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-452/R-24-010b
March 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

U.S. Environmental Protection Agency

Office of Air Quality Planning and Standards
Health and Environmental Impacts Division
and
Center for Public Health and Environmental Assessment
Office of Research and Development

Research Triangle Park, NC

DISCLAIMER

This document serves as a public information document and as a management tool for the U.S. Environmental Protection Agency's (EPA's) Center for Public Health and Environmental Assessment and the Office of Air Quality Planning and Standards in conducting the review of the health-based air quality criteria and the primary national ambient air quality standards for oxides of nitrogen. This document is being circulated to facilitate discussion with the Clean Air Scientific Advisory Committee and for public comment to inform the EPA's current review of the health-based air quality criteria and the primary national ambient air quality standards for oxides of nitrogen. It does not represent and should not be construed to represent an Agency determination or policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

TABLE OF CONTENTS

PREFACE

The planning phase of the U.S. Environmental Protection Agency's (EPA's) reviews of the air quality criteria and the national ambient air quality standards (NAAQS) includes development of an integrated review plan (IRP), which is made available for public comment and provided to the Clean Air Scientific Advisory Committee (CASAC) for consultation. As a result of recent efforts to improve the efficiency of the planning phase and to facilitate the receipt of timely input from the CASAC and the public, the IRP for the current review of the primary NAAQS for oxides of nitrogen is comprised of three volumes. Volume 1 provides background information on the health-based air quality criteria and the primary NAAQS for oxides of nitrogen and may serve as a reference for the public and the CASAC in their consideration of the subsequent two volumes. Volume 2 (this document) addresses the general approach for the review and planning for the integrated science assessment (ISA) and will be the subject of a consultation with the CASAC. This volume identifies policy-relevant issues in the review and describes key considerations in the EPA's development of the ISA. Volume 3 is the planning document for quantitative analyses to be considered in the policy assessment (PA), including exposure and risk analyses as warranted. It will describe key considerations in the EPA's planning with regard to any quantitative exposure/risk analyses to inform the review. To ensure that the availability of new evidence is taken into account when developing the current review, the development and public release of Volume 3 will generally coincide with the availability of the draft ISA and it will be the subject of a consultation with the CASAC at that time.

1 INTRODUCTION

The U.S. Environmental Protection Agency (EPA) is conducting a review of the health-based air quality criteria and the primary (health-based) national ambient air quality standards (NAAQS) for oxides of nitrogen. Ambient concentrations of oxides of nitrogen are influenced by both direct nitrogen dioxide (NO_2) emissions and by emissions of nitric oxides (NO), with the subsequent conversation of NO to NO_2 primarily through reaction with ozone (O_3). A large number of oxidized nitrogen species in the atmosphere are formed from the oxidation of NO and NO_2. These include nitrate radicals (NO_3), nitrous acid (HONO), nitric acid (HNO_3), dinitrogen pentoxide (N_2O_5), nitryl chloride ($ClNO_2$), peroxynitric acid (HNO_4), peroxyacetyl nitrate and its homologues (PANs), other organic nitrates, such as alkyl nitrates (including isoprene nitrates), and particulate nitrate (pNO_3). The sum of these reactive oxidation products and NO plus NO_2 comprise the oxides of nitrogen.[1, 2] Consistent with the reviews completed in 2010 and 2018, this review focuses on health effects associated with gaseous oxides of nitrogen[3] and the protection afforded by the primary NO_2 standards. The gaseous oxides of nitrogen include NO_2 and NO, as well as their gaseous reaction products. Total oxides of nitrogen include these gaseous species as well as particulate species (e.g., nitrates). Health effects and non-ecological welfare effects associated with the particulate species are addressed in the review of the NAAQS for particulate matter (PM).[4] The EPA is separately reviewing the ecological welfare effects associated with and the secondary standards for oxides of nitrogen, oxides of sulfur, and PM.[5]

This Volume (2) of the integrated review plan (IRP) contains the current plans for the general approach for the review, as well as key planning considerations for the development of the integrated science assessment (ISA). The NAAQS review process provides an integrative assessment of relevant scientific information and will focus on key aspects of the NAAQS,

[1] The focus is on NO_2 in this document, as this is in the indicator for the current standards and is most relevant to the evaluation of health evidence.

[2] Section 108(c) of the Clean Air Act specifies that: "Such criteria [for oxides of nitrogen] shall include a discussion of nitric and nitrous acids, nitrites, nitrates, nitrosamines, and other carcinogenic and potentially carcinogenic derivatives of oxides of nitrogen." By contrast, within air pollution research and control communities, the terms "nitrogen oxides" and NO_X are often restricted to refer to only to the sum of NO and NO_2.

[3] These gaseous oxides of nitrogen can also be referred to as "nitrogen oxides" and include a broad category of gaseous oxides of nitrogen (i.e., oxidized nitrogen compounds), including NO_2, NO, and their various reaction products.

[4] Additional information on the PM NAAQS is available at: *https://www.epa.gov/naaqs/particulate-matter-pm-air-quality-standards.*

[5] Additional information on the currently ongoing and prior reviews of the secondary NAAQS for oxides of nitrogen, oxides of sulfur, and PM is available at: *https://www.epa.gov/naaqs/nitrogen-dioxide-no2-and-sulfur-dioxide-so2-secondary-air-quality-standards.*

including the basic elements of the standards: the indicator,[6] averaging time, form,[7] and level. These elements, which together serve to define each ambient air quality standard, are considered collectively in evaluating the protection to public health afforded by the standards.

This document is the second of three volumes that will comprise the IRP for the primary NO_2 NAAQS review. Volume 1 includes introductory or background information on the legislative requirements for reviews of the NAAQS, an overview of the review process, background information on prior reviews of the health-based air quality criteria and primary standards for oxides of nitrogen and a summary of key aspects of the basis for the existing primary NO_2 NAAQS, and a summary of the status and anticipated milestones for the current review. Volume 1 also includes an appendix that includes an overview of the key aspects of existing ambient air monitoring requirements for NO_X. Volume 2 (this document) presents the general approach for this review, the policy-relevant questions guiding the review, and the plans for the development of the ISA. Specifically, Chapter 2 of Volume 2 outlines the general approach of the NAAQS review and details a set of policy-relevant questions intended to focus this review on the critical scientific and policy issues. Chapter 3 of Volume 2 presents plans for the ISA, including the document organization, scope, and specific questions for consideration in light of the overarching policy-relevant questions for the review. Together, Volumes 1 and 2 provide the current information regarding this review of the primary NAAQS for oxides of nitrogen. Volume 3 of the IRP, the planning document for quantitative analyses to be considered in the policy assessment (PA), will be developed with consideration of the availability of new evidence as identified in the development of the ISA. Accordingly, the public release of Volume 3 of the IRP will generally coincide with that of the draft ISA and it will be the subject of a consultation with the CASAC at that time.

[6] The "indicator" of a standard defines the chemical species or mixture that is to be measured in determining whether an area attains the standard. For example, the indicator of the current NAAQS for photochemical oxidants is ozone (O_3).

[7] The "form" of a standard defines the air quality statistic that is to be compared to the level of the standard in determining whether an area attains the standard. For example, the form of the annual $PM_{2.5}$ NAAQS is the 3-year average of the weighted annual mean $PM_{2.5}$ concentrations, while the form of the current 3-month Pb NAAQS is a 3-month average concentration not to be exceeded during a 3-year period.

2 POLICY-RELEVANT ISSUES IN THE CURRENT REVIEW

The approach to considering the information available in this review of the health-based air quality criteria and the current primary NO_2 standards is framed by a series of questions, the answers to which are intended to inform the Administrator's judgment as to whether the current standards provide requisite protection of public health, and his decisions as to whether to retain or revise these standards. The ISA and PA developed in this new review of the primary NO_2 NAAQS will provide the basis for addressing these questions. These assessments focus on policy-relevant scientific information and analyses intended to address key questions related to the adequacy of these standards.

The overarching question in each NAAQS review is:

- **Do the currently available scientific evidence and exposure/risk-based information support or call into question the adequacy of the protection afforded by the current standard(s)?**

As appropriate, a NAAQS review also addresses a second overarching question:

- **What alternative standards, if any, are supported by the currently available scientific evidence and exposure/risk-based information and are appropriate for consideration?**

In considering these overarching questions in the PA, a series of key policy-relevant issues particular to a given review are addressed. The policy-relevant issues thus far identified for this review of the primary NO_2 standards are presented in section 2.1 as a series of questions.

2.1 REVIEW OF THE PRIMARY NO_2 STANDARDS

The approach planned for this review of the primary standards is fundamentally based on using the Agency's assessment of the current scientific evidence, quantitative assessments of exposures and/or risks, and other associated analyses (e.g., air quality analyses) to inform the Administrator's judgments regarding primary standards that are requisite to protect public health with an adequate margin of safety. This approach involves translating scientific and technical information into the basis for addressing a series of key policy-relevant questions using both evidence- and exposure-/risk-based considerations. This series of key questions related to the primary standards is presented below, in the context of the general approach for the review.

The planned approach for this review of the primary NO_2 standards will build on the substantial body of work developed during the course of the prior reviews and the associated conclusions, taking into account the more recent scientific information and air quality data now

available to inform our understanding of the key policy-relevant issues in this review. Key aspects of the basis for the decision establishing the primary annual NO_2 standard in 1971 and the primary 1-hour NO_2 standard in 2010, and retaining them without revision in 2018 are summarized in Volume 1. The ISA, risk and exposure analyses (as warranted), and PA developed in this review will provide the basis for addressing the key policy-relevant questions in the review, and these assessments and analyses will help inform the Administrator's decisions as to whether to retain or revise the primary NO_2 standards.

The final decision on the primary standards is largely a public health policy judgment by the Administrator.[8] Final decisions must draw upon scientific information and analyses about health effects and risks, as well as judgments about how to deal with the range of uncertainties that are inherent in the scientific evidence and analyses. The approach of the PA to informing these judgments is based on a recognition that the available health effects evidence generally reflects continuums that include ambient air exposures for which scientists generally agree health effects are likely to occur through lower levels at which the likelihood and magnitude of response become increasingly uncertain. This approach is consistent with the requirements of the NAAQS provisions of the Clean Air Act (CAA) and with how the EPA and the courts have historically interpreted the Act. These provisions require the Administrator to establish standards that are requisite to protect public health with an adequate margin of safety. In so doing, the Administrator seeks to establish standards that are neither more nor less stringent than necessary for this purpose. The provisions do not require that standard be set at a zero-risk level, but rather at a level that avoids unacceptable risks to public health, including the health of sensitive groups.[9]

Evaluations in the PA are intended to inform the Administrator's public health policy judgments and decisions. In so doing, the PA considers the potential implications of various aspects of the scientific evidence, the exposure/risk-based information, and the associated uncertainties and limitations. The Agency's consideration of the full set of evidence and information available in this review will inform the answer to the following initial overarching question for the review:

[8] Key aspects of the decisions made in the last review, including the Agency's consideration of important policy judgments concerning the scientific and exposure/risk information and associated uncertainties and limitations, as well as the Administrator's public health policy judgments regarding an adequate margin of safety are summarized in section 3 of Volume 1 of this IRP.

[9] More than one population group may be identified as sensitive or at risk in a NAAQS review. The decision in the review of the primary standards will reflect consideration of the degree to which protection is provided for these sensitive population groups. To the extent that any particular population group is not among the identified sensitive groups, a decision that provides protection for the sensitive groups would be expected to also provide protection for other population groups.

- **Do the currently available scientific evidence and exposure-/risk-based information support or call into question the adequacy of the public health protection afforded by the current primary NO_2 standards?**

In reflecting on this question, we[10] will consider the available body of scientific evidence, assessed in the ISA and used as a basis for developing and/or interpreting the risk/exposure analyses, including whether it supports or calls into question the scientific conclusions reached in the last review regarding health effects related to exposure to oxides of nitrogen in ambient air. Information available in this review that may be informative to public health judgments regarding significance or adversity of key effects will also be considered. Additionally, the currently available exposure and risk information, whether newly developed in this review or predominantly developed in the past and interpreted in light of current information, will be considered, including the extent to which it may continue to support judgments made in the last review. Further, in considering this question with regard to the primary NO_2 standards, as in all NAAQS reviews, we give particular attention to exposures and health risks to at-risk populations.[11] As in past reviews of the primary NO_2 NAAQS, this will likely include a focus on people with pre-existing respiratory disease, children, and older adults.

Evaluation of the available scientific evidence and risk/exposure information with regard to this consideration of the current primary standards will focus on key policy-relevant issues by addressing a series of questions such as the following:

- To what extent has new information strengthened or otherwise altered the scientific support for the occurrence of adverse health effects as a result of short- and/or long-term exposure to gaseous oxides of nitrogen in ambient air?
  - What evidence is available from recent studies to inform our understanding of the nature of exposures to oxides of nitrogen that are linked to various health outcomes?

[10] The PA, like the OAQPS Staff Paper in earlier reviews, is a document that provides a transparent OAQPS staff analysis and conclusions regarding the adequacy of the current standards and potential alternatives that are appropriate to consider before the issuance of proposed and final decisions. This evaluation of policy implications is intended to help ''bridge the gap'' between (1) the Agency's scientific and technical assessments (as presented in the ISA and the quantitative exposure and risk analyses) and (2) the judgments required of the EPA Administrator in determining whether it is appropriate to retain or revise the NAAQS. In this way, the PA integrates and interprets the information from the ISA and quantitative exposure and risk analyses to frame policy options for consideration by the Administrator. Consistent with this context for the PA, the term "we" throughout this chapter refers to staff in the EPA's Office of Air Quality Planning and Standards (OAQPS).

[11] As used here and similarly throughout this document, the term population (in the context of health and the primary standards) refers to persons having a quality or characteristic in common, such as a specific pre-existing illness or a specific age or lifestage. Identifying at-risk populations involves consideration of *susceptibility* and *vulnerability*. *Susceptibility* refers to innate (e.g., genetic or developmental aspects) or acquired (e.g., disease or smoking status) sensitivity that increases the risk of health effects occurring with exposure to oxides of nitrogen. *Vulnerability* refers to an increased risk of oxides of nitrogen-related health effects due to factors such as those related to socioeconomic status, reduced access to health care or exposure.

- What does the available evidence, including that recently available, indicate about health effects associated with specific oxides of nitrogen (e.g., NO_2, NO)?
- To what extent is key scientific evidence available to improve or alter our understanding of the health effects associated with various time periods of exposures, including short-term (e.g., 1-hour) and long-term exposures (e.g., more than one month to years) to oxides of nitrogen?
    - At what pollutant concentrations do these health effects occur?
    - To what extent is new information available to improve our understanding of the range of ambient air concentrations within which oxides of nitrogen contribute to health effects?
    - Is there evidence of effects at oxides of nitrogen exposure concentrations lower than those at which effects were previously observed or in areas that would likely have met the current primary NO_2 standards?
    - To what extent are health effects found to be associated with oxides of nitrogen in epidemiologic studies being elicited by oxides of nitrogen exposure versus exposure to one or more co-occurring pollutants (e.g., $PM_{2.5}$, CO, O_3, SO_2, other traffic-related pollutants)?
    - To what extent is new information available to improve the characterization of the severity and/or potential adversity of NO_2-induced respiratory effects reported in controlled human exposure studies? To what extent does such information inform an understanding of effects in at-risk populations?
- Has new information altered our understanding of human lifestages and populations that are particularly at increased risk for experiencing health effects associated with exposure to oxides of nitrogen?
    - What new information is available to inform our understanding of potential health effects in at-risk populations and lifestages living, working, playing, or going to school near ambient air sources of oxides of nitrogen (e.g., near roads)?
    - To what extent is new information available regarding co-occuring risk factors that may be related to increased risk for experiencing health effects associated with exposure to oxides of nitrogen (e.g., children with asthma)?
    - Is there new information on the nature of the exposure-response relationship in different at-risk lifestages and/or populations?

- To what extent is new information available to improve our understanding of the NO_2 concentration gradients around important sources, such as major roads and combustion sources, and how those gradients relate to ambient air monitoring concentrations across larger areas?
- To what extent does risk or exposure information suggest that exposures of concern are likely to occur with recent ambient air NO_2 concentrations in the U.S. or with concentrations that just meet the current primary NO_2 standards?

  - Are the estimated exposures/risks considered in this review of sufficient magnitude such that the health effects might reasonably be judged to be important from a public health perspective?
  - What new information is available to improve our understanding of exposure measurement error and the role of exposure in epidemiologic inference, particularly for interpreting long-term exposure studies?
  - What are the important uncertainties associated with any exposure/risk estimates?
- To what extent have important uncertainties identified in the last review been reduced and/or have new uncertainties emerged?
- To what extent does the newly available information reinforce or call into question any of the basic elements (i.e., indicator, form, averaging time, and level) of the current primary NO_2 standards?

If the information in the current review suggests that revision of the current primary standards would be appropriate to consider, the PA will evaluate how the standards might be revised based on the available scientific information, air quality assessments, and exposure/risk information and will consider what the available information indicates as to the health protection expected to be afforded by the current or potential alternative standards. Such an evaluation may consider the effect of revision of one or more elements of a standard (indicator, averaging time, form, and level), with the effect being evaluated based on the resulting potential standard and all of its elements collectively. Based on such evaluations, the PA would then identify potential alternative standards (specified in terms of indicator, averaging time, form, and level) intended to reflect a range of alternative policy judgments as to the degree of protection that is requisite to protect public health with an adequate margin of safety, as well as options for standards expected to achieve it. Evaluation of what revision(s) of the standard(s) might be appropriate to consider would be framed by specific policy-relevant questions such as the following:

- Does the currently available information call into question the use of NO_2 as the indicator for the primary standards for oxides of nitrogen? Is support provided for considering a different indicator?
- Does the currently available information call into question the current averaging times? Is support provided for considering different averaging times for the standards?
- What does the currently available information indicate with regard to the range of levels and forms of alternative standards that may be supported, and what are the uncertainties and limitations in that information?
- What do the available analyses indicate with regard to exposures and risks associated with specific alternative standards? What are the associated important uncertainties? To what extent might such alternatives be expected to reduce adverse impacts attributable to oxides of nitrogen in ambient air, and what are the associated uncertainties in the estimated reductions?

The approach to reaching conclusions on the current primary standards and, as appropriate, on potential alternative standards is summarized in general terms in Figure 2-1.

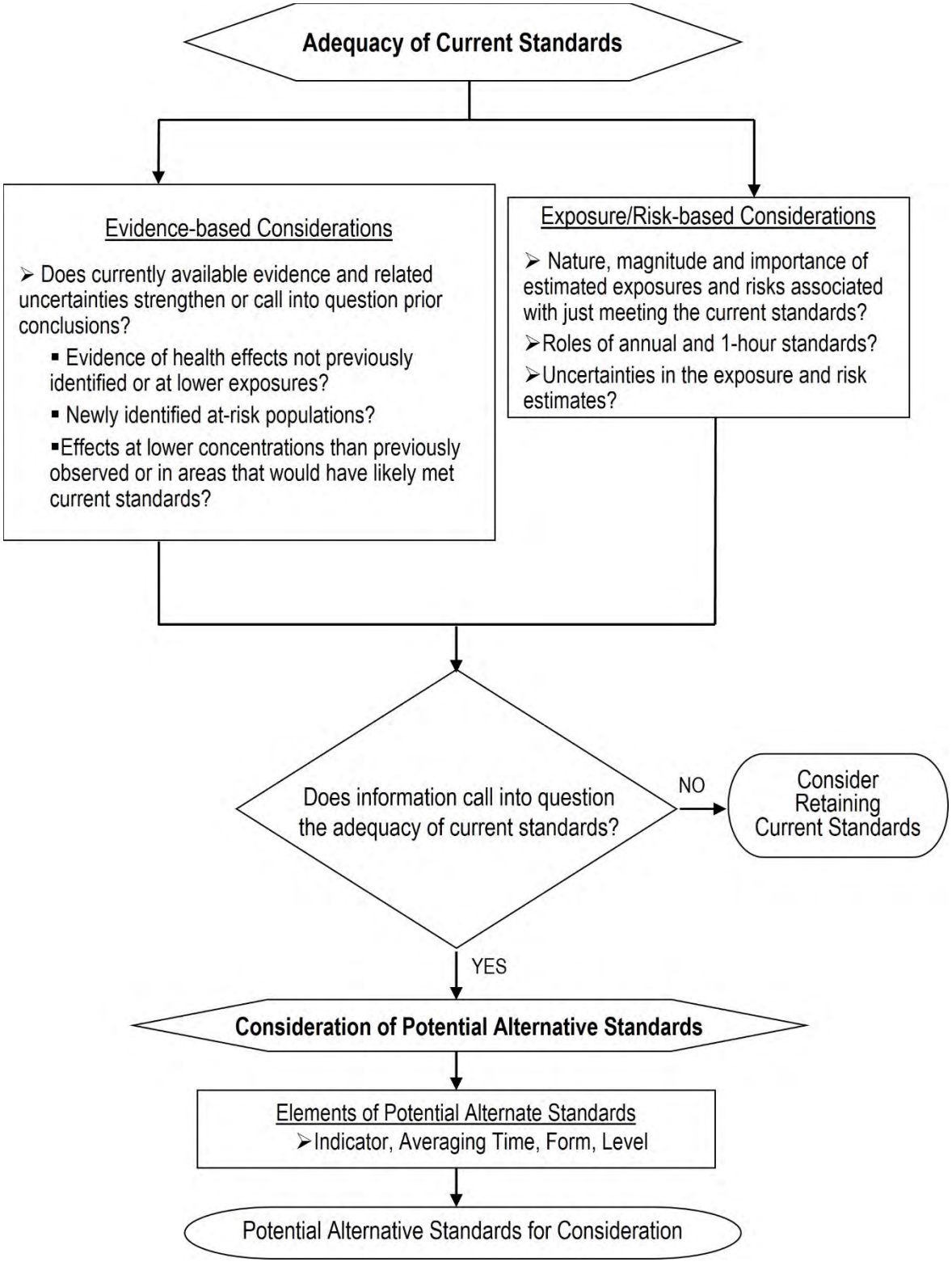


Figure 2-1. Overview of general approach for review of the primary NO_2 standards.

3 DEVELOPMENT OF THE INTEGRATED SCIENCE ASSESSMENT

The ISAs are intended to summarize and assess the scientific evidence related to public health or welfare effects of air pollutant exposures, consistent with the air quality criteria defined in Section 108 of the CAA and with the EPA's obligation to periodically review, and revise as appropriate, those air quality criteria under section 109. The content of the ISA, in conjunction with additional technical and policy assessments and advice from the CASAC and input from the public, provides the scientific basis for the EPA's decisions on the NAAQS. This section provides information relevant to the development of the ISA for Oxides of Nitrogen – Health Criteria as part of the current review of the primary NO_2 NAAQS. Sections 3.1 and 3.2 provide overviews of the anticipated organization and scope of the ISA, respectively. Section 3.3 summarizes the planned approach to developing the ISA, including preliminary results of the literature search and screening effort. Section 3.4 presents scientific questions to guide the development of the ISA in the current review.

3.1 ORGANIZATION OF THE ISA IN THE CURRENT REVIEW

The organization of the ISA for Oxides of Nitrogen - Health Criteria will be consistent with that used in the recent assessments for other criteria pollutants (e.g., U.S EPA, 2020a; U.S EPA, 2020b). It will be organized around a series of detailed, topic-specific chapters[12] and an Integrated Synthesis drawn from the information in those chapters. Chapters will provide thorough assessments of the scientific evidence pertaining to specific topic areas including atmospheric science, exposure and dosimetry, and various human health outcomes. Each chapter will contain an evaluation of results from recent studies integrated with evidence from previous assessments. Chapters for each health outcome category (e.g., respiratory effects) will include detailed conclusions reflecting the overall strength of the evidence supporting cause-effect relationships between pollutant exposures and particular health effects. These "causality determinations" will be based on consideration of various aspects of the evidence, including consistency within a scientific discipline, coherence across disciplines, biological plausibility, and other factors as discussed in section 3.3.4 and Appendix A. Causality determinations will additionally consider the populations in which health effects have been demonstrated to occur and the evidence that certain populations are at increased risk of pollutant-related effects because

[12] Recent ISAs used the term "appendices" to denote individual sections of the assessment. In this ISA for Oxides of Nitrogen, and future ISAs, the term "chapter(s)" will be used to make a clear distinction between the main body of the document and any attachments to the ISA containing supporting information.

they are more sensitive to pollutant exposures and/or because they experience higher exposures. Chapters will additionally present targeted evaluations of the evidence on other scientific issues that may be particularly relevant for subsequent policy considerations. These other issues may include the concentration-, exposure-, or dose-response relationships for particular health effects; the strengths and limitations of various exposure estimation approaches and study designs; the appropriate time lags between exposure and effect or the appropriate exposure periods for particular effects; and the public health significance of effects associated with exposures to NO_2 and other oxides of nitrogen.

Drawing from supporting chapters, the Integrated Synthesis will provide a concise synopsis of ISA conclusions and a synthesis of key findings considered in characterizing pollutant exposures and relationships with health effects. The Integrated Synthesis will include summaries of information for each topic area, including information on pollutant-related sources, emissions, and atmospheric science; exposures and biokinetics; and health effects. For the health effects evidence, the Integrated Synthesis will summarize ISA causality determinations, conclusions on the populations and/or lifestages that may be at increased risk of pollutant-related effects, and other chapter conclusions on policy-relevant scientific issues.

In addition to the topic-specific chapters and the Integrated Synthesis, the ISA for Oxides of Nitrogen – Health Criteria will include a Preface that summarizes major legal and historical aspects of prior NAAQS reviews, an Executive Summary written to be accessible to a wide range of audiences, and a Process Chapter. The Process Chapter will describe the approach taken to develop the ISA, including the methods for literature search and review, documentation, evaluation of individual study quality, public engagement, and quality assurance. The Process Chapter will draw from the general approach described in Appendix A of this IRP and from comments on Appendix A from members of the CASAC Oxides of Nitrogen Health Panel. The approach described in Appendix A builds on the 2015 Preamble to the ISAs (U.S. EPA, 2015), with updates reflecting advances implemented in recent ISAs (U.S EPA, 2020a; U.S EPA, 2020b) and the EPA's consideration of recommendations on the ISA causality framework from an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (NASEM) (NASEM, 2022). The Process Chapter will also provide a general description of the CASAC review process and information on any supplementary materials, such as information accessible through the Health and Environmental Research Online (HERO) database for the ISA, with updates reflecting advances implemented in recent ISAs (U.S EPA, 2020a; U.S EPA, 2020b) and the EPA's consideration of recommendations on the ISA causality framework from an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (NASEM) (NASEM, 2022). The Process Chapter will also provide a general description of the CASAC review process and information on any supplementary materials, such as information

accessible through the Health and Environmental Research Online (HERO) database for the ISA.[13]

3.2 SCOPE OF THE ISA IN THE CURRENT REVIEW

The primary NO_2 NAAQS are intended to protect public health from exposures to NO_2 and other gaseous oxides of nitrogen (see section 3.2.2 for a description of oxide of nitrogen compounds).[14] Thus, the ISA developed in this review will evaluate the atmospheric science, human exposure and dosimetry, and human health effects evidence for the gaseous oxides of nitrogen. The evidence for human health effects associated with organic and inorganic nitrates was evaluated in the Integrated Science Assessment for Particulate Matter (U.S. EPA, 2019a), and considered in the reconsideration of the particulate matter NAAQS (89 FR 16202, March 6, 2024). The evidence for ecological effects of oxides of nitrogen was reviewed in conjunction with the evidence for ecological effects of sulfur oxides and particulate matter in the ISA for Oxides of Nitrogen, Oxides of Sulfur, and Particulate Matter – Ecological Effects (U.S EPA, 2020a).

