



**EPA**

**United States  
Environmental  
Protection Agency**

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# **Draft Plan for the Development of the Integrated Science Assessment for Nitrogen Oxides – Health Criteria**

*Draft - May 2013*

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U. S. Environmental Protection Agency  
Office of Research and Development; National Center for Environment Assessment  
Office of Air and Radiation; Office of Air Quality Planning and Standards  
Research Triangle Park, North Carolina

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# 1. INTRODUCTION

## 1.1 OVERVIEW OF THE PROCESS

1 The U.S. Environmental Protection Agency (EPA) is conducting a review of the air quality  
2 criteria for the health effects of nitrogen oxides (NO<sub>x</sub>) and the primary (health-based) national ambient air  
3 quality standards (NAAQS) for nitrogen dioxide (NO<sub>2</sub>). Figure 1.1 illustrates the four major phases of the  
4 NAAQS review process: (1) planning, (2) science assessment, (3) risk/exposure assessment, as  
5 warranted<sup>1</sup>, and (4) policy assessment and rulemaking. An Integrated Review Plan (IRP) is being  
6 developed for this NAAQS review, and a draft IRP will be released for review by the Clean Air Scientific  
7 Advisory Committee (CASAC) and the public later in 2013. The IRP will characterize the review of the  
8 primary NAAQS for NO<sub>2</sub>, including discussion of the four major phases listed above, the schedule for the  
9 entire review, the process for conducting the review, and the key policy-relevant science issues that will  
10 guide the review.

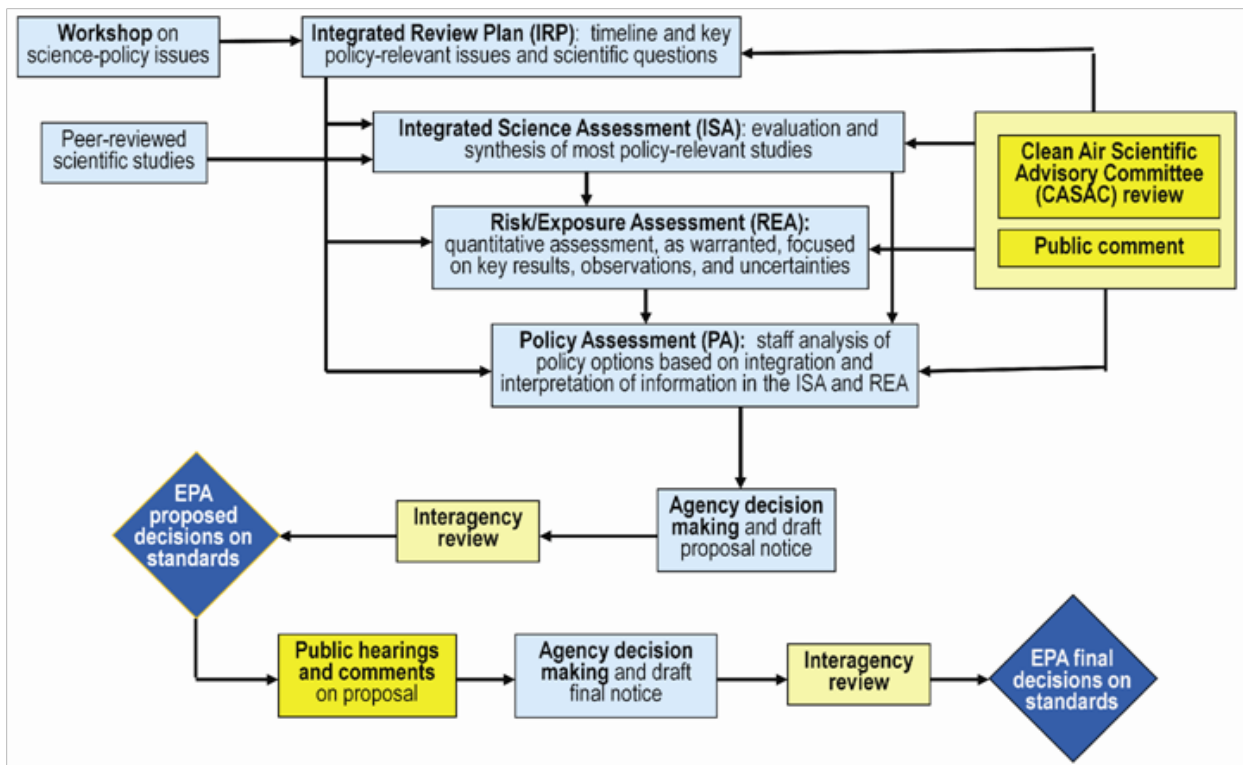
11 The purpose of this document is to communicate the draft plan for the development of the  
12 Integrated Science Assessment (ISA) for NO<sub>x</sub> health criteria which will comprise the science assessment  
13 phase for the review of the primary NAAQS for NO<sub>2</sub>. An ISA is intended to provide a concise review,  
14 synthesis, and assessment of the most policy-relevant science, including key science judgments that are  
15 important to the design and scope of exposure and risk assessments, as well as other aspects of the  
16 NAAQS reviews. An ISA is intended to provide a comprehensive assessment of the current scientific  
17 literature pertaining to known and anticipated effects on public health and welfare associated with the  
18 presence of the pollutant in the ambient air, emphasizing information that has become available since the  
19 last air quality criteria review in order to reflect the current state of knowledge. As such, an ISA provides  
20 the scientific foundation for each NAAQS review and is intended to provide information useful in  
21 forming judgments about the air quality indicator(s), form(s), averaging time(s) and level(s) for the  
22 NAAQS. The current review process generally includes production of a first and second draft ISA, both  
23 of which undergo CASAC and public review prior to completion of the final ISA.

24 The plan for development of an ISA usually is included as part of the IRP. However, a [separate](#)  
25 [draft plan for ISA development](#) is being released for CASAC and public consultation prior to completion  
26 of the draft IRP so that EPA may benefit from advice and comments as the first draft ISA is developed.  
27 EPA intends to release the first draft NO<sub>x</sub> health effects ISA for CASAC and public review in August

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<sup>1</sup>EPA staff will consider the extent to which information and conclusions presented in the ISA support the development of quantitative estimates of NO<sub>2</sub> risks and/or exposures for the current review.

- 1 2013. This draft plan for ISA development includes discussion of the history of the primary NAAQS for  
 2 NO<sub>2</sub> and relevant legislative requirements as background material.



