EPA/600/R-25/232
July 2026
www.epa.gov/isa

Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

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

External Review Draft

July 2026

U.S. Environmental Protection Agency

Disclaimer

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

Document Guide

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

Table of Contents

List of Tables

List of Figures

Acronyms and Abbreviation

AQCD	Air Quality Criteria Documents
CASAC	Clean Air Scientific Advisory Committee
COVID-19	Coronavirus Disease 2019
CPHEA	Center for Public Health and Environmental Assessment
EPA	U.S. Environmental Protection Agency
ES	Executive Summary
FRN	Federal Register Notice
HERO	Health and Environmental Research Online
HISA	Highly Influential Scientific Assessments
IACUC	Institutional Animal Care and Use Committee
IRB	Institutional Review Board
IS	Integrated Synthesis
ISA	Integrated Science Assessment
IRP	Integrated Review Plan
LLR	Living Literature Review
NAAQS	National Ambient Air Quality Standard
NASEM	National Academies of Science, Engineering and Medicine
NO_2	nitrogen dioxide
NO_X	the sum of NO_2 + NO
NO_Y	the sum of all oxides of nitrogen
ORD	Office of Research and Development
PECOS	population, exposure, comparison, outcome, study design
ppb	parts per billion
ppm	parts per million
PQAPP	program quality assurance project plan
STEM	sources, transport and transformation, exposure/extent, and measurement and modeling
SWIFT-AS	SWIFT-Active Screener
QA	quality assurance
QAPP	quality assurance project plans
QC	quality control
U.S.	United States

CHAPTER 14 Process For Developing the Oxides of Nitrogen Integrated Science Assessment

Summary of Public Resources for the Oxides of Nitrogen ISA

This chapter describes the process for developing the Oxides of Nitrogen ISA, including literature search and screening methods; peer input and peer review; and public participation. This table summarizes the publicly available resources related to this ISA and its development. Readers looking for Federal Register Notices (FRN) may search http://www.regulations.gov by either the document citation number (the reference number to the specific FRN) or the Docket ID number (reference number for the overall docket that may house multiple FRNs, as well as public comments in response to those FRNs). EPA's webpage for the primary standards for oxides of nitrogen is also a useful resource.

Oxides of Nitrogen ISA External Review Draft	[forthcoming]
Clean Air Scientific Advisory Committee	https://casac.epa.gov/ords/sab/f?p=113:1
Federal Register Notices	http://www.regulations.gov
Call for Information	Document Citation: 87 FR 75625 Docket ID: ORD-2022-0831
Integrated Review Plan, Volume 2	Document Citation: 89 FR 19308 Docket ID: EPA-HQ-OAR-2023-0317
Peer Input Workshop	Document Citation: 89 FR 73414 Docket ID: EPA-HQ-ORD-2022-0831
Integrated Review Plan	https://www.epa.gov/naaqs/nitrogen-dioxide-no2-primary-standards-planning-documents-current-review
ISA Preamble	https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244
Literature	https://hero.epa.gov/hero/index.cfm/project/page/project_id/4866
Peer Input Workshops	https://www.epa.gov/isa/workshops-obtain-input-preliminary-draft-materials-oxides-nitrogen-integrated-science

14.1 Introduction

The U.S. Environmental Protection Agency's (EPA) Integrated Science Assessments (ISA) provide the scientific foundation for the review of the National Ambient Air Quality Standards (NAAQS). ISAs contain a synthesis and evaluation of the most policy-relevant science using methods and approaches described in the Preamble to the Integrated Science Assessments (U.S. EPA, 2015b) (hereafter referred to as Preamble) which provides an overview of the ISA development process. For this ISA, updates to the Preamble described in Volume 2 of the Integrated Review Plan (IRP) for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen (U.S. EPA, 2024) were also followed. This ISA's development steps are presented in Figure 14-1.

The first two volumes of the IRP for the primary NAAQS for oxides of nitrogen review were released by EPA in March 2024, with subsequent consultation on Volume 2 with the Clean Air Scientific Advisory Panel (CASAC) Oxides of Nitrogen Panel. Volume 1 provides background information on the air quality criteria and standards for oxides of nitrogen. Volume 2 addresses the general approach for the review and planning of the ISA including identification of policy-relevant issues (see Section 14.4) and key considerations in EPA's development of this ISA (see Section 14.7.2). Additionally, this ISA builds on the conclusions and scientific evidence from the 2008 and 2016 Integrated Science Assessment for Oxides of Nitrogen - Health Criteria (U.S. EPA, 2016, 2008) (hereafter referred to as the 2008 and 2016 Oxides of Nitrogen ISAs) and the prior Air Quality Criteria Document (AQCD) for NO_X from 1993 (U.S. EPA, 1993).

This chapter supplements Volume 2 of the IRP (U.S. EPA, 2024) and the 2015 ISA Preamble (U.S. EPA, 2015b), further describing the process of developing this ISA, including methods for documentation, literature review, study quality evaluation, public engagement, and quality assurance (QA).

