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Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

Chapter 12: Cancer

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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.

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Acronyms and Abbreviation

µg	microgram
AQCD	Air Quality Criteria Document
avg	average
BC	black carbon
BHPN	N-bis(2-hydroxy-propyl) nitrosamine
BMI	body mass index
CanCHEC	Canadian Census Health and Environment Cohort
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPS-II	Cancer Prevention Study II
d	day(s)
DNA	deoxyribonucleic acid
DTR	distance to road
e.g.	exempli gratia (for example)
EC	elemental carbon
EE	effect estimate
EEM	effect measure modification
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
ELF	epithelial lining fluid
EMR	electronic medical records
EPA	U.S. Environmental Protection Agency
ER	estrogen receptor
ESCAPE	European Study of Cohorts for Air Pollution Effects
etc.	et cetera
ETS	environmental tobacco smoke
F	female(s)
g	gram(s)
H_2SO_4	sulfuric acid
hr	hour(s)
HR	hazard ratio
i.e.	id est (that is)
IARC	International Agency for Research on Cancer
ICD	international classification of diseases
IDW	inverse distance weighting
IQR	interquartile range
ISA	Integrated Science Assessment
IVIVE	in vitro to in vivo extrapolation
L	liter(s)
ln	natural log
LRT	likelihood-ratio test
LUR	land use regression
M	male
m	milligram
m	meter(s)
Max	maximum
MEC	Multiethnic Cohort Study
Min	minimum
min	minute(s)
mL	milliliter
mo	month(s)
MRR	mortality rate ratio
n	sample size
N	population size
NA	not applicable
NDVI	Normalized Difference Vegetation Index
NDVI	Normalized Difference Vegetation Index
NO	nitric oxide
NO_2	nitrogen dioxide
NO_X	NO_2 + NO
NR	not reported
NSES	neighborhood socioeconomic status
O_3	ozone
ONPHEC	Ontario Population Health and Environment Cohort
OR	odds ratio
P10	10^{th} percentile
P25	25^{th} percentile
P5	5^{th} percentile
P75	75^{th} percentile
P95	95^{th} percentile
PAN	Peroxyacetyl nitrate
PECOS	Population, Exposure, Comparison, Outcome, and Study Design
PM	particulate matter
PM_{10}	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
ppb	parts per billion
ppm	parts per million
PR	progestogen receptor
PUFAs	polyunsaturated fatty acids
RR	relative risk or risk ratio
SD	standard deviation
SE	standard error
SES	socioeconomic status
SO_2	sulfur dioxide
TDAR	T-dependent antibody response
TK	thymidine kinase
TRANSPHORM	Transport related Air Pollution and Health impacts – Integrated Methodologies for Assessing Particulate Matter
TWA	time weighted average
U.K.	United Kingdom
U.S.	United States
UFP	ultra fine particles
UFP	ultrafine particles
vs.	versus
WBC	white blood cells
WHI	Women's Health Initiative

wk	week(s)	$\mu g/m^3$	micrograms per cubic meter
yr	year(s)	µm	micrometer
β	beta	ρ	rho

CHAPTER 12 Cancer

Summary of Causality Determinations for Oxides of Nitrogen Exposure and Cancer

This chapter characterizes the scientific evidence that supports causality determinations for oxides of nitrogen exposure and cancer. The types of studies evaluated within this chapter are consistent with the overall scope of the Integrated Science Assessments (ISA) as detailed in Chapter 14 (see Section 14.4.3.2). In assessing the overall evidence, the strengths and limitations of individual studies were evaluated based on scientific considerations detailed in Table 14-5 of Chapter 14 (see Section 14.4.3.2). More details on the approach used to make causality determinations is included in Appendix A of the Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen, Volume 2 (U.S. EPA, 2024), which builds on the approach described in the 2015 Preamble to the Integrated Science Assessments (U.S. EPA, 2015). The evidence presented throughout this chapter supports the following causality conclusion(s):

Outcome	Causality Determination
Cancer	Suggestive of, but not sufficient to infer, a causal relationship

The Executive Summary, Integrated Synthesis, and all other chapters of this ISA can be found at https://www.epa.gov/isa/integrated-science-assessment-isa-oxides-nitrogen-health-criteria.

12.1 Introduction

12.1.1 Summary of the Previous ISA

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) included a causality determination for the effects of oxides of nitrogen exposure and cancer (U.S. EPA, 2016). The evidence underpinning this causality determination is briefly summarized below.

The 2016 Oxides of Nitrogen ISA concluded that the evidence is "suggestive of, but not sufficient to infer, a causal relationship" between long-term nitrogen dioxide (NO_2) exposure and cancer. The strongest evidence for long-term NO_2 exposure and cancer was derived from epidemiologic studies of lung cancer incidence and mortality conducted in the United States, Canada, and Europe. These studies were generally supportive of a relationship but were inconsistent, with multiple studies reporting positive

associations, but some reporting no associations. Among the studies that reported positive associations with lung cancer incidence or mortality, there was variability in the annual average NO_2 concentrations, multi-year exposure averages, and across geographies. Additionally, among the studies that reported positive associations with lung cancer incidence or mortality, a variety of exposure metrics were used to estimate NO_2 concentrations, such as land use regression models, air dispersion models, spatiotemporal models, and central monitors. The remaining uncertainties from the 2016 Oxides of Nitrogen ISA regarding epidemiologic studies of NO_2 exposure and cancer effects were related to copollutant confounding. At the time of the 2016 Oxides of Nitrogen ISA, evidence derived from toxicological studies did little to address the uncertainty regarding copollutant confounding associated with epidemiologic studies. Exposure to ambient-relevant NO_2 had not been shown to independently induce lung tumors, and there was inconsistent evidence that ambient-relevant NO_2 exposures promote lung tumors when given in conjunction with a known carcinogen. Results from genotoxicity studies with NO_2 were mixed. Due to the small number of toxicological studies, lack of replication of study findings, and mixed results obtained, it was difficult to draw conclusions from these studies and to evaluate consistency and coherence across the evidence base. The 2016 Oxides of Nitrogen ISA additionally highlighted the importance of particulate matter (PM) with a nominal mean aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$), diesel exhaust, polycyclic aromatic hydrocarbons, volatile organic compounds, or other traffic-related pollutants as potential confounders when evaluating cancer effects.

12.1.2 Chapter Organization and Conventions

This chapter evaluates recent evidence examining the relationship between oxides of nitrogen exposure and cancer. Its conclusions are drawn from the integration of the full body of evidence available in the 2016 Oxides of Nitrogen ISA and the evidence that has become available since the 2016 Oxides of Nitrogen ISA. The following sections provide an overview of study inclusion criteria for this chapter (see Section 12.2), summaries of the health effects evidence from past ISAs and from recent studies (see Sections 12.3 to 12.5), a discussion of biological plausibility (see Section 12.6), a summary of the evidence for lifestages and populations (see Section 12.7, Table 12-1), and a discussion of the causality determination for oxides of nitrogen exposure and cancer effects (see Section 12.8, Table 12-2). Only the sections that have multiple lines of evidence include a "Synthesis Across Lines of Evidence" subsection. Evidence inventories include study-specific details for the epidemiologic and toxicological studies including, for example, study population characteristics, exposure details (assessment metrics, temporal scale, and spatial scale), potential confounders, and select results are located in Appendix A – Appendix Tables. Additional information on the organization and conventions for this chapter are discussed below for epidemiologic studies and animal toxicological studies.

12.1.2.1 Epidemiologic Studies

In sections assessing the epidemiologic evidence, this chapter summarizes the evidence from previous ISAs and from recent studies that have become available since the last ISA. When relevant information is available from older or more recent epidemiologic studies, these sections additionally include targeted discussion of available analyses examining concentration-response relationships, effects in particular lifestages and populations, and the potential for confounding by copollutants. For apical endpoints with no or limited evidence on these topics, the subsections addressing them are not included.

In the assessment of the recent epidemiologic evidence, the "Lifestages and Populations" sections, as well as "Summary of Lifestage and Populations" section, discuss analyses of effect measure modification. Effect measure modification occurs when the effect of a pollutant exposure on a health outcome of interest differs between subgroups or strata of risk factors (Rothman and Greenland, 1998). When a risk factor is an effect modifier, it changes the magnitude of the association between the pollutant exposure and the health outcome in stratified analyses. For risk factors that modify the association, effect estimates for each stratum will differ from one another and from the overall estimate, indicating there to be different quantitative relationships between exposure metric and outcome for populations represented by these variables.

In the assessment of recent epidemiologic evidence, the "Copollutants" section discussed examination of potential confounding by copollutants. Copollutant modeling, sometimes referred to as two-pollutant models or co-adjusted models, can reduce concern for confounding by copollutants when correlations between the copollutants is relatively low (e.g., correlation coefficent rho (ρ) <0.4). However, when correlations are high (e.g., ρ >0.7), collinearity between pollutants make copollutant modeling less informative, leading to greater uncertainty in the degree to which reported associations reflect health effects of exposure to oxides of nitrogen independently. Additionally, exposure measurement error can contribute to effect transfer in copollutant models from the pollutant measured with more error to the better measured pollutant (Evangelopoulos et al., 2021).

Unless otherwise specified, throughout this chapter, epidemiologic studies examine long-term exposures to oxides of nitrogen (e.g., more than 30 days). Additionally, in the summaries of the recent epidemiologic evidence, the abbreviation "NO_X" is widely used in the epidemiologic literature and is assumed to be the sum of nitric oxide (NO) and NO_2, which are the dominant forms of oxides of nitrogen emitted from major sources (see Chapter 1, Section 1.3.1 and Chapter 2, Section 2.2).

To increase comparability of results across epidemiologic studies, this Oxides of Nitrogen ISA presents effect estimates for associations with health outcomes scaled to the same increment of oxide of nitrogen concentration.[1] For long-term exposure metrics, effect estimates are scaled to a 10 ppb increase in NO_2, a 15 ppb increase in NO, and a 20 ppb increase in NO_X. These increments were derived by

[1]This is in contrast with reported effect estimates that are scaled to various changes in concentration, such as interquartile range for the study period or an arbitrary unit such as 10 ppb.

calculating the U.S. nationwide percentile distributions for annual average concentrations and then calculating the approximate difference between the median (a typical pollution year) and the 95th percentile (a more polluted year) concentrations among monitors in the State and Local Air Monitoring Stations network. Long-term averages of ambient oxides of nitrogen are less variable across time, and do not differ widely among multi-month averages, annual averages, or multi-year averages. Thus, all long-term exposure metrics were scaled to the same increment.

Some epidemiologic studies reported effect estimates in terms of μg/m^3 increases in oxides of nitrogen, which could be converted to ppb and standardized for NO_2 and NO but not NO_X. This conversion could not be made for NO_X because the proportions of NO_2 and NO are unknown for the various NO_X metrics. Also, data are not available to calculate the percentiles of NO_X concentrations in μg/m^3 at a national scale for the United States or other countries. Therefore, the ISA presents effect estimates based on μg/m^3 of NO_X as they are reported in their respective studies.

12.1.2.2 Animal Toxicological Studies

In sections assessing the animal toxicological evidence, this chapter summarizes the evidence from previous ISAs and from recent studies that have become available since the last ISA. When relevant information is available from older or more recent animal toxicological studies, these sections additionally include targeted discussions of analyses examining dose-response relationships, relevance of toxicological responses to human responses, and multipollutant exposures. For apical endpoints with no or limited evidence on these topics, subsections addressing them are not included.

Unless otherwise specified, throughout this chapter animal studies examine long-term exposures to oxides of nitrogen (e.g., more than 30 days).

12.2 Scope

The evidence that has become available since the 2016 Oxides of Nitrogen ISA has been evaluated for relevance using scoping criteria defined by Population, Exposure, Comparison, Outcome, and Study Design (PECOS) statements. The PECOS statements help to define the scope of the assessment and establish study inclusion criteria, thereby facilitating the identification of the relevant literature for this Oxides of Nitrogen ISA.[2] In order to identify the most relevant literature, the body of evidence from

[2]The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review (narrative, scoping, systematic, and meta-analyses of systematic reviews) articles (which typically present summaries or interpretations of existing studies rather than bringing forward recent information in the form of original research or recent analyses), risk or benefits analyses (e.g., that apply concentration-response functions or effect estimates to exposure estimates for differing cases), and health impact assessments (an assessment tool used to designed to investigate how a proposed program, project, policy, or plan may impact health and well-being and inform decision-makers of these potential outcomes before the decision is made).

the 2016 Oxides of Nitrogen ISA was considered in the development of the PECOS statements for this chapter. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2016 Oxides of Nitrogen ISA inform the scope of this chapter. Except for supporting evidence used to examine the biological plausibility of oxides of nitrogen-associated cancer, recent studies were only included if they meet all components of the discipline-specific PECOS statements (see below) and satisfy discipline-specific study quality criteria (see Chapter 14).

Epidemiologic Studies:

Population: Any human population, including populations or lifestages that might be at increased risk.

Exposure: Exposure to oxides of nitrogen concentrations relevant to ambient air in the United States.[3]

Comparison: Per unit increase (in ppb) for humans exposed to lower concentrations of oxides of nitrogen compared to higher concentrations (e.g., categorical comparisons between different exposure metric quantiles).

Outcome: Change or difference in risk (incidence/prevalence) of cancer health effects.

Study Design: Epidemiologic studies, such as panel, case-crossover, time-series, case-control, cohort, cross-sectional studies, and quasi-experimental, with appropriate timing of exposure for the health outcome of interest.

Animal Toxicological Studies:

Population: Laboratory nonhuman mammalian animal species (e.g., nonhuman primate, mouse, rat, guinea pig, minipig, rabbit, cat, dog) of any lifestage including models of increased susceptibility.

Exposure: Inhalation exposure to relevant oxides of nitrogen concentrations (i.e., 5 ppm or below).[4]

[3]Epidemiologic studies examining associations with NO_2 that report an overall average of NO_2 exposures (i.e., averaged across study populations/locations and over study periods) above 22 ppb were flagged for additional study quality evaluation. This concentration cutoff reflects the 98th percentile of annual average NO_2 concentrations measured at ambient monitors in the United States during the most recent 15 years of available data (i.e., 2008 to 2022) (U.S. EPA, 2023). Studies reporting average NO_2 exposures greater than 22 ppb are considered for inclusion in the ISA if they meet additional study quality criteria described in Chapter 14.

[4]Five ppm is approximately two orders of magnitude higher than peak NO_2 concentrations in the ambient air in the United States. As discussed in the 2015 Preamble to the ISAs (U.S. EPA, 2015) and in the Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen Volume 2 (U.S. EPA, 2024), animal exposures within one to two orders of magnitude of recent ambient air concentrations are considered relevant to

Comparison: An appropriate control group exposed to clean air (e.g., room air, filtered air).

Outcome: Cancer and cancer-related outcomes, such as genotoxic and epigenetic effects.

Study Design: Controlled exposure studies of animals in vivo meeting the above criteria.

12.3 Lung Cancer

In the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016), the evidence from the epidemiologic studies was generally supportive, but inconsistent, for associations between NO_2 and lung cancer incidence or mortality. While there were generally positive associations with lung cancer incidence or mortality in multiple studies conducted in the United States, Canada, and Europe, there was a lack of examination of potential confounding by $PM_{2.5}$ or traffic-related copollutants. Among the studies that reported positive associations with lung cancer incidence or mortality (Carey et al., 2013; Cesaroni et al., 2013; Hystad et al., 2013; Jerrett et al., 2013), there was variability in the annual average NO_2 concentrations, multi-year averages, and across geographical regions. Evidence was inconsistent particularly among studies that estimated subjects' residential ambient NO_2 exposure with well-validated models. Although epidemiologic findings for NO_2-related lung cancer mortality were not entirely consistent, among the studies in the 2016 Oxides of Nitrogen ISA, more studies reported positive associations than in the 2008 Oxides of Nitrogen ISA. Many studies reporting positive associations with lung cancer mortality estimated NO_2 exposure with land use regression (LUR) or dispersion models that were shown to predict well ambient NO_2 concentrations in the study areas.

12.3.1 Epidemiologic Studies of Lung Cancer

In the recent epidemiologic literature, several studies have examined associations between oxides of nitrogen, mostly NO_2 but also NO_X, and lung cancer incidence and lung cancer mortality. The recent studies are divided into studies of lung cancer incidence (see Section 12.3.1.1) and lung cancer mortality (see Section 12.3.1.2).

12.3.1.1 Lung Cancer Incidence

Similar to the 2016 Oxides of Nitrogen ISA, recent studies are generally supportive of associations between NO_2 and lung cancer incidence, though inconsistencies across studies remain. The majority of the recent evidence estimated exposure to NO_2 or NO_X through validated LUR models. In the

ambient air exposures. This concentration cutoff is also consistent with that used in the 2016 Oxides of Nitrogen (U.S. EPA, 2016). Experimental studies investigating the effects of concentrations greater than 5 ppm may be considered for inclusion in the ISA if they provide insight into biological plausibility.

2016 Oxides of Nitrogen ISA, the evidence was inconsistent among studies that estimated residential NO_2 exposure from LUR models with lung cancer incidence. Among the recent evidence, however, the associations were more consistent for lung cancer incidence with NO_2 estimated from LUR models. Additionally, most of the studies had relatively short lag periods (range: 3–18 years), while reporting generally positive associations. While there was some examination of factors that modify associations (e.g., race/ethnicity, genetic factors, dietary), there are remaining uncertainties regarding differences across lifestages, sex, smoking status, and exposure windows (lag periods between exposure and outcome), and there is still limited evidence on concentration response and the potential for copollutant confounding.

The strongest recent evidence is from cohort studies in North America and the United Kingdom (U.K.), which reported generally positive associations between NO_2 and lung cancer incidence (Chen et al., 2023; Liang et al., 2023; Cheng et al., 2022; Letellier et al., 2022; Huang et al., 2021; Hvidtfeldt et al., 2021; Wong et al., 2021; Bai et al., 2019; Weichenthal et al., 2017); however, there was a single study that reported a negative association (Gowda et al., 2019). The single cohort study reporting a negative association differed from the other cohort studies in that the underlying population was postmenopausal, never-smoking women of the Women's Health Initiative (WHI) study rather than the general population (Gowda et al., 2019). Among the studies of lung cancer incidence, long-term NO_2 exposure was estimated from LUR models (Chen et al., 2023; Liang et al., 2023; Cheng et al., 2022; Huang et al., 2021; Hvidtfeldt et al., 2021; Wong et al., 2021; Bai et al., 2019; Weichenthal et al., 2017) or inverse distance weighting (IDW) and kriging of monitored data (Letellier et al., 2022). Associations were reported across various exposure periods, ranging from 3 to 18 years. Historically, in the epidemiologic literature, the relevant exposure period for lung cancer was thought to be 30 years or more (U.S. EPA, 2008), but the recent literature is reporting effects for shorter exposure periods.

The recent evidence also evaluated associations between long-term exposure to NO_X and lung cancer incidence. Overall, there were consistent positive associations between exposure to NO_X and lung cancer incidence (Chen et al., 2023; Liang et al., 2023; Cheng et al., 2022; Huang et al., 2021). These positive associations were reported among large United States or United Kingdom cohorts with estimated NO_X exposure from LUR models.

Evidence from recent studies is summarized in the bullets below. Some of these recent studies include analyses specifically examining concentration-response relationships, lifestages and populations, and the potential for confounding by copollutants. These analyses are discussed in greater detail in Sections 12.3.1.1.1, 12.3.1.1.2, and 12.3.1.1.3, respectively. Study specific details including study population characteristics, exposure details (assessment metrics, temporal scale, and spatial scale), potential confounders, and select results are in Appendix A – Appendix Table 12-1.

- To quantify the association between air pollution and aggressive somatic lung cancer tumors, Letellier et al. (2022) focused on three non-small cell lung cancer somatic tumor mutations (TP53, KRAS, and KRAS G12C/V) in association with exposure to NO_2, using inverse distance weighting approach among patients from a hospital in California. There was a

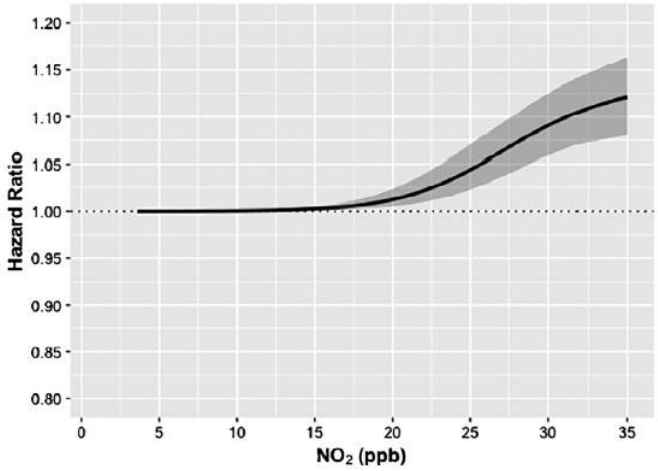
pattern of increased risk for TP53 mutation status (OR: 1.30 [95% CI: 0.99, 1.71] per 1.86 ppb for NO_2 exposure 5-years before diagnosis and OR: 1.30 [95% CI: 0.97, 1.76] per 1.86 ppb for NO_2 exposure 10-years before diagnosis), but the associations were null for KRAS mutation status and KRAS G12C/V mutation status.

- Among participants in the Multiethnic Cohort Study (MEC), LUR models estimated 10-year exposure to NO_2 and NO_X and lung cancer incidence (Cheng et al., 2022). There was a pattern of positive associations with NO_2 (HR: 1.06 [95% CI: 0.97, 1.15] per 10 ppb NO_2) and NO_X (HR: 1.06 [95% CI: 1.00, 1.12] per 20 ppb NO_X).
- Among participants for the Ontario Population Health and Environment Cohort (ONPHEC), (Weichenthal et al., 2017) estimated long-term exposure to NO_2 from LUR models to create a 3-year moving average based on place of residence with a 5-year lag. There was an increased risk for lung cancer associated with exposure to NO_2 (HR: 1.18 [95% CI: 1.10, 1.26] per 4.1 ppb increase in NO_2). In the same ONPHEC cohort, Bai et al. (2019) reported an increased incidence of lung cancer for a 3-year moving average with a 4-year time lag for NO_2 (HR: 1.04 [95% CI: 1.02, 1.05] per 13.9 ppb increase in NO_2). When using a 10-year lag in exposure, the association was slightly attenuated (HR: 1.03 [95% CI: 1.01, 1.04]).
- Hvidtfeldt et al. (2021) pooled seven cohorts from across Europe that are part of the ELAPSE collaboration to assess the relationship between exposure to NO_2 and lung cancer incidence. There were positive, but imprecise, associations for incidence for all lung cancers (HR: 1.04 [95% CI: 0.95, 1.14] per 5.31 ppb increase in NO_2) and adenocarcinoma (HR: 1.04 [95% CI: 0.90, 1.20]), and a negative but imprecise association for incidence of squamous-cell carcinomas (HR: 0.94 [95% CI: 0.76, 1.18]).
- Among the studies that evaluated associations with NO_2 and/or NO_X in the UK Biobank cohort, there were consistent positive associations with lung cancer incidence (Chen et al., 2023; Liang et al., 2023; Huang et al., 2021; Wong et al., 2021).
- There was a single recent epidemiologic study that reported negative associations with NO_2 and lung cancer incidence. Gowda et al. (2019) evaluated associations between NO_2 and lung cancer incidence among postmenopausal, never-smoking women of the WHI study. There was a negative association (HR: 0.92 [95% CI: 0.74, 1.15] per 10 ppb increase in NO_2) for lung cancer incidence overall and there was also a negative association between NO_2 and adenocarcinoma (HR: 0.93 [95% CI: 0.71, 1.23] per 10 ppb increase in NO_2).

