncertainty to the exposure estimate if it is not characterized by the monitors. These errors, in turn, can be broadly categorized as classical or Berkson errors. Classical errors tend to bias effect estimates and reduce precision in epidemiologic studies. In contrast, Berkson errors generally reduce precision but do not introduce bias. Simulation studies conducted for both short-term and long-term health effect studies generally indicate that exposure measurement error reduces precision and biases the health effect estimates toward null in majority of the situations, although positive bias emerges in simulation analyses for both short-term and long-term exposure studies under rare conditions when estimated exposures exhibit high correlation with true exposures while demonstrating substantially reduced variability compared to the true exposure values.

Exposure or air quality models have the potential to capture the spatial and temporal variability of NO₂, therefore enhancing exposure assessment and reducing exposure measurement error in epidemiologic studies. However, the selection of an appropriate model is critically important. The structure of the chosen model must be well-justified, and its applicability to the specific study context should be clearly established. Otherwise, metrics such as cross-validation or goodness-of-fit cannot guarantee improved accuracy in exposure assignment. It is also essential to recognize that reduced precision in exposure assessment decreases the likelihood of detecting statistically significant associations. Furthermore, bias toward the null suggests that the true health effect may be larger than what the epidemiologic model indicates. the epidemiologic model. Pollutants characterized by greater exposure measurement error, such as NO₂ compared with PM_{2.5}, may exhibit attenuated effect sizes in multipollutant models, complicating the detection of associations. Therefore, the identification of associations between NO₂ and adverse health outcomes in such analyses strengthens the evidence for a robust relationship between NO₂ exposure and negative health effects.

Personal exposure to oxides of nitrogen in ambient air is influenced by a variety of sources and factors, with traffic being the predominant contributor in urban areas. Certain populations experience elevated exposures to NO₂ in ambient air due to a complex interplay of factors, with proximity to roads

being a primary driver of several factors. Urban areas and locations near major roads consistently show higher NO₂ concentrations. Our comparative analysis of the percentage of children in near-road versus away-from-road populations across 12 major U.S. metropolitan areas indicates that differences are generally minimal, typically less than 1%.

Recent research investigating differential NO₂ exposure across socioeconomic and sociodemographic groups in the United States indicates that lower-income populations are generally subjected to long-term exposures to higher concentrations of NO₂.

Likewise, recent studies have also documented differential NO₂ exposure across various racial and ethnic groups in the United States, indicating that minority populations often experience elevated levels of this pollutant. National-scale analyses suggest that long-term exposure differences across racial and ethnic groups typically fall within a range of 10 ppb, with considerable variation observed between studies. Among school-age students at the national level, the difference in NO₂ exposure between racial and ethnic groups is approximately 2 ppb for long-term exposures. However, it is important to note that these patterns can vary significantly depending on study methodologies.

Neighborhood characteristics, especially the presence of vegetation, have a moderating effect on NO₂ concentrations. Areas with more vegetation tend to have lower NO₂ concentrations, highlighting the potential role of urban planning in exposure mitigation. Indoor environments add another layer of complexity to differential exposures. Indoor combustion sources and building characteristics can significantly influence personal NO₂ exposures, with factors such as ventilation and infiltration playing important roles in overall exposure levels.

The association between NO₂ in ambient air and personal exposure is complex and influenced by a number of factors, including proximity to traffic and other local sources, indoor/outdoor air exchange rates, time spent in different microenvironments (such as indoors and in vehicles), the presence of indoor sources, seasonal variations in ventilation and source strengths, individual activity patterns and study design (e.g., longitudinal vs. pooled studies). Due to these inter- and intra-personal variations, as well as differences in study design, the correlation between NO₂ in ambient air and personal exposure is often low to moderate. Studies have found poor to moderate correlations, with correlation coefficients typically ranging from near zero to 0.6, depending on the season, indoor sources, and time-activity patterns. However, a low correlation between personal NO₂ exposure and NO₂ concentrations in ambient air does not necessarily mean NO₂ in ambient air is inadequate to serve as a surrogate for the ambient component of personal exposure because the strength of a correlation coefficient can be largely impacted by the design of an exposure assessment. Notably, daily-average correlations, which are directly applicable to exposure estimation approaches employed in community time-series and long-term cohort epidemiologic studies, demonstrate more robust correlations.

NO₂ is a significant component of traffic emissions and is widely used as an indicator of traffic-related air pollution. Recent lines of evidence support the use of NO₂ as a traffic emission indicator. NO₂

shows strong correlations with other traffic-related pollutants such as CO, BC, and UFPs. These correlations are particularly evident near roadways, where traffic emissions are highest, particularly in urban environments with high traffic density. NO₂ concentrations exhibit clear diurnal patterns, with peaks during morning and evening rush hours, reflecting traffic activity. Spatially, NO₂ concentrations are significantly higher near major roadways and decrease with distance, although the gradient is less steep compared to some other primary traffic pollutants. NO₂ also shows moderate to strong correlations with particulate matter (PM_{2.5} and PM₁₀) and VOCs. The strength of these correlations can vary by season and location. The correlations between NO₂ and other pollutants are generally stronger in short-term studies. Long-term studies using LUR and other modeling techniques also show moderate correlations, particularly with PM_{2.5} and BC. Emerging and limited number of studies demonstrate moderate associations between NO₂ and nonchemical stressors, such as traffic noise and the lack of green spaces or blue spaces.

2.7.2 Dosimetry conclusions

The uptake of inhaled NO₂ in the respiratory tract is governed by “reactive absorption,” which involves chemical reactions with antioxidants, unsaturated lipids, and other compounds in the ELF. In vitro studies have clearly illustrated the role of antioxidants in mediating NO₂ uptake. The rapid reactions of NO₂ with tracheobronchial ELF substrates provides a net driving force for NO₂ mass transfer from the gas phase into the ELF. Concentrations of “free” solute NO₂ are likely negligible due to its reaction-mediated removal. Thus, it is not NO₂ itself, but rather its reaction products that are believed to interact with the apical surfaces of the tracheobronchial epithelium. At high substrate concentrations, oxidants/cytotoxic products are at least partially quenched due to secondary antioxidant reactions. At low substrate concentration, ELF-derived oxidants/cytotoxic products have a lower probability of being intercepted by unreacted antioxidants and instead may reach underlying targets.

Within the alveolar region, much of the inhaled NO₂ entering the ELF will diffuse through this thin lining layer rapidly enough to avoid reactions and will reach underlying tissue surfaces. A principal component of pulmonary surfactant, DPPC, may partially reduce the uptake of NO₂ by slowing its diffusion and decreasing reaction with substrates in the subphase fluid. Reducing the reactive absorption increases diffusive resistance and back diffusion into the air phase, thereby reducing uptake from the gas phase. Nonetheless, rapid reactions of NO₂ with tissues will maintain a concentration gradient for NO₂ through the alveolar ELF to the underlying tissues.

Exercise, relative to rest, increases the dose rate of NO₂ to the respiratory tract because of greater NO₂ penetration through the extrathoracic airways and a greater intake rate of NO₂. The uptake of NO₂ by the upper respiratory tract decreases with increasing ventilation rates occurring with activity. This causes a greater proportion of inhaled NO₂ to be delivered to the lower respiratory tract. In humans, exercise results in a shift in the breathing pattern from nasal to oronasal relative to rest. Because the nasal passages

scrub gas-phase NO₂ more efficiently than the mouth and because uptake efficiency decreases with increasing flow, exercise delivers a disproportionately greater quantity of the inhaled mass to the lower respiratory tract, where the NO₂ is readily absorbed. Experimental studies have shown that exercise increases the dose rate of NO₂ to the respiratory tract by three to five times compared to resting exposures.

Current dosimetry models for NO₂ do not adequately consider reactive absorption and secondary reactions that affect the probability of oxidants and/or cytotoxic products reaching target sites. Differences in potential NO₂ reactive substrates and reaction products among species have not been considered in modeling efforts. Although the models predict similar total NO₂ dose in the tracheobronchial airways and sites of maximal NO₂ tissue dose (i.e., near the beginning of the gas exchange region) among several mammalian species, the models do not sufficiently link these NO₂ doses to specific reaction products and downstream events. It is unclear to what extent environmental exposures at current ambient NO₂ concentrations might affect the overall balance of nitrite and nitrate in the respiratory tract or how ambient NO₂ uptake compares with endogenous production rates/amounts in the respiratory tract. Systemic nitrite and nitrate concentrations are highly dependent on diet and not likely affected by ambient NO₂ exposures. However, inhalation of high NO₂ concentrations (200–300 ppb) can cause small increases (<20%) in plasma nitrite.

The uptake of inhaled NO occurs against the background of endogenous NO production in the respiratory tract. In the distal lung, NO rapidly diffuses from the airway lumen across the alveolar-capillary membrane into the vascular compartment. Subsequent reactions with hemoglobin in red blood cells lead to the generation of circulating nitrate, nitrite, and methemoglobin. Blood acts as a practically operationally infinite sink for NO. The interception of NO due to reactions in surfactant is not expected to consume appreciable amounts of NO compared to mass transfer from the alveoli to the vascular space. Due to its rapid transport from the alveolar lumen to the blood, NO is used along with CO to measure diffusing capacity of the lung parenchyma.

Due to endogenous production, the NO concentration in the alveolar region at the end of a breath may exceed or be similar to inhaled exogenous NO near a major roadway. In healthy individuals, endogenous NO production within the respiratory tract is greatest in the nasal/sinus region, a slightly lower production rate occurs in the alveolar region (despite its vastly larger surface area), and the lowest production occurs in the tracheobronchial region. At low concentrations of inhaled NO (a few ppb), due to endogenous production, humans commonly exhale more NO than inhaled. Exhaled NO in the clinical setting usually reflects NO production in the tracheobronchial airways due to measurement during a low expiratory rate of only 50 mL/s. Concentrations of eNO are affected by a variety of factors including disease state, diet, sex (or height), species, smoking history, and environmental exposures. With regard to disease state, eNO is increased with airway inflammation and acute infection. eNO is also decreased in smokers relative to healthy controls.

In the respiratory tract, endogenous NO is a pulmonary vasodilator that can reduce pulmonary hypertension, increase blood oxygenation, induce bronchodilation, and plays a role in host defense. NO in the nasal airways plays a role in sinus host defense through bacteriostatic activity. Macrophage and inflammatory neutrophils may also upregulate NO synthesis as part of their antimicrobial response. Additionally, NO affects ciliary beat frequency and flow direction. Nasal NO production is decreased in individuals with immotile ciliary syndrome and in patients with cystic fibrosis. Tracheobronchial NO production is also reduced in smokers and in increase in NOS activity following garlic supplementation has been shown to improve their lung function as measured by spirometry. These properties of endogenous NO have led to the use of inhaled NO experimentally and in the clinical setting. Experimental and therapeutic treatments involve very high inhaled NO concentrations (typically 20–160 ppm) relative to ambient NO (<100 ppb 1-hour average) and endogenous NO concentrations (typically a few hundred ppb; up to 10 ppm in the sinus region). Experimentally, inhaled NO has reversed, or partially reversed bronchoconstriction induced by nonspecific challenge agents (e.g., histamine) in animals and humans, including those with asthma. Therapeutically, inhaled NO has improved oxygenation and effectively treated both bacterial and fungal infections in patients with cystic fibrosis.

2.8 References

- [.\(2010\).](#) Quantitative Risk and Exposure Assessment for Carbon Monoxide. (NTIS/12010114).
- [.\(2018\).](#) Risk and Exposure Assessment for the Review of the Primary National Ambient Air Quality Standard for Sulfur Oxides.
- [Adgent, MA; Squadrito, GL; Ballinger, CA; Krzywanski, DM; Lancaster, JR, Jr; Postlethwait, EM.](#) (2012). Desferrioxamine inhibits protein tyrosine nitration: Mechanisms and implications. *Free Radic Biol Med* 53: 951-961. <http://dx.doi.org/10.1016/j.freeradbiomed.2012.06.003>
- [Adza, WK; Hursthouse, AS; Miller, J; Boakye, D.](#) (2022). Exploring the combined association between road traffic noise and air quality using QGIS. *Int J Environ Res Public Health* 19: 17057. <http://dx.doi.org/10.3390/ijerph192417057>
- [Ahmad, T; Mabalirajan, U; Sharma, A; Aich, J; Makhija, L; Ghosh, B; Agrawal, A.](#) (2011). Simvastatin improves epithelial dysfunction and airway hyperresponsiveness: From asymmetric dimethyl-arginine to asthma. *Am J Respir Cell Mol Biol* 44: 531-539. <http://dx.doi.org/10.1165/rcmb.2010-0041OC>
- [Alexanderson, C; Olin, AC; Dahlman-Höglund, A; Finizia, C; Torén, K.](#) (2012). Nasal nitric oxide in a random sample of adults and its relationship to sensitization, cat allergen, rhinitis, and ambient nitric oxide. *Am J Rhinol Allergy* 26: e99-e103. <http://dx.doi.org/10.2500/ajra.2012.26.3777>
- [Alexeeff, SE; Carroll, RJ; Coull, B.](#) (2016). Spatial measurement error and correction by spatial SIMEX in linear regression models when using predicted air pollution exposures. *Biostatistics* 17: 377-389. <http://dx.doi.org/10.1093/biostatistics/kxv048>
- [Alexeeff, SE; Roy, A; Shan, J; Ray, GT; Quesenberry, CQ; Apte, J; Portier, CJ; Van Den Eeden, SK.](#) (2022). Association between traffic related air pollution exposure and direct health care costs in Northern California. *Atmos Environ* 287: 119271. <http://dx.doi.org/10.1016/j.atmosenv.2022.119271>
- [Alexeeff, SE; Schwartz, J; Kloog, I; Chudnovsky, A; Koutrakis, P; Coull, BA.](#) (2015). Consequences of kriging and land use regression for PM_{2.5} predictions in epidemiologic analyses: insights into spatial variability using high-resolution satellite data. *J Expo Sci Environ Epidemiol* 25: 138-144. <http://dx.doi.org/10.1038/jes.2014.40>
- [Allen, JD; Miller, EM; Schwark, E; Robbins, JL; Duschka, BD; Annex, BH.](#) (2009). Plasma nitrite response and arterial reactivity differentiate vascular health and performance. *Nitric Oxide* 20: 231-237. <http://dx.doi.org/10.1016/j.niox.2009.01.002>
- [Alving, K; Weitzberg, E; Lundberg, JM.](#) (1993). Increased amount of nitric oxide in exhaled air of asthmatics. *Eur Respir J* 6: 1368-1370.
- [Andersen, ZJ; Stafoggia, M; Weinmayr, G; Pedersen, M; Galassi, C; Jørgensen, JT; Oudin, A; Forsberg, B; Olsson, D; Oftedal, B; Marit Aasvang, G; Aamodt, G; Pyko, A; Pershagen, G; Korek, M; De Faire, U; Pedersen, NL; Östenson, CG; Fratiglioni, L; Eriksen, KT; Tjønneland, A; Peeters, PH; Bueno-De-Mesquita, B; Plusquin, M; Key, TJ; Jaensch, A; Nagel, G; Lang, A; Wang, M; Tsai, MY; Fournier, A; Boutron-Ruault, MC; Baglietto, L; Grioni, S; Marcon, A; Krogh, V; Ricceri, F; Sacerdote, C; Migliore, E; Tamayo-Uria, I; Amiano, P; Dorronsoro, M; Vermeulen, R; Sokhi, R; Keuken, M; de Hoogh, K; Beelen, R; Vineis, P; Cesaroni, G; Brunekreef, B; Hoek, G; Raaschou-Nielsen, O.](#) (2017). Long-term exposure to ambient air pollution and incidence of postmenopausal breast cancer in 15 European cohorts within the ESCAPE project. *Environ Health Perspect* 125: 107005. <http://dx.doi.org/10.1289/EHP1742>
- [Anderson, JT; Zeng, M; Li, Q; Stapley, R; Moore, DR; Chenna, B; Fineberg, N; Zmijewski, J; Eltoum, IE; Siegal, GP; Gaggar, A; Barnes, S; Velu, SE; Thannickal, VJ; Abraham, E; Patel, RP; Lancaster, J. R.; Chaplin, DD; Dransfield, MT; Deshane, JS.](#) (2011). Elevated levels of NO are localized to distal airways in asthma. *Free Radic Biol Med* 50: 1679-1688. <http://dx.doi.org/10.1016/j.freeradbiomed.2011.03.015>

- Antonczak, B; Thompson, TM; Depaola, MW; Rowangould, G. (2023). 2020 Near-roadway population census, traffic exposure and equity in the United States. *Transport Res Transport Environ* 125: 103965. <http://dx.doi.org/10.1016/j.trd.2023.103965>
- Apte, JS; Messier, KP; Gani, S; Brauer, M; Kirchstetter, TW; Lunden, MM; Marshall, JD; Portier, CJ; Vermeulen, RCH; Hamburg, SP. (2017). High-resolution air pollution mapping with Google street view cars: Exploiting big data [Abstract]. *Environ Sci Technol* 51: 6999-7008. <http://dx.doi.org/10.1021/acs.est.7b00891>
- Araín, MA; Blair, R; Finkelstein, N; Brook, J; Jerrett, M. (2009). Meteorological influences on the spatial and temporal variability of NO₂ in Toronto and Hamilton. *Can Geogr* 53: 165-190. <http://dx.doi.org/10.1111/j.1541-0064.2009.00252.x>
- ATS/ERS (American Thoracic Society and European Respiratory Society). (2005). ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 171: 912-930. <http://dx.doi.org/10.1164/rccm.200406-710ST>
- Azmi, WNF, W; Pillai, TR; Latif, MT; Koshy, S; Shaharudin, R. (2023). Application of land use regression model to assess outdoor air pollution exposure: A review. *Environ Adv* 11: 100353. <http://dx.doi.org/10.1016/j.envadv.2023.100353>
- Baldwin, N; Gilani, O; Raja, S; Batterman, S; Ganguly, R; Hopke, P; Berrocal, V; Robins, T; Hoogterp, S. (2015). Factors affecting pollutant concentrations in the near-road environment. *Atmos Environ* 115: 223-235. <http://dx.doi.org/10.1016/j.atmosenv.2015.05.024>
- Barrington, KJ; Finer, N; Pennaforte, T; Altit, G. (2017). Nitric oxide for respiratory failure in infants born at or near term [Review]. *Cochrane Database Syst Rev* 1: CD000399. <http://dx.doi.org/10.1002/14651858.CD000399.pub3>
- Bartley, BL; Gardner, KJ; Spina, S; Hurley, BP; Campeau, D; Berra, L; Yonker, LM; Carroll, RW. (2020). High-Dose Inhaled Nitric Oxide as Adjunct Therapy in Cystic Fibrosis Targeting *Burkholderia multivorans*. 2020: 1536714. <http://dx.doi.org/10.1155/2020/1536714>
- Bartolomei, V; Sörgel, M; Gligorovski, S; Alvarez, EG; Gandolfo, A; Strekowski, R; Quivet, E; Held, A; Zetzsch, C; Wortham, H. (2014). Formation of indoor nitrous acid (HONO) by light-induced NO₂ heterogeneous reactions with white wall paint. *Environ Sci Pollut Res Int* 21: 9259-9269. <http://dx.doi.org/10.1007/s11356-014-2836-5>
- Basagaña, X; Rivera, M; Aguilera, I; Agis, D; Bouso, L; Elosua, R; Foraster, M; de Nazelle, A; Nieuwenhuijsen, M; Vila, J; Künzli, N. (2012). Effect of the number of measurement sites on land use regression models in estimating local air pollution. *Atmos Environ* 54: 634-642. <http://dx.doi.org/10.1016/j.atmosenv.2012.01.064>
- Bastacky, J; Lee, CY; Goerke, J; Koushafar, H; Yager, D; Kenaga, L; Speed, TP; Chen, Y; Clements, JA. (1995). Alveolar lining layer is thin and continuous: Low-temperature scanning electron microscopy of rat lung. *J Appl Physiol* (1985) 79: 1615-1628. <http://dx.doi.org/10.1152/jappl.1995.79.5.1615>
- Bauer, MA; Utell, MJ; Morrow, PE; Speers, DM; Gibb, FR. (1986). Inhalation of 0.30 ppm nitrogen dioxide potentiates exercise-induced bronchospasm in asthmatics. *Am Rev Respir Dis* 134: 1203-1208. <http://dx.doi.org/10.1164/arrd.1986.134.6.1203>
- Bechle, M, atthew J.; Millet, D, ylan B.; Marshall, J, ulian D. (2023). Ambient NO₂ Air Pollution and Public Schools in the United States: Relationships with Urbanicity, Race-Ethnicity, and Income. *Environ Sci Technol Lett* 10: 844-850. <http://dx.doi.org/10.1021/acs.estlett.3c00507>
- Bechle, MJ; Millet, DB; Marshall, JD. (2013). Remote sensing of exposure to NO₂: Satellite versus ground-based measurement in a large urban. *Atmos Environ* 69: 345-353. <http://dx.doi.org/10.1016/j.atmosenv.2012.11.046>
- Beckman, JS; Koenol, WH. (1996). Nitric oxide, superoxide, and peroxynitrite: The good, the bad, and the ugly. *Am J Physiol Cell Physiol* 271: C1424-C1437.
- Beelen, R; Hoek, G; Vienneau, D; Eeftens, M; Dimakopoulou, K; Pedeli, X; Tsai, MY; Künzli, N; Schikowski, T; Marcon, A; Eriksen, KT; Raaschou-Nielsen, O; Stephanou, E; Patelarou, E;