14.2 Literature Database

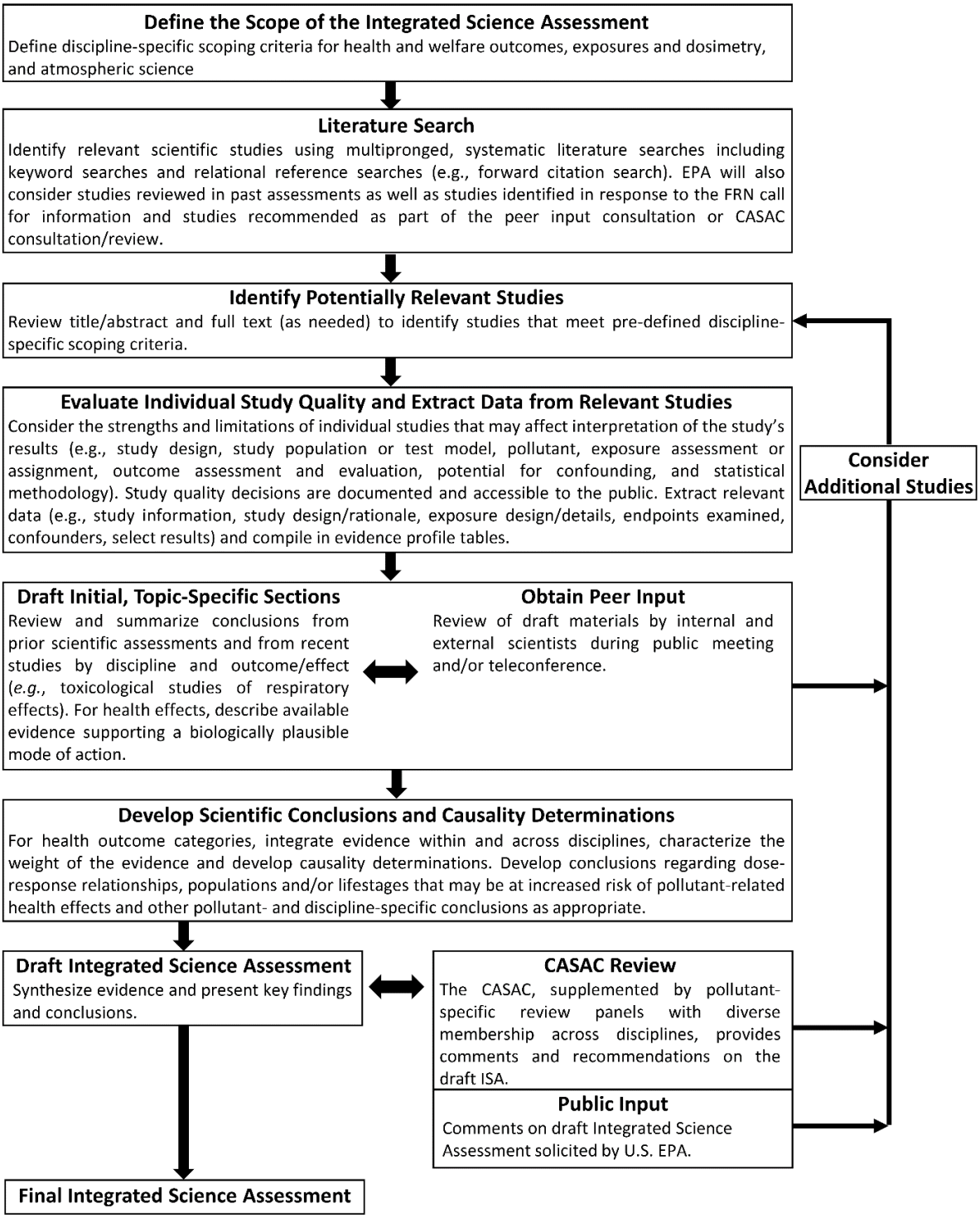
14.2.1 Health and Environmental Research Online

Studies considered in developing the ISAs are documented in EPA's Health and Environmental Research Online (HERO) database to ensure transparency. Upon the completion of this ISA, references considered for inclusion, including those cited in the final ISA, will be publicly accessible through the HERO ISA-NOX 2024 project page. Each reference has a unique HERO ID and the HERO record includes metadata and bibliographic information for the reference. References can be viewed individually or filtered by the chapter or draft in which they are cited.

The HERO project page documents studies identified in the literature search and the inclusion and exclusion decisions for references at each screening stage. In general, a two-step screening process consisting of title and abstract screening followed by full-text screening was used for screening references included and excluded in this ISA; subsequent sections of this chapter discuss the screening process in greater detail. References included at the title and abstract screening step are tagged in HERO as "Title-Abstract Screening Included." Studies selected for inclusion during full-text screening are tagged in HERO as "Full-Text Screening Included" or "Full-Text Screening Excluded." References identified from sources other than the literature searches (e.g., recommendations from CASAC or the public) are also documented on the HERO project page. All references were screened using discipline-specific criteria that were developed a priori. Study specific data, such as concentrations, experimental design, and study results, are reported within the respective ISA chapters.

14.3 Overview of the Process Steps for Developing Integrated Science Assessments

As described in the Preamble and shown in Figure 14-1, developing this ISA consists of the following steps: scoping, literature search and study selection; evaluation of study quality and data extraction; development of initial draft materials for peer input consultation; evaluation, synthesis, and integration of evidence; development of causality determinations and other scientific conclusions, and CASAC review with public input (U.S. EPA, 2015b). Further details on these steps used to develop this ISA are described in the sections that follow.



Source: Modified from Figure II of the Preamble to the Integrated Science Assessments (U.S. EPA, 2015b).

Figure 14-1 Process for developing the Oxides of Nitrogen Integrated Science Assessments.

14.4 Relevance and Scope

As a synthesis and evaluation of the most policy-relevant science, this ISA includes information on atmospheric science, exposure assessment, experimental health studies, and epidemiologic health studies. For this ISA, "policy-relevant" science is described in Volume 2 of the IRP (U.S. EPA, 2024) as "the results of scientific studies that inform ISA conclusions such as causality determinations and conclusions on the populations that may be at increased risk of pollutant-related health effects, as well as conclusions on other policy-relevant issues. These other issues vary by pollutant and discipline and often include characterization of concentration-response relationships, strengths and limitations of various exposure estimates and study designs, impact of potential confounders on health effect associations, timing of effects, etc." The key questions are also laid out in the [Volume 2 of the] IRP. As stated in the Preamble (U.S. EPA, 2015b), "The key policy-relevant questions included in the IRP serve to clarify and focus the NAAQS review on the critical scientific and policy issues, including addressing uncertainties discussed during the previous review and newly emerging literature."

The sections below describe the approaches and scoping statements used to identify relevant studies in each discipline. The use of scoping statements to define study relevance is consistent with recommendations by the National Academies of Sciences, Engineering, and Medicine (NASEM) for improving the design of risk assessment through planning, scoping, and problem formulation to better meet the needs of decision makers (NASEM, 2018). The following sections present additional discipline-specific literature scoping criteria for studies on atmospheric science (see Section 14.4.1), exposure and dosimetry (see Section 14.4.2) and human health effects (see Section 14.4.3).