The ISA for Oxides of Nitrogen – Health Criteria will evaluate relevant studies that have become available since the cutoff-date for the 2016 ISA (i.e., March 2014) in the context of studies evaluated in previous assessments (i.e., U.S. EPA, 2016; U.S. EPA, 2008; U.S. EPA, 1993; U.S EPA, 1982). For topic areas in which research efforts have subsided and older studies remain the definitive works available in the literature, those older studies from previous assessments will be the primary focus of the ISA's evaluation. The sections below define the scoping criteria used to screen the available scientific literature and evaluate studies for their potential to inform the evidence assessment in the ISA. To meet ISA scoping criteria, studies must present new information or analyses and must have undergone scientific peer review. Review articles that are limited to summarizing and interpreting existing studies, without presenting new information or analyses, are outside the scope of the ISA. The following sections present additional discipline-specific literature scoping criteria for studies of human health effects (3.2.1), atmospheric science (3.2.2), and exposure and dosimetry (3.2.3).

[13] HERO is a database of scientific studies and other references used to develop EPA assessments and is available at is available at: *https://heronet.epa.gov*.

[14] Section 108(c) of the CAA indicates that the air quality criteria relating to NO_2 include consideration of "nitric and nitrous acids, nitrites, nitrates, nitrosamines, and other carcinogenic and potentially carcinogenic derivatives of oxides of nitrogen."

3.2.1 Health Effects

The ISA will use discipline-specific population, exposure, comparison, outcome, study design (PECOS) statements to define the set of relevant health effects studies (see Table 3-1 through Table 3-3 and Appendix A). The PECOS statements help to identify the objectives of the assessment and establish criteria that should be met to consider a study for inclusion in the ISA, thereby facilitating identification of the potentially relevant literature and informing the integration and synthesis of study results. The PECOS statements are informed by the body of evidence from previous ISAs and air quality criteria documents (AQCDs),[15] expert knowledge of the relevant scientific literature, and by recent ambient air quality information (i.e., as described for exposure criteria in Tables 3-1 and 3-3). Studies meeting all five aspects of the PECOS statement will be considered for inclusion in the ISA.

The health chapters of the ISA will evaluate the scientific literature related to a range of health outcomes associated with exposures to oxides of nitrogen including, but not limited to, respiratory effects, cardiovascular effects, reproductive and developmental effects, cancer, and mortality. Building upon the 2016 ISA, the EPA will review the available epidemiologic, controlled human exposure, and animal toxicological evidence related to these and other health outcome categories to the extent data are available. The results of recent studies will be integrated with the findings from the 2016 ISA along with any new interpretations of previous findings that the recent studies may support. The ISA will also integrate previous information on the populations and lifestages at increased risk with new evidence for existing and any newly identified risk factors.

[15] The last AQCD was published by the EPA in 2006. Moving forward the science assessments supporting the NAAQS review were renamed the Integrated Science Assessments.

Table 3-1. PECOS statement to define the criteria and framework for identifying relevant oxides of nitrogen epidemiologic studies.

Exposure Duration	Population, Exposure, Comparison, Outcome, Study Design (PECOS)
Short-term exposure	Population (P): Any human population, including populations or lifestages that might be at increased risk;
	Exposure (E): Short-term exposure (i.e., up to 30 days) to oxides of nitrogen concentrations relevant to ambient air in the U.S.;[16]
	Comparison (C): Per unit increase (i.e., 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 (O): Change or difference in risk (incidence/prevalence) of health effects (e.g., respiratory, cardiovascular, metabolic syndrome and diabetes, total mortality, reproductive and developmental);
	Study Design (S): 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.
Long-term exposure	Population (P): Any human population, including populations or lifestages that might be at increased risk;
	Exposure (E): Long-term exposure (i.e., longer than 30 days) to oxides of nitrogen concentrations relevant to ambient air in the U.S.;[16]
	Comparison (C): Per unit increase (i.e., 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 (O): Change or difference in risk (incidence/prevalence) of health effects (e.g., respiratory, cardiovascular, metabolic syndrome and diabetes, total mortality, reproductive and developmental, cancer);
	Study Design (S): 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 endpoint of interest.

[16] The ISA for Oxides of Nitrogen – Health Criteria will focus 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 U.S. during the most recent 15 years of available data (i.e., 2008-2022) (U.S EPA, 2023b). Consistent with the PECOS exposure criteria for animal toxicology studies (Table 3-3), 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 under-represented locations, etc.).

Table 3-2. PECOS statement to define the criteria and framework for identifying relevant oxides of nitrogen controlled human exposure studies.

Exposure Duration	Population, Exposure, Comparison, Outcome, Study Design (PECOS)
Single or repeated short-term exposures	Population (P): 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 (E): 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 (C): 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 (O): 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 (S): 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).

Table 3-3. PECOS statement to define the criteria and framework for identifying relevant oxides of nitrogen animal toxicological studies.

Exposure Duration	Population, Exposure, Comparison, Outcome, Study Design (PECOS)
Short-term exposure	Population (P): 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 (E): Short-term (i.e., up to 30 days) inhalation exposure to relevant oxides of nitrogen concentrations (i.e., 5 ppm or below);[17]
	Comparison (C): An appropriate control group exposed to clean air (e.g., room air, filtered air) control;
	Outcome (O): 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 (S): Controlled exposure studies of animals *in vivo* meeting the above criteria.
Long-term exposure	Population (P): 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 (E): Long-term (i.e., longer than 30 days) inhalation exposure to relevant oxides of nitrogen concentrations (i.e., 5 ppm or below);[17]
	Comparison (C): An appropriate control group exposed to clean air (e.g., room air, filtered air) control;
	Outcome (O): 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 (S): Controlled exposure studies of animals *in vivo* meeting the above criteria.

3.2.2 Atmospheric Science

The term "oxides of nitrogen" refers to oxidized nitrogen compounds, including nitric oxide (NO), NO_2, and other oxidized nitrogen-containing compounds formed from NO and NO_2. Nitrogen dioxide can also react with a variety of atmospheric species to produce organic and inorganic nitrates, which contribute to atmospheric particulate matter (U.S. EPA, 2016; U.S.

[17] Five ppm is approximately two orders of magnitude higher than peak NO_2 concentrations in the ambient air in the U.S. As discussed in Appendix A (A.5.3.4) and in the 2015 Preamble to the ISAs (U.S. EPA, 2015), 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 ISA for Oxides of Nitrogen – Health Criteria (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.

EPA, 2019a). This review of the primary NO_2 NAAQS focuses on evaluating the health effects associated with exposure to the gaseous oxides of nitrogen. The atmospheric chemistry, exposure, and health effects associated with nitrogen compounds present in particulate matter (PM) were most recently considered in the U.S. EPA's review of the NAAQS for PM (U.S. EPA, 2019a). Based on definitions commonly used in the atmospheric science literature, the abbreviation NO_Y will be used to refer to all oxides of nitrogen and NO_X will be used to refer specifically to the sum of NO_2 and NO concentrations (40 CFR Part 58.1).

The ISA will use discipline-specific scoping statements to identify potentially relevant atmospheric science studies (see Table 3-4 and Appendix A). Importantly, application of scoping statements that consider pollutant sources, transport and transformation, exposure/extent, and measurement and modeling (STEM) is consistent with current best practices for reporting or evaluating health science data as recommended by the NASEM. The STEM statement defines the objectives of the atmospheric science assessment and establishes criteria that should be met to be considered for inclusion in the ISA. A study meeting any of the four aspects of the STEM statement will be considered for inclusion in the ISA. The STEM statement for the ISA shown in Table 3-4 has been informed by the body of evidence from the previous ISAs/AQCDs[18] and by expert knowledge of the relevant scientific literature.

With the focus provided by the STEM statement, the Atmospheric Science chapter will present and evaluate the latest data related to emissions sources of oxides of nitrogen, emissions chemistry and concentration trends, spatial and temporal patterns for oxides of nitrogen in ambient air, and the spatial and temporal trends in oxides of nitrogen emissions and concentrations. The impact of the COVID-19 pandemic on emissions and ambient air NO_Y concentrations will be discussed. In addition, the assessment will include information about near-road NO_2 monitoring in the U.S. and advances in measurement and modeling methods, including new studies of Federal Reference Method and Federal Equivalent Method performance, improvements in more advanced spectroscopic measurements methods, and recent innovations in atmospheric modeling of oxides of nitrogen.

[18] The last AQCD was published by the EPA in 2006. Moving forward the science assessments supporting the NAAQS review were renamed the Integrated Science Assessments.

Table 3-4. 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 as well as observations of physical and chemical characteristics that add to our understanding of sources and emissions of oxides of nitrogen.
Transport and Transformation (T)	Studies investigating atmospheric fate and transport, transformation, and deposition processes involving oxides of nitrogen, including transport of air pollutants at various scales (i.e., national/global, regional, urban, neighborhood), chemical transformations in the atmosphere, and estimates of atmospheric deposition that add to our understanding of atmospheric processes.
Exposure/Extent (E)	Studies reporting observations and estimates of ambient air concentrations and their trends for oxides of nitrogen relevant to U.S. conditions, including spatial variability on various scales (i.e., national/global, 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 equivalency methods, satellite remote sensing estimates, low-cost sensor estimates, or research methods; and 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 intercomparisons that are relevant to the NAAQS or to studies in this ISA.

3.2.3 Exposure Science & Dosimetry

Similar to the Atmospheric Science chapter, the scope of the Exposure Science chapter will be defined by a discipline-specific STEM statement (see Table 3-5 and Appendix A). The ISA will present and evaluate 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). The ISA will consider key uncertainties from the last review and the extent to which new scientific evidence may inform our ability to characterize and/or reduce those uncertainties during the current review. The ISA will also evaluate the literature relating to dosimetry of inhaled oxides of nitrogen.

Table 3-5. 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 U.S, 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.

3.3 PROCESS FOR DEVELOPING THE ISA

Appendix A to this volume of the IRP presents planned updates to the ISA development approach described in the 2015 Preamble to the ISAs (U.S. EPA, 2015). As noted previously, the process described in Appendix A builds on the approach described in the 2015 Preamble to the ISAs, with updates reflecting advances implemented in recent ISAs and the EPA's consideration of recommendations on the ISA causality framework from an ad hoc committee of the NASEM (NASEM, 2022). Comments on the process described in Appendix A provided by members of the CASAC Oxides of Nitrogen Health Panel will be considered in developing the draft ISA for Oxides of Nitrogen – Health Criteria in this review. The sections below provide a high-level overview of the updated ISA development process as it is being applied in the current review and an overview of initial results of the literature search and screening efforts.

The process for developing the ISA for Oxides of Nitrogen – Health Criteria began when the Call for Information was published in the Federal Register (87 FR 75625, December 9, 2022). At that time, the public was invited to contribute to the review by commenting on policy-

relevant issues and by submitting potentially relevant research studies.[19]Public comments have been considered in developing this IRP, and research studies identified by public commenters have been included in initial literature screening efforts. The sections below summarize key steps involved in developing the ISA for Oxides of Nitrogen – Health Criteria in this review, including searching the scientific literature and identifying potentially relevant studies, evaluating individual study quality, integrating evidence, developing causality determinations, quality management, and obtaining the CASAC's advice. Each of these steps is discussed in greater detail in Appendix A of this IRP.

3.3.1 Literature Search

The EPA works to identify potentially relevant new studies for inclusion in the ISA by conducting multipronged systematic searches that include extensive mining of literature databases on specific topics in a variety of disciplines. As noted above, the process for identifying relevant literature began with a Call for Information published in the Federal Register Notice inviting the public to submit relevant scientific research studies and data that have been published or accepted for publication (87 FR 75625, December 9, 2022). As part of the public comments in response to this invitation, 149 peer-reviewed research studies published in scientific journals were submitted for the EPA's consideration. Research studies submitted by the public in response to this Call for Information, along with other studies being considered for the ISA, can be viewed in the project page in EPA's HERO database.[20] The EPA reviewed these studies for relevance following the literature screening process described below.

In addition to studies submitted in response to the Call for Information, the EPA applied systematic review methodologies to identify peer-reviewed scientific studies relevant to this ISA. To maximize identification of pertinent published papers for each discipline, literature search strategies were guided by the discipline-specific scoping statements described above in section 3.2. The literature searching and screening methodology used for this ISA generally followed the process depicted in Figure A-1 of Appendix A. The EPA used a combination of forward citation searches and keyword searches to find relevant literature in PubMed and Web of Science published between March 2014 and June 2023. This date range provides overlap with the literature publication dates for the 2016 ISA, facilitating the identification of studies that may have become available soon after the literature search was conducted in the last review. For the

[19] Public comments were submitted to the docket for the Integrated Science Assessment as a part of the review of the primary NAAQS for NO_X (Docket ID Number: EPA-HQ-ORD-2022-0831). This docket can be accessed at: *https://www.regulations.gov/docket/EPA-HQ-ORD-2022-0831*.

[20] The HERO database for this review is available at: *https://heronet.epa.gov/heronet/index.cfm/project/page/project_id/4767*.

forward citation searches, relevant published studies cited in previous ISAs or AQCDs were identified as a seed set and then more recent literature that cited any of the references in the seed set were identified and considered for inclusion. Keyword searches were developed using strings of relevant search terms and exclusion terms to capture literature relevant to oxides of nitrogen for each discipline (i.e., atmospheric science, exposure science, dosimetry, epidemiology, controlled human exposure, and animal toxicology). For search results focused on human health effects, automatic topic classification was used to separate studies with relevant keywords related to ambient air pollution exposure and health outcomes from studies without such keywords. This process uses machine learning to classify references based on a set of already identified relevant papers. Finally, a small number of references were also identified for consideration in this ISA by EPA expert scientists and by review of citations included in previous assessments or in newly identified literature.

Applying this process, the EPA identified a total of 210,904 unique new studies for title and abstract screening across disciplines (Figure 3-1). To provide a high-level view of the volume and types of studies identified at this stage, the number of new studies identified was further refined by scientific discipline. Studies identified by the literature search are documented in the project page in the HERO database.

3.3.2 Identifying Potentially Relevant Studies

New studies identified during the literature search have been evaluated for potential relevance using a multipronged literature screening approach designed to maximize efficiency and the likelihood that relevant studies are identified. Initially, studies have been evaluated by comparing their titles and abstracts to the discipline-specific scoping criteria defined by PECOS or STEM statements. Reflecting the large number of studies identified, machine ranking tools (e.g., SWIFT-Active Screener (Sciome, RTP, NC, USA) (Howard et al., 2020) and Living Literature Review (U.S. EPA, Durham, NC, USA) (U.S EPA, 2023a) were used to maximize efficiency. Title and abstract screening resulted in exclusion of a total of 203,619 studies deemed out of scope, leaving a total of 7,285 potentially relevant new studies (Figure 3-1).[21]

[21] The number of records excluded at the full text level for scoping and study quality deficiencies will be added to the figure after completion of screening at the full text level. At that time, the number of studies included in the ISA will also be added to the figure. The final figure, including all values, will be included in the Process chapter of the ISA for Oxides of Nitrogen – Health Criteria.

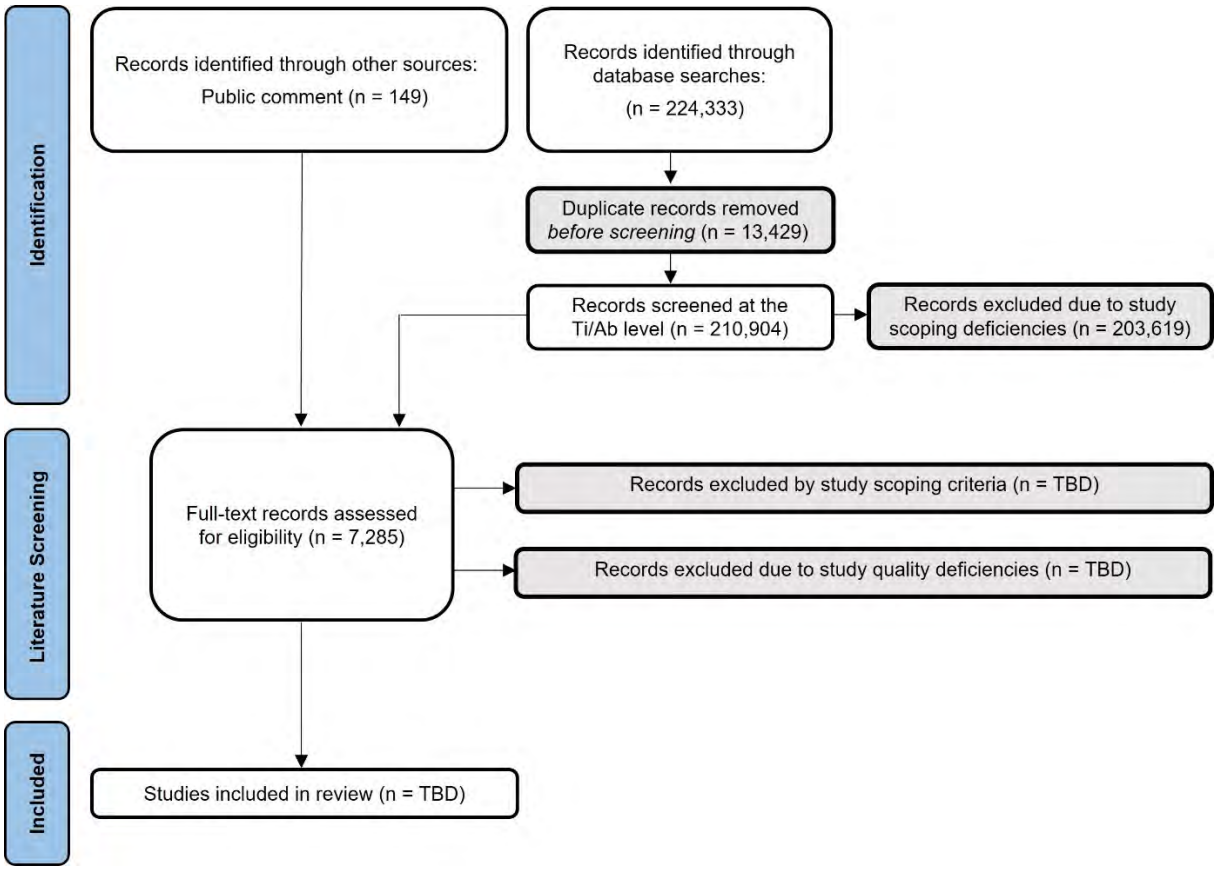


Figure 3-1. Preliminary literature flow diagram for the oxides of nitrogen ISA. Detailed literature screening results and include/exclude decisions can be found in the HERO database. (Available at: *https://heronet.epa.gov/heronet/index.cfm/project/page/project_id/4767*). TBD, to be determined; Ti/Ab, title and abstract.

A preliminary breakdown of the number of new studies currently under consideration for inclusion in the ISA, organized by discipline, is shown in Table 3-6. The specific types of studies being considered for inclusion can be visualized using evidence maps (Figure 3-2 and Figure 3-3).

Table 3-6. Preliminary literature search and screening results by scientific discipline.

Discipline	Number of Studies Identified by Literature Search	Potentially Relevant Studies Identified by Ti/Ab Screening	Number of Studies Considered for Inclusion
Atmospheric Science	90,126	728	TBD
Exposure Science	58,296	2,316	TBD
Epidemiology	48,026	4,078	TBD
Controlled Human Exposure	614	12	TBD
Animal toxicology	13,842	151	TBD
Total number unique studies = 210,904 (duplicates removed)			
Notes: TBD = to be determined; Ti/Ab = title and abstract.			

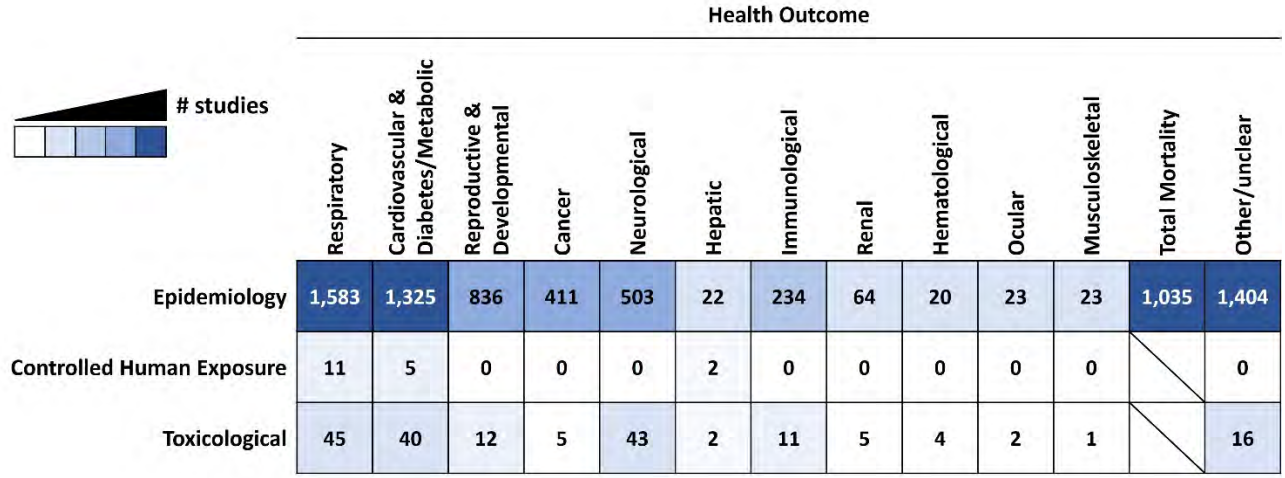


Figure 3-2. Preliminary evidence map depicting potentially relevant epidemiologic, controlled human exposure, and toxicological studies identified during title and abstract literature screening.

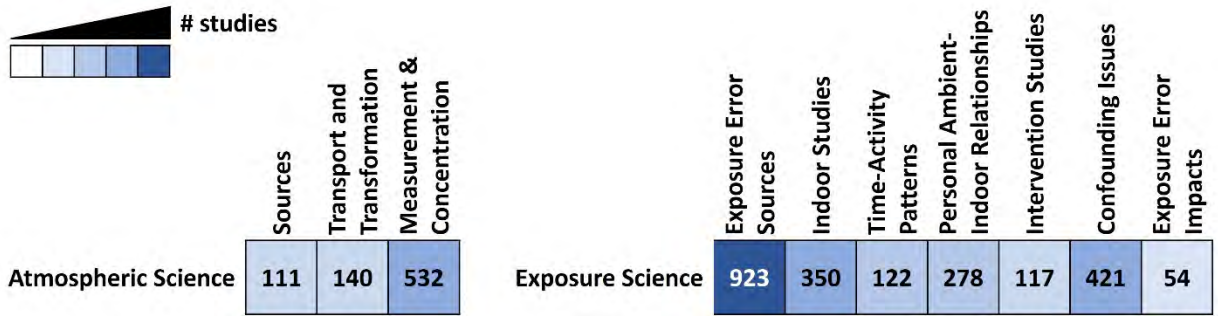


Figure 3-3. Preliminary evidence map depicting potentially relevant atmospheric science and exposure studies identified during title and abstract literature screening.

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, will be further evaluated at the full text level. Studies ultimately deemed out of scope will be eliminated from further consideration. Retained studies will be tagged in HERO as "considered for inclusion" in the ISA. Inclusion and exclusion decisions are documented in the HERO database. Appendix A provides a more detailed description of the process for identifying relevant studies.

3.3.3 Evaluation of Individual Study Quality

New studies that meet the ISA scoping criteria will be further evaluated for individual study quality as described in Appendix A. Individual study quality is evaluated by considering the design, methods, conduct, and documentation of each study, but not the study results. The 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 (Appendix A, Section A.5).

The large number of potentially relevant epidemiologic studies (Table 3-6) led EPA to implement a preliminary study quality evaluation to efficiently identify those epidemiologic studies most likely to inform causality determinations and other ISA conclusions. This preliminary evaluation of study quality is being conducted concurrent with the full-text evaluation of PECOS criteria, with a focus on validated models used to estimate exposures,[22]

[22] Specifically, models used to estimate oxides of nitrogen exposures in epidemiologic studies (e.g., land use regression models or ensemble machine learning models) should be validated for the location(s) and population(s)

appropriate consideration of confounders in studies conducted during COVID-related lockdowns,[23] and strength of study design.[24] Preliminary evaluation of epidemiologic study quality will be followed by the full study quality evaluation, across all disciplines, as described in Appendix A. The full study quality evaluation will be the final step in full-text screening to identify studies for inclusion in the ISA and to inform the level of confidence to be placed in inferences that can be drawn from particular studies.

Literature review software such as DistillerSR (Ottawa, Ontario, Canada) (Hamel et al., 2020) or HAWC (U.S EPA, 2021a) is used for management of individual study quality evaluations. Studies that are determined to meet scoping criteria and that are judged of sufficient quality based on the approach described in Appendix A (section A.5) are tagged in HERO for inclusion in the ISA. When fully available, results of the literature search and screening efforts and the evaluation of individual study quality will be captured in flow diagrams that document the number of references identified from each database searched (i.e., PubMed and Web of Science), the number of references evaluated in each screening step, and general reasons for reference exclusion (Figure 3-1).

3.3.4 Integration of Evidence and Determination of Causality

The ISA for Oxides of Nitrogen – Health Criteria will evaluate and integrate the recent scientific evidence on the health effects of oxides of nitrogen exposures with evidence from previous assessments. Based on this integration, the ISA will reach conclusions on the weight of evidence supporting cause-effect relationships between oxides of nitrogen exposures and various health outcomes. These "causality determinations" reflect overall confidence in such cause-effect relationships based on integrating the full body of evidence within and across disciplines. The ISA framework for reaching these causality determinations recognizes that, compared to any single study, the availability of multiple studies evaluating a particular topic, each with different

---

under investigation. The lack of such validation was an important uncertainty in some epidemiologic studies evaluated in the last review of the primary NO_2 NAAQS (e.g., 83 FR 17268, April 18, 2018).

[23] Studies described as "natural experiments" conducted during COVID lockdown(s) should explicitly consider potential confounders common during lockdown periods, such as changes in employment status, activity patterns (e.g., time spent outdoors versus indoors, driving, working, exercising), stress levels, access to health care, and/or mask wearing.

[24] Specifically, epidemiologic studies that examine populations outside North America should be multicity and/or multi-country and they should address policy-relevant topics (e.g., studies that use alternative methods for confounder control (causal inference methods, quasi-experimental studies), copollutant confounding, effect measure modification for potential at-risk factors (race/ethnicity, age, SES indicators, etc.), exposure-/concentration-response relationships). Studies with these characteristics are most likely to be influential in ISA causality determinations and other conclusions. Studies that examine populations in North America will not be excluded from the ISA based on these study characteristics alone as such studies may be useful for evaluating potential policy options in subsequent steps of the NAAQS review.

strengths and limitations, provides a more robust foundation for evaluating the overall strength of the evidence. To aid in forming weight-of-evidence judgments, the ISAs consider various aspects of the scientific evidence including consistency and coherence across studies, support for biological plausibility, support for exposure- or dose-response relationships, and several others (Appendix A, section A.7.2.1). Limitations in the evidence base can result from the presence of similar uncertainties within a particular subset of studies (e.g., studies similarly affected by confounding, exposure error, species extrapolation, etc.) or uncertainties that exist across the broader body of evidence (e.g., inconsistent evidence across disciplines). When the evidence base includes a group of studies with the same or similar uncertainties of a particular type, caution is used when developing causality determinations so as not to misrepresent and perpetuate errors (Savitz and Forastiere, 2021, Savitz et al., 2019).