- [Lanki, T; Yli-Toumi, T; Declercq, C; Falq, G; Stempfelet, M; ... de Hoogh, K. \(2013\). Development of NO₂ and NO_x land use regression models for estimating air pollution exposure in 36 study areas in Europe - The ESCAPE project. Atmos Environ 72: 10-23. <http://dx.doi.org/10.1016/j.atmosenv.2013.02.037>](#)
- [Belvisi, MG; Stretton, CD; Miura, M; Verleden, GM; Tadjkarimi, S; Yacoub, MH; Barnes, PJ. \(1992\). Inhibitory NANC nerves in human tracheal smooth muscle: A quest for the neurotransmitter. J Appl Physiol \(1985\) 73: 2505-2510.](#)
- [Bennett, EE; Song, Z; Lynch, KM; Liu, C; Stapp, EK; Xu, X; Park, ES; Ying, Q; Smith, RL; Stewart, JD; Whitsel, EA; Mosley, TH; Wong, DF; Liao, D; Yanosky, JD; Szpiro, AA; Kaufman, JD; Gottesman, RF; Power, MC. \(2023\). The association of long-term exposure to criteria air pollutants, fine particulate matter components, and airborne trace metals with late-life brain amyloid burden in the Atherosclerosis Risk in Communities \(ARIC\) study. Environ Int 180: 108200. <http://dx.doi.org/10.1016/j.envint.2023.108200>](#)
- [Bergen, S; Sheppard, L; Sampson, PD; Kim, SY; Richards, M; Vedal, S; Kaufman, JD; Szpiro, AA. \(2013\). A national prediction model for PM_{2.5} component exposures and measurement error-corrected health effect inference. Environ Health Perspect 121: 1017-1025. <http://dx.doi.org/10.1289/ehp.1206010>](#)
- [Berneron, B; Yang, JA; Jankowska, MM; Benmarhnia, T; Letellier, N. \(In Press\) Combined impact of dynamic air pollution and transportation noise on cardiometabolic disorders in San Diego County. Am J Epidemiol. <http://dx.doi.org/10.1093/aje/kwae117>](#)
- [Bernhard, W; Haslam, PL; Floros, J. \(2004\). From birds to humans: New concepts on airways relative to alveolar surfactant \[Review\]. Am J Respir Cell Mol Biol 30: 6-11. <http://dx.doi.org/10.1165/rcmb.2003-0158TR>](#)
- [Bessagnet, B; Pisoni, E; de Meij, A; Letinois, L; Thunis, P. \(2023\). A simple and fast method to downscale chemistry transport model output fields from the regional to the urban/district scale. Environ Modell Softw 164: 105692. <http://dx.doi.org/10.1016/j.envsoft.2023.105692>](#)
- [Bhaskar, KR; O'Sullivan, DD; Seltzer, J; Rossing, TH; Drazen, JM; Reid, LM. \(1985\). Density gradient study of bronchial mucus aspirates from healthy volunteers \(smokers and nonsmokers\) and from patients with tracheostomy. Exp Lung Res 9: 289-308. <http://dx.doi.org/10.3109/01902148509057529>](#)
- [Bidani, A; Postlethwait, EM. \(1998\). Kinetic determinants of inhaled reactive gas absorption. In MP Hlastala; HT Robertson \(Eds.\), Complexity in structure and function of the lung \(pp. 243-296\). New York, NY: Marcell Dekker Inc.](#)
- [Bigi, A; Mueller, M; Grange, SK; Ghermandi, G; Hueglin, C. \(2018\). Performance of NO, NO₂ low cost sensors and three calibration approaches within a real world application. Atmos Meas Tech 11: 3717.](#)
- [Blanco-Alegre, C; Calvo, AI; Alves, C; Fialho, P; Nunes, T; Gomes, J; Castro, A; Oduber, F; Coz, E; Fraile, R. \(2020\). Aethalometer measurements in a road tunnel: A step forward in the characterization of black carbon emissions from traffic. Sci Total Environ 703: 135483. <http://dx.doi.org/10.1016/j.scitotenv.2019.135483>](#)
- [Blanco, MN; Gasset, A; Gould, T; Doubleday, A; Slager, DL; Austin, E; Seto, E; Larson, T; Marshall, JD; Sheppard, L. \(2022\). Characterization of Annual Average Traffic-Related Air Pollution Concentrations in the Greater Seattle Area from a Year-Long Mobile Monitoring Campaign. Environ Sci Technol 56: 11460-11472. <http://dx.doi.org/10.1021/acs.est.2c01077>](#)
- [Bloemsma, LD; Wijga, AH; Klompmaker, JO; Hoek, G; Janssen, NAH; Lebret, E; Brunekreef, B; Gehring, U. \(2022\). Green space, air pollution, traffic noise and mental wellbeing throughout adolescence: Findings from the PIAMA study. Environ Int 163: 107197. <http://dx.doi.org/10.1016/j.envint.2022.107197>](#)
- [Bonacci, G; Baker, PR; Salvatore, S. R.; Shores, D; Khoo, NK; Koenitzer, J. R.; Vitturi, DA; Woodcock, S. R.; Golin-Bisello, F; Cole, MP; Watkins, S; St Croix, C; Batthyany, CI; Freeman, BA;](#)

- Schopfer, FJ. (2012). Conjugated linoleic acid is a preferential substrate for fatty acid nitration. *J Biol Chem* 287: 44071-44082. <http://dx.doi.org/10.1074/jbc.M112.401356>
- Borland, C; Bottrill, F; Jones, A; Sparkes, C; Vuylsteke, A. (2014). The significant blood resistance to lung nitric oxide transfer lies within the red cell. *J Appl Physiol* (1985) 116: 32-41. <http://dx.doi.org/10.1152/japplphysiol.00786.2013>
- Borland, C, olin; Patel, R, uhi. (2024). Comparing in vitro nitric oxide blood uptake to its pulmonary diffusing capacity. *Nitric Oxide* 143: 29-43. <http://dx.doi.org/10.1016/j.niox.2023.11.006>
- Bourgeois, I; Peischl, J; Neuman, JA; Brown, SS; Allen, HM; Campuzano-Jost, P; Coggon, MM; Digangi, JP; Diskin, GS; Gilman, JB; Gkatzelis, G; Guo, H; Halliday, HA; Hanisco, TF; Holmes, CD; Huey, LG; Jimenez, JL; Lamplugh, AD; Lee, YR; ... Ryerson, TB. (2022). Comparison of airborne measurements of NO, NO₂, HONO, NO_y, and CO during FIREX-AQ. *Atmos Meas Tech* 15: 4901-4930. <http://dx.doi.org/10.5194/amt-15-4901-2022>
- Bozkurt, Z; Doğan, G; Arslanbaş, D; Pekey, B; Pekey, H; Dumanoglu, Y; Bayram, A; Tuncel, G. (2015). Determination of the personal, indoor and outdoor exposure levels of inorganic gaseous pollutants in different microenvironments in an industrial city. *Environ Monit Assess* 187: 590. <http://dx.doi.org/10.1007/s10661-015-4816-8>
- Bradley, A, lexander C.; Croes, B, art E.; Harkins, C, olin; McDonald, B, rian C.; de Gouw, J, oost A. (2024). Air Pollution Inequality in the Denver Metroplex and its Relationship to Historical Redlining. *Environ Sci Technol* 58. <http://dx.doi.org/10.1021/acs.est.3c03230>
- Bramble, K, aya; Blanco, M, agali N.; Doubleday, A, nnie; Gassett, A, manda J.; Hajat, A, njum; Marshall, J, ulian D.; Sheppard, L, ianne. (2023). Exposure Disparities by Income, Race and Ethnicity, and Historic Redlining Grade in the Greater Seattle Area for Ultrafine Particles and Other Air Pollutants. *Environ Health Perspect* 131: 77004-. <http://dx.doi.org/10.1289/ehp11662>
- Brantley, HL; Hagler, GSW; Herndon, SC; Massoli, P; Bergin, MH; Russell, AG. (2019). Characterization of Spatial Air Pollution Patterns Near a Large Railway Area in Atlanta, Georgia. *Int J Environ Res Public Health* 16. <http://dx.doi.org/10.3390/ijerph16040535>
- Brauer, M; Brook, JR; Christidis, T; Chu, Y; Crouse, DL; Erickson, A; Hystad, P; Li, C; Martin, RV; Meng, J; Pappin, AJ; Pinault, LL; Tjepkema, M; van Donkelaar, A; Weichenthal, S; Burnett, RT. (2019). Mortality-air pollution associations in low-exposure environments (MAPLE): Phase 1 (pp. 1-87). (ISSN 1041-5505 EISSN 2688-6855). Boston, MA: Health Effects Institute.
- Brauer, M; Koutrakis, P; Keeler, GJ; Spengler, JD. (1991). Indoor and outdoor concentrations of inorganic acidic aerosols and gases. *J Air Waste Manag Assoc* 41: 171-181. <http://dx.doi.org/10.1080/10473289.1991.10466834>
- Brauer, M; Ryan, PB; Suh, HH; Koutrakis, P; Spengler, JD; Leslie, NP; Billick, IH. (1990). Measurements of nitrous acid inside two research houses. *Environ Sci Technol* 24: 1521-1527. <http://dx.doi.org/10.1021/es00080a011>
- Breen, M; Chang, SY; Breen, M; Xu, Y; Isakov, V; Arunachalam, S; Carraway, MS; Devlin, R. (2020). Fine-Scale Modeling of Individual Exposures to Ambient PM_{2.5}, EC, NO_x, CO for the Coronary Artery Disease and Environmental Exposure (CADEE) Study. *Atmosphere (Basel)* 11: 65. <http://dx.doi.org/10.3390/atmos11010065>
- Breen, MS; Long, T; Schultz, B; Williams, R; Richmond-Bryant, J; Breen, M; Langstaff, JE; Devlin, RB; Schneider, A; Burke, J; Batterman, SA; Meng, Q. (2015). Air pollution exposure model for individuals (EMI) in health studies: Evaluation for ambient PM_{2.5} in central North Carolina. *Environ Sci Technol Web*: 14184-14194. <http://dx.doi.org/10.1021/acs.est.5b02765>
- Briant, R; Korsakissok, I; Seigneur, C. (2011). An improved line source model for air pollutant dispersion from roadway traffic. *Atmos Environ* 45: 4099-4107. <http://dx.doi.org/10.1016/j.atmosenv.2010.11.016>
- Briggs, DJ; Collins, S; Elliott, P; Fischer, P; Kingham, S; Lebre, E; Pryl, K; Van Reeuwijk, H; Smallbone, K; Van Der Veen, A. (1997). Mapping urban air pollution using GIS: A regression-based approach. *Int J Geogr Inform Sci* 11: 699-718. <http://dx.doi.org/10.1080/136588197242158>

- [Brown, RH; Zerhouni, EA; Hirshman, CA. \(1994\).](#) REVERSAL OF BRONCHOCONSTRICTION BY INHALED NITRIC-OXIDE - HISTAMINE VERSUS METHACHOLINE. *Am J Respir Crit Care Med* 150: 233-237.
- [Buess, A; Van Muylen, A; Nonclercq, A; Haut, B. \(2020\).](#) Modeling of the Transport and Exchange of a Gas Species in Lungs With an Asymmetric Branching Pattern. Application to Nitric Oxide. *Front Physiol* 11. <http://dx.doi.org/10.3389/fphys.2020.570015>
- [Burkart, S; Parker, H; Weaver, RG; Beets, MW; Jones, A; Adams, EL; Chaput, JP; Armstrong, B. \(2022\).](#) Impact of the COVID-19 pandemic on elementary schoolers' physical activity, sleep, screen time and diet: A quasi-experimental interrupted time series study. *Pediatr Obes* 17: e12846. <http://dx.doi.org/10.1111/ijpo.12846>
- [Butland, BK; Samoli, E; Atkinson, RW; Barratt, B; Beevers, SD; Kitwiroon, N; Dimakopoulou, K; Rodopoulou, S; Schwartz, JD; Katsouyanni, K. \(2020\).](#) Comparing the performance of air pollution models for nitrogen dioxide and ozone in the context of a multilevel epidemiological analysis. *Environ Epidemiol* 4: e093. <http://dx.doi.org/10.1097/EE9.0000000000000093>
- [Butland, BK; Samoli, E; Atkinson, RW; Barratt, B; Katsouyanni, K. \(2019\).](#) Measurement error in a multi-level analysis of air pollution and health: A simulation study. *Environ Health* 18: 13. <http://dx.doi.org/10.1186/s12940-018-0432-8>
- [Button, B; Cai, LH; Ehre, C; Kesimer, M; Hill, DB; Sheehan, JK; Boucher, RC; Rubinstein, M. \(2012\).](#) A periciliary brush promotes the lung health by separating the mucus layer from airway epithelia. *Science* 337: 937-941. <http://dx.doi.org/10.1126/science.1223012>
- [Buzica, D; Gerboles, M; Plaisance, H. \(2008\).](#) The equivalence of diffusive samplers to reference methods for monitoring O₃, benzene and NO₂ in ambient air. *J Environ Monit* 10: 1052-1059. <http://dx.doi.org/10.1039/b802260g>
- [Byun, D; Schere, KL. \(2006\).](#) Review of the governing equations, computational algorithms, and other components of the models-3 community multiscale air quality (CMAQ) modeling system [Review]. *Appl Mech Rev* 59: 51-77. <http://dx.doi.org/10.1115/1.2128636>
- [Cape, JN; Tang, YS; van Dijk, N; Love, L; Sutton, MA; Palmer, SCF. \(2004\).](#) Concentrations of ammonia and nitrogen dioxide at roadside verges, and their contribution to nitrogen deposition. *Environ Pollut* 132: 469-478. <http://dx.doi.org/10.1016/j.envpol.2004.05.009>
- [Carruthers, DJ; Stocker, JR; Ellis, A; Seaton, MD; Smith, SE. \(2017\).](#) Evaluation of an explicit NO_x chemistry method in AERMOD. *J Air Waste Manag Assoc* 67: 702-712. <http://dx.doi.org/10.1080/10962247.2017.1280096>
- [Cassidy-Bushrow, AE; Burmeister, C; Lamerato, L; Lemke, LD; Mathieu, M; O'Leary, BF; Sperone, FG; Straughen, JK; Reiners, JJ. \(2020\).](#) Prenatal airshed pollutants and preterm birth in an observational birth cohort study in Detroit, Michigan, USA. *Environ Res* 189: 109845. <http://dx.doi.org/10.1016/j.envres.2020.109845>
- [Castell, N; Dauge, FR; Schneider, P; Vogt, M; Lerner, U; Fishbain, B; Broday, D; Bartonova, A. \(2016\).](#) Can commercial low-cost sensor platforms contribute to air quality monitoring and exposure estimates? *Environ Int* 99: 293-302. <http://dx.doi.org/10.1016/j.envint.2016.12.007>
- [Cavanagh, DG; Morris, JB. \(1987\).](#) Mucus protection and airway peroxidation following nitrogen dioxide exposure in the rat. *J Toxicol Environ Health* 22: 313-328. <http://dx.doi.org/10.1080/15287398709531074>
- [Centro di Ricerche Ambientali \(Centro di Ricerche Ambientali di Padova\). \(2006\).](#) Radiello(R) manual. Padova, Italy: Fondazione Salvatore Maugeri Clinica del Lavoro e Della Riabilitazione I.R.C.C.S., Centro di Ricerche Ambientali. <http://www.radiello.com/english/Radiello%27s%20manual%2001-06.pdf>
- [Chakraborty, J. \(2022\).](#) Children's exposure to vehicular pollution: Environmental injustice in Texas, USA. *Environ Res* 204: 112008. <http://dx.doi.org/10.1016/j.envres.2021.112008>
- [Chakraborty, J; Aun, JJ. \(2023\).](#) Social inequities in exposure to traffic-related air and noise pollution at public schools in Texas. *Int J Environ Res Public Health* 20: 5308. <http://dx.doi.org/10.3390/ijerph20075308>

Chambliss, SE; Campmier, MJ; Audirac, M; Apte, JS; Zigler, CM. (2023). Local exposure misclassification in national models: relationships with urban infrastructure and demographics. J Expo Sci Environ Epidemiol 34: 761-769. <http://dx.doi.org/10.1038/s41370-023-00624-z>

Chambliss, SE; Pinon, CPR; Messier, KP; Lafranchi, B; Upperman, CR; Lunden, MM; Robinson, AL; Marshall, JD; Apte, JS. (2021). Local- and regional-scale racial and ethnic disparities in air pollution determined by long-term mobile monitoring. Proc Natl Acad Sci USA 118: e2109249118. <http://dx.doi.org/10.1073/pnas.2109249118>

Chase, MW, Jr. (1998). NIST-JANAF thermochemical tables, monograph 9 (Fourth Edition ed.). Washington DC: American Chemical Society. <http://www.nist.gov/srd/monogr.cfm>

Cheeseman, MJ; Ford, B; Anenberg, SC; Cooper, MJ; Fischer, E; Hammer, MS; Magzamen, S; Martin, R; van Donkelaar, A; Volckens, J; Pierce, JR. (2022). Disparities in air pollutants across racial, ethnic, and poverty groups at US public schools. Geohealth 6: e2022GH000672. <http://dx.doi.org/10.1029/2022GH000672>

Chiu, Y, u-Chen; Wille, U, ta; Nathanael, J, oses G. (2024). The Environmental Pollutant NO₃• Rapidly Damages Alkene Moieties in Lipids Through Electron Transfer. European Journal of Organic Chemistry 27. <http://dx.doi.org/10.1002/ejoc.202400155>

Choi, Y. (2014). The impact of satellite-adjusted NO_x emissions on simulated NO_x and O₃ discrepancies in the urban and outflow areas of the Pacific and Lower Middle US. Atmos Chem Phys 14: 675-690. <http://dx.doi.org/10.5194/acp-14-675-2014>

Clark, LP; Harris, MH; Apte, JS; Marshall, JD. (2022). National and intraurban air pollution exposure disparity estimates in the United States: Impact of data-aggregation spatial scale. Environ Sci Technol Lett 9: 786-791. <http://dx.doi.org/10.1021/acs.estlett.2c00403>

Clary-Meinesz, C; Mouroux, J; Huitorel, P; Cosson, J; Schoevaert, D; Blaive, B. (1997). Ciliary beat frequency in human bronchi and bronchioles. Chest 111: 692-697. <http://dx.doi.org/10.1378/chest.111.3.692>

Cole-Hunter, T; So, R; Amini, H; Backalarz, C; Brandt, J; Brauner, EV; Hertel, O; Jensen, SS; Jorgensen, JT; Ketzel, M; Laursen, JE; Lim, YH; Loft, S; Mehta, A; Mortensen, LH; Simonsen, MK; Sissgaard, T; Westendorp, R; Andersen, ZJ. (2022). Long-term exposure to road traffic noise and all-cause and cause-specific mortality: A Danish Nurse Cohort study. Sci Total Environ 820: 153057. <http://dx.doi.org/10.1016/j.scitotenv.2022.153057>

Colville, R, .N; Woodfield, N, .K; D.J, C; B.E.A, F; Rickard, A; Neville, S; Hughes, A. (2002). Uncertainty in dispersion modelling and urban air quality mapping. Environ Sci Pol 5: 207-220. [http://dx.doi.org/10.1016/S1462-9011\(02\)00039-4](http://dx.doi.org/10.1016/S1462-9011(02)00039-4)

Connor, LM; Ballinger, CA; Albrecht, TB; Postlethwait, EM. (2004). Interfacial phospholipids inhibit ozone reactive absorption-mediated cytotoxicity in vitro. Am J Physiol 286: L1169-L1178. <http://dx.doi.org/10.1152/ajplung.00397.2003>

Connor, LM; Bidani, A; Goerke, J; Clements, JA; Postlethwait, EM. (2001). NO₂ interfacial transfer is reduced by phospholipid monolayers. J Appl Physiol (1985) 91: 2024-2034.