12.3.1.1.1 Concentration-Response

There were only a few recent studies of lung cancer incidence that evaluated concentration-response relationship between exposure to NO_2 and lung cancer incidence. Overall, the results were inconsistent. Among participants in the ONPHEC, Bai et al. (2019) used a shape constrained health impact function to estimate the concentration-response relationship between exposure to NO_2 and lung cancer incidence. There was some evidence of a threshold at 15 ppb for NO_2 for a 3-year moving average with a 4-year time lag for NO_2 (see Figure 12-1). Among patients from a hospital in California, there was no evidence of associations between tertiles of exposure to NO_2 (either 5-years before diagnosis or 10-years before diagnosis) and tumor mutation (Letellier et al., 2022). In a UK Biobank study, Wong et al. (2021) reported evidence of a positive concentration response relationship between residential quartiles of exposure to NO_2 and lung cancer risk (p-trend = 3.1×10^{-3}). However, among postmenopausal, never-

smoking women of the WHI study Gowda et al. (2019) reported that there no evidence of a linear concentration response across quartiles of exposure to NO_2 and lung cancer incidence. Overall, there was not a clear pattern in the shape for concentration-response for exposure to NO_2 and lung cancer incidence.



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; ppb = parts per billion.
Source: Bai et al. (2019). Copyright permission pending.

Figure 12-1 Concentration-response curve for the association of incidence of lung cancer with exposure to nitrogen dioxide (NO_2).

12.3.1.1.2 Lifestages and Populations

Genetic Factors

A few recent epidemiologic studies evaluated associations between NO_2 and/or NO_X and lung cancer incidence impacted by genetics (see Table 12-3). In a single study among patients from a hospital in California, Letellier et al. (2022) focused on evaluating three non-small cell lung cancer somatic tumor mutations (TP53, KRAS, and KRAS G12C/V) in association with aggressive somatic lung cancer tumors and NO_2. There was an increased risk of lung cancer incidence for TP53 mutation, but not for KRAS or KRAS G12C/V. Overall, there is limited evidence that some genetic variants may impact the associations between NO_2 and/or NO_X and lung cancer incidence, but there were differences in the genetic variants evaluated in the recent evidence.

Lifestage

A few recent studies evaluated the effect of lifestage on the associations between exposure to NO_2 and lung cancer incidence (Huang et al., 2021; Weichenthal et al., 2017). The associations did not change in stratified analyses across three age categories (<60, 60–74, and ≥75) among participants in the ONPHEC cohort (Weichenthal et al., 2017). Additionally, there was no evidence of effect measure modification for lifestages (≥60 or <60) among participants of the UK Biobank (Huang et al., 2021).

Overall, there was no evidence that lifestage impacts the associations between exposure to NO_2 and lung cancer incidence (see Table 12-3).

Socioeconomic Status

There were a few recent studies that evaluated effect measure modification by socioeconomic status (SES) on the associations between exposure to NO_2 and NO_X and lung cancer incidence (Cheng et al., 2022; Huang et al., 2021). Among those living in low SES neighborhoods, Cheng et al. (2022) reported similar risk of lung cancer associated with NO_2 exposure and NO_X exposure (see Table 12-3). Among those living in high SES neighborhoods, the associations were null for associations with exposures to NO_2 and NO_X (see Table 12-3). Huang et al. (2021) did not find evidence of effect measure modification by household income, a proxy measure for SES, among participants in the UK Biobank cohort. Overall, there was limited evidence for effect measure modification by SES and the inconsistent associations overall.

Race/ethnicity

A recent single study assessed differences by race/ethnicity in lung cancer incidence from long-term exposure in NO_2 (Cheng et al., 2022). Among participants in the MEC, there were no differences among race/ethnicity subgroups of Black (author reported as African American), Japanese American, or Native Hawaiian for exposure to NO_2 or NO_X, but the risk was increased for Latino Americans, although the confidence intervals (CI) were wide (included the null) and slightly decreased for European American, but the CIs included the null (see Table 12-3).

Sex

A few recent studies evaluated the effect of sex on the association between exposure to NO_2 and lung cancer incidence (Huang et al., 2021; Weichenthal et al., 2017). Overall, there was no evidence of effect measure modification by sex (see Table 12-3). Additionally, Huang et al. (2021) also did not find evidence of effect measure modification by sex in the association between exposure to NO_X and lung cancer incidence.

Smoking

A few recent studies evaluated the effect of smoking as a confounder on lung cancer incidence and exposure to NO_2 and NO_X (see Table 12-3). Among participants in the MEC, Cheng et al. (2022), reported positive, but imprecise, associations for those who were never smokers when adjusting for smoking as a confounder; however, there was no formal testing for heterogeneity of effects by smoking status. Weichenthal et al. (2017) indirectly adjusted for smoking by leveraging data from another cohort that had smoking status (never, former, and current cigarette smoking) as a confounder, resulting in attenuation of the risk of lung cancer incidence and exposure to NO_2. Among participants in the UK Biobank cohort, Huang et al. (2021) reported similar positive associations among current or past smokers, but for never smokers, the associations between exposure to NO_2 or NO_X and lung cancer incidence were

attenuated. Overall, there was inconsistent evidence of smoking status on the associations between exposure to NO_2 and NO_X and lung cancer incidence.

Diet

Only a single recent study evaluated the impact of diet on the associations between NO_2 and lung cancer incidence (Chen et al., 2023). Chen et al. (2023) assessed whether the intake of omega-3 polyunsaturated fatty acids (PUFAs) and omega-6 PUFAs modified the association between exposure to NO_2 and NO_X and lung cancer incidence. While there was a positive association between NO_2 and lung cancer incidence (HR: 1.07 [95% CI: 0.98, 1.16]) and a positive association with NO_X (HR: 1.04 [95% CI: 1.01, 1.08]), the associations were unchanged in analyses stratifying by polyunsaturated fatty acids levels, regardless of omega-3 or omega-6 intake (see Table 12-3).

Table 12-3 Epidemiologic studies evaluating effect measure modification between long-term oxides of nitrogen exposure and lung cancer incidence

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Genetic Factors					
Exposure to NO_2					
†Letellier et al. (2022)	2013–2018	NR	OR (95% CI)[c] Lung cancer incidence - Exposure 5-yrs before diagnosis for TP53 mutation (Main Effect): 1.30 (0.99, 1.71)	NA	Individual
			Lung cancer incidence - Exposure 10-yrs before diagnosis for TP53 mutation (Main Effect): 1.30 (0.97, 1.76)	NA	
			Lung cancer incidence - Exposure 5-yrs before diagnosis for KRAS mutation (Main Effect): 0.93 (0.69, 1.26)	NA	
			Lung cancer incidence - Exposure 10-yrs	NA	

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			before diagnosis for KRAS mutation (Main Effect): 0.96 (0.69, 1.33)		
			Lung cancer incidence - Exposure 5-yrs before diagnosis for KRAS G12C/V mutation (Main Effect): 0.95 (0.65, 1.42)	NA	
			Lung cancer incidence - Exposure 10-yrs before diagnosis for KRAS G12C/V mutation (Main Effect): 0.94 (0.62, 1.44)	NA	
Lifestage					
Exposure to NO_2					
†Huang et al. (2021)	UK Biobank Baseline: 2006–2010	HR (95% CI)[b] Lung cancer incidence - Age <60: 1.16 (0.98, 1.36)	HR (95% CI)[b] Lung cancer incidence - Age ≥60: 1.22 (1.10, 1.35)	≈	Individual
†Weichenthal et al. (2017)	Ontario Population Health and Environment Cohort (ONPHEC) Enrollment start: April 1, 1996 Start of follow-up: April 1, 2001 End of follow-up: December 31, 2012	HR (95% CI)[b] Lung cancer incidence - Age <60: 1.10 (1.01, 1.19)	HR (95% CI)[b] Lung cancer incidence - Age 60–74: 1.18 (1.10, 1.26)	≈	Individual
			HR (95% CI)[b] Lung cancer incidence - Age ≥75: 1.05 (0.86, 1.29)	≈	
Exposure to NO_X					
†Huang et al. (2021)	UK Biobank Baseline: 2006–2010	HR (95% CI)[c] Lung cancer incidence - Age <60: 1.08 (0.95, 1.19)	HR (95% CI)[c] Lung cancer incidence - Age ≥60: 1.14 (1.08, 1.21)	≈	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
SES					
Exposure to NO_2					
†Cheng et al. (2022)	The Multiethnic Cohort Study (MEC) Enrollment: 1993–1996 Follow-up: end of December 2013	HR (95% CI)[b] Lung cancer incidence (Main Effect): 1.06 (0.97, 1.15)	HR (95% CI)[b] Lung cancer incidence - Low neighborhood SES: 1.10 (0.99, 1.22)	≈	Individual
			Lung cancer incidence - High neighborhood SES: 1.00 (0.86, 1.16)	≈	
†Huang et al. (2021)	UK Biobank Baseline: 2006–2010	HR (95% CI)[b] Lung cancer incidence - household income above £31,000: 1.18 (0.99, 1.40)	HR (95% CI)[b] Lung cancer incidence - household income below £31,000: 1.10 (1.04, 1.16)	≈	Individual
Exposure to NO_X					
†Cheng et al. (2022)	The Multiethnic Cohort Study (MEC) Enrollment: 1993–1996 Follow-up: end of December 2013	HR (95% CI)[b] Lung cancer incidence (Main Effect): 1.06 (1.00, 1.12)	HR (95% CI)[b] Lung cancer incidence - Low neighborhood SES: 1.08 (1.00, 1.15)	≈	Individual
			Lung cancer incidence - High neighborhood SES: 1.00 (0.90, 1.12)	≈	
†Huang et al. (2021)	UK Biobank Baseline: 2006–2010	HR (95% CI)[c] Lung cancer incidence - household income above £31,000 : 1.16 (1.05, 1.29)	HR (95% CI)[c] Lung cancer incidence - household income below £31,000: 1.11 (1.05, 1.18)	≈	Individual
Race/ethnicity					
Exposure to NO_2					
†Cheng et al. (2022)	The Multiethnic Cohort Study (MEC)	HR (95% CI)[b] Lung cancer incidence (Main	HR (95% CI)[b] Lung cancer incidence - Black (author reported as	≈	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	Enrollment: 1993–1996 Follow-up: end of December 2013	Effect): 1.06 (0.97, 1.15)	African American): 1.06 (0.94, 1.19)		
			Lung cancer incidence - European American: 0.91 (0.74, 1.11)	↓	
			Lung cancer incidence - Japanese American: 1.09 (0.79, 1.50)	≈	
			Lung cancer incidence - Latino American: 1.14 (0.92, 1.43)	↑	
Exposure to NO_X					
†Cheng et al. (2022)	The Multiethnic Cohort Study (MEC) Enrollment: 1993–1996 Follow-up: end of December 2013	HR (95% CI)[b] Lung cancer incidence (Main Effect): 1.06 (1.00, 1.12)	HR (95% CI)[b] Lung cancer incidence - Black (author reported as African American): 1.05 (0.97, 1.13)	≈	
			Lung cancer incidence - European American: 0.95 (0.81, 1.10)	↓	
			Lung cancer incidence - Japanese American: 0.93 (0.73, 1.18)	↓	
			Lung cancer incidence - Latino American: 1.11 (0.96, 1.29)	≈	
Sex					
Exposure to NO_2					
†Huang et al. (2021)	UK Biobank Baseline: 2006–2010	HR (95% CI)[b] Lung cancer incidence - Male: 1.26 (1.11, 1.43)	HR (95% CI)[b] Lung cancer incidence - Female: 1.12 (0.98, 1.27)	≈	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
†Weichenthal et al. (2017)	Ontario Population Health and Environment Cohort (ONPHEC) Enrollment start: April 1, 1996 Start of follow-up: April 1, 2001 End of follow-up: December 31, 2012	HR (95% CI)[b] Lung cancer incidence - Males (Author reported as men): 1.23 (1.14, 1.33	HR (95% CI)[b] Lung cancer incidence - Females (Author reported as women): 1.15 (1.05, 1.26)	≈	Individual
Exposure to NO_X					
†Huang et al. (2021)	UK Biobank Baseline: 2006–2010	HR (95% CI)[c] Lung cancer incidence - Male: 1.17 (1.10, 1.24)	HR (95% CI)[c] Lung cancer incidence - Female: 1.06 (0.98, 1.15)	≈	Individual
Smoking					
Exposure to NO_2					
†Cheng et al. (2022)	The Multiethnic Cohort Study (MEC) Enrollment: 1993–1996 Follow-up: end of December 2013	HR (95% CI)[b] Lung cancer incidence - Never smokers: 1.15 (0.89, 1.49)	HR (95% CI)[b] Lung cancer incidence - Former smokers: 1.07 (0.94, 1.22)	≈	Individual
			Lung cancer incidence - Current smokers: 1.06 (0.94, 1.20)	≈	
†Huang et al. (2021)	UK Biobank Baseline: 2006–2010	HR (95% CI)[b] Lung cancer incidence - smoking status; never smoker: 0.96 (0.74, 1.26)	HR (95% CI)[b] Lung cancer incidence - smoking status; current or past smoker: 1.24 (1.13, 1.36)	↑	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
†Weichenthal et al. (2017)	Ontario Population Health and Environment Cohort (ONPHEC) Enrollment start: April 1, 1996 Start of follow-up: April 1, 2001 End of follow-up: December 31, 2012	HR (95% CI)[b] Lung cancer incidence (Main Effect): 1.18 (1.10, 1.26)	HR (95% CI)[b] Lung cancer incidence - Smoking: 1.05 (0.92, 1.20)	↓	Individual
Exposure to NO_X					
†Cheng et al. (2022)	The Multiethnic Cohort Study (MEC) Enrollment: 1993–1996 Follow-up: end of December 2013	HR (95% CI)[b] Lung cancer incidence - Never smokers: 1.14 (0.95, 1.38)	HR (95% CI)[b] Lung cancer incidence - Former smokers: 1.05 (0.96, 1.15)	≈	Individual
			Lung cancer incidence - Current smokers: 1.05 (0.97, 1.15)	≈	
†Huang et al. (2021)	UK Biobank Baseline: 2006–2010	HR (95% CI)[c] Lung cancer incidence - smoking status; never smoker: 1.05 (0.90, 1.22)	HR (95% CI)[c] Lung cancer incidence - smoking status; current or past smoker: 1.14 (1.08, 1.20)	≈	Individual
Diet					
Exposure to NO_2					
†Chen et al. (2023)	UK Biobank Baseline: 2006–2010 Follow-up: through September 30, 2021 for England and Wales Follow-up: through October 31, 2021 for Scotland	HR (95% CI)[b] Lung cancer incidence (Main Effect): 1.07 (0.98, 1.16)	HR (95% CI)[b] Lung cancer incidence - Low omega-3 fatty acids: 1.12 (0.89, 1.39)	≈	Individual
			Lung cancer incidence - High omega-3 fatty acids: 1.16 (0.91, 1.46)	≈	
			Lung cancer incidence - Low omega-6 fatty acids: 1.07 (0.96, 1.20)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			Lung cancer incidence - High omega-6 fatty acids: 1.12 (0.88, 1.42)	≈	
Exposure to NO_X					
†Chen et al. (2023)	UK Biobank Baseline: 2006–2010 Follow-up: through September 30, 2021 for England and Wales Follow-up: through October 31, 2021 for Scotland	HR (95% CI)[c] Lung cancer incidence (Main Effect): 1.04 (1.01, 1.08)	HR (95% CI)[c] Lung cancer incidence - High omega-3 fatty acids: 1.04 (0.98, 1.10)	≈	Individual
			Lung cancer incidence - Low omega-3 fatty acids: 1.05 (1.00, 1.10)	≈	
			Lung cancer incidence - High omega-6 fatty acids: 1.04 (0.99, 1.10)	≈	
			Lung cancer incidence - Low omega-6 fatty acids: 1.05 (1.00, 1.10)	≈	

List of abbreviations in alphabetical order: EMM = effect measure modification; HR = hazard ratio; MEC = Multiethnic Cohort Study; NO_2 = nitrogen dioxide; ONPHEC = Ontario Population Health and Environment Cohort; OR = odds ratio; UK = United Kingdom; yr = year.
[a]An up-facing arrow (and yellow shading) indicate that the effect of NO_2 or NO_X is greater (e.g., larger risk of cancer) in the group with the factor evaluated than in the reference group. A down-facing arrow (and blue shading) indicate that the effect of NO_2 or NO_X is smaller in the group with the factor evaluated than in the reference group. An almost equal sign (and grey shading) indicates that the effect of NO_2 or NO_X is comparable between groups.
[b]Effect estimates are standardized and are presented as a 10 ppb change in NO_2 for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_X for annual average averaging time
[c]Estimates are not standardized
†Studies published since the 2016 Oxides of Nitrogen ISA.

12.3.1.1.3 Copollutants

Among the recent evidence, there was only a single study that evaluated the potential for copollutant confounding. Weichenthal et al. (2017) reported an increased risk for lung cancer incidence (HR: 1.21 [95% CI: 1.10, 1.26] per 4.1 ppb increase in NO_2), and the risk was slightly strengthened when co-adjusted ($\rho = 0.22$) for $PM_{2.5}$ (HR: 1.21 [95% CI: 1.13, 1.29]).

12.3.1.2 Lung Cancer Mortality

In the recent epidemiologic literature, there were several studies that examined associations between NO_2 and lung cancer mortality. Similar to the 2016 Oxides of Nitrogen ISA, there were generally positive, but inconsistent, associations between NO_2 and lung cancer mortality. While several studies reported positive associations, a few reported null associations, and a few reported inverse (negative) associations. There were varying exposure assessment metrics (central site monitors, LUR models, dispersion models, ensemble machine learning, and geospatial models) and lag periods examined. Evidence from recent studies is summarized in the bullets below. Some of these recent studies include analyses specifically examining the concentration response relationships, lifestages and population differences, and potential confounding by copollutants. These analyses are discussed in greater detail in Sections 12.3.1.2.1, 12.3.1.2.2, and 12.3.1.2.3, respectively. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 12-1.

Of the recent studies that included smoking as a potential confounder, there was generally a consistent pattern of increased risk of lung cancer mortality with exposure to NO_2 (Huang et al., 2023; So et al., 2022; Klompmaker et al., 2020; Hvidtfeldt et al., 2019); with only a single study reporting a null association (Turner et al., 2016). The strongest evidence comes from multiple large cohort studies with associations robust across exposure assessment models (LUR, hybrid, and ensemble machine learning), and geographies (Denmark, China, and Netherlands).

- In a national Danish administrative cohort, So et al. (2022) reported a positive association between exposure to NO_2 estimated from an LUR model and lung cancer mortality (HR: 1.26 [95% CI: 1.22, 1.30] per 5.31 ppb increase in NO_2) with a mean follow-up period of 15.3 years.
- Among participants of the Danish Diet, Cancer and Health cohort, Hvidtfeldt et al. (2019) reported a positive, but imprecise, association (HR: 1.08 [95% CI: 0.92, 1.26] per 5.31 ppb increase in NO_2) between lung cancer mortality and 15-year exposure lag for NO_2, estimated from a hybrid model using data from DEHM/UBM/OSPM/ AirGIS.
- Among participants in a Dutch national health survey, a LUR model estimated long-term exposure to NO_2 (Klompmaker et al., 2020). There was increased risk of lung cancer mortality (HR: 1.08 [95% CI: 0.90, 1.29] per 4.04 ppb increase in NO_2); however, the association was imprecise.
- Huang et al. (2023) assessed long-term exposure to NO_2, estimated from machine learning models, in association with lung cancer mortality in a Chinese cohort with 22 years of follow-up. There was a positive association for lung cancer mortality (HR: 1.32 [95% CI: 1.17, 1.49] per 5.31 ppb increase in NO_2). Huang et al. (2023) also considered different lag years (0–1, 0–2, 0–3, 0–4, 0–5), with all the associations slightly increased (HR range: 1.37–1.48).

There were several recent studies that examined the associations between NO_2 and lung cancer mortality, but without adjustment for smoking as a confounder (Bouma et al., 2023; Eum et al., 2022; Klompmaker et al., 2021a; Klompmaker et al., 2021b; Raaschou-Nielsen et al., 2020; Eckel et al., 2016;

Crouse et al., 2015). While there were consistent positive associations among these studies, there could be bias in estimates without consideration of smoking as a confounder. The consistency in the associations was robust to variation in the average NO_2 concentration, exposure lag periods for multiple years, different exposure assessment metrics (LUR, dispersion, and hybrid models), among large cohorts, and across geographies (United States, Canada, Denmark, Netherlands).

- A single study evaluated whether exposure to NO_2, based data obtained from EPA's Air Quality System (AQS), was associated with the survival of patients with lung cancer in California (Eckel et al., 2016). There was an increased risk of lung cancer mortality overall and by stage at diagnosis, with localized only stage at diagnosis having have strongest associations (HR: 1.70 [95% CI: 1.65, 1.75] per 10.2 ppb NO_2).
- Among participants in the Canadian Census Health and Environment Cohort (CanCHEC), Crouse et al. (2015) a national LUR model was used to examine exposure to NO_2 in association with lung cancer mortality over a 16-year follow-up period. There was an increased risk of lung cancer mortality (HR: 1.092 [95% CI: 1.064, 1.121] per 8.1 ppb increase in NO_2).
- In a nested-case control study in Denmark, there was a positive association between a 5-year time-weighted average exposure period of NO_2 and lung cancer mortality (mortality rate ratio (MRR): 1.17 [95% CI: 1.15, 1.18] per 5.31 ppb increase in NO_2) (Raaschou-Nielsen et al., 2020).
- Three exposure assessment metrics (hybrid, LUR, and dispersion models) were used to evaluate associations between NO_2 and lung cancer mortality in a national Dutch cohort (Klompmaker et al., 2021a). Regardless of the exposure assessment metric, there was an increased risk for lung cancer mortality (HRs ranged from 1.154 to 1.178), with the strongest association with the hybrid model (HR: 1.178 [95% CI: 1.133, 1.225] per 5.31 ppb in NO_2).
- In another study of an administrative Dutch cohort, Klompmaker et al. (2021b) estimated exposure to NO_2 by taking the average from all three exposure assessment models, LUR, hybrid, and dispersion. There was an increased risk of lung cancer mortality per 4.41 ppb increase in NO_2 (HR: 1.176 [95% CI: 1.131, 1.223]). While there were still positive associations for each of the exposure models individually, the risk was attenuated toward the null (HR for LUR: 1.131 [95% CI: 1.092, 1.172], HR for hybrid: 1.139 [95% CI: 1.103, 1.176], and HR for dispersion: 1.103 [95% CI: 1.068, 1.138]). In the two-exposure model for Normalized Difference Vegetation Index (NDVI), national land-use database of the Netherlands (TOP10NL), and road traffic noise, there were positive associations, but the associations were attenuated towards the null with less precision (HR range: 1.081–1.149).

There were a few studies that reported inverse (negative) associations between exposure to NO_2 and lung cancer mortality, (Eum et al., 2019; Chen et al., 2016), with a single study reporting null associations (Kang et al., 2023). These studies were conducted among cohorts in China, the United States, and South Korea, with exposure to NO_2 estimated from monitors from EPA's AQS, over different latency periods (ranging from 12-months to 10-years).

- In a cohort study in four northern Chinese cities, NO_2 concentrations were estimated from the nearest monitor station and then two methods were used to assign exposure: assigning the 1998 air pollution exposure for all and time-varying exposures for both deaths and survivors through 2008 (Chen et al., 2016). Regardless of the method to assign exposure, there were

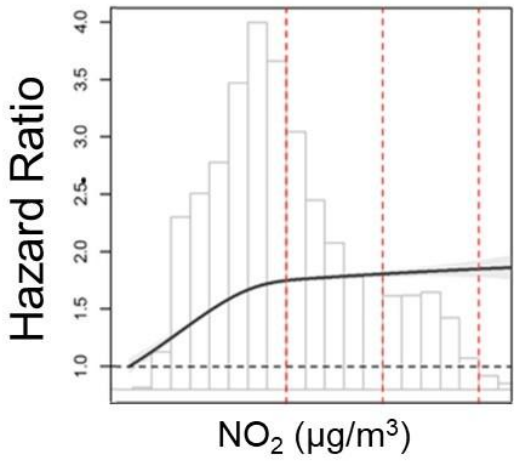
slightly negative associations between NO_2 and lung cancer mortality (HR for 1998 exposure: 0.898 [95% CI: 0.821, 0.982] and HR for time-varying exposure: 0.969 [95% CI: 0.953, 0.984]).