14.4.1 Atmospheric Sciences

Atmospheric science studies were considered relevant for inclusion in this ISA if they presented and evaluated the latest data related to one or more of the following topics: emissions sources of oxides of nitrogen; emissions chemistry and concentration trends; spatial and temporal patterns for oxides of nitrogen in ambient air; and spatial and temporal trends in oxides of nitrogen emissions and concentrations. Recent research related to specific policy-relevant topics, such as impacts of the COVID-19 pandemic on emissions and ambient air the sum of all oxides of nitrogen (NO_Y) concentrations; near-road nitrogen dioxide (NO_2) monitoring in the United States and advances in measurement and modeling methods, and new studies of Federal Reference Method and Federal Equivalent Method performance; improvements in spectroscopic measurements methods; and innovations in atmospheric modeling of oxides of nitrogen were also of interest. Determining study relevance involved assessing whether a research subject area had the potential to inform policy related to the NAAQS, and whether a study published in that area offered sufficiently original results to be evaluated in this ISA.

Table 14-1 shows the relevance criteria used for broadly identifying recent environmental research advances and knowledge gaps. Application of scoping statements that consider pollutant sources, transport and transformation, extent (concentration), and measurement and modeling (STEM) is consistent with current best practices for reporting or evaluating health science data, as recommended by NASEM (NASEM, 2022). The STEM statement for the Atmospheric Science chapter of the ISA was informed by the body of evidence from the previous ISAs, AQCD, and expert knowledge of the relevant scientific literature. It defines the objectives of the Atmospheric Science chapter and establishes criteria to be met for published studies to be considered in the ISA. A study meeting any of the four aspects of the STEM statement was considered for inclusion.

Table 14-1 STEM statement to define the criteria and framework for identifying relevant oxides of nitrogen atmospheric studies

Statement	Description
Source (S)	Studies reporting quantitative emissions estimates of oxides of nitrogen or observations of physical and chemical characteristics that add to our understanding of pollutant sources and emissions of oxides of nitrogen.
Transport and Transformation (T)	Studies investigating atmospheric fate and transport, transformation, or deposition processes involving oxides of nitrogen, including transport of air pollutants at various scales (i.e., global, national, regional, urban, neighborhood), atmospheric chemical transformations in the atmosphere, or estimates of atmospheric deposition that add to our understanding of atmospheric processes.
Exposure/Extent (E)	Studies reporting observations and estimates of ambient air concentrations or their trends for oxides of nitrogen, including spatial variability on various scales (i.e., global, national, regional, urban, neighborhood); temporal trends such as diurnal, weekday/weekend, seasonal, and long-term trends; or characteristics, such as composition or relationship with atmospheric properties that provide up-to-date concentrations and estimates or add to our understanding of spatiotemporal concentration trends.
Measurement and Modeling (M)	Studies describing methods of measurement of oxides of nitrogen by federal reference and equivalent methods, satellite remote sensing estimates, low-cost sensor estimates, research methods, or modeling techniques (e.g., chemical transport modeling) for characterizing oxides of nitrogen concentrations in ambient air, including the evaluation of measurement principles and modeling assumptions, examination of potential bias and uncertainties, and method comparisons that are relevant to the NAAQS or to studies in this ISA.

List of abbreviations in alphabetical order: ISA = Integrated Science Assessment; NAAQS = National Ambient Air Quality Standards.
Note: A study must meet at least one requirement listed in the description field of one of these statements to be considered for inclusion in the chapter.

14.4.2 Exposure and Dosimetry

This ISA presents and evaluates relevant evidence related to exposure continuums for NO_2 and other oxides of nitrogen, characterization of oxides of nitrogen exposures, the impacts of exposure measurement error on epidemiologic findings, and exposures to factors that may confound associations in epidemiologic studies (e.g., copollutants). This ISA considers key uncertainties from the last review and the extent to which recent scientific evidence may inform our ability to characterize and/or reduce those

uncertainties during the current review. The ISA also evaluates the literature relating to dosimetry of inhaled oxides of nitrogen.

The following guidelines were used to judge the relevance of studies examining exposures to oxides of nitrogen. Studies were included if they provided original data and substantially advanced understanding of the inhalation exposure to oxides of nitrogen from the ambient air; inhalation exposure to oxides of nitrogen in various microenvironments; exposure measurement errors associated with various exposure surrogates; the impact of exposure measurement error on epidemiologic findings; correlations of ambient air oxides of nitrogen with other air pollutants; populations potentially experiencing elevated exposures oxides of nitrogen in ambient air; or NO_X toxicokinetics including uptake, distribution, metabolism, and elimination from the body.

Exposure studies pertaining to the U.S. population and U.S.-based oxides of nitrogen sources were considered most informative to this ISA. Studies were included from outside the United States (e.g., Canada and Europe) if they were judged to have important findings (i.e., similar air quality and exposure conditions to the United States).

Similar to Chapter 1, the scope of the Exposure Science chapter was defined by a discipline-specific STEM statement (see Table 14-2). This ISA presents and evaluates relevant evidence related to exposure continuums for NO_2 and other oxides of nitrogen, characterization of oxides of nitrogen exposures, and exposures to factors that may confound associations in epidemiologic studies (e.g., copollutants).

Table 14-2 STEM statement to define the criteria and framework for identifying relevant oxides of nitrogen exposure studies

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

Note: A study must meet at least one requirement listed in the description field of one of these statements to be considered for inclusion in the chapter.

14.4.3 Health

Relevance of studies that evaluate the relationship between oxides of nitrogen exposure and health effects was assessed using scoping statements that defined the relevant Population, Exposure, Comparison, Outcome, and Study Design (PECOS). The use of PECOS statements is widely accepted and often applied in the health disciplines for systematic review in risk assessment.