Cooper, MJ; Martin, RV; McLinden, CA; Brook, JR. (2020). Inferring ground-level nitrogen dioxide concentrations at fine spatial resolution applied to the TROPOMI satellite instrument. Environ Res Lett 15: 104013. <http://dx.doi.org/10.1088/1748-9326/aba3a5>

Crouse, DL; Goldberg, MS; Ross, NA. (2009). A prediction-based approach to modelling temporal and spatial variability of traffic-related air pollution in Montreal, Canada. Atmos Environ 43: 5075-5084. <http://dx.doi.org/10.1016/j.atmosenv.2009.06.040>

Dahl, KL; Chen, TJ; Nakayama, JY; West, M; Hamner, HC; Whitfield, GP; Dooyema, C. (2024). Time Playing Outdoors Among Children Aged 3-5 Years: National Survey of Children's Health, 2021. Am J Prev Med 66: 1024-1034. <http://dx.doi.org/10.1016/j.amepre.2023.12.011>

de Foy, B; Lu, Z; Streets, DG. (2016). Impacts of control strategies, the Great Recession and weekday variations on NO₂ columns above North American cities. Atmos Environ 138: 74-86. <http://dx.doi.org/10.1016/j.atmosenv.2016.04.038>

- de Hoogh, K; Chen, J; Gulliver, J; Hoffmann, B; Hertel, O; Ketzel, M; Bauwelinck, M; van Donkelaar, A; Hvidtfeldt, UA; Katsouyanni, K; Klompmaker, J; Martin, RV; Samoli, P; Schwartz, PE; Stafoggia, M; Bellander, T; Strak, M; Wolf, K; Vienneau, D; Brunekreef, B; Hoek, G. (2018). Spatial PM_{2.5}, NO₂, O₃ and BC models for Western Europe - Evaluation of spatiotemporal stability. *Environ Int* 120: 81-92. <http://dx.doi.org/10.1016/j.envint.2018.07.036>
- de Hoogh, K; Gulliver, J; Donkelaar, AV; Martin, RV; Marshall, JD; Bechle, MJ; Cesaroni, G; Pradas, MC; Dedele, A; Eeftens, M; Forsberg, B; Galassi, C; Heinrich, J; Hoffmann, B; Jacquemin, B; Katsouyanni, K; Korek, M; Künzli, N; Lindley, SJ; Lepeule, J; Meleux, F; de Nazelle, A; Nieuwenhuijsen, M; Nystad, W; Raaschou-Nielsen, O; Peters, A; Peuch, VH; Rouil, L; Udvardy, O; Slama, R; Stempfelet, M; Stephanou, EG; Tsai, MY; Yli-Tuomi, T; Weinmayr, G; Brunekreef, B; Vienneau, D; Hoek, G. (2016). Development of West-European PM_{2.5} and NO₂ land use regression models incorporating satellite-derived and chemical transport modelling data. *Environ Res* 151: 1-10. <http://dx.doi.org/10.1016/j.envres.2016.07.005>
- De Santis, F; Allegrini, I; Fazio, MC; Pasella, D. (1996). Characterization of indoor air quality in the Church of San Luigi Dei Francesi, Rome, Italy. *Int J Environ Anal Chem* 64: 71-81. <http://dx.doi.org/10.1080/03067319608028336>
- Defner, V; Küchenhoff, H; Breitner, S; Schneider, A; Cyrus, J; Peters, A. (2018). Mixtures of Berkson and classical covariate measurement error in the linear mixed model: Bias analysis and application to a study on ultrafine particles. *Biom J* 60: 480-497. <http://dx.doi.org/10.1002/bimj.201600188>
- Denby, BR; Kiesewetter, G; Nyiri, A; Klimont, Z; Fagerli, H; Waersted, EG; Wind, P. (2024). Sub-grid Variability and its Impact on Exposure in Regional Scale Air Quality and Integrated Assessment Models: Application of the uEMEP Downscaling Model. *Atmos Environ* 333. <http://dx.doi.org/10.1016/j.atmosenv.2024.120586>
- Dennekamp, M; Howarth, S; Dick, CAJ; Cherrie, JW; Donaldson, K; Seaton, A. (2001). Ultrafine particles and nitrogen oxides generated by gas and electric cooking. *Occup Environ Med* 58: 511-516.
- Deppisch, C; Herrmann, G; Graepler-Mainka, U; Wirtz, H; Heyder, S; Engel, C; Marschal, M; Miller, CC; Riethmüller, J. (2016). Gaseous nitric oxide to treat antibiotic resistant bacterial and fungal lung infections in patients with cystic fibrosis: a phase I clinical study. *Infection* 44: 513-520. <http://dx.doi.org/10.1007/s15010-016-0879-x>
- DeWinter, JL; Brown, SG; Seagram, AF; Landsberg, K; Eisinger, DS. (2018). A national-scale review of air pollutant concentrations measured in the US near-road monitoring network during 2014 and 2015. *Atmos Environ* 183: 94-105. <http://dx.doi.org/10.1016/j.atmosenv.2018.04.003>
- Di, Q; Amini, H; Shi, L; Kloog, I; Silvern, R; Kelly, J; Sabath, MB; Choirat, C; Koutrakis, P; Lyapustin, A; Wang, Y; Mickley, LJ; Schwartz, J. (2020). Assessing NO₂ concentration and model uncertainty with high spatiotemporal resolution across the contiguous United States using ensemble model averaging. *Environ Sci Technol* 54: 1372-1384. <http://dx.doi.org/10.1021/acs.est.9b03358>
- Dickerson, RR; Stratton, P; Ren, X; Kelley, P; Heaney, CD; Deanes, L; Aubourg, M; Spicer, K; Dreessen, J; Auvil, R; Sawtell, G; Thomas, M; Campbell, S; Sanchez, C. (In Press) Mobile laboratory measurements of air pollutants in Baltimore, MD elucidate issues of environmental justice. *Journal of the Air & Waste Management Association* (1995) 74: 1-18. <http://dx.doi.org/10.1080/10962247.2024.2393178>
- Dionisio, KL; Baxter, LK; Burke, J; Ozkaynak, H. (2016a). The importance of the exposure metric in air pollution epidemiology studies: When does it matter, and why? *Air Qual Atmos Health* 9: 495-502. <http://dx.doi.org/10.1007/s11869-015-0356-1>
- Dionisio, KL; Baxter, LK; Chang, HH. (2014). An empirical assessment of exposure measurement error and effect attenuation in bipollutant epidemiologic models. *Environ Health Perspect* 122: 1216-1224. <http://dx.doi.org/10.1289/ehp.1307772>

- Dionisio, KL; Chang, HH; Baxter, LK. (2016b). A simulation study to quantify the impacts of exposure measurement error on air pollution health risk estimates in copollutant time-series models. Environ Health 15: 114. <http://dx.doi.org/10.1186/s12940-016-0186-0>
- Dionisio, KL; Isakov, V; Baxter, LK; Sarnat, JA; Sarnat, SE; Burke, J; Rosenbaum, A; Graham, SE; Cook, R; Mulholland, J; Oezkaynak, H. (2013). Development and evaluation of alternative approaches for exposure assessment of multiple air pollutants in Atlanta, Georgia. J Expo Sci Environ Epidemiol 23: 581-592. <http://dx.doi.org/10.1038/jes.2013.59>
- Dons, E; Van Poppel, M; Int Panis, L; De Prins, S; Berghmans, P; Koppen, G; Matheeuissen, C. (2014). Land use regression models as a tool for short, medium and long term exposure to traffic related air pollution. Sci Total Environ 476-477: 378-386. <http://dx.doi.org/10.1016/j.scitotenv.2014.01.025>
- Downen, RS; Dong, Q; Chorvinsky, E; Li, B; Tran, N; Jackson, JH; Pillai, DK; Zaghloul, M; Li, Z. (2022). Personal NO2 sensor demonstrates feasibility of in-home exposure measurements for pediatric asthma research and management. J Expo Sci Environ Epidemiol 32: 312-319. <http://dx.doi.org/10.1038/s41370-022-00413-0>
- Dressel, IM; Demetillo, MAG; Judd, LM; Janz, SJ; Fields, KP; Sun, K; Fiore, AM; McDonald, BC; Pusede, SE. (2022). Daily satellite observations of nitrogen dioxide air pollution inequality in New York City, New York and Newark, New Jersey: Evaluation and application. Environ Sci Technol 56: 15298-15311. <http://dx.doi.org/10.1021/acs.est.2c02828>
- Duan, X; Buckpitt, AR; Pinkerton, KE; Ji, C; Plopper, CG. (1996). Ozone-induced alterations in glutathione in lung subcompartments of rats and monkeys. Am J Respir Cell Mol Biol 14: 70-75. <http://dx.doi.org/10.1165/ajrcmb.14.1.8534488>
- Duan, X; Buckpitt, AR; Plopper, CG. (1993). Variation in antioxidant enzyme activities in anatomic subcompartments within rat and rhesus monkey lung. Toxicol Appl Pharmacol 123: 73-82. <http://dx.doi.org/10.1006/taap.1993.1223>
- Ducret-Stich, RE; Tsai, MY; Ragetti, MS; Ineichen, A; Kuenzli, N; Phuleria, HC. (2013). Role of highway traffic on spatial and temporal distributions of air pollutants in a Swiss Alpine valley. Sci Total Environ 456-457: 50-60. <http://dx.doi.org/10.1016/j.scitotenv.2013.03.065>
- Dweik, RA; Boggs, PB; Erzurum, SC; Irvin, CG; Leigh, MW; Lundberg, JO; Olin, AC; Plummer, AL; Taylor, DR. (2011). An official ats clinical practice guideline: interpretation of exhaled nitric oxide levels (FE(NO)) for clinical alications. Am J Respir Crit Care Med 184: 602-615. <http://dx.doi.org/10.1164/rccm.912011ST>
- East, JD; Henderson, BH; Napelenok, SL; Koplit, SN; Sarwar, G; Gilliam, R; Lenzen, A; Tong, DQ; Pierce, RB; Garcia-Menendez, F. (2022). Inferring and evaluating satellite-based constraints on NOx emissions estimates in air quality simulations. Atmos Chem Phys 22: 15981-16001. <http://dx.doi.org/10.5194/acp-22-15981-2022>
- Ebelt, S, tefanie T.; D'Souza, R, ohan R.; Yu, H, aofei; Scovronick, N, oah; Moss, S, hannon; Chang, H, oward H. (2023). Monitoring vs. modeled exposure data in time-series studies of ambient air pollution and acute health outcomes. J Expo Sci Environ Epidemiol 33: 377-385. <http://dx.doi.org/10.1038/s41370-022-00446-5>
- El-Sayed, MMH; Elshorbany, YF; Koehler, K. (2021). On the impact of the COVID-19 pandemic on air quality in Florida. Environ Pollut 285: 117451. <http://dx.doi.org/10.1016/j.envpol.2021.117451>
- England, C; Corcoran, WH. (1974). Kinetics and mechanisms of the gas-phase reaction of water vapor and nitrogen dioxide. Ind Eng Chem Fundam 13: 373-384. <http://dx.doi.org/10.1021/i160052a014>
- Evangelopoulos, D; Katsouyanni, K; Keogh, RH; Samoli, E; Schwartz, J; Barratt, B; Zhang, H; Walton, H. (2020). PM2.5 and NO2 exposure errors using proxy measures, including derived personal exposure from outdoor sources: A systematic review and meta-analysis. Environ Int 137: 105500. <http://dx.doi.org/10.1016/j.envint.2020.105500>
- Evangelopoulos, D; Katsouyanni, K; Schwartz, J; Walton, H. (2021). Quantifying the short-term effects of air pollution on health in the presence of exposure measurement error: a simulation study of

- multi-pollutant model results. *Environ Health* 20: 1-13. <http://dx.doi.org/10.1186/s12940-021-00757-4>
- Eze, IC; Jeong, A; Schaffner, E; Rezwan, FI; Ghantous, A; Foraster, M; Vienneau, D; Kronenberg, F; Herceg, Z; Vineis, P; Brink, M; Wunderli, JM; Schindler, C; Cajochen, C; Röösli, M; Holloway, JW; Imboden, M; Probst-Hensch, N. (2020). Genome-wide DNA methylation in peripheral blood and long-term exposure to source-specific transportation noise and air pollution: The SAPALDIA study. *Environ Health Perspect* 128: 67003. <http://dx.doi.org/10.1289/EHP6174>
- Fabisiak, JP; Jackson, EM; Brink, LL; Presto, AA. (2020). A risk-based model to assess environmental justice and coronary heart disease burden from traffic-related air pollutants. *Environ Health* 19: 34. <http://dx.doi.org/10.1186/s12940-020-00584-z>
- Fallah-Shorshani, M, asoud; Fruin, S, cott; Yin, X, iaozhe; McConnell, R, ob; Franklin, M, eredith. (2024). Estimating near-roadway air pollution from multi-frequency noise measurements. *Sci Total Environ* 944: 173900-. <http://dx.doi.org/10.1016/j.scitotenv.2024.173900>
- Fallah-Shorshani, M; Hatzopoulou, M; Ross, NA; Patterson, Z; Weichenthal, S. (2018). Evaluating the impact of neighborhood characteristics on differences between residential and mobility-based exposures to outdoor air pollution. *Environ Sci Technol* 52: 10777-10786. <http://dx.doi.org/10.1021/acs.est.8b02260>
- Fang, H; Michalski, G. (2022). Assessing the roles emission sources and atmospheric processes play in simulating $\delta^{15}\text{N}$ of atmospheric NO_x and NO_3^- using CMAQ (version 5.2.1) and SMOKE (version 4.6). *GMD* 15: 4239-4258. <http://dx.doi.org/10.5194/gmd-15-4239-2022>
- Farmer, DK; Vance, ME; Abbatt, JPD; Abeleira, A; Alves, MR; Arata, C; Boedicker, E; Bourne, S; Cardoso-Saldaña, F; Corsi, R; Decarlo, PF; Goldstein, AH; Grassian, VH; Hildebrandt Ruiz, L; Jimenez, JL; Kahan, TF; Katz, EF; Mattila, JM; Nazaroff, WW; Novoselac, A; O'Brien, RE; Or, VW; Patel, S; Sankhyam, S; Stevens, PS; Tian, Y; Wade, M; Wang, C; Zhou, S; Zhou, Y. (2019). Overview of HOMEChem: House Observations of Microbial and Environmental Chemistry. *Environ Sci Process Impacts* 21: 1280-1300. <http://dx.doi.org/10.1039/c9em00228f>
- Fattoruso, G; Nocerino, M; Toscano, D; Pariota, L; Sorrentino, G; Manna, V; De Vito, S; Carteni, A; Fabbriano, M; Di Francia, G. (2020). Site Suitability Analysis for Low Cost Sensor Networks for Urban Spatially Dense Air Pollution Monitoring. *Atmosphere (Basel)* 11: 1215. <http://dx.doi.org/10.3390/atmos11111215>
- Fernandez-Somoano, A, na; Llop, S; Aguilera, I; Tamayo-Uria, I; Dolores Martinez, M; Foraster, M; Ballester, F; Tardon, A. (2015). Annoyance Caused by Noise and Air Pollution during Pregnancy: Associated Factors and Correlation with Outdoor NO_2 and Benzene Estimations. *Int J Environ Res Public Health* 12: 7044-7058. <http://dx.doi.org/10.3390/ijerph120607044>
- Fernando, HJS. (2010). Fluid dynamics of urban atmospheres in complex terrain. *Annu Rev Fluid Mech* 42: 365-389. <http://dx.doi.org/10.1146/annurev-fluid-121108-145459>
- Finlayson-Pitts, BJ; Wingen, LM; Sumner, AL; Syomin, D; Ramazan, KA. (2003). The heterogeneous hydrolysis of NO_2 in laboratory systems and in outdoor and indoor atmospheres: An integrated mechanism. *Phys Chem Chem Phys* 5: 223-242. <http://dx.doi.org/10.1039/b208564j>
- Floyd, CN; Shahed, F; Ukah, F; Mcneill, K; O'Gallagher, K; Mills, CE; Evangelopoulos, D; Lim, S; Mudway, I; Barratt, B; Walton, H; Webb, AJ. (2020). Acute blood pressure-lowering effects of nitrogen dioxide exposure from domestic gas cooking via elevation of plasma nitrite concentration in healthy individuals [Letter]. *Circ Res* 127: 847-848. <http://dx.doi.org/10.1161/CIRCRESAHA.120.316748>
- Foraster, M; Esnaola, M; López-Vicente, M; Rivas, I; Álvarez-Pedrerol, M; Persavento, C; Sebastian-Galles, N; Pujol, J; Dadvand, P; Sunyer, J. (2022). Exposure to road traffic noise and cognitive development in schoolchildren in Barcelona, Spain: A population-based cohort study. *PLoS Med* 19: e1004001. <http://dx.doi.org/10.1371/journal.pmed.1004001>
- Ford, E; Hughes, MN; Wardman, P. (2002). Kinetics of the reactions of nitrogen dioxide with glutathione, cysteine, and uric acid at physiological pH. *Free Radic Biol Med* 32: 1314-1323. [http://dx.doi.org/10.1016/S0891-5849\(02\)00850-X](http://dx.doi.org/10.1016/S0891-5849(02)00850-X)

Förstermann, U; Sessa, WC. (2012). Nitric oxide synthases: Regulation and function [Review]. Eur Heart J 33: 829-837. <http://dx.doi.org/10.1093/eurheartj/ehr304>

Frampton, MW; Balmes, JR; Bromberg, PA; Arjomandi, M; Hazucha, MJ; Thurston, SW; Alexis, NE; Ganz, P; Zareba, W; Koutrakis, P; Thevenet-Morrison, K; Rich, DQ. (2022). Effects of short-term increases in personal and ambient pollutant concentrations on pulmonary and cardiovascular function: A panel study analysis of the Multicenter Ozone Study in older subjects (MOSES 2). Environ Res 205: 112522. <http://dx.doi.org/10.1016/j.envres.2021.112522>

Franklin, M; Fruin, S. (2017). The role of traffic noise on the association between air pollution and children's lung function. Environ Res 157: 153-159. <http://dx.doi.org/10.1016/j.envres.2017.05.024>

Fuentes, M. (2009). Statistical issues in health impact assessment at the state and local levels. Air Qual Atmos Health 2: 47-55. <http://dx.doi.org/10.1007/s11869-009-0033-3>

Fuks, KB; Weinmayr, G; Basagaña, X; Gruzieva, O; Hampel, R; Oftedal, B; Sørensen, M; Wolf, K; Aamodt, G; Aasvang, GM; Aguilera, I; Becker, T; Beelen, R; Brunekreef, B; Caracciolo, B; Cyrus, J; Elosua, R; Eriksen, KT; Foraster, M; ... Hoffmann, B. (2017). Long-term exposure to ambient air pollution and traffic noise and incident hypertension in seven cohorts of the European study of cohorts for air pollution effects (ESCAPE). Eur Heart J 38: 983-990. <http://dx.doi.org/10.1093/eurheartj/ehw413>

Fukuto, J; Carrington, SJ; Tantillo, DJ; Harrison, JG; Ignarro, LJ; Freeman, BA; Chen, A; Wink, DA. (2012). Small molecule signaling agents: The integrated chemistry and biochemistry of nitrogen oxides, oxides of carbon, dioxygen, hydrogen sulfide, and their derived species [Review]. Chem Res Toxicol 25: 769-793. <http://dx.doi.org/10.1021/tx2005234>

Gair, AJ; Penkett, SA; Oyola, P. (1991). Development of a simple passive technique for the determination of nitrogen-dioxide in remote continental locations. Atmos Environ 25A: 1927-1939. [http://dx.doi.org/10.1016/0960-1686\(91\)90274-B](http://dx.doi.org/10.1016/0960-1686(91)90274-B)

Gandolfo, A; Bartolomei, V; Alvarez, EG; Tlili, S; Gligorovski, S; Kleffmann, J; Wortham, H. (2015). The effectiveness of indoor photocatalytic paints on NO_x and HONO levels. Appl Catal B-Environ 166: 84-90. <http://dx.doi.org/10.1016/j.apcatb.2014.11.011>

Gandolfo, A; Bartolomei, V; Truffier-Boutry, D; Temime-Roussel, B; Brochard, G; Bergé, V; Wortham, H; Gligorovski, S. (2020). The impact of photocatalytic paint porosity on indoor NO_x and HONO levels. Phys Chem Chem Phys 22: 589-598. <http://dx.doi.org/10.1039/c9cp05477d>

Gantt, B; Owen, RC; Watkins, N. (2021). Characterizing nitrogen oxides and fine particulate matter near major highways in the United States using the national near-road monitoring network. Environ Sci Technol 55: 2831-2838. <http://dx.doi.org/10.1021/acs.est.0c05851>

Gao, D; Esenther, S; Minet, L; De Jesus, A; Hudson, S; Leaderer, B; Hatzopoulou, M; Godri Pollitt, KJ. (2023). Assessment of children's personal and land use regression model-estimated exposure to NO₂ in Springfield, Massachusetts. Sci Total Environ 892: 164681. <http://dx.doi.org/10.1016/j.scitotenv.2023.164681>

Geigel, EJ; Hyde, RW; Perillo, IB; Torres, A; Perkins, PT; Pietropaoli, AP; Frasier, LM; Frampton, MW; Utell, MJ. (1999). Rate of nitric oxide production by lower alveolar airways of human lungs. J Appl Physiol (1985) 86: 211-221.

George, SC; Hogman, M; Permutt, S; Silkoff, PE. (2004). Modeling pulmonary nitric oxide exchange [Review]. J Appl Physiol (1985) 96: 831-839. <http://dx.doi.org/10.1152/japplphysiol.00950.2003>

Gianni, S; Morais, CCA; Larson, G; Pinciroli, R; Carroll, R; Yu, B; Zapol, WM; Berra, L. (2020). Ideation and assessment of a nitric oxide delivery system for spontaneously breathing subjects. Nitric Oxide 104-105: 29-35. <http://dx.doi.org/10.1016/j.niox.2020.08.004>

Gilbert, NL; Goldberg, MS; Brook, JR; Jerrett, M. (2007). The influence of highway traffic on ambient nitrogen dioxide concentrations beyond the immediate vicinity of highways. Atmos Environ 41: 2670-2673. <http://dx.doi.org/10.1016/j.atmosenv.2006.12.007>

Goldberg, DL; Anenberg, SC; Kerr, GH; Mohegh, A; Lu, Z; Streets, DG. (2021). TROPOMI NO₂ in the United States: A detailed look at the annual averages, weekly cycles, effects of temperature, and