- In another study among Medicare beneficiaries in the United States, there were inverse associations between 12-month moving average NO_2 exposure and lung cancer mortality (MRR: 0.983 [95% CI: 0.976, 0.991] per 10 ppb increase in NO_2) overall; however, these estimates were not adjusted for smoking (Eum et al., 2019). Furthermore, when different regions were considered, there was an increased MRR of 1.058 (95% CI: 1.034, 1.082) for the Center region (between the Mississippi River and the Sierra Nevada Mountain range) of the United States, but the West and East were mostly unchanged.
- Among those who have chronic obstructive pulmonary disease in a South Korean cohort, there were null associations between the 1-year, 3-year, and 5-year exposure period for NO_2 and lung cancer mortality (HR: 0.990 [95% CI: 0.966, 1.014] per 10 $\mu g/m^3$, HR: 0.984 [95% CI: 0.960, 1.009], and HR: 0.995 [95% CI: 0.968, 1.022], respectively) (Kang et al., 2023).

Additionally, there was a single recent study reporting null associations with lung cancer mortality. Among participants of the NIH-AARP Diet and Health Study, there was a null association (HR: 1.00 [95% CI: 0.97, 1.04] per 10 ppb increase in NO_2) with a mean follow-up period of 17-years (Lim et al., 2019).

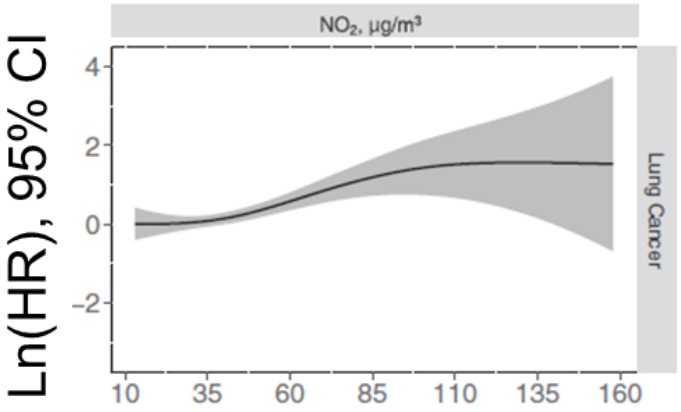
12.3.1.2.1 Concentration-Response

There were a few recent studies that evaluated the concentration-response for exposure to NO_2 and lung cancer mortality, controlling for smoking (Huang et al., 2023; So et al., 2022; Klompmaker et al., 2020) and not controlling for smoking (Klompmaker et al., 2021a; Klompmaker et al., 2021b). Several studies (Huang et al., 2023; So et al., 2022; Klompmaker et al., 2021a) reported a supralinear concentration-response curve for NO_2 and lung cancer mortality, with no evidence of a threshold (see Figure 12-2 to Figure 12-4). Additionally, Klompmaker et al. (2021a) noted that there were steeper slopes at lower concentrations.



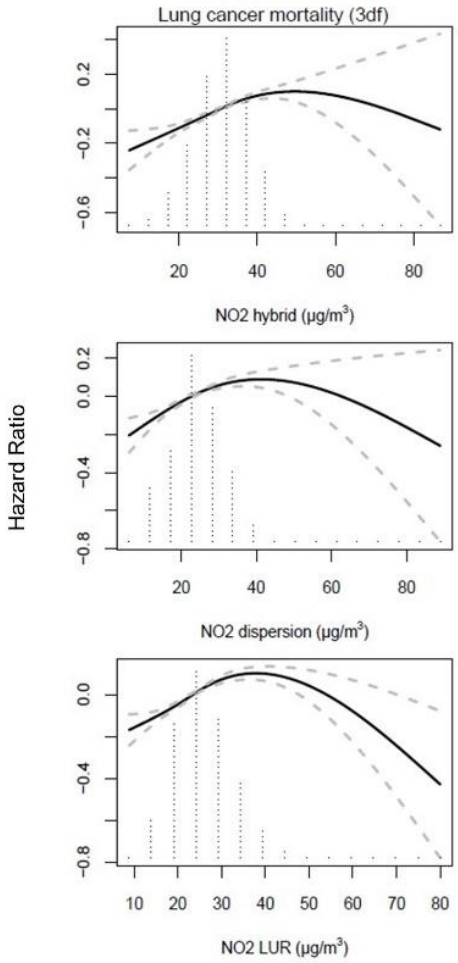
List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; µg/m^3 = micrograms per cubic meter.
Notes: Red vertical dashed lines show values used for subset analyses: 40 (the EU standard), 30, and 20 µg/m^3. The upper limit of the x-axis was truncated at 99.5 percentile of the distribution of NO_2. Associations were obtained from models adjusting for age (underlying time scale), sex (strata), household income in decile, occupational status, immigrant status, marital status, and highest completed education level, regional mean household income, regional percentage of unemployment, and the difference of mean household income and percentage of unemployment, between parish and region.
Source (adapted from): So et al. (2022). Copyright permission pending.

Figure 12-2 Concentration-response curve for the association of incidence of lung cancer with exposure to nitrogen dioxide (NO_2).



List of abbreviations in alphabetical order: CI = confidence interval; Ln = natural logarithm; NO_2 = nitrogen dioxide; µg/m^3 = micrograms per cubic meter.
Notes: Models were adjusted for age, sex, BMI, level of education, income, occupational exposure, physical exercise, and status of marital, smoking and drinking.
Source (adapted from): Huang et al. (2023). Copyright permission pending.

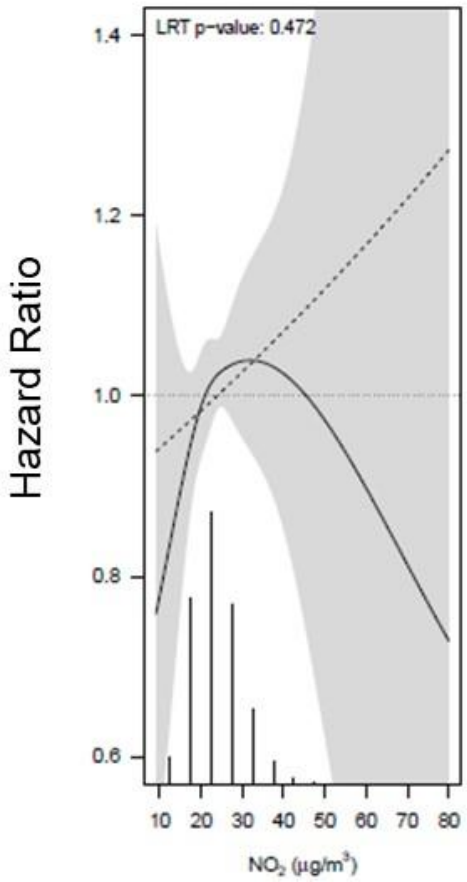
Figure 12-3 Concentration-response curve for the association of NO_2 and lung cancer mortality.



List of abbreviations in alphabetical order: df = degrees of freedom; LUR = land use regression; NO_2 = nitrogen dioxide; µg/m³ = micrograms per cubic meter.
Source (adapted from): Klompmaker et al. (2021a). Copyright permission pending.

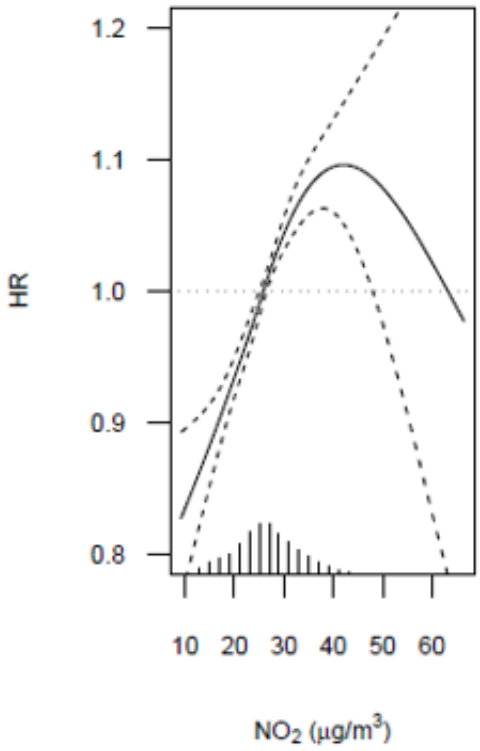
Figure 12-4 Concentration-response curves with natural splines (3 degrees of freedom) of NO_2 based on a hybrid, LUR, and dispersion model with lung cancer mortality.

However, in studies among Dutch cohorts, Klompmaker et al. (2020) and Klompmaker et al. (2021b) reported linear concentration response between 10 to 40 µg/m³ (5 to 212 ppb), but above 40 µg/m³, the shape becomes more U-shaped, which may be the result of very limited data above 40 µg/m³ (see Figure 12-5 and Figure 12-6). Overall, there was no clear shape of the concentration-response curves for NO_2 and lung cancer mortality.



List of abbreviations in alphabetical order: LRT = likelihood-ratio test**;** NO_2 = nitrogen dioxide; $\mu g/m^3$ = micrograms per cubic meter.
Notes: Estimated concentration response curve and 95% CIs (dashed lines) for lung cancer mortality (df = 3) (dashed line = estimated exposure−response curves with 1 df, density bars are shown on y−axis).
Source (adapted from): Klompmaker et al. (2020). Copyright permission pending.

Figure 12-5 Estimated concentration-response curve for NO_2 and lung cancer mortality.



List of abbreviations in alphabetical order: CI = confidence interval; df = degrees of freedom; HR = hazard ratio; NO_2 = nitrogen dioxide; $\mu g/m^3$ = micrograms per cubic meter.
Source (adapted from): Klompmaker et al. (2021b). Copyright permission pending.

Figure 12-6 Estimated concentration-response curve and 95% CIs (dashed lines) for lung cancer mortality (df = 3).

12.3.1.2.2 Lifestages and Populations

Smoking

While smoking is widely known as a potential confounder for lung cancer incidence and mortality, there were some inconsistencies in whether smoking was included as a potential confounder in the recent epidemiologic evidence, more specifically in studies examining associations with lung cancer mortality. Generally, there was a consistent pattern of increased risk of lung cancer mortality in association with NO_2 and NO_X. However, among the studies that did control for smoking as a potential confounder (Huang et al., 2023; So et al., 2022; Klompmaker et al., 2020; Hvidtfeldt et al., 2019), the positive associations were smaller in magnitude than those that did not control for smoking (Bouma et al., 2023; Eum et al., 2022; Klompmaker et al., 2021a; Klompmaker et al., 2021b; Raaschou-Nielsen et al., 2020; Eckel et al., 2016; Crouse et al., 2015) (see Table 12-4). For instance, in a Danish nationwide administrative cohort, So et al. (2022) reported an increased risk of lung cancer mortality (HR: 1.16 [95% CI: 1.13, 1.19]) when indirectly adjusting for smoking at the municipality level rather than the individual

level; however, when not adjusting for smoking, the association was strengthened (HR: 1.26 [95% CI: 1.22, 1.30]).

Lifestage

A few recent studies evaluated whether lifestage modified the association between exposure to NO_2 and lung cancer mortality. So et al. (2022) reported a larger magnitude of association among those 65 years and younger, compared to those over 65 years. Klompmaker et al. (2020) reported increased risk for those ≥65 years compared to <65 years, the magnitude of the association was large and the CI included the null. However, Huang et al. (2023) did not report evidence of effect measure modification among ages <60 versus ≥60. There are a limited number of recent studies that evaluated the modification of lifestage on the association between exposure to NO_2 and lung cancer mortality, and the associations were inconsistent (see Table 12-4).

Sex

There were a few recent studies evaluating the impact of sex differences on the association between exposure to NO_2 and lung cancer mortality (see Table 12-4). So et al. (2022) reported a larger magnitude of associations among males compared to females in a Danish national administrative cohort. Among participants in a Chinese cohort, Huang et al. (2023) did not report evidence of effect measure modification by sex, but the magnitude of the association was slightly stronger among females. Overall, there was limited evidence that evaluated the modification of sex on the association between exposure to NO_2 and lung cancer mortality and the recent evidence is inconsistent

Table 12-4 Epidemiologic studies evaluating effect measure modification between long-term NO_2 exposure and lung cancer mortality

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Smoking					
†So et al. (2022)	Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) January 1, 2000–December 31, 2017	HR (95% CI)[b] Lung cancer mortality - No smoking: 1.26 (1.22, 1.30)	HR (95% CI)[b] Lung cancer mortality - Indirect adjustment for smoking: 1.16 (1.13, 1.19)	↓	Individual
Lifestage					
†Huang et al. (2023)	January 1998 – December 2019	HR (95% CI)[b] Lung cancer mortality (Main Effect): 1.32 (1.17, 1.49)	HR (95% CI)[b] Lung cancer mortality - Age <60: NR	≈	Individual
			Lung cancer mortality - Age ≥60: NR	≈	
†Klompmaker et al. (2020)	Public Health Monitor Enrollment: September–November 2012 Follow-up: 2013–2017	HR (95% CI)[b] Lung cancer mortality - Adults (<65 years): 0.90 (0.62, 1.31)	HR (95% CI)[b] Lung cancer mortality - Older Adults (≥65 years): 1.21 (0.83, 1.76)	↓	Individual
†So et al. (2022)	Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) 1 January 2000–31 December 2017	HR (95% CI)[b] Lung cancer mortality - Age <65: 1.22 (1.20, 1.24)	HR (95% CI)[b] Lung cancer mortality - Age ≥65: 1.08 (1.07, 1.09)	↓	Individual
Sex					
†Huang et al. (2023)	January 1998–December 2019	HR (95% CI)[b] Lung cancer mortality (Main Effect): 1.32 (1.17, 1.49)	HR (95% CI)[b] Lung cancer mortality - Males: NR	≈	Individual
			Lung cancer mortality - Females: NR	≈	
†So et al. (2022)	Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) January 1, 2000–December 31, 2017	HR (95% CI)[b] Lung cancer mortality - Male (author reported as men): 1.18 (1.17, 1.19)	HR (95% CI)[b] Lung cancer mortality - Female (author reported as women): 1.06 (1.06, 1.06)	↓	Individual

List of abbreviations in alphabetical order: CI = confidence interval; EMM = effect measure modification; HR = hazard ratio.
[a]An up-facing arrow (and yellow shading) indicate that the effect of NO_2 or NO_X is greater (e.g., larger risk of cancer) in the group with the factor evaluated than in the reference group. A down-facing arrow (and blue shading) indicates that the effect of NO_2 or NO_X is smaller in the group with the factor evaluated than in the reference group. An almost equal sign (and grey shading) indicates that the effect of NO_2 or NO_X is comparable between groups.
[b]Effect estimates are standardized and are presented as a 10 ppb change in NO_2 for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_X for annual average averaging time.
[c]Estimates are not standardized.
†Studies published since the 2016 Oxides of Nitrogen ISA.

12.3.1.2.3 Copollutants

Among the recent epidemiologic studies evaluating the associations between exposure to NO_2 and lung cancer mortality, the impact of confounding by copollutants such as $PM_{2.5}$, particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm (PM_{10}), ultrafine particles (UFPs), ozone (O_3), and sulfur dioxide (SO_2), were also evaluated (see Table 12-5). Overall, there were inconsistent patterns of association among the recent studies that examined the effect of copollutants on the associations between exposure to NO_2 and lung cancer mortality.

Several recent studies evaluated the effect of particulate matter, including $PM_{2.5}$, PM_{10}, UFPs. When adjusting for $PM_{2.5}$, the association between exposure to NO_2 and lung cancer mortality remained robust among a Danish nationwide administrative cohort study (So et al., 2022) and in Medicare cohort (Eum et al., 2022), with both studies reporting moderate correlations (0.60 and 0.59, respectively) between NO_2 and $PM_{2.5}$. In another study in the Medicare cohort, there was a slight attenuation in the association when using a two-stage approach to adjust for $PM_{2.5}$ (Eum et al., 2019). In a national Dutch cohort, Klompmaker et al. (2021a) reported attenuation in the association when adjusting for $PM_{2.5}$ across three different exposure metrics (LUR, hybrid, dispersion). Black carbon (BC), a component of $PM_{2.5}$, was also evaluated as a copollutant in recent studies; however, there were inconsistencies, with individual studies reporting a stronger association (So et al., 2022), no change (Eum et al., 2022), and attenuation towards the null (Klompmaker et al., 2021a). These inconsistent associations may be the result of moderate to high correlations between NO_2 and BC. In addition, a single recent study evaluated potential copollutant confounding by PM_{10}. Chen et al. (2016) used two different exposure assignment methods in four cities in China. Adjustment for PM_{10} did not change the association for the 1998 exposure assignment, but there was an increased risk for the average air pollutant concentration for the surviving period (HR: 1.65 [95% CI: 1.30, 2.09]). There was a single recent study that evaluated the potential confounding by UFPs Bouma et al. (2023), and this study reported attenuation of the association between exposure to NO_2 and lung cancer mortality.

In addition to PM as a copollutant, there were a few recent studies that evaluated the effects of O_3 and SO_2 as copollutants. When O_3 was evaluated as a copollutant, there were consistently stronger associations between exposure to NO_2 and lung cancer mortality in the copollutant models (Huang et al., 2023; So et al., 2022). In a single study in China, SO_2 was adjusted as a copollutant and the risk of lung cancer mortality, and the association was robust as the HR was relatively unchanged from the single exposure estimates for NO_2 (Chen et al., 2016).

There were a limited number of studies that evaluated multipollutant effects of $PM_{2.5}$ and O_3 on the associations between exposure to NO_2 and lung cancer mortality. While Turner et al. (2016) reported a slightly smaller magnitude in the association, Crouse et al. (2015) reported a similar risk for lung cancer mortality in the multipollutant model with $PM_{2.5}$ and O_3 compared to the risk in the single exposure for NO_2.

Lastly, other co-exposures, greenness, and road traffic noise was assessed for its effect on the associations with exposure to NO_2 and lung cancer mortality, but the evidence is limited. Two metrics of greenness, the Normalized Difference Vegetation Index (NDVI) and the national land-use database of the Netherlands (TOP10NL) of 2010, were evaluated in two-exposure models with NO_2 among a Dutch national cohort (Klompmaker et al., 2021b). The NDVI was used to assess surrounding greenness, or the average density of green vegetation within a circular buffer of each residential address. TOP10NL was used to assess surrounding green space, or the proportion of green space within a buffer around the participant's residential address. In either the two-exposure model with NO_2 and NDVI or NO_2 and TOP10NL, the risk of lung cancer mortality was attenuated towards the null. In the two-exposure model with NO_2 and road traffic noise, there was a similar risk of lung cancer mortality as in the single-exposure model with NO_2.

Table 12-5 Epidemiologic studies evaluating copollutants on the associations between exposure to NO_2 and lung cancer mortality

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
†Bouma et al. (2023)	Statistics Netherlands (CBS) Enrollment: 2013 Follow-up: 2013–2019	UFP	UFP: 0.81	Cox proportional hazard models Cox proportional hazard models – co-adjusted for UFPs	↓	HR (95% CI)[b] Lung cancer mortality (Main Effect): 1.19 (1.14, 1.25) Lung cancer mortality - UFP: 1.10 (1.04, 1.17)
†Chen et al. (2016)	January 1998 to December 2009	SO_2	SO_2: NR	Cox proportional hazard model co-adjusted for SO_2	≈	HR (95% CI)[b] Lung cancer mortality - time-varying exposures for both deaths and controls (Main Effect) 0.94 (0.91, 0.97) Lung cancer mortality - time-varying exposures for both deaths and controls with SO_2: 0.96 (0.93, 0.99)
					≈	Lung cancer mortality - assigned 1998 air pollution exposure (Main

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
						Effect) 0.82 (0.69, 0.97) Lung cancer mortality - assigned 1998 air pollution exposure with SO_2: 0.82 (0.69, 0.98)
					≈	Lung cancer mortality - average concentration for the surviving period (Main Effect): 0.72 (0.58, 0.89) Lung cancer mortality - average concentration for the surviving period with SO_2: 0.90 (0.72, 1.13)
†Chen et al. (2016)	January 1998 to December 2009	PM_{10}	PM_{10}: NR	Cox proportional hazard model co-adjusted for PM_{10}	↑	HR (95% CI)[b] Lung cancer mortality - time-varying exposures for both deaths and controls (Main Effect) 0.94 (0.91, 0.97) Lung cancer mortality - time-varying exposures for both deaths and controls with PM_{10}: 1.01 (0.97, 1.05)
					≈	Lung cancer mortality - assigned 1998 air pollution exposure (Main Effect) 0.82 (0.69, 0.97) Lung cancer mortality -

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
						assigned 1998 air pollution exposure with PM_{10}: 0.80 (0.68, 0.95)
					↑	Lung cancer mortality - average concentration for the surviving period (Main Effect): 0.72 (0.58, 0.89) Lung cancer mortality - average NO_2 for the surviving period with PM_{10}: 1.65 (1.30, 2.09)
†Crouse et al. (2015)	Canadian Census Health and Environment Cohort (CanCHEC) Enrollment: 1991 Follow-up: 1991–2006	$PM_{2.5}$; O_3	$PM_{2.5}$; O_3: NR	Cox proportional hazard model	≈	HR (95% CI)[b] Lung cancer mortality: Trachea, bronchus, and lung cancers (Main Effect): 1.09 (1.06, 1.12) Lung cancer mortality: Trachea, bronchus, and lung cancers with $PM_{2.5}$ and O_3: 1.08 (1.05, 1.11)
†Eum et al. (2019)	Medicare Enrollment: 2000–2008 Follow-up: 2000–2008	$PM_{2.5}$	$PM_{2.5}$: NR	Poisson regression models - two-stage approach for $PM_{2.5}$ adjustment	≈	MRR (95% CI)[b] Lung cancer mortality (Main Effect): 0.98 (0.98, 0.99) Lung cancer mortality - additionally adjusted for $PM_{2.5}$: 0.96 (0.95, 0.97)
†Eum et al. (2022)	Medicare Enrollment: 2001–2008	$PM_{2.5}$	$PM_{2.5}$: 0.59	Cox proportional hazard model co-adjusted for $PM_{2.5}$	≈	HR (95% CI)[b] Lung cancer mortality (Main Effect): 1.04 (1.02, 1.07) Lung cancer