Discipline-specific PECOS statements for epidemiologic and experimental studies (i.e., controlled human exposure and animal toxicology studies) were developed to establish inclusion criteria based on the objectives of this ISA and facilitate identifying the most relevant literature (Table 14-3 and Table 14-4; PECOS statements are also included in each health effects chapter). In some cases, PECOS statements differed by health outcome depending on 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 (U.S. EPA, 2016). Additionally, some epidemiologic PECOS statements were further refined to emphasize the strongest recent epidemiologic studies addressing key uncertainties from the previous review; these PECOS refinements are identified and described in detail in the relevant chapters.

14.4.3.1 Experimental Studies

For experimental studies, relevance evaluation focused on controlled human exposure and animal toxicological studies with appropriate study designs and relevant exposure concentrations (Table 14-3 and Table 14-4). The scope of the experimental evidence included in this ISA encompassed studies of controlled exposures to humans and short-term and long-term exposures to nonhuman mammalian animal species that are relevant to the range of human exposures (i.e., 5 ppm or below). As discussed in previous chapters and in the 2015 Preamble to the ISAs (U.S. EPA, 2015b), 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 ISA (U.S. EPA, 2016). Animal studies investigating the effects of concentrations greater than 5 ppm were considered for inclusion in the ISA if they provide insight into biological plausibility.

Table 14-3 Population, Exposure, Comparison, Outcome, and Study Design statement to define the criteria and framework for identifying relevant oxides of nitrogen controlled human exposure studies

Exposure Duration	Concept	Application
Single or repeated short-term exposures	**Population**	Human volunteers enrolled in controlled exposure studies, including volunteers representing populations or lifestages that might be at increased risk of pollutant-related health effects.
	Exposure	Controlled inhalation exposure to NO_2 or other oxide of nitrogen – pollutant exposures must be controlled by the experimenters and not simply a measure of ambient or occupational exposure.
	Comparison	An appropriate control exposure to filtered air or room air for each study participant or an appropriately matched comparison group exposed to filtered air or room air.
	Outcome	Outcomes of interest are those that relate to human health, including effects on the respiratory system, cardiovascular system, immune system, nervous system, diabetes, cancer, or reproduction and development. Effects of interest include changes in indicators or measures of physiological function, health-relevant biomarkers, and organ structure. Effects can be directly measured in exposed study participants or in cells, tissues, or fluids isolated from study participants.
	Study Design	Studies that perform controlled human exposures meeting the above criteria or that analyze data from previously conducted controlled human exposures (e.g., reanalysis, meta-analysis).

List of abbreviations in alphabetical order: NO_2 = nitrogen dioxide.

Table 14-4 Population, Exposure, Comparison, Outcome, and Study Design statement to define the criteria and framework for identifying relevant oxides of nitrogen animal toxicological studies

Exposure Duration	Concept	Application
Short-term exposure	**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	Short-term (i.e., up to 30 days) inhalation exposure to relevant oxides of nitrogen concentrations (i.e., 5 ppm or below).[1]
	Comparison	An appropriate control group exposed to clean air (e.g., room air, filtered air) control.
	Outcome	Outcomes of interest are those that relate to human health, including effects on the respiratory system, cardiovascular system, immune system, nervous system, diabetes, cancer, reproduction and development, or other human health effects (e.g., nervous system). Effects of interest include changes in indicators or measures of physiological function, health-related biomarkers, and organ structure. Effects can be directly measured in exposed animals or in cells, tissues, or fluids isolated from animals.
	Study Design	Controlled exposure studies of animals in vivo meeting the above criteria.
Long-term exposure	**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	Long-term (i.e., longer than 30 days) inhalation exposure to relevant oxides of nitrogen concentrations (i.e., 5 ppm or below).[1]
	Comparison	An appropriate control group exposed to clean air (e.g., room air, filtered air) control.
	Outcome	Outcomes of interest are those that relate to human health, including effects on the respiratory system, cardiovascular system, immune system, nervous system, diabetes, cancer, reproduction and development, or other human health effects (e.g., nervous system). Effects of interest include changes in indicators or measures of physiological function, health-related biomarkers, and organ structure. Effects can be directly measured in exposed animals or in cells, tissues, or fluids isolated from animals.
	Study Design	Controlled exposure studies of animals in vivo meeting the above criteria.

List of abbreviations in alphabetical order: ppm = parts per million.
[1]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 previous chapters and in the 2015 Preamble to the ISAs (U.S. EPA, 2015b), 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 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.

14.4.3.2 Epidemiologic Studies

To identify the most relevant epidemiologic literature, evidence from the 2016 Oxides of Nitrogen ISA (U.S. EPA, 2016) was considered in developing the epidemiologic PECOS statements. Specifically, the scope of the current assessment was informed by well-established areas of research, gaps in the literature, inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2016 Oxides of Nitrogen ISA. The evaluation of epidemiologic studies focused on the association between exposure to NO_2 and other oxides of nitrogen and various health

effects, including, but not limited to, respiratory, cardiovascular, metabolic, nervous system, and reproductive and developmental effects, cancer, and total mortality (see Table 14-5).

Table 14-4 Population, Exposure, Comparison, Outcome, and Study Design statement to define the criteria and framework for identifying relevant oxides of nitrogen epidemiologic studies

Exposure Duration	Concept	Application
Short-term or long-term exposure	**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[1]
	Comparison	Per unit increase (i.e., in ppb) or 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., respiratory, cardiovascular, metabolic syndrome and diabetes, nervous system, total mortality, reproductive and developmental, cancer).
	Study Design	Epidemiologic studies, such as panel, case-crossover, time-series, case-control studies, cohort, cross-sectional studies, and quasi-experimental, with appropriate timing of exposure for the health outcome of interest.