**Figure 1.1 Overview of Process for Reviewing the NAAQS**

## 1.2 HISTORY OF REVIEWS OF THE PRIMARY NAAQS FOR NO<sub>2</sub>

3 The establishment and revision of the NAAQS is governed by two sections of the Clean Air Act,  
 4 as described in more detail in the Appendix. On April 30, 1971, EPA promulgated identical primary and  
 5 secondary NAAQS for NO<sub>2</sub>, under section 109 of the Act, set at 0.053 parts per million (ppm), annual  
 6 average (36 FR 8186). EPA concluded the first review of the NAAQS with a final decision to retain these  
 7 standards published on June 19, 1985 (50 FR 25532). The next review was initiated in 1987 and  
 8 culminated October 8, 1996 in a final determination by the Administrator not to revise the NAAQS for  
 9 NO<sub>2</sub> (61 FR 52852).

10 EPA initiated the most recent review of the air quality criteria for the health effects of NO<sub>x</sub> and  
 11 the NO<sub>2</sub> primary NAAQS on December 9, 2005 (70 FR 73236) with a general call for information. Upon  
 12 completion of the Integrated Science Assessment for Oxides of Nitrogen-Health Criteria and the Risk and  
 13 Exposure Assessment to Support the Review of the NO<sub>2</sub> Primary National Ambient Air Quality Standard  
 14 (Risk and Exposure Assessment), EPA proposed to supplement the existing annual primary standard for

1 NO<sub>2</sub> by establishing a new short-term standard on July 15, 2009 (74 FR 34404). On February 9, 2010,  
2 EPA finalized a new short-term primary NO<sub>2</sub> standard with a level of 100 parts per billion (ppb), based on  
3 the 3-year average of the 98<sup>th</sup> percentile of the yearly distribution of 1-hour daily maximum  
4 concentrations. In that rulemaking, EPA also retained the existing annual primary standard, with a level of  
5 53 ppb<sup>2</sup> (75 FR 6474). The Administrator signed a notice of final rulemaking on January 22, 2010.

### 1.3 SCOPE OF THE CURRENT REVIEW

6 As noted above, in reviewing the NO<sub>2</sub> NAAQS, EPA has historically focused its review of  
7 relevant scientific information on a broad category of nitrogen oxides, while finding it appropriate to  
8 specify the indicator of the standard specifically in terms of NO<sub>2</sub>. As specified in Section 108(c) of the  
9 Clean Air Act, EPA considers the term nitrogen oxides to refer to all forms of oxidized nitrogen including  
10 multiple gaseous (e.g., NO<sub>2</sub>, nitric oxide [NO]) and particulate (e.g., nitrate) species. 42 U.S.C. 21  
11 7408(c). EPA has evaluated the atmospheric chemistry, exposure, and health effects associated with  
12 nitrogen compounds present as particulate matter within the context of ambient particles in the Agency's  
13 review of the NAAQS for particulate matter. Thus, the current review of the NO<sub>2</sub> NAAQS will focus on  
14 the gaseous species of nitrogen oxides, which in this document are abbreviated as NO<sub>x</sub><sup>3</sup>.

15 Although it is likely that the majority of the information available to inform the current review,  
16 particularly with regard to human exposures and health effects, will be specifically for NO<sub>2</sub>, evidence on  
17 the other gaseous nitrogen oxides will be considered to the extent that information is available and  
18 relevant to the review of the NO<sub>2</sub> NAAQS. In addition, evidence will be considered on the possible  
19 influence of atmospheric pollutants other than the NO<sub>x</sub> (e.g., sulfur oxides, carbon monoxide, ozone,  
20 particulate matter) on the role of the NO<sub>x</sub> in health effects.

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<sup>2</sup>At standard temperature (25°C) and pressure (1 atm), 53 ppb NO<sub>2</sub> is equivalent to 100 micrograms per cubic meter of air (µg/m<sup>3</sup>), and 100 ppb NO<sub>2</sub> is equivalent to 188 µg/m<sup>3</sup>.

<sup>3</sup>In the fields of air pollution research and control, the term NO<sub>x</sub> can refer more narrowly to the sum of NO and NO<sub>2</sub>.

## 2. REVIEW SCHEDULE

1           On February 10, 2012, EPA's National Center for Environmental Assessment in Research  
 2 Triangle Park, NC (NCEA-RTP) announced the initiation of the current periodic review of the air quality  
 3 criteria for the health effects of NO<sub>x</sub> and the primary NO<sub>2</sub> NAAQS and issued a call for information in  
 4 the Federal Register (77 FR 7149). EPA held a workshop February 29 to March 1, 2012, to discuss with  
 5 invited scientific experts, key science and policy issues relevant to the review of the health effects of NO<sub>x</sub>  
 6 (77 FR 7149). Table 2-1 outlines the anticipated schedule for development of the ISA. The anticipated  
 7 schedule for the remainder of the review of the primary NO<sub>2</sub> NAAQS will be included in the draft IRP,  
 8 which will be released later in 2013.

**Table 2-1. Anticipated Schedule for the Development of the Integrated Science Assessment for NO<sub>x</sub> – Health Criteria**

<b>Major Milestone</b>	<b>Projected Target Dates</b>
CASAC/public consultation on draft plan for ISA development	June 2013
Final plan for ISA development (to be incorporated into draft IRP)	August 2013
First draft of ISA	August 2013
CASAC/public review of first draft ISA and draft IRP	November 2013
Second draft of ISA	April 2014
CASAC/public review of second draft ISA	July 2014
Final ISA	November 2014

## 3. DEVELOPMENT OF THE INTEGRATED SCIENCE ASSESSMENT

### 3.1 SCOPE AND ORGANIZATION

1           The ISA comprises the science assessment phase of the NO<sub>2</sub> NAAQS review. The ISA may be  
2 supplemented with additional materials if additional documentation is required to support information  
3 contained within the ISA. These supplementary materials may include more detailed and comprehensive  
4 coverage of relevant publications and may accompany the ISA or be available in electronic form as output  
5 from the Health and Environmental Research Online (HERO) database developed by EPA  
6 (<http://hero.epa.gov/>). Supplementary information available in the HERO database will be presented as  
7 electronic links in the ISA.

8           The ISA will critically evaluate and integrate the scientific information on exposure and health  
9 effects associated with NO<sub>x</sub> in ambient air in the discipline areas of atmospheric science, human  
10 exposure, epidemiology, controlled human exposure, toxicology, and dosimetry.<sup>4</sup> The purpose of the  
11 discussions within the ISA is not to provide a detailed literature review but to draw upon the existing  
12 body of evidence to synthesize the current state of knowledge on the most relevant issues pertinent to the  
13 review of the NAAQS for NO<sub>2</sub>. The ISA discussions will be designed to focus on the key policy-relevant  
14 questions described in Section 3.2.