The ISA causality framework for this review builds on the established framework described in the 2015 Preamble to the ISAs, with updates reflecting advances implemented in the recent ISAs and in consideration of recent NASEM recommendations (NASEM, 2022). It includes a five-level hierarchy to classify the weight-of-evidence for causation as either causal; likely to be causal; suggestive of, but not sufficient to infer, a causal relationship; inadequate to infer a causal relationship; and not likely to be a causal relationship (Table 3-7). The updated draft of the ISA causality framework is described in detail in Appendix A (Section A.7.2.1) to this IRP.

Table 3-7. Causality determinations for health outcomes.

Descriptor	Evidence Characteristics
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant exposures have been shown to result in health effects in studies in which chance, confounding, and other biases can be ruled out with reasonable confidence. A "causal" relationship is generally based on multiple high-quality studies conducted by different research groups. Evidence supporting this determination can include controlled human exposure studies that consistently demonstrate effects and/or observational studies reporting consistent health effect associations that, when considered in light of study quality and coherence with other lines of evidence (i.e., controlled human exposure studies, animal toxicological studies, and mode of action information), cannot be explained by plausible alternatives.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. That is, the pollutant exposures have been shown to result in health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. A "likely to be causal" relationship is generally based on multiple high-quality studies conducted by different research groups. Evidence supporting this determination can include 1) multiple high-quality observational studies consistently reporting health effect associations, but with uncertainty remaining related to potential confounding and/or limited coherence with other lines of evidence (i.e., controlled human exposure studies, animal toxicological studies, mode of action information) or 2) consistent evidence in animal models and/or *in vitro* models (e.g., for cancer-related effects) that can be reasonably extrapolated to human health, but limited availability of human data.
Suggestive of, but not sufficient to infer, a causal relationship	Evidence is suggestive of, but not sufficient to infer, a causal relationship with relevant pollutant exposures. That is, the pollutant exposures have been shown to result in health effects, but chance, confounding, and bias cannot be confidently ruled out. Evidence supporting a "suggestive" relationship can be comprised of studies of varying quality that may be generally supportive of pollutant-related effects, but not entirely consistent and with limited coherence across lines of evidence. A suggestive determination can be reached with relatively small bodies of evidence, or, in rare cases, one high quality study.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. That is, the evidence supporting an "inadequate" relationship is limited and available studies are of insufficient quantity, quality, consistency, and/or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations and lifestages, are consistent in not showing an effect at any level of exposure.

3.3.5 Quality Management

The EPA has an agency-wide quality assurance (QA) policy outlined in the EPA Quality Manual for Environmental Programs (see CIO 2105-P-01.1) and follows the specifications outlined in EPA Order CIO 2105.1. As required by CIO 2105.1, the EPA Office of Research and

Development (ORD) maintains a Quality Management Program, which is documented in an internal Quality Management Plan. The ISAs are designated as Highly Influential Scientific Assessments (HISA) and are classified as ORD QA Category A. As such, the oxides of nitrogen ISA is subject to the EPA's Quality Management Program requirements for a Quality Management Plan and adheres to the *Program Quality Assurance Project Plan (PQAPP) for the Integrated Science Assessment Program,* (*QAPP ID: L-HEEAD-0030253-QP-1-6*). The ISA will be subjected to management and QA clearance review, and during this step, the CPHEA QA Manager verifies that the EPA QA requirements are met (see Appendix A for more detail).

3.3.6 CASAC Peer Review

Section 109(d) of the CAA establishes the requirement for an independent scientific committee to review the Air Quality Criteria (i.e., the ISA in the current process) and the NAAQS, and to recommend to the EPA Administrator any new NAAQS and any revisions to existing criteria and NAAQS that may be appropriate (see 42 U.S.C. 7409(d)(2)). The CASAC was established to fulfill these requirements, and a draft of the ISA will be sent to the CASAC for review. Coincident with the CASAC review, the draft ISA will also be made available to the public, with a *Federal Register* notice announcing public availability and providing instructions for submitting comments on the draft ISA to the public docket.

As described in Appendix A (Section A.8), the CASAC will be supplemented by a panel that includes broad scientific expertise related to oxides of nitrogen and on the science-policy issues important for this review of the primary NO_2 NAAQS. The panel will develop a draft advisory report with recommendations for the EPA Administrator on the draft ISA. The report will be transmitted to the CASAC for discussion and deliberation. If the CASAC determines the contents of the report are appropriate, the committee will adopt the report and transmit it to the EPA Administrator to reflect its statutorily mandated advice to the Agency.

The EPA will carefully consider advice received from the CASAC and comments from the public in revising and updating the draft ISA. After appropriate revisions are made, the final ISA will be made available on the EPA website. A notice announcing the availability of the final ISA will be published in the *Federal Register*.

3.4 SCIENTIFIC QUESTIONS TO GUIDE EVALUATION OF THE EVIDENCE

As noted above, the ISA for Oxides of Nitrogen – Health Criteria being developed in this review will build upon the evidence assessed and the conclusions reached in the 2016 ISA and prior assessments. Studies that have become available since the 2016 ISA will be integrated with the older studies that have been evaluated in previous assessments. Based on the recent evidence,

conclusions from the 2016 ISA will be re-evaluated. A series of scientific questions will guide the evaluation of the recent literature, with a focus on 1) whether new scientific evidence reinforces or calls into question the conclusions reached in the 2016 ISA; 2) whether uncertainties from the last review have been reduced and/or whether new uncertainties have emerged; and 3) the degree to which new lines of evidence have become available to support areas of evaluation not considered in previous assessments. The specific scientific questions that will guide the evaluation of the literature for each discipline are described in the sections below.

3.4.1 Source to Concentration – Air Quality, Atmospheric Science, Fate, and Transport

The ISA will present and evaluate data related to ambient air concentrations of oxides of nitrogen; sources leading to the presence of oxides of nitrogen in the atmosphere; and physical and chemical processes that determine the formation, degradation, and lifetime of oxides of nitrogen in the atmosphere. The following questions will guide the evaluation of the scientific literature for air quality, atmospheric science, and fate and transport.

- What new information is available to inform our understanding of the atmospheric chemistry of oxides of nitrogen? How does new information characterize the role of atmospheric chemistry in determining relationships among oxides of nitrogen species? What new information is available with respect to formation, transport, and transformation of oxidized nitrogen species that may be important in assessing health effects from multipollutant exposures? How does the near-source environment (e.g., near major highways or large combustion sources) influence chemistry and spatiotemporal variability of oxides of nitrogen?
- What new information exists regarding characterization of sources of oxides of nitrogen to ambient air in both urban and rural environments? What are the relevant spatial and temporal scales for considering emissions of oxides of nitrogen to ambient air? What new information is available regarding existing and emerging energy, industrial, transportation, and agricultural sources and their impacts on emissions of oxides of nitrogen?
- To what extent have new methods been developed to improve measurements of oxides of nitrogen in ambient air, particularly those that measure NO_2 directly? How have these new methods reduced interference problems in measuring oxides of nitrogen? What advances have taken place in the development of low-cost community sensor technologies? What advances have taken place in the development of satellite-based remote sensing technologies? What limitations still remain?
- What new modeling methods and refinements have been developed that improve our understanding and predictive capabilities of spatial and temporal patterns of NO_2 and, more broadly, NOy?
- Based on recent air quality and emissions data, what is known about recent emissions and resulting ambient air concentrations of oxides of nitrogen? How have emissions and concentrations of NO_X and of NO_2 changed since the 2016 ISA? To what extent can new data sources (e.g., satellites, community sensors) or air quality analyses be used to improve the characterization of ambient air concentrations of oxides of nitrogen?

- What spatial and temporal patterns can be seen in ambient air concentrations of NO_2 and the broader category of NOy concentrations? In particular, what spatial and temporal patterns can be seen on a micro-scale near sources including major roadways, industrial operations, residential fuel combustion, or wildland fires? What do ambient air quality characterizations (including examinations of the influence of meteorological parameters) indicate about spatial patterns on neighborhood, urban, regional, and national scales?
- Based on air quality and emissions data for oxides of nitrogen and atmospheric chemistry models, what improvements have been made in estimating background concentrations of oxides of nitrogen, and what are likely background concentrations in the absence of anthropogenic emissions?
- What information is available on interactions between oxides of nitrogen and copollutants in the atmosphere that may alter the spatial distributions of oxides of nitrogen?
- To what extent have uncertainties in data, modeling, and satellite measurements been reduced from the previous reviews?
- What effects have pandemic related lockdowns, increasing environmental temperatures, and increasing wildland fire activity had on NO_X emissions and ambient air concentrations of NO_2 and other oxides of nitrogen?

3.4.2 Exposure

The ISA will evaluate the factors that influence exposure to oxides of nitrogen in ambient air and the measurement error and other uncertainties associated with extrapolation of ambient air concentrations to personal exposures to oxides of nitrogen of ambient air origin, particularly in the context of interpreting results from epidemiologic studies. The following questions will guide the evaluation of the scientific literature for exposures to NO_2 and other oxides of nitrogen.

- How have personal or microenvironmental exposure measurement techniques for oxides of nitrogen, such as sensors and passive samplers, been advanced in recent years? What measurement errors are associated with these emerging techniques?
- How have modeling or hybrid modeling techniques such as sub-grid scale modeling within chemical transport models, air quality dispersion models, and land use regression models been advanced in recent years? What new information is available regarding modeled estimates of spatially-resolved (at the micro-, middle-, and neighborhood-scales) ambient air NO_2 and other oxides of nitrogen species concentrations used for exposure assessment?
- To what extent have data fusion approaches that combine ambient air concentrations with air quality models been recently developed to improve the spatial and temporal resolution of exposure estimates within a community? What advancements have been made regarding validation of data fusion and their ability to estimate source attribution for exposures to NO_2 or other oxides of nitrogen species?
- How do instrumentation errors (e.g., interference in measurements of ambient air NO_2 concentrations from other nitrogen compounds) affect assessing health effects of exposures to oxides of nitrogen in epidemiologic studies?

- To what extent do recent studies examine the relationship between near-road oxides of nitrogen, on-road oxides of nitrogen, and in-vehicle exposures to oxides of nitrogen?
- What new information is available regarding the interaction of indoor oxides of nitrogen with organic compounds emitted indoors to form organic nitrogen compounds?
- What new information exists regarding characterization of exposure measurement error in assessment of short-term and long-term exposures to oxides of nitrogen and how that error influences personal-ambient air exposure relationships? What implications does exposure measurement error have on inference about epidemiologic associations observed between oxides of nitrogen and health effects? Do the implications vary according to factors such as exposure duration, study design, and exposure assessment method?
- What are the relationships between oxides of nitrogen measured at stationary monitoring sites and personal short-term and long-term exposure? What evidence is available regarding these relationships in environments near roads or other sources?
- What new information exists regarding exposure to oxides of nitrogen in a multipollutant context with other gaseous pollutants (e.g., carbon monoxide), particle phase pollutants (e.g., ultrafine particles, black carbon, organic carbon, transition metals) generated by traffic or other combustion sources, or of a mixture of traffic-related pollutants?
  - How does information about pollutant co-exposures aid in evaluation of potential confounders in epidemiologic associations between oxides of nitrogen and health effects?
  - What new information exists about the relationship between NO, NO_2, NO_X, and NOy concentrations and indicators of near-source pollution including distance to sources (e.g., major roadways) and source activity levels (e.g., traffic counts)?
- What new information is available regarding differences in exposure patterns for oxides of nitrogen and personal-ambient air exposure relationships among various lifestages and specific groups within populations?
  - What new information is available on spatial and temporal trends in exposures to oxides of nitrogen in ambient air, particularly for groups and lifestages that may be at increased risk of health effects?
  - To what extent is information available characterizing how well the current area-wide and near-road NO_2 monitoring sites represent exposures to populations living near major roads?
  - What implications do potential differences in exposure measurement error have on inferences about relationships with health effects observed in general population studies versus those conducted in specific lifestages and groups within the population (e.g., people with underlying health condition)?

3.4.3 Dosimetry

The ISA will evaluate literature focusing on dosimetry that may underlie the health outcomes associated with exposure to NO_2, NO, and other oxides of nitrogen. These topic areas will be

evaluated using both human and animal data. The following questions will guide the evaluation of the scientific literature for dosimetry.

- What are the effects of host factors such as lifestage, sex, pre-existing disease, genetic background, and physical activity on the uptake of NO_2 and/or NO and cellular and tissue responses that may underlie health effects associated with exposure to oxides of nitrogen?
- What information is available to discern the relative contributions to local NO_2 and/or NO of: (1) ambient air exposures to NO_2 and/or NO; (2) dietary consumption of nitrite and nitrate which undergo transformation to NO; and (3) endogenous formation of NO_2 and/or NO?
- What NO_2 and/or NO reaction products, including oxides of nitrogen metabolites, can be found in the cells, tissues, or fluids of the respiratory tract and in the systemic circulation that may serve as markers of NO_2 and/or NO exposure and effect?
- To what extent can the inhalation dosimetry of NO_2 and/or NO be extrapolated between species, qualitatively or quantitatively?
- To what extent is information available on dosimetry of oxides of nitrogen other than NO_2 and NO?

3.4.4 Biological Plausibility

The ISA will evaluate literature focusing on modes of action that may underlie the health outcomes associated with exposure to NO_2, NO, and other oxides of nitrogen. These topic areas will be evaluated using both human and animal data. The following questions will guide the evaluation of the scientific literature related to biological plausibility.

- What new information is available to inform our understanding of the potential biological mechanisms underlying responses to NO_2 and/or NO exposures, or exposures to other oxides of nitrogen, at concentrations defined in the ISA to be policy relevant (see Tables 3-1 to 3-3), with a focus on response pathway(s) and exposure-dose-response relationships?
- What information is available to characterize intra- and inter-individual variability in biological responses following exposure to NO_2, NO, and/or other oxides of nitrogen?
- What are the effects of host factors such as lifestage, sex, pre-existing disease, and genetic background on cellular and tissue responses, as well as biological mechanisms, that may underlie health effects associated with exposure to oxides of nitrogen?
- What biological processes, from the molecular to whole organ level, can be qualitatively or quantitatively compared across species (i.e., human vs. animal)?
- Do interactions with other inhaled pollutants influence the mechanisms underlying the health effects of NO_2, NO, and/or other oxides of nitrogen? If so, how might this information provide understanding of the potential for a copollutant to act as an effect measure modifier of health effects related to oxides of nitrogen?

3.4.5 Health Outcomes

The ISA will evaluate health effects that occur following both short- and long-term exposures to oxides of nitrogen (predominantly NO_2) as examined in epidemiologic, controlled

human exposure, and animal toxicological studies. The health effects evidence will be integrated with available information on exposure, dosimetry, and biological plausibility to inform the key ISA conclusions, including causality determinations. The evidence integration will focus on (1) whether recent studies support or call into question the causality determinations made in the 2016 ISA, (2) whether recent evidence supports causality determinations or other conclusions for health outcomes not included in the 2016 ISA, and (3) whether new evidence reduces uncertainties identified in the last review and whether additional uncertainties have been identified.

Causality determinations from the 2016 ISA are summarized in Table 3-8 below. The strongest evidence was for relationships between NO_2 exposures and asthma exacerbation (short-term exposures) and asthma development (long-term exposures), likely through the formation of secondary oxidation products in the respiratory tract (U.S. EPA, 2016, Section 4.3.2.1) and the induction of oxidative stress, inflammation, allergic responses, and altered immune function (U.S. EPA, 2016, Figures 1-2 and 4-1). Epidemiologic studies reported associations between short-term increases in ambient air NO_2 concentrations and increased incidence of hospital admissions and emergency department visits for asthma, increases in respiratory symptoms and airway inflammation in people with asthma, and decreases in lung function in children with asthma. The biological plausibility of NO_2-induced asthma exacerbation was supported by controlled human exposure studies that showed increased airway reactivity and allergic inflammation in adults with asthma exposed at rest to NO_2 at ambient air-relevant concentrations. Support for effects of long-term NO_2 exposures came from epidemiologic studies indicating associations with asthma incidence in children and from experimental studies characterizing a potential mode of action for NO_2. Remaining uncertainties included the lack of an apparent dose-response relationship in controlled human exposure studies examining NO_2-induced airway reactivity and the potential for epidemiologic associations to be confounded by co-occurring pollutants (e.g., other traffic-related pollutants). Compared to the evidence for asthma-related effects, the evidence supporting other health outcomes was subject to greater uncertainty as reflected in “suggestive” or “inadequate” causality determinations (Table 3-8).

Table 3-8. Summary of causality determinations from the 2016 ISA organized by health outcome.

Health Outcome	Causality Determination
Respiratory Effects	
Respiratory Effects and Short-Term Exposure	Causal
Respiratory Effects and Long-Term Exposure	Likely to be causal
Cardiovascular Effects and Diabetes	
Cardiovascular Effects and Short-Term Exposure	Suggestive
Cardiovascular Effects and Diabetes and Long-Term Exposure	Suggestive
Total Mortality	
Total Mortality and Short-Term Exposure	Suggestive
Total Mortality and Long-Term Exposure	Suggestive
Reproductive and Developmental Effects	
Fertility, Reproduction, & Pregnancy	Inadequate
Birth Outcomes	Suggestive
Postnatal Development	Inadequate
Cancer	
Cancer and Long-Term Exposure	Suggestive

In the current review, the causality determinations from the 2016 ISA will be revisited in light of recent evidence, and evidence for any additional outcomes will be examined. The following questions will guide the evaluation of the health effects literature for short-term and long-term exposure to NO_2 and other oxides of nitrogen.

- What do studies across scientific disciplines (i.e., epidemiologic, controlled human exposure, animal toxicological) indicate about the strength of evidence supporting health effects of short-term and long-term exposures to NO_2 and other oxides of nitrogen? To what extent has the strength of evidence changed for effects examined in previous reviews (i.e., respiratory effects, cardiovascular effects and diabetes, reproductive and developmental effects, total mortality, and cancer)? Does recent evidence support additional health effect outcome categories of exposures to oxides of nitrogen?
- To what extent have recent studies addressed key uncertainties identified in the evidence in the 2016 ISA, including uncertainty in the epidemiologic evidence due to potential confounding by copollutants and potential exposure measurement error, and uncertainty in the controlled human exposure evidence due to the lack of an apparent dose-response relationship for airway hyperresponsiveness at NO_2 exposure concentrations near those occurring in ambient air?
- To what extent do recent epidemiologic, controlled human exposure, and animal toxicological studies provide information on health effects related to specific oxides of nitrogen including, but not limited to, NO_2 and NO?

- How does recent evidence for health effects associated with oxides of nitrogen compare among healthy individuals, those with pre-existing disease states (e.g., people with asthma or cardiovascular disease), particular lifestages, or groups characterized by other factors that potentially modify risk (e.g., genetics, nutritional status)?
- Do recent studies provide new information on the range of ambient air and exposure concentrations over which NO_2-related health effects, or effects associated with other oxides of nitrogen, are most well-characterized?
- To what extent does the new scientific evidence support the occurrence of health effects of exposure to oxides of nitrogen at lower ambient air or exposure concentrations than those previously demonstrated? What are the uncertainties in the evidence for health effects at relatively low exposure or ambient air concentrations (e.g., uncertainty in occurrence, adversity, public health importance of effects)?
- What recent evidence is available regarding the shape of concentration-response relationships between exposure to oxides of nitrogen and various health endpoints? Is there evidence to support the identification of a discernible threshold below which adverse health effects do not occur?
- What do recent studies indicate regarding the health impacts of reductions in concentrations of oxides of nitrogen in ambient air (e.g., due to policy intervention) or reductions in exposures (e.g., due to changes to indoor sources)?
- To what extent does new evidence indicate that observed health effect associations are attributable specifically to ambient air oxides of nitrogen versus other pollutants contained in the complex ambient air pollution mixture? What information about the independent health effects of exposure to oxides of nitrogen can be gleaned from the various lines of available evidence, including epidemiologic, controlled human exposure, and animal toxicological studies?
- How does confounding by other traffic-related copollutants (e.g., particulate matter, carbon monoxide) or meteorological factors influence relationships observed between health effects and both short- and long-term exposures to oxides of nitrogen? To what extent do other factors serve as potential confounding factors in epidemiologic studies (e.g., age, socioeconomic status (SES), and other exposures such as noise)? In such studies, to what extent can health impacts due to oxides of nitrogen be separated from the health impacts of these other factors?
- What new information is available to assess the influence of exposure measurement error on uncertainty in epidemiologic study results?
    - How can the influence of exposure measurement error be assessed through the examination of various study designs, study populations, exposure assessment methods, spatial and/or temporal variability in ambient air concentrations, spatial alignment of study population and ambient measurements, and analytical models?
    - To what extent can monitored ambient air NO_2 concentrations used in epidemiologic studies reflect oxides of nitrogen exposures in study populations under various environmental conditions, such as a near-source environment?

  - To what extent can recent data from near-road monitors better characterize or reduce exposure measurement error in epidemiologic studies?
  - What information is available regarding the time-activity patterns of study subjects including time spent outdoors, spatial distribution of study subjects, and ambient air monitors?

- What evidence is available regarding the nature of health effects from exposures to ambient air pollutant mixtures that include oxides of nitrogen? To what extent does the evidence support attributing these health effects to exposures to NO_2 or other oxides of nitrogen, another ambient air pollutant that is correlated with oxides of nitrogen, or to the pollutant mixtures that oxides of nitrogen may be representing?
- What new information is available on the health effects of oxides of nitrogen exposures in populations spending time or living near roads or other sources? To what extent do findings from experimental studies provide biological plausibility for the effects observed in epidemiologic studies?
- To what extent does recent evidence indicate that particular exposure patterns, such as repeated short-term NO_2 exposures versus persistent long-term exposures, contribute to disease development?

Specific Questions Related to Short-Term Exposures

- How do results of recent studies or new interpretations of previous findings expand our understanding of the relationship between short-term exposure to oxides of nitrogen and airway hyperresponsiveness or other lung function changes, inflammation, host defense against infectious disease, respiratory symptoms, and asthma exacerbations?
- What new information is available on the effects of short-term exposure to oxides of nitrogen on acute cardiovascular events in humans such as myocardial infarction, stroke, increases in blood pressure, and arrhythmias?
- To what extent do recent studies of short-term exposure to oxides of nitrogen indicate associations with total mortality or with health effects beyond the respiratory and cardiovascular systems?
- What is the extent of coherence of findings for effects such as hospital admissions, emergency department visits, and mortality with changes in lung function, airway hyperresponsiveness, heart rate variability, and vasomotor function? What other biomarkers of early effect may be used in the assessment of health effects?
- To what extent does recent information across epidemiologic, controlled human exposure, and animal toxicological studies on the pattern of exposure to oxides of nitrogen (e.g., peak, repeated peak, average) provide understanding of the time course for changes in health effects? What new information is available on time-activity patterns of study subjects such as time spent outdoors or activity levels that can aid in understanding key aspects of exposure to or dosimetry of ambient air oxides of nitrogen that are associated with health effects?
- To what extent does recent data from epidemiologic, controlled human exposure, and animal toxicological studies provide information on health effects related to various short-term exposure durations (e.g., 1-hour, 24-hour, multi-day)?

Specific Questions Related to Long-Term Exposures

- How do the results of recent studies expand our understanding of the relationships between long-term exposure to oxides of nitrogen and chronic respiratory effects manifested as a reduction in lung function, a reduction in lung development, or morphological changes in the lung?
- To what extent do recent studies indicate that long-term exposure to oxides of nitrogen promotes exacerbation and/or development of asthma or other chronic lung diseases, cardiovascular diseases, and other health conditions?
- To what extent do recent studies find that long-term exposure to oxides of nitrogen contribute to changes in molecular and cellular processes that could result in adverse cognitive, behavioral, reproductive, developmental, cancer, or other effects?
- What information is available on the effects of exposures to oxides of nitrogen on health outcomes in populations living near major roads or working on or near major roads? To what extent do recent studies disentangle the effects of NO_2 and other oxides of nitrogen from co-occurring traffic-related pollutants?
- What information is available regarding the effect of long-term, low-concentration exposure to oxides of nitrogen on an individual's sensitivity to short-term but higher concentration exposures?
- Do recent studies provide information on health effects related to long-term exposure windows other than annual or lifetime average (e.g., preconception, pregnancy average, pregnancy trimester average)? What data are available comparing associations of health effects among various long-term oxides of nitrogen exposure metrics (e.g., annual, seasonal, pregnancy average)?

3.4.6 At-Risk Lifestages and Populations

The EPA has developed a framework to provide a consistent and transparent basis for informing the level of confidence for conclusions that specific lifestages or populations may be at increased risk of pollutant-related health effects according to one of four levels: adequate evidence, suggestive evidence, inadequate evidence, and evidence of no effect (see Appendix A, Section A.7.2.3). Conclusions from the 2016 ISA on populations potentially at increased risk are summarized in Table 3-9 below.[25]

[25] Table 3-9 was extracted directly from the (U.S. EPA, 2016).

Table 3-9. Summary of evidence for potential increased nitrogen dioxide exposure and increased risk of nitrogen dioxide-related health effects.[26]

Evidence Classification	Factor Evaluated
Adequate evidence	Asthma Lifestage: Children Older adults
Suggestive evidence	SES: Low SES Sex: Females Diet: Reduced antioxidant intake
Inadequate evidence	COPD Cardiovascular disease Diabetes Genetic factors Obesity Smoking Physical activity Race/ethnicity Residence in urban areas Proximity to roadways

The ISA in this review will evaluate an array of factors that characterize potential "at-risk" populations and lifestages: intrinsic factors (biological factors such as age or genetic variants), acquired factors (e.g., pre-existing disease), extrinsic factors (nonbiological factors such as nutritional status, SES), and/or factors affecting dose or exposure (e.g., sex, age, outdoor activity or work, SES, physical activity). The various factors listed above may influence risk by increasing exposure, dose, or biological effect at a given dose, and some factors (e.g., SES) may contribute to risk in multiple ways. In the current review, the ISA will evaluate whether new information supports or calls into question our previous understanding of the human populations and lifestages that may be at increased risk for experiencing health effects associated with exposures to oxides of nitrogen. The following questions will guide the evaluation of the human health evidence for potential at-risk populations and lifestages.

- Does recent information on the health risks of NO_2 exposure, or exposure to other oxides of nitrogen, support the 2016 ISA conclusions for people with asthma or other pre-existing respiratory disease, children and older adults, and people with low SES? Is there new

[26] Table modified from the 2016 oxides of nitrogen ISA (U.S. EPA, 2016).

evidence supporting increased risk from exposure to other oxides of nitrogen or new evidence for additional potential at-risk populations or lifestages?

