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Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

Chapter 13: Health Effects with Limited Evidence

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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

AR	Allergic rhinitis
avg	average
β	beta
BC	black carbon
CI	confidence interval
CKD	Chronic kidney disease
cm^2	Square centimeters
d	day(s)
dL	Deciliters
EE	effect estimate
e.g.	exempli gratia (for example)
etc.	et cetera
EPA	Environmental Protection Agency
F	female(s)
g	gram(s)
hr	hour(s)
HR	hazard ratio
ID	identification
IgE	Immunoglobulin E
IgM	Immunoglobulin M
i.e.	id est (that is)
IRR	incidence rate ratio
IQR	Interquartile range
ISA	Integrated Science Assessment
Km^2	Square kilometer
L	liter(s)
LUR	Land-use regression
M	male
Max	maximum
m	milligram
Min	minimum
M/F	male/female
m	meter(s)
µg	microgram
min	minute(s)
mL	milliliter
mo	month(s)
m^2	Square meters
n	sample size
N	population size
NO_2	nitrogen dioxide
NO_X	NO_2 + NO
NO	nitric oxide
NR	not reported
O_3	ozone
OR	odds ratio
PECOS	Population, Exposure, Comparison, Outcome, and Study Design
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
Q	quantile (could be quartile or quintile)
RR	relative risk or risk ratio
SD	standard deviation
SE	standard error
SES	socioeconomic status
T	tertile
U/L	Units per liter
U.K.	United Kingdom
U.S.	United States
wk	week(s)
yr	year(s)
vs.	versus

CHAPTER 13 Health Effects with Limited Evidence

Summary of Causality Determinations for Oxides of Nitrogen Exposure and Health Effects with Limited Evidence

This chapter characterizes the scientific evidence that supports causality determinations for oxides of nitrogen exposure and health effects with limited evidence. The types of studies evaluated within this chapter are consistent with the overall scope of the 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 Volume 2 of the Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen (U.S. EPA, 2024), which builds on the approach described in the 2015 Preamble to the Integrated Science Assessments (U.S. EPA, 2015a). The evidence presented throughout this chapter supports the following causality conclusion(s):

Outcome	Causality Determination
Immune Effects	Inadequate to infer a causal relationship
Renal Effects	Inadequate to infer a causal relationship
Hepatic Effects	Inadequate to infer a causal relationship
Ocular Effects	Inadequate to infer a causal relationship
Gastrointestinal Effects	Inadequate to infer a causal relationship
Musculoskeletal Effects	Inadequate to infer a causal relationship
Other Effects	Inadequate 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.

13.1 Introduction

13.1.1 Chapter Organization and Conventions

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) did not include causality determinations for these health outcome categories. The health effects included in this

chapter are part of an emerging evidence base that has become available since the 2016 Oxides of Nitrogen ISA.

This chapter evaluates recent studies examining the relationships between oxides of nitrogen exposure and health effects with limited evidence, including immune effects, renal effects, hepatic effects, ocular effects, gastrointestinal effects, musculoskeletal effects, and other effects. The following sections provide an overview of study inclusion criteria for recent studies evaluated in this chapter (see Section 13.2) and summaries of recent health effects evidence for oxides of nitrogen exposure and immune effects (see Section 13.3), renal effects (see Section 13.4), hepatic effects (see Section 13.5), ocular effects (see Section 13.6), gastrointestinal effects (see Section 13.7), musculoskeletal effects (see Section 13.8), and other health effects (see Section 13.9) and a discussion of the causality determinations for oxides of nitrogen exposure and immune effects (see Section 13.3.2 and Table 13-1), renal effects (see Section 13.4.2 and Table 13-2), hepatic effects (see Section 13.5.4 and Table 13-3), ocular effects (see Section 13.6.2 and Table 13-4), gastrointestinal effects (see Section 13.7.2 and Table 13-5), and musculoskeletal effects (see Section 13.8.2 and Table 13-6). 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. For outcomes supported by evidence from multiple disciplines, subsections titled "Synthesis Across Lines of Evidence" are included.

13.1.1.1 Epidemiologic Studies

In sections assessing the epidemiologic evidence, this chapter summarizes the evidence from recent studies that have become available since the last ISA. When relevant information is available from 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 "Copollutant" 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 are relatively low (e.g., correlation coefficent rho (ρ) <0.4). However, when correlations are high (e.g., ρ>0.7), collinearity between pollutants makes 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).

Throughout this chapter, short-term exposure to oxides of nitrogen is assumed to be approximately 30 days or less, while long-term exposure to oxides of nitrogen is assumed to be approximately 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 nitrogen dioxide (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] The increments for standardization for short-term exposure vary by averaging time (e.g., 24-hour avg, 8-hour max, 1-hour max) and oxide of nitrogen. For 24-hour average, effect estimates were scaled to a 20 ppb increase for NO_2 or NO and a 30 ppb increase for NO_X. For a 1-hour maximum, effect estimates were scaled to a 25 ppb increase for NO_2, a 60 ppb increase for NO, and an 80 ppb increase for NO_X. For an 8-hour maximum, the increments for standardization are 25 ppb increase for NO_2, 40 ppb increase for NO, and 55 ppb increase for NO_X. These increments were derived by calculating the U.S.-wide percentile distributions for a given averaging time and then calculating the approximate difference between the median (a typical pollution day) and the 95th percentile (a more polluted day) for a given averaging time (U.S. EPA, 2015b). There were common exceptions to this standardization method. Averaging times other than 24-hour average or 1-hour maximum were examined, for example, 2- to 15-hour averages. Effect estimates based on these averaging times were not standardized but are presented in the ISA as reported in their respective studies.

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 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 average concentrations of oxides of nitrogen in ambient air are less variable across time, and

[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.

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 studies reported effect estimates in terms of $\mu g/m^3$ 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 $\mu g/m^3$ at a national scale for the United States or other countries. Therefore, the ISA presents effect estimates based on $\mu g/m^3$ of NO_X as they are reported in their respective studies.

13.1.1.2 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 recent animal toxicological studies, targeted discussions of analyses examining dose-response relationships, relevance of toxicological responses to human responses, and multipollutant exposures are included. For apical endpoints with no or limited evidence on these topics, the subsections addressing them are not included.

13.2 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 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. Studies that were included in the 2016 Oxides of Nitrogen ISA, including studies that do not meet the current PECOS criteria, are discussed in this chapter to establish the state of the evidence prior to this assessment. Except for supporting evidence used to

[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 new information in the form of original research or new 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).

examine the biological plausibility of oxides of nitrogen-associated health effects, recent studies were only included if they met all components of the discipline-specific PECOS statements (see below) and satisfied 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 health effects (e.g., immune effects, renal effects, hepatic effects, ocular effects, gastrointestinal effects, musculoskeletal effects, or other 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, 2015a) and in Volume 2 of the Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen (U.S. EPA, 2024), animal exposures within one to two orders of magnitude of recent ambient air concentrations are considered relevant to ambient air exposures. This concentration cutoff is also consistent with that used in the 2016 Oxides of Nitrogen

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

Outcome: Outcomes of interest are those that relate to human health which are not discussed in other chapters, including immune effects, renal effects, hepatic effects, dermal effects, ocular effects, gastrointestinal effects, and musculoskeletal effects.

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

13.3 Immune Effects

This section evaluates evidence for the effects of oxides of nitrogen exposure on the immune system. The 2016 Oxides of Nitrogen ISA did not find sufficient evidence to include potential impacts of exposure on the immune system, and the recent evidence is limited to epidemiologic studies. Immunological evidence for this ISA is organized to reflect disease categories most relevant to sensitization and allergic responses (see Section 13.3.1), including eczema, rhinitis and rhinoconjunctivitis, and allergic sensitization. These categories encapsulate the immune-related endpoints as reflected by the available literature. As detailed in the World Health Organization's Guidance for Immunotoxicity Risk Assessment for Chemicals, data from endpoints observed in the absence of an immune stimulus (e.g., levels of serum immunoglobulins, white blood cell) are not sufficient on their own to draw a conclusion regarding immune hazard but may provide useful supporting evidence, especially when evaluated in the broader context of functional data (IPCS, 2012). Consequently, this section evaluates available epidemiologic research focused on the perturbance of immune function. There were no recent PECOS-relevant toxicological studies available for exposure to oxides of nitrogen and immune effects.