- correlation with surface NO₂ concentrations. *Earths Future* 9: e2020EF001665. <http://dx.doi.org/10.1029/2020EF001665>
- Goldberg, DL; Lamsal, L; Loughner, CP; Swartz, WH; Lu, Z; Streets, DG. (2017). A high-resolution and observationally constrained OMI NO₂ satellite retrieval. *Atmos Chem Phys* 17: 11403-11421. <http://dx.doi.org/10.5194/acp-17-11403-2017>
- Goldman, GT; Mulholland, JA; Russell, AG; Gass, K; Strickland, MJ; Tolbert, PE. (2012). Characterization of ambient air pollution measurement error in a time-series health study using a geostatistical simulation approach. *Atmos Environ* 57: 101-108. <http://dx.doi.org/10.1016/j.atmosenv.2012.04.045>
- Goldman, GT; Mulholland, JA; Russell, AG; Srivastava, A; Strickland, MJ; Klein, M; Waller, LA; Tolbert, PE; Edgerton, ES. (2010). Ambient air pollutant measurement error: characterization and impacts in a time-series epidemiologic study in Atlanta. *Environ Sci Technol* 44: 7692-7698. <http://dx.doi.org/10.1021/es101386r>
- Goldstein, S; Lind, J; Merenyi, G. (2004). Reaction of organic peroxy radicals with •NO₂ and •NO in aqueous solution: Intermediacy of organic peroxyxynitrate and peroxyxynitrite species. *J Phys Chem A* 108: 1719-1725. <http://dx.doi.org/10.1021/jp037431z>
- Gonzales, M; Qualls, C; Hudgens, E; Neas, L. (2005). Characterization of a spatial gradient of nitrogen dioxide across a United States-Mexico border city during winter. *Sci Total Environ* 337: 163-173. <http://dx.doi.org/10.1016/j.scitotenv.2004.07.010>
- Gualtieri, G; Crisci, A; Tartaglia, M; Toscano, P; Gioli, B. (2015). A Statistical Model to Assess Air Quality Levels at Urban Sites. *Water Air Soil Pollut* 226. <http://dx.doi.org/10.1007/s11270-015-2663-4>
- Ha, S; Nobles, C; Kanner, J; Sherman, S; Cho, SH; Perkins, N; Williams, A; Grobman, W; Biggio, J; Subramaniam, A; Ouidir, M; Chen, Z; Mendola, P. (2020). Air Pollution Exposure Monitoring among Pregnant Women with and without Asthma. *Int J Environ Res Public Health* 17: 1-16. <http://dx.doi.org/10.3390/ijerph17134888>
- Hagenbjork-Gustafsson, A; Eriksson, K; Forsberg, B. (2009). Field evaluation of the Ogawa Diffusive Sampler for NO₂/NO(x) in a cold climate [Abstract]. *Epidemiology* 20: S161. <http://dx.doi.org/10.1097/01.ede.0000362548.83420.d7>
- Hamid, Q; Springall, DR; Riveros-Moreno, V; Chanez, P; Howarth, P; Redington, A; Bousquet, J; Godard, P; Holgate, S; Polak, JM. (1993). Induction of nitric oxide synthase in asthma. *Lancet* 342: 1510-1513. [http://dx.doi.org/10.1016/S0140-6736\(05\)80083-2](http://dx.doi.org/10.1016/S0140-6736(05)80083-2)
- Hanigan, IC; Williamson, GJ; Knibbs, LD; Horsley, J; Rolfe, MI; Cope, M; Barnett, AG; Cowie, CT; Heyworth, JS; Serre, ML; Jalaludin, B; Morgan, GG. (2017). Blending multiple nitrogen dioxide data sources for neighborhood estimates of long-term exposure for health research. *Environ Sci Technol* 51: 12473-12480. <http://dx.doi.org/10.1021/acs.est.7b03035>
- Hart, JE; Spiegelman, D; Beelen, R; Hoek, G; Brunekreef, B; Schouten, LJ; van den Brandt, P. (2015). Long-term ambient residential traffic-related exposures and measurement error-adjusted risk of incident lung cancer in the Netherlands cohort study on diet and cancer. *Environ Health Perspect* 123: 860-866. <http://dx.doi.org/10.1289/ehp.1408762>
- Hatch, GE. (1992). Comparative biochemistry of airway lining fluid. In RA Parent (Ed.), *Comparative biology of the normal lung*, vol 1: Treatise on pulmonary toxicology (pp. 617-632). Boca Raton, FL: CRC Press.
- Hazlehurst, MF; Spalt, EW; Nicholas, TP; Curl, CL; Davey, ME; Burke, GL; Watson, KE; Vedal, S; Kaufman, JD. (2018). Contribution of the in-vehicle microenvironment to individual ambient-source nitrogen dioxide exposure: the Multi-Ethnic Study of Atherosclerosis and Air Pollution. *J Expo Sci Environ Epidemiol* 28: 371-380. <http://dx.doi.org/10.1038/s41370-018-0025-1>
- Heal, MR. (2008). The effect of absorbent grid preparation method on precision and accuracy of ambient nitrogen dioxide measurements using Palmes passive diffusion tubes. *J Environ Monit* 10: 1363-1369. <http://dx.doi.org/10.1039/b811230d>

- Heal, MR; Laxen, DPH; Marner, BB. (2019). Biases in the measurement of ambient nitrogen dioxide (NO₂) by Palmes passive diffusion tube: A review of current understanding. Atmosphere (Basel) 10: 357. <http://dx.doi.org/10.3390/atmos10070357>
- HEI (Health Effects Institute). (2010). Traffic-related air pollution: A critical review of the literature on emissions, exposure, and health effects. (Special Report 17). Boston, MA: Health Effects Institute (HEI). <https://www.healtheffects.org/system/files/SR17Traffic%20Review.pdf>
- Heintzelman, A; Filippelli, G; Lulla, V. (2021). Substantial decreases in US cities' ground-based NO₂ concentrations during COVID-19 from reduced transportation. Sustainability 13: 9030. <http://dx.doi.org/10.3390/su13169030>
- Helen, GS; Aguilar-Villalobos, M; Adetona, O; Cassidy, B; Bayer, CW; Hendry, R; Hall, DB; Naeher, LP. (2013). Exposure of pregnant women to cookstove related household air pollution in urban and peri-urban Trujillo, Peru. Arch Environ Occup Health 70: 10-18. <http://dx.doi.org/10.1080/19338244.2013.807761>
- Hill, BG; Dranka, BP; Bailey, SM; Lancaster, JR; Darley-Usmar, VM. (2010). What part of NO don't you understand? Some answers to the cardinal questions in nitric oxide biology [Review]. J Biol Chem 285: 19699-19704. <http://dx.doi.org/10.1074/jbc.R110.101618>
- Hjortebjerg, D; Andersen, AMN; Ketzel, M; Pedersen, M; Raaschou-Nielsen, O; Sørensen, M. (2016). Associations between maternal exposure to air pollution and traffic noise and newborn's size at birth: A cohort study. Environ Int 95: 1-7. <http://dx.doi.org/10.1016/j.envint.2016.07.003>
- Hoek, G; Beelen, R; de Hoogh, K; Vienneau, D; Gulliver, J; Fischer, P; Briggs, D. (2008). A review of land-use regression models to assess spatial variation of outdoor air pollution [Review]. Atmos Environ 42: 7561-7578. <http://dx.doi.org/10.1016/j.atmosenv.2008.05.057>
- Hoek, G, erard; Vienneau, D, anielle; de Hoogh, K, ees. (2024). Does residential address-based exposure assessment for outdoor air pollution lead to bias in epidemiological studies? Environ Health 23: 75-. <http://dx.doi.org/10.1186/s12940-024-01111-0>
- Hohenberger, TL; Che, W; Sun, Y; Fung, JCH; Lau, AKH. (2022). Assessment of the impact of sensor error on the representativeness of population exposure to urban air pollutants. Environ Int 165: 107329. <http://dx.doi.org/10.1016/j.envint.2022.107329>
- Hohlfeld, JM. (2002). The role of surfactant in asthma. Respir Res 3: 4. <http://dx.doi.org/10.1186/rr176>
- Holloway, T; Miller, D; Anenberg, S; Diao, M; Duncan, B; Fiore, AM; Henze, DK; Hess, J; Kinney, PL; Liu, Y; Neu, JL; O'Neill, SM; Odman, MT; Pierce, RB; Russell, AG; Tong, D; West, JJ; Zondlo, MA. (2021). Satellite monitoring for air quality and health. Annu Rev Biomed Data Sci 4: 417-447. <http://dx.doi.org/10.1146/annurev-biodatasci-110920-093120>
- Hong, JH; Lee, JH; Park, SS. (2007). Application of an in-situ measurement system to determine HONO levels in an indoor environment. Journal of Korean Society for Atmospheric Environment 23: 191-202. <http://dx.doi.org/10.5572/KOSAE.2007.23.2.191>
- Hsu, H, siao-Hsien Leon; Wilson, A, nder; Schwartz, J, oel; Kloog, I, tai; Wright, R, obert O.; Coull, B, rent A.; Wright, R, osalind J. (2023). Prenatal Ambient Air Pollutant Mixture Exposure and Early School-age Lung Function. Environmental epidemiology (Philadelphia, Pa) 7: e249-. <http://dx.doi.org/10.1097/ee9.0000000000000249>
- Hu, Y; Yao, M; Liu, Y; Zhao, B. (2020). Personal exposure to ambient PM_{2.5}, PM₁₀, O₃, NO₂, and SO₂ for different populations in 31 Chinese provinces. Environ Int 144: 106018. <http://dx.doi.org/10.1016/j.envint.2020.106018>
- Hu, Y; Zhao, B, in. (2020). Relationship between indoor and outdoor NO₂: A review. Build Environ 180: 106909. <http://dx.doi.org/10.1016/j.buildenv.2020.106909>
- Huang, K; Zhu, Q; Lu, X; Gu, D; Liu, Y. (2023). Satellite-Based Long-Term Spatiotemporal Trends in Ambient NO₂ Concentrations and Attributable Health Burdens in China From 2005 to 2020. Geohealth 7: e2023GH000798. <http://dx.doi.org/10.1029/2023GH000798>
- Huang, R; Zhai, X; Ivey, CE; Friberg, MD; Hu, X; Liu, Y; Di, Q; Schwartz, J; Mulholland, JA; Russell, AG. (2018). Air pollutant exposure field modeling using air quality model-data fusion methods

and comparison with satellite AOD-derived fields: application over North Carolina, USA. *Air Qual Atmos Health* 11: 11-22. <http://dx.doi.org/10.1007/s11869-017-0511-y>

Hudda, N; Durant, LW; Fruin, SA; Durant, JL. (2020). Impacts of aviation emissions on near-airport residential air quality. *Environ Sci Technol* 54: 8580-8588. <http://dx.doi.org/10.1021/acs.est.0c01859>

Hudda, N; Simon, MC; Zamore, W; Brugge, D; Durant, JL. (2016). Aviation emissions impact ambient ultrafine particle concentrations in the greater Boston area. *Environ Sci Technol* 50: 8514-8521. <http://dx.doi.org/10.1021/acs.est.6b01815>

Hughes, JMB. (2013). Invited editorial on "Lung membrane conductance and capillary volume derived from the NO and CO transfer in high altitude newcomers" [Editorial]. *J Appl Physiol* (1985) 115: 153-154. <http://dx.doi.org/10.1152/japplphysiol.00581.2013>

Hummel, SG; Fischer, AJ; Martin, SM; Schafer, FQ; Buettner, GR. (2006). Nitric oxide as a cellular antioxidant: A little goes a long way. *Free Radic Biol Med* 40: 501-506. <http://dx.doi.org/10.1016/j.freeradbiomed.2005.08.047>

Ichinose, T; Arakawa, K; Shimojo, N; Sagai, M. (1988). Biochemical effects of combined gases of nitrogen dioxide and ozone: II. Species differences in lipid peroxides and antioxidative protective enzymes in the lungs. *Toxicol Lett* 42: 167-176.

Ishibashi, Y; Takahashi, N; Tokumaru, A; Karino, K; Sugamori, T; Sakane, T; Kodani, N; Kunizawa, Y; Yoshitomi, H; Sato, H; Oyake, N; Murakami, Y; Shimada, T. (2008). Activation of inducible NOS in peripheral vessels and outcomes in heart failure patients. *J Card Fail* 14: 724-731. <http://dx.doi.org/10.1016/j.cardfail.2008.06.450>

Islam, NM; Yadav, RL; Yadav, PK. (2017). Modulation of lung function by increased nitric oxide production. *JCDR* 11: CC09-CC12. <http://dx.doi.org/10.7860/JCDR/2017/24650.9981>

Ivy, D; Mulholland, JA; Russell, AG. (2008). Development of ambient air quality population-weighted metrics for use in time-series health studies. *J Air Waste Manag Assoc* 58: 711-720. <http://dx.doi.org/10.3155/1047-3289.58.5.711>

Jaffe, D, aniel A.; Creekmore, A, melie. (2024). Emissions and exposure to NO_x, CO, CO₂ and PM_{2.5} from a gas stove using reference and low-cost sensors. *Atmos Environ* 331. <http://dx.doi.org/10.1016/j.atmosenv.2024.120564>

Jain, B; Rubinstein, I; Robbins, RA; Leise, KL; Sisson, JH. (1993). Modulation of airway epithelial cell ciliary beat frequency by nitric oxide. *Biochem Biophys Res Commun* 191: 83-88. <http://dx.doi.org/10.1006/bbrc.1993.1187>

Jarvis, DL; Leaderer, BP; Chinn, S; Burney, PG. (2005). Indoor nitrous acid and respiratory symptoms and lung function in adults. *Thorax* 60: 474-479. <http://dx.doi.org/10.1136/thx.2004.032177>

Jeong, CH; Hilker, N; Wang, JM; Deboz, J; Healy, RM; Sofowote, U; Munoz, T; Herod, D; Evans, GJ. (2022). Characterization of winter air pollutant gradients near a major highway. *Sci Total Environ* 849: 157818. <http://dx.doi.org/10.1016/j.scitotenv.2022.157818>

Jerrett, M; Arain, A; Kanaroglou, P; Beckerman, B; Potoglou, D; Sahuvaroglu, T; Morrison, J; Giovis, C. (2005). A review and evaluation of intraurban air pollution exposure models [Review]. *J Expo Anal Environ Epidemiol* 15: 185-204. <http://dx.doi.org/10.1038/sj.jea.7500388>

Jiao, A; Sun, Y; Avila, C; Chiu, V; Molitor, J; Slezak, J; Sacks, DA; Chen, JC; Benmarhnia, T; Getahun, D; Wu, J. (2023). Maternal exposure to ambient air pollution mixture and premature rupture of membranes: Evidence from a large cohort in Southern California (2008-2018). *Environ Int* 177: 108030. <http://dx.doi.org/10.1016/j.envint.2023.108030>

Jiao, J; Wang, H; Lou, W; Jin, S; Fan, E; Li, Y; Han, D; Zhang, L. (2011). Regulation of ciliary beat frequency by the nitric oxide signaling pathway in mouse nasal and tracheal epithelial cells. *Exp Cell Res* 317: 2548-2553. <http://dx.doi.org/10.1016/j.yexcr.2011.07.007>

Jomova, K, laudia; Alomar, S, uliman Y.; Alwasel, S, aleh H.; Nepovimova, E, ugenie; Kuca, K, amil; Valko, M, arian. (2024). Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. *Arch Toxicol* 98: 1323-1367. <http://dx.doi.org/10.1007/s00204-024-03696-4>

- Jörres, RA. (2000). Modelling the production of nitric oxide within the human airways [Review]. *Eur Respir J* 16: 555-560. <http://dx.doi.org/10.1034/j.1399-3003.2000.016003555.x>
- Kacmarek, RM; Ripple, R; Cockrill, BA; Bloch, KJ; Zapol, WM; Johnson, DC. (1996). Inhaled nitric oxide: a bronchodilator in mild asthmatics with methacholine-induced bronchospasm. *Am J Respir Crit Care Med* 153: 128-135.
- Kamboj, K; Sisodiya, S; Mathur, AK; Zare, A; Verma, P. (2022). Assessment and Spatial Distribution Mapping of Criteria Pollutants. *Water Air Soil Pollut* 233. <http://dx.doi.org/10.1007/s11270-022-05522-y>
- Kang, I; McCreery, A; Azimi, P; Gramigna, A; Baca, G; Abromitis, K; Wang, M; Zeng, Y; Scheu, R; Crowder, T; Evens, A; Stephens, B. (2022). Indoor air quality impacts of residential mechanical ventilation system retrofits in existing homes in Chicago, IL. *Sci Total Environ* 804: 150129. <http://dx.doi.org/10.1016/j.scitotenv.2021.150129>
- Karamaoun, C; Van Muylem, A; Haut, B. (2016). Modeling of the Nitric Oxide Transport in the Human Lungs. *Front Physiol* 7: 255. <http://dx.doi.org/10.3389/fphys.2016.00255>
- Karner, AA; Eisinger, DS; Niemeier, DA. (2010). Near-roadway air quality: Synthesizing the findings from real-world data. *Environ Sci Technol* 44: 5334-5344. <http://dx.doi.org/10.1021/es100008x>
- Kashtan, Y; Nicholson, M; Finnegan, CJ; Ouyang, Z; Garg, A; Lebel, ED; Rowland, ST; Michanowicz, DR; Herrera, J; Nadeau, KC; Jackson, RB. (2024). Nitrogen dioxide exposure, health outcomes, and associated demographic disparities due to gas and propane combustion by U.S. stoves. *Sci Adv* 10: eadm8680-. <http://dx.doi.org/10.1126/sciadv.adm8680>
- Kashtan, YS; Nicholson, M; Finnegan, C; Ouyang, Z; Lebel, ED; Michanowicz, DR; Shonkoff, SBC; Jackson, RB. (2023). Gas and propane combustion from stoves emits benzene and increases indoor air pollution. *Environ Sci Technol* 57: 9653-9663. <http://dx.doi.org/10.1021/acs.est.2c09289>
- Keller, JP; Olives, C; Kim, SY; Sheppard, L; Sampson, PD; Szpiro, AA; Oron, AP; Lindström, J; Vedal, S; Kaufman, JD. (2015). A unified spatiotemporal modeling approach for predicting concentrations of multiple air pollutants in the multi-ethnic study of atherosclerosis and air pollution. *Environ Health Perspect* 123: 301-309. <http://dx.doi.org/10.1289/ehp.1408145>
- Kelly, FJ; Blomberg, A; Frew, A; Holgate, ST; Sandstrom, T. (1996a). Antioxidant kinetics in lung lavage fluid following exposure of humans to nitrogen dioxide. *Am J Respir Crit Care Med* 154: 1700-1705. <http://dx.doi.org/10.1164/ajrccm.154.6.8970358>
- Kelly, FJ; Cotgrove, M; Mudway, IS. (1996b). Respiratory tract lining fluid antioxidants: the first line of defence against gaseous pollutants. *Cent Eur J Public Health* 4: 11-14.
- Kelly, FJ; Tetley, TD. (1997). Nitrogen dioxide depletes uric acid and ascorbic acid but not glutathione from lung lining fluid. *Biochemistry* 325: 95-99.
- Kendrick, CM; Koonce, P; George, LA. (2015). Diurnal and seasonal variations of NO, NO₂ and PM_{2.5} mass as a function of traffic volumes alongside an urban arterial. *Atmos Environ* 122: 133-141. <http://dx.doi.org/10.1016/j.atmosenv.2015.09.019>
- Kerr, GH; Goldberg, DL; Emma Knowland, K; Keller, CA; Oladini, D; Kheirbek, I; Mahoney, L; Lu, Z; Anenberg, SC. (2022). Diesel passenger vehicle shares influenced COVID-19 changes in urban nitrogen dioxide pollution. *Environ Res Lett* 17: 074010. <http://dx.doi.org/10.1088/1748-9326/ac7659>
- Kerr, GH; Goldberg, DL; Harris, MH; Henderson, BH; Hystad, P; Roy, A; Anenberg, SC. (2023). Ethnoracial Disparities in Nitrogen Dioxide Pollution in the United States: Comparing Data Sets from Satellites, Models, and Monitors. *Environ Sci Technol* 57: 19532-19544. <http://dx.doi.org/10.1021/acs.est.3c03999>
- Kharitonov, SA; Walker, L; Barnes, PJ. (2005). Repeatability of standardised nasal nitric oxide measurements in healthy and asthmatic adults and children. *Respir Med* 99: 1105-1114. <http://dx.doi.org/10.1016/j.rmed.2005.02.019>
- Khoder, MI. (2002). Nitrous acid concentrations in homes and offices in residential areas in Greater Cairo. *J Environ Monit* 4: 573-578. <http://dx.doi.org/10.1039/b201818g>

- [Kim, YM; Kim, J; Han, Y; Lee, BJ; Choi, DC; Cheong, HK; Jeon, BH; Oh, I; Bae, GN; Lee, JY; Kim, CH; Seo, S; Noh, SR; Ahn, K.](#) (2017). Comparison of diverse estimation methods for personal exposure to air pollutants and associations with allergic symptoms: The Allergy & Gene-Environment Link (ANGEL) study. *Sci Total Environ* 579: 1127-1136. <http://dx.doi.org/10.1016/j.scitotenv.2016.11.090>
- [Kimbrough, S; Owen, RC; Snyder, M; Richmond-Bryant, J.](#) (2017). NO to NO₂ conversion rate analysis and implications for dispersion model chemistry methods using Las Vegas, Nevada near-road field measurements. *Atmos Environ* 165: 23-34. <http://dx.doi.org/10.1016/j.atmosenv.2017.06.027>
- [Kirsch, M; Korth, HG; Sustmann, R; De Groot, H.](#) (2002). The pathobiochemistry of nitrogen dioxide [Review]. *Biol Chem* 383: 389-399. <http://dx.doi.org/10.1515/BC.2002.043>
- [Kleinman, MT; Mautz, WJ.](#) (1991). The effects of exercise on dose and dose distribution of inhaled automotive pollutants. In *Res Rep Health Eff Inst* 1991, Oct(45):1-40; discussion 41-50 [Research report (Health Effects Institute)] (pp. 1-40; discussion 41-50). (Research Report no. 45). Cambridge, MA: Health Effects Institute. <http://pubs.healtheffects.org/view.php?id=45>
- [Klepeis, NE; Nelson, WC; Ott, WR; Robinson, JP; Tsang, AM; Switzer, P; Behar, JV; Hern, SC; Engelmann, WH.](#) (2001). The National Human Activity Pattern Survey (NHAPS): A resource for assessing exposure to environmental pollutants. *J Expo Anal Environ Epidemiol* 11: 231-252. <http://dx.doi.org/10.1038/sj.jea.7500165>
- [Klepeis, NE; Tsang, AM; Behar, JV.](#) (1996). Analysis of the national human activity pattern survey (NHAPS) respondents from a standpoint of exposure assessment [EPA Report]. (EPA/600/R-96/074). Washington, DC: U.S. Environmental Protection Agency. <http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockkey=9101VZRG.txt>
- [Klompaker, JO; Hoek, G; Bloemsa, LD; Marra, M; Wijga, AH; van den Brink, C; Brunekreef, B; Lebret, E; Gehring, U; Janssen, NAH.](#) (2020). Surrounding green, air pollution, traffic noise exposure and non-accidental and cause-specific mortality. *Environ Int* 134: 105341. <http://dx.doi.org/10.1016/j.envint.2019.105341>
- [Klompaker, JO; Hoek, G; Bloemsa, LD; Wijga, AH; van den Brink, C; Brunekreef, B; Lebret, E; Gehring, U; Janssen, NAH.](#) (2019). Associations of combined exposures to surrounding green, air pollution and traffic noise on mental health. *Environ Int* 129: 525-537. <http://dx.doi.org/10.1016/j.envint.2019.05.040>
- [Klompaker, JO; Janssen, N; Andersen, ZJ; Atkinson, R; Bauwelinck, M; Chen, J; de Hoogh, K; Houthuijs, D; Katsouyanni, K; Marra, M; Oftedal, B; Rodopoulou, S; Samoli, E; Stafoggia, M; Strak, M; Swart, W; Wesseling, J; Vienneau, D; Brunekreef, B; Hoek, G.](#) (2021). Comparison of associations between mortality and air pollution exposure estimated with a hybrid, a land-use regression and a dispersion model. *Environ Int* 146: 106306. <http://dx.doi.org/10.1016/j.envint.2020.106306>
- [Kornartit, C; Sokhi, RS; Burton, MA; Ravindra, K.](#) (2010). Activity pattern and personal exposure to nitrogen dioxide in indoor and outdoor microenvironments. *Environ Int* 36: 36-45. <http://dx.doi.org/10.1016/j.envint.2009.09.004>
- [Krajewski, AK; Luben, TJ; Warren, JL; Rappazzo, KM.](#) (2023). Associations between weekly gestational exposure of fine particulate matter, ozone, and nitrogen dioxide and preterm birth in a North Carolina Birth Cohort, 2003-2015. *Environmental epidemiology* (Philadelphia, Pa) 7: e278-. <http://dx.doi.org/10.1097/ee9.0000000000000278>
- [Lal, RM; Ramaswami, A; Russell, AG.](#) (2020). Assessment of the Near-Road (monitoring) Network including comparison with nearby monitors within US cities. *Environ Res Lett* 15: 114026. <http://dx.doi.org/10.1088/1748-9326/ab8156>
- [Lamsal, L; okN; Haffner, D; Swartz, WH; Fisher, B; Bucsele, E; Krotkov, NA; Vasilkov, A; Marchenko, S; Qin, W; Yang, E, unSu; Fasnacht, Z; Joiner, J; Choi, S.](#) (2021). Ozone Monitoring Instrument (OMI) Aura nitrogen dioxide standard product version 4.0 with improved surface and cloud treatments. *Atmos Meas Tech* 14: 455-479. <http://dx.doi.org/10.5194/amt-14-455-2021>