- What new information is available on the health effects in populations spending time near important sources of NO_X emissions (e.g., roads)? To what extent does living, working, attending school or daycare, or otherwise spending time on or near major roads contribute to greater overall exposures to oxides of nitrogen and increase the risk of related health effects? Given the concentration gradients observed for oxides of nitrogen in ambient air with distance to roads, what information is available regarding the sizes and sociodemographic characteristics of populations living near major roads? What does recent evidence indicate regarding the public health importance of NO_X emissions from sources other than roadways?
- What information is available that provides insight as to whether a potential at-risk population or lifestage experiences higher exposures or a higher dose of oxides of nitrogen, has a greater biological response to a given exposure, and/or experiences health effects at lower exposure concentrations?
- What information is available to quantify the magnitude of greater biological response or risk of health effects associated with exposure to oxides of nitrogen in a particular at-risk lifestage or population?
- Is recent evidence supporting potential at-risk lifestages or populations coherent across disciplines?
- What does new evidence on effect measure modification indicate regarding populations at increased risk of health effects from exposure to oxides of nitrogen (e.g., young age, residence near major roads, lower SES, and asthma; older age and pre-existing cardiovascular disease; preexisting respiratory disease or prior respiratory infection)?

4 REFERENCES

Hamel, C, Kelly, SE, Thavorn, K, Rice, DB, Wells, GA and Hutton, B (2020). An evaluation of DistillerSR's machine learning-based prioritization tool for title/abstract screening - impact on reviewer-relevant outcomes. BMC Medical Research Methodology 20(1): 256.

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

NASEM (2022). 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 Standard Reviews. The National Academies Press. Washington, DC. Available at: https://doi.org/10.17226/26612.

Savitz, DA and Forastiere, F (2021). Do pooled estimates from meta-analyses of observational epidemiology studies contribute to causal inference? Occup Environ Med 78(9): 621-622.

Savitz, DA, Wellenius, GA and Trikalinos, TA (2019). The Problem With Mechanistic Risk of Bias Assessments in Evidence Synthesis of Observational Studies and a Practical Alternative: Assessing the Impact of Specific Sources of Potential Bias. Am J Epidemiol 188(9): 1581-1585.

U.S. EPA (1993). Air Quality Criteria for Oxides of Nitrogen. Office of Health and Environmental Assessment. Environmental Criteria and Assessment Office. Washington, DC U.S. EPA. EPA–600/8–91–049aF–cF. August 1993. Available at: *https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=40179*.

U.S. EPA (1982). Air quality criteria for oxides of nitrogen. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. Research Triangle Park, NC. EPA/600/8-82-026.

U.S. EPA (2015). Preamble to the Integrated Science Assessments (ISA). Office of Research and Development, National Center for Environmental Assessment. Washington, DC. U.S. EPA. EPA/600/R-15/067. Available at: *https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=526136*.

U.S. EPA (2016). Integrated Science Assessment for Oxides of Nitrogen-Health Criteria. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. Research Triangle Park, NC. EPA/600/R-15/068. Available at: *https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310879*.

U.S. EPA (2019). Integrated Science Assessment (ISA) for Particulate Matter (Final Report). U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. Washington, DC. U.S. EPA. EPA/600/R-19/188.

December 2019. Available at: *https://www.epa.gov/naaqs/particulate-matter-pm-standards-integrated-science-assessments-current-review*.

U.S. EPA (2020a). Integrated Science Assessment (ISA) for Ozone and Related Photochemical Oxidants (Final). U.S. Environmental Protection Agency, Office of Research and Development. Washington, DC. EPA/600/R-20/012. Available at: *https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=540022*.

U.S. EPA (2020b). Integrated Science Assessment for Oxides of Nitrogen, Oxides of Sulfur, and Particulate Matter—Ecological Criteria (Final). U.S. Environmental Protection Agency, Office of Research and Development, Center for Public Health and Environmental Assessment. Research Triangle Park, NC. EPA/600/R-20/278. Available at: *https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=349473*.

U.S. EPA (2021). Health Assessment Workspace Collaborative (HAWC) Washington, DC.

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

U.S. EPA (2023b). LLR Online (pre-release Version 007EC800) Washington, DC.

U.S. EPA (2008). Integrated Science Assessment for Oxides of Nitrogen – Health Criteria. Office of Research and Development, National Center for Environmental Assessment. Research Triangle Park, NC. U.S. EPA. EPA/600/R-08/071. July 2008. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=194645.

APPENDIX A ISA DEVELOPMENT PROCESS

A.1. INTRODUCTION

The Integrated Science Assessments (ISAs) review, synthesize, and evaluate policy-relevant scientific information[27] and reach key science judgments intended to inform the EPA's reviews of the National Ambient Air Quality Standards (NAAQS). This appendix provides an overview of the ISA development process, with a focus on human health and exposure.[28] It builds on the process described in the 2015 Preamble to the ISAs (U.S. EPA, 2015) and on updates and advancements presented in recently completed ISAs (U.S EPA, 2020a; U.S EPA, 2020b). The process presented in this appendix additionally reflects the EPA's consideration of recommendations made by an ad hoc committee of the National Academies of Science, Engineering, and Medicine (NASEM) charged with reviewing the current ISA framework for reaching causality determinations (U.S. EPA, 2015). Those recommendations are presented in the NASEM report titled *Advancing the Framework for Assessing Causality of Health and Welfare Effects to Inform National Ambient Air Quality Standard Reviews* (NASEM, 2022). It builds on the process described in the 2015 Preamble to the ISAs (U.S. EPA, 2015) and on updates and advancements presented in recently completed ISAs (U.S EPA, 2020a; U.S EPA, 2020b). The process presented in this appendix additionally reflects the EPA's consideration of recommendations made by an ad hoc committee of the National Academies of Science, Engineering, and Medicine (NASEM) charged with reviewing the current ISA framework for reaching causality determinations (U.S. EPA, 2015). Those recommendations are presented in the NASEM report titled *Advancing the Framework for Assessing Causality of Health and Welfare Effects to Inform National Ambient Air Quality Standard Reviews* (NASEM, 2022). It builds on the process described in the 2015 Preamble to the ISAs (U.S. EPA, 2015) and on updates and advancements presented in recently completed ISAs (U.S EPA, 2020a; U.S EPA, 2020b). The process presented in this appendix additionally reflects the EPA's consideration of recommendations made by an ad hoc committee of the National Academies of Science, Engineering, and Medicine (NASEM) charged with reviewing the current ISA framework for

[27] Policy-relevant scientific information includes 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.

[28] The ISA development process for the welfare effects evidence is discussed in the 2015 Preamble to the ISAs (U.S. EPA, 2015) and in recent ISAs (U.S EPA, 2020a; U.S EPA, 2020b).

reaching causality determinations (U.S. EPA, 2015). Those recommendations are presented in the NASEM report titled *Advancing the Framework for Assessing Causality of Health and Welfare Effects to Inform National Ambient Air Quality Standard Reviews* (NASEM, 2022). It builds on the process described in the 2015 Preamble to the ISAs (U.S. EPA, 2015) and on updates and advancements presented in recently completed ISAs (U.S EPA, 2020a; U.S EPA, 2020b). The process presented in this appendix additionally reflects the EPA's consideration of recommendations made by an ad hoc committee of the National Academies of Science, Engineering, and Medicine (NASEM) charged with reviewing the current ISA framework for reaching causality determinations (U.S. EPA, 2015). Those recommendations are presented in the NASEM report titled *Advancing the Framework for Assessing Causality of Health and Welfare Effects to Inform National Ambient Air Quality Standard Reviews* (NASEM, 2022).

As part of the Integrated Review Plan (IRP) for the review of the primary NO_2 NAAQS, this appendix describes the process being applied to develop the ISA for Oxides of Nitrogen – Health Criteria. It will be subject to a consultation with the Clean Air Scientific Advisory Committee (CASAC) Oxides of Nitrogen Primary NAAQS Review Panel. Following CASAC consultation, an updated version of this appendix will be included in the draft ISA for Oxides of Nitrogen – Health Criteria, where it will be subject to CASAC review and public comment. Ultimately, the process used in this review to develop the ISA for Oxides of Nitrogen – Health Criteria will be expanded to include welfare effects and implemented in developing future ISAs. The sections below present an overview of ISA organization and development (A.2), a detailed description of the updated ISA development process (A.3 through A.8), and a summary of the quality management process that governs ISA development (A.9).

A.2. OVERVIEW OF ISA ORGANIZATION AND DEVELOPMENT

A.2.1. ISA Organization

The ISAs are organized around a series of detailed, topic-specific chapters[29] and an Integrated Synthesis that draws from those chapters. Chapters provide thorough assessments of the scientific evidence pertaining to specific topic areas including atmospheric science, exposure and dosimetry, and human health outcomes. Each chapter contains an evaluation of results from recent studies building upon key conclusions and evidence presented in previous assessments. Chapters for each health outcome category (e.g., respiratory effects, cardiovascular effects) reflect full assessments of the causal nature of relationships between pollutant exposures and

[29] In the past, some ISAs have utilized chapters (U.S. EPA, 2013b; U.S. EPA, 2013a), while other ISAs more recently (U.S EPA, 2020a; U.S. EPA, 2024) referred to topic-specific sections as appendices. In the past, some ISAs have utilized chapters (U.S. EPA, 2013b; U.S. EPA, 2013a), while other ISAs more recently (U.S EPA, 2020a; U.S. EPA, 2024; U.S EPA, 2020b) referred to topic-specific sections as appendices.

health effects that result in key science judgments (i.e., causality determinations, see A.7.2.1). These causality determinations are based on the consideration of various aspects of the evidence, including consistency and coherence across studies, biological plausibility, and other aspects as discussed below (A.7.2.2). For human health outcomes, causality determinations also consider the evidence that certain populations and lifestages may experience larger risks of pollutant-related effects because they are "at-risk" to those effects and/or because they experience higher exposures (A.7.2.3). Chapters additionally present targeted evaluations of the evidence on other pollutant-specific policy-relevant issues to support the summary discussion of those issues in the Integrated Synthesis. These other issues vary by pollutant and discipline, and often include conclusions on concentration-, exposure-, and/or dose-response relationships; strengths and limitations of various exposure estimates and study designs; the impact of potential confounding factors on health effect associations; and the timing of effects (i.e., lag structure of associations and/or averaging times of exposures).

Drawing from the detailed assessment of the scientific evidence provided in the chapters, the Integrated Synthesis provides a concise synopsis of the ISA conclusions and synthesizes the key findings considered in characterizing pollutant exposures and relationships with health effects. The Integrated Synthesis typically includes summaries of key information for each topic area, including information on pollutant-related sources, emissions, and atmospheric science; exposures and dosimetry; and health effects. The Integrated Synthesis summarizes the ISA causality determinations, conclusions on the populations and/or lifestages that may be at increased risk of pollutant-related effects, and conclusions on other key policy-relevant issues, including but not limited to pre-existing disease(s), genetic factors, lifestage(s), socioeconomic status (SES), race/ethnicity, sex, urbanicity, proximity to roadways, stress, behavioral factors (diet, smoking, physical activity); copollutant confounding; and/or exposure/concentration response.

In addition to the Integrated Synthesis and supporting chapters, the ISAs also generally include a Preface that summarizes major legal and historical aspects of prior NAAQS reviews, an Executive Summary written to be accessible to a wide range of audiences, and a Process Appendix. The Process Appendix describes the approach taken to develop the ISA, typically including the methods for literature search and review, individual study quality evaluation, public engagement, and quality assurance considerations as well as documentation for these activities.

A.2.2. ISA Development

ISAs are developed principally by scientists within the EPA's CPHEA with extensive knowledge in their respective fields including atmospheric science, exposure science, dosimetry,

human exposure, animal toxicology, and epidemiology.[30] When additional subject matter expertise is required, the EPA solicits extramural scientists to supplement internal expertise, thereby ensuring that each ISA provides an accurate reflection of the most up-to-date scientific knowledge.

The process for developing an ISA begins with a Call for Information published in the Federal Register that announces the start of a NAAQS review and invites the public to contribute to the review by submitting potentially relevant research studies in identified subject areas. At this stage, the public is also given the opportunity to comment on policy-relevant issues to be addressed in the review. Information and comments received from the public inform the planning phase of the review, including the development of an IRP. The IRP presents background information on the NAAQS program in general and on the NAAQS for the pollutant under review, key policy-relevant science issues for the review, the anticipated process and plans for developing the ISA and other assessments, and the anticipated schedule for the review.

The EPA consults with the CASAC and solicits public comment on the assessment plans presented in the IRP. As described further in Section A.8, the CASAC is an independent committee composed of scientific experts charged with providing advice to the EPA Administrator on the NAAQS and on the underlying scientific foundation for the standards. Early in a NAAQS review, the EPA typically supplements the seven-member CASAC with a pollutant-specific review panel to inform the CASAC's advice. Given the breadth of scientific and technical information evaluated during NAAQS reviews, CASAC panels reflect a wide range of expertise. The specific expertise varies across panels, but typically requires members with expert knowledge of atmospheric science, human exposure, dosimetry, toxicology, epidemiology, medicine, public health, biostatistics, and risk assessment. Consistent with NASEM recommendations (NASEM, 2022, p.8), critical disciplines are often represented by multiple panel members in order to facilitate advice from a range of perspectives.

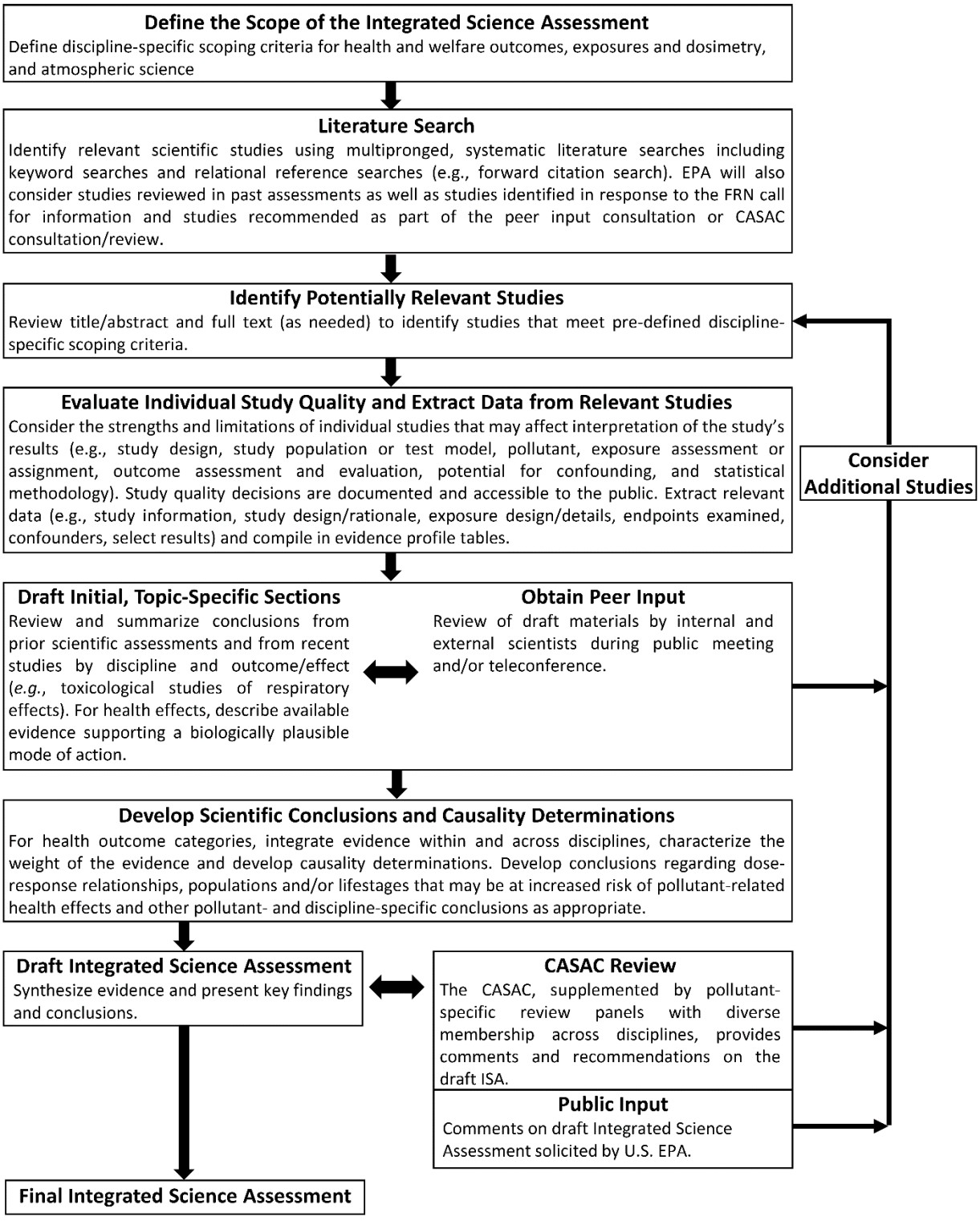
Following the CASAC consultation on the IRP, the EPA develops the ISA to provide the scientific foundation for the review. After public release of the draft ISA, the CASAC reviews the document, recommending revisions as necessary before the final ISA is published. The remainder of this appendix describes the process involved in developing an ISA. The process is summarized in Figure A-1 and described in detail in Sections A.2 through A.8.[31] These sections

[30] For reviews that include secondary standards expertise in ecological and other welfare effects is also included.

[31] Recognizing that the EPA continually strives to innovate and improve both the process for developing ISAs and the ISAs themselves, Agency staff routinely monitor advancements in scientific fields related to evidence integration and weight-of-evidence evaluations, as well as other relevant fields that could improve the ISAs. As a result, the general process outlined in Figure A-1 and discussed in Sections A.2 through A.8 may evolve over time, as has been the case with the framework for ISA development described in the 2015 Preamble (U.S. EPA,

describe the approaches used for defining the scope of the ISA (A.3), conducting the literature search and identifying potentially relevant studies (A.4), evaluating individual study quality (A.5), extracting data from relevant studies (A.6), drafting ISA (A.7), obtaining scientific and public review of the draft ISA (A.8), revising and finalizing the ISA (A.9), and quality management (A.9).

2015). This strategy is consistent with the NASEM recommendation to monitor the scientific literature to determine if emerging approaches to research synthesis and evidence integration "might be adapted to improve Integrated Science Assessment causal determinations" (NASEM, 2022, p. 132).



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

Figure A-1. The general process for Integrated Science Assessment development.

A.3. DEFINING THE SCOPE OF THE ISA

As noted above, the ISAs include a series of topic-specific chapters that provide detailed assessments of the policy-relevant scientific evidence. These chapters focus on integrating policy-relevant studies that have become available since the previous ISA with older studies evaluated in earlier assessments. Emphasis is placed on new and emerging information and studies that address scientific uncertainties and limitations identified in prior reviews. Important older studies (i.e., those included in the previous ISAs) may be discussed in detail to reinforce key concepts and conclusions and are open to reinterpretation considering more recent data. Older studies may be the primary focus of the ISA in some subject areas or scientific disciplines where research efforts have subsided and where these older studies remain the definitive works available in the literature. The ISAs emphasize studies that are most relevant for ambient air-related exposures, including those examining pollutant concentrations that reflect the range of ambient air-related exposures across microenvironments. Studies examining higher exposure concentrations (i.e., one to two orders of magnitude greater than ambient air concentrations) may be included if they provide evidence of the potential biological mechanism(s) for an observed effect. Each ISA identifies specific literature scoping criteria to focus the assessment on the most relevant studies. General criteria that guide the ISA scoping decisions for studies of human health effects, atmospheric science, exposure, and dosimetry are discussed below.[32]

A.3.1. Health Effects Studies

To be considered for inclusion in the ISA, relevant health studies must have undergone scientific peer review and have been published or accepted for publication within the predefined literature search cutoff dates. Studies can be considered for inclusion if they present original research or new analyses of existing data. To further refine criteria for identification of potentially relevant health studies, the ISAs use discipline-specific population, exposure, comparison, outcome, study design (PECOS) statements. PECOS statements help to define the objectives of the assessment and establish relevance criteria that should be met to consider a study for inclusion in the ISA, thereby facilitating identification of the potentially relevant literature. To focus on exposure concentrations most relevant to humans, an upper limit is sometimes used for exposure concentrations tested in epidemiologic and animal toxicological studies. All studies that meet the PECOS criteria during title and abstract and full text review undergo study quality evaluation (A.4 and A.5).

[32] For ISAs that include welfare effects, analogous scoping criteria are developed for scoping decisions on welfare effects studies (e.g., U.S EPA, 2020a).

Meta-analyses may be considered for inclusion in an ISA to the extent that (1) the time period from which the underlying literature is drawn is relevant to the ISA time period (e.g., so that the pooled effect estimates are reflective of current understanding of the literature); (2) the underlying literature would meet the PECOS criteria; and (3) the underlying literature would be policy-relevant. Studies with pooled effect estimates (e.g., meta-analyses and pooled analyses) are considered with caution when evaluating causality so as not to misrepresent and perpetuate errors from approximating estimates (Savitz and Forastiere, 2021, Savitz et al., 2019). Review articles that are out of scope or that are limited to summarizing and interpreting existing studies, without presenting new information or analyses, are not considered for inclusion in the ISA.

PECOS statements are informed by the body of evidence from the previous ISAs and Air Quality Criteria Documents (AQCDs) and by expert knowledge of the policy-relevant scientific issues. Generic examples of PECOS statements are provided below for epidemiologic (see Table A-1), controlled human exposure (see Table A-2), and animal toxicological (see Table A-3) studies. In each ISA, these generic PECOS statements may be modified as appropriate for specific pollutants and health outcome categories.

Table A-1. Generic PECOS statement to define the criteria and framework for identifying relevant epidemiologic studies.

Exposure Duration	Population, Exposure, Comparison, Outcome, Study Design (PECOS)
Short-term exposure	Population (P): Any human population, including populations or lifestages that might be at increased risk;
	Exposure (E): Short-term exposure to the pollutant(s) under evaluation (e.g., up to 30 days) at concentrations relevant to ambient air in the U.S.;
	Comparison (C): Per unit increase in pollutant exposure (e.g., in ppb or $\mu g/m^3$) or populations exposed to lower concentrations of pollutant compared to higher concentrations (e.g., categorical comparisons between different exposure metric quantiles);
	Outcome (O): Change or difference in risk (incidence/prevalence) of health outcome per increase in exposure;
	Study Design (S): 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.
Long-term exposure	Population (P): Any human population, including populations or lifestages that might be at increased risk;
	Exposure (E): Long-term exposure to the pollutant(s) under evaluation (e.g., longer than 30 days) at concentrations relevant to ambient air in the U.S.;
	Comparison (C): Per unit increase in pollutant exposure (in ppb or $\mu g/m^3$) or humans exposed to lower concentrations compared to higher concentrations (e.g., categorical comparisons between different exposure metric quantiles) within or across communities;
	Outcome (O): Change or difference in risk (incidence/prevalence) of health outcome per increase in exposure;
	Study Design (S): 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 endpoint of interest.

Table A-2. Generic PECOS statement to define the criteria and framework for identifying relevant controlled human exposure studies.

Exposure Duration	Population, Exposure, Comparison, Outcome, Study Design (PECOS)
Single or repeated short-term exposures	Population (P): 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 (E): Controlled pollutant exposure – pollutant exposures must be controlled by the experimenters and not simply a measure of ambient air or occupational exposure;
	Comparison (C): 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 (O): 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 (S): 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).

Table A-3. Generic PECOS statement to define the criteria and framework for identifying relevant animal toxicological studies.

Exposure Duration	Population, Exposure, Comparison, Outcome, Study Design (PECOS)
Short-term exposure	Population (P): 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 (E): Short-term (up to 30 days) exposure to relevant pollutant concentrations (i.e., one or two orders of magnitude greater than ambient air concentrations);
	Comparison (C): An appropriate control group exposed to clean air (room air, filtered air) control;
	Outcome (O): 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 (S): Controlled exposure studies of animals *in vivo* meeting the above criteria.
Long-term exposure	Population (P): 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 (E): Long-term (longer than 30 days) exposure to relevant pollutant concentrations (i.e., one or two orders of magnitude greater than ambient air concentrations);
	Comparison (C): An appropriate control group exposed to clean air (room air, filtered air) control;
	Outcome (O): 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 (S): Controlled exposure studies of animals *in vivo* meeting the above criteria.

A.3.2. Atmospheric and Exposure Sciences Studies

To be included in the ISA, relevant atmospheric science and exposure studies must have undergone scientific peer review and been published or accepted for publication within the predefined literature search cutoff dates.[33] Consistent with the health evidence, the ISA uses discipline-specific scoping statements to identify potentially relevant atmospheric and exposure science studies. These scoping statements include consideration of pollutant sources, transport

[33] In the atmospheric science chapter, results of published studies are often supplemented by targeted air quality analyses conducted by the EPA.

and transformation, exposure/extent, and measurement and modeling (STEM). The STEM statements define the objectives of the atmospheric science and exposure evidence assessments and establish criteria that should be met to consider a study for inclusion in the ISA. A study meeting any of the four aspects of the STEM statement could be considered for inclusion in the atmospheric science or exposure assessment.[34]

For atmospheric science, flexibility is built into STEM statement application by maintaining a broad scope for subject areas with few studies identified, but dynamically narrowing the scope as study selection progresses. This is accomplished by iteratively adjusting relevance criteria to account for scientific findings, geographic similarity to the United States, representativeness or diversity of environmental conditions, quality of measurement or modeling method used, or other refinements if the number of identified studies becomes impractical to include.

For most subject areas, study selection is carried out by application of the STEM statement to individual studies. However, if a very large number of relevant studies are identified for a subject area, alternative search strategies can be applied to identify only the most relevant and influential studies. This general approach to focusing on the most influential and relevant atmospheric science studies is consistent with the EPA's approach to inclusion of such studies in the Integrated Risk Information System (IRIS) and Provisional Peer Reviewed Toxicity Value (PPRTV) programs (Thayer et al., 2022).

The STEM statements for a specific ISA are informed by the body of evidence from the previous ISAs and AQCDs and by expert knowledge of the relevant scientific literature. These scoping statements can serve to highlight well-established areas of research as well as gaps in the literature and uncertainties from previous assessments (U.S EPA, 2020a; U.S. EPA, 2016). Importantly, application of STEM statements is consistent with current best practices for reporting or evaluating health science data as recommended by the NASEM (NASEM, 2022) Generic STEM statements for atmospheric science and exposure studies are provided below (see Table A-4 and Table A-5, respectively). These generic statements provide a scoping framework that can be modified as appropriate for specific ISAs.

[34] This contrasts with the PECOS statements used for health effects studies that require all of the listed criteria to be met.

Table A-4. Generic STEM statement to define the criteria and framework for identifying relevant atmospheric science studies.

Statement	Description
Source (S)	Studies reporting quantitative emissions estimates as well as observations of physical and chemical characteristics that add to our understanding of pollutant sources and emissions.
Transport and Transformation (T)	Studies investigating atmospheric fate and transport, transformation, and deposition processes, including transport of air pollutants at various scales (i.e., national/global, regional, urban, neighborhood), atmospheric chemical transformations in the atmosphere, and estimates of atmospheric deposition that add to our understanding of atmospheric processes.
Exposure/Extent (E)	Studies reporting observations and estimates of ambient air concentrations and their trends, including spatial variability on various scales (i.e., national/global, 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 by federal reference and equivalency methods, satellite estimates, low-cost sensor estimates, or research methods, and modeling techniques (e.g., chemical transport modeling) for characterizing pollutant concentrations in ambient air, including the evaluation of measurement principles and modeling assumptions, examination of potential bias and uncertainties, and method intercomparisons that are relevant to the NAAQS or to studies in this ISA.