13.3.1 Sensitization and Allergic Responses

Hypersensitivity responses are the result of an over-reaction of the immune system. Hypersensitivity reactions are organized into four different classes, types I (IgE-mediated hypersensitivity), II (IgG or IgM-mediated cytotoxic hypersensitivity), III (immune complex-mediated hypersensitivity), and IV (cell-mediated hypersensitivity) (Murphy and Weaver, 2016). Irrespective of the type of response, all hypersensitivity responses develop in the same two phases: sensitization and elicitation (or challenge). During the sensitization phase, the immune system is trained to respond to an otherwise innocuous antigen. This phase typically occurs without symptoms. During the elicitation phase, the previously sensitized individual is re-exposed to the antigen precipitating the symptoms of the allergic disease. Important for risk assessors, the concentration of the sensitizing chemical required to elicit an

ISA (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.

allergic response is, in some cases, orders of magnitude lower than the concentration required for sensitization. Consequently, preventing allergic sensitization from developing in the first place is of paramount importance because dangerous, potentially life-threatening allergic reactions can occur in response to exposure to a low concentration of the sensitizer. The sections below summarize recent epidemiology studies examining associations between sensitization and allergic responses. Recent animal toxicological studies have not evaluated oxides of nitrogen exposure and sensitization and allergic responses to diseases.

13.3.1.1 Epidemiologic Studies of Sensitization and Allergic Responses

Epidemiologic studies of sensitization and allergic response generally cover studies of atopic diseases, including asthma, rhinitis, and eczema, as well as studies examining antibodies that mediate these diseases, such as immunoglobulin E (IgE). There were no studies in the 2016 Oxides of Nitrogen ISA that examined associations with sensitization and allergic responses (U.S. EPA, 2016). Recent epidemiologic studies examining these endpoints are summarized below. 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 13-1.

Eczema and Atopic Dermatitis

There were only a few recent epidemiologic studies that examined the associations between exposure to NO_2 or NO_X and eczema or atopic dermatitis. The recent epidemiologic studies are details below, with 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 13-1.

- A pooled study of European cohorts examined associations between air pollution and eczema among children. NO_2 and NO_X were estimated from land-use regression (LUR) models following the steps in the European Study of Cohorts for Air Pollution Effects (ESCAPE) study commonly used in European cohort studies (Fuertes et al., 2020). Annual exposure to NO_X and NO_2 were inversely associated with eczema. For example, per 10 $\mu g/m^3$ increase in NO_2 the reported odds ratios (ORs) for associated eczema were 0.92 (95% CI: 0.80, 1.07) and 0.88 (95% CI: 0.74, 1.04) in four- and eight-year-olds, respectively.
- In addition, a study from China, in the Hubei province, examined potential associations between air pollution and childhood eczema (Deng et al., 2019). After adjusting for sociodemographic covariates, the authors reported that during the gestational period, as well as during the first year of life, exposure to NO_2 is positively associated with childhood eczema (see Appendix A – Appendix Table 13-1**Error! Reference source not found.**).
- A single study in the Taiwan Birth Cohort Study, Huang et al. (2015) estimated prenatal exposure periods for NO_2 in association with atopic dermatitis. From fixed-site stations, NO_2 exposure was estimated for each trimester, three months after birth, whole gestational period, and from conception to three months postnatal. The strongest association with atopic dermatitis was with the whole gestational period, with trimester one and from conception to

three months postnatal reporting positive associations (see Appendix A – Appendix Table 13-1).

Rhinitis and Rhinoconjunctivitis

There were a limited number of recent epidemiologic studies that evaluated associations between exposure to oxides of nitrogen and rhinitis and rhinoconjunctivitis. Overall, the associations were inconsistent, with a few studies reporting positive associations with exposure to NO_2 (Marchetti et al., 2023; Burte et al., 2020), inverse associations (Fuertes et al., 2020), and null associations (Burte et al., 2018). Additionally, a few studies evaluated associations between exposure to NO_X and rhinitis and rhinoconjunctivitis, but the associations were inconsistent (Fuertes et al., 2020; Chung et al., 2016). The recent epidemiologic studies are details below, with 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 13-1.

- A study based in Taiwan examined associations between allergic rhinitis (AR) and air pollution, specifically NO_X (Chung et al., 2016). Using data from National Health Insurance of Taiwan from 2007 to 2011, the authors had a large sample size of children (n = 9,960), 0–6 years old. This was a short-term exposure study that examines one and two-week exposure periods and incident AR. Adjustment was minimal in this study, with the only adjustments made for age and sex so results should be interpreted as such. After dividing exposure concentrations into three tertiles, with tertile 1 as the referent, NO_X was positively associated with incidence AR at both one-week (tertile 2: 1.83 [95% CI: 1.38, 2.53], tertile 3: 1.94 [95% CI: 1.41, 2.71]) and two-week (tertile 2: 1.50 [95% CI: 1.19, 2.03], tertile 3: 1.41 [95% CI: 1.11, 1.89]) time intervals before diagnosis. Results should be interpreted with caution as this study has some limitations, including the linkage of exposure to clinics and lack of individual information to control for confounding.
- A European study examined associations between the incidence of self-reported adult rhinitis and air pollution in two cohorts, the Genetics and Environment of Asthma (EGEA) and the European Community Respiratory Health Survey (ECRHS) (Burte et al., 2018). Similar to many European studies, the authors use the ESCAPE framework for estimating exposure concentrations, with annual averages assigned to individual residences. It is important to note that estimates for NO_2 were only available for 17 cities within the study (results reported per 10 $\mu g/m^3$ increase). Following this the authors used meta-regression between cities to examine associations between air pollution and rhinitis and found null results (adjusted incidence rate ratio (aIRR): 1.00 [95% CI: 0.91, 1.09]).
- A pooled study of European cohorts showed largely inverse, but imprecise, associations between exposure to both NO_2 and NOx and rhinoconjunctivitis (Fuertes et al., 2020). Effect estimates, when exposure was assigned to residence at time of outcome, were 0.91 (95% CI: 0.75, 1.10) at age four and 0.87 (95% CI: 0.62, 1.22) at age eight for NO_2, and 0.96 (95% CI: 0.77, 1.19) at age four and 0.98 (95% CI: 0.63, 1.52) at age eight for NO_X. Similar results were seen when exposures were assigned to the residence at birth.
- A study examining two European cohorts (EGEA and ECRHS) examined associations between air pollution/traffic density and severity of rhinitis (Burte et al., 2020). Similar to other studies examining rhinitis, the outcome is derived from self-report data, along with severity scores. ESCAPE methods were used to assign exposure concentrations to residential addresses during the study period. The authors adjusted for age, sex, smoking status, asthma,

and allergic sensitization in the main models. NO_2 was associated with all severity levels of rhinitis in the total study population. When stratified by study, associations were heterogeneous in the EGEA study, while there were consistent positive associations in the ECRHS study. For the population with allergic sensitization, ORs for mild, moderate, and high severity of rhinitis were 1.15 (95% CI: 1.02, 1.30), 1.17 (95% CI: 1.02, 1.34), and 1.14 (95% CI: 1.00, 1.3) respectively. For those without allergic sensitization, effect estimates were similar for the same categories of rhinitis with ORs of 1.24 (95% CI: 1.06, 1.44), 1.29 (95% CI: 1.09, 1.53), and 1.38 (95% CI: 1.16, 1.64). Lastly, for those without asthma ORs reported were 1.14 (95% CI: 1.00, 1.29), 1.37 (95% CI: 1.17, 1.59), and 1.19 (95% CI: 1.03, 1.39).

- A cross-sectional Italian study reported on observed associations between long-term exposure to air pollution and rhinitis, asthma with/without rhinitis, and chronic bronchitis/chronic obstructive pulmonary disease (CB/COPD) with/without rhinitis (Marchetti et al., 2023). The authors combined data from two studies, the Gene Environment Interactions in Respiratory Diseases (GEIRD) study and the Pisa study (a longitudinal study carried out in Pisa and Cascina, Tuscany, Italy). Annual NO_2 exposure, derived from daily averages, was assigned to residential addresses (1 km^2 resolution) from 2013 to 2015, in a cross-validated model. There was a positive association between NO_2, per 10 $\mu g/m^3$ increase, and rhinitis (OR: 1.21 [95% CI: 1.07, 1.37]). In analyses to explore the effect modification by sex, associations were stronger in males than in females (OR: 1.30 [95% CI: 1.04, 1.64] and OR: 0.98 [95% CI: 0.76, 1.26], respectively). In contrast to some other studies, larger effects were observed for those <50 years of age (OR: 1.46 [95% CI: 1.17, 1.84] compared to older adults (OR: 1.17 [95% CI: 0.94, 1.45]).