- [Lane, HM; Morello-Frosch, R; Marshall, JD; Apte, JS. \(2022\). Historical Redlining Is Associated with Present-Day Air Pollution Disparities in U.S. Cities. Environ Sci Technol Lett 9: 345-350. <http://dx.doi.org/10.1021/acs.estlett.1c01012>](#)
- [Languille, B; Gros, V; Nicolas, B; Honoré, C; Kaufmann, A; Zeitouni, K. \(2022\). Personal exposure to black carbon, particulate matter and nitrogen dioxide in the Paris region measured by portable sensors worn by volunteers. Toxics 10: 33. <http://dx.doi.org/10.3390/toxics10010033>](#)
- [Larkin, A; Geddes, JA; Martin, RV; Xiao, Q; Liu, Y; Marshall, JD; Brauer, M; Hystad, P. \(2017\). Global land use regression model for nitrogen dioxide air pollution. Environ Sci Technol 51: 6957-6964. <http://dx.doi.org/10.1021/acs.est.7b01148>](#)
- [Leaderer, BP; Naeher, L; Jankun, T; Balenger, K; Holford, TR; Toth, C; Sullivan, J; Wolfson, JM; Koutrakis, P. \(1999\). Indoor, outdoor, and regional summer and winter concentrations of PM₁₀, PM₂₅, SO₄₂₋, H⁺, NH₄⁺, NO₃₋, NH₃, and nitrous acid in homes with and without kerosene space heaters. Environ Health Perspect 107: 223-231. <http://dx.doi.org/10.1289/ehp.99107223>](#)
- [Leavey, A; Reed, N; Patel, S; Bradley, K; Kulkarni, P; Biswas, P. \(2017\). Comparing on-road real-time simultaneous in-cabin and outdoor particulate and gaseous concentrations for a range of ventilation scenarios. Atmos Environ 166: 130-141. <http://dx.doi.org/10.1016/j.atmosenv.2017.07.016>](#)
- [Lebel, ED; Finnegan, CJ; Ouyang, Z; Jackson, RB. \(2022\). Methane and NO_x emissions from natural gas stoves, cooktops, and ovens in residential homes. Environ Sci Technol 56: 2529-2539. <http://dx.doi.org/10.1021/acs.est.1c04707>](#)
- [Lee, HJ; Liu, Y; Chat, RB. \(2023\). Neighborhood-scale ambient NO₂ concentrations using TROPOMI NO₂ data: Applications for spatially comprehensive exposure assessment. Sci Total Environ 857: 159342. <http://dx.doi.org/10.1016/j.scitotenv.2022.159342>](#)
- [Lee, K; Xue, J; Geyh, AS; Ozkaynak, H; Leaderer, BP; Weschler, CJ; Spengler, JD. \(2002\). Nitrous acid, nitrogen dioxide, and ozone concentrations in residential environments. Environ Health Perspect 110: 145-150. <http://dx.doi.org/10.1289/ehp.02110145>](#)
- [Lelieveld, S; teven; Lelieveld, J; os; Mishra, A, shmi; Daiber, A, ndreas; Pozzer, A, ndrea; Poeschl, U, lrich; Berkemeier, T, homas. \(2024\). Endogenous Nitric Oxide Can Enhance Oxidative Stress Caused by Air Pollutants and Explain Higher Susceptibility of Individuals with Inflammatory Disorders. Environ Sci Technol 58: 1823-1831. <http://dx.doi.org/10.1021/acs.est.3c07010>](#)
- [Letellier, N; Zamora, S; Spoon, C; Yang, JA; Mortamais, M; Escobar, GC; Sears, DD; Jankowska, MM; Benmarhnia, T. \(2022\). Air pollution and metabolic disorders: Dynamic versus static measures of exposure among Hispanics/Latinos and non-Hispanics. Environ Res 209: 112846. <http://dx.doi.org/10.1016/j.envres.2022.112846>](#)
- [Li, J; Dai, L; Deng, X; Zhang, J; Song, C; Xu, J; Wang, A; Xiong, Z; Shan, Y; Huang, X. \(2023a\). Association between long-term exposure to low level air pollutants and incident end-stage kidney disease in the UK Biobank: A prospective cohort. Chemosphere 338: 139470. <http://dx.doi.org/10.1016/j.chemosphere.2023.139470>](#)
- [Li, J; Song, H; Luo, T; Cao, Y; Zhang, L; Zhao, Q; Li, Z; Hu, X; Gu, J; Tian, S. \(2024\). Exposure to O₃ and NO₂ on the interfacial chemistry of the pulmonary surfactant and the mechanism of lung oxidative damage. Chemosphere 362: 142669-. <http://dx.doi.org/10.1016/j.chemosphere.2024.142669>](#)
- [Li, Y; Xie, T; Cardoso Melo, RD; de Vries, M; Lakerveld, J; Zijlema, W; Hartman, CA. \(2023b\). Longitudinal effects of environmental noise and air pollution exposure on autism spectrum disorder and attention-deficit/hyperactivity disorder during adolescence and early adulthood: The TRAILS study. Environ Res 227: 115704. <http://dx.doi.org/10.1016/j.envres.2023.115704>](#)
- [Liang, D; Golan, R; Moutinho, JL; Chang, HH; Greenwald, R; Sarnat, SE; Russell, AG; Sarnat, JA. \(2018\). Errors associated with the use of roadside monitoring in the estimation of acute traffic pollutant-related health effects. Environ Res 165: 210-219. <http://dx.doi.org/10.1016/j.envres.2018.04.013>](#)

- Lima, ES; Bonini, MG; Augusto, O; Barbeiro, HV; Souza, HP; Abdalla, DS. (2005). Nitrate lipids decompose to nitric oxide and lipid radicals and cause vasorelaxation. Free Radic Biol Med 39: 532-539. <http://dx.doi.org/10.1016/j.freeradbiomed.2005.04.005>
- Lindström, J; Szpiro, AA; Sampson, PD; Oron, AP; Richards, M; Larson, TV; Sheppard, L. (2013). A flexible spatio-temporal model for air pollution with spatial and spatio-temporal covariates. Environ Ecol Stat 21: 411-433. <http://dx.doi.org/10.1007/s10651-013-0261-4>
- Lipfert, FW. (2016). A critical review of the ESCAPE project for estimating long-term health effects of air pollution [Review]. Environ Int 99: 87-96. <http://dx.doi.org/10.1016/j.envint.2016.11.028>
- Lippai, I; Magliozzo, RS; Peisach, J. (1999). EPR spectroscopic reinvestigation of the activation of iron complexes of PMAH as a bleomycin model. J Am Chem Soc 121: 780-784.
- Liu, C; Liang, L; Xu, W; Ma, Q. (2024). A review of indoor nitrous acid (HONO) pollution: Measurement techniques, pollution characteristics, sources, and sinks. Sci Total Environ 921: 171100. <http://dx.doi.org/10.1016/j.scitotenv.2024.171100>
- Liu, CS; Wei, Y; Danesh Yazdi, M; Qiu, X; Castro, E; Zhu, Q; Li, L; Koutrakis, P; Ekenga, CC; Shi, L; Schwartz, JD. (2023). Long-term association of air pollution and incidence of lung cancer among older Americans: A national study in the Medicare cohort. Environ Int 181: 108266. <http://dx.doi.org/10.1016/j.envint.2023.108266>
- Liu, F, ei; Ronald, J, vanderA; Eskes, H; Ding, J; Mijling, B, as. (2018). Evaluation of modeling NO₂ concentrations driven by satellite-derived and bottom-up emission inventories using in situ measurements over China. Atmos Chem Phys 18: 4171-4186. <http://dx.doi.org/10.5194/acp-18-4171-2018>
- Liu, J; Deng, H; Lakey, PSJ; Jiang, H; Mekic, M; Wang, X; Shiraiwa, M; Gligorovski, S. (2020). Unexpectedly high indoor HONO concentrations associated with photochemical NO₂ transformation on glass windows. Environ Sci Technol 54: 15680-15688. <http://dx.doi.org/10.1021/acs.est.0c05624>
- Loupa, G; Rapsomanikis, S. (2008). Air pollutant emission rates and concentrations in medieval churches. J Atmos Chem 60: 169-187. <http://dx.doi.org/10.1007/s10874-008-9116-z>
- Lovasi, GS; Treat, CA; Fry, D; Shah, I; Clougherty, JE; Berberian, A; Perera, FP; Kioumourtoglou, MA. (2022). Clean fleets, different streets: Evaluating the effect of New York City's clean bus program on changes to estimated ambient air pollution. J Expo Sci Environ Epidemiol 33: 332-338. <http://dx.doi.org/10.1038/s41370-022-00454-5>
- Lovich, MA; Bruno, NK; Plant, CP; Wei, AE; Vasquez, GB; Johnson, BJ; Fine, DH; Gilbert, RJ. (2011). Use of ultra pure nitric oxide generated by the reduction of nitrogen dioxide to reverse pulmonary hypertension in hypoxemic swine. Nitric Oxide 24: 204-212. <http://dx.doi.org/10.1016/j.niox.2011.04.006>
- Lu, T; Marshall, JD; Zhang, W; Hystad, P; Kim, SY; Bechle, MJ; Demuzere, M; Hankey, S. (2021). National empirical models of air pollution using microscale measures of the urban environment. Environ Sci Technol 55: 15519-15530. <http://dx.doi.org/10.1021/acs.est.1c04047>
- Lucht, S; Glaubitz, L; Moebus, S; Schramm, S; Jockwitz, C; Caspers, S; Hoffmann, B. (2022). Long-term air pollution, noise, and structural measures of the Default Mode Network in the brain: Results from the 1000BRAINS cohort. Int J Hyg Environ Health 239: 113867. <http://dx.doi.org/10.1016/j.ijheh.2021.113867>
- Lundberg, JON; Farkas-Szallasi, T; Weitzberg, E; Rinder, J; Lidholm, J; Änggård, A; Hökfelt, T; Lundberg, JM; Alving, K. (1995). High nitric oxide production in human paranasal sinuses. Nat Med 1: 370-373. <http://dx.doi.org/10.1038/nm0495-370>
- Lundberg, JON; Settergren, G; Gelinder, S; Lundberg, JM; Alving, K; Weitzberg, E. (1996). Inhalation of nasally derived nitric oxide modulates pulmonary function in humans. Acta Physiol Scand 158: 343-347. <http://dx.doi.org/10.1046/j.1365-201X.1996.557321000.x>
- Luo, H; Zhang, Q; Yu, K; Meng, X; Kan, H; Chen, R. (2022). Long-term exposure to ambient air pollution is a risk factor for trajectory of cardiometabolic multimorbidity: A prospective study in the UK Biobank. EBioMedicine 84: 104282. <http://dx.doi.org/10.1016/j.ebiom.2022.104282>

- [Madej, E; Folkes, LK; Wardman, P; Czapski, G; Goldstein, S. \(2008\). Thiyl radicals react with nitric oxide to form S-nitrosothiols with rate constants near the diffusion-controlled limit. Free Radic Biol Med 44: 2013-2018. <http://dx.doi.org/10.1016/j.freeradbiomed.2008.02.015>](#)
- [Mage, D; Wilson, W; Hasselblad, V; Grant, L. \(1999\). Assessment of human exposure to ambient particulate matter. J Air Waste Manag Assoc 49: 1280-1291. <http://dx.doi.org/10.1080/10473289.1999.10463964>](#)
- [Mallach, G; Shutt, R; Thomson, EM; Valcin, F; Kulka, R; Weichenthal, S. \(2023\). Randomized cross-over study of in-vehicle cabin air filtration, air pollution exposure, and acute changes to heart rate variability, saliva cortisol, and cognitive function. Environ Sci Technol 57: 3238-3247. <http://dx.doi.org/10.1021/acs.est.2c06556>](#)
- [Mann, JK; Lutzker, L; Holm, SM; Margolis, HG; Neophytou, AM; Eisen, EA; Costello, S; Tyner, T; Holland, N; Tindula, G; Prunicki, M; Nadeau, K; Noth, EM; Lurmann, F; Hammond, SK; Balmes, JR. \(2021\). Traffic-related air pollution is associated with glucose dysregulation, blood pressure, and oxidative stress in children. Environ Res 195: 110870. <http://dx.doi.org/10.1016/j.envres.2021.110870>](#)
- [Matte, TD; Ross, Z; Kheirbek, I; Eisl, H; Johnson, S; Gorczynski, JE; Kass, D; Markowitz, S; Pezeshki, G; Clougherty, JE. \(2013\). Monitoring intraurban spatial patterns of multiple combustion air pollutants in New York City: Design and implementation. J Expo Sci Environ Epidemiol 23: 223-231. <http://dx.doi.org/10.1038/jes.2012.126>](#)
- [Matthaios, VN; Kang, CM; Wolfson, JM; Greco, KF; Gaffin, JM; Hauptman, M; Cunningham, A; Petty, CR; Lawrence, J; Phipatanakul, W; Gold, DR; Koutrakis, P. \(2022\). Factors influencing classroom exposures to fine particles, black carbon, and nitrogen dioxide in inner-city schools and their implications for indoor air quality. Environ Health Perspect 130: 47005. <http://dx.doi.org/10.1289/EHP10007>](#)
- [Matthaios, VN; Kramer, LJ; Crilley, LR; Sommariva, R; Pope, FD; Bloss, WJ. \(2020\). Quantification of within-vehicle exposure to NO_x and particles: Variation with outside air quality, route choice and ventilation options. Atmos Environ 240: 117810. <http://dx.doi.org/10.1016/j.atmosenv.2020.117810>](#)
- [Matthaios, VN; Rooney, D; Harrison, RM; Koutrakis, P; Bloss, WJ. \(2023\). NO₂ levels inside vehicle cabins with pollen and activated carbon filters: A real world targeted intervention to estimate NO₂ exposure reduction potential. Sci Total Environ 860: 160395. <http://dx.doi.org/10.1016/j.scitotenv.2022.160395>](#)
- [McConnell, R; Islam, T; Shankardass, K; Jerrett, M; Lurmann, F; Gilliland, F; Gauderman, J; Avol, E; Künzli, N; Yao, L; Peters, J; Berhane, K. \(2010\). Childhood incident asthma and traffic-related air pollution at home and school. Environ Health Perspect 118: 1021-1026. <http://dx.doi.org/10.1289/ehp.0901232>](#)
- [Mccurdy, T; Graham, SE. \(2003\). Using human activity data in exposure models: Analysis of discriminating factors. J Expo Anal Environ Epidemiol 13: 294-317. <http://dx.doi.org/10.1038/sj.jea.7500281>](#)
- [Meng, Q; Williams, R; Pinto, JP. \(2012a\). Determinants of the associations between ambient concentrations and personal exposures to ambient PM_{2.5}, NO₂, and O₃ during DEARS. Atmos Environ 63: 109-116. <http://dx.doi.org/10.1016/j.atmosenv.2012.09.019>](#)
- [Meng, QY; Svendsgaard, D; Kotchmar, DJ; Pinto, JP. \(2012b\). Associations between personal exposures and ambient concentrations of nitrogen dioxide: A quantitative research synthesis. Atmos Environ 57: 322-329. <http://dx.doi.org/10.1016/j.atmosenv.2012.04.035>](#)
- [Mercer, RR; Russell, ML; Roggli, VL; Crapo, JD. \(1994\). Cell number and distribution in human and rat airways. Am J Respir Cell Mol Biol 10: 613-624. <http://dx.doi.org/10.1165/ajrcmb.10.6.8003339>](#)
- [Mikhailik, A; Michurina, TV; Dikranian, K; Hearn, S; Maxakov, VI; Siller, SS; Takemaru, KI; Enikolopov, G; Peunova, N. \(2021\). nNOS regulates ciliated cell polarity, ciliary beat frequency, and directional flow in mouse trachea. 4. <http://dx.doi.org/10.26508/lsa.202000981>](#)

- Milando, CW; Batterman, SA. (2018). Sensitivity analysis of the near-road dispersion model RLINE - an evaluation at Detroit, Michigan. Atmos Environ 181: 135-144. <http://dx.doi.org/10.1016/j.atmosenv.2018.03.009>
- Miller, DJ; Actkinson, B; Padilla, L; Griffin, RJ; Moore, K; Lewis, PGT; Gardner-Frolick, R; Craft, E; Portier, CJ; Hamburg, SP; Alvarez, RA. (2020). Characterizing elevated urban air pollutant spatial patterns with mobile monitoring in Houston, Texas. Environ Sci Technol 54: 2133-2142. <http://dx.doi.org/10.1021/acs.est.9b05523>
- Miller, FJ; Overton, JH, Jr; Jaskot, RH; Menzel, DB. (1985). A model of the regional uptake of gaseous pollutants in the lung: I. The sensitivity of the uptake of ozone in the human lung to lower respiratory tract secretions and exercise. Toxicol Appl Pharmacol 79: 11-27. [http://dx.doi.org/10.1016/0041-008X\(85\)90364-3](http://dx.doi.org/10.1016/0041-008X(85)90364-3)
- Miller, FJ; Overton, JH; Myers, ET; Graham, JA. (1982). Pulmonary dosimetry of nitrogen dioxide in animals and man. In T Schneider; L Grant (Eds.), Air pollution by nitrogen oxides (pp. 377-386). Amsterdam: Elsevier Scientific Publishing Company.
- Miller, L; Xu, X; Lemke, LD; Wheeler, AJ. (2019). Interannual variation of air quality across an international airshed in Detroit (USA) and Windsor (Canada): A comparison of two sampling campaigns in both cities. Atmos Environ 198: 417-426. <http://dx.doi.org/10.1016/j.atmosenv.2018.11.017>
- Mishra, A; Lelieveld, S; Pöschl, U; Berkemeier, T. (2023). Multiphase Kinetic Modeling of Air Pollutant Effects on Protein Modification and Nitrotyrosine Formation in Epithelial Lining Fluid. Environ Sci Technol 57: 12642-12653. <http://dx.doi.org/10.1021/acs.est.3c03556>
- Miyanishi, K; Kinouchi, T; Kataoka, K; Kanoh, T; Ohnishi, Y. (1996). In vivo formation of mutagens by intraperitoneal administration of polycyclic aromatic hydrocarbons in animals during exposure to nitrogen dioxide. Carcinogenesis 17: 1483-1490. <http://dx.doi.org/10.1093/carcin/17.7.1483>
- Moitra, S; Foraster, M; Arbillaga-Etxarri, A; Marín, A; Barberan-Garcia, A; Rodríguez-Chiaradia, DA; Balcells, E; Koreny, M; Torán-Monserrat, P; Vall-Casas, P; Rodríguez-Roisin, R; Garcia-Aymerich, J. (2022). Roles of the physical environment in health-related quality of life in patients with chronic obstructive pulmonary disease. Environ Res 203: 111828. <http://dx.doi.org/10.1016/j.envres.2021.111828>
- Mölter, A; Lindley, S; de Vocht, F; Agius, R; Kerry, G; Johnson, K; Ashmore, M; Terry, A; Dimitroulopoulou, S; Simpson, A. (2012). Performance of a microenvironmental model for estimating personal NO₂ exposure in children. Atmos Environ 51: 225-233. <http://dx.doi.org/10.1016/j.atmosenv.2012.01.030>
- Morris, EA; Speroni, S; Taylor, BD. (2024). Going nowhere faster: did the covid-19 pandemic accelerate the trend toward staying home? J Am Plann Assoc 1. <http://dx.doi.org/10.1080/01944363.2024.2385327>
- Moutinho, JL; Liang, D; Golan, R; Sarnat, SE; Weber, R; Sarnat, JA; Russell, AG. (2020). Near-road vehicle emissions air quality monitoring for exposure modeling. Atmos Environ 224: 117318. <http://dx.doi.org/10.1016/j.atmosenv.2020.117318>
- Mukerjee, S; Smith, L; Brantley, H; Stallings, C; Neas, L; Kimbrough, S; Williams, R. (2015). Comparison of modeled traffic exposure zones using on-road air pollution measurements. Atmos Pollut Res 6: 82-87. <http://dx.doi.org/10.5094/APR.2015.010>
- Mullen, NA; Li, J; Russell, ML; Spears, M; Less, BD; Singer, BC. (2015). Results of the California healthy homes indoor air quality study of 2011-2013: Impact of natural gas appliances on air pollutant concentrations. Indoor Air 26: 231-245. <http://dx.doi.org/10.1111/ina.12190>
- Namba, T; Masaki, N; Hitomi, Y; Ishinoda, Y; Iwashita, M; Yumita, Y; Kagami, K; Yasuda, R; Ikegami, Y; Toya, T; Nagatomo, Y; Takase, B; Soejima, K; Adachi, T. (2022). Association of serum nitric oxide metabolite level with mortality in patients undergoing coronary angiography. J Cardiol 80: 578-584. <http://dx.doi.org/10.1016/j.jjcc.2022.07.020>
- Nathan, C. (1992). Nitric oxide as a secretory product of mammalian cells [Review]. FASEB J 6: 3051-3064. <http://dx.doi.org/10.1096/fasebj.6.12.1381691>