15           The focus of the ISA will be on literature published since the 2008 NO<sub>x</sub> ISA. Key findings and  
16 conclusions from the 2008 ISA for NO<sub>x</sub> will be briefly summarized at the beginning of the ISA and of  
17 individual sections. The results of recent studies will be integrated with previous findings. Important  
18 studies reviewed in previous assessments will be discussed in greater detail if they are open to  
19 reinterpretation in light of newer data or if they provide the most informative evidence in the available  
20 literature. Generally, only information that has undergone scientific peer review and that has been  
21 published (or accepted for publication) in the open literature will be considered. In evaluation of  
22 controlled human exposure and animal toxicological studies, emphasis will be placed on studies  
23 conducted at or near NO<sub>x</sub> concentrations that represent the range of human exposures in the ambient  
24 environment across various microenvironments. However, in recognition of the fact that controlled  
25 human exposure and animal toxicological studies do not necessarily reflect effects in the most sensitive

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<sup>4</sup>Note that evidence related to environmental effects of NO<sub>x</sub> will be considered separately in the science assessment conducted as part of the review of the secondary NAAQS for NO<sub>2</sub> and SO<sub>2</sub>.



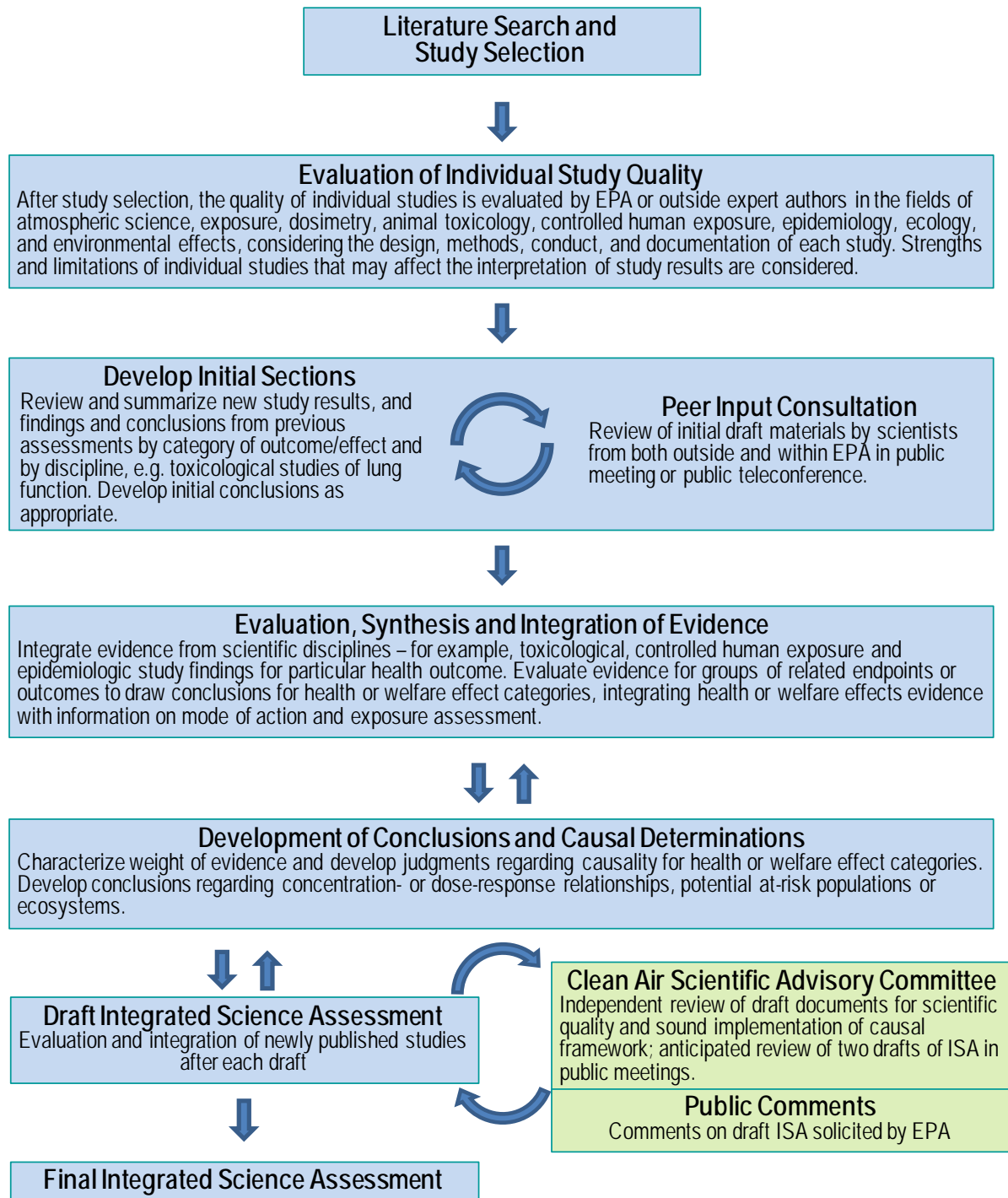
1 populations, studies at higher exposure concentrations will be included when they provide information  
2 relevant to previously unreported effects, evidence of the potential biological mechanism for an observed  
3 effect, or information on exposure-response relationships.

## 3.2 ASSESSMENT APPROACH

### Introduction

4 The NCEA-RTP is responsible for preparing the ISA for NO<sub>x</sub> health criteria. In each NAAQS  
5 review, development of the science assessment begins with a “Call for Information” published in the  
6 Federal Register. This notice announces EPA’s initiation of activities in the preparation of the ISA for the  
7 specific NAAQS review and invites the public to assist through the submission of research studies in the  
8 identified subject areas. This and subsequent key components of the process currently followed for the  
9 development of an ISA (i.e., the development process) are presented in Figure 3.1 and are described in  
10 greater detail in the [Preamble to the ISA for Ozone and Related Photochemical Oxidants \(U.S. EPA,  
11 2013\)](#). How the ISA fits into the larger NAAQS review process is briefly described in Section 1.1, the  
12 Overview of the Review Process.

## Integrated Science Assessment Development Process



**Figure 3.1. General process for development of Integrated Science Assessments (ISAs)**

(Modified from Figure III of the [Preamble to the ISA for Ozone and Related Photochemical Oxidants](#), U.S. EPA, 2013).