Other Immune Effects

- Kousha and Castner (2016) used a case-crossover study design to evaluate the association between short-term exposure to NO_2 and otitis media (a continuum of inflammation in the middle ear) emergency department visits in Windsor, Ontario, Canada. There were increased ED visits for otitis media with exposure to NO_2 on lag day 3 (OR: 1.12 [95% CI: 0.97, 1.30]). While there were increased ED visits for lag days 4 and 5, the associations were near null for lag days 0, 1, 6, and 7 (see Appendix A – Appendix Table 13-1).

13.3.1.2 Epidemiologic Studies of Autoimmune Diseases

There were no studies in the 2016 Oxides of Nitrogen ISA that examined associations between exposure to oxides of nitrogen and autoimmune diseases. There was only a single recent study that examined that associations between exposure to NO_2 and autoimmune diseases, with 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 13-1.

- A recent Canadian study examined associations between exposure to air pollution and anti-nuclear antibodies, a marker of systemic autoimmune rheumatic disease, utilizing the CARTaGENE study (Zhao et al., 2020). NO_2 exposures were estimated at the 10 km^2 resolution and then linked to the postal code associated with each participant in the study. In a single pollutant model, there was a near null association between exposure to NO_2 and anti-nuclear antibodies (ANA) positivity (OR: 0.99 [95% CI: 0.98, 1.01]).

- Honda et al. (2023) examined the associations between long-term exposure to NO_2 and type 1 diabetes related mortality among U.S. Medicare beneficiaries. Using a LUR model, 12-month moving average NO_2 concentrations were estimated across the conterminous U.S. In a single pollutant model, there was increased risk of mortality from Type I diabetes (HR: 1.25 [95% CI: 1.09, 1.43] per 10 ppb increase in NO_2). When adjusted for $PM_{2.5}$, the risk of mortality from Type I diabetes was similar (HR: 1.27 [95% CI: 1.09, 1.48] per 10 ppb increase in NO_2).

13.3.1.3 Conclusions and Remaining Uncertainties

There were a limited number of recent epidemiologic studies that evaluated the associations between exposure to oxides of nitrogen and immune effects, including markers of inflammation and cell regulation. 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. In addition, there are uncertainties related to potential copollutant confounding, lifestages and population differences, the concentration-response relationship, and biological plausibility.

13.3.2 Summary and Causality Determination

The 2016 Oxides of Nitrogen ISA did not include studies of immune effects. In the recent evidence, there were a limited number of epidemiologic studies evaluating the relationship between oxides of nitrogen exposure and immune effects (see Table 13-1). A small number of studies from the United States and Europe showed consistent positive associations between exposure to NO_2 and rhinitis and rhinoconjunctivitis, but given a lack of evaluation of copollutant confounding, controlling for individual variables, and concentration-response curves, and a lack of supporting experimental evidence, there remain critical uncertainties in the evidence. **Overall, the evidence is *inadequate to infer the presence or absence of a causal relationship* between oxides of nitrogen exposure and immune effects.**

Table 13-1 Summary of evidence contributing to causality determinations for oxides of nitrogen exposure and immune effects

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Eczema and Atopic Dermatitis			
Limited epidemiologic evidence for eczema and atopic dermatitis	Limited evidence of associations for eczema. Uncertainties regarding concentration response and exposure response, lifestages and population differences, and copollutant confounding.	Fuertes et al. (2020)	Median NO_2: 5.95–22.86 ppb for annual avg Median NO_X: 16.3–65.9 µg/m^3 for annual avg
		Deng et al. (2019)	Mean NO_2: 20.40–20.70 ppb for annual avg
		Huang et al. (2015)	Mean NO_2: 17.3 ppb for monthly average
Rhinitis and Rhinoconjunctivitis			
Limited epidemiologic evidence for rhinitis and rhinoconjunctivitis	Some positive associations with incidence of rhinitis and rhinoconjunctivitis across North American and international studies. Uncertainties regarding concentration response and exposure response, lifestages and population differences, and copollutant confounding.	Chung et al. (2016)	Median NO_X: 19.6 ppb for 24-hr avg
		Burte et al. (2018)	Mean NO_2: 15.57 ppb for annual average
		Marchetti et al. (2023)	Mean NO_2: 14.46 ppb for 6-month period
		Burte et al. (2020)	Mean NO_2: 15.89 ppb for annual average
Autoimmune			
Limited epidemiologic evidence for autoimmune effects	Limited evidence of associations for autoimmune effects.	Zhao et al. (2020)	Mean NO_2: 14 ppb for annual average
		Honda et al. (2023)	Mean NO_2: 10.9 ppb for annual average

List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; NO_X = oxides of nitrogen; ppb: = parts per billion.
[a]Based on the 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.

13.4 Renal Effects

There were no studies of renal effects in the 2016 Oxides of Nitrogen ISA. The recent epidemiologic studies examining the associations between exposure to oxides of nitrogen and renal effects are summarized below. 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 13-1. There were no recent PECOS-relevant toxicological studies available for exposure to oxides of nitrogen and renal effects.

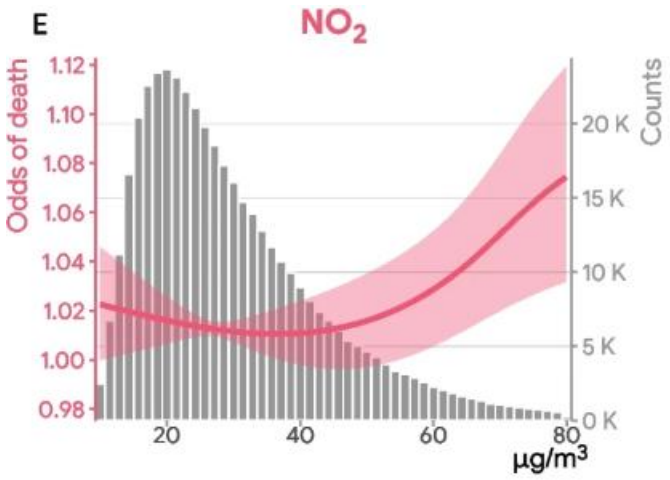
13.4.1 Epidemiologic Studies of Renal Effects

A limited number of recent epidemiologic studies examined associations between exposure to oxides of nitrogen and renal effects. Overall, there were positive associations with renal disease in North American studies with mixed evidence from international studies. Recent epidemiologic studies examining these endpoints are summarized below. 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 13-1.

- A study based in New York State examined kidney-related conditions and air pollution in a case-crossover study using data from 2007 to 2016 (Chu et al., 2023). Exposures were estimated using an ensemble machine learning algorithm based on a 1-hour maximum NO_2 and assigned at 1 km^2 grids. This study employed a symmetric bi-directional case-crossover design with conditional logistic regression to examine associations between renal outcomes and NO_2. NO_2 was positively associated across cumulative lags (lag 0 through 0–6) for acute kidney failure, urolithiasis, volume depletion, glomerular disease, and dysnatremia (though CIs for these last two outcomes consistently crossed the null). Negative, null, and positive associations were seen for renal tubulo-interstitial diseases and chronic kidney disease (CKD). In three pollutant models, with $PM_{2.5}$ and O_3, positive associations were consistently seen for exposure to NO_2 with acute kidney failure, urolithiasis, dysnatremia, and volume depletion across a zero to five day cumulative lag. This study compared exposures while adjusting for environmental conditions using several intraday measures of temperature, including daily mean, daily minimum, daily maximum, nighttime mean, and daytime mean. Results remained relatively stable across outcomes and when controlling for different environmental conditions.
- A second U.S.-based study evaluating populations in the Atlanta metropolitan area examined associations with a primary diagnosis of all renal disease and acute kidney failure (CKD was excluded because short-term exposure was determined unlikely to be associated) (Bi et al., 2021). Short-term exposure to NO_2 and NO_X were estimated using the Community Multi-Scale Air Quality (CMAQ) modeling system (1-hour maximum) and assigned to 2010 census Zip Code Tabulation Areas (ZCTAs) corresponding to residence. Time series models were adjusted for cubic terms for daily maximum air temperature and mean dew-point temperature, indicator variables for a season, day of week and holidays, and hospital participation. Both NO_2 and NO_X were positively associated with emergency department (ED) visits for all renal disease in the cumulative lag estimates but hovered around the null for 1-day lags (rate ratios

(RRs) 1.018 [95% CI: 0.997, 1.039] and 1.017 [95% CI: 0.999, 1.034], respectively). When examining single day lags for renal specific ED visits, there were few positive associations for both NO_2 and NO_X per Interquartile Range (IQR) increase in concentrations. The most consistent association measures were lag days 2 and 3 for both NO_2 and NO_X for all renal diseases as the primary diagnosis.