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
						mortality - $PM_{2.5}$: 1.05 (1.03, 1.08)
†Eum et al. (2022)	Medicare Enrollment: 2001–2008	BC	BC: 0.54	Cox proportional hazard model co-adjusted for BC	≈	HR (95% CI)[b] Lung cancer mortality (Main Effect): 1.04 (1.02, 1.07) Lung cancer mortality - BC: 1.04 (1.02, 1.07)
†Huang et al. (2023)	January 1998 to December 2019	O_3	O_3: NR	Cox proportional hazard model with adjustment for O3	≈	HR (95% CI)[b] Lung cancer mortality (Main Effect): 1.32 (1.17, 1.49) Lung cancer mortality with O_3: 1.39 (1.20, 1.60)
†Klompmaker et al. (2021b)	Follow-up period: January 1, 2013 to December 31, 2018	NDVI	NDVI: NR	Cox proportional hazard model co-adjusted for NDVI 300m	≈	HR (95% CI)[b] Lung cancer mortality: 1.08 (0.90, 1.29) Lung cancer mortality - NDVI 300 m: 1.13 (0.92, 1.38)
†Klompmaker et al. (2021b)	Follow-up period: January 1, 2013 to December 31, 2018	TOP10NL	TOP10NL: NR	Cox proportional hazard model co-adjusted for TOP10NL 1000 m	≈	HR (95% CI)[b] Lung cancer mortality: 1.08 (0.90, 1.29) Lung cancer mortality - TOP10NL 1000 m: 1.12 (1.08, 1.17)
†Klompmaker et al. (2021b)	Follow-up period: January 1, 2013 to December 31, 2018	Road traffic noise	Road traffic noise: NR	Cox proportional hazard model co-adjusted for road traffic noise	≈	HR (95% CI)[b] Lung cancer mortality: 1.08 (0.90, 1.29) Lung cancer mortality - road traffic noise: 1.15 (1.10, 1.20)
†Klompmaker et al. (2021a)	January 1, 2008 to December 31, 2012	$PM_{2.5}$	Lung cancer mortality - hybrid model with $PM_{2.5}$: 0.58 Lung cancer	Cox proportional hazard model co-adjusted for $PM_{2.5}$	≈	HR (95% CI)[b] Lung cancer mortality - hybrid model (Main Effect): 1.18 (1.13, 1.22)

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
			mortality - LUR model with $PM_{2.5}$: 0.52 Lung cancer mortality - Dispersion model with $PM_{2.5}$: 0.71			Lung cancer mortality - hybrid model with $PM_{2.5}$: 1.12 (1.07, 1.18)
					≈	Lung cancer mortality - LUR model (Main Effect): 1.17 (1.13, 1.22) Lung cancer mortality - LUR model with $PM_{2.5}$: 1.14 (1.09, 1.19)
					↓	Lung cancer mortality - dispersion model (Main Effect): 1.15 (1.11, 1.20) Lung cancer mortality - dispersion model with $PM_{2.5}$: 1.03 (0.97, 1.10)
†Klompmaker et al. (2021a)	January 1, 2008 to December 31, 2012	BC	Lung cancer mortality - hybrid model with BC: 0.88 Lung cancer mortality - LUR model with BC: 0.78 Lung cancer mortality - Dispersion model with BC: 0.75	Cox proportional hazard model co-adjusted for BC	≈	Lung cancer mortality - hybrid model (Main Effect): 1.18 (1.13, 1.22) Lung cancer mortality - hybrid model with BC: 1.15 (1.07, 1.23)
					≈	Lung cancer mortality - LUR model (Main Effect): 1.17 (1.13, 1.22) Lung cancer mortality - LUR model with BC: 1.14 (1.07, 1.22)
					↓	Lung cancer mortality - dispersion

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of association[a]	Effect Estimate (95% CI)
						model (Main Effect): 1.15 (1.11, 1.20) Lung cancer mortality - dispersion model with BC: 1.08 (0.97, 1.20)
†So et al. (2022)	Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) January 1, 2000 to December 31, 2017	BC	BC: 0.89	Cox proportional hazard model - co-adjusted for BC	↑	HR (95% CI)[b] Lung cancer mortality (Main Effect): 1.26 (1.22, 1.30) Lung cancer mortality - BC: 1.34 (1.27, 1.42)
†So et al. (2022)	Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) January 1, 2000 to December 31, 2017	$PM_{2.5}$	$PM_{2.5}$: 0.6	Cox proportional hazard model co-adjusted for $PM_{2.5}$	≈	HR (95% CI)[b] Lung cancer mortality (Main Effect): 1.26 (1.22, 1.30) Lung cancer mortality - $PM_{2.5}$: 1.24 (1.19, 1.29)
†So et al. (2022)	Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) January 1, 2000 to December 31, 2017	O_3	O_3: -0.65	Cox proportional hazard model - co-adjusted for O_3	↑	HR (95% CI)[b] Lung cancer mortality (Main Effect): 1.26 (1.22, 1.30) Lung cancer mortality - O_3: 1.34 (1.27, 1.42)
†Turner et al. (2016)	Cancer Prevention Study II Enrollment: 1982 Follow-up: through 2004	O_3, regional $PM_{2.5}$, near-source $PM_{2.5}$	O_3, regional $PM_{2.5}$, near-source $PM_{2.5}$: O_3: -0.08; regional $PM_{2.5}$: 0.21; near-source $PM_{2.5}$: 0.60	Cox proportional hazard model with co-adjustment for multipollutant	≈	HR (95% CI)[b] Lung cancer mortality (Main Effect): 0.99 (0.95, 1.03) Lung cancer mortality - Multipolluant (O_3, regional $PM_{2.5}$, near-source $PM_{2.5}$): 0.94 (0.90, 0.99)

List of abbreviations: BC = black carbon; CI = confidence interval; HR = hazard ratio; LUR = land use regression; MRR = mortality risk ratio; NDVI = Normalized Difference Vegetation Index; NO_2 = nitrogen dioxide; O_3 = ozone; ppb = parts per billion; $PM_{2.5}$ = particulate matter with a nominal mean aerodynamic diameter less than equal to 2.5 μm; PM_{10} = particulate matter with a nominal mean aerodynamic diameter less than equal to 10 μm.
[a]Up facing arrow (and yellow shading) indicate that the effect of NO_2 is greater (e.g., larger risk of lung cancer mortality) with the copollutant evaluated than in the single pollutant model. Down facing arrow (and blue shading) indicate that the effect of NO_2 is smaller with the copollutant evaluated than in the single pollutant model. An almost equal sign (and grey shading) indicates that the effect of NO_2 is comparable between the single pollutant analysis and copollutant analysis.
[b]Effect estimates are standardized and are presented as a 10 ppb change in NO_2 for annual average averaging time.
[c]Estimates are not standardized.
†Studies published since the 2016 Oxides of Nitrogen ISA.

12.3.1.3 Conclusions and Remaining Uncertainties

Overall, there was a consistent pattern of positive associations between exposure to NO_2 and lung cancer incidence and mortality, but a few studies did report null associations. In the recent epidemiologic literature, there were several studies that examined associations between oxides of nitrogen, mostly NO_2 but also NO_X. The majority of the recent evidence estimated exposure to NO_2 or NO_X through validated LUR models. Additionally, most of the studies had relatively short latency periods (range: 3–18 years). While there was some examination of factors modifying association (smoking, race/ethnicity, genetic factors, dietary), the evidence was limited and inconsistent. The recent studies evaluated the potential effect of confounding by copollutants, but there were inconsistent impacts on the associations overall. Among the studies that considered copollutants, co-adjusted exposures were the common way to account for potential copollutant confounding, but this could have led to bias in the estimates, especially with moderately or highly correlated copollutants. There were a few recent studies of concentration-response, but overall, there was no clear shape of the concentration response curves for NO_2 and lung cancer mortality.

12.3.2 Animal Toxicological Studies of Lung Cancer

Available animal toxicological evidence evaluated in the 1993 Oxides of Nitrogen Air Quality Criteria Document (AQCD) and the 2008 and 2016 Oxides of Nitrogen ISAs reported a lack of evidence that NO_2 acts as a direct carcinogen, and only limited evidence that ambient-relevant NO_2 exposures promote lung tumors when given in conjunction with a known carcinogen. NO_2 exposure was shown to facilitate colonization of the lung by tumor cells (U.S. EPA, 2016, 2008, 1993). No recent animal toxicological studies investigating the effects of NO_2 exposure on lung cancer have been identified. Therefore, this section focuses on key studies that have been evaluated in previous Oxides of Nitrogen ISAs and AQCDs. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below and summarized in Appendix A – Appendix Table 12-2.

Lung Tumors with Co-exposure with Known Carcinogens or Copollutants

Compared to clean air exposure, continuous exposure to 4 ppm NO_2 for 17 months after injection with the carcinogen N-bis(2-hydroxy-propyl) nitrosamine (BHPN) led to a fivefold increase in the number of rats that developed adenomas or adenocarcinomas in the lungs, but the results were not analyzed for potential statistical significance (Ichinose et al., 1991). However, the combination of 0.4 ppm NO_2 and 0.05 ppm O_3 significantly increased the number of rats with lung tumors after BHPN injection (Ichinose and Sagai, 1992). In this study, BHPN injection alone did not induce lung tumors, and the tumor increases reported with BHNP and O_3 exposure and with BHNP and NO_2 plus sulfuric acid (H_2SO_4; 0.1 mg/m^3) exposure were not statistically significant. Rats were not exposed to NO_2 alone in this study.

Higher than ambient-relevant NO_2 exposure (6 ppm, 8 months) combined with diesel exhaust particle extract-coated black carbon particles (DEPcCBP) increased the number of F344 rats with lung tumors (alveolar adenomas) (Ohyama et al., 1999). When given weekly for 4 weeks by intratracheal installation, DEPcCBP exposure alone did not induce lung tumors.

Cancer in the Lungs of Animals with Spontaneously High Tumor Rates

The 2008 and 2016 Oxides of Nitrogen ISAs reviewed two studies that investigated the effect of NO_2 exposure on tumors in the lungs of animals with spontaneously high tumor rates (U.S. EPA, 2016, 2008). In AKR/cum mice, 0.25 ppm NO_2 inhalation exposure for up to 26 weeks decreased the progression of spontaneous T cell lymphoma in the lungs, thymus, spleen, lymph nodes, and liver and increased survival rates (Richters and Damji, 1990). The investigators attributed the protective effect to adverse effects on CD4+ T cells induced by NO_2 exposure. A similar duration of exposure (i.e., 6 months) to 1 or 5 ppm NO_2 had no effect on pulmonary adenomas in A/J mice, but higher than ambient-relevant NO_2 exposures (i.e., 10 ppm) induced a small, but statistically significant increase in pulmonary adenomas (Adkins et al., 1986). In CAF1/Jax mice, continuous exposure to 5 ppm NO_2 produced statistically significant increases in the number of mice with pulmonary tumors when compared with controls after 12 months but not after 14 or 16 months (Wagner et al., 1965).

Facilitation of Lung Cancer Metastases

The 2008 and 2016 Oxides of Nitrogen ISAs reviewed three studies that investigated the ability of NO_2 to facilitate tumor metastasis of lung cancer, or more accurately, colonization of the lung by tumor cells (U.S. EPA, 2016, 2008). Richters and Kuraitis (1983, 1981) and Richters et al. (1985) exposed mice to 0.3–0.8 ppm NO_2 for 8, 10, or 12 weeks before injecting them intravenously with the B16 melanoma cell line. Melanoma nodules in the lungs were then counted. All three studies reported increases in the number of melanoma nodules in the lungs of mice exposed to NO_2. Richters and Kuraitis (1981) and Richters and Kuraitis (1983) reported a statistically significant increase in the number of melanoma nodules in the lungs of mice exposed to 0.4 ppm NO_2. Those studies also reported statistically significant results for additional NO_2 concentrations (i.e., 0.3 ppm and 0.8 ppm). Richters et al. (1985) also reported

that the number of melanoma nodules was increased in the lungs of the mice exposed to 0.4 ppm NO_2 for 12 weeks, though the increase was not statistically significant.

12.3.2.1 Relevance of Animal Responses to Human Responses

Three studies provided evidence that the lungs of mice previously exposed to NO_2 were more susceptible to colonization by metastatic cancer cells (Richters et al., 1985; Richters and Kuraitis, 1983, 1981). Metastasis is a potentially life-threatening event where cancer cells spread from a primary tumor to other parts of the body. Recognizing that many common cancers metastasize to the lung (Stella et al., 2019) and that there are examples where exposure to other agents contributes to metastasis in rodent models and increases risk of metastasis in humans (e.g., ionizing radiation, arsenic, parabens) (Tong et al., 2023; Schmidlin et al., 2020; Lee et al., 2017). These findings support the human relevance of rodent models of metastasis and the relevance of NO_2 results in rodent models.

12.3.2.2 Conclusions and Remaining Uncertainties

Animal toxicological evidence related to lung cancer provided no evidence that NO_2 acts as a direct carcinogen, and inconsistent evidence that ambient-relevant NO_2 exposures promote lung tumors at the site of contact. The strongest toxicological evidence for lung cancer is derived from inhalation studies where rodents were exposed to ambient-relevant NO_2 concentrations prior to being injected with metastatic cancer cells leading to an increased number of rodents with lung tumors. In addition, co-exposure to a known carcinogen (BHPN) increased the number of rodents with lung tumors, but the one study examining co-exposures did not include an important control (i.e., no NO_2 exposure), limiting the interpretation of study findings. Mixed results were observed following NO_2 exposures in rodents with spontaneously high tumor rates, with some studies reporting protective effects and others reporting harmful effects. Taken together, animal toxicological studies provide some support for the conclusion that NO_2 exposure can promote tumor growth, but the evidence base is highly limited in breadth and depth, and none of the available studies have been replicated. The potential effects of multipollutant exposures on lung cancer are similarly limited, further reducing the real-world relevance of the available evidence. Consequently, additional studies are needed to better understand the effects of NO_2 on lung cancer.

12.3.3 Synthesis Across Lines of Evidence

Similar to the 2016 Oxides of Nitrogen ISA, the recent epidemiologic evidence is generally supportive of positive associations between NO_2 and lung cancer incidence and lung cancer mortality. Compared to studies in the 2016 Oxides of Nitrogen ISA, recent epidemiologic studies that estimated NO_2 exposures with validated LUR models have consistently reported positive associations for these

outcomes. Most of the recent studies had relatively short lag periods (range: 3–18 years), while reporting generally positive associations. While there has been some examination of factors modifying associations (e.g., smoking, race/ethnicity, genetic factors, dietary), the evidence supporting these factors is limited and inconsistent. Recent epidemiologic studies that evaluated the potential for confounding by $PM_{2.5}$ or other copollutants report inconsistent results, with some analyses indicating attenuation of associations in copollutant models and others indicating either stronger or unchanged associations. The evidence on concentration-response relationships remains limited, with the few available studies indicating linear increases in risk with increasing NO_2 exposure at lower concentrations and plateaus or inverse associations at higher concentrations. In addition, no animal toxicological studies examining NO_2 exposures and lung cancer have become available since the 2016 Oxides of Nitrogen ISA. The existing animal evidence does not provide support for NO_2 acting as a direct carcinogen, and there is only limited and inconsistent evidence that ambient-relevant NO_2 exposures promote lung tumors at the site of contact.

12.4 Cancers of Sites Outside the Lungs

In the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016), evidence for several site-specific cancers was reviewed. Overall, the limited epidemiologic studies reported inconsistent associations, and there was uncertainty regarding an independent effect of NO_2 due to the lack of examination of potential confounding by $PM_{2.5}$ or traffic-related copollutants by any of the studies. Studies published since the 2016 Oxides of Nitrogen ISA are evaluated in this section in the context of the older evidence.

12.4.1 Leukemia

There was a small number of studies that evaluated associations between oxides of nitrogen and leukemia in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016). Overall, the limited epidemiologic evidence reported inconsistent associations, and there was uncertainty regarding an independent effect of NO_2 due to the lack of examination of potential confounding by $PM_{2.5}$ or traffic-related copollutants by any of the studies. There was particularly limited evidence of associations between exposure to oxides of nitrogen and leukemia in adults, as the majority of studies examined the relationships among children. The evidence that has become available since the 2016 Oxides of Nitrogen ISA includes a small number of epidemiologic studies examining associations with leukemia in adults. No animal toxicological studies examining NO_2 or NO_X exposures and leukemia have been published since the 2016 Oxides of Nitrogen ISA.

12.4.1.1 Epidemiologic Studies of Leukemia

A limited number of recent epidemiologic studies have examined the relationship between exposures to NO_2 or NO_X and leukemia. These recent studies examined adults in Denmark and the United States, and they considered a variety of exposure periods and exposure metrics. Study specific details including study population characteristics, exposure details (assessment metrics, temporal scale, and spatial scale), potential confounders, and select results are in Appendix A – Appendix Table 12-3.

- Raaschou-Nielsen et al. (2015) investigated the associations between long-term exposure to NO_2 and NO_X and risk of leukemia in Denmark. To estimate NO_2 and NO_X exposure, Raaschou-Nielsen et al. (2015) used the residential addresses of each participant with the Danish AirGIS dispersion modeling system for three exposure periods: 5-year exposure, 10-year exposure, and mean exposure from 1971 (time-weighted average that accounts for all addresses during the study period). In this case-control study, cases were identified from the Danish Cancer Registry, which had complete residential histories since 1971. For NO_2 and NO_X, there were inverse associations for lymphocytic leukemia for the three exposure periods (OR range of 0.91–0.94 per 5.32 ppb increase in NO_2 and OR range of 0.96–0.97 per 20 $\mu g/m^3$ increase in NO_X) and chronic myeloid leukemia (OR range: 0.69–0.80 for NO_2 and OR range of 0.91–0.93 for NO_X). While there was a consistent pattern of decreased odds for any myeloid leukemia and acute myeloid leukemia with exposure to NO_2 and NO_X, the associations were imprecise regardless of the exposure period. Furthermore, there was no evidence of effect modification of the associations between NO_X exposure and acute myeloid leukemia based on sex (male vs. female), age (<65 vs. ≥65 years), or income. However, there were increased odds of acute myeloid leukemia for females (OR: 1.31 [95% CI: 1.08, 1.59] per 20 $\mu g/m^3$ increase in NO_X), those ≥65 years (OR: 1.27 [95% CI: 1.06, 1.52] per 20 $\mu g/m^3$ increase in NO_X) and among those in the highest tertile of disposable income (OR: 1.34 [95% CI: 1.05, 1.72] per 20 $\mu g/m^3$ increase in NO_X).
- In another case-control study in Denmark, Danish National Cancer Registry data and Danish DEHM-UBM-AirGIS system-modelled air pollution exposures were used to examine the relationship between NO_2 averaged over 1-year, 5-year, or 10-year and adult leukemia overall and for subtypes (Puett et al., 2020). Overall, there were null associations between NO_2 and adult leukemia, regardless of the average exposure period. The odds of leukemia incidence were attenuated when only including adults up to age 69, while the odds were slightly increased among adults over the age of 70. Among the subtypes of leukemia, the associations were near null for associations between NO_2 and acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myeloid leukemia, or chronic myeloid leukemia, regardless of exposure period.
- Among participants in the U.S. Cancer Prevention Study II (CPS-II), Turner et al. (2017) examined whether exposure to NO_2 was associated with specific types of cancer mortality other than lung cancer. NO_2 exposure was estimated from a national LUR model and associations with leukemia mortality and multiple myeloma mortality were evaluated. There were null associations between NO_2 and leukemia (HR: 1.00 [95% CI: 0.90, 1.10] per 6.5 ppb of NO_2) and multiple myeloma (HR: 1.00 [95% CI: 0.92, 1.09]).

12.4.1.1.1 Conclusions and Remaining Uncertainties

Overall, there remains a limited number of epidemiologic studies evaluating the associations between oxides of nitrogen and leukemia incidence and mortality. While the recent studies were among adults, which addresses a gap from the 2016 Oxides of Nitrogen ISA, these studies generally did not report positive associations with leukemia. In addition, there are several remaining uncertainties including factors modifying associations for lifestages and population differences (e.g., lifestages, sex, genetics), the potential for copollutant confounding, and the shape of concentration-response relationships. In general, among the recent studies, there were consistent inverse associations between oxides of nitrogen and leukemia, accounting for several different exposure periods and exposure metrics, and conducted in different countries.

12.4.2 Bladder Cancer

There were a limited number of epidemiologic studies reviewed in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016) that examined the associations between oxides of nitrogen and bladder cancer. While a single study reported no associations between NO_X exposure and bladder cancer incidence, a single study reported increased odds of bladder cancer mortality with increased NO_2 concentrations. However, there was remaining uncertainty regarding the independent effect of NO_2, as potential confounding by copollutants such as $PM_{2.5}$ was not examined. Additionally, there was uncertainty regarding exposure assessment and whether concurrent NO_2 concentrations at a single central site monitor in a municipality adequately represent exposure contrasts between subjects. The evidence that has become available since the 2016 Oxides of Nitrogen ISA includes several epidemiologic studies examining associations with bladder cancer in populations from Europe and the United States. No animal toxicological studies examining bladder cancer have been published since the 2016 Oxides of Nitrogen ISA.

12.4.2.1 Epidemiologic Studies of Bladder Cancer

A limited number of recent epidemiologic studies evaluate the associations between exposure to NO_2 or NO_X and bladder cancer incidence, and a single recent study examines bladder cancer mortality. Recent studies evaluated exposure to NO_2 and bladder cancer incidence in countries across Europe, consistently reporting near null associations (HR range of 0.98–1.13), while using LUR exposure models developed with similar methodologies (Chen et al., 2022; Turner et al., 2019; Pedersen et al., 2018). Study specific details including study population characteristics, exposure details (assessment metrics, temporal scale, and spatial scale), potential confounders, and select results are in Appendix A – Appendix Table 12-3.

- Pedersen et al. (2018) reported a null association between exposure to NO_2 and bladder cancer incidence (HR: 0.96 [95% CI: 0.80, 1.15] per 5.31 ppb increase in NO_2) across the 15 cohorts in the European Study of Cohorts for Air Pollution Effects (ESCAPE), with inconsistent patterns of associations among the individual cohorts. In addition, Pedersen et al. (2018) reported a null association between exposure to NO_X and bladder cancer incidence (HR: 0.99 [95% CI: 0.91, 1.09] per 20 $\mu g/m^3$ increase in NO_X) across 15 cohorts in ESCAPE.
- In the Spanish Bladder Cancer Study, there were consistent null associations between NO_2 and bladder cancer incidence, whether exposure to NO_2 was evaluated continuously (HR: 0.91 [95% CI: 0.57, 1.46] per 5.9 ppb increase in NO_2) or categorized into tertiles (HR range: 1.04–1.13) (Turner et al., 2019).
- Among six of eight cohorts from the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project study, Chen et al. (2022) reported a null association between NO_2 and bladder cancer incidence (HR: 1.01 [95% CI: 0.91, 1.12] per 5.31 ppb in NO_2).
- Among participants of the Cancer Prevention Study II (CPS-II) in the United States, Turner et al. (2017) examined whether exposure to NO_2 was associated with specific types of cancer other than lung cancer mortality. There was an imprecise, positive association between NO_2 and bladder cancer mortality (HR: 1.03 [95% CI: 0.94, 1.12] per 6.5 ppb of NO_2).

Several of the studies summarized above evaluated the potential for copollutant confounding or effect modification. In analyses that adjusted for the copollutants $PM_{2.5}$ or O_3, associations were attenuated toward the null (Chen et al., 2022). In a single study that adjusted for black carbon, Chen et al. (2022) reported the risk of bladder cancer was slightly increased compared to the single pollutant model but the association was imprecise (HR: 1.06 [95% CI: 0.84, 1.34]). Furthermore, only a single study examined potential effect modification (Turner et al., 2019). This study reported no clear evidence for effect modification by age, sex, region, education, cigarette smoking status, or pack-years (see Appendix A – Appendix Table 12-3).

12.4.2.1.1 Conclusions and Remaining Uncertainties

Several recent studies evaluated the exposure to NO_2 and bladder cancer incidence across Europe, consistently reporting null associations, while using similar LUR exposure models. In the few studies that evaluated potential confounding by copollutants, generally, there was attenuation of the effect estimates. There remains limited epidemiologic evidence, and similar to the conclusions to the 2016 Oxides of Nitrogen ISA, overall, the associations between exposure to NO_2 and bladder cancer were null.