Table A-5. Generic STEM statement to define the criteria and framework for identifying relevant exposure science studies.

Statement	Description
Source (S)	Emissions from outdoor or indoor sources (e.g., traffic or cookstove emissions), anthropogenic sources or natural sources (e.g., industrial emission or wildfire).
Transport and Transformation (T)	Atmospheric and environmental processes, including the transport of air pollutants at various scales (i.e., national/global, regional, urban, neighborhood, middle, micro scales, and microenvironments), 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 characterized by various surrogates (e.g., ambient air measurement, near-source measurement, microenvironmental measurement, personal exposure measurement and modeling, biomarkers of exposure) and exposure determinants (i.e., factors leading 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 (e.g., federal reference and equivalent methods, passive samplers, remote sensing, and biomonitoring approach) and modeling techniques (e.g., Stochastic Human Exposure and Dose Simulation) 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.

A.4. APPROACH TO LITERATURE SEARCH AND LITERATURE SCREENING

A.4.1. Literature Search

The EPA uses a multipronged approach to identify scientific studies that may be relevant for inclusion in a particular ISA. As described below, this approach employs both targeted and broad literature search strategies (e.g., forward citation searches and keyword searches, respectively). It also includes consideration of studies identified by public commenters, studies recommended during the peer input workshop or during the CASAC review/consultation process (A.7 and A.8), and studies identified by EPA scientists based on professional expertise.

One targeted approach to literature identification that may be employed is forward citation searching. For this approach, a set of relevant published references are identified as a seed set and then databases (e.g., PubMed and Web of Science) are queried to identify recently published literature that has cited any of the references in the seed set. The seed set for the new ISA literature search is comprised of data-containing peer-reviewed references cited in the previous ISAs or AQCDs. Each topic area (e.g., atmospheric science, epidemiology) has its own

seed set(s). Because the seed set is highly relevant to the topic of interest, this targeted approach to reference identification can be more precise than keyword searches, and it further allows for relevance ranking based on the number of references in a bibliography that match references in the seed set.

A broader approach to literature identification is the use of keywords to query literature databases. When this approach is applied, a set of broad keywords is carefully curated for each pollutant and/or topic and then used to search relevant databases (e.g., PubMed and Web of Science). The results of the broad keyword search can then be further categorized by scientific discipline (e.g., epidemiology, toxicology) using automatic topic classification. This step employs machine learning where positive and negative seed references for a particular discipline are used to train an algorithm to identify discipline-specific references based on word use and frequency in titles and abstracts. This method varies in effectiveness across disciplines due to the broad range of topics and variability in term usage in some evidence bases. Discipline-specific keyword searches (e.g., related to pollutant sources, atmospheric science, exposure assessment, dosimetry/toxicokinetics, epidemiology, controlled human exposure, or animal toxicology) may also be used to capture literature pertinent to the pollutant of interest in citation databases (i.e., PubMed and Web of Science). Results of the keyword search and forward citation search are combined and deduplicated to form the set to be screened as described below.

A.4.2. Literature Screening

Studies identified during the literature search described above are evaluated for potential relevance using a multipronged literature screening approach designed to maximize efficiency while simultaneously ensuring relevant studies are identified. Studies are initially evaluated for potential relevance by comparing their titles and abstracts to the discipline-specific scoping criteria defined by PECOS or STEM statements (A.3). Because the number of criteria pollutant-related studies identified in initial literature searches can be very large (e.g., typically hundreds of thousands of studies across disciplines and outcomes), machine ranking literature review software tools (e.g., DistillerSR [Ottawa, Ontario, Canada] Hamel et al., 2020, SWIFT-Active Screener [Sciome, RTP, NC, USA] Howard et al., 2020, Living Literature Review [U.S. EPA, Durham, NC, USA] (U.S EPA, 2023a) are employed to maximize screening efficiency. Final study inclusion and exclusion decisions reached while using these tools are documented in the HERO database.[35] 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, are retained for further evaluation of the full text. For atmospheric science, a second round of title and abstract screening is often required to accommodate the iterative revision of STEM criteria

[35] *https://hero.epa.gov*

or to further restrict the form of the STEM statement if the initial number of studies is too large for effective full text screening.

Following title and abstract screening, ISA-relevance is further evaluated by comparing the full text of documents to the predefined PECOS and STEM scoping criteria described above. Studies not meeting the scoping criteria are excluded from further consideration and are tagged in HERO as not PECOS- or STEM-relevant. Retained studies are tagged in HERO as "considered for inclusion" in the ISA.

Studies identified as PECOS- or STEM-relevant are further evaluated for individual study quality as described below (A.5). The approach described below can be adapted as appropriate for an individual ISA, and the specific study quality criteria for a given assessment are informed by expert knowledge of the literature from previous reviews and by recommendations from a peer input workshop, the CASAC, and members of the public during initial phases of planning and ISA development. Studies that are determined to meet scoping criteria and that are judged of sufficient quality are tagged in HERO for inclusion in the ISA. Studies that do not meet study quality criteria are tagged in HERO for exclusion.

Results of the literature search and screening efforts and the evaluation of individual study quality can be captured in flow diagrams that document the number of references identified from each database searched (i.e., PubMed and Web of Science), the number of references evaluated in each screening step, and general reasons for reference exclusion (see Figure A-2 for an example of anticipated formatting). The specific types of studies selected for inclusion in an ISA may additionally be visualized using evidence maps (see Figure A-3 for anticipated content). Evidence maps are commonly used to visualize evidence derived from systematic literature search and screening approaches. Evidence maps can also be used to identify emerging areas of research, knowledge gaps, and to inform staffing needs.

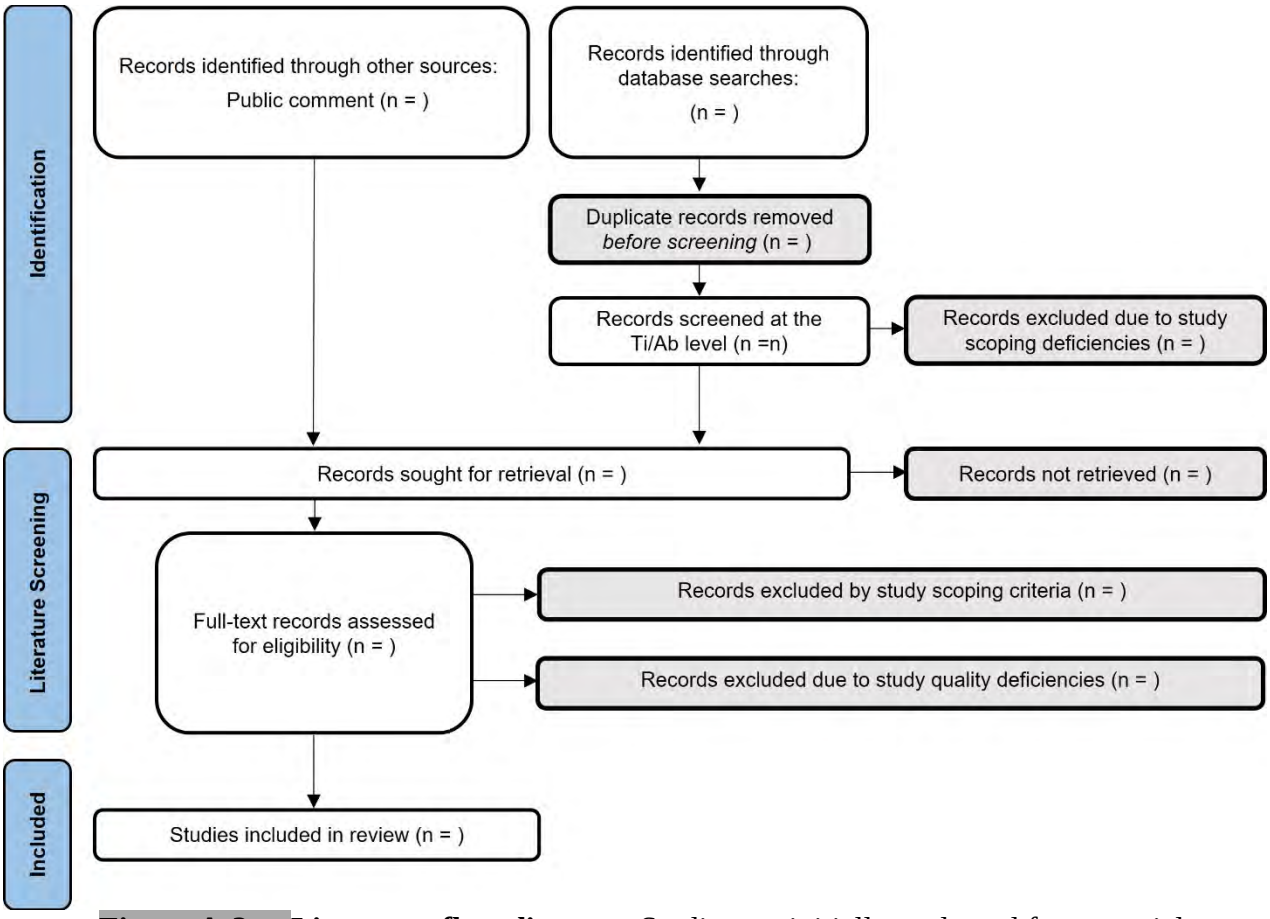


Figure A-2. Literature flow diagram. Studies are initially evaluated for potential relevance by comparing their titles and abstracts to the discipline-specific scoping criteria defined by PECOS or STEM statements. Following title and abstract screening, the ISA relevance is further evaluated by comparing the full text of documents to the predefined PECOS and STEM scoping criteria. Studies not meeting the scoping criteria are excluded from further consideration and tagged in HERO as not PECOS or STEM relevant. Retained studies are tagged in HERO as "considered for inclusion" in the ISA. Detailed literature screening results and include/exclude decisions can be found on the ISA-specific HERO project page (*https://hero.epa.gov*). CASAC, Clean Air Scientific Advisory Committee; Ti/Ab, title and abstract; WoS, Web of Science.

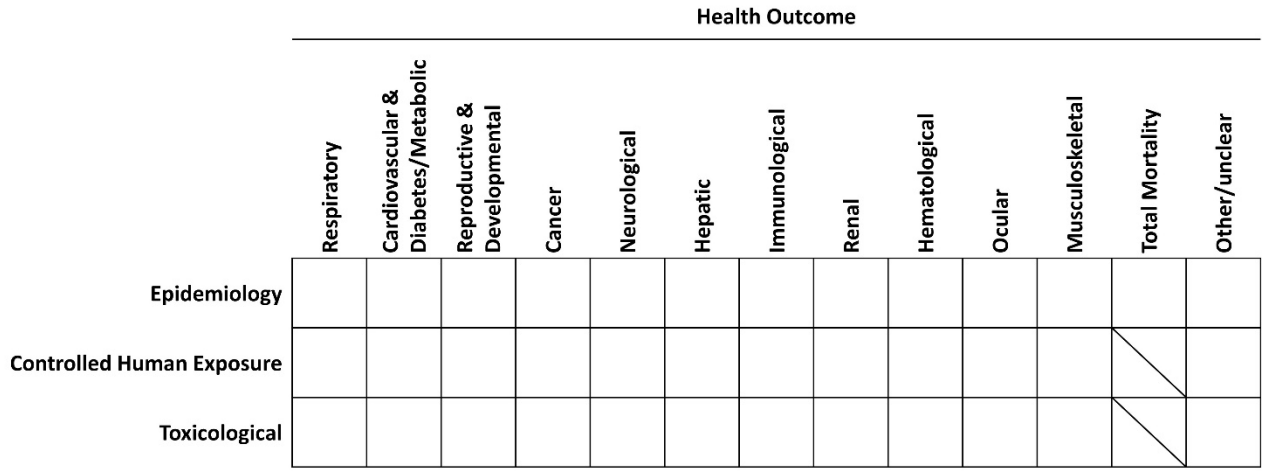


Figure A-3. Number of PECOS-relevant health studies identified during literature screening and organized by health outcome. Health outcome tags will be added to studies during literature screening. The number of studies identified for each health outcome will be tabulated and used to build evidence maps (example health outcomes shown, actual health outcomes will vary by pollutant).

In addition to identifying studies reporting health outcomes, EPA scientists may also seek supplementary scientific information to support biologically plausible modes of action between air pollutant exposures and health effects. Results from experimental *in vivo* studies involving animal models and humans, as well as from *in vitro* studies when appropriate, may be used to evaluate biological plausibility. Given the range of data types used to support biological plausibility, supplementary scientific information may be derived from studies deemed out of scope of PECOS/STEM statements (e.g., exposure concentrations higher than PECOS-defined cut-offs, alternative model systems that do not meet PECOS criteria).

A.5. EVALUATING INDIVIDUAL STUDY QUALITY

Studies that are determined to be PECOS- or STEM-relevant are evaluated for study quality. Individual study quality is evaluated by considering the design, methods, and documentation of each study, but not 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, p. 5), the sections below identify foundational study design attributes and analysis approaches that are considered when evaluating studies and describe how these attributes and approaches can influence the inference drawn from individual studies.

Effective evaluation of study quality relies most fundamentally on transparency, including the clear reporting of key data, assumptions, methods, formulas, input parameters, QA/QC procedures, statistical models/coding, reasoning process, and limitations. Such transparency can increase confidence in individual study results (NASEM, 2022, p. 6-7). The sufficiency of study documentation and reporting can be evaluated based on (1) whether a person with a general knowledge of the research area can understand the described approach, (2) whether the study can, in principle, be independently verified/replicated based on the reported methodology, and (3) whether the limitations can be characterized based on the reported assumptions and uncertainties (WHO, 2008). For studies of health effects in particular, the specific attributes considered in evaluating study quality include (1) study design, (2) study population or test model, (3) pollutant, (4) exposure assessment or assignment, (5) outcome assignment evaluation, (6) potential confounding (i.e., for epidemiology), and (7) statistical methodology. These attributes, described further below, are informed by existing EPA guidelines related to cancer, neurotoxicity, reproductive toxicity, developmental toxicity, and exposure assessment (U.S EPA, 2005; U.S EPA, 1998; U.S EPA, 1996; U.S EPA, 1991; U.S EPA, 2019b); and are consistent with current best practices for reporting or evaluating health science data as recommended by the NASEM (NASEM, 2022). The ISA assessment of the scientific quality of individual studies is 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, are not used as a checklist in evaluating study quality, and the identification of uncertainties that may influence study interpretation does not necessarily lead to a conclusion that the study should be excluded from the ISA. Rather, strengths and limitations identified during study quality evaluation provide context for the broader process of evidence integration and inform the development of ISA conclusions such as causality determinations. Final study inclusion and exclusion decisions reached as a result of study quality evaluation are documented in the HERO database or HAWC.[36] The sections below provide a general discussion of the study attributes considered in the ISA's evaluation of individual study quality for epidemiology (A.5.1), controlled human exposure (A5.2), animal toxicological (A.5.3), and atmospheric science and exposure science studies (A.5.4). These attributes can be adapted for specific ISAs, as appropriate.

A.5.1. Epidemiology

Epidemiologic studies report associations between pollutant exposures and a spectrum of health effects (e.g., changes in heart or lung function) and outcomes (e.g., hospital admissions, mortality) in the general population and in groups potentially at increased risk of pollutant-related effects. When integrated with other lines of scientific evidence (i.e., controlled human exposure and animal toxicology), epidemiologic studies can provide information that supports the elucidation of the exposure to effect continuum, including the lag structure of associations (i.e., lag time between exposure and effect) and the concentration-response relationships across the range of ambient air pollutant concentrations experienced by populations. When evaluating epidemiologic studies, inference is stronger for studies that clearly describe the primary and any secondary aims of the study, or specific hypotheses being tested. In evaluating the quality of epidemiologic studies, the ISAs additionally consider the appropriateness of the (1) study design, (2) study population, (3) pollutant, (4) exposure assessment or assignment, (5) outcome assignment evaluation, (6) potential confounding, and (7) statistical methodology. Each of these study attributes is discussed below.

A.5.1.1. Study Design

Study designs that focus on environmental exposures, such as air pollution, vary depending on the data available and the exposure duration examined, but broadly can encompass cohort, cross-sectional, time-series, case-crossover, panel, and ecological designs. In addition, quasi-experimental designs have been used to mimic randomized experiments and reduce potential bias. Such studies can be informative in the assessment of causality and can include

[36] *https://hero.epa.gov* and *https://hawc.epa.gov/*

intervention studies, studies of natural experiments, and accountability studies. Across designs, studies with larger sample sizes and those conducted over longer time periods reduce selection bias among the study population and increase generalizability, and such studies are therefore considered to produce more reliable results than studies with smaller sample sizes. Because multicity studies examine associations of health effects across cities and in larger and broader populations, the ISAs generally emphasize multicity studies when available.

Air pollution epidemiologic studies examining short-term exposure (i.e., up to 30 days) employ time-series, case-crossover, or panel designs to evaluate the relationships between short-term (e.g., day-to-day) changes in air pollution exposures and specific health outcomes at the population level (e.g., mortality, hospital admissions, or emergency department visits). Some of these study designs examine temporal relationships (e.g., time-series studies) and others allow individuals or populations to serve as their own controls (e.g., a panel study with repeated measurements or a case crossover study), which make them less prone than cross-sectional studies to confounding by factors that differ between individuals (e.g., SES, age, smoking status). Therefore, among epidemiologic studies of short-term exposures, case-crossover and panel designs in which individuals or populations serve as their own controls are emphasized. Inference from these study designs is stronger when they include appropriate controls for factors that vary temporally and that are correlated with the exposure of interest and the health outcome (e.g., daily temperature, day of the week, seasonal illness rates, etc.). Panel studies can be particularly informative if they employ clearly defined scripted activity patterns (e.g., study participants walk the same routes at the same times of day), measure personal exposures to the ambient air pollutant, and measure outcomes at consistent, well-defined lags after exposures.

Air pollution epidemiologic studies examining long-term exposures (i.e., longer than 30 days) and specific health outcomes at the population level (e.g., disease incidence or progression, mortality) often employ cross-sectional or ecological study designs, which measure exposures and outcome(s) at a single point in time, or prospective cohort designs, which assess exposure before the outcome(s) occur. Because prospective designs can better inform the temporality of the relationship between long-term pollutant exposures and outcomes, inference is generally stronger for prospective cohort studies, including case-control studies nested within a prospective cohort (e.g., for rare diseases), than for cross-sectional studies, ecological studies, or case-control studies not nested within a prospective cohort. Long-term exposure studies that do not employ a prospective cohort design can have uncertainties related to potential reverse causality (i.e., cross-sectional studies), the appropriateness of the control group, and the validity of inference about individuals from aggregated or group-level data (i.e., ecologic studies). Because studies of long-term exposures evaluate associations based on spatial and/or temporal variation, inference from

cohort studies is stronger when they address the potential for confounding by factors that vary spatially across populations (e.g., smoking rates, SES, etc.) and temporally (e.g., trends for time).

Additionally, some epidemiologic studies employ study designs and/or statistical approaches that, compared to traditional regression models, are intended to better account for confounders and to mimic randomized experiments and reduce potential bias. In the peer-reviewed literature, these epidemiologic studies are often referred to as causal inference studies,[37] studies that use causal modeling methods, or quasi-experimental studies. Examples of such statistical approaches include, but are not limited to, general propensity scores, inverse probability weighting models, and instrument variables. When evaluating studies that employ these alternative methods for confounder control, the ISA uses an approach consistent with that used for evaluating traditional regression models. As described further below (Section A.5.1.8), this approach considers the clarity, plausibility, internal consistency, and validity of study assumptions; the degree to which confounding has been appropriately considered and addressed; and the degree to which statistical uncertainties are appropriately characterized and quantified.

A.5.1.2. Study Population

The population evaluated in an epidemiologic study can impact the strength of inference drawn from that study. The bullets below describe the attributes of epidemiologic study populations considered as part of the ISA study quality evaluations.

- **Representativeness:** There is greater confidence in results for study populations that are recruited from, and representative of, the target population. Selection bias can influence the results in either direction and may not affect the internal validity of results but rather reduce the generalizability (external validity) of findings to the target population.
- **Inclusion and exclusion criteria for participants:** Clearly specified criteria for including and excluding subjects and the reporting of baseline information on participants that are lost to follow-up can aid in evaluating potential selection bias.
- **Participation rates:** Studies with high participation and low loss to follow-up over time that is not dependent on exposure or health status are considered to have low potential for selection bias.
- **Health conditions:** For studies that evaluate populations with underlying health conditions, independent clinical assessment of the health condition is considered to be the most reliable approach to identifying the study population, though self-report of physician diagnosis could also be considered a reliable approach for some conditions (e.g., respiratory and cardiovascular diseases). Comparison groups with and without an underlying health condition are more informative if groups are from the same source population.

[37] To prevent confusion with the main scientific conclusions presented within an ISA (i.e., the causality determinations), this document refers to such studies as employing alternative methods for confounder control.

A.5.1.3. Pollutant

The primary NAAQS are set to protect public health against exposures to the "criteria" air pollutants. To inform decisions on the NAAQS, each ISA focuses on studies that evaluate the effects of exposures to the particular criteria pollutant(s) under evaluation. Thus, emphasis is placed on epidemiologic studies that evaluate associations with individual criteria pollutants, or with components of a criteria pollutant that are particularly relevant for reviewing the NAAQS (e.g., fine particulate matter ($PM_{2.5}$) in the case of the criteria pollutant particulate matter). Studies only reporting associations with undefined mixtures (e.g., diesel exhaust) or their surrogates (e.g., distance to roadway) are generally not used to inform ISA conclusions.

Studies of mixtures can be informative in an ISA if health effect associations with the particular criteria pollutant under evaluation are also presented. Such studies reflect real-world exposures and can provide insight into combinations of effects or potential modification of the criteria pollutant's effect by the broader pollutant mixture. Inference in the context of the ISA is generally strongest from mixtures studies that present (1) independent effect estimates for the pollutant of interest that adequately control for, or otherwise address, the potential for confounding by co-occurring pollutants (Section A.5.1.6, below) and (2) formal analyses examining how co-occurring pollutants and/or the broader pollution mixture may modify the independent effects of the pollutant of interest. In contrast, studies only presenting associations with mixtures (i.e., no independent effect estimates for the criteria pollutant under evaluation) are typically not policy-relevant in the context of the ISA.

A.5.1.4. Exposure Assessment or Assignment

The primary NAAQS are intended to protect the public health against effects of exposures to criteria pollutants in ambient air. However, information about ambient air exposures is rarely available for individual study participants. Often, epidemiologic studies use surrogates for personal exposures. For most criteria pollutants, ambient air concentrations may be used. Other exposure surrogates commonly used in epidemiologic studies include indoor pollutant concentrations, total personal exposures, and biomarker concentrations. The ISAs emphasize epidemiologic studies with clear justifications for their exposure surrogates (e.g., in terms of capturing spatiotemporal variation in exposures), as well as studies that compare results across multiple valid exposure assessment methods. The bullets below describe attributes of epidemiologic study exposure estimates that are considered as part of the ISA study quality evaluations.

- **Spatiotemporal variability:** Ambient air concentrations of criteria pollutants vary spatially and temporally. Exposure estimates typically have smaller biases and smaller reductions in precision for pollutants with less spatial variation, compared with spatially heterogeneous pollutants (Sheppard et al., 2005). For pollutants with lower spatial

variability, exposure measurement error typically causes health effect estimates to be underestimated (Zeger et al., 2000). In these situations, biases and decreases in the precision of the association (i.e., wider 95% CIs) tend to be relatively small (Rothman and Greenland, 1998; Zeger et al., 2000). In the ISAs, studies with validated exposure estimation methods that capture spatiotemporal variability appropriate for the study design and location carry greater weight, especially for studies involving pollutants with relatively large spatiotemporal variabilities (e.g., traffic-related pollutants, such as NO_2).

- **Exposure duration:** Regardless of the approach to estimating pollutant exposures, inference is stronger when the exposure duration corresponds with the time course for physiological changes in the outcome (e.g., short-term exposures can result in respiratory symptoms while multi-year exposures may be appropriate for cancer and other diseases elicited by long-term exposures).
- **Lag Time:** When examining outcomes associated with short-term exposures, evaluation of the evidence may focus on specific lags between exposure and outcome based on the evidence related to the health outcome being analyzed. When the existence of a lag between exposure and outcome is supported, the following hierarchy is used in the process of selecting results from individual studies of short-term exposures:

  (1) Distributed lag models;

  (2) Average of multiple days (e.g., 0−2);

  (3) If *a priori* lag days were used by the study authors, these are the effect estimates presented; or

  (4) If a study focuses on only a series of individual lag days, expert judgment is applied to select the appropriate result to focus on considering the time course for physiologic changes for the health effect or outcome being evaluated.

- **Source of exposure estimates:** Epidemiologic studies often estimate exposures to ambient air pollutants using fixed-site ambient air monitors, remote sensing approaches, modeling, or using a combination of inputs from multiple sources. For some pollutants, studies use biomarker concentrations as estimates of exposure (e.g., blood lead concentrations). Each of these is discussed below.
  - **Fixed-site monitors:** Concentrations reported from fixed-site monitors are most informative if they are correlated with personal exposures; if monitors are located close to study subjects; if monitored concentrations within a location are correlated; or if monitored concentrations are combined with time-activity information. Some studies use (low-cost) sensors to estimate pollutant exposures. Sensors can provide relatively high spatial and temporal resolution, though sensor validation and calibration can be a challenge, and both should be considered when interpreting studies that use them.
  - **Personal monitoring:** Personal monitoring characterizes exposures at the individual level and provides exposure data attributable to both ambient air and non-ambient-air sources. Measurement errors (e.g., instrument error and

representativeness of exposures to ambient air) associated with personal monitoring should be documented.

- **Remote sensing:** Remote sensing-based approaches can use data from satellites to estimate ground-level concentrations of some pollutants (e.g., $PM_{2.5}$, NO_2, and O_3). Remote sensing approaches should be calibrated using ground-level monitoring networks and their accuracy, precision, and any interferences should be clearly documented.
- **Models:** Some epidemiologic studies use atmospheric models to estimate exposures, either in place of or to supplement measurements from ambient air monitors. These models may include land use regression models, chemical transport models (e.g., EPA's Community Multiscale Air Quality (CMAQ) modeling system), dispersion models, geostatistical models (e.g., kriging), population stochastic models, and hybrid models that use inputs from multiple sources of information (e.g., including models, satellites, and monitors). Uncertainty in exposure predictions from these models is largely influenced by model formulations and the quality of model input data pertaining to precursor emissions or meteorology, which tends to vary on a study-by-study basis. Studies that use these models to estimate exposures should clearly document the procedures for model development and validation, as well as model performance under the conditions of the study.
- **Biomarkers:** For some pollutants, epidemiologic studies use biomarkers to estimate exposures. As noted above for personal monitoring, biomarkers provide exposure estimates at the individual level and that are attributable to both ambient air and non-ambient-air sources. Depending on the biomarker used, exposure biomarkers may be quite limited with regard to the specific timing and duration of the exposure represented. When used, biomarkers should be clearly justified and measured using valid, reliable methods with appropriate characterization of variability.