- A time series analysis from Australia and New Zealand examined air pollution and short-term outcomes including acute renal failure (Groves et al., 2020). The authors utilized health data from the Australia and New Zealand Intensive Care Society (ANZICS), Adult Patient Database (APD), ANZICS modification of the Acute Physiology and Chronic Health Evaluation (APACHE) III diagnostic codes, and air pollution concentrations were assigned to postcode centroids from the Environment Protection Authority of Victoria and the Office of Environment and Heritage of New South Wales (NSW). The adjusted relative risk for acute kidney failure was 0.912 (95% CI: 0.786, 1.059).
- A cohort from Denmark, part of the ELAPSE project, was examined for all-cause and cause-specific mortality in association with air pollution. Renal outcomes were assessed using International Classification of Disease 10th Revision (ICD-10 codes) and exposures were estimated at a resolution of 100 m^2, via a validated LUR model, and geolocated to a residential address. For sensitivity analyses, the authors used exposures extrapolated with the Danish Eulerian Hemispheric Model (DEHM) that provided estimates at 26 km^2 (So et al., 2022). Per 5.31 ppb increase in annual average NO_2 concentrations, the incidence of CKD was positive with a hazard ratio (HR) of 1.05 (95% CI: 1.00, 1.11), this was robust across copollutant models ($PM_{2.5}$ and BC), with the exception of O_3 (HR: 0.98 [95% CI: 0.90, 1.08]).
- A retrospective cohort study composed of patients with pre-end stage renal disease (ESRD), defined by estimated glomerular filtration rate (eGFR) <45 ml/min/1.73/m^2, from Taichung Veterans General Hospital focused on associations between annual NO_2 concentrations and eGFR (Wu et al., 2022). Exposures were assigned using a validated hybrid model at the patient's primary residence. NO_2 (ppb) exposures were categorized into tertiles with the lowest as the reference group, where both middle and upper tertile exposure groups were positively associated with HRs of 1.08 (95% CI: 0.98, 1.19) and 1.60 (95% CI: 1.46, 1.76), respectively. When conducting sensitivity analyses to exclude patients with eGFR deterioration within 7-, 30-, and 90-days, the results were consistent and authors reported positive HRs, particularly with the highest tertile.
- A study from China examined short-term exposure to air pollution and relative percent increase in mortality related to CKD in a time-stratified case-crossover design (Cai et al., 2023). Evaluating exposures with short lag periods, concentration-response (C-R) curves, stratified analyses, and copollutant models, this study examined associations between NO_2 and outcomes in a variety of ways. Adjusted relative percent increase in mortality with NO_2 was 1.26 (95% CI: 0.29, 2.24) per 5.31 ppb. When adjusted for $PM_{2.5}$, the results remain consistently positive at 1.27 (95% CI: 0.02, 2.55). The effect estimates are positive but cross the null in copollutant models with particulate matter <1 micron (PM_1) and PM_{10}. In analyses stratified by categorical variables (age, sex, education, marriage, occupation, disease type, season, year, and region), overall, the results are consistently positive between NO_2 exposure and CKD mortality. Furthermore, the C-R curve is non-linear and has a downward slope until approximately 21.26 ppb, at which point it increases positively consistently (see Figure 13-1).



List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide; $\mu g/m^3$ = micrograms per cubic meter.
Note: The solid lines with shaded regions represent the odds of death from kidney diseases and the associated 95% confidence intervals.
Source: adapted from Cai et al. (2023). Copyright permission pending.

Figure 13-1 Concentration-response association of short-term exposure to nitrogen dioxide with death from kidney disease in China.

- A study using the UK Biobank health data employed a multistate model to examine how exposures to ambient air pollution potentially impacts progression and mortality related to CKD (Wu et al., 2023). ESCAPE LUR methods were used to estimate long-term exposures for NO_2 and NO_X. The authors reported on incident CKD in healthy individuals, CKD to multimorbidity, and CKD to death. See Appendix A – Appendix Table 13-1 for effect estimates.
- In another study in the UK Biobank, Wang et al. (2022) investigated the associations between long-term exposure to NO_2 and NO_X, estimated from LUR, with risk of incident CKD. There was increased risk for incident CKD with exposure to NO_2 (HR: 1.05 [95% CI: 1.03, 1.07] per 11.00 $\mu g/m^3$) and NO_X (HR: 1.06 [95% CI: 1.04, 1.08] per 16.55 $\mu g/m^3$).

13.4.1.1 Conclusions and Remaining Uncertainties

In general, there were consistent patterns of association between exposure to oxides of nitrogen and both reduced renal function and the incidence of early end stage kidney disease (ESKD) as well as ESKD (also reported in some studies as ESRD). These results were consistent in both North American studies as well as international studies (including those from Europe and Asia). Because there were relatively few studies examining associations between exposure to oxides of nitrogen and renal effects, the ability to judge coherence and consistency across the various outcomes is somewhat limited. Additionally, there are remaining uncertainties regarding concentration-response relationship, lifestages and population differences, copollutant confounding, and biological plausibility.

13.4.2 Summary and Causality Determination

The 2016 Oxides of Nitrogen ISA did not include studies of renal effects. In the recent evidence, there were a limited number of studies evaluating the relationship between oxides of nitrogen exposure and renal effects. Recent epidemiologic evidence in the United States, Europe, and other regions reported consistent positive associations between exposure to oxides of nitrogen and reduced renal function as well as ED visits for kidney-related disease (see Table 13-2). Two U.S. based studies reported positive associations between exposure to both NO_2 and NO_X and a variety of renal issues including acute kidney failure, urolithiasis, and hospital admissions for kidney disease. Results for associations between exposure to oxides of nitrogen and kidney function from studies in Europe, Asia, and Australia and New Zealand were mixed. A cohort study from Denmark reported positive associations between exposure to NO_2 and incident CKD, while a UK Biobank study reported null associations. A single study conducted in China examined copollutant models and reported largely positive associations. However, there are many remaining data gaps and uncertainties that the available literature has not effectively addressed. In particular, available epidemiologic studies have not sufficiently teased apart implications of potential copollutant confounding (e.g., mixtures models that address collinearity, interactions, etc.) across heterogeneous geographic regions, evidence from experimental studies and other studies that could support biological plausibility is lacking, and the shapes of concentration-response relationship for renal effects have not been characterized for ambient air quality that is clearly relevant to concentrations in the United States. **Overall, the evidence is *inadequate to infer the presence or absence of a causal relationship* between oxides of nitrogen exposure and renal effects.**

Table 13-2 Summary of evidence contributing to causality determinations for oxides of nitrogen exposure and renal effects

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Limited epidemiologic evidence of renal effects	Positive associations with renal disease in North American studies with mixed evidence from international studies. Uncertainties regarding concentration response and exposure response, lifestages and population differences, and copollutant confounding.	Chu et al. (2023)	Mean NO_2: 11.2 ppb for 1-hr max
		Bi et al. (2021)	Mean NO_2: 21.58 ppb for 1-hr max Mean NO_X: 45.63 ppb for 1-hr max
		So et al. (2022)	Mean NO_2: 20.3 µg/m^3 for annual average

List of abbreviations in alphabetical order: µg/m^3 = micrograms per cubic meter; NO_2 = nitrogen dioxide; NO_X = oxides of nitrogen; ppb: = parts per billion.
[a]Based on the 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.