12.4.3 Female Reproductive Cancers: Breast, Cervical, Ovarian, and Uterine

In the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016), there were a limited number of epidemiologic studies examining associations between long-term exposure to oxides of nitrogen and breast cancer. Overall, the associations were inconsistent, with some studies reporting increased risk, but wide confidence intervals, and others reporting no associations. The studies considered a variety of

exposure metrics (LUR models, central site monitors) and examined populations in several different locations (Canada, Denmark, and the United States). There were uncertainties regarding the exposure window, potential selection bias, inclusion of all breast cancer cases or post-menopausal breast cancer cases only, and limited information on copollutant confounding. Other than breast cancer, no other female reproductive cancers were included in the 2016 Oxides of Nitrogen ISA. Epidemiologic studies that have become available since the 2016 Oxides of Nitrogen ISA examine associations with breast, cervical, ovarian, and uterine cancers. No animal toxicological studies examining female reproductive cancers have been published since the 2016 Oxides of Nitrogen ISA.

12.4.3.1 Epidemiologic Studies of Female Reproductive Cancers: Breast, Cervical, Ovarian, and Uterine

Breast Cancer Incidence and Mortality

There were several recent epidemiologic studies evaluating the associations between exposure to oxides of nitrogen and breast cancer. While all the recent epidemiologic studies evaluated associations between exposure to NO_2 and breast cancer, a few studies additionally evaluated associations with exposure to NO_X. Overall, the associations were inconsistent, with some studies reporting positive associations, others reporting null associations, and a single study reporting a negative (inverse) association. Among the breast cancer studies, there were different types of exposure metrics (LUR modes, spatiotemporal models, chemical transport models, central site monitors, and ensemble machine learning models), different geographic locations (Denmark, United States, United Kingdom, Canada), large study populations, and differences in exposure periods (timing between exposure and outcome). Study specific details including study population characteristics, exposure details (assessment metrics, temporal scale, and spatial scale), potential confounders, and select results are in Appendix A – Appendix Table 12-3.

A few recent studies evaluated the associations between oxides of nitrogen and breast cancer incidence among all women and a single recent study examined breast cancer mortality. Overall, there was no clear pattern of association across the recent evidence.

- A few recent studies in Denmark reported inconsistent associations between exposure to NO_2 and breast cancer incidence. While a nationwide case-control study reported increased odds of breast cancer incidence (OR: 1.06 [95% CI: 1.01, 1.11] per 5.31 ppb increase in NO_2) (Poulsen et al., 2023), a study among participants in the Danish Nurse Cohort reported a null association (HR: 1.00 [95% CI: 0.85, 1.18] per 3.93 ppb increase of NO_2) (Andersen et al., 2016). In the nationwide case-control study, Poulsen et al. (2023) derived NO_2 exposure from the Danish DEHM/UBM/AirGIS modeling system and calculated a time-weighted average over all residential addresses held during the 20 years prior to the index date. However, in the Danish Nurse Cohort, Andersen et al. (2016) used the Danish integrated air pollution modeling system (THOR and AirGIS) to estimate a 3-year running mean. Despite these differences, the mean NO_2 concentration for cases was the same for both studies (mean: 11 ppb). While the study population includes both pre-and post-menopausal women in the Danish Nurse Cohort, there was an adjustment for menopausal status, as well as other

important confounders (age at menarche, age at first birth, parity, hormone therapy use, oral contraceptive use).

- Hvidtfeldt et al. (2023b) used data from six of nine cohorts from the ELAPSE collaboration. Exposure to NO_2 was estimated from the Europe-wide hybrid LUR model. In the pooled analysis, there was a positive association for risk of breast cancer incidence (HR: 1.03 [95% CI: 1.00, 1.06] per 5.31 ppb increase in NO_2). There was no distinction by menopausal status or hormone receptor subtype, and studies did not adjust for potential confounders such as age at menarche, use of oral contraception, postmenopausal hormone use, or parity.
- Among participants of the Cancer Prevention Study II (CPS-II), Turner et al. (2017) examined whether exposure to NO_2 based on a national LUR model was associated with breast cancer mortality in the United States. There was a positive but imprecise association with exposure to NO_2 (HR: 1.05 [95% CI: 0.96, 1.14] per 6.5 ppb increase in NO_2).

Among studies that evaluated associations between oxides of nitrogen and breast cancer specifically for premenopausal and/or postmenopausal women, there were inconsistent associations, with several studies reporting increased risk of breast cancer incidence, but some studies reporting null or near-null associations. These recent epidemiologic studies all estimated exposure to NO_2 and/or NO_X through established, validated LUR models.

- Andersen et al. (2017b) examined the associations between NO_2 and the incidence of postmenopausal breast cancer in European women across 15 cohorts from nine European countries. Estimates of NO_2 and NO_X concentration at the residence were estimated by standardized LUR models developed within the ESCAPE and Transport related Air Pollution and Health impacts – Integrated Methodologies for Assessing Particulate Matter (TRANSPHORM) projects. There was increased incidence for postmenopausal breast cancer with NO_X (HR: 1.04 [95% CI: 1.00, 1.08] per 20 $\mu g/m^3$ increase in NO_X), and increased, but imprecise, incidence with NO_2 (HR: 1.04 [95% CI: 0.96, 1.13] per 5.31 ppb increase in NO_2). The increased incidence postmenopausal breast cancer with NO_X was robust to adjustment for potential confounding of long-term residents, non-movers, and urbanization, and to model specifications.
- In a Canadian cohort, Goldberg et al. (2019) reported positive but imprecise associations between NO_2, estimated from a national LUR model, and risk of breast cancer in postmenopausal women for two age cutoffs, over the age of 50 or over the age of 52. There was an increased rate of incidence of breast cancer in relation to an IQR (9.7 ppb) increase in NO_2 for women under the age of 52 (RR: 1.20 [95% CI: 1.06, 1.36]), with a slight attenuation towards the null and decreased precision for women under the age of 50 (HR: 1.15 [95% CI: 0.99, 1.35]).
- In another cohort study in Canada, there was a positive association between exposure to NO_2, as a 3-year moving average with 4-year time lag, and incidence of breast cancer (HR: 1.02 [95% CI: 1.00, 1.04] per 8.2 ppb increase in NO_2) (Bai et al., 2019). When using a 10-year exposure lag, the association was slightly strengthened (HR: 1.03 [95% CI: 1.01, 1.05]). Due to a lack of information on menopausal status, Bai et al. (2019) conducted a stratified analysis by using 51 years of age, the average age of menopause in Canada, as the cutoff to further investigate whether there were potential differences for pre- and postmenopausal breast cancer risk. While the risk for women <51 years of age was slightly larger in magnitude (HR: 1.04 [95% CI: 1.00, 1.07]) than for women ≥51 years of age (HR: 1.01 [95% CI: 0.98, 1.04]), there was no evidence of modification. Additionally, adjusting for a history of hormonal

replacement therapy among women aged 65 years or older resulted in a similar risk of incidence of breast cancer.

- In the UK Biobank cohort, annual averages for NO_2 (2005, 2006, 2007, and 2010) and NO_X (2010) were available for the baseline assessment period (Smotherman et al., 2023). NO_2 and NO_X were modeled as continuous variables and as quartiles, and NO_2 also had cumulative average exposure as a continuous variable and quartile. Additionally, a 2-year lag and 5-year lag were considered. Regardless of how NO_2 was modeled, there were null associations with breast cancer among postmenopausal women, and there was no evidence of linear concentration response. For NO_X, there were null associations across each quartile and no evidence of a linear concentration response.

There were several recent studies that examined associations between NO_2 and/or NO_X and hormonal subtypes (estrogen receptor, ER, and progesterone receptor, PR) of breast cancer. Across these studies, there was a consistent pattern of increased risk of ER+/PR+ breast cancer with exposure to NO_2 and/or NO_X.

- Among participants of the U.S. Sister Study, Reding et al. (2015) estimated NO_2 exposure from a validated regionalized universal kriging model and assessed the associations between exposure to NO_2 and breast cancer overall and subtype. While there were positive but imprecise association between NO_2 and invasive breast cancer (HR: 1.03 [95% CI: 0.95, 1.13] per 10 ppb NO_2), there was a positive association between NO_2 and ER+/PR+ breast cancer (RR: 1.20 [95% CI: 1.03, 1.30] per 10 ppb NO_2), but an imprecise inverse association with ER-/PR- breast cancer (RR: 0.87 [95% CI: 0.64, 1.17] per 10 ppb NO_2). While menopausal hormone therapy was adjusted for in the models, other confounders such as age, menopausal status, age at menarche, and parity were not included.
- In a population-based case-control study in Montreal, Goldberg et al. (2017) reported a positive but imprecise association of breast cancer incidence for all postmenopausal women (OR: 1.14 [95% CI: 0.71, 1.82] per 3.84 ppb increase in NO_2), and the association was further increased for women living at their current address for 10 years or more at time of recruitment, but the CIs included the null (OR: 1.22 [95% CI: 0.66, 2.25]). For ER+/PR+ cases, there was a positive, but imprecise, association for breast cancer incidence (OR: 1.20 [95% CI: 0.72, 1.98] per 3.84 increase in NO_2), and the association was strengthened if subjects were living at their current dwelling at least 10 years prior to the year of diagnosis (OR: 1.38 [95% CI: 0.72, 1.98]), however the CIs include the null.
- In the French E3N cohort, to estimate the association with breast cancer incidence in a nested case-control study two different exposure assessment metrics were used to estimate NO_2 exposures (Amadou et al., 2023). An LUR model was developed based on average NO_2 measurements from 2010 to 2013 and then back extrapolated until 1990. A chemistry-transport model, CHIMERE, was also used to estimate NO_2 in sensitivity analyses. The overall (premenopausal and postmenopausal) breast cancer risk was positively associated with exposure to NO_2, whether using concentration estimates from either the LUR model (OR: 1.07 [95% CI: 0.99, 1.17] per 9.46 ppb increase in NO_2) or CHIMERE model (OR: 1.16 [95% CI: 1.08, 1.25] per 11.05 ppb increase in NO_2). Subgroup analyses by hormone receptor status showed an increased risk for ER+/PR+ breast cancer, but CIs included the null. By menopausal status at the index date, the risk of breast cancer among premenopausal women was attenuated towards the null, but the increased risk remained for postmenopausal women. There was some heterogeneity when stratifying by breast cancer histology, with a stronger,

but still imprecise, association for ductal-lobular breast cancer. There were no differences in the results by stage of disease or grade of differentiation at diagnosis.

- Cheng et al. (2020) applied three commonly used methods (kriging interpolation, LUR, CALINE4) to estimate long-term exposure to NO_X and risk of breast cancer (incidence) in California, primarily Los Angeles County. Additionally, NO_2 was estimated with two commonly used methods (kriging interpolation, LUR). Among all women, there was increased, but imprecise, risk of breast cancer with NO_X exposures estimated by kriging (HR: 1.12 [95% CI: 0.96, 1.31] per 50.2 ppb of NO_X) and LUR (HR: 1.08 [95% CI: 0.96, 1.22] per 45.6 ppb), but a null association with CALINE4 (HR: 0.97 [95% CI: 0.73, 1.26] per 8.7 ppb). Although there was no formal statistical evidence of heterogeneity in effects by race/ethnicity, there was an increased risk of breast cancer associated with LUR-estimated NO_X for Black (HR: 1.26 [95% CI: 1.01, 1.58]) and Japanese Americans (HR: 1.42 [95% CI: 1.05, 1.91]). When considering hormone receptor status, there was an increased risk of ER+/PR+ breast cancer with NO_X estimated by kriging (HR: 1.54 [95% CI: 1.07, 2.21]). With LUR-estimated NO_2, there was an increased risk for ER-/PR- breast cancer (HR: 1.80 [95% CI: 0.97, 3.34]).

Cervical, Ovarian, and Uterine Cancers

There were a limited number of recent epidemiologic studies that evaluated associations between oxides of nitrogen exposure and other female reproductive cancers (cervical, ovarian, and uterine). Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 12-3.

- Among the CPS-II cohort, Turner et al. (2017) reported positive, but imprecise, associations between NO_2 and cervical cancer mortality (HR: 1.38 [95% CI: 0.87, 2.18] per 6.5 ppb increase in NO_2), ovarian cancer mortality (HR: 1.05, [95% CI: 0.89, 1.22]), and uterine cancer mortality (HR: 1.06 [95% CI: 0.94, 1.21]).
- Villanueva et al. (2021) examined whether exposure to NO_2 impacted ovarian cancer-specific survival among women in California. Compared to women with overall NO_2 concentrations of <20.0 ppb (referent tertile), women who had average exposures between 20.0 and 30.0 ppb (HR: 1.30 [95% CI, 1.25, 1.36]) and those with exposures >30.0 ppb (HR: 2.48 [95% CI, 2.32, 2.66]) had greater mortality from ovarian cancer.

Several of the studies summarized above have conducted analyses specifically evaluating the factors (e.g., genetics, lifestage) modifying associations between exposure to NO_2 or NO_X and female reproductive cancers. Additionally, some recent epidemiologic studies evaluated the potential confounding of copollutants on the associations between exposure to NO_2 or NO_X and female reproductive cancers. These topics are discussed in more detail in Section 12.4.3.1.1 and Section 12.4.3.1.2, respectively.

12.4.3.1.1 Lifestages and Population Differences

Genetics

Among women with receptor positive (ER+/PR+) breast cancer, there was a consistent pattern of increased risk of breast cancer in association with NO_2 and NO_X (Amadou et al., 2023; Cheng et al., 2020; Goldberg et al., 2017; Reding et al., 2015). The consistent pattern of increased risk of breast cancer among women with receptor positive (ER+/PR+) breast cancer is based on evidence from studies conducted in the United States, France, and Canada, with both premenopausal and postmenopausal women, and different exposure assessment metrics (kriging, LUR model, and dispersion model), but the CIs include the null (see Table 12-6). However, among the studies that evaluate receptor negative breast cancer, there was no clear pattern of association (Amadou et al., 2023; Cheng et al., 2020; Reding et al., 2015).

Lifestages

There were a limited number of studies that examined the effect of lifestages on the associations between exposure to NO_2 and breast cancer incidence (see Table 12-6). Of the recent studies that restricted analyses to particular age groups, there was a consistent pattern of increased risk in breast cancer incidence (Hvidtfeldt et al., 2023b; Poulsen et al., 2023; Goldberg et al., 2019). More specifically, Goldberg et al. (2019) reported increased risk of breast cancer in postmenopausal women at two cutoffs, restricted to over the age of 50 or restricted to over the age of 52 in a Canadian cohort. In women under the age of 50 the association was positive but there was a slight attenuation towards the null and decreased precision (HR: 1.15 [95% CI: 0.99, 1.35]). There was more limited evidence of the effect of age over 55 years on the associations between exposure to NO_2 and breast cancer incidence (Hvidtfeldt et al., 2023b; Poulsen et al., 2023). Additionally, there were similar associations reported when stratified by menopausal status (Amadou et al., 2023).

Table 12-6 Epidemiologic studies evaluating effect measure modification between long-term NO_2 exposure and breast cancer incidence

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
Genetic Factors					
Exposure to NO_2					
†Amadou et al. (2023)	Etude Epidémiologique auprés de femmes de la Mutuelle Générale	OR (95% CI)[b] Breast cancer - Overall, LUR (Main	OR (95% CI)[b] Breast cancer - Overall, LUR, ER+: 1.07 (0.96, 1.20)	≈	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	de lá Education Nationale (E3N) Baseline: 1990 Follow-up: 1997, 2000, 2002, 2005, 2008, and 2011	Effect): 1.07 (0.99, 1.17)	Breast cancer - Overall, LUR, ER-: 1.06 (0.83, 1.36)	≈	
			Breast cancer - Overall, LUR, PR+: 1.05 (0.93, 1.19)	≈	
			Breast cancer - Overall, LUR, PR-: 1.06 (0.90, 1.25)	≈	
			Breast cancer - Overall, LUR, ER+PR+: 1.04 (0.91, 1.19)	≈	
			Breast cancer - Overall, LUR, ER-PR-: 0.98 (0.74, 1.29)	≈	
			Breast cancer - Overall, LUR, ER+PR-: 1.10 (0.88, 1.36)	≈	
			Breast cancer - Overall, LUR, ER-PR+: 1.35 (0.69, 2.63)	↑	
†Cheng et al. (2020)	The Multiethnic Cohort Study (MEC) Recruitment: 1993–1996 Follow-up through 2010	HR (95% CI)[b] Breast cancer incidence - Kriging - ER+/PR+(Main Effect): 1.03 (0.92, 1.15)	HR (95% CI)[b] Breast cancer incidence - Kriging - Black (author reported African American) - ER+/PR+: 1.01 (0.85, 1.20)	≈	Individual
			Breast cancer incidence - Kriging - Japanese American - ER+/PR+: 1.04 (0.74, 1.47)	≈	
			Breast cancer incidence - Kriging - Latinos - ER+/PR+: 1.11 (0.87, 1.43)	≈	
			Breast cancer incidence - Kriging - White - ER+/PR+: 1.08 (0.86, 1.35)	≈	
†Cheng et al. (2020)	The Multiethnic Cohort Study (MEC)	HR (95% CI)[b] Breast cancer incidence - Kriging - ER-/PR-(Main	HR (95% CI)[b] Breast cancer incidence - Kriging - Black (author reported African	≈	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	Recruitment: 1993–1996 Follow-up through 2010	Effect): 0.97 (0.77, 1.23)	American) - ER-/PR-: 1.02 (0.72, 1.45)		
			Breast cancer incidence - Kriging - Japanese American - ER-/PR-: 2.07 (0.88, 4.84)	↑	
			Breast cancer incidence - Kriging - Latinos - ER-/PR-: 0.86 (0.54, 1.38)	≈	
			Breast cancer incidence - Kriging - White - ER-/PR-: 0.75 (0.45, 1.27)	↓	
†Cheng et al. (2020)	The Multiethnic Cohort Study (MEC) Recruitment: 1993–1996 Follow-up through 2010	HR (95% CI)[b] Breast cancer incidence - LUR - ER+/PR+(Main Effect): 0.99 (0.88, 1.23)	HR (95% CI)[b] Breast cancer incidence - LUR - Black (author reported African American) - ER+/PR+: 1.03 (0.67, 1.59)	≈	Individual
			Breast cancer incidence - LUR - Japanese American - ER+/PR+: 1.05 (0.62, 1.80)	≈	
			Breast cancer incidence - LUR - Latinos - ER+/PR+: 0.92 (0.60, 1.41)	≈	
			Breast cancer incidence - LUR - White - ER+/PR+: 1.01 (0.67, 1.54)	≈	
†Cheng et al. (2020)	The Multiethnic Cohort Study (MEC) Recruitment: 1993–1996 Follow-up through 2010	HR (95% CI)[b] Breast cancer incidence - LUR – ER-/PR-(Main Effect): 1.10 (0.91, 1.31)	HR (95% CI)[b] Breast cancer incidence - LUR - Black (author reported African American) - ER-/PR-: 1.12 (0.82, 1.53)	≈	Individual
			Breast cancer incidence - LUR - Japanese American - ER-/PR-: 1.95 (1.21, 3.14)	↑	
			Breast cancer incidence - LUR - Latinos - ER-	↓	

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			/PR-: 0.88 (0.62, 1.23)		
			Breast cancer incidence - LUR - White - ER-/PR-: 0.98 (0.65, 1.48)	≈	
†Goldberg et al. (2017)	2008–2011	OR (95% CI)[b] Breast cancer - ER+/PR+ Overall: 1.20 (0.72, 1.98)	OR (95% CI)[b] Breast cancer - ER+/PR+ Living at current dwelling at least 10 years: 1.38 (0.72, 2.65)	≈	Individual
†Reding et al. (2015)	Sister Study cohort August 2003 to July 2009	RR (95% CI)[b] Breast cancer incidence (Main Effect): 1.03 (0.95, 1.13)	RR (95% CI)[b] Breast cancer incidence - ER+/PR+: 1.18 (1.03, 1.35)	↑	Individual
			Breast cancer incidence - ER-/PR-: 0.87 (0.64, 1.17)	↓	
Exposure to NO_x					
†Cheng et al. (2020)	The Multiethnic Cohort Study (MEC) Recruitment: 1993–1996 Follow-up through 2010	HR (95% CI)[b] Breast cancer incidence - Kriging - ER+/PR+(Main Effect): 1.05 (0.97, 1.13)	HR (95% CI)[b] Breast cancer incidence - Kriging - Black (author reported African American) - ER+/PR+: 1.07 (0.95, 1.21)	≈	Individual
			Breast cancer incidence - Kriging - Japanese American - ER+/PR+: 1.06 (0.81, 1.39)	≈	
			Breast cancer incidence - Kriging - Latinos - ER+/PR+: 1.07 (0.91, 1.26)	≈	
			Breast cancer incidence - Kriging - White - ER+/PR+: 1.04 (0.88, 1.24)	≈	
†Cheng et al. (2020)	The Multiethnic Cohort Study (MEC) Recruitment: 1993–1996	HR (95% CI)[b] Breast cancer incidence - LUR - ER+/PR+(Main Effect): 1.03 (0.97, 1.09)	HR (95% CI)[b] Breast cancer incidence - LUR - Black (author reported African American) - ER+/PR+: 1.10 (0.98, 1.23)	≈	Individual

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
	Follow-up through 2010		Breast cancer incidence - LUR - Japanese American - ER+/PR+: 1.11 (0.96, 1.27)	≈	
			Breast cancer incidence - LUR - Latinos - ER+/PR+: 1.00 (0.89, 1.12)	≈	
			Breast cancer incidence - LUR - White - ER+/PR+: (0.98, 0.86 (1.11)	≈	
†Cheng et al. (2020)	The Multiethnic Cohort Study (MEC) Recruitment: 1993–1996 Follow-up through 2010	HR (95% CI)[b] Breast cancer incidence - CALINE4 - ER+/PR+(Main Effect): 0.96 (0.84, 1.11)	HR (95% CI)[b] Breast cancer incidence - CALINE4- Black (author reported African American) - ER+/PR+: 1.05 (0.80, 1.36)	≈	Individual
			Breast cancer incidence - CALINE4- Japanese American - ER+/PR+: 1.06 (0.77, 1.47)	≈	
			Breast cancer incidence - CALINE4- Latinos - ER+/PR+: 0.76 (0.59, 0.98)	↓	
			Breast cancer incidence - CALINE4- White - ER+/PR+: 1.00 (0.85, 1.19)	≈	
†Cheng et al. (2020)	The Multiethnic Cohort Study (MEC) Recruitment: 1993–1996 Follow-up through 2010	HR (95% CI)[b] Breast cancer incidence - Kriging – ER-/PR-(Main Effect): 0.95 (0.81, 1.10)	HR (95% CI)[b] Breast cancer incidence - Kriging - Black (author reported African American) - ER-/PR-: 0.93 (0.74, 1.16)	≈	Individual
			Breast cancer incidence - Kriging - Japanese American - ER-/PR-: 1.00 (0.53, 1.90)	≈	
			Breast cancer incidence - Kriging - Latinos - ER-PR-: 1.07 (0.78, 1.47)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			Breast cancer incidence - Kriging - White - ER-/PR-: 0.83 (0.56, 1.24)	≈	
†Cheng et al. (2020)	The Multiethnic Cohort Study (MEC) Recruitment: 1993–1996 Follow-up through 2010	HR (95% CI)[b] Breast cancer incidence - LUR - ER-/PR-(Main Effect): 1.08 (0.96, 1.22)	HR (95% CI)[b] Breast cancer incidence - LUR - Black (author reported African American) - ER-/PR-: 1.12 (0.91, 1.38)	≈	Individual
			Breast cancer incidence - LUR - Japanese American - ER-/PR-: 1.32 (0.95, 1.84)	↑	
			Breast cancer incidence - LUR - Latinos - ER-/PR-: 1.01 (0.82, 1.25)	≈	
			Breast cancer incidence - LUR - White - ER-/PR-: 1.06 (0.78, 1.44)	≈	
†Cheng et al. (2020)	The Multiethnic Cohort Study (MEC) Recruitment: 1993–1996 Follow-up through 2010	HR (95% CI)[b] Breast cancer incidence - CALINE4 - ER-/PR-(Main Effect): 0.98 (0.74, 1.30)	HR (95% CI)[b] Breast cancer incidence - CALINE4- Black (author reported African American) - ER-/PR-: 0.87 (0.51, 1.46)	≈	Individual
			Breast cancer incidence - CALINE4- Japanese American - ER-/PR-: 1.48 (0.73, 3.02)	↑	
			Breast cancer incidence - CALINE4- Latinos - ER-/PR-: 0.83 (0.52, 1.34)	≈	
			Breast cancer incidence - CALINE4- White - ER-/PR-: 0.98 (0.71, 1.37)	≈	
Lifestage					
Exposure to NO_2					