List of abbreviations in alphabetical order: ppb = parts per billion.
[1]The Oxides of Nitrogen ISA focuses on the studies most likely to inform scientific and policy conclusions relevant to ambient air quality in the United States. To efficiently identify such studies during screening, PECOS exposure criteria for epidemiologic studies include a concentration cutoff. Specifically, epidemiologic studies of NO_2 should report overall average NO_2 exposures (e.g., averaged across study populations/locations and over study periods) at or below 22 ppb. This concentration cutoff reflects the 98th percentile of annual average NO_2 concentrations measured at ambient air monitors in the United States during the most recent 15 years of available data (i.e., 2008 to 2022) (U.S. EPA, 2023d). Consistent with the PECOS exposure criteria for animal toxicology studies (Table 14-), epidemiologic studies reporting average NO_2 concentrations above 22 ppb will be considered for inclusion in the ISA if those studies provide valuable and/or unique insights into policy-relevant issues (e.g., studies that examine unique endpoints, use alternative methods for confounder control [causal inference methods], examine potentially at-risk populations, examine associations in underrepresented locations).

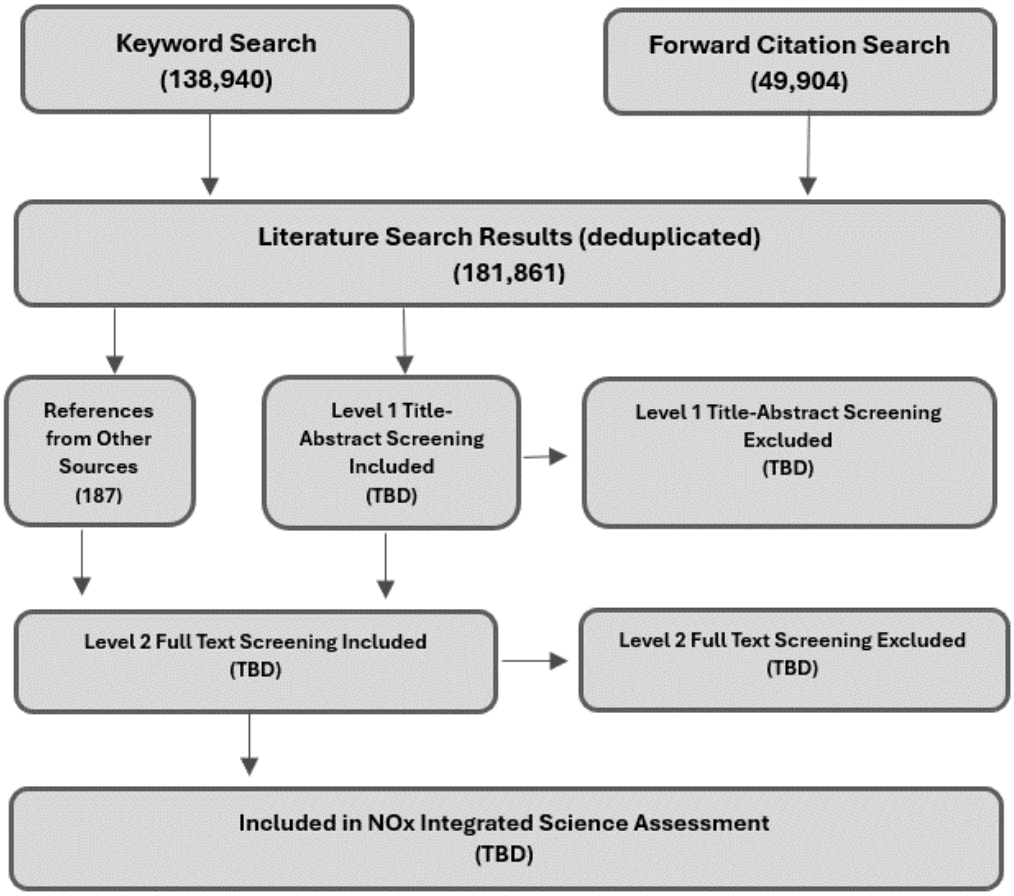
14.5 Literature Search and Screening

14.5.1 Literature Search

EPA uses a structured approach to identify relevant studies for consideration and inclusion in the ISAs. The search for relevant literature for this review began with publication of a Call for Information Federal Register Notice (FRN) (December 9, 2022, 87 FR 75625). This FRN announced initiation of this review of the NAAQS for oxides of nitrogen and invited the public to submit relevant research studies and data published, accepted for publication, or presented at a public scientific meeting since May 15, 2015. Literature submitted by the public in response to this FRN can be viewed at the HERO ISA- NOx 2024 project page. EPA reviewed these studies for relevance following the literature screening process described in this chapter.

In addition to the Call for Information FRN, EPA applied systematic review methodologies to identify peer-reviewed scientific literature relevant to this ISA. The literature searching and screening methodology used generally followed the process depicted in Figure 14-2. The process began with a combination of keyword searches and forward citation searches in PubMed and Web of Science to find relevant literature published between March 2014 and June 2023. This literature search strategy was designed to maximize precision and recall for each discipline (i.e., health, atmospheric sciences, and exposure). The forward citation searches for each discipline were updated in November 2024 after the Peer Input Workshop. This update was done to capture any literature published since the June 2023 cut from the original search.

Keyword searches were developed for each discipline using strings of relevant search terms to capture literature relevant to oxides of nitrogen and the specific topics in each chapter. In addition to keyword searches, topic-specific forward citation searches for all disciplines were used to identify publications that cited references included in the 2016 Oxides of Nitrogen ISA. In addition, a small number of potentially relevant studies were identified for consideration in the ISA by the CASAC NO_X Panel (FRN: 89 FR 15989; CASAC NOx Panel IRP Meeting), by reviewers at the Peer Input Workshop, by expert scientists at EPA, and/or in public comments received in response to the Call for Information FRN (87 FR 75625).



List of abbreviations in alphabetical order: NO_X = the sum of NO_2 + NO; TBD = to be determined.

*Figure under development with final numbers updated for the release of the final Oxides of Nitrogen ISA.

Figure 14-2 Literature flow diagram for the Oxides of Nitrogen Integrated Science Assessment.