13.5 Hepatic Effects

There were no epidemiologic or toxicological studies of hepatic effects in the 2016 Oxides of Nitrogen ISA. The recent studies examining the associations between exposure to oxides of nitrogen and hepatic effects are summarized in the text below. Study details of the recent evidence are included in Appendix A – Appendix Table 13-1 for the epidemiologic studies and Appendix A – Appendix Table 13-2 for the animal toxicological studies. Evidence for metabolic effects other than non-alcoholic fatty liver disease (NAFLD) is discussed in Chapter 8 Metabolic Effects.

13.5.1 Epidemiologic Studies of Hepatic Effects

In the 2016 Oxides of Nitrogen ISA, there were no epidemiologic studies that evaluated hepatic effects. A limited number of recent studies evaluated the associations between exposure to oxides of nitrogen and hepatic effects, including different markers for enzyme levels. 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. Study details including study population characteristics, exposure details (assessment metrics, temporal, and spatial scale), potential confounders, and select results are in Appendix A – Appendix Table 13-1.

- Hsieh et al. (2017) investigated the relationship between residential two-year annual average NO_2, estimated from a geospatial model, and liver health in a sample (n = 74) of overweight and obese youth with characterized markers for NAFLD and markers for non-alcoholic steatohepatitis (NASH). An increase of one IQR in average NO_2 (1.91 ppb) was associated with 11.4 U/L (SE: 5.4) greater plasma cytokeratin-18 (CK-18), a protein byproduct of hepatocyte apoptosis that has been found to be an indicator of NASH risk in a pediatric population.
- In a cross-sectional study in the UK Biobank, Liu et al. (2023) explored the association between air pollution, estimated from a LUR model, and liver enzyme levels and whether alcohol intake impacts the association. A 20 $\mu g/m^3$ increase in long-term exposure to NO_X was associated with a 0.1745% (95% CI: 0.125, 0.223) increase in aspartate aminotransferase (AST) liver enzyme levels, a 0.369% (95% CI: 0.267, 0.472) increase in gamma-glutamyl transferase (GGT), but no association with alanine aminotransferase (ALT) (β: 0.068% [95% CI: -0.008, 0.145]) or alkaline phosphatase (ALP) (β: 0.039% [95% CI: -0.011, 0.089]). A 10 ppb increase in NO_2 was associated with a 0.418% (95% CI: 0.323, 0.513) change in AST liver enzyme levels and a 0.566% (95% CI: 0.369, 0.764) change in GGT, but no association with ALT (β: 0.143% [95% CI: -0.005, 0.291]) or ALP (β: 0.0.36% [95% CI: -0.061, 0.133]). With an increase in frequency of drinking, the influence of NO_X and NO_2 on AST, ALT, and GGT levels also increased. There was also evidence of effect measure modification by age (≤60 and >60) for both NOx (lower ALP for ≤60) and NO_2 (lower ALP for ≤60) with ALP, but not with any other liver enzyme. Additionally, there was evidence of effect measure modification by sex for both NO_X and NO_2 and all liver enzymes, AST, ALT, GGT, and ALP, with stronger associations among men.

13.5.1.1 Conclusions and Remaining Uncertainties

A limited number of recent epidemiologic studies evaluated the associations between exposure to oxides of nitrogen and hepatic effects, including different markers for enzyme levels. The large cross-sectional study provides some insight into the associations between exposure to oxides of nitrogen in ambient air and hepatic effects, but the temporality of exposure and outcome cannot be established. 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, concentration-response relationship, and biological plausibility.

13.5.2 Animal Toxicological Studies of Hepatic Effects

There were no studies evaluating oxides of nitrogen exposure and hepatic function in the 2016 Oxides of Nitrogen ISA. Recently, a single study has investigated the effects of NO_2 on hepatic outcomes. Study specific details, exposure conditions, and endpoints examined are highlighted in the text below and in Appendix A – Appendix Table 13-2.

- Serum AST, ALT, and ALP activity was significantly elevated in female C57BL/6 mice following 2.5 ppm NO_2 exposure for 28 days (5 hours/day) (Guo et al., 2023).
- The same study found that liver tissue from NO_2-exposed female mice had significantly increased lipid content (oil red O stain), and H&E-stained liver sections showed evidence of inflammasome aggregation and steatosis. In contrast, hepatic collagen fibers were not significantly altered when visualized using Sirius red.
- Male C57BL/6 mice were also investigated by Guo et al. (2023) using the same exposure paradigm, but no statistically significant changes were noted.

13.5.2.1 Conclusions and Remaining Uncertainties

In summary, there is limited evidence from a single study that NO_2 exposure increased serum activity of liver enzymes (AST, ALT, and ALP) and hepatic histopathological changes in female mice, but not in males. This finding has not been replicated, however, and other endpoints relevant to hepatotoxicity have not been investigated (e.g., bilirubin and gamma-glutamyl transpeptidase). There is also a significant gap in understanding the potential impact of NO_2 on male mice, as current data is insufficient to draw definitive conclusions about sex-specific differences. Furthermore, additional studies are needed to characterize the dose-response relationship and the impact of exposure duration.

13.5.3 Synthesis Across Lines of Evidence

A limited number of studies investigating the effects of oxides of nitrogen exposure on hepatic effects were available. Findings from a single cross-sectional epidemiologic study reported that NOx and NO_2 were associated with changes in some liver enzymes (AST and GGT), but not others (ALT and ALP). A single study in rodents also reported that exposure to NO_2 increased the serum activity of AST, ALT, and ALP in female mice, though GGT was not investigated. The difference in these findings could result from higher NO_2-exposure concentrations in the rodent study (i.e., 2,500 ppb versus 14.13 ppb [mean]) or from biological differences between rodents and humans. Another epidemiologic study reported associations with a marker of NASH in youth, and there is some support from animal toxicologic studies showing hepatic fat accumulation.

13.5.4 Summary and Causality Determination

The 2016 Oxides of Nitrogen ISA did not evaluate studies on hepatic effects. Recent epidemiologic and animal toxicological studies have reported associations with liver enzymes and NASH which provides some support for coherence across disciplines; however, the limited availability of studies limits conclusions about consistency within disciplines (see Table 13-3). There are many remaining data gaps and uncertainties that the available literature has not effectively addressed. In particular, the largest and most comprehensive evaluation of hepatic effects comes from a cross-sectional epidemiologic study, and recent epidemiologic studies have not examined potential copollutant confounding by traffic-related pollutants across heterogeneous geographic regions. Furthermore, there is limited evidence from experimental studies and other toxicological studies that could support biological plausibility, and the shapes of concentration-response functions for hepatic effects have not been characterized for air quality that is clearly relevant to ambient air concentrations in the United States. **Overall, the evidence is *inadequate to infer the presence or absence of a causal relationship* between oxides of nitrogen exposure and hepatic effects.**

Table 13-3 Summary of evidence contributing to causality determinations for oxides of nitrogen exposure and hepatic effects

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Limited and inconsistent epidemiologic evidence of hepatic effects	Positive associations with liver enzyme levels in a single cross-sectional study. Uncertainties regarding concentration response and exposure response, lifestages and population differences, and copollutant confounding.	Liu et al. (2023)	Mean NO_2: 14.13 ppb for annual average Mean NO_X: 43.90 µg/m^3 for annual average
Limited evidence of hepatic effects from animal toxicological studies provides some coherence	Increased serum activity of liver enzymes and histopathological changes in female mice.	Guo et al. (2023)	2,500 ppb NO_2

List of abbreviations in alphabetical order: µg/m^3 = micrograms per cubic meter; NO_2 = nitrogen dioxide; NO_X = oxides of nitrogen; ppb = parts per billion; ppm = parts per million.
[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.

13.6 Ocular Effects

In the 2016 Oxides of Nitrogen, there were no studies of ocular effects. Recent epidemiologic studies examining the associations between exposure to oxides of nitrogen and ocular effects are summarized in the text below. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 13-1. There were no recent PECOS-relevant toxicological studies available for exposure to oxides of nitrogen and ocular effects.

13.6.1 Epidemiologic Studies of Ocular Effects

Recent epidemiologic studies of ocular effects evaluated a variety of outcomes, such as conjunctivitis, visual acuity, retinal morphology, microvascular disease, and dry eye disease. 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 13-1.