- Nathanael, JG; Wille, U. (2023). Phenylalanine Residues Are Very Rapidly Damaged by Nitrate Radicals (NO₃ center dot) in an Aqueous Environment. Chembiochem 24. <http://dx.doi.org/10.1002/cbic.202200731>
- Nathanael, JG; Yuan, B; Wille, U. (2022). Oxidative Damage of Aliphatic Amino Acid Residues by the Environmental Pollutant NO₃.: Impact of Water on the Reactivity. Environ Sci Technol 56: 7687-7695. <http://dx.doi.org/10.1021/acs.est.2c00863>
- Ng, AW; Bidani, A; Heming, TA. (2004). Innate host defense of the lung: effects of lung-lining fluid pH [Review]. Lung 182: 297-317. <http://dx.doi.org/10.1007/s00408-004-2511-6>
- Niepsch, D; Clarke, LJ; Tzoulas, K; Cavan, G. (2022). Spatiotemporal variability of nitrogen dioxide (NO₂) pollution in Manchester (UK) city centre (2017-2018) using a fine spatial scale single-NO_x diffusion tube network. Environ Geochem Health 44: 3907-3927. <http://dx.doi.org/10.1007/s10653-021-01149-w>
- Nieuwenhuijsen, MJ; Gascon, M; Martinez, D; Ponjoan, A; Blanch, J; Garcia-Gil, MDM; Ramos, R; Foraster, M; Mueller, N; Espinosa, A; Cirach, M; Khreis, H; Dadvand, P; Basagaña, X. (2018). Air Pollution, Noise, Blue Space, and Green Space and Premature Mortality in Barcelona: A Mega Cohort. Int J Environ Res Public Health 15. <http://dx.doi.org/10.3390/ijerph15112405>
- Nobile, F; Forastiere, A; Michelozzi, P; Forastiere, F; Stafoggia, M. (2023). Long-term exposure to air pollution and incidence of mental disorders. A large longitudinal cohort study of adults within an urban area. Environ Int 181: 108302. <http://dx.doi.org/10.1016/j.envint.2023.108302>
- Ntarladima, AM; Karssenbergh, D; Vaartjes, I; Grobbee, DE; Schmitz, O; Lu, M; Boer, J; Koppelman, G; Vonk, J; Vermeulen, R; Hoek, G; Gehring, U. (2021). A comparison of associations with childhood lung function between air pollution exposure assessment methods with and without accounting for time-activity patterns. Environ Res 202: 111710. <http://dx.doi.org/10.1016/j.envres.2021.111710>
- O'Donnell, VB; Eiserich, JP; Chumley, PH; Jablonsky, MJ; Krishna, NR; Kirk, M; Barnes, S; Darley-Usmar, VM; Freeman, BA. (1999). Nitration of unsaturated fatty acids by nitric oxide-derived reactive nitrogen species peroxynitrite, nitrous acid, nitrogen dioxide, and nitronium ion. Chem Res Toxicol 12: 83-92. <http://dx.doi.org/10.1021/tx980207u>
- Ohlwein, S; Hennig, F; Lucht, S; Matthiessen, C; Pundt, N; Moebus, S; Jöckel, KH; Hoffmann, B. (2019). Indoor and outdoor road traffic noise and incident diabetes mellitus: Results from a longitudinal German cohort study. Environ Epidemiol 3: e037. <http://dx.doi.org/10.1097/EE9.0000000000000037>
- Olin, AC; Bake, B; Torén, K. (2007). Fraction of exhaled nitric oxide at 50 mL/s: Reference values for adult lifelong never-smokers. Chest 131: 1852-1856. <http://dx.doi.org/10.1378/chest.06-2928>
- Ouidir, M; Giorgis-Allemand, L; Lyon-Caen, S; Morelli, X; Cracowski, C; Pontet, S; Pin, I; Lepeule, J; Siroux, V; Slama, R. (2015). Estimation of exposure to atmospheric pollutants during pregnancy integrating space-time activity and indoor air levels: Does it make a difference? Environ Int 84: 161-173. <http://dx.doi.org/10.1016/j.envint.2015.07.021>
- Pacher, P; Beckman, JS; Liaudet, L. (2007). Nitric oxide and peroxynitrite in health and disease [Review]. Physiol Rev 87: 315-424. <http://dx.doi.org/10.1152/physrev.00029.2006>
- Park, SS; Hong, JH; Lee, JH; Kim, YJ; Cho, SY; Kim, SJ. (2008). Investigation of nitrous acid concentration in an indoor environment using an in-situ monitoring system. Atmos Environ 42: 6586-6596. <http://dx.doi.org/10.1016/j.atmosenv.2008.05.023>
- Pattinson, W; Langstaff, J; Longley, I, an; Kingham, S. (2016). Use of an exposure model to explore the impact of residential proximity to a highway on exposures to air pollutants of an ambient origin. Air Qual Atmos Health 9: 335-357. <http://dx.doi.org/10.1007/s11869-015-0343-6>
- Patton, AP; Laumbach, R; Ohman-Strickland, P; Black, K; Alimokhtari, S; Liroy, P; Kipen, HM. (2016). Scripted drives: A robust protocol for generating exposures to traffic-related air pollution. Atmos Environ 143: 290-299. <http://dx.doi.org/10.1016/j.atmosenv.2016.08.038>
- Pedersen, M; Halldorsson, TI; Ketzel, M; Grandström, C; Raaschou-Nielsen, O; Jensen, SS; Grunnet, LG; Vaag, A; Sørensen, M; Olsen, SF. (2019). Associations between ambient air pollution and

noise from road traffic with blood pressure and insulin resistance in children from Denmark. *Environ Epidemiol* 3: e069. <http://dx.doi.org/10.1097/EE9.0000000000000069>

Physick, W; Powell, J; Cope, M; Boast, K; Lee, S. (2011). Measurements of personal exposure to NO₂ and modelling using ambient concentrations and activity data. *Atmos Environ* 45: 2095-2102. <http://dx.doi.org/10.1016/j.atmosenv.2011.01.063>

Pietropaoli, AP; Perillo, IB; Perkins, PT; Frasier, LM; Speers, DM; Frampton, MW; Utell, MJ; Hyde, RW. (2007). Smokers have reduced nitric oxide production by conducting airways but normal levels in the alveoli. *Inhal Toxicol* 19: 533-541. <http://dx.doi.org/10.1080/08958370701260673>

Pietropaoli, AP; Perillo, IB; Torres, A; Perkins, PT; Frasier, LM; Utell, MJ; Frampton, MW; Hyde, RW. (1999). Simultaneous measurement of nitric oxide production by conducting and alveolar airways of humans. *J Appl Physiol* (1985) 87: 1532-1542. <http://dx.doi.org/10.1152/jappl.1999.87.4.1532>

Pleijel, H; Karlsson, GP; Gerdin, EB. (2004). On the logarithmic relationship between NO₂ concentration and the distance from a highroad. *Sci Total Environ* 332: 261-264. <http://dx.doi.org/10.1016/j.scitotenv.2004.03.020>

Plopper, CG; Hatch, GE; Wong, V; Duan, X; Weir, AJ; Tarkington, BK; Devlin, RB; Becker, S; Buckpitt, AR. (1998). Relationship of inhaled ozone concentration to acute tracheobronchial epithelial injury, site-specific ozone dose and glutathione depletion in rhesus monkeys. *Am J Respir Cell Mol Biol* 19: 387-399. <http://dx.doi.org/10.1165/ajrcmb.19.3.3183>

Poddubny, VA; Yushketova, NA. (2013). A physicochemical model of sorption processes in NO₂ passive sampling with air humidity effects. *Environ Monit Assess* 185: 3819-3829. <http://dx.doi.org/10.1007/s10661-012-2830-7>

Polidori, A; Fine, PM. (2012). Ambient concentrations of criteria and air toxic pollutants in close proximity to a freeway with heavy-duty diesel traffic. Final report. South Coast Air Quality Management District. <http://www.aqmd.gov/docs/default-source/air-quality/air-quality-monitoring-studies/near-roadway-study.pdf?sfvrsn=2>

Ponzi, E; Vineis, P; Chung, KF; Blangiardo, M. (2020). Accounting for measurement error to assess the effect of air pollution on omic signals. *PLoS ONE* 15: e0226102. <http://dx.doi.org/10.1371/journal.pone.0226102>

Postlethwait, EM; Bidani, A. (1989). Pulmonary disposition of inhaled NO₂-nitrogen in isolated rat lungs. *Toxicol Appl Pharmacol* 98: 303-312. [http://dx.doi.org/10.1016/0041-008x\(89\)90235-4](http://dx.doi.org/10.1016/0041-008x(89)90235-4)

Postlethwait, EM; Bidani, A. (1990). Reactive uptake governs the pulmonary air space removal of inhaled nitrogen dioxide. *J Appl Physiol* (1985) 68: 594-603.

Postlethwait, EM; Bidani, A. (1994). Mechanisms of pulmonary NO₂ absorption [Review]. *Toxicology* 89: 217-237. [http://dx.doi.org/10.1016/0300-483x\(94\)90099-x](http://dx.doi.org/10.1016/0300-483x(94)90099-x)

Postlethwait, EM; Langford, SD; Bidani, A. (1991a). Interfacial transfer kinetics of NO₂ into pulmonary epithelial lining fluid. *J Appl Physiol* (1985) 71: 1502-1510.

Postlethwait, EM; Langford, SD; Bidani, A. (1991b). Transfer of NO₂ through pulmonary epithelial lining fluid. *Toxicol Appl Pharmacol* 109: 464-471. [http://dx.doi.org/10.1016/0041-008X\(91\)90009-4](http://dx.doi.org/10.1016/0041-008X(91)90009-4)

Postlethwait, EM; Langford, SD; Bidani, A. (1992). Kinetics of NO₂ air space absorption in isolated rat lungs. *J Appl Physiol* (1985) 73: 1939-1945.

Postlethwait, EM; Langford, SD; Jacobson, LM; Bidani, A. (1995). NO₂ reactive absorption substrates in rat pulmonary surface lining fluids. *Free Radic Biol Med* 19: 553-563. [http://dx.doi.org/10.1016/0891-5849\(95\)00058-6](http://dx.doi.org/10.1016/0891-5849(95)00058-6)

Postlethwait, EM; Mustafa, MG. (1981). Fate of inhaled nitrogen dioxide in isolated perfused rat lung. *J Toxicol Environ Health* 7: 861-872. <http://dx.doi.org/10.1080/15287398109530029>

Postlethwait, EM; Mustafa, MG. (1989). Effect of altered dose rate on NO₂ uptake and transformation in isolated lungs. *J Toxicol Environ Health* 26: 497-507. <http://dx.doi.org/10.1080/15287398909531272>

Pryor, WA. (1992). How far does ozone penetrate into the pulmonary air/tissue boundary before it reacts? *Free Radic Biol Med* 12: 83-88. [http://dx.doi.org/10.1016/0891-5849\(92\)90060-T](http://dx.doi.org/10.1016/0891-5849(92)90060-T)

- Qi, M; Dixit, K; Marshal, JD; Zhang, W; Hankey, S. (2022). National land use regression model for NO₂ using street view imagery and satellite observations. *Environ Sci Technol* 56: 13499-13509. <http://dx.doi.org/10.1021/acs.est.2c03581>
- Que, LG; Yang, Z; Stamler, JS; Lugogo, NL; Kraft, M. (2009). S-nitrosoglutathione reductase: An important regulator in human asthma. *Am J Respir Crit Care Med* 180: 226-231. <http://dx.doi.org/10.1164/rccm.200901-0158OC>
- Radi, R. (2013). Protein tyrosine nitration: biochemical mechanisms and structural basis of functional effects. *Acc Chem Res* 46: 550-559. <http://dx.doi.org/10.1021/ar300234c>
- Ragettli, MS; Phuleria, HC; Tsai, MY; Schindler, C; de Nazelle, A; Ducret-Stich, RE; Ineichen, A; Perez, L; Braun-Fahrlander, C; Probst-Hensch, N; Künzli, N. (2014). The relevance of commuter and work/school exposure in an epidemiological study on traffic-related air pollution. *J Expo Sci Environ Epidemiol* 25: 474-481. <http://dx.doi.org/10.1038/jes.2014.83>
- Rangel, A; Raysoni, AU; Chavez, MC; Jeon, S; Aguilera, J; Whigham, LD; Li, WW. (2022). Assessment of traffic-related air pollution (TRAP) at two near-road schools and residence in El Paso, Texas, USA. *Atmos Pollut Res* 13: 101304. <http://dx.doi.org/10.1016/j.apr.2021.101304>
- Rattigan, OV; Carpenter, AC; Civerolo, KL; Felton, HD. (2020). Pollutant measurements at near road and urban background sites in New York, USA. *Atmos Pollut Res* 11: 859-870. <http://dx.doi.org/10.1016/j.apr.2020.01.014>
- Reis, S; Liška, T; Vieno, M; Carnell, EJ; Beck, R; Clemens, T; Dragosits, U; Tomlinson, SJ; Leaver, D; Heal, MR. (2018). The influence of residential and workday population mobility on exposure to air pollution in the UK. *Environ Int* 121: 803-813. <http://dx.doi.org/10.1016/j.envint.2018.10.005>
- Rich, DQ; Frampton, MW; Balmes, JR; Bromberg, PA; Arjomandi, M; Hazucha, MJ; Thurston, SW; Alexis, NE; Ganz, P; Zareba, W; Koutrakis, P; Thevenet-Morrison, K. (2020). Multicenter Ozone Study in older Subjects (MOSES): Part 2. Effects of Personal and Ambient Concentrations of Ozone and Other Pollutants on Cardiovascular and Pulmonary Function (pp. 1-90). (ISSN 1041-5505 EISSN 2688-6855 Health Report 192, Part 2). Boston, MA: Health Effects Institute. <https://www.healtheffects.org/publication/multicenter-ozone-study-older-subjects-moses-part-2-effects-personal-and-ambient>
- Richmond-Bryant, J; Long, TC. (2020). Influence of exposure measurement errors on results from epidemiologic studies of different designs [Review]. *J Expo Sci Environ Epidemiol* 30: 420-429. <http://dx.doi.org/10.1038/s41370-019-0164-z>
- Richmond-Bryant, J; Owen, RC; Graham, S; Snyder, M; McDow, S; Oakes, M; Kimbrough, S. (2017a). Estimation of on-road NO₂ concentrations, NO₂/NO_x ratios, and related roadway gradients from near-road monitoring data. *Air Qual Atmos Health* 10: 611-625. <http://dx.doi.org/10.1007/s11869-016-0455-7>
- Richmond-Bryant, JS; Owen, RC; Kimbrough, S. (2017b). Factors associated with NO₂ and NO_x concentration gradients near a highway. *Atmos Environ* 174: 214-226. <http://dx.doi.org/10.1016/j.atmosenv.2017.11.026>
- Riley, EA; Gould, T; Hartin, K; Fruin, SA; Simpson, CD; Yost, MG; Larson, T. (2016). Ultrafine particle size as a tracer for aircraft turbine emissions. *Atmos Environ* 139: 20-29. <http://dx.doi.org/10.1016/j.atmosenv.2016.05.016>
- Robinson, O; Tamayo, I; de Castro, M; Valentin, A; Giorgis-Allemand, L; Krog, NH; Aasvang, GM; Ambros, A; Ballester, F; Bird, P; Chatzi, L; Cirach, M; Dédèlè, A; Donaire-Gonzalez, D; Gražuleviciene, R; Iakovidis, M; Ibarluzea, J; Kampouri, M; Lepeule, J; ... Basagaña, X. (2018). The urban exposome during pregnancy and its socioeconomic determinants. *Environ Health Perspect* 126: 077005. <http://dx.doi.org/10.1289/EHP2862>
- Ross, Z; Ito, K; Johnson, S; Yee, M; Pezeshki, G; Clougherty, JE; Savitz, D; Matte, T. (2013). Spatial and temporal estimation of air pollutants in New York City: Exposure assignment for use in a birth outcomes study. *Environ Health* 12: 51. <http://dx.doi.org/10.1186/1476-069X-12-51>

- Ross, Z; Kheirbek, I; Clougherty, JE; Ito, K; Matte, T; Markowitz, S; Eisl, H. (2011). Noise, air pollutants and traffic: Continuous measurement and correlation at a high-traffic location in New York City. *Environ Res* 111: 1054-1063. <http://dx.doi.org/10.1016/j.envres.2011.09.004>
- Rossi, R; Ceccato, R; Gastaldi, M. (2020). Effect of Road Traffic on Air Pollution. *Experimental Evidence from COVID-19 Lockdown. Sustainability* 12: 8984. <http://dx.doi.org/10.3390/su12218984>
- Roswall, N; Raaschou-Nielsen, O; Ketzel, M; Gammelmark, A; Overvad, K; Olsen, A; Sørensen, M. (2017). Long-term residential road traffic noise and NO₂ exposure in relation to risk of incident myocardial infarction - A Danish cohort study. *Environ Res* 156: 80-86. <http://dx.doi.org/10.1016/j.envres.2017.03.019>
- Roughton, FJ; Forster, RE. (1957). Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. *J Appl Physiol* (1985) 11: 290-302.
- Rubenchik, BL; Glavin, AA; Galenko, PM; Kilichko, AA; Olenick, IO; Artemov, KV. (1995). Gaseous nitrogen dioxide increases the endogenous synthesis of carcinogenic N-nitrosodimethylamine in animals. *J Environ Pathol Toxicol Oncol* 14: 111-115.
- Rudolph, V; Rudolph, TK; Schopfer, FJ; Bonacci, G; Woodcock, SR; Cole, MP; Baker, PR; Ramani, R; Freeman, BA. (2010). Endogenous generation and protective effects of nitro-fatty acids in a murine model of focal cardiac ischaemia and reperfusion. *Cardiovasc Res* 85: 155-166. <http://dx.doi.org/10.1093/cvr/cvp275>
- Safaei Fakhr, B; Di Fenza, R; Gianni, S; Wiegand, SB; Miyazaki, Y; Araujo Morais, CC; Gibson, LE; Chang, MG; Mueller, AL; Rodriguez-Lopez, JM; Ackman, JB; Arora, P; Scott, LK; Bloch, DB; Zapol, WM; Carroll, RW; Ichinose, F; Berra, L; Investigators, NOS. (2021). Inhaled high dose nitric oxide is a safe and effective respiratory treatment in spontaneous breathing hospitalized patients with COVID-19 pneumonia. *Nitric Oxide* 116: 7-13. <http://dx.doi.org/10.1016/j.niox.2021.08.003>
- Sagai, M; Arakawa, K; Ichinose, T; Shimojo, N. (1987). Biochemical effects on combined gases of nitrogen dioxide and ozone: I. Species differences of lipid peroxides and phospholipids in lungs. *Toxicology* 46: 251-265. [http://dx.doi.org/10.1016/0300-483X\(87\)90207-1](http://dx.doi.org/10.1016/0300-483X(87)90207-1)
- Saha, PK; Khlystov, A; Snyder, MG; Grieshop, AP. (2018). Characterization of air pollutant concentrations, fleet emission factors, and dispersion near a North Carolina interstate freeway across two seasons. *Atmos Environ* 177: 143-153. <http://dx.doi.org/10.1016/j.atmosenv.2018.01.019>
- Salman, AK; Choi, Y; Park, J; Mousavinezhad, S; Payami, M; Momeni, M; Ghahremanloo, M. (2024). Deep learning based emulator for simulating CMAQ surface NO₂ levels over the CONUS. *Atmos Environ* 316: 120192. <http://dx.doi.org/10.1016/j.atmosenv.2023.120192>
- Samoli, E; Butland, BK. (2017). Incorporating measurement error from modeled air pollution exposures into epidemiological analyses [Review]. *Curr Environ Health Rep* 4: 472-480. <http://dx.doi.org/10.1007/s40572-017-0160-1>
- Samoli, E; Butland, BK; Rodopoulou, S; Atkinson, RW; Barratt, B; Beevers, SD; Beddows, A; Dimakopoulou, K; Schwartz, JD; Yazdi, MD; Katsouyanni, K. (2020). The impact of measurement error in modeled ambient particles exposures on health effect estimates in multilevel analysis: A simulation study. *Environ Epidemiol* 4: e094. <http://dx.doi.org/10.1097/EE9.0000000000000094>
- Samoli, E; Stergiopoulou, A; Santana, P; Rodopoulou, S; Mitsakou, C; Dimitroulopoulou, C; Bauwelinck, M; de Hoogh, K; Costa, C; Mari-Dell'Olmo, M; Corman, D; Vardoulakis, S; Katsouyanni, K. (2019). Spatial variability in air pollution exposure in relation to socioeconomic indicators in nine European metropolitan areas: A study on environmental inequality. *Environ Pollut* 249: 345-353. <http://dx.doi.org/10.1016/j.envpol.2019.03.050>