1           Important aspects of the development of the ISA are described in the sections below, including the  
2 approach for searching the literature and identifying relevant publications and forming specific policy-  
3 relevant questions that are intended to guide the assessment. These responsibilities are undertaken by  
4 expert authors of the ISA chapters which include EPA staff with extensive knowledge in their respective  
5 fields and extramural scientists solicited by EPA for their expertise in specific fields. The process for  
6 scientific and public review of drafts of the ISA is described in Section 3.3.

### **Literature Search and Identification of Relevant Studies**

7           The NCEA-RTP uses a structured approach to identify relevant studies for consideration and  
8 inclusion in the ISA. A Federal Register Notice is published to announce the initiation of a review and  
9 request information, including relevant literature, from the public. In addition, publications are identified  
10 by EPA through a recurrent multi-tiered literature search process that includes extensive manual and  
11 computer-aided citation mining of computer databases on specific topics in a variety of disciplines using  
12 as keywords terms such as NO<sub>x</sub>, NO<sub>2</sub>, NO, nitric acid, peroxyacetyl nitrate, or total reactive nitrogen. The  
13 search strategies are iteratively modified to optimize identification of pertinent published papers. Papers  
14 are identified for inclusion in several additional ways: searches for recent publications that have cited  
15 references included in the previous ISA, independent review of tables of contents for journals in which  
16 relevant papers may be published or reference lists from key publications, independent identification of  
17 relevant literature by external expert authors, and identification of relevant publications by both the public  
18 and CASAC during the external review process. The studies identified will include research published or  
19 accepted for publication from January 2008, which was the publication end date for studies reviewed in  
20 the 2008 NO<sub>x</sub> ISA, through approximately two months before the release of the second external review  
21 draft of the ISA (target of February 2014, see Table 2-1). Once identified, studies are reviewed with  
22 regard to inclusion criteria described below before including them in the ISA. Publications considered for  
23 inclusion in the ISA are added to the HERO database; the references in the ISA include a hyperlink to the  
24 database. The combination of approaches described above is intended to produce the comprehensive  
25 collection of pertinent studies needed to address the key scientific issues that form the basis of the ISA.

26           Studies that have undergone scientific peer review and have been published or accepted for  
27 publication and reports that have undergone review are considered for inclusion in the ISA. Analyses  
28 conducted by EPA using publicly available data, for example, air quality and emissions data, are also  
29 considered for inclusion in the ISA.

## Evaluation of Individual Study Quality

1           The ISA will emphasize studies published since the 2008 NO<sub>x</sub> ISA; however, evidence from  
2 previous studies will be included to integrate with results from recent studies, and in some cases,  
3 characterize the key policy-relevant evidence in a particular subject area. Several general benchmarks are  
4 used to evaluate the quality and policy-relevance of studies included in the ISA. Policy-relevant and  
5 informative studies include those that provide a basis for or describe the relationship between the criteria  
6 pollutant and effects, such as studies that offer innovation in method or design and studies that reduce  
7 uncertainty on critical issues, for example, analyses of potential confounding or effect modification by  
8 copollutants or other variables, analyses of concentration-response or dose-response relationships, or  
9 analyses related to time between exposure and response. In assessing the scientific quality and relevance  
10 of studies, the following parameters are considered:

- 11 • To what extent are the air quality data, exposure, or dose metrics of adequate quality and sufficiently  
12 representative to serve as credible exposure indicators?
- 13 • Were the study populations, subjects, or animal models adequately selected, and are they sufficiently  
14 well defined to allow for meaningful comparisons between study or exposure groups?
- 15 • Are the statistical analyses appropriate, properly performed, and properly interpreted?
- 16 • Are likely covariates (i.e., potential confounding factors, effect modifiers) adequately controlled for or  
17 taken into account in the study design or statistical analyses?
- 18 • Are the health endpoint measurements meaningful, valid, and reliable?
- 19 • Are the reported findings internally consistent, biologically plausible, and coherent in terms of  
20 consistency with other known facts?

21           In evaluating epidemiologic studies for the present assessment, EPA also will consider whether a  
22 given study contains information on (1) short- or long-term exposures that represent ambient  
23 concentrations of NO<sub>x</sub> across various microenvironments; (2) health effects of specific NO<sub>x</sub> species; (3)  
24 lifestages or populations that potentially are at increased risk of NO<sub>x</sub>-related health effects; (4) potential  
25 copollutant interactions (e.g., are there synergistic effects of NO<sub>x</sub> with other pollutants) or confounding  
26 (e.g., are associations observed between NO<sub>x</sub> and health endpoints biased by the effects of copollutants);  
27 and/or (5) important methodological issues (e.g., lag or time period between exposure and effects, model  
28 specifications, thresholds, mortality displacement) related to the health effects of NO<sub>x</sub> exposure. Among  
29 the epidemiologic studies, particular emphasis will be given to those relevant to standard setting in the  
30 U.S. Specifically, studies conducted in the U.S. or Canada generally will be accorded more text  
31 discussion than those from other geographic regions because of the greater relevance of the population  
32 sociodemographic characteristics and air pollution mixture. In addition, emphasis will be placed on

1 discussion of (1) multicity studies that employ standard methodological analyses for evaluating NO<sub>x</sub>  
2 effects, provide overall estimates for effects based on combined analyses of information pooled across  
3 cities, and examine results for consistency across cities; (2) studies that provide quantitative effect  
4 estimates for populations of interest; and (3) studies that regard NO<sub>x</sub> as a component of a complex  
5 mixture of air pollutants by considering the concentrations of copollutants, correlations of NO<sub>x</sub> with these  
6 copollutants, and results of copollutant analyses.

7 A set of additional explicit criteria also will be used to evaluate the quality and relevance of  
8 experimental studies included in the ISA. The discussion of research evaluating controlled exposures of  
9 laboratory animals will focus primarily on those studies conducted with NO<sub>x</sub> exposures representative of  
10 exposure concentrations and durations that humans experience across various ambient  
11 microenvironments. In animal models, relevant exposures will depend on the toxicokinetics and  
12 biological sensitivity of the particular laboratory animal examined. With respect to the mechanisms of  
13 NO<sub>x</sub> toxicity, studies conducted under environmentally-relevant conditions will be emphasized, but  
14 studies at higher concentrations also will be considered, because of species-to-species differences and  
15 potential differences in sensitivity between humans or animals included in experimental studies and at-  
16 risk human lifestages and populations. Other considerations for the evaluation of animal toxicological  
17 studies include: (1) investigation of animal models of disease that can provide information on human  
18 lifestages and populations potentially at increased risk of NO<sub>x</sub>-related health effects; (2) examination of  
19 concentration-response or time-course of responses; and (3) demonstration of sufficient statistical power  
20 to assess responses to exposures. Results from in vitro studies also may be included if they provide  
21 mechanistic insight or further inform effects demonstrated in vivo. For research evaluating controlled  
22 human exposures to NO<sub>x</sub>, emphasis will be placed on studies that (1) examine NO<sub>x</sub> exposures that  
23 approximate the range of human exposure concentrations and durations across various ambient  
24 microenvironments; (2) compare responses following NO<sub>x</sub> exposure and control or filtered air exposure  
25 and thus have subjects serve as their own controls; (3) investigate effects in potential at-risk populations  
26 such as people with asthma and compare to responses in age-matched healthy subjects; (4) address issues  
27 such as concentration-response or time-course of responses; (5) investigate exposure to NO<sub>x</sub> separately  
28 and in combination with other pollutants such as ozone and sulfur dioxide; and (6) have sufficient  
29 statistical power to adequately assess responses to NO<sub>x</sub> exposures.