- A Canadian study, using a case-crossover study design, and utilizing the NAPS exposure data, found positive associations (OR: 1.276 [95%CI: 1.173, 1.388]) between NO_2 and

conjunctivitis at single and multiple day lags for both men and women, under and above 18 years of age, as well as during the warm season (Szyszkowicz et al., 2016).

- A multiregional study conducted in China reported on air pollution and visual acuity/impairment in school-age children. Exposure concentrations were estimated at 0.1 degrees and were assigned to the centroids of 94 schools. Environmental confounders of greenness and temperature were controlled for along with individual covariates assessed through self-report questionnaires. Based on long-term averages (three to five years), NO_2 was associated with visual impairment with an OR of 1.276 (95% CI: 1.173, 1.388) and with decreased eyesight scores in both eyes. In stratified analyses for age (6–11 years and 12–18 years; sex; outdoor exercise time; residential area (urban vs. rural); parental education; and parental tobacco smoking) NO_2 remained consistently associated with visual impairment in all tests of visual acuity (Yang et al., 2021).
- A UK Biobank study examined associations between retinal morphology and NO_2 and NOx exposures. Both were inversely associated with retinal thickness suggesting that exposure to NO_2 and NO_X are associated with reduced retinal thickness (Chua et al., 2020).
- A study based in Taiwan examined dry eye disease and air pollution using a highly spatially resolved model with 50 m^2 resolution. After controlling for sociodemographic variables, those in the greater exposed group had a prevalence ratio higher than those in the lower exposed group (above and below 17.02 ppb), acting as the reference group, of 1.43 (95% CI: 1.15, 1.78) per SD increase (Chung et al., 2021).
- A second Taiwanese study examined air pollution's role in uveitis incidence. Modeling the exposures as quartiles, with the lowest as the reference group, both NO and NO_X were associated with increasing incidence of uveitis as concentrations increased. Additionally, looking at cumulative yearly exposure, both pollutants were associated with the incidence of uveitis (Bai et al., 2021).
- A third study from Taiwan examined central retinal artery occlusion using a time-series stratified design and examining single day lag periods. Null associations were observed during lag 0, but positive associations were reported through lag day 6. When adjusted for other baseline pollutants, NO_2 was associated at a 5 day lag (per 1% increase in concentration) with an OR of 1.03 (95% CI: 1.01, 1.05) (Cheng et al., 2016).

13.6.1.1 Conclusions and Remaining Uncertainties

There were a limited number of recent studies that evaluated the associations between exposure to oxides of nitrogen and ocular effects. 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, concentration-response relationship, and biological plausibility.

13.6.2 Summary and Causality Determination

The 2016 Oxides of Nitrogen ISA did not include studies of ocular effects. In the recent evidence, there were a limited number of studies evaluating the relationship between oxides of nitrogen exposure

and ocular effects (see Table 13-4). There was a singular study from North America that reported positive associations between exposure to NO_2 and ED visits for conjunctivitis, with stronger associations for those ≤18 years of age. International studies based out of Europe and Asia reported consistent positive associations between exposure to both NO_2 and NO_X and a variety of ocular diseases including dry eye disease, retinal thickness, and uveitis. However, there are many remaining data gaps and uncertainties that the available literature has not effectively addressed. In particular, available epidemiologic studies have not examined potential copollutant confounding by traffic-related pollutants across heterogeneous geographic regions, evidence from experimental studies and other studies that could support biological plausibility is lacking, and the shapes of concentration-response relationships for ocular effects have not been characterized for air quality that is clearly relevant to ambient air concentrations in the United States. **Overall, the evidence is *inadequate to infer the presence or absence of a causal relationship* between oxides of nitrogen exposure and ocular effects.**

Table 13-4 Summary of evidence contributing to causality determinations for oxides of nitrogen exposure and ocular effects

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Limited epidemiologic evidence of ocular effects	Positive associations with visual impairment, altered retinal morphology, uveitis, and dry eye disease in North American and international studies. Uncertainties regarding concentration response and exposure response, lifestages and population differences, and copollutant confounding.	Szyszkowicz et al. (2016)	Mean NO_2: 5.2–18.5 ppb for 24-hr avg
		Chua et al. (2020)	Median NO_2: 32.38 μg/m^3 for annual average Median NO_X: 44.72 μg/m^3 for annual average
		Chung et al. (2021)	Mean NO_2: 15.24 μg/m^3 for annual average

List of abbreviations in alphabetical order: μg/m^3 = micrograms per cubic meter; NO_2 = nitrogen dioxide; NO_X = oxides of nitrogen; ppb = parts per billion.
[a]Based on the 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.

13.7 Gastrointestinal Effects

There were no studies of gastrointestinal effects in the 2016 Oxides of Nitrogen ISA. Recent epidemiologic studies examining the associations between exposure to oxides of nitrogen and gastrointestinal effects are summarized in the text below. Study specific details including study population characteristics, exposure details (assessment metrics, temporal, and spatial scale), potential confounders, and select results are in Appendix A – Appendix Table 13-1. There were no recent PECOS-relevant toxicological studies available for exposure to oxides of nitrogen and gastrointestinal effects.

13.7.1 Epidemiologic Studies of Gastrointestinal Effects

In the 2016 Oxides of Nitrogen ISA, there were no epidemiologic studies that evaluated gastrointestinal outcomes. There are a limited number of recent studies that evaluated the associations between exposure to oxides of nitrogen in ambient air and gastrointestinal outcomes, including inflammatory bowel diseases (IBD), colitis, and pediatric-onset inflammatory bowel disease (Elten et al., 2020; Opstelten et al., 2016; Szyszkowicz, 2015). The recent epidemiologic studies of gastrointestinal effects are summarized in the following bullets.

- Among participants in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, Opstelten et al. (2016) reported a pattern of positive, but imprecise associations between IBD and disease subtypes overall with exposure to NO_2 and NO_X, which was estimated from an LUR model developed for the ESCAPE project. There were increased odds of IBD associated with long-term exposure to NO_2 (OR: 1.10 [95% CI: 0.83, 1.40] per 10 ppb increase in NO_2) and NO_X (OR: 1.08 [95% CI: 0.83, 1.40] per 20 $\mu g/m^3$ increase in NO_X) exposures, but the CIs included the null. For Crohn's disease, there was similar pattern of increased odds, but the CIs included the null (NO_2 OR: 1.26 [95% CI: 0.37, 4.27] per 10 ppb increase in NO_2 and NO_X OR: 1.17 [95% CI: 0.67, 2.03] per 20 $\mu g/m^3$ increase in NO_X). Additionally, there was a null association between NO_2 and ulcerative colitis (OR: 0.98 [95% CI: 0.51, 1.90] per 10 ppb increase in NO_2) and a positive, but imprecise, association with NO_X (OR: 1.03 [95% CI: 0.76, 1.35] per 20 $\mu g/m^3$ increase in NO_X). The imprecise associations may be the result of a small number of cases for IBD (n = 142), Crohn's disease (n = 38), and ulcerative colitis (n = 104).
- In a case-crossover study, Szyszkowicz (2015) reported positive associations between short-term exposure to NO_2, estimated from monitoring station data, and emergency department visits for colitis in Canada. The strongest association was for lag day 3 with OR of 1.10 (95% CI: 1.03, 1.16) per 10 ppb increase in NO_2.
- In a study in Canada, Elten et al. (2020) evaluated the associations between maternal and early-life exposures to NO_2, estimated from a national LUR model, and risk of pediatric-onset of IBD among children in Ontario. Overall, there were null associations between exposure to NO_2 and IBD, regardless of exposure period (trimester 1, trimester 2, trimester 3, pregnancy, or childhood), with HRs ranging from 0.96 to 1.03. For Crohn's disease and ulcerative colitis, there were similar patterns of association across the different exposures, with mostly null associations.

13.7.1.1 Conclusions and Remaining Uncertainties

Because of the small number of studies and the various apical endpoints of gastrointestinal effects, the ability to judge coherence and consistency across the outcomes evaluated in these studies is limited. There remain uncertainties regarding copollutant confounding, lifestages and population differences, concentration-response relationship, and biological plausibility.