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
†Amadou et al. (2023)	Etude Epidémiologique auprés de femmes de la Mutuelle Générale de lá Education Nationale (E3N) Baseline: 1990 Follow-up: 1997, 2000, 2002, 2005, 2008, and 2011	OR (95% CI)[b] Breast cancer incidence – Overall, Chemical transport model (CHIMER): 1.16 (1.08, 1.25)	Breast cancer incidence- Overall, Chemical transport model (CHIMERE), Premenopausal: 1.00 (0.78, 1.27)	↓	Individual
			Breast cancer incidence - Overall, Chemical transport model (CHIMERE), Postmenopausal: 1.15 (1.05, 1.27)	≈	
†Amadou et al. (2023)	Etude Epidémiologique auprés de femmes de la Mutuelle Générale de lá Education Nationale (E3N) Baseline: 1990 Follow-up: 1997, 2000, 2002, 2005, 2008, and 2011	OR (95% CI)[b] Breast cancer incidence – Overall, LUR: 1.07 (0.99, 1.17)	OR (95% CI)[b] Breast cancer incidence - Overall, LUR, Premenopausal women: 1.02 (0.80, 1.31)	≈	Individual
			Breast cancer incidence - Overall, LUR, Postmenopausal women: 1.07 (0.97, 1.19)	≈	
†Hvidtfeldt et al. (2023b)	Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) Enrollment: 1985–2005 Follow-up: 2011–2015	HR (95% CI)[b] Breast cancer incidence - Overall(Main Effect): 1.10 (1.04, 1.16)	HR (95% CI)[b] Breast cancer incidence - Overall, less than 50 years of age: 1.04 (0.83, 1.29)	≈	Individual
			Breast cancer incidence - Overall, 50-54 years of age: 1.16 (0.99, 1.35)	↑	
			Breast cancer incidence - Overall, greater than or equal to 55 years of age: 1.06 (0.99, 1.13)	≈	
†Poulsen et al. (2023)	Denmark National Administrative and Health Registers 2000–2014	OR (95% CI)[b] Breast cancer incidence - Overall (Main Effect): 1.06 (1.01, 1.11)	OR (95% CI)[b] Breast cancer incidence - Overall, Diagnosis age less than 55 years: 1.10 (1.01, 1.19)	≈	Individual
			Breast cancer incidence - Overall, Diagnosis age greater than or equal to 55 years: 1.06 (1.01, 1.11)	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
†Poulsen et al. (2023)	Denmark National Administrative and Health Registers 2000–2014	OR (95% CI)[b] Breast cancer incidence - TWA period of 5 years, all cases (Main Effect): 1.04 (1.00, 1.08)	OR (95% CI)[b] Breast cancer incidence - TWA period of 5 years, age of diagnosis less than 45 years: 0.89 (0.76, 1.04)	↓	Individual
			Breast cancer incidence - TWA period of 5 years, age of diagnosis less than 55 years: 1.04 (0.95, 1.14)	≈	
			Breast cancer incidence - TWA period of 5 years, age of diagnosis greater than or equal to 55 years: 1.04 (0.98, 1.10)	≈	
†Poulsen et al. (2023)	Denmark National Administrative and Health Registers 2000–2014	OR (95% CI)[b] Breast cancer incidence - TWA period of 10 years, all cases (Main Effect): 1.06 (1.01, 1.11)	OR (95% CI)[b] Breast cancer incidence - TWA period of 10 years, age of diagnosis less than 45 years: 0.93 (0.79, 1.08)	↓	Individual
			Breast cancer incidence - TWA period of 10 years, age of diagnosis less than 55 years: 1.06 (0.96, 1.16)	≈	
			Breast cancer incidence - TWA period of 10 years, age of diagnosis greater than or equal to 55 years: 1.06 (1.01, 1.11)	≈	
†Poulsen et al. (2023)	Denmark National Administrative and Health Registers 2000–2014	OR (95% CI)[b] Breast cancer incidence - TWA period of 20 years, all cases (Main Effect): 1.06 (1.01, 1.11)	OR (95% CI)[b] Breast cancer incidence - TWA period of 20 years, age of diagnosis less than 45 years: 1.00 (0.86, 1.16)	≈	Individual
			Breast cancer incidence - TWA period of 20 years, age of diagnosis less than 55 years: 1.10 (1.01, 1.19)	≈	
			Breast cancer incidence - TWA period of 20	≈	

Study	Cohort [Enrollment, Follow-up]	EMM Reference Factor	EMM Comparison Factor	Direction of EMM[a]	Spatial Scale of Effect Modifier
			years, age of diagnosis greater than or equal to 55 years: 1.06 (1.01, 1.11)		

List of abbreviations in alphabetical order: CI = confidence interval; EMM = effect measure modification; HR = hazard ratio; NO_2 = nitrogen dioxide; NO_X = oxides of nitrogen; OR = odds ratio; RR = relative risk; TWA = time weighted average.
[a]An up-facing arrow (and yellow shading) indicates that the effect of NO_2 or NO_X is greater (e.g., larger risk of cancer) in the group with the factor evaluated than in the reference group. A down-facing arrow (and blue shading) indicates that the effect of NO_2 or NO_X is smaller in the group with the factor evaluated than in the reference group. An almost equal sign (and grey shading) indicates that the effect of NO_2 or NO_X is comparable between groups.
[b]Effect estimates are standardized and are presented as a 10 ppb change in NO_2 for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_X for annual average averaging time.
†Studies published since the 2016 Oxides of Nitrogen ISA.

12.4.3.1.2 Copollutants

Among the recent epidemiologic studies evaluating the associations between exposure to NO_2 and female reproductive cancers, the impact of confounding by copollutants were also evaluated (see Table 12-7). Poulsen et al. (2023) co-adjusted for $PM_{2.5}$ and elemental carbon (EC), a component of $PM_{2.5}$. Compared to the single pollutant model for NO_2, co-adjusting for $PM_{2.5}$ attenuated the risk for breast cancer incidence overall, but adjusting for EC strengthened the association (single pollutant NO_2 model OR: 1.06 [95% CI: 1.01, 1.11] per 5.31 ppb increase in NO_2 and two-pollutant NO_2 and EC model OR: 1.10 [95% CI: 0.77, 1.56]). This same pattern held for the two pollutants for $PM_{2.5}$ and EC when stratifying by diagnosis age ≥55 years, and diagnosis age <55 years.

In a recent epidemiologic study evaluating the associations between exposure to NO_2 and ovarian cancer mortality, the associations were unchanged with adjustment for O_3 or distance to road (Villanueva et al., 2021).

Table 12-7 Epidemiologic studies evaluating copollutants on the associations between exposure to NO_2 and breast cancer incidence

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of Association[a]	EE (95% CI)
Breast Cancer Incidence						
†Poulsen et al. (2023)	Denmark National Administrative and Health Registers 2000–2014	$PM_{2.5}$	$PM_{2.5}$: 0.6	Logistic regression model	↓	OR (95% CI)[b] Single pollutant: 1.06 (1.01, 1.11) Copollutant: 1.00 (0.95, 1.06)
†Poulsen et al. (2023)	Denmark National Administrative and Health Registers 2000–2014	EC	EC: 0.86	Logistic regression model	↑	OR (95% CI)[b] Single pollutant: 1.06 (1.01, 1.11) Copollutant: 1.10 (0.77, 1.56)
Ovarian Cancer Mortality						
†Villanueva et al. (2021)	California Cancer Registry (CCR) Enrollment: 1996–2014 Follow-up: 2016	O_3	O_3: -0.17	Cox proportional hazard model	≈	HR (95% CI)[b] Single pollutant: Ovarian cancer mortality - T1 (<20 ppb): Reference Ovarian cancer mortality - T2 (20-30 ppb): 1.30 (1.25 , 1.36) Ovarian cancer mortality - T3 (>30 ppb): 2.48 (2.32, 2.66) Copollutant: Ovarian cancer mortality - T1 (<20 ppb), model with NO_2 and Ozone: Reference Ovarian cancer mortality - T2 (20-30 ppb), model with NO_2 and Ozone: 1.30 (1.25, 1.36) Ovarian cancer mortality - T3 (>30 ppb), model with NO_2 and Ozone: 2.49 (2.32, 2.67)

Study	Cohort [Enrollment, Follow-up]	Copollutant	Correlation Value (ρ)	Modeling Method	Direction of Association[a]	EE (95% CI)
†Villanueva et al. (2021)	California Cancer Registry (CCR) Enrollment: 1996–2014 Follow-up: 2016	Distance to road:	Distance to road: -0.09	Cox proportional hazard model	≈	HR (95% CI)[b] Single pollutant: Ovarian cancer mortality - T1 (<20 ppb): Reference Ovarian cancer mortality - T2 (20-30 ppb): 1.30 (1.25 , 1.36) Ovarian cancer mortality - T3 (>30 ppb): 2.48 (2.32, 2.66) Copollutant: Ovarian cancer mortality - T1 (<20 ppb), model with NO_2 and DTR: Reference Ovarian cancer mortality - T2 (20-30 ppb), model with NO_2 and DTR: 1.30 (1.25, 1.36) Ovarian cancer mortality - T3 (>30 ppb), model with NO_2 and DTR: 2.50 (2.33, 2.68)
†Villanueva et al. (2021)	California Cancer Registry (CCR) Enrollment: 1996–2014 Follow-up: 2016	O_3, DTR	O_3zone, DTR: NR	Cox proportional hazard model	≈	HR (95% CI)[b] Single pollutant: Ovarian cancer mortality - T1 (<20 ppb): Reference Ovarian cancer mortality - T2 (20-30 ppb): 1.30 (1.25 , 1.36) Ovarian cancer mortality - T3 (>30 ppb): 2.48 (2.32, 2.66) Copollutant: Ovarian cancer mortality - T1 (<20 ppb), model with NO_2, Ozone, and DTR: Reference Ovarian cancer mortality - T2 (20-30 ppb), model with NO_2, Ozone, and DTR: 1.30 (1.25, 1.36) Ovarian cancer mortality - T3 (>30 ppb), model with NO_2, Ozone, and DTR: 2.50 (2.33, 2.69)

List of abbreviations in alphabetical order: CI = confidence interval; DTR = distance to road; EC = elemental carbon; EE = effect estimate; HR = hazard ratio; NO_2 = nitrogen dioxide; NR = not reported; O_3 = ozone; $PM_{2.5}$ = fine particulate matter.

[a]An up-facing arrow (and yellow shading) indicates that the effect of NO_2 is greater (e.g., larger risk of cancer) with the copollutant evaluated than in the single pollutant model. A down-facing arrow (and blue shading) indicates that the effect of NO_2 is smaller with the copollutant evaluated than in the single pollutant model. An almost equal sign (and grey shading) indicates that the effect of NO_2 is comparable between the single pollutant analysis and copollutant analysis.
[b]Effect estimates are standardized and are presented as a 10 ppb change in NO_2 for annual average averaging time; 15 ppb change in NO for annual average averaging time; and 20 ppb change in NO_X for annual average averaging time.
†Studies published since the 2016 Oxides of Nitrogen ISA.

12.4.3.1.3 Conclusions and Remaining Uncertainties

In the recent epidemiologic evidence, there are inconsistent patterns of association between exposure to NO_2 and NO_X and breast cancer incidence and mortality overall. However, there was consistently increased risk with exposure to NO_2 and NO_X and breast cancer incidence among the studies that evaluated the effect of hormone receptor status (ER+/PR+). Overall, there was a consistent pattern of increased risk of exposure to NO_2 and NO_X and breast cancer incidence across lifestages, with only limited evidence that age modifies these associations. There remains uncertainty regarding the potential for copollutant confounding as the recent evidence is limited and inconsistent. The recent evidence for cervical, ovarian, and uterine cancers is limited overall, and there are uncertainties regarding the evaluation of lifestages and populations, and potential for copollutant confounding. Lastly, there is no recent evidence evaluating concentration-response relationships for exposure to oxides of nitrogen and female reproductive cancers overall.

12.4.4 Male Reproductive Cancers: Prostate and Testicular

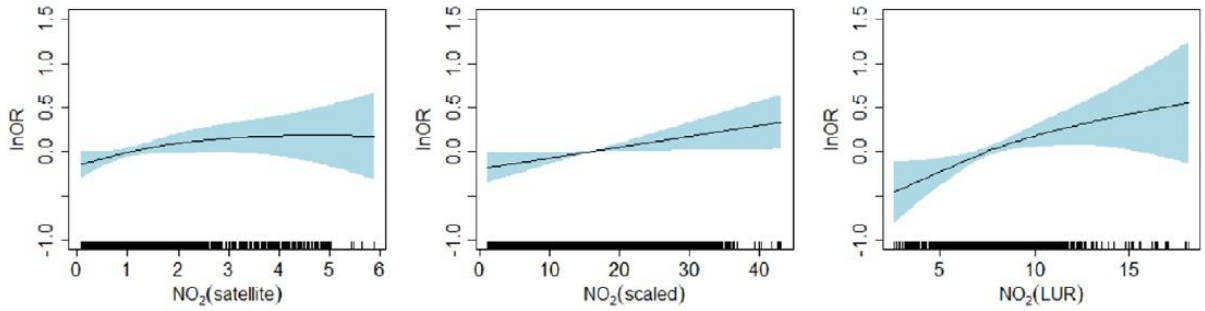
The 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016) included a limited number of studies that evaluated associations between exposure to oxides of nitrogen and prostate cancer. While a single study reported positive associations between exposure to NO_2 and prostate cancer, another study reported no associations between NO_X and prostate cancer. A key uncertainty in the studies of prostate cancer was the lack of examination of copollutants. No other male reproductive cancer studies were available for review in the 2016 Oxides of Nitrogen ISA. The evidence that has become available since the 2016 Oxides of Nitrogen ISA remains limited, with few epidemiologic studies and no animal toxicological studies.

12.4.4.1 Epidemiologic Studies of Male Reproductive Cancers: Prostate and Testicular

The recent epidemiologic evidence is still limited for prostate cancer. Study specific details including study population characteristics, exposure details (assessment metrics, temporal scale, and spatial scale), potential confounders, and select results are in Appendix A – Appendix Table 12-3.

- Using three different exposure assessment methods to estimate NO_2 in a Canadian case-control study, Youogo et al. (2022) investigated the association with risk of prostate cancer. Exposure to NO_2 was estimated from (1) satellite-derived observations; (2)

satellite-derived observations scaled with historical fixed-site measurements (scaled model); and (3) a national LUR model. Regardless of the exposure assessment metric, there was a pattern of increased odds for prostate cancer (ORs range 1.12–1.81), with the satellite model resulting in the widest CIs. Except for the satellite NO_2 exposure-response for which the ORs increase up to a concentration of about 2 ppb, beyond which they remain stable, the exposure-response functions for other exposures were consistent with linearity and ORs increased proportionally to the concentration of the pollutant, with wider confidence intervals at the extremes due to the small number of subjects (see Figure 12-7).



List of abbreviations in alphabetical order: df = degrees of freedom; ln = natural logarithm; LUR = land use regression; NO_2 = nitrogen dioxide; OR = odds ratio.
Notes: NO_2 concentrations are the solid lines and the 95% CIs are the blue shade
Source: Youogo et al. (2022). Copyright permission pending.

Figure 12-7 Concentration-response curves for the relationship between NO_2 concentrations and 95% CI over the period from 1975 to 1994 and prostate cancer generated obtained using cubic smoothing splines at four degrees of freedom.

- Among male participants in the CPS-II study, exposure to NO_2 was estimated from a national LUR model (Turner et al., 2017). There was a positive, but imprecise, association between prostate cancer and exposure to NO_2 (HR: 1.02 [95% CI: 0.87, 1.18]).
- In addition to prostate cancer, there was a single study that examined the associations between exposure to NO_2 and testicular cancer incidence (Taj et al., 2022). In a nationwide register-based case-control study in Denmark, a hybrid model was used to estimate time-weighted average exposure to NO_2 for four different exposure windows (the year before birth; the first 10 years of life; 10–20 years before diagnosis (10-year lag); and the 10-years before diagnosis) in association with risk for testicular cancer. All exposure windows were inversely (negatively) associated with risk for testicular cancer (year before birth OR: 0.77 [95% CI: 0.62, 0.96], first 10 years of life OR: 0.84 [95% CI: 0.68, 1.03], respectively), but the 10–20 years before diagnosis (10-year lag) (OR: 0.96 [95% CI: 0.87, 1.07]) and the 10 years before diagnosis (OR: 0.98 [95% CI: 0.89, 1.08]) were null. When stratified by age, those aged 36 and above have a slightly increased risk (OR: 1.06 [95% CI: 0.92, 1.21]), but the CIs included the null, while those aged 35 and below were null (OR: 0.91 [95% CI: 0.80, 1.03]), with no evidence of interaction (p = 0.29).

12.4.4.1.1 Conclusions and Remaining Uncertainties

Overall, there remains limited epidemiologic evidence on associations between exposure to oxides of nitrogen and male reproductive cancers. While the recent evidence evaluated different exposure assessment metrics and exposure windows, there remains uncertainty regarding the potential for copollutant confounding, lifestages and populations, and concentration-response relationships.

12.4.5 Other Cancers

In the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016), there were a limited number of studies that examined incidence or mortality for various cancers, including cervical, brain, buccal cavity/pharynx, esophageal, stomach, colon, rectal, liver, pancreatic, laryngeal, kidney, melanoma, non-Hodgkin lymphoma, and myeloma. In addition, there was an array of tumor types examined, including central nervous system tumors, intracranial and intraspinal embryonal tumors, primitive neuroectodermal tumors, other gliomas, neuroblastoma, retinoblastoma, unilateral retinoblastoma, Wilms tumor, hepatoblastoma, rhabdomyosarcomas, germ cell tumors, extracranial and extragonadal germ cell tumors, and teratoma). A single study reported positive associations between NO_2 and mortality from all cancers, and there were positive associations with cervical and brain cancers in adults and retinoblastoma in children. The 2016 Oxides of Nitrogen ISA noted the challenges in judging consistency and coherence across all the various cancer outcomes.

12.4.5.1 Epidemiologic Studies of Other Cancers

There continues to be limited evidence in the recent epidemiologic studies for associations between oxides of nitrogen and incidence or mortality for cancer overall and other site-specific cancers. There remains uncertainty regarding copollutant confounding, examining of lifestage and population differences, and concentration response relationship. Study specific details including study population characteristics, exposure details (assessment metrics, temporal scale, and spatial scale), potential confounders, and select results are in Appendix A – Appendix Table 12-3.

- A single study evaluated associations with overall cancer incidence. Cohen et al. (2016) reported positive, but imprecise associations for overall cancer incidence and NO_X among myocardial infarction survivors in Israel, with the association strengthening when excluding heavy smokers. There were also positive associations for aggregated site-specific (lung, prostate, kidney, or bladder) cancer incidence.
- Among the recent studies of exposure to NO_2 and cancer mortality, there were generally positive associations (HR range 1.04–1.21) (Li et al., 2023; Eum et al., 2022; Eum et al., 2019; Cohen et al., 2016), but a single study reporting a null association (Kang et al., 2023).
- Among the recent studies assessing the associations of NO_2 and brain cancer incidence, there was a general pattern of positives, but some included the null in the CIs (Hvidtfeldt et al.,

2023a; Poulsen et al., 2020; Weichenthal et al., 2020; Wu et al., 2020; Andersen et al., 2017a; Jørgensen et al., 2016; Poulsen et al., 2016). These studies were conducted in well-established cohorts but there were differences in the exposure assessment metrics used (dispersion, LUR) and type of outcomes (e.g., brain, meninges, malignant, non-malignant). The single study of exposure to NO_2 and brain cancer mortality reported a near-null association (Turner et al., 2017).

- Among the recent studies assessing the associations of NO_X and brain cancer incidence, there was a general pattern of positive, but imprecise, associations (Poulsen et al., 2020; Wu et al., 2020; Andersen et al., 2017a; Poulsen et al., 2016).
- There were a limited number of studies that evaluated associations between oxides of nitrogen (NO_2, NO_X, and NO) and childhood cancers (Kreis et al., 2022; Lavigne et al., 2020; Hall et al., 2019; Lavigne et al., 2017; Janitz et al., 2016). There were several different apical outcomes including childhood germ cell tumors, childhood acute leukemia, lymphoma, malignant bone tumors, Wilms tumors, and brain tumors, with exposure to oxides of nitrogen measured at different periods (different trimesters, childhood) making it difficult to judge consistency across studies. There were also a small number of cases in most studies, which may have resulted in some of the imprecise associations (see Appendix A – Appendix Table 12-3**Error! Reference source not found.**). However, in the studies that evaluated a ssociations with childhood leukemias, there was a general pattern of increased risk with exposure to NO_2 (Kreis et al., 2022; Lavigne et al., 2020; Janitz et al., 2016).
- There were a few studies evaluating the risk of gastrointestinal cancers, but the different subtypes make it difficult to assess the consistency of associations (Chen et al., 2023; Nagel et al., 2018; Turner et al., 2017).
- There was a pattern of positive associations among the limited studies examining exposure to NO_2 and liver cancer incidence (So et al., 2021; Pedersen et al., 2017), but the small number of studies limit the ability to judge coherence and consistency across the studies. In addition, a single study reported a positive, but imprecise, association between exposure to NO_2 and liver cancer mortality (Turner et al., 2017).
- Among the studies of kidney cancer incidence, there were consistent positive, but imprecise, associations in the ESCAPE and ELAPSE cohorts and exposure to NO_2 (Hvidtfeldt et al., 2022; Raaschou-Nielsen et al., 2016). Additionally, in a single study reported a null association between exposure NO_2 and kidney cancer mortality (Turner et al., 2017).
- There were a few studies evaluating the risk of laryngeal cancers and there were consistent positive associations between exposure to NO_2 and laryngeal cancers (Wang et al., 2023; Turner et al., 2017).

12.4.5.1.1 Conclusions and Remaining Uncertainties

There were a limited number of recent studies that evaluated the associations between exposure to oxides of nitrogen and other cancers. Because of the small number of studies and the various apical outcomes, the ability to judge coherence and consistency across the outcomes evaluated in these studies is limited. There are uncertainties regarding copollutant confounding, lifestages and population differences, and concentration response relationships.

12.5 Genotoxicity

Genotoxicity is a broad term that refers to mutations, which are irreversible changes to the genetic material, and deoxyribonucleic acid (DNA) damage that may be reversed by various mechanisms. Safety assessment of chemicals generally involves tests that address three major genotoxicity-related endpoints: 1) gene mutation (i.e., point mutations or insertions/deletions), 2) clastogenicity (i.e., chromosome breaks and rearrangements), and 3) aneuploidy (i.e., gain or loss of whole chromosome(s)) (IPCS, 2020). A limited number of studies included in the 2016 Oxides of Nitrogen ISA investigated the effect of NO_2 exposure on these forms of genotoxicity. These studies include animal and in vitro toxicological investigations.[5] Exposure to NO_2 induced genotoxic effects including gene mutations and clastogenicity in vitro and in a limited number of animal models. However, the results reported were not always consistent and our ability to relate in vitro outcomes to responses in animal models is limited.