30 NCEA participates in the Agency-wide Quality Management System, which requires the  
31 development of a Quality Management Plan (QMP). Implementation of the NCEA QMP ensures that all  
32 data generated or used by NCEA scientists are “of the type and quality needed and expected for their  
33 intended use” and that all information disseminated by NCEA adheres to a high standard for quality  
34 including objectivity, utility, and integrity. Quality assurance (QA) measures detailed in the QMP are

1 being employed for the current NO<sub>x</sub> review, including the development of the ISA for NO<sub>x</sub> health  
2 criteria. The NCEA QA staff is responsible for the review and approval of quality-related documentation.  
3 NCEA scientists are responsible for the evaluation of all inputs to the ISA, including primary (new) and  
4 secondary (existing) data, to ensure their quality is appropriate for their intended purpose. NCEA adheres  
5 to Data Quality Objectives, which identify the most appropriate inputs to the science assessment and  
6 provide QA instruction for researchers citing secondary information. The approaches utilized to search  
7 the literature and criteria for study selection and evaluation were detailed in the two preceding  
8 subsections. Generally, NCEA scientists rely on scientific information found in peer-reviewed journal  
9 articles, books, and government reports. Where information is integrated or reduced from multiple  
10 sources to create new figures, tables, or summation, the data generated are considered to be new and  
11 subject to rigorous quality assurance measures to ensure their accuracy.

### **Content and Organization of the ISA**

12 The organization of the ISA for NO<sub>x</sub> health criteria will be consistent with that used in the recent  
13 assessments for other criteria pollutants (e.g., [ISA for Ozone and Related Photochemical Oxidants, U.S.  
14 EPA, 2013](#)). Development of the ISA will be guided by policy-relevant questions that frame the entire  
15 review of the primary NO<sub>2</sub> NAAQS. These policy-relevant questions will be discussed in more detail in  
16 the IRP but are related to two overarching issues. The first issue is whether new evidence reinforces or  
17 calls into question the evidence presented and evaluated in the last NAAQS review with respect to factors  
18 such as the concentrations of NO<sub>x</sub> exposure associated with health effects and plausibility of health  
19 effects caused by NO<sub>x</sub> exposure. The second issue is whether uncertainties from the last review have been  
20 reduced and/or whether new uncertainties have emerged. Specific questions that will be addressed in the  
21 ISA are listed subsequently by topic area.

1 A. Air Quality and Atmospheric Chemistry: The ISA will present and evaluate data related to  
2 ambient concentrations of NO<sub>x</sub>; sources leading to the presence of NO<sub>x</sub> in the atmosphere;  
3 and chemical reactions that determine the formation, degradation, and lifetime of NO<sub>x</sub> in  
4 the atmosphere.

- 5 • What progress has been made in improving measurements and reducing  
6 interference problems in measuring NO<sub>x</sub>? What limitations still remain?
- 7 • Based on recent air quality and emissions data, what are current concentrations  
8 and emissions of NO<sub>x</sub>? How have emissions and concentrations of NO<sub>x</sub> and of  
9 NO<sub>2</sub> changed since the 2008 NO<sub>x</sub> ISA? To what extent can satellite data be used  
10 to improve the characterization of NO<sub>x</sub> concentrations?
- 11 • What spatial and temporal patterns can be seen in the air quality data for NO<sub>x</sub>? In  
12 particular, what patterns can be seen on a micro-scale for near road environments  
13 and on a national scale based on satellite data?
- 14 • Based on air quality and emissions data on NO<sub>x</sub> and atmospheric chemistry  
15 models, what are likely policy relevant background concentrations of NO<sub>x</sub> in the  
16 absence of anthropogenic emissions?

17 B. Exposure: The ISA will evaluate the factors that influence exposure to ambient NO<sub>x</sub> and  
18 the uncertainties associated with extrapolation from ambient concentrations to personal  
19 exposures to NO<sub>x</sub> of ambient origin, particularly in the context of interpreting results from  
20 epidemiologic studies. The issues of uncertainty differ by the exposure period of interest as  
21 most short-term exposure studies (e.g., population-level studies using time-series analyses,  
22 field/panel studies) rely on temporal variation in exposure while long-term exposure  
23 studies (e.g., longitudinal cohort studies) rely on spatial variability of exposure.

- 24 • What are the relationships between NO<sub>x</sub> measured at stationary monitoring sites  
25 and personal exposure to NO<sub>x</sub>? What evidence is available regarding these  
26 relationships in environments near roads or other sources?
- 27 • What new information exists regarding characterization of error in NO<sub>x</sub> exposure  
28 assessment and how it influences personal-ambient exposure relationships?
- 29 • What information is available regarding differences in NO<sub>x</sub> exposure patterns and  
30 personal-ambient exposure relationships among various lifestyles and  
31 populations?
- 32 • What new information exists regarding NO<sub>x</sub> measurements in a multipollutant  
33 context? To what extent do NO<sub>2</sub> measurements serve as surrogates of exposure to

1 other gaseous pollutants (including carbon monoxide and nitrous acid) and  
 2 particle phase pollutants generated by traffic or other combustion sources?

- 3 • What new information is available about the interaction of NO<sub>x</sub> with organic  
 4 compounds that may influence human exposure?

5 C. Dosimetry and Modes of Action: The ISA will evaluate literature focusing on dosimetry  
 6 and modes of action that may underlie the health outcomes associated with exposure to  
 7 NO<sub>x</sub>. These topic areas will be evaluated using both human and animal data.