13.7.2 Summary and Causality Determination

The 2016 Oxides of Nitrogen ISA did not include studies of gastrointestinal effects. In the recent evidence, there were a limited number of studies evaluating the relationship between oxides of nitrogen exposure and gastrointestinal effects (see Table 13-5). There was a pattern of positive, but imprecise, associations between IBD and disease subtypes overall with exposure to NO_2 and NO_X in the small cohort in Europe. A case-crossover study in Canada reported a similar pattern of associations with exposure to NO_2 and colitis. However, there were inconsistent associations between exposure to NO_2 and pediatric-onset IBD. Given the limited evidence in the epidemiologic studies, it is difficult to judge coherence and consistency across studies. Additionally, there is lack of evaluation of copollutant confounding, lifestages and population differences, and concentration-response relationship. Furthermore, there is no supporting experimental evidence, or a biologically plausible mechanism is remaining uncertainties. **Overall, the evidence is *inadequate to infer the presence or absence of a causal relationship* between oxides of nitrogen exposure and gastrointestinal effects.**

Table 13-5 Summary of evidence contributing to causality determinations for oxides of nitrogen exposure and gastrointestinal effects

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Limited epidemiologic evidence of gastrointestinal effects.	A pattern of positive associations with IBD in adults. Uncertainties regarding concentration response and exposure response, lifestages and population differences, and copollutant confounding.	See Section 13.7.1	Median NO_2: 8.03–14.72 ppb for annual averages Median NO_X: 21.7–40.1 µg/m^3 for annual averages Mean NO_2: 12.73 ppb for 24-hr avg

List of abbreviations in alphabetical order: µg/m^3 = microgram per cubic meter; NO_2 = nitrogen dioxide; NO_X = oxides of nitrogen; 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.

13.8 Musculoskeletal Effects

In the 2016 oxides of nitrogen ISA, there were no studies of musculoskeletal effects. The recent epidemiologic studies examining the associations between exposure to oxides of nitrogen and musculoskeletal effects are summarized in the text below. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 13-1. There were no recent PECOS-relevant toxicological studies available for exposure to oxides of nitrogen and musculoskeletal effects.

13.8.1 Epidemiologic Studies of Musculoskeletal Effects

In the 2016 Oxides of Nitrogen ISA, there were no epidemiologic studies that evaluated musculoskeletal effects. There were a limited number of recent studies that evaluated the associations between exposure to oxides of nitrogen and musculoskeletal effects, including bone mineral density (BMD), osteoporosis, and sarcopenia.

Bone Mineral Density

- In a cohort study in a subset of people in the Taiwan Biobank, Lin et al. (2020) evaluated associations between bone mineral density and average annual exposure to NO_2, NO, and NO_X, estimated from monitoring stations from the Taiwan Air Quality Monitoring Database. Overall, there were decreased bone mineral density T-scores associated with NO_2 (β: -0.230 [95% CI: -0.305, -0.155] per 10 ppb NO_2), NO (β: -0.0600 [95% CI: -0.760, -0.440] per 15 ppb NO), and NO_X (β: −-0.340 [95% CI: -0.440, -0.240] per 20 ppb NO_X). There were also differences between males and females, with strongest effects reported in women (NO_2 β: -0.26 [95% CI: -0.36, -0.16] per 10 ppb NO_2, NO β: -0.645 [95% CI: -0.848, -0.443] per 15 ppb NO, NO_X β: -0.38 [95% CI: -0. 50, -0.26] per 20 ppb NO_X).
- Yang et al. (2023) examined the associations between average annual exposure to NO_2 and NO_X, estimated from the ESCAPE project LUR model, and estimated bone mineral density among participants in the UK Biobank study. There were decreases in estimated bone mineral density at baseline (2006–2010) for NO_2 (β: -0.0037 g/cm^2 [95% CI: -0.0042, -0.0031] per 10.9 μg/m^3 in NO_2) and NO (β: -0.0021 g/cm^2 [95% CI: -0.0026, -0.0016] per 10.6 μg/m^3 in NO).
- Among the Women's Health Initiative Study participants, NO_2 and NO concentrations were assessed in association with bone mineral density (Prada et al., 2023). NO_2 and NO were estimated from kriging for three exposure windows, 1-, 3-, and 5-year averages before BMD assessments. There was decreased bone mineral density in the whole body for NO across all exposure windows, with the strongest association of a decrease of -0.022 (95% CI: -0.027, -0.017) g/cm^2 per year per 10% increase in 3-year average NO concentration. There were more inconsistent associations for bone mineral density for total hip, femoral neck, and lumbar spine across the three exposure windows for NO. With NO_2, there were inconsistent associations with bone mineral density in the whole body, total hip, femoral neck, and lumbar spine across all exposure periods.

Osteoporosis

In general, there was a consistent pattern of positive association between NO_2 and NO_X and osteoporosis. All recent evaluations of osteoporosis were conducted in the UK Biobank study.

- Yang et al. (2023) examined the associations between exposure to NO_2 and NO_X, estimated from the ESCAPE project LUR model, and osteoporosis among participants in the UK Biobank study. There was an increased risk of osteoporosis prevalence at baseline (2006–2010) with NO_2 (OR: 1.12 [95% CI: 1.07, 1.18] per 10 ppb increase in NO_2) and NO_X (OR: 1.04 [95% CI: 1.01, 1.06] per 16.6 μg/m^3 increase in NO_X). After the follow-up period (2021), the increased risk for osteoporosis remained.
- Xu et al. (2022) evaluated the association between ambient air pollutants and osteoporosis. There was increased risk of osteoporosis for NO_2 (HR: 1.12 [95% CI: 1.04, 1.20] per 10 ppb increase in NO_2) and NO_X (HR: 1.03 [95% CI: 1.01, 1.04] per 10 μg/m^3 increase in NO_X).

- Yu et al. (2023) conducted a similar study, evaluating associations between long-term exposure to NO_2 and NO_X, estimated from LUR developed for ESCAPE, and risk of osteoporosis and fractures. There were positive associations with the risk of osteoporosis for exposure to NO_2 (HR: 1.712 [95% CI: 1.177, 2.492] per 10 ppb NO_2) and NO_X (HR: 1.029 [95% CI: 1.011, 1.048] per 1 $\mu g/m^3$ NO_X). There were also positive associations with the risk of fracture with exposure to NO_2 (HR: 1.506 [95% CI: 1.101, 2.06] per 10 ppb NO_2) and NO_X (HR: 1.023 [95% CI: 1.007, 1.038] per 1 $\mu g/m^3$ NO_X).

Other Musculoskeletal Outcomes

- Among participants in the UK Biobank, average annual exposure to NO_2 and NO_X, estimated from a LUR model developed for ESCAPE, were assessed in association with sarcopenia, a progressive and generalized loss of skeletal muscle mass and strength (Lai et al., 2022). There was an increased risk of sarcopenia with exposure to NO_2 (OR: 1.21 [95% CI: 1.18, 1.25] per 10 ppb in NO_2) and NO_X (OR: 1.06 [95% CI: 1.05, 1.08] per 16.59 $\mu g/m^3$ in NO_X).
- Qi et al. (2023) evaluated whether the association between air pollution and risk of fractures was mediated by lower circulating 25-hydroxyvitamin D (25[OH]D) in serum, which emerging evidence suggests as an underlying mechanism for air pollution leading to fractures. NO_2 and NO_X were estimated from an ESCAPE LUR model. There was an association between increased risk for fractures and NO_2 (HR: 1.16 [95% CI: 1.12, 1.20] per 10 ppb increase in NO_2) and NO_X (HR: 1.04 [95% CI: 1.03, 1.05] per 10 $\mu g/m^3$ increase in NO_X). The mediation analysis demonstrated that serum 25(OH)D accounted for 4.09% (95% CI: 2.40, 6.00) of the estimated effects on NO_2 and 5.45% (95% CI: 3.29, 8.00) of the estimated effects on NO_X.

13.8.1.1 Conclusions and Remaining Uncertainties

In general, there was a consistent pattern of positive associations between exposure to NO_2 and NO_X and osteoporosis. All recent evaluations of osteoporosis were conducted in the UK Biobank study, so the ability to judge coherence and consistency across different geographical locations, exposure distributions, and exposure assessment metrics in these studies is limited. There were limited recent epidemiologic studies that evaluated associations between NO_2 and NO_X and bone mineral density, a single study of sarcopenia, and a single study for fractures. There are remaining uncertainties regarding copollutant confounding, lifestages and population differences, concentration-response relationship, and biological plausibility.