A.5.1.5. Outcome Assessment and Evaluation

Confidence in study results is greater when outcomes are based on independent clinical assessments of the health condition, without knowledge of exposure status. This can include data from clinical examinations conducted as part of the study as well as data obtained from hospitals, insurance providers or other health care organizations. Outcomes based on interviews, self-reports, or analysis of biological indicators, and defined by consistent criteria and collected by validated, reliable methods without knowledge of exposure status are generally viewed with relatively high confidence. For example, independent, clinical assessment is valuable for outcomes like lung function or incidence of disease, but self-report of physician diagnosis may be adequate for outcomes for which validation studies have been conducted that demonstrate good reliability of self-reported health outcomes (Murgia et al., 2014; Weakley et al., 2013; Barr et al., 2002; Muhajarine et al., 1997; Toren et al., 1993). For biological samples, the stability of the biomarker(s) of interest and the sensitivity and precision of the analytical method is

considered. In general, if errors in the outcome assessment are not correlated with exposure status, those errors tend to bias results toward the null.

A.5.1.6. Potential Confounding

Confounding is "…a confusion of effects. Specifically, the apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect (which may be null)" (Rothman and Greenland, 1998). A confounder is associated with both the exposure and the outcome. Factors are considered to be potential confounders if demonstrated in the scientific literature to be associated with both the exposure and outcome being evaluated. Not accounting for confounders can introduce bias and may produce artifactual associations, thus emphasizing the importance of evaluating the approaches used in individual studies to account for potential confounders and how the strengths of those approaches might influence weight of evidence considerations in causality determinations (NASEM, 2022, pp. 5-6). Inference is stronger for epidemiologic studies that explicitly identify confounders and their potential impacts on results and that take steps to minimize those impacts, often through statistical adjustment and/or study design. In assessing studies that have considered confounders, ISAs give preference to those studies that clearly document the appropriateness of models selected, the validity of methods employed, and the assumptions underlying those methods. Studies that only provide unadjusted effect estimates are not considered.

Potential confounders vary by study population, exposure, and outcome. To control for potential confounders, a variety of statistical methods can be employed. Potential confounders included in statistical analyses should be based on a thoughtful review of published literature and the evidence of potential relationships between variables. In considering the issue of potential confounding on study conclusions, studies in the ISA may utilize different approaches for identifying potential confounders, controlling for the role of such confounders, and accounting for unknown confounders, as described below.

- **Identification of potential confounders**: Strategies for identifying potential confounders can include *a priori* biological considerations, published literature, causal diagrams (e.g., directed acyclic graphs), and/or statistical analyses.
- **Approach to controlling for confounders:** Scientific judgment is needed to identify the likely sources and extent of confounding and to determine how effectively selected study designs and analyses control for potential confounders. Multivariable regression models are often used to detect and control for potential confounders by adjusting for factors that might confound results. These models attempt to control for characteristics that may differ systematically between exposed and unexposed study participants. Other approaches that have been applied include matching and weighting methods Stuart, 2010, g-computation and substitution estimators Keil et al., 2020, doubly robust estimators (Díaz, 2019), bounding approaches Richardson et al., 2014, quantitative bias analysis

approaches (Lash et al., 2014, Weuve et al., 2018), and sensitivity analyses. The approach selected should avoid post-treatment confounding caused by inappropriate adjustment for post-treatment variables (e.g., collider bias).

- **Unknown confounders:** Approaches to handling unknown confounders include, but are not limited to, instrumental variables (Greenland, 2000), bounding approaches Richardson et al., 2014, quantitative bias analysis approaches (Lash et al., 2014, Weuve et al., 2018, and sensitivity analyses. In prioritizing studies for inclusion in the ISA, preference is given to studies with clear discussions of the assumptions underlying selected approaches, the robustness of those assumptions, and any sensitivity analyses conducted. Confidence that unmeasured confounders are not responsible for study findings is increased when multiple studies are conducted in various settings using different subjects or exposures, each of which might eliminate different sources of confounding. Multicity studies can provide insight into the potential impact of unknown confounders on study results through the use of a consistent method to analyze data from across locations with different concentrations of copollutants and other covariates.

For studies of short-term exposure, concern is greatest for potential confounders that vary temporally on time scales similar to the variation in exposures and health outcomes. Confounders commonly considered in studies of short-term exposures include, but are not limited to, the following:

- Meteorology,
- Copollutants, particularly those arising from the same source(s) as the pollutant of interest,
- Day of week and season,
- Medication use,
- Stress and noise,
- Allergen exposure, and
- Long-term temporal trends.

For studies of long-term exposures, concern is greatest for potential confounders that vary spatially. Confounders commonly considered in studies of long-term exposures include, but are not limited to, the following:

- SES, race/ethnicity, and age,
- Smoking rates,
- Stress and noise,
- Historic sources,
- Residential housing age,
- Occupational exposures, and
- Short-term exposures.

Additionally, studies of long-term exposure that do not also appropriately address relevant time-varying confounders (e.g., societal patterns and trends in smoking rates, medication use) can lead to erroneous conclusions regarding support for causal relationships. A number of methods have been employed to handle time-varying confounders in studies of long-term exposure, including but not limited to marginal structural models (Robins et al., 2000), regression adjustment using the longitudinal g-computation formula (Bang and Robins, 2005; Hernán and Robins, 2016) longitudinal inverse probability weighting (Ertefaie and Stephens, 2010), doubly robust sequential regression estimators (Díaz et al., 2023; Stitelman et al., 2012), and difference-in-differences designs (Wing et al., 2018).

For epidemiologic studies that utilize biomarkers (e.g., blood Pb) to estimate exposures, there is additional concern regarding the representation of the specific timing, duration, and/or frequency of exposures. Depending on the biomarker used, there may be limitations in the conclusions that can be drawn about the relationship between the exposure and outcome.

Across exposure durations, the ISAs additionally evaluate the degree to which co-occurring ambient air pollutants may confound health effect associations with the criteria pollutant(s) under evaluation. An emphasis on epidemiologic studies that attempt to minimize such potential "copollutant" confounding may increase confidence in conclusions regarding outcomes associated with the pollutant under evaluation. Copollutant modeling (i.e., two-pollutant models) can reduce concern for this confounding, particularly when correlations between copollutants are relatively low (e.g., $r < 0.4$). However, when correlations are high (e.g., $r > 0.7$), 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 the specific criteria pollutant(s) under evaluation.

A.5.1.7. 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 example, the presence of a pre-existing disease or indicator of low SES (e.g., educational attainment, household income) may act as an effect modifier if it is associated with increased risk of effects from air pollution exposure. It is often possible to stratify the association between health outcome and exposure by one or more of these potential effect modifiers. 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.

Inference can be particularly strong from studies that consider the potential impacts of effect measure modification, especially when the modifying factors are coherent with information from other lines of evidence regarding the biological pathways connecting pollutant exposures with particular health effects (e.g., larger pollutant-related effects in human populations with pre-existing cardiovascular disease would be coherent with animal evidence of cardiovascular effects). Such studies can also be important for quantitatively assessing risks to populations and lifestages at increased risk of health effects for the criteria pollutant evaluated (section A.7.2.3). Uncertainty in inference is lower from studies that articulate and justify assumptions of treatment effect heterogeneity and that include appropriate diagnostics (e.g., multiple comparisons) to account for potentially spurious findings.

Evaluation of effect measure modification in the evidence base informs causality determinations in several ways. First, the presence of effect measure modification can help identify potentially at-risk populations. Consistent evidence that at least one population subgroup is at risk is a category of pollutant-related health effects provides strong support for a causality determination for that health effect category, though the lack of evidence for effect measure modification where there is otherwise evidence of a pollutant-related health effect in the general population does not weaken the support for a causality determination. Evidence for effect measure modification can also explain heterogeneity in results across studies, which could reduce uncertainties regarding inconsistent evidence. Finally, effect measure modification can provide supporting information on mechanisms (e.g., genetic polymorphisms or microbiome profiles) contributing to pollutant-related health effects.

A.5.1.8. Statistical Methodology

Statistical assumptions should be articulated in the context of a study design description. Statistical methods that are appropriate for the power of the study carry greater weight. For example, categorical analyses with small sample sizes can be prone to biasing results toward or away from the null. Statistical tests such as correlations, t-tests and chi-squared tests are not considered sensitive enough for adequate inferences regarding health effect associations. For all methods, the pattern of effect estimates and precision of the estimates (i.e., width of 95% CI) across studies are important considerations for assessing the strength and/or patterns of associations, rather than relying only on statistical significance which is highly dependent on study design (Gelman and Greenland, 2019; Greenland et al., 2016; Wasserstein and Lazar, 2016; Wasserstein et al., 2019). Appropriateness and limitations in statistical approaches should be clearly articulated. Sensitivity analyses with alternative statistical models or specifications can inform the stability of findings and aid in judgments of the strength of inference that can be

drawn from results. In the case of multiple comparisons, consistency in the pattern of association can increase confidence that associations are not due to chance alone.

Some epidemiologic studies employ alternative methods for confounder control that are intended to better account for confounders and to mimic randomized experiments and reduce potential bias. As discussed above (A.5.1.1), in the peer-reviewed literature these studies are often referred to as causal inference studies or studies that used causal modeling methods.[38] In its review of the ISA weight-of-evidence framework, the NASEM committee noted that "the utility of a causal inference framework in an individual study depends on its appropriate use" and "[t]he ability to show mathematical equivalence between statistical and causal parameters does not make the assumptions required for such equivalence true" (NASEM, 2022). Furthermore, the NASEM noted that well-designed studies "1) articulate the scientific question in terms of potential and counterfactual outcomes, 2) specify available data and a causal model, 3) articulate a set of assumptions on the causal model that allow the identification of the causal parameter of interest as an observable statistical quantity, 4) analyze the data to estimate the identified statistical quantity, and 5) interpret the statistical results as causal relations according to the validity of the assumptions made in steps 3 and 4, and quantify the statistical uncertainties" (NASEM, 2022, pp. 163-164). Thus, consistent with the approach to evaluating epidemiologic studies that employ traditional regression models, when evaluating studies that use such alternative methods for confounder control the ISA considers whether study assumptions are clear and plausible, whether confounding has been carefully considered and addressed with appropriate approaches, whether study assumptions are internally consistent and valid, and whether statistical uncertainties are appropriately quantified.

A.5.2. Controlled Human Exposure

Controlled human exposure studies (also known as human clinical studies) evaluate the health effects of experimental exposures in human volunteers under highly controlled and carefully regulated environmental conditions and activity levels. These studies provide direct evidence of physiological and/or biomolecular effects following air pollution exposures and help to identify the biological pathways linking exposures to health effects in humans. They can provide strong support for the biological plausibility of relationships between air pollutant exposures and health effects that may be indicated by epidemiologic study associations, and precise information on exposure- or dose-response relationships in homogeneous populations, often at exposure concentrations at or near those common in ambient air. Thus, data from controlled human exposure studies can provide direct evidence of cause-and-effect relationships

[38] To prevent confusion with the main scientific conclusions presented within an ISA (i.e., the causality determinations), this document refers to such studies as employing alternative methods for confounder control.

in humans and can help compensate for some of the limitations in epidemiologic studies (e.g., potential confounding by co-occurring pollutants or other factors, exposure error, etc.) (NASEM, 2017). For ethical and practical reasons, controlled human exposure studies are generally limited to examining relatively healthy people or those with mild or moderate diseases; short exposure durations; and exposure concentrations expected to elicit no more than mild, transient effects. As a result, these studies do not include individuals who may be at the highest risk of pollutant-related health effects (e.g., children, older adults, people with more severe disease or comorbidities).

Controlled human exposure studies should clearly describe the primary and any secondary aims of the study, or specific hypotheses being tested. In evaluating the quality of these studies, the ISAs additionally consider the appropriateness of the study design, study population, pollutants examined, approach to assigning exposures, outcome assessment, control for potential confounders and statistical analysis. Each of these study attributes is discussed below.

A.5.2.1. Study Design

In prioritizing studies for inclusion in the ISA, preference is given to balanced crossover (repeated measures) or parallel study designs that include control exposures to clean air. In a crossover design, each study participant is exposed to both the air pollutant under evaluation and to clean air, under the same conditions (e.g., ventilation rate), as a control. In this design, each study participant serves as their own control, minimizing inter-individual confounders. In crossover studies, a sufficient and specified time between exposure days should be provided to avoid carry over effects from prior exposure days. In studies using a parallel design, all arms should be matched for individual characteristics, such as age, sex, race/ethnicity, anthropometric properties, and health status. In studies evaluating effects of disease, appropriately matched healthy controls are preferred to aid interpretation of study results. The evaluation of study design generally includes consideration of factors that minimize bias in results such as randomization; blinding; allocation concealment of study subjects, investigators, and research staff; and withdrawal/exclusion of subjects. Studies must include appropriate control groups to allow for accurate interpretation of results relative to criteria pollutant exposure.

A.5.2.2. Study Population

Depending on the study design, subjects recruited into study groups should be matched for age, sex, race/ethnicity, anthropometric properties, and health status. In studies evaluating effects of specific subject characteristics (e.g., disease, genetic polymorphism, etc.), appropriately matched healthy controls are preferred. Relevant characteristics and health status should be reported for each experimental group. For the examination of populations with an

underlying health condition (e.g., asthma), independent, clinical assessment of the health condition is ideal, but self-report of physician diagnosis generally is considered reliable for respiratory and cardiovascular disease outcomes. Criteria for including and excluding subjects should be indicated clearly, and the loss or withdrawal of recruited subjects during the course of a study should be reported.

A.5.2.3. Pollutant

As described above for epidemiologic studies, each ISA focuses on studies that evaluate the effects of exposures to the particular criteria pollutant(s) under evaluation. Thus, emphasis is placed on controlled human exposure studies that evaluate individual criteria pollutants or components of a criteria pollutant that are particularly relevant for reviewing the NAAQS (e.g., $PM_{2.5}$ in the case of particulate matter). Studies of pollutant mixtures (e.g., ozone as part of an oxidant mixture) can be informative if health effects of exposure to the criteria pollutant under evaluation, presumably a component of the mixture, are also examined separately. Such studies can provide insight into potential modification of the effect of the criteria pollutant by other individual pollutants or by a broader pollutant mixture. Ideally, studies should report the source, purity, and form of the pollutant(s) examined.

A.5.2.4. Exposures

Controlled human exposure studies that approximate expected human exposures in terms of concentration, duration, exercise level, ventilation rate and method of exposure are of particular interest. In prioritizing studies for inclusion in the ISA, preference is given to studies that evaluate pollutant exposure concentrations close to existing ambient air concentrations, though studies that use higher exposure concentrations may still provide information relevant to consideration of the biological plausibility of effects associated with lower exposures and/or dosimetry. Studies should have measures in place to adequately monitor and control the exposure conditions, including pollutant concentrations, temperature, and relative humidity. The method of exposure (e.g., chamber, facemask, etc.) should be specified, and activity level of subjects during exposures should be well-characterized. Preference is also given to studies that include control exposures (e.g., to filtered air or room air). Study subjects should be randomly exposed without knowledge of the exposure condition, and exposure metrics should be well characterized, including external exposure, intake dose, dosing regimen, and exposure route.

A.5.2.5. Outcome Assessment and Evaluation

For each experiment and each experimental group, including controls, precise details should be provided describing the endpoints examined, how they are measured, and when and where they are evaluated. Endpoints should be assessed in the same manner for control and exposure groups using valid, reliable methods. This includes using the same procedures in terms

of time after exposure, methods, endpoint evaluator, etc. Blinding of endpoint evaluators is ideal, especially for qualitative endpoints such as histopathology. Time of the endpoint evaluations is a key consideration that will vary depending on endpoint evaluated. Endpoints should be assessed at time points that are appropriate for the research questions, and those time points should be clearly justified.

A.5.2.6. Potential Confounding

To limit potential for confounding, studies included in the ISA use either a crossover repeated measures design, in which each study participant serves as their own control, or a parallel exposure design in which experimental and control groups are matched for individual level characteristics (e.g., race/ethnicity, sex, body weight, smoking history, age) and time-varying factors (e.g., seasonal and diurnal patterns). Exposures should be well-characterized to evaluate independent effects of the pollutant(s) under study.

A.5.2.7. Statistical Methodology

Statistical methods should be described clearly and be appropriate for the study design and research question, including correction for multiple comparisons when appropriate. Statistical significance is generally used to evaluate the findings of controlled human exposure studies. Detection of statistical significance is influenced by a variety of factors including, but not limited to, the size of the study, exposure and outcome measurement error, and statistical model specifications. Sample size is not a criterion for exclusion, though the sample size should provide adequate power to detect hypothesized effects. Because statistical tests have limitations, consideration is also given to trends in data and reproducibility of results. Consistent trends across studies can informative, even if results of individual studies are not statistically significant.

A.5.3. Experimental Animal Studies and Emerging Approaches in Toxicology

Animal toxicological studies evaluate the health effects of controlled pollutant exposures in animal models (e.g., non-human primates, mice, rats, guinea pig). Investigators expose non-human mammalian animal species to known concentrations of air pollutants under carefully regulated laboratory conditions. Experimental animal studies provide critical information on potential human health effects, exposure- and dose-response relationships, and underlying toxicological pathways and mechanisms of action. One major uncertainty associated with animal studies is the representativeness of responses in animals to humans, given the potential differences in metabolism, hormonal regulation, breathing patterns, lung structure, physiology, and anatomy. When these differences are appropriately characterized, experimental animal studies can inform and improve our understanding of biological mechanisms, providing support

for biological plausibility of relationships between air pollutant exposures and health effects that may be indicated by epidemiologic studies, and address uncertainties in other lines of evidence (e.g., confounding in epidemiologic studies). In addition, depending on the animal model used and the study design employed, experimental animal studies may help inform an understanding of the potential for biological responses and health effects in certain populations that may be at increased risk of a criteria pollutant-related health effect.

Another emerging line of evidence in toxicological studies comes from new approach methodologies (NAMs), a term which refers to any technology, methodology, approach, or combination of these tools that can inform chemical hazard and risk assessment while avoiding the use of animal testing, including *in silico*, *in chemico*, *in vitro*, and *ex vivo* approaches (ECHA, 2016; U.S EPA, 2018; U.S EPA, 2021b).[39] While the EPA has historically relied on *in vitro* and/or *in vivo* studies to provide mechanistic insight, data collected using well-validated NAMs may also provide insight into the occurrence of health effects when guidelines are established for use of these methods in air pollution studies.

Toxicological studies should clearly describe the primary and any secondary aims of the study, or specific hypotheses being tested. In evaluating the quality of these studies, the ISAs additionally consider the appropriateness of the study design, test model, pollutant(s) examined, exposure assignment and approach, outcome assessment, variable control, and statistical analysis. Each of these study attributes is discussed below.

A.5.3.1. Study Design

Toxicological studies should include appropriately time-matched control exposures, should randomize assignment to exposure groups and, where possible, should blind research personnel from endpoint evaluation and analysis. Blinding of research personnel to study group may not be possible due to animal welfare and experimental considerations; however, differences in the monitoring or handling of animals across groups by research personnel should be minimized. Studies should use methods to limit differences in baseline characteristics of control and exposure groups, and groups should be subjected to identical experimental procedures and conditions to the extent possible (e.g., in animal care including housing, husbandry, etc.). The evaluation of study design generally includes consideration of factors that minimize bias in results, such as randomization, blinding, and unexplained loss of animals.

[39] Experimentation performed using a computer are referred to as an *in silico* approach (Cronin, 2009). Chemical reactivity tests that are performed in the absence of biological materials are referred to as *in chemico* approaches (Cronin, 2009). *In vitro* tests are performed outside of a living organism using established cell lines while *ex vivo* approaches are those that involve the collection of cells/tissues/organs from living organisms for use in experimentation (European Commission et al., 2020).

Where applicable, approval of study protocols by appropriate institutional animal care and use committees must be obtained (European Commission et al., 2020; Cronin et al., 2009).

A.5.3.2. Test Model

Toxicological studies should provide a clear justification for their chosen model system. Unless data indicate otherwise, laboratory nonhuman mammalian animal species of any lifestage, stock, and strain are considered appropriate for evaluating effects of pollutant exposure. Ideally, studies should report species, strain, substrain, genetic background, age, sex, and weight. It is preferred that the authors test for effects in both sexes and multiple lifestages and report the result for each group separately. All animals used in a study should be accounted for, and rationale for exclusion of animals or data should be specified.

A.5.3.3. Pollutant

As described above for other disciplines, each ISA focuses on studies that examine the effects of exposures to the particular criteria pollutant(s) under evaluation. Thus, emphasis is placed on toxicological studies that examine individual criteria pollutants or components of a criteria pollutant that are particularly relevant for reviewing the NAAQS (e.g., $PM_{2.5}$ in the case of particulate matter). Studies of pollutant mixtures can be informative if health effects of exposure to the criteria pollutant under evaluation, presumably a component of the mixture, are also examined separately. Such studies can provide insight into potential modification of the effect of the criteria pollutant by other individual pollutants or by a broader pollutant mixture. Ideally, studies should report the source, purity, and form of the pollutant(s) examined.

A.5.3.4. Exposures

Animal toxicological studies should have measures in place to adequately control exposure conditions, including the identity of the target pollutant, exposure concentrations, temperature, and relative humidity. Studies that approximate expected human exposures in terms of concentration, duration, timing of exposure, and method of pollutant administration are of particular interest, though pollutant exposures within two orders of magnitude of recent ambient air concentrations may be considered relevant, e.g., if they assess a previously unreported effect or mode of action for an observed effect or examine multiple concentrations to elucidate exposure-response relationships. This range in relevant exposures is meant to account for differences in dosimetry, toxicokinetics, and biological sensitivity between humans, including groups at increased risk, and the various animal species and strains used in toxicological studies. Studies using exposure concentrations or doses at the higher end of this range may be considered to the extent that they provide information relevant to understanding mode of action or mechanisms, inter-species variation, or factors that may confer increased risk in human populations.

The focus is generally on inhalation exposure, but oral and intravenous exposures may also be informative in studies that examine a relevant biomarker (e.g., blood lead concentrations). Non-inhalation exposure experiments that target the respiratory tract (e.g., intratracheal instillation [IT]) may be informative if they provide information relevant to biological plausibility and dosimetry. As discussed above, *in vitro* studies in validated model systems may be considered for inclusion in an ISA, though the relevance of *in vitro* exposure concentrations to human inhalation exposures are often an additional source of uncertainty. All studies should include exposure control groups (e.g., filtered air or room air).

A.5.3.5. Outcome Assessment and Evaluation

For each treatment group, including controls, precise details should be provided describing the endpoints examined, how they are measured, and when and where they are evaluated. Endpoints should be assessed in the same manner for control and exposure groups using valid, reliable methods. This includes using the same procedures in terms of time after exposure, methods, endpoint evaluator, etc. Limits of detection should be provided for quantitative assays, when available. Blinding of endpoint evaluators is ideal, especially for qualitative endpoints such as histopathology. Timing of the endpoint evaluations is a key consideration that will vary depending on the endpoint under investigation. Endpoints should be assessed at time points that are appropriate for the research questions.

A.5.3.6. Variable Control

To limit potential impact of other variables on study results, studies included in the ISA match experimental and control groups for individual-level characteristics and time-varying factors. Individual characteristics include strain, sex, body weight, litter size, feed, and water consumption. Exposures should be well characterized to evaluate independent effects of the pollutant(s) under study.

A.5.3.7. Statistical Methodology

Statistical methods should be described clearly and should be appropriate for the study design and research question, including correction for multiple comparisons when appropriate. Results should be reported with sufficient detail to allow for independent interpretation (e.g., quantitatively with a measure of variance). Statistical significance is generally used to evaluate study findings. Detection of statistical significance is influenced by a variety of factors including, but not limited to, the sample size used in the study, exposure and outcome measurement error, and statistical model specifications. Sample size is not a criterion for exclusion, though the sample size should provide adequate power to detect hypothesized effects. Because statistical tests have limitations, the ISAs also consider trends in results across studies and reproducibility

of study results. Consistent trends across studies can be informative for weight-of-evidence evaluations, even if results of individual studies are not statistically significant.

A.5.4. Atmospheric, Environmental, and Exposure Science

Information from atmospheric and exposure sciences can inform the ISA interpretation of health effects evidence. Atmospheric sciences provide information on air pollutant sources, atmospheric transport and transformation, ambient air concentrations, and techniques for measuring or modeling air pollutants and their precursors. Human exposures to air pollutants is contact with the pollutant(s) at the interface of the breathing zone over a specified length of time (U.S EPA, 2019b).

Atmospheric and exposure sciences provide health effects studies with information on emissions, ambient air concentrations, properties, processes, and constituents of criteria air pollutants (e.g., in the case of photochemical oxidants and oxides of nitrogen); spatiotemporal variations; various exposure surrogates (e.g., ambient air concentration, indoor concentration, and total personal exposure); and variability and uncertainty associated with exposure estimates. Of particular interest is understanding the strengths and limitations of exposure surrogates commonly used in studies of health effects, including information on errors in measuring or modeling the exposure surrogate and errors resulting from using the surrogate to approximate true exposure.

The ISA study quality evaluation for atmospheric and exposure science studies considers the applicability and utility of the study, the soundness of the study approach, clarity and completeness of the study, and its treatment of uncertainty and variability. These study attributes are adopted from the EPA exposure assessment guidelines (U.S EPA, 2019b).[40] They are not mutually exclusive and can be used collectively to inform conclusions on study quality.

A.5.4.1. Applicability and Utility

Applicability and utility refer to the extent to which information presented in a study is relevant for its intended use (U.S EPA, 2019b). To be considered for inclusion in an ISA, atmospheric and exposure science studies should evaluate the pollutant in ambient air (and in other media, as relevant), and/or exposure pathways (e.g., emissions, transformation, transport) pertinent to U.S. populations, with a focus on the policy-relevant issues that help frame the assessment of the health effects evidence. These issues can vary across the ISAs and generally include characterizing emissions sources, transport and transformation processes, measurement and modeling methods, temporal and spatial patterns of ambient air pollutant concentrations and

[40] Analogous study quality evaluation guidelines have not previously been developed for atmospheric science. Thus, the ISA study quality evaluation of atmospheric science studies is based on adaptation of the study attributes described in the EPA exposure assessment guidelines (U.S EPA, 2019b).

exposures, meteorological impacts on pollutant concentrations, relationships and correlations between pollutants within complex mixtures, infiltration to indoor environments, transfers to other media, as relevant, and the strengths and limitations of various exposure estimation approaches. For studies examining exposure surrogates, the ISA examines various aspects of exposure measurement error, some of which have been discussed above in the context of the health evidence (e.g., errors in measurements, inherent assumptions in exposure modeling, uncertainties in model input parameters, spatiotemporal variations in pollutant concentrations, activity patterns and building ventilation). The ISA assessment of applicability and utility is aided by clear documentation of study design, data collection/generation techniques, and any underlying assumptions.

A.5.4.2. Soundness

Soundness refers to the extent to which the scientific and technical procedures, measures, methods, or models employed to generate information are reasonable for, and consistent with, the intended application (U.S EPA, 2019b). In evaluating soundness, the ISAs focus on atmospheric or environmental science and exposure studies that use quality-assured measurement and/or modeling techniques. Studies should include or reference clear and comprehensive descriptions of the measurement or modeling techniques used, evaluation procedures and performance metrics, strengths and limitations of techniques, and quality-control procedures. The ISAs place more weight on studies that use methodologies appropriate for meeting study goals and that clearly justify those methodological decisions. For example, considerations when evaluating soundness of measurement- and model-based atmospheric science or exposure studies are described below.