- Sampson, PD; Szpiro, AA; Sheppard, L; Lindstrom, J; Kaufman, JD. (2011). Pragmatic estimation of a spatio-temporal air quality model with irregular monitoring data. Atmos Environ 45: 6593-6606. <http://dx.doi.org/10.1016/j.atmosenv.2011.04.073>
- Sanna, A; Kurtansky, A; Veriter, C; Stanescu, D. (1994). BRONCHODILATOR EFFECT SF INHALED NITRIC-OXIDE IN HEALTHY-MEN. Am J Respir Crit Care Med 150: 1702-1704.
- Sarnat, JA; Russell, A; Liang, D; Moutinho, JL; Golan, R; Weber, RJ; Gao, D; Sarnat, SE; Chang, HH; Greenwald, R; Yu, T. (2018). Developing multipollutant exposure indicators of traffic pollution: The Dorm Room Inhalation to Vehicle Emissions (DRIVE) Study. (Research Report 196). Boston, MA: Health Effects Institute.
- Sarwar, G; Corsi, R; Kumura, Y; Allen, D; Weschler, CJ. (2002). Hydroxyl radicals in indoor environments. Atmos Environ 36: 3973-3988. [http://dx.doi.org/10.1016/S1352-2310\(02\)00278-9](http://dx.doi.org/10.1016/S1352-2310(02)00278-9)
- Sather, ME; Slonecker, ET; Mathew, J; Daughtrey, H; Williams, DD. (2007). Evaluation of ogawa passive sampling devices as an alternative measurement method for the nitrogen dioxide annual standard in El Paso, Texas. Environ Monit Assess 124: 211-221. <http://dx.doi.org/10.1007/s10661-006-9219-4>
- Sawyer, K; Brown, J; HazuchaM; Bennett, WD. (2007). The effect of exercise on nasal uptake of ozone in healthy human adults. J Appl Physiol (1985) 102: 1380-1386. <http://dx.doi.org/10.1152/japplphysiol.00269.2006>
- Sayegh, A; Tate, JE; Ropkins, K. (2016). Understanding how roadside concentrations of NO_x are influenced by the background levels, traffic density, and meteorological conditions using Boosted Regression Trees. Atmos Environ 127: 163-175. <http://dx.doi.org/10.1016/j.atmosenv.2015.12.024>
- Schneider, P; Castell, N; Vogt, M; Dauge, FR; Lahoz, WA; Bartonova, A. (2017). Mapping urban air quality in near real-time using observations from low-cost sensors and model information. Environ Int 106: 234-247. <http://dx.doi.org/10.1016/j.envint.2017.05.005>
- Schwartz, SE; White, WH. (1983). Kinetics of reactive dissolution of nitrogen oxides into aqueous solution. In SE Schwartz (Ed.), Trace atmospheric constituents: Properties, transformations, and fates (pp. 1-116). New York, NY: Wiley.
- Seagram, AF; Brown, SG; Huang, S; Landsberg, K; Eisinger, DS. (2019). National assessment of near-road air quality in 2016: Multi-year pollutant trends and estimation of near-road PM_{2.5} increment. Trans Res Rec 2673: 161-171. <http://dx.doi.org/10.1177/0361198119825538>
- See, KC; Christiani, DC. (2013). Normal values and thresholds for the clinical interpretation of exhaled nitric oxide levels in the US general population: Results from the National Health and Nutrition Examination Survey 2007-2010. Chest 143: 107-116. <http://dx.doi.org/10.1378/chest.12-0416>
- Štrevičienė, V; Paliulis, D. (2012). Influence of temperature and relative humidity on the performance of nitrogen dioxide diffusive sampler. Res J of Chem Sci 2: 89-92.
- Servais, S; Boussouar, A; Molnar, A; Douki, T; Pequignot, JM; Favier, R. (2005). Age-related sensitivity to lung oxidative stress during ozone exposure. Free Radic Res 39: 305-316. <http://dx.doi.org/10.1080/10715760400011098>
- Shafran-Nathan, R; Yuval; Broday, DM. (2018). Impacts of personal mobility and diurnal concentration variability on exposure misclassification to ambient pollutants. Environ Sci Technol 52: 3520-3526. <http://dx.doi.org/10.1021/acs.est.7b05656>
- Shafran-Nathan, R; Yuval; Levy, I; Broday, DM. (2016). Exposure estimation errors to nitrogen oxides on a population scale due to daytime activity away from home. Sci Total Environ 580: 1401-1409. <http://dx.doi.org/10.1016/j.scitotenv.2016.12.105>
- Shairsingh, KK; Jeong, CH; Wang, JM; Evans, GJ. (2018). Characterizing the spatial variability of local and background concentration signals for air pollution at the neighbourhood scale. Atmos Environ 183: 57-68. <http://dx.doi.org/10.1016/j.atmosenv.2018.04.010>
- Shakeri, F; Amin, F; Marefati, N; Roshan, NM; Boskabady, M; Boskabady, MH. (2023). Effect of Allium cepa extract on total and differential WBC, TP level, oxidant and antioxidant biomarkers, and

- lung pathology in ovalbumin-sensitized rats. *Allergol Immunopathol* 51: 153-162.
<http://dx.doi.org/10.15586/aei.v51i3.532>
- Shekarzifard, M; Faghih-Imani, A; Crouse, D; Goldberg, M; Ross, N; Eluru, N; Hatzopoulou, M.
 (2016a). Individual exposure to traffic related air pollution across land-use clusters. *Transport Res Transport Environ* 46: 339-350. <http://dx.doi.org/10.1016/j.trd.2016.04.010>
- Shekarzifard, M; Faghih-Imani, A; Hatzopoulou, M. (2016b). An examination of population exposure to traffic related air pollution: Comparing spatially and temporally resolved estimates against long-term average exposures at the home location. *Environ Res* 147: 435-444.
<http://dx.doi.org/10.1016/j.envres.2016.02.039>
- Shen, Y, ouchen; de Hoogh, K, ees; Schmitz, O, liver; Gulliver, J, ohn; Vienneau, D, anielle; Vermeulen, R, oel; Hoek, G, erard; Karssenber, D, erek. (2024). Europe-wide high-spatial resolution air pollution models are improved by including traffic flow estimates on all roads. *Atmos Environ* 335. <http://dx.doi.org/10.1016/j.atmosenv.2024.120719>
- Shetty, S, hobitha; Schneider, P, hilipp; Stebel, K, erstin; Hamer, P, aul David; Kylling, A, rve; Berntsen, T, erje Koren. (2024). Estimating surface NO₂ concentrations over Europe using Sentinel-5P TROPOMI observations and Machine Learning. *Rem Sens Environ* 312.
<http://dx.doi.org/10.1016/j.rse.2024.114321>
- Shmool, JLC; Michanowicz, DR; Cambal, L; Tunno, B; Howell, J; Gillooly, S; Roper, C; Tripathy, S; Chubb, LG; Eisl, HM; Gorczynski, JE; Holguin, FE; Shields, KN; Clougherty, JE. (2014). Saturation sampling for spatial variation in multiple air pollutants across an inversion-prone metropolitan area of complex terraing. *Environ Health* 13: 28. <http://dx.doi.org/10.1186/1476-069X-13-28>
- Simon, H, eather; Hogrefe, C, hristian; Whitehill, A, ndrew; Foley, K, risten M.; Liljegren, J, ennifer; Possiel, N, orm; Wells, B, enjamin; Henderson, B, arron H.; Valin, L, ukas C.; Tonnesen, G, ail; Appel, K, . Wyat; Koplitz, S, hannon. (2024). Revisiting day-of-week ozone patterns in an era of evolving US air quality. *Atmos Chem Phys* 24. <http://dx.doi.org/10.5194/acp-24-1855-2024>
- Simon, PK; Dasgupta, PK. (1995). Continuous automated measurement of the soluble fraction of atmospheric particulate matter. *Anal Chem* 67: 71-78. <http://dx.doi.org/10.1021/ac00097a012>
- Singer, BC; Chan, WR; Kim, YS; Offermann, FJ; Walker, IS. (2020). Indoor air quality in California homes with code-required mechanical ventilation. *Indoor Air* 30: 885-899.
<http://dx.doi.org/10.1111/ina.12676>
- Singer, BC; Pass, RZ; Delp, WW; Lorenzetti, DM; Maddalena, RL. (2017). Pollutant concentrations and emission rates from natural gas cooking burners without and with range hood exhaust in nine California homes. *Build Environ* 122: 215-229. <http://dx.doi.org/10.1016/j.buildenv.2017.06.021>
- Singh, A; Guo, T; Bush, T; Abreu, P; Leach, FCP; Stacey, B; Economides, G; Anderson, R; Cole, S; Thomas, GN; Pope, FDD; Bartington, SEE. (2022). Impacts of COVID-19 lockdown on traffic flow, active travel and gaseous pollutant concentrations; Implications for future emissions control measures in Oxford, UK. *Sustainability* 14: 16182. <http://dx.doi.org/10.3390/su142316182>
- Singh, K; Armstrong, SC; Wagner, BE; Counts, J; Skinner, A; Kay, M; Li, JS; Shah, S; Zucker, N; Neshteruk, C; Story, M; Suarez, L; Kraus, WE; Zizzi, AR; Dunn, J. (2024). Physical activity and sleep changes among children during the COVID-19 pandemic. *NPJ DIGITAL MEDICINE* 7: 70. <http://dx.doi.org/10.1038/s41746-024-01041-8>
- Slade, R; Crissman, K; Norwood, J; Hatch, G. (1993). Comparison of antioxidant substances in bronchoalveolar lavage cells and fluid from humans, guinea pigs, and rats. *Exp Lung Res* 19: 469-484. <http://dx.doi.org/10.3109/01902149309064358>
- Smith, JD; Mitsakou, C; Kitwiroon, N; Barratt, BM; Walton, HA; Taylor, JG; Anderson, HR; Kelly, FJ; Beevers, SD. (2016). The London Hybrid Exposure Model (LHEM): Improving human exposure estimates to NO₂ and PM_{2.5} in an urban setting. *Environ Sci Technol* 50: 11760-11768.
<http://dx.doi.org/10.1021/acs.est.6b01817>
- Smith, RB; Beevers, SD; Gulliver, J; Dajnak, D; Fecht, D; Blangiardo, M; Douglass, M; Hansell, AL; Anderson, HR; Kelly, FJ; Toledano, MB. (2020). Impacts of air pollution and noise on risk of

- preterm birth and stillbirth in London. *Environ Int* 134: 105290. <http://dx.doi.org/10.1016/j.envint.2019.105290>
- So, R; Andersen, ZJ; Chen, J; Stafoggia, M; de Hoogh, K; Katsouyanni, K; Vienneau, D; Rodopoulou, S; Samoli, E; Lim, YH; Jørgensen, JT; Amini, H; Cole-Hunter, T; Mahmood Taghavi Shahri, S; Maric, M; Bergmann, M; Liu, S; Azam, S; Loft, S; ... Mehta, AJ. (2022). Long-term exposure to air pollution and mortality in a Danish nationwide administrative cohort study: Beyond mortality from cardiopulmonary disease and lung cancer. *Environ Int* 164: 107241. <http://dx.doi.org/10.1016/j.envint.2022.107241>
- So, R; Jørgensen, JT; Lim, YH; Mehta, AJ; Amini, H; Mortensen, LH; Westendorp, R; Ketzel, M; Hertel, O; Brandt, J; Christensen, JH; Geels, C; Frohn, LM; Sjøgaard, T; Bräuner, EV; Jensen, SS; Backalarz, C; Simonsen, MK; Loft, S; Cole-Hunter, T; Andersen, ZJ. (2020). Long-term exposure to low levels of air pollution and mortality adjusting for road traffic noise: A Danish Nurse Cohort study. *Environ Int* 143: 105983. <http://dx.doi.org/10.1016/j.envint.2020.105983>
- Song, Y; Namkung, W; Nielson, DW; Lee, JW; Finkbeiner, WE; Verkman, AS. (2009). Airway surface liquid depth measured in ex vivo fragments of pig and human trachea: Dependence on Na⁺ and Cl⁻ channel function. *Am J Physiol Lung Cell Mol Physiol* 297: L1131-L1140. <http://dx.doi.org/10.1152/ajplung.00085.2009>
- Sørensen, M; Poulsen, AH; Hvidtfeldt, UA; Brandt, J; Frohn, LM; Ketzel, M; Christensen, JH; Im, U; Khan, J; Münzel, T; Raaschou-Nielsen, O. (2022a). Air pollution, road traffic noise and lack of greenness and risk of type 2 diabetes: A multi-exposure prospective study covering Denmark. *Environ Int* 170: 107570. <http://dx.doi.org/10.1016/j.envint.2022.107570>
- Sørensen, M; Poulsen, AH; Hvidtfeldt, UA; Frohn, LM; Ketzel, M; Christensen, JH; Brandt, J; Geels, C; Raaschou-Nielsen, O. (2022b). Exposure to source-specific air pollution and risk for type 2 diabetes: A nationwide study covering Denmark. *Int J Epidemiol* 51: 1219-1229. <http://dx.doi.org/10.1093/ije/dyac040>
- Sousan, S; Koehler, K; Thomas, G, eb; Park, J; Hillman, M; Halterman, A; Peters, TM. (2016). Inter-comparison of low-cost sensors for measuring the mass concentration of occupational aerosols. *Aerosol Sci Technol* 50: 462-473. <http://dx.doi.org/10.1080/02786826.2016.1162901>
- Souza, PAF; Kroptavich, CR; Zhou, S; Kahan, TF. (2024). Oxidant concentrations and photochemistry in a vehicle cabin. *Environ Sci Process Impacts*. <http://dx.doi.org/10.1039/d4em00319e>
- Spector, B, arak M. M.; Shusterman, D, ennis J. J.; Zhao, K, ai. (2023). Nasal nitric oxide flux from the paranasal sinuses. *Curr Opin Allergy Clin Immunol* 23: 22-28. <http://dx.doi.org/10.1097/aci.0000000000000871>
- Spengler, JD; Brauer, M; Samet, JM; Lambert, WE. (1993). Nitrous acid in Albuquerque, New Mexico, homes. *Environ Sci Technol* 27: 841-845. <http://dx.doi.org/10.1021/es00042a005>
- Spicer, CW; Coutant, RW; Ward, GF; Joseph, DW; Gaynor, AJ; Billick, IH. (1989). Rates and mechanisms of NO₂ removal from indoor air by residential materials. *Environ Int* 15: 643-654. [http://dx.doi.org/10.1016/0160-4120\(89\)90087-1](http://dx.doi.org/10.1016/0160-4120(89)90087-1)
- Spicer, CW; Kenny, DV; Ward, GF; Billick, IH. (1993). Transformations, lifetimes, and sources of NO₂, HONO, and HNO₃ in indoor environments. *J Air Waste Manag Assoc* 43: 1479-1485.
- Spinelle, L; Gerboles, M; Villani, MG; Aleixandre, M; Bonavitacola, F. (2017). Field calibration of a cluster of low-cost commercially available sensors for air quality monitoring. Part B: NO, CO and CO₂. *Sens Actuators B* 238: 706-715. <http://dx.doi.org/10.1016/j.snb.2016.07.036>
- Squadrito, GL; Postlethwait, EM. (2009). On the hydrophobicity of nitrogen dioxide: Could there be a "lens" effect for NO(2) reaction kinetics. *Nitric Oxide* 21: 104-109. <http://dx.doi.org/10.1016/j.niox.2009.05.008>
- Squadrito, GL; Postlethwait, EM; Matalon, S. (2010). Elucidating mechanisms of chlorine toxicity: Reaction kinetics, thermodynamics, and physiological implications [Review]. *Am J Physiol Lung Cell Mol Physiol* 299: L289-L300. <http://dx.doi.org/10.1152/ajplung.00077.2010>

- Squizzato, S; Masiol, M; Rich, DQ; Hopke, PK. (2018). PM2.5 and gaseous pollutants in New York State during 2005-2016: Spatial variability, temporal trends, and economic influences. *Atmos Environ* 183: 209-224. <http://dx.doi.org/10.1016/j.atmosenv.2018.03.045>
- Stafoggia, M; Oftedal, B; Chen, J; Rodopoulou, S; Renzi, M; Atkinson, RW; Bauwelinck, M; Klompmaker, JO; Mehta, A; Vienneau, D; Andersen, ZJ; Bellander, T; Brandt, J; Cesaroni, G; de Hoogh, K; Focht, D; Gulliver, J; Hertel, O; Hoffmann, B; ... Janssen, NAH. (2022). Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project. *The Lancet Planetary Health* 6: e9-e18. [http://dx.doi.org/10.1016/S2542-5196\(21\)00277-1](http://dx.doi.org/10.1016/S2542-5196(21)00277-1)
- Stavrakou, T; Müller, JF; Bauwens, M; Boersma, KF; van Geffen, J. (2020). Satellite evidence for changes in the NO2 weekly cycle over large cities. *Sci Rep* 10: 10066. <http://dx.doi.org/10.1038/s41598-020-66891-0>
- Stieb, DM; Chen, L; Hystad, P; Beckerman, BS; Jerrett, M; Tjepkema, M; Crouse, DL; Omariba, DW; Peters, PA; van Donkelaar, A; Martin, RV; Burnett, RT; Liu, S; Smith-Doiron, M; Dugandzic, RM. (2016). A national study of the association between traffic-related air pollution and adverse pregnancy outcomes in Canada, 1999-2008. *Environ Res* 148: 513-526. <http://dx.doi.org/10.1016/j.envres.2016.04.025>
- Stucki, L, ara; Betner, S, taffan; Selander, J, enny; Lohmus, M, are; Akesson, A, gnet; Eriksson, C, harlotta. (2023). Sociodemographic inequalities in long-term exposure to air pollution, road traffic noise, and greenness: A population-based cohort study of women. *Environmental epidemiology (Philadelphia, Pa)* 7: e279-. <http://dx.doi.org/10.1097/ee9.0000000000000279>
- Sun, Y; Headon, KS; Jiao, A; Slezak, JM; Avila, CC; Chiu, VY; Sacks, DA; Molitor, J; Benmarhnia, T; Chen, JC; Getahun, D; Wu, J. (2023). Association of antepartum and postpartum air pollution exposure with postpartum depression in Southern California. *JAMA Netw Open* 6: e2338315. <http://dx.doi.org/10.1001/jamanetworkopen.2023.38315>
- Sun, Y; Li, X; Benmarhnia, T; Chen, JC; Avila, C; Sacks, DA; Chiu, V; Slezak, J; Molitor, J; Getahun, D; Wu, J. (2022). Exposure to air pollutant mixture and gestational diabetes mellitus in Southern California: Results from electronic health record data of a large pregnancy cohort. *Environ Int* 158: 106888. <http://dx.doi.org/10.1016/j.envint.2021.106888>
- Szpiro, AA; Paciorek, CJ. (2013). Measurement error in two-stage analyses, with application to air pollution epidemiology. *Environmetrics* 24: 501-517. <http://dx.doi.org/10.1002/env.2233>
- Szpiro, AA; Paciorek, CJ; Sheppard, L. (2011). Does more accurate exposure prediction necessarily improve health effect estimates? *Epidemiology* 22: 680-685. <http://dx.doi.org/10.1097/EDE.0b013e3182254cc6>
- Szpiro, AA; Sampson, PD; Sheppard, L; Lumley, T; Adar, SD; Kaufman, JD. (2010). Predicting intra-urban variation in air pollution concentrations with complex spatio-temporal dependencies. *Environmetrics* 21: 606-631. <http://dx.doi.org/10.1002/env.1014>
- Tessum, MW; Larson, T; Gould, TR; Simpson, CD; Yost, MG; Vedal, S. (2018). Mobile and Fixed-Site Measurements To Identify Spatial Distributions of Traffic-Related Pollution Sources in Los Angeles. *Environ Sci Technol* 52: 2844-2853. <http://dx.doi.org/10.1021/acs.est.7b04889>
- Thornadtsson, A; Drca, N; Ricciardolo, F; Högman, M. (2017). Increased levels of alveolar and airway exhaled nitric oxide in runners. *Ups J Med Sci* 122: 85-91. <http://dx.doi.org/10.1080/03009734.2017.1317886>
- Topp, R; Cyrus, J; Gebefugi, I; Schnelle-Kreis, J; Richter, K; Wichmann, HE; Heinrich, J. (2004). Indoor and outdoor air concentrations of BTEX and NO2: correlation of repeated measurements. *J Environ Monit* 6: 807-812. <http://dx.doi.org/10.1039/b405537c>
- Toro, C; Foley, K; Simon, H; Henderson, B; Baker, KR; Eyth, A; Timin, B; Appel, W; Luecken, D; Beardsley, M; Sonntag, D; Possiel, N; Roberts, S. (2021). Evaluation of 15 years of modeled atmospheric oxidized nitrogen compounds across the contiguous United States. *Elementa Sci Anthropocene* 9. <http://dx.doi.org/10.1525/elementa.2020.00158>

- Trees, IR; Saha, A; Putnick, DL; Clayton, PK; Mendola, P; Bell, EM; Sundaram, R; Yeung, EH. (2024). Prenatal exposure to air pollutant mixtures and birthweight in the upstate KIDS cohort. *Environ Int* 187: 108692-. <http://dx.doi.org/10.1016/j.envint.2024.108692>
- Tsoukias, NM; Dabdub, D; Wilson, AF; George, SC. (2000a). Effect of alveolar volume and sequential filling on the diffusing capacity of the lungs: II. Experiment. *Respir Physiol* 120: 251-271. [http://dx.doi.org/10.1016/S0034-5687\(00\)00104-3](http://dx.doi.org/10.1016/S0034-5687(00)00104-3)
- Tsoukias, NM; George, SC. (1998). A two-compartment model of pulmonary nitric oxide exchange dynamics. *J Appl Physiol* (1985) 85: 653-666.
- Tsoukias, NM; Wilson, AF; George, SC. (2000b). Effect of alveolar volume and sequential filling on the diffusing capacity of the lungs: I. theory. *Respir Physiol* 120: 231-249.
- Tsujino, I; Kawakami, Y; Kaneko, A. (2005). Comparative simulation of gas transport in airway models of rat, dog, and human. *Inhal Toxicol* 17: 475-485. <http://dx.doi.org/10.1080/08958370590964476>
- U.S. BLS (U.S. Bureau of Labor Statistics). (2023). Table 11A. Time spent in leisure and sports activities for the civilian population by selected characteristics, averages per day, 2023 annual averages [Database]. Retrieved from <https://www.bls.gov/news.release/atus.t11a.htm>
- U.S. EPA (U.S. Environmental Protection Agency). (1993). Air quality criteria for oxides of nitrogen (final, 1993) [EPA Report]. (EPA/600/8-91/049aF-cF). Washington, DC: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=40179>
- U.S. EPA (U.S. Environmental Protection Agency). (2008a). Integrated science assessment for oxides of nitrogen – Health criteria (Final report, 2008) [EPA Report]. (EPA/600/R-08/071). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP Division. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=194645>
- U.S. EPA (U.S. Environmental Protection Agency). (2008b). Risk and exposure assessment to support the review of the NO₂ primary national ambient air quality standard [EPA Report]. (EPA-452/R-08-008a). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. http://www.epa.gov/ttn/naaqs/standards/nox/data/20081121_NO2_REA_final.pdf
- U.S. EPA (U.S. Environmental Protection Agency). (2011). Exposure factors handbook: 2011 edition [EPA Report]. (EPA/600/R-090/052F). Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. <https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100F2OS.txt>
- U.S. EPA (U.S. Environmental Protection Agency). (2013). Integrated science assessment for ozone and related photochemical oxidants [EPA Report]. (EPA/600/R-10/076F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment-RTP Division. <http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=247492>
- U.S. EPA (U.S. Environmental Protection Agency). (2014a). Health risk and exposure assessment for ozone. Final report. (EPA-452/P-14-004a). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air And Radiation, Office of Air Quality Planning and Standards. <http://nepis.epa.gov/exe/ZyPURL.cgi?Dockey=P100KBUF.txt>
- U.S. EPA (U.S. Environmental Protection Agency). (2014b). Welfare Risk and Exposure Assessment for Ozone, Final. (EPA-452/P-14-005a). Research Triangle Park, NC: Office of Air Quality Planning and Standards. <https://www3.epa.gov/ttn/naaqs/standards/ozone/data/20141021welfarerea.pdf>
- U.S. EPA (U.S. Environmental Protection Agency). (2016). Integrated science assessment for oxides of nitrogen: Health criteria (Final report, Jan 2016) [EPA Report]. (EPA/600/R-15/068). Washington, DC. <https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310879>
- U.S. EPA (U.S. Environmental Protection Agency). (2019a). Air pollutants exposure model documentation (APEX, version 5.2) volume I: User's guide [EPA Report]. (EPA-452/R-19-