14.5.2 Title and Abstract Screening

For health and exposure studies, EPA used SWIFT-Active Screener (SWIFT-AS; Sciome) to perform a first-level screening of the search results for relevance, based on the title and abstract. SWIFT-AS is a web-based literature screening software application that uses machine learning to allow screeners to efficiently screen literature for relevance (Howard et al., 2020). Using a process similar to that in (Howard et al., 2016), search results were ranked in descending order of relevance through machine learning methods. EPA then used this sets of "seed references" (references known to be relevant from the 2016 ISA) for each discipline. As references are screened and tagged as relevant or not relevant, the ranking model is further trained to sort the remaining literature, pushing predicted relevant literature to the top of the queue of references to be screened. EPA screened literature until SWIFT-AS estimated that

95% of relevant literature was included, a threshold considered comparable to human error rates (Howard et al., 2020; Cohen et al., 2006).

For atmospheric science studies, EPA screened titles and abstracts using Living Literature Review (LLR), an application developed by EPA scientists, librarians, and developers. LLR integrates searching and screening of references in one platform. It employs ranking techniques similar to those used in SWIFT-AS and other software to assist the screening by ranking references in descending order of their likely relevance, based on both a set of curated seed references (in this case, references cited in the 2016 ISA and therefore known to be relevant) and references marked for inclusion by the screener as screening progresses. As screening progresses down the ranked search results, the software uses the method of (Howard et al., 2020) that is also used in SWIFT-AS to estimate the proportion of total relevant references that have already been identified as such (i.e., recall). EPA scientists screened until a recall estimate of 95% was achieved.

14.6 Study Selection: Full-Text Screening and Evaluation of Study Quality

Studies that appear to meet the ISA scoping criteria based on the title and abstract screen, together with studies that cannot be definitively identified as out of scope, were evaluated at the full text level. Studies ultimately deemed out of scope were eliminated from further consideration. Retained studies were tagged in HERO as "considered for inclusion" in this ISA. Inclusion and exclusion decisions are documented in the HERO database.

New studies that met the ISA scoping criteria were further evaluated for individual study quality as described in Section 14.6.1. Individual study quality was evaluated by considering the design, methods, conduct, and documentation of each study, but not the study results. This ISA's study quality evaluation considers the strengths and limitations of individual studies, including the possible roles of chance, confounding, and bias that may affect study interpretation and the strength of inference that can be drawn from study results. For the human health literature, the specific attributes considered in evaluating study quality include study design, study population or test model, exposure estimation or assignment, outcome evaluation, potential for confounding, and statistical methodology.

14.6.1 Individual Study Quality

After selecting studies for inclusion based on relevance, individual study quality was evaluated by considering the design, methods, conduct, and documentation of each study, but not the study results. The ISA's general approach to study quality evaluation considers the strengths and limitations of individual studies, including the possible role of chance, confounding, and other biases that may affect study interpretation and the strength of inference that can be drawn from study results. Consistent with NASEM

advice (NASEM, 2022), the sections below identify foundational study design attributes and analysis approaches that were considered when evaluating studies and describe how these attributes and approaches can influence the inference drawn from individual studies. Assessing the scientific quality of individual studies was framed by the following general questions:

- Were the study design, study groups, methods, data, and results adequately justified and clearly presented in relation to the study objectives to allow for study evaluation, including evaluating underlying assumptions and study limitations?
- Are the air quality, exposure, and/or dose metrics sufficiently representative of, or pertinent to, ambient air and are they adequately documented?
- Do the analytical methods used in the study provide adequate sensitivity and precision?
- Are the statistical analyses appropriate, properly performed, and appropriately interpreted?
- For studies of health effects specifically:
    - Were the study populations, participants, or organism model systems appropriately selected and sufficiently well-defined to allow for meaningful comparisons between study or exposure groups?
    - Are the effect measurements meaningful and valid?
    - Were likely confounders controlled for and modifying factors examined in the study design and/or statistical analysis?
    - Were the studies conducted with appropriate oversight by ethics boards or committees (e.g., documenting approval from an Institutional Review Board [IRB] for human studies or from an Institutional Animal Care and Use Committee [IACUC] for animal studies)?

Answers to these questions, and the presence or absence of particular study attributes, were not used as a checklist in evaluating study quality, and the identification of uncertainties that may influence study interpretation did not lead to a conclusion that the study was excluded from the ISA. Rather, strengths and limitations identified during study quality evaluation provided context for the broader process of evidence integration and informed developing ISA's conclusions such as causality determinations. Final study inclusion and exclusion decisions were reached because of study quality evaluation are documented in the HERO database. Further details surrounding how discipline specific studies were evaluated are described in Appendix A of Volume 2 of the IRP (U.S. EPA, 2024).

14.7 Peer Review and Public Participation

Peer review is an essential component of any scientific assessment, as formalized in the guidance in EPA's Peer Review Handbook (U.S. EPA, 2015a). This ISA follows the policies and procedures identified therein. Additionally, this ISA is a Highly Influential Scientific Assessment (HISA), which the

Office of Management and Budget's Final Information Quality Bulletin for Peer Review (hereafter, "Peer Review Bulletin") defines as:

> A subset of Influential Scientific Information that is a scientific assessment (i.e., an evaluation of a body of scientific or technical knowledge, which typically synthesizes multiple factual inputs, data, models, and assumptions and applies the best professional judgment to bridge uncertainties in the available information) that "could have a potential impact of more than $500 million in any year on either the public or private sector" or "is novel, controversial, or precedent-setting, or has significant interagency interest." (U.S. OMB, 2004)

As such, additional steps for review and transparency are required to release this information (e.g., public comment). These steps are described in the subsequent sections.

14.7.1 Call for Information

Consistent with the Preamble (U.S. EPA, 2015b), a Call for Information was published in the Federal Register on December 9, 2022 (87 FR 75625). The purpose of this Call for Information was to announce the beginning of the review cycle for the oxides of nitrogen air quality criteria and the primary NO_2 NAAQS and to invite the public to submit relevant research studies and data that had been published, accepted for publication, or presented at a public scientific meeting since May 15, 2015. The public was given 60 days to submit public comments to the docket. EPA received eight comments via the Federal eRulemaking Portal (http://www.regulations.gov, Docket ID: ORD-2022-0831). Literature submitted by the public in response to this FRN can be viewed at the HERO ISA- NOX 2024 project page.