- **Measurement studies**: The ISAs place more weight on studies that document or reference high quality measurement data, including uncertainty, bias, sensitivity, specificity, stability, repeatability, and data management practices consistent with best practices among similar measurement studies. Also included are innovative, newly developed methods with less developed data quality documentation that show promise as potential alternative methods that could have advantages over current methods, and methods that contribute unique insight into atmospheric processes and concentration trends that complement established, high quality measurement methods.
- **Modeling studies**: The ISAs place more weight on studies that include or reference clear descriptions of acceptable rationales for model selection and model assumptions, model input parameters (e.g., data source for input parameters, rationale for input data selection, quality of input data (including accuracy, precision, representativeness, completeness, and consistency)), model calibration/validation procedures (e.g., goodness-of-fit criteria for acceptance of the parameter value, the procedure to handle outliers, procedures to validate results, model parameter sensitivity analysis, impact of parameter uncertainty on results), model evaluation results (e.g., for chemical transport models) as well as data transfer, transformation and storage procedures.

A.5.4.3. Clarity and Completeness

Clarity and completeness refer to study transparency and is a crosscutting attribute (WHO, 2008). Transparency is essential for evaluating other attributes of data/study quality. For example, documenting and reporting key assumptions, methods, formulas, input parameters, reasoning processes, and limitations would increase the transparency of a study. Key aspects of a study for purposes of evaluating transparency are summarized below.

- **Study Rationale**: Study transparency is greater for studies presenting clear rationales for study design, location, population selection (in the case of exposure studies), method selection, and conclusions.
- **Assumptions**: The most informative studies clearly articulate assumptions related to study design and methods used (e.g., dispersion model assumptions, and assumptions associated with using central monitoring sites for exposure assignment), as well as assumptions associated with chemistry, transport, dispersion, and/or exposure modeling techniques, and strengths and limitations of a study.
- **Data and procedures**: Studies that clearly describe QA and QC procedures, key data, data sources and methods, and statistical methods (e.g., methods for missing data and imputation, and quantitative relationships between and within pollutant measurements, such as regression slopes, intercepts, and fit statistic), are considered most informative.

A.5.4.4. Uncertainty and Variability

Uncertainty in environmental or exposure assessment studies comes from incomplete or incorrect information about an environmental measurement or true exposure and variability describes the natural heterogeneity of measurements/estimates. Uncertainty and variability are associated with each element of atmospheric/environmental analyses and exposure assessments. Evaluation of uncertainty and variability can increase our understanding of the reliability of analyses and the data needs for improving them.

In considering studies for inclusion in the ISA, preference is given to studies that characterize uncertainties in measurement and/or modeling approaches and the factors contributing to uncertainties in these analyses. Studies can be of particular use in the ISAs if they characterize exposure errors relevant to interpreting epidemiologic study designs or if they examine the potential for differential exposures across various populations. For example, classical error in the exposure surrogate of an epidemiologic study, defined as error scattered about the true exposure and independent of the true exposure, is generally expected to reduce precision and to negatively bias health effect associations between air pollution and health effects. In contrast, Berkson error, in which the true value varies randomly around the measured value and the measurement error is independent of the measured value, reduces precision but is not expected to bias the health effect estimate (Goldman et al., 2011).

Studies of differential exposures can identify populations with elevated exposures, characterize exposures for populations at higher risk of pollutant-related effects (e.g., due to pre-existing disease), and can evaluate the factors contributing to variability in exposures (e.g., activity patterns, proximity to sources, etc.).

A.6. EXTRACTING DATA FROM RELEVANT STUDIES

For studies determined to be appropriate for inclusion in an ISA, relevant study data are extracted into evidence tables.[41] Data are extracted using literature review software tools (e.g., DistillerSR) or directly into spreadsheets by the EPA scientists or other personnel trained to perform this task. In all cases, the integrity of extracted data is confirmed by quality control checks performed as described below (A.9). Extracted study summary data are compiled in evidence tables that provide a high-level overview of the evaluated studies and are used to assist with data analysis, evidence synthesis, and formulation of conclusions. Example formats for example data extraction tables are provided below (see Tables A-7 through A-9).

Table A-6. Example Data Extraction Table – Epidemiologic Studies.

Study Reference	Study Population	Exposure Assessment	Concentration and Co-pollutant Examination	Outcome Assessment	Statistical Methods	Effect Estimates 95% CI
HERO ID, author(s), year N Location Years (recruitment) (follow-up) Study design	Population details	Exposure model, monitor data Annual, monthly Model development and validation	Mean/median value (reported by study and/or standardized) Min, Max Pearson or Spearman rho value(s) for each co-pollutant	Description of outcome	Model type and list of confounders	ORs, RRs, β

Max, maximum; min, minimum; N, sample size; ORs, odds ratio; RRs, risk or rate ratios.

[41] If a potentially informative study is missing information relevant to extraction endpoints, the EPA may contact the corresponding author to request that information. The request and author's response will be included in the docket for that ISA. If the missing information is not available, the study may be deemed inappropriate for inclusion in the ISA.

Table A-7. Example Data Extraction Table – Animal Toxicological Studies.

Study Reference	Study Population	Exposure Details	Endpoints Examined
HERO ID, author(s), year	Species/strain, age, & sample size	Exposure route, concentration, duration, timing of exposure, control group composition, exposure biomarker (if relevant)	Outcome(s) measured, timing of outcome measurement, results summary

Table A-8. Example Data Extraction Table – Controlled Human Exposure Studies.

Study Reference	Study Population	Exposure Details	Endpoints Examined
HERO ID, author(s), year	Population details (i.e., Sample size, age, sex, disease state, etc.)	Target pollutant concentration or range, subject activity, duration of exposure, frequency of exposure	Outcome(s) measured, timing of outcome measurement, results summary

Table A-9. Example Data Extracted Table – Exposure Science Studies.

Study Reference	Study Rationale	Sampling and Modeling	Data Analysis	Exposure Factors	Results
HERO ID, author(s), year	Hypothesis; Study location selection; Inclusion and exclusion criteria for study participants (age, gender, ethnic group, health status, SES, etc.); Sample size determination; Data quality objectives	Exposure indicators; sampling frequency and duration; Sampling methods; model input parameters	Statistical analyses methods; summary statistics; uncertainty and variability in the findings; model performance	Exposure factor data and the basis for choosing certain values of exposure factors	Exposure levels for various populations; sources and extent of exposure errors; correlations with copollutants exposures

A.7. DRAFTING ISA SECTIONS

A.7.1. Draft Chapters and Obtain Peer Input

After completing data extraction, the ISA authors draft topic-specific chapters in two stages. During the first stage, initial drafts are developed and used to inform discussions during a peer-input workshop as described below. Initial draft chapters typically include an introduction, a summary of the previous ISA conclusions, an overview of the scope of the assessment in the

current ISA, and a review of the available science. Initial drafts of human health outcome chapters often additionally include a biological plausibility section. The integrated summary and policy-relevant conclusions (e.g., causality determinations, conclusions on at-risk populations) are not developed in this initial drafting stage.

The peer input workshop brings together the EPA and external subject matter experts from a variety of disciplines to review the draft chapters. The purpose of the workshop is to obtain early feedback from experts in relevant fields to ensure that the draft ISA reflects the most up-to-date policy-relevant science. The discussion at the peer-input workshop also can provide a foundation for initial integration of evidence within and across disciplines. During the peer input workshop, expert panelists are asked to address several overarching questions, often including, but not limited to the following:

- To what extent do the initial draft materials capture the key studies published since the cutoff date of the prior ISA?
- What are panelists' views on the specific issues that should be considered or highlighted and that will be important for integrating evidence across disciplines?
- To what degree are study results accurately reported and appropriately interpreted?

The EPA staff may ask workshop panelists additional questions related to the organization and content of specific draft chapters. The public is invited to listen in on the discussion during the workshop, but no draft ISA materials are shared publicly, and comments are not solicited from the public at this time. After the workshop, the ISA authors update the initial draft chapters, integrate evidence across disciplines, and develop policy-relevant scientific conclusions including causality determinations and conclusions on populations that may be at increased risk. The approaches to integrating evidence and developing these conclusions are discussed in detail in the following sections.

A.7.2. Develop Policy-Relevant Scientific Conclusions

Drawing upon the results of studies determined to be relevant and of adequate quality, the ISAs reach a number of policy-relevant conclusions intended to inform the NAAQS review. Most prominently, the ISAs use structured frameworks to reach conclusions on the strength of the scientific evidence supporting cause-effect relationships between pollutant exposures and adverse health effects (i.e., causality determinations) and on the populations that may be at increased risk of such adverse health effects (i.e., at-risk populations).[42] While discussed

[42] The ISAs also typically present findings on other policy-relevant issues, which vary by pollutant and discipline and can include concentration-, exposure-, and/or dose-response relationships; the exposure concentrations below which evidence for effects is limited; on the potential adversity of particular effects; the effects of particular pollutant components (e.g., for $PM_{2.5}$); etc. These are described more fully in individual assessments.

separately, these frameworks are carefully integrated within the ISA, with the evidence for increased risk in certain populations often providing substantial support for causality determinations. The ISA frameworks for reaching conclusions on causality and at-risk populations are described further below.

A.7.2.1. Causality Determinations

The 1964 Surgeon General's report on tobacco smoking defined "cause" as a "significant, effectual relationship between an agent and an associated disorder or disease in the host" (Hew, 1964). More generally, a cause is an agent that brings about an effect or a result. Unlike an association, a causal claim supports the creation of counterfactual claims; that is, a claim about what the world would have been like under different or changed circumstances (IOM, 2008).

The ISAs evaluate and integrate scientific evidence on health effects of criteria pollutant exposures, and based on this integration and the weight of the evidence in support of causation, present a determination regarding the existence of a causal relationship between pollutant exposure and various health effects. Evaluating the potential for cause-effect relationships between criteria pollutant exposures and health effects is made more challenging by the fact that many of the outcomes evaluated in the ISAs have complex etiologies. Diseases such as asthma, coronary heart disease, and cancer are typically initiated by multiple environmental and biological factors. Outcomes in a given individual can depend on factors such as age, genetic background, nutritional status, immune competence, and social factors (IOM, 2008; Gee and Payne-Sturges, 2004). Further, exposure to a combination of agents could cause synergistic or antagonistic effects. Thus, the observed risk may represent the net effect of many actions and counteractions.

The ISA framework for reaching causality determinations recognizes that, compared to any single study, the availability of multiple studies evaluating a particular topic, each with different strengths and limitations, provides a more robust foundation for evaluating the overall strength of the evidence. The existing framework is described in the 2015 Preamble to the ISAs (U.S. EPA, 2015). That framework was informed by the weight-of-evidence approaches formulated by other regulatory and science agencies, including the National Academy of Sciences (NAS) Institute of Medicine IOM, 2008 , the International Agency for Research on Cancer (IARC, 2006), the EPA *Guidelines for Carcinogen Risk Assessment* (U.S EPA, 2005), the Centers for Disease Control and Prevention (CDC, 2004), Integrated Risk Information System [IRIS] (U.S EPA, 2022), and World Health Organization (WHO, 2021). The frameworks used by each of these organizations are similar in nature, although adapted to different purposes, and have proven effective in providing uniform structure and language for causality

determinations. The framework described below builds on that in the 2015 Preamble to the ISAs (U.S. EPA, 2015), with updates reflecting CASAC feedback over multiple ISAs since 2015 and reflecting consideration of recent NASEM recommendations (NASEM, 2022).

A.7.2.1.1. Aspects of the evidence important to judging causality

In making judgments regarding the potential for causal relationships, the ISAs consider various aspects of causality drawn from previous efforts focused largely on epidemiology studies. The 1964 Surgeon General's report on tobacco smoking discussed criteria for the evaluation of epidemiologic studies, focusing on consistency, strength, specificity, temporal relationship, and coherence (Hew, 1964). Sir Austin Bradford Hill (Hill, 1965) articulated similar aspects of causality in epidemiology and public health that have been widely adopted (IOM, 2008; IARC, 2006; U.S EPA, 2005; CDC, 2004). The EPA has adapted this list of characteristics for use in the ISA causality determinations specific to effects of criteria pollutant exposures (U.S. EPA, 2015).

Table A-10 and the accompanying text describe the key aspects of the evidence base that the ISA considers in judging causality. Although the list of aspects provides a framework for assessing the evidence, it does not lend itself to being considered in terms of simple formulas or fixed rules leading to conclusions about causality (Hill, 1965). For example, one cannot simply count the number of studies reporting statistically significant results or statistically nonsignificant results and reach credible conclusions about the relative weight of evidence and the likelihood of causality. The aspects cannot be used as a strict checklist, and not meeting one or more of the principles does not automatically preclude a determination of causality [see discussion in (CDC, 2004). Rather, these aspects provide a framework for systematic appraisal of a body of evidence, informed by peer input and public comment, which includes weighing alternative views on controversial issues. Additional context for interpreting the aspects in Table A-10 is provided in subsequent sections.

Table A-10. Aspects of the evidence important to judging causality.

Aspect	Description
Consistency	An inference of causation is strengthened when a pattern of elevated risks is observed across multiple independent studies. The reproducibility of findings in different groups and using different study designs constitutes one of the strongest arguments for causation. Statistical significance is not the sole criterion by which the presence or absence of an effect is determined. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.
Coherence	An inference of causation is strengthened when multiple lines of evidence independently support the occurrence of related effects following pollutant exposure. Such coherence can be demonstrated by evidence across various disciplines and/or across a variety of study designs.
Biological plausibility	An inference of causation is strengthened by results from experimental studies or other sources demonstrating biologically plausible mechanisms by which pollutant exposures could lead to adverse outcomes.
Biological gradient (i.e., exposure-response relationship)	A well-characterized exposure- or dose-response relationship (e.g., larger, more serious effects associated with increasing exposure/dose) can strongly support cause and effect, especially when such relationships are observed across multiple disciplines and durations of exposure, including the observation of larger and/or more serious effects following longer exposures.
Strength of the observed association	The finding of large, precise risks increases confidence that an association is not likely due to chance, bias, or other factors. However, an effect estimate that is small in magnitude does not necessarily indicate a lack of causation.
Experimental evidence	Strong evidence supporting causation can be provided by experimental studies (i.e., controlled human exposure, animal toxicological) and by studies of "natural experiments" when a change in exposure is found to result in a change in occurrence or frequency of health effects.
Temporality of the observed association	Evidence that pollutant exposure precedes the appearance of the effect, and that the interval between exposure and effect are reasonable based on available science, supports causation.
Specificity of the observed association	Evidence linking exposure to a specific outcome can provide strong support for causation. However, lack of specificity does not necessarily indicate a lack of causation since it is rarely expected that a pollutant exposure will invariably predict the occurrence of an outcome, and since a given outcome may have multiple causes.

A.7.2.1.1.1. Consistency

In assessing the consistency of findings across studies for evaluating the weight of the evidence, the ISAs emphasize the pattern of results in a body of epidemiologic or experimental studies examining related outcomes. Consistency of findings is informed by the repeated observation of effects or associations across multiple independent studies. Results that are replicable across variations in study designs or analytic choices "can be viewed as more robust and as stronger evidence for a causal relationship" (NASEM, 2022, p. 7). Thus, the strength of the evidence is increased when similar findings are reported in different populations under

different circumstances. For epidemiologic studies, the ISA's evaluation of consistency includes consideration of the direction and magnitude of associations across independent studies with greater emphasis on the pattern of results across studies than on the statistical significance of results in individual studies. Statistical significance is influenced by a variety of factors including, but not limited to, the size of the study population, exposure and outcome measurement error, and statistical model specifications. Statistical significance may be informative; however, it is just one of the means of evaluating confidence in the observed relationship and assessing the probability of chance as an explanation. As statistical inferences may result in both false positives and false negatives, the ISAs emphasize the pattern of associations across epidemiologic studies. Statistical significance of results is traditionally given greater emphasis on the evaluation of consistency across controlled human exposure and animal toxicological studies, though the pattern of results across such experimental studies with similar designs and examining related effects can also be informative. Discordant results among independent studies may be explained by differences in study methods, random errors, exposure errors, confounding factors, or study power, and the ISAs explore such potential explanations for studies with results that are not consistent.

A.7.2.1.1.2. Coherence

In evaluating coherence of the evidence base, the ISAs examine the degree to which studies from different disciplines, or studies from the same discipline with fundamentally different designs, support the occurrence of effects as a result of pollutant exposures. For example, evidence base may include epidemiologic evidence reporting positive associations between pollutant exposures and cardiovascular events which are coherent with controlled human exposure and/or experimental animal studies demonstrating changes in cardiac or vascular function following exposures. Evidence that is coherent across disciplines and/or study designs provides stronger support for a causality determination than any of the individual lines of evidence alone.

A.7.2.1.1.3. Experimental Evidence and Biological Plausibility

In making judgments regarding causality, the ISAs specifically consider the extent to which experimental studies provide evidence of effects resulting from air pollutant exposures, which can also provide biological plausibility for associations reported in epidemiologic studies to be indicative of causal relationships. Experimental studies provide valuable information on the relationship between exposures and observed effects under well-defined conditions. Biological plausibility for a causal relationship between pollutant exposure and a particular type of effect can be supported by experimental studies, including those that provide an understanding of the

mode of action through which pollutant exposures lead to health effects. This understanding may span multiple levels of biological organization including, but not limited to, molecular and cellular events in the pathways leading to disease. A complete understanding of the mode of action is rarely available and is not necessary for it to be biologically plausible that an exposure-effect relationship reflects a causal relationship. Rather, experimental studies demonstrating a pollutant to elicit key physiological events in the pollutant exposure-to-response pathway, and the relationships between those events, can provide strong support for cause-effect interpretations of health effect associations reported in epidemiologic studies. Due to the complexities and uncertainties related to extrapolation from non-human experimental model systems, the ISA may draw upon studies that use exposure concentrations higher than those considered relevant for typical ambient air exposures in human populations to inform consideration of biological plausibility of relationships between pollutant exposures and various health effects.

A.7.2.1.1.4. Biological Gradient

The presence of concentration-, exposure-, and/or dose-response relationships in the study dataset can increase confidence in a finding that exposure may be causative, particularly when such relationships are demonstrated across multiple independent studies or across disciplines and potential confounders have been addressed. The shapes of concentration-, exposure-, or dose-response curves, and whether those curves are linear across the range of ambient air exposures, can also be an important consideration in characterizing the public health impacts associated with pollutant exposures. The shapes of these curves across ambient air exposures occurring under air quality conditions that meet existing standards may be of particular interest in the NAAQS reviews. Sources of variability and uncertainty in interpreting concentration-, exposure-, and dose-response relationships can include a limitation in the data available toward the lower and upper ends of the concentration range, the possible influence of exposure measurement error over the range of concentrations, and variability in response among individuals with respect to air pollution health effects. These sources of uncertainty and variability tend to smooth and “linearize” concentration-, exposure-, and dose-response functions and thus can obscure the existence of nonlinear relationships and thresholds. These sources of variability and uncertainty may explain why the available exposure-response data from epidemiologic studies of ambient air concentrations for some environmental pollutants (e.g., PM, O_3, Pb, environmental tobacco smoke, radiation) do not exhibit population-level thresholds for cancer or noncancer health effects, even though likely mechanisms include nonlinear processes for some key events.

A.7.2.1.1.5. Strength and Specificity of Associations

In evaluating the strength of an observed association in epidemiologic studies, the ISAs consider the magnitude, statistical precision (i.e., informed by width of confidence intervals), and the specificity of health outcomes across multiple studies. In large studies that adequately account for potential confounding factors, strong associations can serve to increase confidence that findings are not due to a weak unmeasured confounder, chance, or other biases. However, the health effects evaluated in the ISAs tend to have multiple contributing factors (e.g., genetics, disease, lifestyle, environmental), and the magnitude of the contribution from air pollution exposures will depend on the prevalence of other risk factors in the study population. Thus, in studies that appropriately account for potential confounding factors and other sources of bias a small effect size does not rule out there being a causal relationship with the air pollutant, and such an effect can be important from a public health perspective if it impacts large segments of the population. A small effect can represent a shift in the distribution of responses in the study population and may increase the proportion of individuals with clinically important outcomes.

A.7.2.1.1.6. Temporality of the Observed Association

Temporality of an observed association refers to the temporal sequence of exposure and observed effects. For a causal relationship, pollutant exposure must happen before effects. Experimental animal and controlled human exposure studies demonstrating exposure-induced health effects provide strong support for appropriate temporal relationships between exposures and effects reported in observational epidemiologic studies. Not all observational studies provide evidence of temporality. For example, cohort studies, by design, generally better suited to address the consideration of the temporal sequence of exposure and effect than cross-sectional studies.

A.7.2.2. ISA framework for making causality determinations

Using the aspects of the evidence described above to make judgments related to causality, the ISAs assess the relevant scientific literature to draw conclusions on the causal nature of the relationships between relevant pollutant exposures and health effects. These "causality determinations" reflect overall confidence in cause-effect relationships based on the strengths and limitations of the full body of evidence, integrated within and across disciplines. In its review of the current ISA causality framework, the NASEM supported this approach, noting that "[a] weight of evidence approach, which combines assessment of the scientific literature with expert judgment to weigh that complex literature, is a scientifically defensible approach for the ISA causal determination framework" (NASEM, 2022, p. 126). The ISAs evaluate evidence for major health outcome categories or groups of related endpoints (e.g., respiratory effects), characterizing the strengths and limitations of evidence for individual endpoints within the broader category. Limitations in the evidence base can result from the consistent presence of

uncertainties within a group of studies (e.g., studies similarly affected by confounding, exposure error, species extrapolation, etc.) or uncertainties that exist across the broader body of evidence (e.g., inconsistent evidence across disciplines, lack of coherence). The ISAs generally rely on qualitative uncertainty evaluations, though quantitative analysis approaches such as meta-regression are used in some situations. Rigorous external peer-review by the CASAC and pollutant-specific expert panels is critical to informing ISA conclusions on uncertainty and/or bias in the body of evidence supporting causality determinations.

The ISA causality determinations are articulated using a framework with a five-level hierarchy based on the weight of the evidence for causation (Table A-11). The NASEM endorsed this approach, noting that the five categories for classifying causality determinations "are scientifically defensible given the precautionary nature of the CAA" (NASEM, 2022, p. 3). The standardized language used in the framework to describe specific determinations is adapted from sources across the federal government and the wider scientific community, especially the EPA *Guidelines for Carcinogen Risk Assessment* (U.S EPA, 2005), U.S. Surgeon General's report, *The Health Consequences of Smoking* CDC, 2004, and NAS IOM document, *Improving the Presumptive Disability Decision-Making Process for Veterans* (IOM, 2008). Table A-11 presents the human health descriptors for each of the determinations in the ISA causality framework.[43]

[43] Characteristics of the ecological and other welfare effects evidence supporting each of the five causal determinations are presented in the 2015 Preamble to the ISAs (U.S. EPA, 2015).

Table A-11. Causality determinations for health outcomes.

Descriptor	Evidence Characteristics
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant exposures have been shown to result in health effects in studies in which chance, confounding, and other biases can be ruled out with reasonable confidence. A "causal" relationship is generally based on multiple high-quality studies conducted by different research groups. Evidence supporting this determination can include controlled human exposure studies that consistently demonstrate effects and/or observational studies reporting consistent health effect associations that, when considered in light of study quality and coherence with other lines of evidence (i.e., controlled human exposure studies, animal toxicological studies, and mode of action information), cannot be explained by plausible alternatives.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. That is, the pollutant exposures have been shown to result in health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. A "likely to be causal" relationship is generally based on multiple high-quality studies conducted by different research groups. Evidence supporting this determination can include 1) multiple high-quality observational studies consistently reporting health effect associations, but with uncertainty remaining related to potential confounding and/or limited coherence with other lines of evidence (i.e., controlled human exposure studies, animal toxicological studies, mode of action information) or 2) consistent evidence in animal models and/or *in vitro* models (e.g., for cancer-related effects) that can be reasonably extrapolated to human health, but limited availability of human data.
Suggestive of, but not sufficient to infer, a causal relationship	Evidence is suggestive of, but not sufficient to infer, a causal relationship with relevant pollutant exposures. That is, the pollutant exposures have been shown to result in health effects, but chance, confounding, and bias cannot be confidently ruled out. Evidence supporting a "suggestive" relationship can be comprised of studies of varying quality that may be generally supportive of pollutant-related effects, but not entirely consistent and with limited coherence across lines of evidence. A suggestive determination can be reached with relatively small bodies of evidence, or, in rare cases, one high quality study.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. That is, the evidence supporting an "inadequate" relationship is limited and available studies are of insufficient quantity, quality, consistency, and/or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of exposures that human beings are known to encounter and considering at-risk populations and lifestages, are consistent in not showing an effect at any level of exposure concentration.

Each level of the causality hierarchy is delineated by the degree to which chance, confounding, and other biases can be ruled out as explanations of study results with reasonable confidence. A conclusion on which level within the hierarchy best fits a particular body of

evidence is informed by considering the aspects of the evidence described above (i.e., consistency, coherence, biological plausibility, biological gradient, strength of associations, experimental evidence, temporality, and specificity). ISAs use these aspects to guide evidence integration both across populations and within groups that share characteristics with the potential to modify exposure-response relationships, particularly characteristics that may place a group at higher risk. As noted by the NASEM, "[h]eightened human response can be due to age, comorbidities, or other environmental, socio-economic, behavioral, epigenetic or genetic factors" NASEM, 2022, p. 4). Given this, the NASEM cautioned that "considering, or highlighting, only overall average population or broad ecosystem effects can obscure causal relationships that exist for more sensitive subgroups, subspecies, communities, or ecosystems" (NASEM, 2022, p. 128). Consistent with this advice, the ISAs take into consideration the heterogeneity in exposure-response relationships often demonstrated between individuals and populations. When studies informing causality determinations consistently demonstrate elevated pollutant-related risks in populations with particular characteristics, the resulting determinations reflect the strength of the evidence for effects in those populations.

A.7.2.3. At-risk populations

As noted above, some populations and lifestages may be at greater risk of criteria pollutant-related health effects than the general population. Higher risks could be due to intrinsic, extrinsic, and/or exposure-related factors. Intrinsic factors such as genetics, lifestage, or disease status can contribute to larger or more serious responses to a particular pollutant exposure, and physiological differences between groups (e.g., differences in breathing patterns between children and adults) can contribute to higher internal pollutant doses in some populations. Extrinsic factors (e.g., nutritional status) and exposure-related factors (e.g., working outdoors, living near roadways or other pollution sources) can also contribute to increased risk, and many of the characteristics commonly used to classify populations potentially at increased risk (e.g., race, SES, educational attainment) are surrogates for the combined impact of several intrinsic, extrinsic, and exposure-related factors. The co-occurrence of risk factors in some populations, including those with environmental justice concerns or minority groups who may have legacy impacts for some risk factors, presents a complex public health challenge. A critical part of characterizing the public health impacts of criteria pollutant exposures under the NAAQS is identifying the specific populations that are at greater risk of pollutant-related health effects and understanding, where possible, the combinations of intrinsic, extrinsic, and exposure-related factors that confer the greatest risk.