13.8.2 Summary and Causality Determination

The 2016 Oxides of Nitrogen ISA did not include studies of musculoskeletal effects. A limited number of recent studies evaluated the relationship between oxides of nitrogen exposure and musculoskeletal effects (see Table 13-6). The main musculoskeletal effects evaluated in the epidemiologic studies were bone mineral density and osteoporosis. Among the limited number of studies evaluating the relationship between exposure to oxides of nitrogen and bone mineral density, there was a consistent pattern of associations with decreased bone mineral density in large cohorts in Taiwan and

Europe but inconsistent associations in a cohort of women in the United States. In general, there was a consistent pattern of positive association between NO_2 and NO_X and osteoporosis; however, all of the recent evaluations of osteoporosis were conducted in a single cohort in the United Kingdom. There are many remaining data gaps and uncertainties that the available literature has not effectively addressed. In particular, available epidemiologic studies have not examined potential copollutant confounding by traffic-related pollutants, evidence from experimental studies and other animal toxicological studies that could support biological plausibility is lacking, and the shapes of concentration-response functions for musculoskeletal effects have not been characterized for air quality that is clearly relevant to concentrations in the United States. **Overall, the evidence is *inadequate to infer the presence or absence of a causal relationship* between oxides of nitrogen exposure and musculoskeletal effects.**

Table 13-6 Summary of evidence contributing to causality determinations for oxides of nitrogen exposure and musculoskeletal effects

Rationale for Causality Determination[a]	Key Evidence[b]	Key References	Oxides of Nitrogen Concentrations Associated with Effects
Bone Mineral Density			
Limited epidemiologic evidence for musculoskeletal effects of bone mineral density.	Limited number of epidemiologic studies with limited evidence of decreased bone mineral density with exposure to NO_2 and NOx. Uncertainties regarding concentration response and exposure response, lifestages and population differences, and copollutant confounding.	Yang et al. (2023)	Mean NO_2: 29.07 µg/m^3 for annual average Mean NO_X: 43.65 µg/m^3 for annual average
		Lin et al. (2020)	Mean NO_2: 15.1 ppb for annual average Mean NO_X: 19.3 ppb for annual average
Osteoporosis			
Limited but consistent evidence for musculoskeletal effects of osteoporosis.	Limited but consistent pattern of positive associations between exposure to NO_2 and NOx and osteoporosis; however, the recent evaluations of osteoporosis were conducted in a single cohort in the U.K. Uncertainties regarding concentration response and exposure response, lifestages and population differences, and copollutant confounding. No support from toxicological studies and no information about potential biological mechanisms.	Yang et al. (2023)	Mean NO_2: 29.07 µg/m^3 for annual average Mean NO_X: 43.65 µg/m^3 for annual average
		Xu et al. (2022)	Median NO_2: 25.6 µg/m^3 for annual average Median NO_X: 41.5 µg/m^3 for annual average
		Yu et al. (2023)	Mean NO_2: 29.12 µg/m^3 for annual average Mean NO_X: 43.86 µg/m^3 for annual average

List of abbreviations in alphabetical order: µg/m^3 = micrograms per cubic meter; NO_2 = nitrogen dioxide; NO_X = oxides of nitrogen; 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.

13.9 Other Health Effects

This Section summarizes recent studies examining associations between exposure to oxides of nitrogen in ambient air and olfactory dysfunction, sleep health, hemoglobin levels, and genitourinary effects. Study specific details including study population characteristics, exposure assessment metrics, potential confounders, and select results are in Appendix A – Appendix Table 13-1.

13.9.1 Epidemiologic Studies of Other Health Effects

There were a limited number of recent studies that evaluated the associations between exposure to oxides of nitrogen and apical outcomes of olfactory dysfunction, sleep health, hemoglobin levels, and genitourinary effects, which none of these outcomes were included in the 2016 Oxides of Nitrogen ISA. Because of the small number of studies examining each of these health outcomes, the ability to judge coherence and consistency across studies is limited.

- Among participants from the National Social Life, Health, and Aging Project (U.S.), Adams et al. (2016) investigated associations between exposure to a 365 day moving average of NO_2, estimated from EPA's Aerometric Information Retrieval System (AIRS), and olfactory dysfunction. There were increased odds of olfactory dysfunction per an 8.9 ppb increase in NO_2 (OR: 1.35 [95% CI: 1.07, 1.72]).
- Honda et al. (2017) examined the relationship between long-term air pollution exposure and hemoglobin levels in a sample of the National Social Life, Health, and Aging Project participants. In addition, mediation by C-reactive protein (CRP) on the association between NO_2 exposures and hemoglobin levels was also explored. NO_2 exposure was estimated from the nearest AQS monitor for five different exposure windows based on 1- to 5-year moving averages. Across all exposure windows, there were decreased hemoglobin levels in association with NO_2, with the strongest associations for the 1-year exposure window (prevalence ratio (PR): 1.43 [95% CI: 1.25, 1.63] per 9.61 ppb increase in NO_2). In the mediation analysis, -0.09 g/dL of the observed -0.73 g/dL decrease in hemoglobin levels per IQR increase in NO_2 was mediated by CRP.
- Li et al. (2022) assessed the associations between annual average exposure to NO_X and NO_2 with overall sleep health among participants in the UK Biobank cohort. Sleep patterns were defined by five individual sleep behaviors (snoring, chronotype, sleep duration, excessive daytime sleepiness, and insomnia). Low-risk sleep behaviors were assessed as follows: reported never/rarely insomnia symptoms; "morning" person or "morning than evening" person; normal (≥7 and <9 hours a day) sleep duration; without snoring; and without ("never/rarely" or "sometimes") frequent daytime sleepiness. The respective sleep behavior was coded as 1 if it was classified as low risk and coded as 0 if it was classified as high risk. A healthy sleep score was created by summing five component scores with a range from 0 to 5, with higher scores denoting a healthier sleep pattern. Then, according to their healthy sleep score, participants were classified into three categories. Participants who scored 0 or 1 were

defined as “poor sleep pattern”; those who scored 2 or 3 were defined as “intermediate sleep pattern”; and those who scored 4 or 5 were defined as “healthy sleep pattern”. There was increased risk of poor sleep patterns (OR: 1.12 [95% CI: 1.09, 1.15] per 10 ppb increase in NO_2) and intermediate sleep patterns (OR: 1.06 [95% CI: 1.05, 1.07] per 10 ppb increase in NO_2) with NO_2, compared to good sleep patterns. There was also an increased risk of poor sleep patterns (OR: 1.05 [95% CI: 1.04, 1.07] per 10 μg/m^3 increase in NO_X) and intermediate sleep patterns (OR: 1.12 [95% CI: 1.08, 1.15] per 10 μg/m^3 increase in NO_X) with NO_X, compared to good sleep patterns.

- Szyszkowicz et al. (2021) evaluated associations between ambient air pollution and the number of ED visits for genitourinary tract diseases in a case-crossover study in Toronto, Canada. Exposure to NO_2 was estimated from the National Air Pollution Surveillance (NAPS) program, with lags for days 0, 1, and 2. The strongest risk of ED visits for diseases of the genitourinary tract with NO_2 was with lag 0 (RR: 1.067 [95% CI: 1.048, 1.086] per 20 ppb of NO_2). There was also an increased risk of ED visits for diseases of the genitourinary tract with NO_2 with lag 0 among women (RR: 1.060 [95% CI: 1.041, 1.079] per 20 ppb of NO_2) and men (RR: 1.077 [95% CI: 1.053, 1.101] per 20 ppb NO_2) separately.

13.9.1.1 Conclusions and Remaining Uncertainties

The recent epidemiologic studies in this Section evaluate potential emerging health outcomes that may be associated with exposure to oxides of nitrogen in ambient air, including olfactory dysfunction, sleep health, hemoglobin levels, and genitourinary effects. However, because of the small number of studies examining each apical outcome, the ability to judge coherence and consistency across studies within each outcome is limited. There are many remaining uncertainties that the available literature has not effectively characterized or addressed, including concentration-response relationship, copollutant confounding, lifestages and population differences, and biological plausibility.

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