14.7.2 Integrated Review Plan

Following the Call for Information, EPA prepared a multi-volume IRP: Volume 1 provides background information on the air quality criteria and standards for oxides of nitrogen and Volume 2 addresses the general approach for the review and planning of the ISA. Volume 2 of the IRP (U.S. EPA, 2024, 2022) was released for consultation with the CASAC and public comment via a Notice of Availability in the Federal Register on March 18, 2024 (89 FR 19308). The public was provided opportunity to submit written comments to the docket, and EPA received two public comments via the Federal eRulemaking Portal (http://www.regulations.gov, Docket ID: EPA-HQ-OAR-2023-0317) that were addressed.

14.7.3 Peer Input

The role of peer input is described in Volume 2 of the IRP (U.S. EPA, 2024), the Preamble (U.S. EPA, 2015b), and the Peer Review Handbook (U.S. EPA, 2015a). After a thorough literature search and screening process, EPA developed preliminary draft chapters for peer input. Peer input is a process that allows EPA to gather early-in-the-process feedback from subject-matter experts, internal and external to EPA, to ensure that the ISA captures relevant new literature and focuses on the most policy-relevant findings. Peer input supplements other peer-review mechanisms and does not replace a review by the CASAC.

Peer input for this ISA occurred as a series of four webinar workshops, which EPA announced in an FRN on September 10, 2024 (89 FR 73414, Docket ID: EPA-HQ-ORD-2022-0831). The four workshops were organized by subject: Atmospheric Science, Exposure and Dosimetry, and two sessions on Health. ICF International Inc. facilitated these workshops under contract with EPA. Peer input reviewers were selected by the contractor, with input from EPA, in accordance with the Peer Review Handbook (U.S. EPA, 2015a).

Peer input reviewers were given the following general charge:

- Correct technical errors and identify critical gaps.
- Consider how clearly and logically the chapters and content within the sections are organized.
- Indicate how accurately scientific information is characterized, whether advances in recent literature have been adequately highlighted, and whether the emphasis was placed on the most informative, policy-relevant literature.
- Identify any key studies missing (including those published after the literature search dates for the draft materials), especially any associated with the effects of oxides of nitrogen from ambient air. Provide complete citations for suggested references.
- Indicate any specific issues that should be considered or highlighted that will be important for integrating evidence across disciplines.

Additional discipline-specific changes were determined by EPA scientists, as needed.

During the workshops, peer input reviewers affirmed that EPA included the relevant literature, though some additional studies were identified for consideration. Following the workshop, EPA considered comments and incorporated revisions based on the reviewers' feedback. Suggested studies were screened for relevance as described in the initial literature searches and incorporated if they met the inclusion criteria (see Sections 14.4 and 14.5).

14.7.4 Internal Technical Review

EPA guidelines, such as the Peer Review Handbook (U.S. EPA, 2015a), recommend an internal technical review process before any external dissemination of scientific information. Consistent with this guidance, EPA subject-matter experts reviewed this draft ISA. Following the technical review, EPA revised the document based on consideration of internal reviewer comments.

14.7.5 Clean Air Scientific Advisory Committee Peer Review

Sections 108 and 109 of the Clean Air Act [42 U.S.C. 7408 and 7409] govern the periodic review and establishment of the NAAQS (U.S. EPA, 2023a). Concerning the CASAC, section 109(d)(2) addresses the appointment and advisory functions of an independent scientific review committee. Section 109(d)(2)(A) requires the Administrator to appoint this committee, which is to be composed of "seven members including at least one member of the National Academy of Sciences, one physician, and one person representing State air pollution control agencies." Section 109(d)(2)(B) provides that the independent scientific review committee periodically "shall complete a review of the criteria… and the national primary and secondary ambient air quality standards… and shall recommend to the Administrator any new… standards and revisions of existing criteria and standards as may be appropriate…" Since the early 1980s, the CASAC has performed this independent review function.

The CASAC serves as the official peer review mechanism for this ISA. As a HISA, the Peer Review Bulletin also governs the review process (U.S. OMB, 2004). All requirements in the Peer Review Bulletin regarding the selection of reviewers, information access, opportunity for public participation, transparency, and management of the peer-review process and reviewer selection will be met for the CASAC to review this ISA.

14.8 Quality Assurance and Quality Control

Quality Assurance (QA) helps ensure that EPA conducts high-quality science that can be used to inform policymakers, industry, and the public. Agency-wide, EPA's Quality Program provides the framework for planning, implementing, documenting, and assessing work performed by the Agency, as well as for carrying out required quality assurance and quality control (QA/QC) activities. Additionally, the Quality Program covers the implementation of EPA's Information Quality Guidelines and EPA's Environmental Information Quality Policy and Procedures (U.S. EPA, 2023b, c, 2002). This ISA follows all Agency guidelines to ensure a high-quality document.

Quality Assurance Project Plans (QAPPs) are developed within EPA to ensure that all Agency materials meet a high-quality standard. EPA has developed a Program-Level QAPP (PQAPP) for the ISA Program to describe the technical approach and associated QA/QC procedures related to the ISA Program

(Programmatic Quality Assurance Project Plan (PQAPP) for the ISA Program; L-HEEAD-0030253-QP-1-6). All QA objectives and measurement criteria detailed in the PQAPP will be employed in developing this ISA. QC checks will be conducted on numerical entries throughout the Final ISA[1]. Each discipline team will perform their specific numeric control evaluation, and this is specified in chapters. At a minimum, numerical values from 20% of citations (i.e., every fifth reference) will be verified for accuracy by an independent EPA staff member against the source, and errors will be subsequently corrected. Furthermore, EPA's HERO database has its own QC processes, as documented in HERO's QAPP.