The scientific community has used a variety of terms to classify the populations that may be at increased risk of pollutant-related health effects. These terms, which have been defined

inconsistently across the scientific literature, include susceptible, vulnerable, and sensitive (Vinikoor-Imler et al., 2014; Sacks et al., 2011; U.S. EPA, 2009; U.S EPA, 2010). The lack of consensus in terminology across the scientific community led previous reviews and early ISAs to adopt the term "susceptible populations" to encompass the various factors that could confer increased risk (Vinikoor-Imler et al., 2014; Sacks et al., 2011; U.S. EPA, 2009; U.S EPA, 2010). However, this terminology proved problematic because the broader scientific community often describes susceptible populations as those at increased risk specifically due to biological or intrinsic factors such as pre-existing disease or lifestage. Therefore, starting with the 2013 ISA for Ozone and Related Photochemical Oxidants (U.S. EPA, 2013b) the term "at-risk" was adopted to encompass the broad range of intrinsic, extrinsic, and exposure-related factors that may confer increased risk of criteria pollutant-related health effects in particular populations and lifestages.

In assessing the overall public health impact of criteria pollutant exposures, the ISA identifies, evaluates, and characterizes risk factors to inform conclusions on the populations and lifestages that may be at increased risk. As described further below, the ISA uses a structured framework to characterize potential risk factors and guide evaluation of the evidence across scientific disciplines to assess the overall confidence that a specific factor may result in a population or lifestage being at increased risk of an air pollutant-related health effect. In doing so, the ISA draws from the evidence integration underlying causality determinations, with a focus on the epidemiologic, controlled human exposure, and animal toxicological studies that provide information on pollutant-related effects in particular populations or lifestages as well as available information on differential exposures and dosimetry.

Regarding epidemiologic studies, the ISA focuses particularly on studies that include stratified analyses, or analyses of effect measure modification, and on studies that examine effects that are overwhelmingly or exclusively present in specific populations. Stratified analyses and analyses of effect measure modification can compare various populations or lifestages exposed to similar air pollutant concentrations within the same study design. Studies that evaluate effects in specific populations or lifestages can provide evidence of increased risk in populations that are uniquely affected (e.g., lung function development in children; heart failure, heart attacks, or strokes in people with pre-existing cardiovascular disease). When evaluating results across epidemiologic studies, consistent with the approach to informing causality determinations, emphasis is placed on patterns or trends in results in the various populations evaluated.

Some controlled human exposure and animal toxicological studies evaluate potential risk factors, such as genetic background or health status (e.g., pre-existing asthma), though study participants with serious health conditions are usually excluded from controlled human exposure

studies and limitations in animal models of human disease often result in important uncertainties. However, when available, these experimental studies are important for establishing coherence across disciplines. They can provide information about the independent effects of the air pollutant under evaluation as well as the biological plausibility of effects observed in epidemiologic studies examining specific populations. Additionally, dosimetry studies can further inform the plausibility of a population being at increased risk by demonstrating whether the deposition and distribution of an air pollutant within the body varies across populations or lifestages.

An important consideration in evaluating the health evidence for potential at-risk populations or lifestages is variability across studies in how those groups are defined. For example, risk in populations with well-controlled pre-existing disease (e.g., asthma, hypertension) could be substantially different from the risk in populations with uncontrolled disease. Variability across studies in how potential at-risk populations are defined can similarly exist for other factors (e.g., body mass index vs. other indicators of body composition, various indicators of SES, and various age ranges used to define lifestages). A related consideration is variability within populations or lifestages, such as behavioral differences, biological differences, and adherence to medical treatments. ISAs consider such sources of variation where relevant because they may affect the extent to which studies can reliably identify a population or lifestage that may be at increased risk of pollutant-related effects.

In addition to the health evidence, ISAs consider evidence for differential exposures when evaluating support in the evidence for the identification of populations and lifestages that may be at increased risk. When available, data from studies examining pollutant exposures in specific populations can be integrated with data for health effects in those populations. Such combinations of exposure and health data can inform the ISA's evaluation of the intrinsic, extrinsic, and exposure-related factors that may confer the greatest risk to criteria pollutant-related health effects.

The ISA's characterization of risk factors consists of evaluating the evidence across scientific disciplines and assessing overall confidence that a specific factor may result in a population or lifestage being at increased risk of an air pollutant-related health effect. The ISA uses a structured framework with four categories to characterize the evidence for at-risk populations. Categories are "adequate evidence," "suggestive evidence," "inadequate evidence," and "evidence of no effect." These categories are described below in Table A-12.

Table A-12. Characterization of evidence for factors potentially increasing the risk of pollutant-related health effects.

Classification	Health Effects
Adequate evidence	There is substantial, consistent evidence within a discipline to conclude that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, this evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.
Suggestive evidence	The collective evidence suggests that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage, but the evidence is limited due to inconsistency within a discipline or, where applicable, a lack of coherence across disciplines.
Inadequate evidence	The collective evidence is inadequate to determine whether a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. The available studies are of insufficient quantity, quality, consistency, and/or statistical power to permit a conclusion to be drawn.
Evidence of no effect	There is substantial, consistent evidence within a discipline to conclude that a factor does not result in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, the evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.

A.7.3. Develop the Integrated Synthesis

The Integrated Synthesis draws from the detailed assessment of the evidence in the ISA chapters. It provides a concise synopsis of the ISA conclusions and synthesis of key information and findings considered in characterizing pollutant exposures and relationships with health effects. The Integrated Synthesis includes summaries of policy-relevant information for each topic area covered in the ISA chapters, including atmospheric science, sources, and environmental distribution; exposure, biomarkers, and toxicokinetics; the nature of health effects associated with pollutant exposure, including causality determinations; and the human populations and lifestages at increased risk of the effects of pollutant exposure. The Integrated Synthesis also summarizes the evidence and conclusions for other policy-relevant issues. These vary across assessments and can include the exposure durations, metrics, and concentrations eliciting health effects; the shapes and statistical precision of concentration-, exposure-, or dose-response functions; and the potential adversity and public health significance of certain health effects.

A.8. PEER REVIEW OF AND PUBLIC COMMENT ON THE DRAFT ISA

Section 109(d)(2) of the Clean Air Act (CAA) 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 "shall complete a review of the criteria...and the national primary and secondary ambient air quality standards…and shall recommend to the Administrator any new…standards and revisions of existing criteria and standards as may be appropriate …" Since the early 1980s, this independent review function has been performed by the CASAC of the EPA's Science Advisory Board.

Most preliminary work of the CASAC in reviewing the draft ISA is done by an ad hoc panel of independent subject matter experts. Ad-hoc panels for each review consist of members of the CASAC supplemented by additional independent experts in the subject matter for that review. CASAC panels are convened to provide broad expertise related to the particular criteria pollutant under evaluation and the science-policy issues important for the review. Given the breadth of scientific and technical information evaluated during NAAQS reviews, CASAC panels reflect a wide range of expertise. The specific expertise varies across panels, but typically includes expert knowledge of atmospheric science, human exposure, dosimetry, toxicology, epidemiology, medicine, public health, biostatistics, and risk assessment. Consistent with NASEM recommendations (NASEM, 2022, p. 8), critical disciplines are often represented by multiple panel members in order to facilitate advice from a range of perspectives. Ad-hoc CASAC panels are generally chaired by a CASAC member. The CASAC panels convene at public meetings that are announced in the *Federal Register* and that provide an opportunity for public comment. Draft advisory reports, conveying recommendations to the EPA on the draft ISA, are prepared by the ad-hoc panels and are transmitted to the full CASAC for discussion and deliberation. These reports convey advice to the EPA regarding the ISA conclusions (e.g., causality determinations, at-risk populations, exposure-response relationships, etc.) and the ISA's approaches to evaluating, weighing, and integrating evidence to reach those conclusions, and they often identify additional studies that the CASAC believes should be included in the ISA. If the full CASAC determines the contents of a report are appropriate, the CASAC will adopt the report and transmit it to the EPA to reflect its statutorily mandated advice to the Agency.

The EPA carefully considers advice received from the CASAC and comments from the public in revising and updating the draft ISA document. This may include consideration of

additional studies identified during peer review that meet the ISA's scoping and study quality criteria. After appropriate revisions are made, the final document is made available on the EPA website. A notice announcing the availability of the final ISA is published in the *Federal Register*. More information on EPA's peer review practices can be found in EPA's Peer Review Handbook and via the EPA CASAC peer review website (*https://casac.epa.gov/ords/sab/r/sab_apex/casac/home*).

A.9. QUALITY MANAGEMENT

The EPA has an agency-wide quality assurance (QA) policy outlined in the *EPA Quality Manual for Environmental Programs* (see CIO 2105-P-01.1) and follows the specifications outlined in EPA Order CIO 2105.1. As required by CIO 2105.1, the EPA Office of Research and Development (ORD) maintains a Quality Management Program, which is documented in an internal Quality Management Plan (QMP). All environmental information operations (EIO), including the ISAs, are subject to the EPA's Quality Management Program requirements for a Quality Management Plan (QMP) and a Quality Assurance Project Plan (QAPP). Adherence to the ORD QMP and the ISA program-level QAPP, ensures that all data generated, collected, evaluated, or used in an ISA are "of the type and quality needed and expected for their intended use" and that all information disseminated by the ISAs adhere to a high standard for quality including objectivity, utility, and integrity. The EPA's Center for Public Health and Environmental Assessment (CPHEA) QA managers (QAMs) are responsible for the review and approval of quality-related documentation. The CPHEA ISA scientists are responsible for the evaluation of all inputs to the ISAs, including primary (new) and secondary (existing) data from others, to ensure their quality is appropriate for use in the ISAs. CPHEA adheres to Data Quality Objectives, which identify the most appropriate inputs to the science assessment, and CPHEA provides QA instruction to researchers involved with environmental information operations.

The approaches utilized to search the literature and to select and evaluate studies were detailed in the preceding subsections. Generally, the ISA scientists rely on scientific information found in peer-reviewed journal articles, books, and government reports. The ISAs can integrate information that is extracted from multiple sources to create new figures, tables, or summation, which is subject to rigorous quality assurance measures to ensure their accuracy. Documentation of the quality of extracted information includes the types of QA/QC checks performed and the approach to verifying information extractions (e.g., verification by a second individual). The QA/QC checks for extracted information include comparison of entries to information from the original publication, checking conversions (e.g., ppm to $\mu g/m^3$), confirming effect levels, and inserting and verifying electronic citations that are converted to HERO links. In addition, QA

reviews of key information from all types of health effect studies are performed. Furthermore, publicly available databases (e.g., HERO) have their own QA processes.

The ISAs are designated as Highly Influential Scientific Assessments (HISA) and classified as ORD QA Category A. Category A designations require reporting of all critical QA activities, including audits. During assessment development, the ISAs undergo periodic quality audits. A Technical Systems Audit (TSA) of each ISA is conducted by the EPA or an independent contractor to verify that all QA/QC procedures were adequately performed and documented. The ISAs are subjected to management and QA clearance review, and during this step, the CPHEA QA Manager verifies that the EPA QA requirements are met.

The EPA is committed to providing public access to environmental information. The *EPA's Information Quality Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency* reflects our commitment to the quality of the information we disseminate.

A.10. REFERENCES

Bang, H and Robins, JM (2005). Doubly robust estimation in missing data and causal inference models. Biometrics 61(4): 962-972.

Barr, RG, Herbstman, J, Speizer, FE and Camargo, CA, Jr. (2002). Validation of self-reported chronic obstructive pulmonary disease in a cohort study of nurses. Am J Epidemiol 155(10): 965-971.

CDC (2004). *National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. U.S. Department of Health and Human Services. Centers for Disease Control and Prevention Atlanta (GA). Available at: *https://pubmed.ncbi.nlm.nih.gov/24455788/*.

Cronin, MTD, Bajot, F, Enoch, SJ, Madden, JC, Roberts, DW and Schwöbel, J (2009). The In Chemico–In Silico Interface: Challenges for Integrating Experimental and Computational Chemistry to Identify Toxicity. Alternatives to Laboratory Animals 37(5): 513-521.

Díaz, I (2019). Machine learning in the estimation of causal effects: Targeted minimum loss-based estimation and double/debiased machine learning. Biostatistics 21(2): 353-358.

Díaz, I, Williams, N, Hoffman, KL and Schenck, EJ (2023). Nonparametric causal effects based on longitudinal modified treatment policies. Journal of the American Statistical Association 118(542): 846-857.

ECHA (2016). *New approach methodologies in regulatory science: Proceedings of a scientific workshop, Helsinki, 19–20 April 2016.* Helsinki, Finland. *http://dx.doi.org/10.2823/543644.*

Ertefaie, A and Stephens, DA (2010). Comparing approaches to causal inference for longitudinal data: Inverse probability weighting versus propensity scores. The International Journal of Biostatistics 6(2): 14.

European Commission, Joint Research Centre, Adcock, I, Novotny, T, Nic, M, Dibusz, K, Hynes, J, Marshall, L and Gribaldo, L (2020). *Advanced non-animal models in biomedical research – Respiratory tract diseases*. Publications Office of the European Union. Available at: *https://data.europa.eu/doi/10.2760/725821*.

Gee, GC and Payne-Sturges, DC (2004). Environmental health disparities: A framework integrating psychosocial and environmental concepts. Environ Health Perspect 112(17): 1645-1653.

Gelman, A and Greenland, S (2019). Are confidence intervals better termed "uncertainty intervals"? BMJ (Clinical Research Edition) 366: l5381.

Goldman, GT, Mulholland, JA, Russell, AG, Strickland, MJ, Klein, M, Waller, LA and Tolbert, PE (2011). Impact of exposure measurement error in air pollution epidemiology: Effect of error type in time-series studies. Environ Health 10: 61.

Greenland, S (2000). An introduction to instrumental variables for epidemiologists. Int J Epidemiol 29: 722-729.

Greenland, S, Senn, SJ, Rothman, KJ, Carlin, JB, Poole, C, Goodman, SN and Altman, DG (2016). Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. Eur J Epidemiol 31(4): 337-350.

Hamel, C, Kelly, SE, Thavorn, K, Rice, DB, Wells, GA and Hutton, B (2020). An evaluation of DistillerSR's machine learning-based prioritization tool for title/abstract screening - impact on reviewer-relevant outcomes. BMC Medical Research Methodology 20(1): 256.

Hernán, MA and Robins, JM (2016). Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol 183(8): 758-764.

Hew (1964). Smoking and health: Report of the advisory committee to the surgeon general of the public health service. U.S. Department of Health, Education, and Welfare. Washington, DC. *http://profiles.nlm.nih.gov/ps/retrieve/ResourceMetadata/NNBBMQ*.

Hill, AB (1965). The environment and disease: Association or causation? Proceedings of the Royal Society of Medicine 58(5): 295-300.

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

IARC (2006). IARC monographs on the evaluation of carcinogenic risks to humans: Preamble. World Health Organization. Lyon, France. Available at: *http://monographs.iarc.fr/ENG/Preamble/*.

IOM, Ed. (2008). Improving the presumptive disability decision-making process for veterans. National Academies Press Washington, DC.

Keil, AP, Buckley, JP, Katie, MO, Ferguson, KK, Zhao, S and White, AJ (2020). A quantile-based g-computation approach to addressing the effects of exposure mixtures. Environ Health Perspect 128(4): 47004.

Lash, TL, Fox, MP, MacLehose, RF, Maldonado, G, McCandless, LC and Greenland, S (2014). Good practices for quantitative bias analysis. Int J Epidemiol 43(6): 1969-1985.

Muhajarine, N, Mustard, C, Roos, LL, Young, TK and Gelskey, DE (1997). Comparison of survey and physician claims data for detecting hypertension. J Clin Epidemiol 50(6): 711-718.

Murgia, N, Brisman, J, Claesson, A, Muzi, G, Olin, AC and Torén, K (2014). Validity of a questionnaire-based diagnosis of chronic obstructive pulmonary disease in a general population-based study. BMC Pulmonary Medicine 14: 49.

NASEM (2017). *National Academies of Sciences, Engineering, and Medicine 2017. Controlled Human Inhalation-Exposure Studies at EPA.* National Academies Press (US). Washington (DC). Available at: *http://dx.doi.org/10.17226/24618*.

NASEM (2022). 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 Standard Reviews. The National Academies Press. Washington, DC. Available at: *https://doi.org/10.17226/26612*.

Richardson, A, Hudgens, MG, Gilbert, PB and Fine, JP (2014). Nonparametric bounds and sensitivity analysis of treatment effects. Statistical Science 29(4): 596-618.

Robins, JM, Hernán, MA and Brumback, B (2000). Marginal structural models and causal inference in epidemiology. Epidemiology 11(5): 550-560.

Rothman, KJ and Greenland, S (1998). *Modern Epidemiology*. Lippincott-Raven. Philadelphia, PA.

Sacks, JD, Stanek, LW, Luben, TJ, Johns, DO, Buckley, BJ, Brown, JS and Ross, M (2011). Particulate-matter induced health effects: Who is susceptible? Environ Health Perspect 119(4): 446-454.

Savitz, DA and Forastiere, F (2021). Do pooled estimates from meta-analyses of observational epidemiology studies contribute to causal inference? Occup Environ Med 78(9): 621-622.

Savitz, DA, Wellenius, GA and Trikalinos, TA (2019). The Problem With Mechanistic Risk of Bias Assessments in Evidence Synthesis of Observational Studies and a Practical Alternative: Assessing the Impact of Specific Sources of Potential Bias. Am J Epidemiol 188(9): 1581-1585.

Sheppard, L, Slaughter, JC, Schildcrout, J, Liu, JS and Lumley, T (2005). Exposure and measurement contributions to estimates of acute air pollution effects. J Expo Anal Environ Epidemiol 15(4): 366-376.

Stitelman, OM, De Gruttola, V and van der Laan, MJ (2012). A general implementation of TMLE for longitudinal data applied to causal inference in survival analysis. The International Journal of Biostatistics 8(1): 26.

Stuart, EA (2010). Matching methods for causal inference: A review and a look forward. Statistical Science 25(1): 1-21.

Thayer, KA, Angrish, M, Arzuaga, X, Carlson, LM, Davis, A, Dishaw, L, Druwe, I, Gibbons, C, Glenn, B, Jones, R, Kaiser, JP, Keshava, C, Keshava, N, Kraft, A, Lizarraga, L, Persad, A, Radke, EG, Rice, G, Schulz, B and Vetter, N (2022). Systematic Evidence Map

(SEM) template: Report format and methods used for the US EPA Integrated Risk Information System (IRIS) program, Provisional Peer-Reviewed Toxicity Value (PPRTV) program, and other "fit for purpose" literature-based human health analyses. Environ Int 169(Elsevier): 107468.

Toren, K, Brisman, J and Jarvholm, B (1993). Asthma and asthma-like symptoms in adults assessed by questionnaires: A literature review. Chest 104(2): 600-608.

U.S. EPA (1982). Air quality criteria for oxides of nitrogen. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. Research Triangle Park, NC. EPA/600/8-82-026.

U.S. EPA (1991). Guidelines for Developmental Toxicity Risk Assessment. U.S. Environmental Protection Agency. Available at: *https://nepis.epa.gov/exe/ZyPURL.cgi?Dockey=30002L7L.txt*.

U.S. EPA (1993). Air Quality Criteria for Oxides of Nitrogen. Office of Health and Environmental Assessment. Environmental Criteria and Assessment Office. Washington, DC U.S. EPA. EPA–600/8–91–049aF–cF. August 1993. Available at: *https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=40179*.

U.S. EPA (1996). Guidelines for Reproductive Toxicity Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum. Washington, DC. EPA/630/R-96/009. Available at: *https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=30004YQB.txt*.

U.S. EPA (1998). Guidelines for neurotoxicity risk assessment. U.S. Environmental Protection Agency, Risk Assessment Forum. Washington, DC. EPA/630/R-95/001F. Available at: *http://www.epa.gov/risk/guidelines-neurotoxicity-risk-assessment*.

U.S. EPA (2005). Guidelines for carcinogen risk assessment. Risk Assessment Forum. Washington, DC. EPA630P03001F. Available at: *https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf*.

U.S. EPA (2008). Integrated Science Assessment for Oxides of Nitrogen – Health Criteria. Office of Research and Development, National Center for Environmental Assessment. Research Triangle Park, NC. U.S. EPA. EPA/600/R-08/071. July 2008. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=194645.

U.S. EPA (2009). Integrated Science Assessment for Particulate Matter (Final Report). Office of Research and Development, National Center for Environmental Assessment. Research Triangle Park, NC. U.S. EPA. EPA-600/R-08-139F. December 2009. Available at: *https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=216546*.

U.S. EPA (2010). Integrated Science assessment (ISA) for Carbon Monoxide (Final report). U.S. Environmental Protection Agency. Washington, DC. EPA/600/R-09/019F. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=218686.

U.S. EPA (2013a). Integrated Science Assessment (ISA) for Lead (Final Report). Office of Research and Development, National Center for Environmental Assessment. Washington, DC. U.S. EPA. EPA/600/R-10/075F. July 2013. Available at: *https://assessments.epa.gov/isa/document/&deid=255721*.

U.S. EPA (2013b). Integrated Science Assessment of Ozone and Related Photochemical Oxidants (Final Report). Office of Research and Development, National Center for Environmental Assessment. Research Triangle Park, NC. U.S. EPA. EPA-600/R-10-076F. February 2013. Available at: *https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100KETF.txt*.

U.S. EPA (2015). Preamble To The Integrated Science Assessments (ISA). Office of Research and Development, National Center for Environmental Assessment. Washington, DC. U.S. EPA. EPA/600/R-15/067. Available at: *https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=526136*.

U.S. EPA (2016). Integrated Science Assessment for Oxides of Nitrogen-Health Criteria. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. Research Triangle Park, NC. EPA/600/R-15/068. Available at: *https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310879*.

U.S. EPA (2018). Strategic plan to promote the development and implementation of alternative test methods within the TSCA program. Office of Chemical Safety and Pollution Prevention. Washington D.C. EPA-740-R1-8004. Available at: *https://www.epa.gov/sites/production/files/2018-06/documents/epa_alt_strat_plan_6-20-18_clean_final.pdf*.

U.S. EPA (2019a). Integrated Science Assessment (ISA) for Particulate Matter (Final Report). U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. Washington, DC. U.S. EPA. EPA/600/R-19/188. December 2019. Available at: *https://www.epa.gov/naaqs/particulate-matter-pm-standards-integrated-science-assessments-current-review*.

U.S. EPA (2019b). Guidelines for Human Exposure Assessment. Risk Assessment Forum. Washington, DC. EPA/100/B-19/001. Available at: *https://www.epa.gov/sites/production/files/2020-01/documents/guidelines_for_human_exposure_assessment_final2019.pdf*.

U.S. EPA (2020a). Integrated Science Assessment for Oxides of Nitrogen, Oxides of Sulfur, and Particulate Matter—Ecological Criteria (Final). U.S. Environmental Protection Agency, Office of Research and Development, Center for Public Health and Environmental Assessment. Research Triangle Park, NC. EPA/600/R-20/278. Available at: *https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=349473*.

U.S. EPA (2020b). Integrated Science Assessment (ISA) for Ozone and Related Photochemical Oxidants (Final). U.S. Environmental Protection Agency, Office of Research and Development. Washington, DC. EPA/600/R-20/012. Available at: https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=540022.

U.S. EPA (2021a). Health Assessment Workspace Collaborative (HAWC) Washington, DC.

U.S. EPA (2021b). EPA new approach methods work plan: reducing use of vertebrate animals in chemical testing. Washington D.C. Available at: *https://www.epa.gov/chemical-research/epa-new-approach-methods-work-plan-reducing-use-vertebrate-animals-chemical*.

U.S. EPA (2022). ORD staff handbook for developing IRIS assessments. U.S. Environmental Protection Agency, Office of Research and Development, Center for Public Health and Environmental Assessment. Washington, DC. EPA 600/R-22/268. Available at: *https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=356370*.

U.S. EPA (2023a). LLR Online (pre-release Version 007EC800) Washington, DC.

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

U.S. EPA (2024). Integrated Science Assessment (ISA) for Lead (Final Report). Office of Research and Development, Center for Public Health and Environmental Assessment. Washington, DC. U.S. EPA. EPA/600/R-23/375. January 2024. Available at: *https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=548355*.

Vinikoor-Imler, LC, Owens, EO, Nichols, JL, Ross, M, Brown, JS and Sacks, JD (2014). Evaluating potential response-modifying factors for associations between ozone and health outcomes: A weight-of-evidence approach. Environ Health Perspect 122(11): 1166-1176.

Wasserstein, RL and Lazar, NA (2016). The ASA's statement on p-values: Context, process, and purpose. American Statistician 70(2): 129-133.

Wasserstein, RL, Schirm, AL and Lazar, NA (2019). Moving to a world beyond "p<0.05". American Statistician 73(S!): 1-19.

Weakley, J, Webber, MP, Ye, F, Zeig-Owens, R, Cohen, HW, Hall, CB, Kelly, K and Prezant, DJ (2013). Agreement between obstructive airways disease diagnoses from self-report questionnaires and medical records. Preventive Medicine 57(1): 38-42.

Weuve, J, Sagiv, SK and Fox, MP (2018). Quantitative bias analysis for collaborative science. Epidemiology 29(5): 627-630.

WHO (2008). Uncertainty and Data Quality in Exposure Assessment. The Internaltional Programme on Chemical Safety. Geneva. WHO. *https://apps.who.int/iris/handle/10665/44017*.

WHO (2021). *World Health Organization global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide*. World

Health Organization. Geneva. Available at: *https://apps.who.int/iris/handle/10665/345329*.

Wing, C, Simon, K and Bello-Gomez, RA (2018). Designing difference in difference studies: Best practices for public health policy research. Annu Rev Public Health 39(1): 453-469.

Zeger, SL, Thomas, D, Dominici, F, Samet, JM, Schwartz, J, Dockery, D and Cohen, A (2000). Exposure measurement error in time-series studies of air pollution: Concepts and consequences. Environ Health Perspect 108(5): 419-426.

Development Team for Appendix A of Volume 2 the Integrated Review Plan

Executive Direction

Dr. Steven J. Dutton (Division Director)—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Scott Jenkins (Branch Chief)—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

AUTHORS, CONTRIBUTORS, AND REVIEWERS

Authors

Dr. David M. Lehmann—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Qingyu Meng—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Scott Jenkins—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Alison Krajewski—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Christine Alvarez—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Contributors

Dr. Anne Barkley—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. James Brown—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. LaShonda Bunch—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Peter Byrley—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Catheryne Chiang—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Evan Coffman—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Parker Duffney—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Amanda Haddock—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Maxwell Hatala—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Kirstin Hester—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Cheryl Itkin—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Ila Kanneboyina—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Haesoo Kim—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Ellen Kirrane—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Nichole Kulikowski—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Stephen McDow—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Natalia Neal-Walthall—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC[44]

Dr. Nicole Olson—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Mira Sanderson—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Adrien Wilkie—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Reviewers

Dr. Britta Bierwagen—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Washington, DC

Dr. Laura Carlson—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Wayne Cascio—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Tara Greaver—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Nicole Hagan—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Mary Hutson—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Iman Hassan—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Samantha Jones—Center for Public Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Dierdre Murphy—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Liz Naess—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

[44] Dr. Neal-Walthall was affiliated with U.S. EPA at the time of drafting this document.

Dr. Jennifer Nichols—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Erika Sasser—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Dahnish Shams—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Karen Wesson—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

United States Environmental Protection Agency	Office of Air Quality Planning and Standards Health and Environmental Impacts Division Research Triangle Park, NC	EPA-452/R-24-010b March 2024