12.5.1 Animal and In Vitro Toxicological Studies of Genotoxicity

Available toxicological evidence evaluated in the 2008 and 2016 Oxides of Nitrogen ISAs provides evidence that NO_2 exposure induces genotoxic effects (U.S. EPA, 2016, 2008). These studies employed a variety of experimental approaches and includes in vitro[6] assessments conducted using bacteria, rodents, and human primary cells exposed either via a NO_2-containing atmosphere, culture media/broth, or at the air-liquid interface. Fewer studies investigated the effects of NO_2 exposure on genotoxicity endpoints ex vivo and in vivo using rodent and insect models. No recent toxicological studies investigating the effects of NO_2 exposure on genotoxicity have become available since the 2016 Oxides of Nitrogen ISA. Study specific details, exposure conditions, and endpoints examined in the older studies are highlighted in the text below. Sections 12.5.1.1 and 12.5.1.2 summarize the evidence for gene mutations and clastogenicity, respectively. Section 12.5.1.1 further discusses the evidence for dose-response relationships between NO_2 and NO exposure and genotoxicity, and Section 12.5.1.2 discusses the relevance of the available genotoxicity evidence for humans. Section 12.5.1.3 presents conclusions and summarizes the remaining uncertainties in the evidence. Studies supporting the causality determination for genotoxicity assessed in vivo or in vitro are described in more detail in Appendix A – Appendix Table 12-4 and Appendix A – Appendix Table 12-5, respectively.

Gene Mutation

The ability of NO_2 to induce gene mutation was investigated in four animal (DeMarini et al., 2000; Victorin et al., 1990; Isomura et al., 1984; Inoue et al., 1981) and nine in vitro (DeMarini et al.,

[5]EPA has historically considered evidence from in vitro models for cancer-related effects.
[6]For all other health effects reviewed in this ISA, in vitro studies are considered mechanistic evidence and are only discussed in the biological plausibility section. For genotoxicity endpoints, however, in vitro studies, which are often conducted using high doses, are considered primary evidence.

2000; Arroyo et al., 1992; Nguyen et al., 1992; Victorin and Ståhlberg, 1988; Kosaka et al., 1987; Kosaka et al., 1986; Kosaka et al., 1985; Isomura et al., 1984; Sasaki et al., 1980) toxicological studies.

Three studies investigated the potential for oxides of nitrogen exposure to induce forward mutations (Nguyen et al., 1992; Isomura et al., 1984; Inoue et al., 1981). Inhalation exposure to either NO_2 (8–27 ppm) or NO (9–27 ppm) for 1–2 days dose-dependently increased ouabain-resistant forward mutations in rat lung cells (Isomura et al., 1984). The frequency of forward mutations was increased in rat lungs following exposure to NO (0, 9, 19, 27 ppm) (Isomura et al., 1984).

In vitro NO exposure (0.125–0.375 mL NO gas/mL culture media) dose-dependently increased forward mutations human lymphocytes in the thymidine kinase (TK) mutation test (Nguyen et al., 1992). Although the response pattern was inconsistent, NO (2–18 ppm) increased forward mutations in Chinese hamster cells (Don line) (Isomura et al., 1984).

Seven studies investigated the potential for oxides of nitrogen exposure to induce reverse mutations (Arroyo et al., 1992; Victorin and Ståhlberg, 1988; Kosaka et al., 1987; Kosaka et al., 1986; Kosaka et al., 1985; Isomura et al., 1984; Sasaki et al., 1980). When cultured in an atmosphere containing NO_2 (2–20 ppm, specific doses vary by study), reverse mutations were increased, most often dose-dependently, in some strains of *Salmonella tryphimurium* bacteria (i.e., TA100, TA1535), but not others (i.e., TA90, TA1538) (Arroyo et al., 1992; Victorin and Ståhlberg, 1988; Isomura et al., 1984). In contrast, reverse mutations were not induced when *S. tryphimurium* strains TA100 and TA102 were cultured in broth bubbled with 10–180 ppm and NO_2 (Kosaka et al., 1987; Kosaka et al., 1985). When delivered by bubbling, NO_2 exposure induced reverse mutations in WP2 *Escherichia coli* (Kosaka et al., 1987; Kosaka et al., 1986). Reverse mutations were induced in *Bacillis subtillis* spores exposed to an atmosphere containing 500 ppm NO_2 (Sasaki et al., 1980). DNA repair processes were induced when *S. tryphimurium* strains (i.e., TA1535 and mutant strains) were cultured in broth bubbled with NO_2 (0–90 ppm) (Kosaka et al., 1987; Kosaka et al., 1986; Kosaka et al., 1985). In addition, exposure to an NO-containing atmosphere (2–20 ppm, specific doses vary by study) dose-dependently induced bacterial reverse mutations in *S. tryphimurim* (TA100, 1535) (Arroyo et al., 1992; Isomura et al., 1984). A single study investigated the ability of the combination of NO and NO_2 to induce reverse mutations in *S. tryphimurim* (TA1535) exposed for up to 30 minutes (Arroyo et al., 1992). In that study, the concentration of NO_2 remained constant while the amount of NO was increased (4 ppm NO + 2 ppm NO_2; 6 ppm NO + 2 ppm NO_2; 8 ppm NO + 2 ppm NO_2). The investigators reported that bacterial reverse mutations were dose- and time-dependently increased.

The 2008 ISA for Oxides of Nitrogen discussed the possibility that NO_2 could produce cancer via nitrosamine formation (U.S. EPA, 2008). N-nitroso compounds can be generated endogenously in the human body from NO_2 via processes that generate nitrite (NO_2^-) or nitrate. Further, NO_2 is known to react with amines to produce nitrosamines, known animal carcinogens. Such reactions have not been demonstrated with ambient-relevant exposures (U.S. EPA, 2016). Peroxyacetyl nitrate (PAN) is an oxide of nitrogen produced by reactions involving ultraviolet radiation, NO_2, and hydrocarbons (U.S. EPA,

2008). High concentrations of PAN (e.g., 78 ppm) were also shown to be weakly mutagenic in the lungs of the highly susceptible big Blue® mice (DeMarini et al., 2000). Exposure to PAN (273 and 300 ppb) induced reverse mutations in *S. tryphimurim* (DeMarini et al., 2000).

The ability of NO_2 exposure to induce other types of mutations in *Drosophila melanogaster* has been investigated in a small number of other studies. Sex-linked recessive lethal mutations were induced in *D. melanogaster* exposed to 500–700 ppm, 50–280 ppm, or 50–280 ppm NO_2 for 1 hour, 2 days, or a complete generation, respectively (Inoue et al., 1981). NO_2 (50 ppm) did not induce somatic mutations in *D. melanogaster* under any tested condition (Victorin et al., 1990).

Clastogenicity

The ability of NO_2 to induce chromosome breaks and rearrangements was investigated in four animals (Han et al., 2013; Victorin et al., 1990; Isomura et al., 1984; Gooch et al., 1977) and six in vitro (Koehler et al., 2013; Koehler et al., 2011, 2010; Nguyen et al., 1992; Gorsdorf et al., 1990; Shiraishi and Bandow, 1985) toxicological studies.

NO_2 exposure dose-dependently increased chromosomal aberrations in the lungs of rats (8–27 ppm, based on visual inspection of the data) (Isomura et al., 1984) but had no effect on the number of chromosomal aberrations in mouse leukocytes and spermatocytes (0.1–10 ppm) (Gooch et al., 1977). Additionally, NO_2 dose-dependently increased DNA single strand breaks (5–500 ppm, based on visual inspection of the data) (Gorsdorf et al., 1990) and sister chromatid exchanges (0.5–8 ppm, statistical significance observed at exposure concentration ≥1 ppm) (Shiraishi and Bandow, 1985) in Chinese hamster V79 cells.

Following in vivo exposure, micronuclei were dose-dependently induced in the bone marrow of rats exposed to NO_2 (0, 2.7, 5.3, 10.6 ppb (0, 5, 10, 20 mg/m$^{3)}$; 6 hours/day × 7 days) (Han et al., 2013). Micronuclei were not induced in mouse bone marrow by exposure to 20 ppm NO_2 (Victorin et al., 1990). Micronuclei were not induced when primary nasal epithelial cells exposed to NO_2 (0.01, 0.1, 1, 10 ppm) for 30 minutes were cultured at the air: liquid interface (Koehler et al., 2010). Increasing the exposure duration to 3 hours, however, resulted in micronuclei formation in the presence as little as 0.01 ppm NO_2 (Koehler et al., 2013). Under similar conditions, micronuclei were formed in primary nasal mucosal cells (Koehler et al., 2011).

Positive results were reported when using the comet assay to evaluate DNA damage in the brain, lung, liver, kidney, spleen, and heart cells collected from rats exposed to NO_2 (0, 2.7, 5.3, 10.6 ppb (0, 5, 10, 20 mg/m^3); 6 hours/day × 7 days) (Han et al., 2013). In air:liquid interface cultures, exposure to NO_2 dose-dependently (0.01, 0.1, 1, 10 ppm) (Koehler et al., 2013; Koehler et al., 2010) and time-dependently (Koehler et al., 2011) produced DNA fragments (comet assay, which measures multiple indices such as tail length using single-cell electrophoresis) in human primary nasal epithelial and mucosal cells, respectively. The abundance of DNA-protein complexes, an indicator of DNA modification, was dose-dependently increased in the same study.

Two studies investigated the potential for NO exposure to induce DNA strand breaks (Nguyen et al., 1992; Gorsdorf et al., 1990). In vitro NO exposure (0.125–0.375 mL NO gas/mL culture media) dose-dependently increased DNA strand breaks in human TK6 lymphoblasts (Nguyen et al., 1992). There was no effect on the number of DNA single-strand breaks in Chinese hamster V79 cells following exposure to NO (50–500 ppm) (Gorsdorf et al., 1990).

Overall, animal and in vitro toxicological studies provide evidence suggesting that NO_2 exposure induces genotoxic effects including gene mutation (forward and reverse mutations) and clastogenicity (DNA strand breaks, chromosomal aberrations, sister chromatid exchanges).

12.5.1.1 Dose Response

To aid in forming weight-of-evidence judgments, the ISAs consider various aspects of the scientific evidence including, for example, dose-response relationships (see Chapter 14). Dose-response relationships can strongly support cause and effect and be reported for several lines of evidence including reverse mutations in bacteria (Arroyo et al., 1992; Victorin and Ståhlberg, 1988; Isomura et al., 1984) and forward mutations in rat lung cells (Isomura et al., 1984) and human lymphocytes (Nguyen et al., 1992). Dose-response relationships were also reported for measures of clastogenicity and aneugenicity including the production of DNA fragments in human primary nasal epithelial and mucosal cells (Koehler et al., 2013; Koehler et al., 2010), in vivo micronuclei formation in the bone marrow of rats (0, 5, 10, 20 mg/m^3 NO_2; 6 hours/day × 7 days) (Han et al., 2013), DNA single strand breaks (Gorsdorf et al., 1990) and sister chromatid exchanges (Shiraishi and Bandow, 1985) in Chinese hamster V79 cells, and DNA strand breaks in human TK6 lymphoblasts (Nguyen et al., 1992). The majority of studies were conducted in vitro and validated approaches for in vitro to in vivo extrapolation (IVIVE) for these endpoints are not available, limiting their use to hazard identification.

12.5.1.2 Relevance of Toxicological Responses to Human Responses

While the relevance of the evidence for NO_2-induced genotoxicity is strengthened by the application of models that are well-accepted indicators of genotoxicity (i.e., Ames test, comet assay, micronucleus test) (Menz et al., 2023), it is not possible to relate the doses used in in vitro studies to in vivo exposures in animal models or to humans exposures. Irrespective, some of the models employed are commonly used for hazard identification in the regulatory setting. Furthermore, evidence for various forms of mutagenicity, clastogencity, and aneugenicity are generally consistent across studies. Meaning, that an increase in bacterial reverse mutations, bacterial forward mutations, comet formation, and micronuclei were reported in several studies. Although the studies are not replicates because the study's designs varied, confidence in the results is increased because genotoxicity was reported under different experimental conditions. Real-world relevance of the available evidence is diminished by the lack of dose

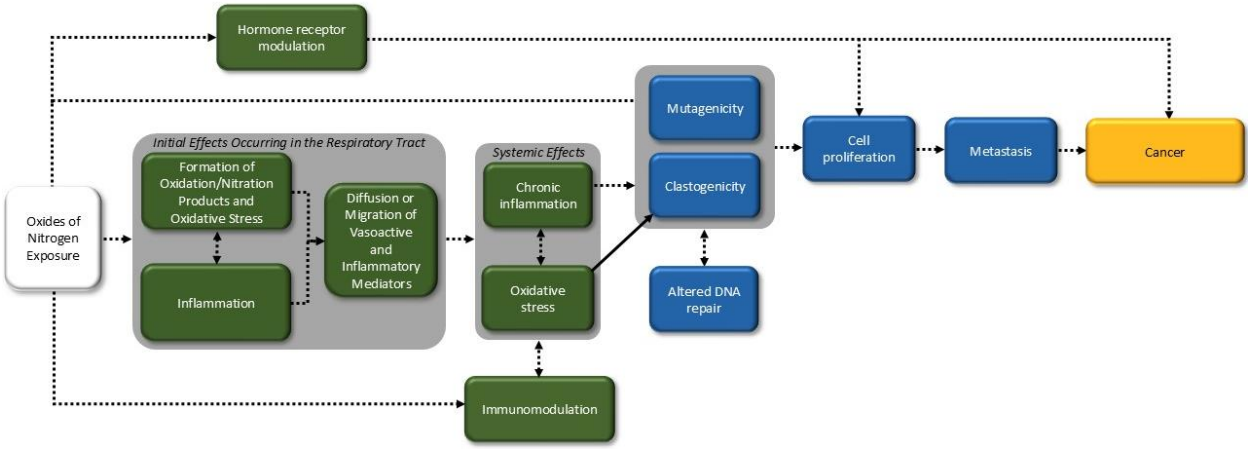
comparability. However, the relevance of the available data to human responses may be enhanced to some extent by the use of human cells cultured at the air-liquid interface. The use of these cultures is gaining in popularity because they more accurately simulate real-world exposure scenarios and utilize human cells, which may improve predictive capacity when compared to two-dimensional animal cell cultures. However, these assumptions have not been rigorously confirmed. Although there are limitations of the genotoxicity evidence, the data indicate that direct exposures to oxides of nitrogen can result in genotoxic effects in cell culture-based model systems. Still, in vivo animal-based toxicological evidence related to lung cancer provided no evidence that NO_2 acts as a direct carcinogen.

12.5.1.3 Conclusions and Remaining Uncertainties

Available toxicological evidence provides evidence that NO_2 exposure induces genotoxic effects including gene mutations and clastogenicity primarily in in vitro models but also in some animal models. Toxicological evidence for genotoxicity is limited, particularly for in vivo studies. For example, the number of studies for any genotoxicity-related endpoint investigated is relatively small and, even though some endpoints have been investigated in multiple studies, the application of disparate study designs prevents direct comparison of studies (i.e., no true replicates). Irrespective, there are several studies providing evidence that NO_2 exposure has the potential to result in genotoxicity and, in many instances, is dose-dependent. However, considerable uncertainty remains regarding the relevance of the mostly in vitro data on genotoxicity for human inhalation of NO_2 or other oxides of nitrogen. The majority of genotoxicity studies assessed in this review were conducted in vitro and, in the absence of validated IVIVE models, doses used in in vitro studies cannot be related to in vivo exposures in humans. Caution in interpreting the in vitro results is further supported by the observation that animal toxicological studies related to lung cancer provided no evidence that NO_2 acts as a direct carcinogen (see Section 12.3.2.2). Consequently, additional studies are needed to better understand the effects of NO_2 on genotoxicity endpoints.

12.6 Biological Plausibility

This section describes biological pathways that potentially underlie the effects of cancer resulting from exposure to oxides of nitrogen. Figure 12-8 depicts the potential pathways as a continuum of upstream events connected by arrows that may lead to downstream events observed in epidemiologic studies. Evidence supporting these proposed pathways was derived from Sections 12.3 to 12.5 of this ISA, evidence reviewed in the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016), and recent evidence collected from studies that may not meet the current PECOS criteria but contain mechanistic information examining these pathways. Discussion of how exposure to oxides of nitrogen may lead to cancer contributes to an understanding of the biological plausibility of epidemiologic study results indicating associations with cancer incidence and/or mortality.



Note: The boxes represent the effects for which there is experimental or epidemiologic evidence related to oxides of nitrogen exposure, and the arrows indicate a proposed relationship between those effects. Solid arrows denote evidence of essentiality as provided, for example, by an inhibitor of the pathway used in an experimental study involving oxides of nitrogen exposure. Dotted arrows denote a possible relationship between effects. Shading around multiple boxes is used to denote a grouping of these effects. Arrows may connect individual boxes, groupings of boxes, and individual boxes within groupings of boxes. Progression of effects is generally depicted from left to right and color-coded (white, exposure; green, initial effect; blue, intermediate effect; orange, effect at the population level or a key clinical effect). Here, population-level effects generally reflect the results of epidemiologic studies. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below. The structure of the biological plausibility sections and the role of biological plausibility in contributing to the weight-of-evidence analysis used in the 2026 Oxides of Nitrogen ISA are discussed in Section 12.8.

Figure 12-8 Potential biological plausibility pathways for cancer effects associated with exposure to oxides of nitrogen.

The human body is composed of trillions of cells that, under normal conditions, multiply as needed. Sometimes, this orderly process breaks down and abnormal cells grow and spread uncontrollably to other parts of the body leading to cancer. The development of cancer is a complex, multistep process that involves the progressive accumulation of mutations in genes leading to upregulation of oncogenes and loss of function of tumor suppressor genes. Consistent with the evidence assessed in the 2016 Oxides of Nitrogen ISA, the currently available evidence for the carcinogenic potential of oxides of nitrogen is limited. There is, however, a consistent body of evidence demonstrating genotoxicity following NO_2 exposure in experimental studies, mostly conducted in vitro, and NO_2 possesses several key characteristics that were identified by the International Agency for Research on Cancer (IARC) that are common to human carcinogens (Smith et al., 2016). The multi-step pathway described in Figure 12-8 connects exposure to NO_2 and cancer incidence via the aforementioned indicators of carcinogenesis.

As detailed in Chapter 2, NO_2 is a highly reactive gas that occurs as a radical that, once inhaled, encounters the epithelial lining fluid (ELF) of the respiratory tract. In the ELF, NO_2 chemically interacts with antioxidants, unsaturated lipids, and other compounds provoking inflammation. These localized effects can result in the diffusion and migration of inflammatory mediators into circulation, potentially affecting other organ systems. Additionally, acting as an electrophile, NO_2 preferentially reacts with nucleophiles (i.e., electron donors) leading to the formation of various reaction products. Importantly, reactions involving electrophiles have the potential to form DNA and protein adducts, which is a common property of human carcinogens (Smith et al., 2016). Although NO_2 is an electrophile, there was no

evidence available for this review investigating whether NO_2 exposure leads to the formation of adducts. However, peroxyacetyl nitrate has been reported to form DNA adducts in bacteria (DeMarini et al., 2000).

There are four potential pathways whereby NO_2 exposure has the potential to lead to the development of cancer. The most direct pathway to NO_2-induced carcinogenesis would involve mutagenesis. As reported by IARC, many carcinogens are genotoxic (IARC, 2012). Importantly, the strongest evidence for NO_2-induced cancer development is derived from genotoxicity studies. In an epidemiology study, potential associations between air pollution exposures and somatic non-small cell lung cancer mutation were investigated (Letellier et al., 2022). In that study, an increase of 1.86 ppb (3.5 mg/m^3) in NO_2 exposure five years before cancer diagnosis was associated with *TP53* tumor mutation whereas no associations were identified for two KRAS mutations (i.e., *KRAS*, and *KRAS G12C/V*) five and ten years before cancer diagnosis (Letellier et al., 2022). In addition, there is consistent evidence that NO_2 exposure has the potential to lead to DNA mutations in experimental models (U.S. EPA, 2016, 2008, 1993). To that point, several studies suggest that NO_2 exposure dose-dependently induced reverse mutations in two different species of bacteria (Arroyo et al., 1992; Victorin and Ståhlberg, 1988; Sasaki et al., 1980) and forward mutations in lung cells harvested from rats exposed in vivo (Isomura et al., 1984). It is not clear if NO_2 acts as a direct mutagen (i.e., interacts directly with DNA) or if it damages DNA indirectly. Notably, a small number of toxicological studies provided evidence that NO_2 exposure induces SOS repair functions in bacteria (Kosaka et al., 1987; Kosaka et al., 1986; Kosaka et al., 1985), which supports other lines of evidence related to mutagenesis.

Acting through additional pathways, NO_2 exposure has the potential to induce inflammation, oxidative stress, and immunomodulation, with intertwined pathophysiological processes that create a cycle leading to chronic inflammation and disease including some forms of cancer (Biswas, 2016; Smith et al., 2016). Markers of inflammation and oxidative stress originating in the respiratory tract have the potential to enter the bloodstream and play a role in non-respiratory health effects (e.g., cancer). As reviewed in the 2016 Oxides of Nitrogen ISA and Chapter 3 of this ISA, short-term ($\leq$30 days) exposure to NO_2 has been shown to alter markers of inflammation (e.g., proinflammatory cytokines) and oxidative stress (e.g., reactive oxygen species, reactive nitrogen species) in the respiratory tract of humans (U.S. EPA, 2016). Long-term NO_2 exposure has also been shown to increase oxidative stress and inflammation in animal studies but not as consistently as short-term exposures (U.S. EPA, 2016). Notably, Arroyo et al. (1992) reported that the mutagenic effects of NO exposure in *S. tryphimurium* bacteria were blocked by antioxidants (i.e., β-carotene and tocopherols). Exposure to NO_2 has also been shown to modulate some functions of the immune system in humans and animal models (see Chapter 3). For example, phagocytosis and superoxide production were reduced in human volunteers exposed to NO_2 though host resistance to viral infection was not affected under the conditions studied. In animal models, host resistance to bacterial and viral infection were both reduced, along with other measures of immunosuppression including the T-dependent antibody response (TDAR) and various ex vivo white

blood cell (WBC) functions (e.g., phagocytosis, superoxide anion production). Notably, modulation of the immune system has the potential to contribute to the development of inflammation and oxidative stress.

Oxidative stress, chronic inflammation, and immunomodulation all have the potential to lead to genotoxicity. As noted above, the strongest evidence for NO_2-induced genotoxicity is derived from studies demonstrating that NO_2 exposure leads to reverse and forward DNA mutations in bacteria and rat lung cells, respectively. In addition, as discussed in Sections 12.3 to 12.5, NO_2 exposure induces clastogenicity in toxicological models. For example, NO_2 dose-dependently induced DNA strand breaks in human primary nasal and mucosal cells as well as several other organs when measured using the comet assay, a well-accepted genotoxicity model. DNA strand breaks were also dose-dependently induced when investigated using another experimental approach. Finally, permanent DNA damage was detected in human primary nasal epithelia cells following NO_2 exposure when evaluated using the well-accepted micronucleus test. Importantly, Bittrich et al. (1993) showed that induction of DNA single strand breaks by NO_2 in V79 cells is inhibited by antioxidant vitamins.

NO_2 exposure also has the potential to lead to cancer development through receptor modulation. Receptor modulation is associated with the development of some cancers (Smith et al., 2016). In the case of NO_2, there were no studies directly investigating receptor modulation available for this review. However, a higher risk of NO_2-associated breast cancer has been observed with ER+/PR+ receptor status compared to ER-/PR-tumors in epidemiology studies (Amadou et al., 2023; Cheng et al., 2020; Reding et al., 2015) suggesting a role for receptor modulation in the development of cancer following NO_2 exposure.