This ISA is classified as QA Category A and a HISA, which requires at least one audit to be completed. During assessment development, the ISA underwent one Technical System audit in July 2024 by an independent contractor, Neptune and Company, Inc. The auditor identified no significant findings and verified that QC procedures were adequately performed and documented by QA procedures.

14.9 Conclusion

This chapter describes the overall process of developing this Oxides of Nitrogen ISA, including literature search and screening methods, study quality evaluation, peer input and peer review, documentation, and QA. Overall, EPA has robust policies and procedures to ensure the highest quality products. In developing this ISA, EPA followed all the appropriate processes and endeavored to add additional steps as practicable and needed (e.g., use of SWIFT-AS, scoping statements, and documentation of individual study quality).

[1]For the External Release Draft ISA, QC checks were conducted on numerical entries (i.e. tables, figures) in Chapter 2 through Chapter 4. For the final release of the ISA, all chapters will have gone through QC checks. All chapters have gone through the HERO QC checks for the External Release Draft ISA.

14.10 References

Cohen, AM; Hersh, WR; Peterson, K; Yen, PY. (2006). Reducing workload in systematic review preparation using automated citation classification. J Am Med Inform Assoc 13: 206-219. http://dx.doi.org/10.1197/jamia.M1929

Howard, BE; Phillips, J; Miller, K; Tandon, A; Mav, D; Shah, MR; Holmgren, S; Pelch, KE; Walker, V; Rooney, AA; Macleod, M; Shah, RR; Thayer, K. (2016). SWIFT-Review: A text-mining workbench for systematic review. Syst Rev 5: 87. http://dx.doi.org/10.1186/s13643-016-0263-z

Howard, BE; Phillips, J; Tandon, A; Maharana, A; Elmore, R; Mav, D; Sedykh, A; Thayer, K; Merrick, BA; Walker, V; Rooney, A; Shah, RR. (2020). SWIFT-Active Screener: Accelerated document screening through active learning and integrated recall estimation. Environ Int 138: 105623. http://dx.doi.org/10.1016/j.envint.2020.105623

NASEM (National Academies of Sciences, Engineering, and Medicine). (2018). Progress toward transforming the Integrated Risk Information System (IRIS) program: A 2018 evaluation. Washington, DC: National Academies Press. http://dx.doi.org/10.17226/25086

NASEM (National Academies of Sciences, Engineering, and Medicine). (2022). Advancing the framework for assessing causality of health and welfare effects to inform National Ambient Air Quality Standards reviews. In Advancing the Framework for Assessing Causality of Health and Welfare Effects to Inform National Ambient Air Quality Standard Reviews. Washington, DC: National Academies Press. http://dx.doi.org/10.17226/26612

U.S. EPA (U.S. Environmental Protection Agency). (1993). Air quality criteria for oxides of nitrogen (final, 1993) [EPA Report]. (EPA/600/8-91/049aF-cF). Washington, DC: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=40179

U.S. EPA (U.S. Environmental Protection Agency). (2002). Guidelines for ensuring and maximizing the quality, objectivity, utility, and integrity of information disseminated by the Environmental Protection Agency [EPA Report]. (EPA/260R-02-008). Washington, DC: U.S. Environmental Protection Agency, Office of Environmental Information. https://www.epa.gov/sites/production/files/2017-03/documents/epa-info-quality-guidelines.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2008). Integrated science assessment for oxides of nitrogen – Health criteria (Final report, 2008) [EPA Report]. (EPA/600/R-08/071). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP Division. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=194645

U.S. EPA (U.S. Environmental Protection Agency). (2015a). Peer review handbook [EPA Report] (4th ed.). (EPA/100/B-15/001). Washington, DC: U.S. Environmental Protection Agency, Science Policy Council. https://www.epa.gov/osa/peer-review-handbook-4th-edition-2015

U.S. EPA (U.S. Environmental Protection Agency). (2015b). Preamble to the Integrated Science Assessments [EPA Report]. (EPA/600/R-15/067). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, RTP Division. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244

U.S. EPA (U.S. Environmental Protection Agency). (2016). Integrated science assessment for oxides of nitrogen: Health criteria (Final report, Jan 2016) [EPA Report]. (EPA/600/R-15/068). Washington, DC. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310879

U.S. EPA (U.S. Environmental Protection Agency). (2022). Integrated review plan for the National Ambient Air Quality Standards for lead. Volume 2: Planning for the review and the Integrated Science Assessment [EPA Report]. (EPA-452/R-22-003b). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards and Office of Research and Development. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P10148PX.txt

U.S. EPA. Definitions, CAA § 302; 42 USC § 7409 (2023a). https://www.govinfo.gov/app/details/USCODE-2023-title42/USCODE-2023-title42-chap85-subchapI-partA-sec7409

U.S. EPA (U.S. Environmental Protection Agency). (2023b). Environmental Information Quality Policy, Directive No: CIO 2105.3. Washington, DC. https://www.epa.gov/system/files/documents/2023-04/environmental_information_quality_policy.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2023c). Environmental Information Quality Procedure, Directive No: CIO 2105-P-01.3. Washington, DC. https://www.epa.gov/system/files/documents/2023-04/environmental_information_quality_procedure.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2023d). Overview of nitrogen dioxide (NO2) air quality in the United States, Updated: June 29, 2023. Washington, DC. https://www.epa.gov/system/files/documents/2023-06/NO2_2022.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2024). Integrated Review Plan for the Primary National Ambient Air Quality Standards for Oxides of Nitrogen. Volume 2: Planning for the Review and the Integrated Science Assessment [EPA Report]. (EPA-452/R-24-010b). Washington, DC.

U.S. OMB (U.S. Office of Management and Budget). (2004). Issuance of OMB's "Final Information Quality Bulletin for Peer Review" [Memorandum]. (M-05-03). Washington, DC: U.S. Office of Management and Budget, Executive Office of the President. https://www.whitehouse.gov/wp-content/uploads/legacy_drupal_files/omb/memoranda/2005/m05-03.pdf