- 8 • What information is available to discern the relative contributions to internal  
 9 NO<sub>x</sub> compounds of NO<sub>x</sub> derived exogenously from ambient exposures and NO<sub>x</sub>  
 10 derived from pathways such as diet or biological processes?
- 11 • What NO<sub>x</sub> reaction products can be found in the respiratory tract cells, tissues, or  
 12 fluids that may serve as markers of NO<sub>x</sub> exposure and effect?
- 13 • What are the potential biological mechanisms underlying responses to NO<sub>x</sub> at or  
 14 near environmentally-relevant exposures, with a focus on response pathway(s)  
 15 and exposure-dose-response relationships?
- 16 • What new information is available related to the modes of action for health  
 17 effects associated with exposure to NO<sub>x</sub>?
- 18 • What mechanisms can be qualitatively compared across species?
- 19 • Do interactions between inhaled NO<sub>x</sub> and other inhaled pollutants influence the  
 20 mechanisms underlying the toxic potential of NO<sub>x</sub>?
- 21 • What are the effects of host factors such as age, sex, pre-existing disease, and  
 22 genetic background on NO<sub>x</sub> uptake and cellular and tissue responses?

23 D. Health Effects: The ISA will evaluate the literature related to respiratory, cardiovascular,  
 24 reproductive, and developmental health effects, mortality, and cancer associated with NO<sub>x</sub>  
 25 exposure. Other health effects also may be evaluated, for example, those related to the  
 26 central nervous system or gastrointestinal system. Health effects that occur following both  
 27 short- and long-term exposures will be evaluated in epidemiologic, controlled human  
 28 exposure, and animal toxicological studies. Efforts will be directed at identifying the lower  
 29 concentrations at which effects are observed, including those in potential at-risk lifestyles  
 30 and populations.

31 Short-Term Exposure:

- 32 • What do controlled human exposure, animal toxicological, and epidemiologic  
 33 studies indicate regarding the relationship between short-term (i.e., hours to



1 weeks) exposures to NO<sub>x</sub> and health effects of concern (e.g., altered lung  
2 function, respiratory symptoms, inflammation, heart rate variability, cardiac  
3 arrhythmias, emergency department visits, hospital admissions, mortality),  
4 including the nature and time course, in healthy individuals and in those with pre-  
5 existing disease states (e.g., people with asthma or cardiovascular disease) or  
6 other potential at-risk factors (e.g., lifestage, genetic, nutritional)?

- 7 • How do results of recent studies expand current understanding of the relationship  
8 between short-term exposure to NO<sub>x</sub> and airway hyperresponsiveness or other  
9 lung function changes?
- 10 • What is the influence of NO<sub>x</sub> on host defense against infectious disease?
- 11 • What are the effects of NO<sub>x</sub> exposure on cardiovascular health in humans (e.g.,  
12 heart rate variability, arrhythmias, vasomotor function, risk of myocardial  
13 infarction)?
- 14 • How do results from recent population-level time-series studies expand  
15 understanding of relationships between exposure to NO<sub>x</sub> and mortality (all-cause,  
16 respiratory, cardiovascular), hospital admissions, or emergency department visits?
- 17 • To what extent does exposure to NO<sub>x</sub> contribute to health effects beyond the  
18 respiratory and cardiovascular systems?
- 19 • What do results from studies conducted in environments near roads or other  
20 sources indicate about the health effects of short-term NO<sub>x</sub> exposure?
- 21 • How are observed responses such as changes in lung function, airway  
22 hyperresponsiveness, heart rate variability, and vasomotor function related to  
23 more overt health effects? What other biomarkers of early effect may be used in  
24 the assessment of health effects?
- 25 • What evidence is available regarding the shape of concentration-response  
26 relationships between short-term NO<sub>x</sub> exposure and health effects?
- 27 • What evidence is available regarding the nature of health effects from interactions  
28 between NO<sub>x</sub> and other ambient air pollutants in comparison to health effects  
29 following exposure to NO<sub>x</sub> alone?
- 30 • What are the potential effects of exposure measurement error on epidemiologic  
31 results?
- 32 • To what extent does information on the pattern of NO<sub>x</sub> exposure (e.g., peak,  
33 repeated peak, average) influence interpretation of the health effects evidence?

- 1 • To what extent do data provide information on health effects related to various  
2 NO<sub>x</sub> exposure indices or averaging times relevant to the 1-hour standard? What  
3 data exist comparing associations of health effects among various short-term NO<sub>x</sub>  
4 exposure metrics (e.g., 1-hour versus 24-hour)?

5 Long-Term Exposure:

- 6 • To what extent does the scientific evidence support the occurrence of health  
7 effects from long-term NO<sub>x</sub> exposure (e.g., months to years) at ambient  
8 concentrations that are lower than those previously observed? If so, what  
9 uncertainties are related to these associations and are the health effects in question  
10 important from a public health perspective?
- 11 • How do results of recent studies expand current understanding of the relationships  
12 between long-term exposure to NO<sub>x</sub> and chronic respiratory effects manifested as  
13 permanent lung tissue damage, a reduction in baseline lung function, or a  
14 reduction in lung function development?
- 15 • To what extent does long-term NO<sub>x</sub> exposure promote exacerbation and  
16 development of asthma or other chronic lung diseases, cardiovascular diseases,  
17 and other conditions? What is the relationship between long-term NO<sub>x</sub> exposure  
18 and all-cause mortality and cause-specific mortality?
- 19 • To what extent does long-term exposure to NO<sub>x</sub> contribute to other health effects,  
20 e.g., cognitive, behavioral, reproductive, developmental effects?
- 21 • What evidence is available regarding the shape of concentration-response  
22 relationships between long-term NO<sub>x</sub> exposure and health effects?
- 23 • What do results from studies conducted in environments near roads or other  
24 sources indicate about the health effects of long-term NO<sub>x</sub> exposure?
- 25 • What evidence is available regarding the nature of health effects from interactions  
26 between NO<sub>x</sub> and other ambient air pollutants in comparison to health effects  
27 attributable to specifically to exposure to NO<sub>x</sub>?
- 28 • What information is available regarding the effect of long-term, low-  
29 concentration exposure to NO<sub>x</sub> on an individual's sensitivity to short-term but  
30 higher concentration exposures?
- 31 • What evidence is available regarding health effects related to long-term exposure  
32 windows other than annual or lifetime average (e.g., preconception, pregnancy  
33 average, pregnancy trimester average)? What data are available comparing

1 associations of health effects among various long-term NO<sub>x</sub> exposure metrics  
2 (e.g., annual, seasonal, pregnancy average)?