Moving further along the continuum connecting NO_2 exposure to cancer are alterations in cell proliferation and cell death (Smith et al., 2016). Short- and long-term exposure to high NO_2 concentrations resulted in increased in proliferation of alveolar septal cells and bronchiolar Clara cells of rats (Fehrenbach et al., 2007; Barth and Müller, 1999). Apoptosis, also known as programmed cell death, plays a role in preventing cancer. Inhibition of apoptosis is a common feature of carcinogens that alter cell replication and/or cell cycle control (Smith et al., 2016). Short-term exposure to high NO_2 concentrations (i.e., 10 ppm) resulted in an 8-fold increase in apoptosis of alveolar septal cells (Fehrenbach et al., 2007). These findings suggest that NO_2 exposure has the potential to increase cell proliferation in the lung and alter apoptosis of alveolar septal cells in animal models.

Metastasis, the spread of cancer cells, is the final step in the path to cancer following exposure to NO_2. NO_2 exposure facilitated tumor metastasis of the lung in three different studies discussed in Section 12.3.2. These findings support the possibility that NO_2 exposure has the potential to be conducive to metastasis of the lung.

The toxicological evidence provides several possible pathways through which NO_2 exposure can result in cancer. The evidence is strongest for pathways leading to mutagenesis through NO_2-induced

inflammation, oxidative stress, and immunomodulation that, in conjunction with altered DNA repair mechanisms, can lead to cell proliferation, metastasis, and ultimately cancer.

12.7 Summary of Lifestages and Populations

Some populations and lifestages may be at greater risk of oxides of nitrogen-related health effects than the general population. Higher risks could be due to intrinsic,[7] extrinsic,[8] and/or exposure-related factors. In assessing the recent evidence, these factors are identified, evaluated, and characterized to inform conclusions on the lifestages and populations that may be at increased risk. The systematic approach used to evaluate factors that may increase the risk of a population or specific lifestage to an air pollutant-related health effect is described in more detail in the Preamble to the ISAs (U.S. EPA, 2015) and the Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen Volume 2 (U.S. EPA, 2024). The evaluation of these factors focuses on health effect studies that conduct stratified analyses to compare populations or lifestages exposed to similar air pollutant concentrations within the same study design. For the evaluation of these studies, important considerations include whether the stratified analyses were planned a priori or were post hoc analyses, whether the study conducted multiple comparisons, and whether there were small sample sizes in individual strata. These study design issues can increase the probability of finding associations by chance or reduce the power to detect associations in subgroup analyses. Experimental studies that examine health effects exclusively in human subjects or animal models with a particular factor, such as pre-existing disease, are also important lines of evidence to evaluate because they inform judgments of the coherence and biological plausibility of effects observed in epidemiologic studies, as well as the independent effect of NO_2 exposure. Additionally, studies examining whether factors may result in differential exposure to NO_2 are included. The sections below evaluate the evidence for genetic factors (see Section 12.7.1), social and demographic factors (see Section 12.7.2), and behavioral factors (see Section 12.7.3). Table 12-1 at the end of this Section Summarizes the evidence for each factor to increase risk of oxides of nitrogen-related health effects.

12.7.1 Genetic Factors

In the 2016 Oxides of Nitrogen ISA, there were no studies available that evaluated the potential for genetic factors to modify the associations between exposure to oxides of nitrogen and cancer. Among

[7]Intrinsic factors such as genetics, lifestage, or disease status can contribute to larger or more serious responses to a particular pollutant exposure, and physiological differences between groups (e.g., differences in breathing patterns between children and adults) can contribute to higher internal pollutant doses in some populations.
[8]Extrinsic factors (e.g., nutritional status) and exposure-related factors (e.g., working outdoors, living near roadways or other pollution sources) can also contribute to increased risk, and many of the characteristics commonly used to classify lifestages and populations (e.g., race, SES, educational attainment) are surrogates for the combined impact of several intrinsic, extrinsic, and exposure-related factors.

the recent evidence, several studies examined genetic factors as potential modifiers of the association between exposure to NO_2 and cancer. In the lung cancer incidence evidence, a single study evaluated three non-small cell lung cancer somatic tumor mutations (TP53, KRAS, and KRAS G12C/V) in association with aggressive somatic lung cancer tumors and exposure to NO_2 (Letellier et al., 2022). There was an increased risk of NO_2-associated lung cancer incidence for TP53 mutation, but not for KRAS or KRAS G12C/V. Overall, there is limited evidence that some genetic variants may impact the associations between NO_2 and/or NO_X and lung cancer incidence, but there were differences in the genetic variants evaluated in recent studies.

Genetic factors were also examined in the breast cancer incidence evidence. Among women, there was a consistent pattern of increased risk of hormone receptor positive (ER+/PR+) breast cancer in association with exposure to NO_2 and NO_X (Amadou et al., 2023; Cheng et al., 2020; Goldberg et al., 2017; Reding et al., 2015). The increased risk of NO_2- and NO_X -associated receptor positive (ER+/PR+) breast cancer was based on evidence from studies conducted in the United States, France, and Canada, with both premenopausal and postmenopausal women, and different exposure assessment metrics (kriging, LUR model, and dispersion model). Among the studies that evaluated receptor negative breast cancer, there was no clear pattern of association (Amadou et al., 2023; Cheng et al., 2020; Reding et al., 2015). Overall, the collective evidence is suggestive that genetic factors result in populations or lifestages being at increased risk of NO_2-related cancer incidence or mortality. The strongest evidence comes from the epidemiologic studies of associations with hormone receptor positive breast cancer incidence, with limited evidence for increased risk of NO_2-associated lung cancer incidence in the presence of the TP53 non-small cell lung cancer somatic tumor mutation. However, the epidemiologic evidence remains limited, and there is a lack of coherence across the epidemiologic and animal and in vitro toxicological studies.

12.7.2 Sociodemographic Factors

Sociodemographic factors encompass the broad categories of lifestages (e.g., children, adults), socioeconomic status (SES), race/ethnicity, sex, residence in urban area, and/or proximity to roadways.

Lifestages

In the 2016 Oxides of Nitrogen ISA, there were no studies available that evaluated the potential for lifestages to modify associations between exposure to oxides of nitrogen and cancer. Among the recent evidence, there were several studies that examined lifestage as a potential modifier of the association between exposure to NO_2 and cancer. A few recent studies evaluated the effect of lifestages on the associations between exposure to NO_2 and lung cancer incidence (Huang et al., 2021; Weichenthal et al., 2017). The associations did not change in stratified analyses with three age categories (<60, 60–74, and ≥75) among participants in the ONPHEC cohort (Weichenthal et al., 2017). Additionally, there was no evidence of effect measure modification by age (≥60 or <60) among participants of the UK Biobank

(Huang et al., 2021). Among the lung cancer mortality studies, So et al. (2022) reported a larger magnitude association among those 65 years and younger, compared to those over 65 years; however, Klompmaker et al. (2020) and Huang et al. (2023) did not report evidence of effect measure modification by age <65 and ≥65 years or age <60 and ≥60, respectively. Furthermore, there were a limited number of studies that examined the effect of lifestages on the associations between exposure to NO_2 and breast cancer incidence. Of the recent studies that evaluated lifestages under 55, there was a consistent pattern of increased NO_2-associated risk in breast cancer incidence (Hvidtfeldt et al., 2023b; Poulsen et al., 2023; Goldberg et al., 2019). More specifically, Goldberg et al. (2019) reported increased risk of NO_2-associated breast cancer in postmenopausal women over the age of 50 or over the age of 52 in a Canadian cohort. For women under the age of 50 there was a slight attenuation towards the null and decreased precision, but the association was still positive (HR: 1.15 [95% CI: 0.99, 1.35]). There was more limited evidence of the effect of age over 55 years on the associations between exposure to NO_2 and breast cancer incidence (Hvidtfeldt et al., 2023b; Poulsen et al., 2023). Despited the limited evidence, there was a consistent pattern of increased risk of breast cancer incidence for women ≥50 years. Overall, the collective evidence is suggestive of certain lifestages being at increased risk of lung cancer mortality and breast cancer incidence, but the evidence is limited.

Socioeconomic Status

SES is a composite measure that usually consists of economic status measured by income, social status measured by education, and work status measured by occupation. Persons with lower SES generally have been found to have a higher prevalence of pre-existing diseases, less access to resources such as healthcare, and possibly increased nutritional deficiencies. Neighborhoods comprising low SES populations are characterized as having fewer resources and more psychosocial stressors and air pollution sources (Diez Roux and Mair, 2010); (O'Neill et al., 2003) thus, community-level SES may influence health. Any or a combination of these factors could link low SES to increased risk for NO_2-related health effects.

In the 2016 oxides of nitrogen, there were no studies available that evaluated the potential for SES to modify the associations between exposure to oxides of nitrogen and cancer. Among the recent epidemiologic studies, there were a few studies that evaluated effect measure modification by SES on the associations between exposure to NO_2 and NO_X and lung cancer incidence (Cheng et al., 2022); (Huang et al., 2021). Among those living in low SES neighborhoods, Cheng et al. (2022) reported increased risk of lung cancer with NO_X exposure, but not with NO_2 exposure. Among those living in high SES neighborhoods, the associations were null for both exposure to NO_2 and NO_X. Huang et al. (2021) did not find evidence effect measure modification by household income, a proxy measure for SES, among participants in the UK Biobank cohort. The inconsistency in the associations overall may be due to the differences in the indicators for SES. Overall, the collective evidence is inadequate to determine whether SES results in populations or lifestages being at increased risk of NO_2-related cancer incidence or mortality as the evidence is limited.

Race/Ethnicity

Race and ethnicity are complex factors that are often closely related with other factors including particular genetics, diet, and SES. Therefore, race and ethnicity may influence NO_2-related health effects through both intrinsic and extrinsic mechanisms. In the 2016 Oxides of Nitrogen ISA, there were no studies available that evaluated the potential for race/ethnicity to modify associations between exposure to oxides of nitrogen and cancer. Among the recent epidemiologic studies, there was only a single study that assessed differences by race/ethnicity in lung cancer incidence from long-term exposure in NO_2 (Cheng et al., 2022). Among participants in the Multiethnic Cohort Study (MEC), there were no differences in NO_2-associated lung cancer among race/ethnicity subgroups of Black (author reported as African American), European American, Japanese American, or Native Hawaiian. Risk was increased for Latino Americans, though the CIs were wide (included the null). Overall, the collective evidence is inadequate to determine whether race/ethnicity results in populations or lifestages being at increased risk of NO_2-related cancer incidence or mortality as the evidence is limited to a single study.

Sex

Several health conditions and diseases have been shown to differ by sex, with some indication that there may be differences by sex in the relationship between air pollution and health effects. In the 2016 oxides of nitrogen, there were no studies available that evaluated the potential for sex to modify associations between exposure to oxides of nitrogen and cancer. The few recent studies that evaluated the effect of sex on the associations between exposure to NO_2 and lung cancer incidence did find evidence of modification by sex (Huang et al., 2021; Weichenthal et al., 2017). Additionally, a single study did not find evidence effect measure modification by sex for associations between exposure to NO_X and lung cancer incidence (Huang et al., 2021). There were a few recent studies evaluating sex differences on the association between exposure to NO_2 and lung cancer mortality. So et al. (2022) reported a larger magnitude of association among males compared to females in a Danish national administrative cohort. Among participants in a Chinese cohort, Huang et al. (2023) did not report evidence of effect measure modification by sex, but the magnitude of the association was slightly larger among females. Overall, the collective evidence is inadequate to determine whether sex results in populations or lifestages being at increased risk of NO_2-related cancer incidence or mortality as the evidence was limited and inconsistent.

12.7.3 Behavioral and Other Factors

Behavioral and other factors such as diet, smoking, and physical activity may modify risk of NO_2-related cancer.

Diet

Diet is an important influence on health and thus, plausibly could influence air pollutant-related health effects. It is not expected that diet would affect oxides of nitrogen exposure, although the two may

be linked through a common relationship with SES. In the 2016 oxides of nitrogen, there were no studies available that evaluated the potential for diet to modify the associations between exposure to oxides of nitrogen and cancer. Among the recent epidemiologic studies, only a single study evaluated the impact of diet on the associations between NO_2 and lung cancer incidence (Chen et al., 2023). Chen et al. (2023) assessed whether the intake of omega-3 PUFAs and omega-6 PUFAs modified the association between exposure to NO_2 and NO_X and lung cancer incidence. While there were positive associations between exposure to NO_2 and NO_X and lung cancer incidence overall, the associations were unchanged in analyses stratifying by polyunsaturated fatty acids levels, regardless of omega-3 or omega-6 intake. Overall, the collective evidence is inadequate to determine whether diet results in populations or lifestages being at increased risk of NO_2-related cancer incidence or mortality as the evidence was limited.

Smoking

Smoking is a well-documented risk factor for many diseases, but it is unclear whether smoking exacerbates health effects associated with air pollutant exposures, including oxides of nitrogen. Information on oxides of nitrogen exposure or internal dose differences between smokers and nonsmokers also is lacking. In the 2016 oxides of nitrogen, there were no studies available that evaluated the potential for smoking to modify associations between exposure to oxides of nitrogen and cancer. Among the recent epidemiologic studies, several studies evaluated the potential effect of smoking on lung cancer incidence and lung cancer mortality. There was inconsistent evidence by smoking status on the associations for exposure to NO_2 and NO_X and lung cancer incidence. A study of participants in the MEC reported positive, but imprecise, associations for those who were never smokers; however, there was no formal evidence for heterogeneity of effects by smoking status (Cheng et al., 2022). The ONPHEC indirectly adjusted for smoking, resulting in attenuation of the risk of lung cancer incidence (Weichenthal et al., 2017). Among participants in the UK Biobank cohort, there were similar positive associations among current and past smokers, but for never smokers the associations between exposure to NO_2 or NO_X and lung cancer incidence were attenuated (Huang et al., 2021).

Among the recent epidemiologic evidence for lung cancer mortality, there were some inconsistencies in whether smoking was included as a potential confounder or assessed as an effect measure modifier. Generally, there was a consistent pattern of increased risk of lung cancer mortality in association with NO_2 and NO_X. However, among the studies that did control for smoking as a potential confounder (Huang et al., 2023; So et al., 2022; Klompmaker et al., 2020; Hvidtfeldt et al., 2019), the positive associations were smaller in magnitude than those that did not control for smoking (Bouma et al., 2023; Eum et al., 2022; Klompmaker et al., 2021a; Klompmaker et al., 2021b; Raaschou-Nielsen et al., 2020; Eckel et al., 2016; Crouse et al., 2015). For instance, in a Danish nationwide administrative cohort, there was an increased risk of lung cancer mortality when indirectly adjusting for smoking at the municipality level rather than the individual level; however, when not adjusting for smoking, the association was strengthened (So et al., 2022). Overall, the collective evidence is inadequate to determine whether smoking results in populations or lifestages being at increased risk of NO_2-related cancer incidence or mortality as the evidence was inconsistent.

Table 12-1 Summary of evidence for populations at increased risk of cancer effects from oxides of nitrogen exposure

	Key Evidence	Key References
Suggestive evidence		
Genetic factors	Breast cancer incidence: Consistent positive associations for ER+PR+ hormone receptor	Reding et al. (2015); Amadou et al. (2023); Cheng et al. (2020)
	Lung cancer incidence: Limited evidence for non-small cell lung cancer somatic tumor mutation TP53	Letellier et al. (2022)
Lifestages	Breast cancer incidence: Consistent positive associations for 50–55 and ≥55 yr of age	Hvidtfeldt et al. (2023b); Poulsen et al. (2023); Goldberg et al. (2019)
	Lung cancer mortality: Limited evidence of for those <65 yr	So et al. (2022)
Inadequate evidence		
Socioeconomic status	Lung cancer incidence: Limited and inconsistent evidence	Cheng et al. (2022); Huang et al. (2021)
Race/ethnicity	Lung cancer incidence: Limited and inconsistent evidence	Cheng et al. (2022)
Sex	Lung cancer incidence and mortality: Limited and inconsistent evidence	Weichenthal et al. (2017); Huang et al. (2021); So et al. (2022); Huang et al. (2023)
Diet	Lung cancer incidence: Limited and inconsistent evidence	Chen et al. (2023)
Smoking	Lung cancer incidence and mortality: Inconsistent evidence	Cheng et al. (2022); Weichenthal et al. (2017); Huang et al. (2021); So et al. (2022); Hvidtfeldt et al. (2019); Huang et al. (2023); Klompmaker et al. (2020); Eckel et al. (2016); Raaschou-Nielsen et al. (2020); Klompmaker et al. (2021a); Bouma et al. (2023); Eum et al. (2022); Klompmaker et al. (2021b); Crouse et al. (2015)

List of abbreviations in alphabetical order: ER = estrogen receptor; PR = progestogen receptor; yr = year.

12.8 Summary and Causality Determination

The 2016 Oxides of Nitrogen ISA concluded that the evidence is "suggestive of, but not sufficient to infer, a causal relationship" between long-term NO_2 exposure and cancer. This causality determination was primarily based on epidemiologic studies of lung cancer incidence and mortality conducted in the United States, Canada, and Europe. These studies were generally supportive of a relationship but were inconsistent, with multiple studies reporting positive associations, but some reporting no associations. The studies that reported positive associations with lung cancer incidence or mortality were robust to variability in the annual average NO_2 concentrations, multi-year averages, and across geographies. Additionally, among the studies that reported positive associations with lung cancer incidence or mortality, a variety of exposure metrics were used to estimate NO_2 concentrations, such as land use regression models, air dispersion models, spatiotemporal models, and central monitors. The remaining uncertainties regarding epidemiologic studies of NO_2 exposure and cancer effects were related to copollutant confounding, particularly $PM_{2.5}$, diesel exhaust, polycyclic aromatic hydrocarbons, volatile organic compounds, and other traffic-related pollutants.

At the time of the 2016 Oxides of Nitrogen ISA, evidence derived from toxicological studies did little to address the uncertainty associated with epidemiologic studies. Exposure to ambient-relevant NO_2 had not been shown to independently induce lung tumors in animal studies, and there was inconsistent evidence that ambient-relevant NO_2 exposures promote lung tumors when given in conjunction with a known carcinogen. Available toxicological studies provided evidence that NO_2 exposure induces genotoxic effects, including the dose-dependent induction of gene mutations and clastogenicity, though this evidence was primarily from in vitro models. A small number of animal inhalation studies also indicated genotoxicity following NO_2 exposures, though most of these studies examined exposure concentrations above those determined in this ISA to be relevant to ambient air. Due to the small number of toxicological studies, lack of replication of study findings, high exposure concentrations in animal models, and mixed results obtained, it was difficult to draw conclusions from these studies and to evaluate consistency and coherence across the evidence base.

Recent epidemiologic evidence demonstrates a generally consistent pattern of positive associations between NO_2 and lung cancer incidence and mortality, but several studies did report null or inverse associations. In the recent epidemiologic literature, there were several studies that examined associations between oxides of nitrogen, mostly NO_2 but also NO_X. The majority of recent evidence estimated exposure to NO_2 or NO_X through validated LUR models, and most of the studies had relatively short latency periods (range: 3–18 years). While there was some examination of factors modify associations (e.g., smoking, race/ethnicity, genetic factors, dietary), the evidence was limited and inconsistent. Some recent studies observed that associations with lung cancer remained positive in copollutant models with $PM_{2.5}$ and O_3. Among the studies that considered copollutants, co-adjusted exposures were the common way to account for potential copollutant confounding, but this could have led

to bias in the estimates, especially with moderately or highly correlated copollutants. There were a few recent studies of concentration-response relationship, but overall, the evidence is limited and inconsistent.

Overall, the evidence is *suggestive of, but not sufficient to infer, a causal relationship* between long-term oxides of nitrogen exposure and cancer. The strongest evidence supporting this relationship comes from epidemiologic studies reporting a generally consistent pattern of positive associations between exposure to NO_2 exposure and lung cancer incidence and mortality (see Table 12-2). While there was limited evidence of positive associations in copollutant models with $PM_{2.5}$ and O_3, the evidence was inconsistent overall. Toxicological studies provide no clear evidence of NO_2 acting as a complete carcinogen (i.e., a compound capable of acting as both an initiator and a promoter). However, a small number of toxicological studies in tumor-prone rodents or with co-exposure with a known carcinogen indicate that ambient-relevant NO_2 exposures can increase lung tumor incidence. The biological plausibility of oxides of nitrogen-induced cancer is supported by toxicological evidence indicating that NO_2 exposure induces genotoxic effects, including gene mutations and clastogenicity, though this evidence comes primarily from in vitro models and animal models exposed to NO_2 concentrations above those identified as ambient-relevant.

Table 12-2 Summary of evidence contributing to causality determinations for oxides of nitrogen exposure and cancer effects

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Lung Cancer			
Evidence from epidemiologic studies generally supportive but not consistent	Positive associations with lung cancer incidence or mortality in multiple studies conducted in the United States, Canada, and Europe.	Carey et al. (2013); Cesaroni et al. (2013); Hystad et al. (2013); Jerrett et al. (2013) Section 12.3.1	Means: 12, 23.2 ppb for annual avg, 12.3, 15.4 ppb for multi-yr avg, 6.4–32.4 ppb across cities in multicity study
	No associations with lung cancer incidence or mortality in multiple studies conducted in the United States and Europe.	Raaschou-Nielsen et al. (2013); Hart et al. (2011); Papathomas et al. (2011); Brunekreef et al. (2009); Beelen et al. (2008) Section 12.3.1	Means: 14.2 ppb for 15-yr avg, 19.6 ppb for 20-yr avg, 2.8–31.8 ppb for annual avg across cities in multicity study
Lack of toxicological evidence for direct effect on carcinogenesis but limited evidence for tumor promotion with ambient-relevant exposures	NO_2 exposure alone does not induce lung tumors. Mixed evidence for tumor promotion with co-exposure to known carcinogen. Limited evidence for facilitation of metastasis.	Adkins et al. (1986); Richters and Damji (1990); Wagner et al. (1965); Richters and Kuraitis (1981); Richters and Kuraitis (1983); Richters and Kuraitis (1983); Ichinose et al. (1991) Section 12.3.2	Tumor promotion with nitrosamine exposure: inconsistent 0.25–5 ppm for 6–17 mo. Facilitation of metastases: 0.3–0.8 ppb for 10 or 12 wk

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Limited evidence for key events in proposed mode of action	Finding of mutagenicity and micronucleus formation in ex vivo culture of primary human nasal epithelial cells exposed to NO_2.	Koehler et al. (2013); Koehler et al. (2011, 2010) Section 12.5.1	0.01, 0.1, 1, 10 ppm
	NO_2 exposure dose-dependently induced genotoxic effects including gene mutations and clastogenicity in rat lungs	Han et al. (2013); Isomura et al. (1984) Section 12.5.1	8–27 ppm
	Evidence of dose-dependent mutagenicity and clastogenicity in vitro	Arroyo et al. (1992); Nguyen et al. (1992); Gorsdorf et al. (1990); Victorin and Ståhlberg (1988); Shiraishi and Bandow (1985) Section 12.5.1	5–500 ppm
Cancers of Sites Outside the Lung			
Limited epidemiologic evidence and uncertainty regarding independent effect of NO_2	Positive associations with leukemia, bladder cancer, female reproductive cancers, and male reproductive cancers.	Ghosh et al. (2013); Parent et al. (2013); Liu et al. (2009) Sections 12.4.1, 12.4.2, 12.4.3, 12.4.4, 12.4.5	Means or medians: 17–24 ppb for annual avg

List of abbreviations in alphabetical order: avg = average; d = day; h = hour; mo = month; NO_2 = nitrogen dioxide; NS = not significant; wk = week; mo = month; ppb = parts per billion.

[a]Based-on application of the causality framework described in Section 3.3.4 of volume 2 of the Integrated Review Plan for the *Integrated Science Assessment for Oxides of Nitrogen – Health Criteria* (U.S. EPA, 2024).

[b]Describes the key evidence and provides references contributing to the causality determination. References to earlier sections indicate where the full body of evidence is described.

12.9 References

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