- 005a). Research Triangle Park, NC: Office of Air Quality Planning and Standards. https://www.epa.gov/sites/production/files/2019-12/documents/apex52_usersguide_vol1_october2019.pdf
- U.S. EPA (U.S. Environmental Protection Agency). (2019b). Air pollutants exposure model documentation (APEX, version 5.2) volume II: Technical support document [EPA Report]. (EPA-452/R-19-005b). Research Triangle Park, NC: Office of Air Quality Planning and Standards. https://www.epa.gov/sites/production/files/2019-12/documents/apex52_usersguide_vol2_october2019.pdf
- U.S. EPA (U.S. Environmental Protection Agency). (2021). 2021 policy on children's health, October 5, 2021 [EPA Report]. Washington, DC.
- U.S. EPA (U.S. Environmental Protection Agency). (2024). Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen. Volume 2: Planning for the Review and the Integrated Science Assessment [EPA Report]. (EPA-452/R-24-010b). Washington, DC.
- Ursino, D; Takama, Y. (2013). A review of data fusion techniques [Review]. TheScientificWorldJournal 2013: 704504. <http://dx.doi.org/10.1155/2013/704504>
- Van As, A. (1977). Pulmonary airway clearance mechanisms: A reappraisal [Editorial]. Am Rev Respir Dis 115: 721-726.
- van den Brekel, L, ieke; Lenters, V, irissa; Mackenbach, J, oreintje; Hoek, G, erard; Wagtendonk, A, lfred; Lakerveld, J, eroen; Grobbee, D, iederick E.; Vaartjes, I, lonca. (2024). Ethnic and socioeconomic inequalities in air pollution exposure: a cross-sectional analysis of nationwide individual-level data from the Netherlands. The Lancet Planetary Health 8: e18-e29. [http://dx.doi.org/10.1016/s2542-5196\(23\)00258-9](http://dx.doi.org/10.1016/s2542-5196(23)00258-9)
- van der Heijden, HHA, CM; Brouwer, ML; Hoekstra, F; van der Pol, P; Merkus, PJF, M. (2014). Reference values of exhaled nitric oxide in healthy children 1-5 years using off-line tidal breathing. Pediatr Pulmonol 49: 291-295. <http://dx.doi.org/10.1002/ppul.22796>
- van der Vliet, A; O'Neill, CA; Cross, CE; Koostra, JM; Volz, WG; Halliwell, B; Louie, S. (1999). Determination of low-molecular-mass antioxidant concentrations in human respiratory tract lining fluids. Am J Physiol 276: L289-L296.
- Van Ryswyk, K; Wheeler, AJ; Grgicak-Mannion, A; Xu, X; Curran, J; Caravaggio, G; Hall, A; Macdonald, P; Brook, JR. (2022). An investigation into which methods best explain children's exposure to traffic-related air pollution. Toxics 10: 284. <http://dx.doi.org/10.3390/toxics10060284>
- Van Stee, EW; Sloane, RA; Simmons, JE; Brunnemann, KD. (1983). In vivo formation of N-nitrosomorpholine in CD-1 mice exposed by inhalation to nitrogen dioxide and by gavage to morpholine. J Natl Cancer Inst 70: 375-379. <http://dx.doi.org/10.1093/jnci/70.2.375>
- Van Stee, EW; Sloane, RA; Simmons, JE; Moorman, MP; Brunnemann, KD. (1995). Endogenous formation of N-nitrosomorpholine in mice from 15NO₂ by inhalation and morpholine by gavage. Carcinogenesis 16: 89-92. <http://dx.doi.org/10.1093/carcin/16.1.89>
- Vardoulakis, S; Lumbreras, J; Solazzo, E. (2009). Comparative evaluation of nitrogen oxides and ozone passive diffusion tubes for exposure studies. Atmos Environ 43: 2509-2517. <http://dx.doi.org/10.1016/j.atmosenv.2009.02.048>
- Velders, GJM; Willers, SM; Wesseling, J; van den Elshout, S; van der Swaluw, E; Mooibroek, D; van Ratingen, S. (2021). Improvements in air quality in the Netherlands during the corona lockdown based on observations and model simulations. Atmos Environ 247: 118158. <http://dx.doi.org/10.1016/j.atmosenv.2020.118158>
- Velsor, LW; Ballinger, CA; Patel, J; Postlethwait, EM. (2003). Influence of epithelial lining fluid lipids on NO₂-induced membrane oxidation and nitration. Free Radic Biol Med 34: 720-733. [http://dx.doi.org/10.1016/S0891-5849\(02\)01370-9](http://dx.doi.org/10.1016/S0891-5849(02)01370-9)
- Velsor, LW; Postlethwait, EM. (1997). NO₂-induced generation of extracellular reactive oxygen is mediated by epithelial lining layer antioxidants. Am J Physiol 17: L1265-L1275.

- Vichi, F; De Santis, F. (2012). The measurement of the sink properties of triethanolamine (TEA) as a coating for collecting NO₂ by using annular diffusion denuders. *Environ Technol* 33: 1065-1069. <http://dx.doi.org/10.1080/09593330.2011.606848>
- Vienneau, D; Stafoggia, M; Rodopoulou, S; Chen, J; Atkinson, RW; Bauwelinck, M; Klompmaker, JO; Oftedal, B; Andersen, ZJ; Janssen, NAH; So, R; Lim, YH; Fluckiger, B; Ducret-Stich, R; Roosli, M; Probst-Hensch, N; Kunzli, N; Strak, M; Samoli, E; De Hoogh, K; Brunekreef, B; Hoek, G. (2023). Association between exposure to multiple air pollutants, transportation noise and cause-specific mortality in adults in Switzerland. *Environ Health* 22: 29. <http://dx.doi.org/10.1186/s12940-023-00983-y>
- Vlaanderen, J; Portengen, L; Chadeau-Hyam, M; Szpiro, A; Gehring, U; Brunekreef, B; Hoek, G; Vermeulen, R. (2019). Error in air pollution exposure model determinants and bias in health estimates. *J Expo Sci Environ Epidemiol* 29: 258-266. <http://dx.doi.org/10.1038/s41370-018-0045-x>
- Wagner, HM. (1970). Absorption von NO und NO₂ in MIK- und MAK-konzentrationen bei der inhalation. [Absorption von NO und NO₂ in MIK- und MAK-konzentrationen bei der inhalation]. *Staub Reinhalt Luft* 30: 380-381.
- Wallace, LA; Emmerich, SJ; Howard-Reed, C. (2004). Source strengths of ultrafine and fine particles due to cooking with a gas stove. *Environ Sci Technol* 38: 2304-2311. <http://dx.doi.org/10.1021/es0306260>
- Wang, C; Bottorff, B; Reidy, E; Rosales, CMF; Collins, DB; Novoselac, A; Farmer, DK; Vance, ME; Stevens, PS; Abbatt, JPD. (2020). Cooking, bleach cleaning, and air conditioning strongly impact levels of HONO in a house. *Environ Sci Technol* 54: 13488-13497. <http://dx.doi.org/10.1021/acs.est.0c05356>
- Wang, C; Soden, BJ; Yang, W; Munir, S; Mayfield, M; Coca, D. (2021). Understanding Spatial Variability of NO₂ in Urban Areas Using Spatial Modelling and Data Fusion Approaches. *Atmosphere (Basel)* 12: 179. <http://dx.doi.org/10.3390/atmos12020179>
- Wang, M; Beelen, R; Eeftens, M; Meliefste, K; Hoek, G; Brunekreef, B. (2012). Systematic evaluation of land use regression models for NO₂. *Environ Sci Technol* 46: 4481-4489. <http://dx.doi.org/10.1021/es204183v>
- Wang, M, eng; Zhou, X, iao-Hua Andrew; Curl, C, ynthia; Fitzpatrick, A, nnette; Vedal, S, verre; Kaufman, J, oel. (2023a). Long-term exposure to ambient air pollution and cognitive function in older US adults The Multi-Ethnic Study of Atherosclerosis. *Environmental epidemiology (Philadelphia, Pa)* 7: e242-. <http://dx.doi.org/10.1097/ee9.0000000000000242>
- Wang, Y; Hu, X; Chang, HH; Waller, LA; Belle, JH; Liu, Y. (1999). A Bayesian downscaler model to estimate daily PM_{2.5} levels in the conterminous US. *Int J Environ Res Public Health* 15. <http://dx.doi.org/10.3390/ijerph15091999>
- Wang, Y; Liu, P; Schwartz, J; Castro, E; Wang, W; Chang, H; Scovronick, N; Shi, L. (2023b). Disparities in ambient nitrogen dioxide pollution in the United States. *Proc Natl Acad Sci USA* 120: e2208450120. <http://dx.doi.org/10.1073/pnas.2208450120>
- Waring, MS; Wells, JR. (2015). Volatile organic compound conversion by ozone, hydroxyl radicals, and nitrate radicals in residential indoor air: Magnitudes and impacts of oxidant sources. *Atmos Environ* 106: 382-391. <http://dx.doi.org/10.1016/j.atmosenv.2014.06.062>
- Wei, Y; Amini, H; Qiu, X; Castro, E; Jin, T; Yin, K; Vu, BN; Healy, J; Feng, Y; Zhang, J; Coull, B; Schwartz, J. (2024). Grouped mixtures of air pollutants and seasonal temperature anomalies and cardiovascular hospitalizations among U.S. Residents. *Environ Int* 187: 108651. <http://dx.doi.org/10.1016/j.envint.2024.108651>
- Wei, Y; Qiu, X; Yazdi, MD; Shtein, A; Shi, L; Yang, J; Peralta, AA; Coull, BA; Schwartz, JD. (2022). The Impact of Exposure Measurement Error on the Estimated Concentration-Response Relationship between Long-Term Exposure to and Mortality. *Environ Health Perspect* 130: 77006. <http://dx.doi.org/10.1289/EHP10389>

- Weichenthal, S; Bélisle, P; Lavigne, E; Villeneuve, PJ; Wheeler, A; Xu, X; Joseph, L. (2015). Estimating risk of emergency room visits for asthma from personal versus fixed site measurements of NO₂. *Environ Res* 137: 323-328. <http://dx.doi.org/10.1016/j.envres.2015.01.006>
- Weissert, LF; Alberti, K; Miskell, G; Pattinson, W; Salmond, JA; Henshaw, G; Williams, DE. (2019). Low-cost sensors and microscale land use regression: Data fusion to resolve air quality variations with high spatial and temporal resolution. *Atmos Environ* 213: 285-295. <http://dx.doi.org/10.1016/j.atmosenv.2019.06.019>
- Weitzberg, E; Hezel, M; Lundberg, JO. (2010). Nitrate-nitrite-nitric oxide pathway: Implications for anesthesiology and intensive care [Review]. *Anesthesiology* 113: 1460-1475. <http://dx.doi.org/10.1097/ALN.0b013e3181fef3cc>
- Weitzberg, E; Lundberg, JO. (2013). Novel aspects of dietary nitrate and human health [Review]. *Annu Rev Nutr* 33: 129-159. <http://dx.doi.org/10.1146/annurev-nutr-071812-161159>
- Werder, E, mily; Lawrence, K, ailyn; Deng, X, inlei; Jackson II, W, . Braxton; Christenbury, K, ate; Buller, I, an; Engel, L, awrence; Sandler, D, ale. (2024). Residential air pollution, greenspace, and adverse mental health outcomes in the US Gulf Long-term Follow-up Study. *Sci Total Environ* 946: 174434-. <http://dx.doi.org/10.1016/j.scitotenv.2024.174434>
- Wesselink, AK; Hystad, P; Kirwa, K; Kaufman, JD; Willis, MD; Wang, TR; Szpiro, AA; Levy, JI; Savitz, DA; Rothman, KJ; Hatch, EE; Wise, LA. (2023). Air pollution and fecundability in a North American preconception cohort study. *Environ Int* 181: 108249. <http://dx.doi.org/10.1016/j.envint.2023.108249>
- Widdicombe, JH. (2002). Regulation of the depth and composition of airway surface liquid [Review]. *J Anat* 201: 313-318. <http://dx.doi.org/10.1046/j.1469-7580.2002.00098.x>
- Widdicombe, JH; Widdicombe, JG. (1995). Regulation of human airway surface liquid [Review]. *Respir Physiol* 99: 3-12. [http://dx.doi.org/10.1016/0034-5687\(94\)00095-H](http://dx.doi.org/10.1016/0034-5687(94)00095-H)
- Willis, MD; Hill, EL; Ncube, CN; Campbell, EJ; Harris, L; Harleman, M; Ritz, B; Hystad, P. (2023). Changes in Socioeconomic Disparities for Traffic-Related Air Pollution Exposure During Pregnancy Over a 20-Year Period in Texas. *JAMA Netw Open* 6: e2328012. <http://dx.doi.org/10.1001/jamanetworkopen.2023.28012>
- Wilson, WE; Brauer, M. (2006). Estimation of ambient and non-ambient components of particulate matter exposure from a personal monitoring panel study. *J Expo Sci Environ Epidemiol* 16: 264-274. <http://dx.doi.org/10.1038/sj.jes.7500483>
- Wilson, WE; Mage, DT; Grant, LD. (2000). Estimating separately personal exposure to ambient and nonambient particulate matter for epidemiology and risk assessment: Why and how. *J Air Waste Manag Assoc* 50: 1167-1183. <http://dx.doi.org/10.1080/10473289.2000.10464164>
- Wong, PY; Su, HJ; Lee, HY; Chen, YC; Hsiao, YP; Huang, JW; Teo, TA; Wu, CD; Spengler, JD; Klemes, JJ. (2021). Using land-use machine learning models to estimate daily NO₂ concentration variations in Taiwan. *J Clean Prod* 317. <http://dx.doi.org/10.1016/j.jclepro.2021.128411>
- Wu, X; Bennett, DH; Lee, K; Cassady, DL; Ritz, B; Hertz-Picciotto, I. (2011). Longitudinal variability of time-location/activity patterns of population at different ages: A longitudinal study in California. *Environ Health* 10: 80-. <http://dx.doi.org/10.1186/1476-069X-10-80>
- Xu, J; Jiang, H, an; Zhao, H; Stephens, B. (2017). Mobile monitoring of personal NO_x exposures during scripted daily activities in Chicago, IL. *Aerosol Air Qual Res* 17: 1999-2009. <http://dx.doi.org/10.4209/aaqr.2017.02.0063>
- Yaghi, A; Zaman, A; Cox, G; Dolovich, MB. (2012). Ciliary beating is depressed in nasal cilia from chronic obstructive pulmonary disease subjects. *Respir Med* 106: 1139-1147. <http://dx.doi.org/10.1016/j.rmed.2012.04.001>
- Yang, T; Hu, X; Wang, J; Rao, S; Cai, YS; Li, G; Huang, J; Rahimi, K. (2023). Long-term exposure to road traffic noise and incident heart failure: evidence from UK Biobank. *JACC: Heart Failure* 11: 986-996. <http://dx.doi.org/10.1016/j.jchf.2023.04.003>
- Yokoyama, E. (1968). Uptake of SO₂ and NO₂ by the isolated upper airways. *Koshu Eisei Kenkyu* 17: 302-306.

- Yu, H; Russell, A; Mulholland, J; Odman, T; Hu, Y; Chang, HH; Kumar, N. (2018). Cross-comparison and evaluation of air pollution field estimation methods. *Atmos Environ* 179: 49-60. <http://dx.doi.org/10.1016/j.atmosenv.2018.01.045>
- Yu, Y; Paul, K; Arah, OA; Mayeda, ER; Wu, J; Lee, E; Shih, IF; Su, J; Jerrett, M; Haan, M; Ritz, B. (2020). Air pollution, noise exposure, and metabolic syndrome – A cohort study in elderly Mexican-Americans in Sacramento area. *Environ Int* 134: 105269. <http://dx.doi.org/10.1016/j.envint.2019.105269>
- Zhang, J; Lim, YH; So, R; Jørgensen, JT; Mortensen, LH; Napolitano, GM; Cole-Hunter, T; Loft, S; Bhatt, S; Hoek, G; Brunekreef, B; Westendorp, R; Ketzel, M; Brandt, J; Lange, T; Kølsen-Fisher, T; Andersen, ZJ. (2023a). Long-term exposure to air pollution and risk of SARS-CoV-2 infection and COVID-19 hospitalisation or death: Danish nationwide cohort study. *Eur Respir J* 62: 2300280. <http://dx.doi.org/10.1183/13993003.00280-2023>
- Zhang, L; Yang, C; Xiao, Q; Geng, G; Cai, J; Chen, R; Meng, X, ia; Kan, H. (2021a). A Satellite-Based Land Use Regression Model of Ambient NO₂ with High Spatial Resolution in a Chinese City. *Remote Sensing* 13. <http://dx.doi.org/10.3390/rs13030397>
- Zhang, X; Craft, E; Zhang, K, ai. (2017). Characterizing spatial variability of air pollution from vehicle traffic around the Houston Ship Channel area. *Atmos Environ* 161: 167-175. <http://dx.doi.org/10.1016/j.atmosenv.2017.04.032>
- Zhang, X; Just, AC; Hsu, HL; Kloog, I; Woody, M; Mi, Z; Rush, J; Georgopoulos, P; Wright, RO; Stroustrup, A. (2021b). A hybrid approach to predict daily NO₂ concentrations at city block scale. *Sci Total Environ* 761: 143279. <http://dx.doi.org/10.1016/j.scitotenv.2020.143279>
- Zhang, X; Zhang, H; Wang, Y; Bai, P; Zhang, L; Wei, Y; Tang, N. (2023b). Characteristics and determinants of personal exposure to typical air pollutants: A pilot study in Beijing and Baoding, China. *Environ Res* 218: 114976. <http://dx.doi.org/10.1016/j.envres.2022.114976>
- Zhang, Y; Ma, C; Xiao, Y; Liu, C; Xu, Q; Wang, Y; Xu, X; Hao, L. (2010). Dual role of vitamin C utilization in NO₂-induced oxidative stress in lung tissues of mice. *Bull Environ Contam Toxicol* 84: 662-666. <http://dx.doi.org/10.1007/s00128-010-0021-1>
- Zhao, H; Chan, WR; Cohn, S; Delp, WW; Walker, IS; Singer, BC. (2021). Indoor air quality in new and renovated low-income apartments with mechanical ventilation and natural gas cooking in California. *Indoor Air* 31: 717-729. <http://dx.doi.org/10.1111/ina.12764>
- Zhou, Y; Levy, JI. (2007). Factors influencing the spatial extent of mobile source air pollution impacts: A meta-analysis [Review]. *BMC Public Health* 7: 89. <http://dx.doi.org/10.1186/1471-2458-7-89>
- Zou, X; Shen, Z; Yuan, T; Yin, S; Cai, J; Chen, L; Wang, W. (2006). Shifted power-law relationship between NO₂ concentration and the distance from a highway: A new dispersion model based on the wind profile model. *Atmos Environ* 40: 8068-8073. <http://dx.doi.org/10.1016/j.atmosenv.2006.09.012>
- Zuidema, C; Bi, J; Burnham, D; Carmona, N; Gassett, A; Slager, D; Schumacher, C; Austin, E; Seto, E; Szpiro, A; Sheppard, L. (In Press) Leveraging low-cost sensors to predict nitrogen dioxide for epidemiologic exposure assessment. *J Expo Sci Environ Epidemiol*. <http://dx.doi.org/10.1038/s41370-024-00667-w>
- Zuidema, C; Schumacher, CS; Austin, E; Carvlin, G; Larson, TV; Spalt, EW; Zusman, M; Gassett, AJ; Seto, E; Kaufman, JD; Sheppard, L. (2021). Deployment, calibration, and cross-validation of low-cost electrochemical sensors for carbon monoxide, nitrogen oxides, and ozone for an epidemiological study. *Sensors* 21: 4214. <http://dx.doi.org/10.3390/s21124214>
- Zusman, M; Gassett, AJ; Kirwa, K; Barr, RG; Cooper, CB; Han, MK; Kanner, RE; Koehler, K; Ortega, VE; Paine, R, III; Paulin, L; Pirozzi, C; Rule, A; Hansel, NN; Kaufman, JD. (2021). Modeling residential indoor concentrations of PM_{2.5}, NO₂, NO_x, and secondhand smoke in the Subpopulations and Intermediate Outcome Measures in COPD (SPIROMICS) Air study. *Indoor Air* 31: 702-716. <http://dx.doi.org/10.1111/ina.12760>