3 E. Causality: The ISA will evaluate the evidence for and against causal relationships between  
4 observed health outcomes and NO<sub>x</sub> exposures. EPA has developed a framework to provide  
5 a consistent and transparent basis for drawing such conclusions. In the framework, key  
6 considerations in drawing conclusions about causality include consistency of findings for  
7 an endpoint across studies, biological plausibility, and coherence of the evidence across  
8 disciplines and across related endpoints, including those related to modes of action (see  
9 Table II in [Preamble to the ISA for Ozone and Related Photochemical Oxidants, U.S.  
10 EPA, 2013](#)). The ISA will place emphasis on studies conducted with NO<sub>x</sub> concentrations  
11 representative of those across various ambient microenvironments, with the exception of  
12 evidence for biological plausibility and modes of action, which in animal or controlled  
13 human exposure study groups with shorter duration (e.g., 2 to 8 hour periods) exposures  
14 may be observed with higher exposure concentrations than those (e.g., lower, 24-hour  
15 average concentrations) typically associated with the health effects and human populations  
16 examined in epidemiologic studies.

- 17 • Does the evidence base from recent studies contain new information to support or  
18 re-evaluate the causal determinations made for relationships between NO<sub>x</sub>  
19 exposure and various health effects in the 2008 NO<sub>x</sub> ISA?
- 20 • What information is available regarding the health impacts of a decrease in  
21 ambient concentrations of NO<sub>x</sub>?

22 F. Uncertainties: The ISA will evaluate uncertainty in the scientific data, particularly in  
23 relation to observed epidemiologic findings.

- 24 • How does confounding by co-exposure to other ambient pollutants (e.g., ozone,  
25 particulate matter, sulfur dioxide, carbon monoxide) or meteorological factors  
26 influence relationships observed between health effects and both short- and long-  
27 term NO<sub>x</sub> exposures? To what extent do other factors serve as potential  
28 confounding factors in epidemiologic studies (e.g., demographic and lifestyle  
29 attributes)?
- 30 • To what extent are the observed health effect associations attributable to ambient  
31 NO<sub>x</sub> or to the pollutant mixtures that NO<sub>x</sub> may be representing? For example, the  
32 possibility that ambient concentrations of NO<sub>2</sub> serve as a surrogate for exposure to  
33 vehicle exhaust pollutants, including various other gases and particles, will be  
34 considered.

- 1           • How does exposure measurement error contribute to uncertainty in epidemiologic  
2           study results?

3       G. At-risk Lifestages and Populations: The ISA will examine exposure and health outcome  
4       data to draw conclusions about specific lifestages or populations that potentially are at  
5       increased risk of NO<sub>x</sub>-related health effects. Potential at-risk lifestages or populations can  
6       be characterized by a variety of factors: intrinsic factors (biological factors such as age,  
7       pre-existing disease, genetic variants), extrinsic factors (nonbiological factors such as diet,  
8       lower socioeconomic status), and/or factors affecting dose or exposure (age, outdoor  
9       activity or work, lower socioeconomic status). As noted above, some factors (e.g., age)  
10      may influence risk through multiple mechanisms. EPA has developed a framework to  
11      provide a consistent and transparent basis for drawing conclusions about at-risk lifestages  
12      or populations (see Table 8-1 of [ISA for Ozone and Related Photochemical Oxidants, U.S.  
13      EPA, 2013](#)). In the framework, key considerations in drawing such conclusions include  
14      consistency of findings for a factor within a discipline and coherence of the evidence  
15      across disciplines.

- 16           • What conclusions can be drawn about at-risk lifestages and populations based on  
17           evidence integrated across disciplines regarding factors that may increase risk of  
18           NO<sub>x</sub>-related health effects?
- 19           • How does new information augment that evaluated in the 2008 NO<sub>x</sub> ISA  
20           regarding people with pre-existing respiratory disease or genetic variants as  
21           potential at-risk populations and children or older adults as potential at-risk  
22           lifestages?
- 23           • What information is available that characterizes whether a factor influences risk  
24           of NO<sub>x</sub>-related health effects by increasing NO<sub>x</sub> exposure or dose or by  
25           increasing biological response given a specific dose of NO<sub>x</sub>?
- 26           • What is the extent of the coherence of evidence regarding potential at-risk  
27           lifestages or populations for both short- and long-term exposures to NO<sub>x</sub>?

28      H. Public Health Impact: The ISA will evaluate what conclusions can be drawn about public  
29      health impacts related to short- and long-term exposure to NO<sub>x</sub>. This will include  
30      evaluation of the potential for health effects of NO<sub>x</sub> exposure to be considered adverse.  
31      Development of these concepts may include, as appropriate, an estimation of the sizes of  
32      potential at-risk lifestages and populations and discussion of the public health significance  
33      of the magnitude of change in health outcomes characterized to result from ambient air  
34      NO<sub>x</sub> exposure.

## 4. SCIENTIFIC AND PUBLIC REVIEW

1           Drafts of the ISA will be made available for review by the CASAC NO<sub>x</sub> primary NAAQS review  
2 panel and public as indicated in Figure 3.1 above; availability of draft documents will be announced in the  
3 Federal Register. The CASAC panel will review the draft ISA documents and discuss their comments in  
4 public meetings that will be announced in the Federal Register. EPA will take into account comments,  
5 advice, and recommendations received from the CASAC panel and from the public in revising draft ISA  
6 documents. EPA has established a public docket for the development of the ISA. After appropriate  
7 revision based on comments received from CASAC and the public, the final document will be made  
8 available on an EPA website and in hard copy. A notice announcing the availability of the final ISA will  
9 be published in the Federal Register.

## 5. REFERENCES

U.S. Environmental Protection Agency. (2013) Integrated Science Assessment for Ozone and Related Photochemical Oxidants (Final Report). U.S. EPA, Washington, DC. EPA/600/R-10/076F. Available at: [http://www.epa.gov/ttn/naaqs/standards/ozone/s\\_o3\\_2008\\_isa.html](http://www.epa.gov/ttn/naaqs/standards/ozone/s_o3_2008_isa.html);

## APPENDIX A.

### LEGISLATIVE REQUIREMENTS

1 Two sections of the Clear Air Act govern the establishment and revision of the National Ambient  
2 Air Quality Standards (NAAQS). Section 108 of the Act directs the Administrator to identify and list air  
3 pollutants that meet certain criteria, including that the air pollutant “in [her] judgment, cause[s] or  
4 contribute[s] to air pollution which may reasonably be anticipated to endanger public health and welfare”  
5 and “the presence of which in the ambient air results from numerous or diverse mobile or stationary  
6 sources.” 42 U.S.C. 21 7408(a)(1)(A) & (B). For those air pollutants listed, section 108 requires the  
7 Administrator to issue air quality criteria that “accurately reflect the latest scientific knowledge useful in  
8 indicating the kind and extent of all identifiable effects on public health or welfare which may be  
9 expected from the presence of [a] pollutant in ambient air . . .” 42 U.S.C. 7408(2).

10 Section 109(a) of the Act directs the Administrator to promulgate “primary” and “secondary”  
11 NAAQS for pollutants for which air quality criteria have been issued. 42 U.S.C. 7409(1).<sup>5</sup> Section  
12 109(b)(1) defines a primary standard as one “the attainment and maintenance of which in the judgment of  
13 the Administrator, based on [the air quality] criteria and allowing an adequate margin of safety, are  
14 requisite to protect the public health.”<sup>6</sup> 42 U.S.C. 7409(b)(1). A secondary standard, in turn, must  
15 “specify a level of air quality the attainment and maintenance of which, in the judgment of the  
16 Administrator, based on [the air quality] criteria, is requisite to protect the public welfare from any known  
17 or anticipated adverse effects associated with the presence of such pollutant in the ambient air.”<sup>7</sup> 42  
18 U.S.C. 7409(b)(2).

19 The requirement that primary standards include an adequate margin of safety is intended to  
20 address uncertainties associated with inconclusive scientific and technical information available at the  
21 time of standard setting. It is also intended to provide a reasonable degree of protection against hazards  
22 that research has not yet identified. *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 (D.C. Cir.  
23 1980), *cert. denied*, 449 U.S. 1042 (1980); *American Petroleum Institute v. Costle*, 665 F.2d 1176,  
24 1186 (D.C. Cir. 1981), *cert. denied*, 455 U.S. 1034 (1982). Both kinds of uncertainties are components  
25 of the risk associated with pollution at concentrations below those at which human health effects can be  
26 said to occur with reasonable scientific certainty. Thus, in selecting primary standards that include an

<sup>5</sup>EPA notes that as the promulgation of a NAAQS is identified in section 307(d)(1) of the Clean Air Act, all of the provisions of this rulemaking are subject to the requirements of section 307(d) of the Clean Air Act.

<sup>6</sup>The legislative history of section 109 indicates that a primary standard is to be set at “the maximum permissible ambient air level . . . which will protect the health of any [sensitive] group of the population,” and that for this purpose “reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group.” S. Rep. No. 91-1196, 91st Cong., 2d Sess. 10 (1970)

<sup>7</sup>EPA will conduct a separate review of the secondary NO<sub>2</sub> NAAQS jointly with a review of the secondary SO<sub>2</sub> NAAQS.

1 adequate margin of safety, the Administrator is seeking not only to prevent pollution concentrations that  
2 have been demonstrated to be harmful but also to prevent lower pollutant concentrations that may pose an  
3 unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree.

4 In addressing the requirement for a margin of safety, EPA considers such factors as the nature and  
5 severity of the health effects involved, the size of the at-risk population(s), and the kind and degree of the  
6 uncertainties that must be addressed. The selection of any particular approach to providing an adequate  
7 margin of safety is a policy choice left specifically to the Administrator's judgment. *Lead Industries*  
8 *Association v. EPA*, *supra*, 647 F.2d at 1161-62.

9 In setting standards that are "requisite" to protect public health and welfare, as provided in section  
10 109(b), EPA's task is to establish standards that are neither more nor less stringent than necessary for  
11 these purposes. In so doing, EPA may not consider the costs of implementing the standards. *Whitman v.*  
12 *American Trucking Associations*, 531 U.S. 457, 471, 475-76 (2001).

13 Section 109(d)(1) of the Act requires the Administrator to periodically undertake a thorough  
14 review of the air quality criteria published under section 108 and the NAAQS and to revise the criteria  
15 and standards as may be appropriate. 42 U.S.C. 7409(d)(1). The Act also requires the Administrator to  
16 appoint an independent scientific review committee composed of seven members, including at least one  
17 member of the National Academy of Sciences, one physician, and one person representing State air  
18 pollution control agencies, to review the air quality criteria and NAAQS and to "recommend to the  
19 Administrator any new ... standards and revisions of existing criteria and standards as may be appropriate  
20 under section 108 and subsection (b) of this section." 42 U.S.C. 7409(d)(2). This independent review  
21 function is performed by the Clean Air Scientific Advisory Committee of EPA's Science Advisory Board.



**U.S. EPA SCIENCE ADVISORY BOARD  
CLEAN AIR SCIENTIFIC ADVISORY COMMITTEE MEMBERS**

**FISCAL YEAR 2013**

1           The Clean Air Scientific Advisory Committee (CASAC) has a statutorily mandated responsibility  
2 to review and offer scientific and technical advice to the Administrator on the air quality criteria and  
3 regulatory documents that form the basis for the National Ambient Air Quality Standards (NAAQS),  
4 which currently include standards for lead, particulate matter, ozone, carbon monoxide, nitrogen dioxide,  
5 and sulfur dioxide. To perform such reviews, in each case the Committee forms a review panel consisting  
6 of CASAC members augmented by selected consultants with expertise in scientific or technical areas  
7 pertinent to the given pollutant or pollutant class under review.

**CHAIR**

Dr. H. Christopher Frey, North Carolina State University, Raleigh, NC

**CHARTERED MEMBERS**

Dr. H. Christopher Frey, North Carolina State University, Raleigh, NC

Mr. George A. Allen, Northeast States for Coordinated Air Use Management, Boston, MA

Dr. Ana Diez-Roux, University of Michigan, Ann Arbor, MI

Dr. Jack Harkema, Michigan State University, East Lansing, MI

Dr. Helen Suh, Northeastern University, Boston, MA

Dr. Kathleen Weathers, Cary Institute of Ecosystem Studies, Millbrook, NY

Dr. Ronald Wyzga, Electric Power Research Institute, Palo Alto, CA

**OXIDES OF NITROGEN PRIMARY NAAQS PANEL**

Dr. H. Christopher Frey, Chair, North Carolina State University, Raleigh, NC

Mr. George A. Allen, Northeast States for Coordinated Air Use Management, Boston, MA

Dr. Matthew Campen, University of New Mexico, Albuquerque, NM

Dr. Ronald Cohen, University of California, Berkeley, CA

Dr. Douglas Dockery, Harvard University, Boston, MA

Dr. Philip Fine, South Coast Air Quality Management District, Diamond Bar, CA

Dr. Panos Georgopoulos, UMDNJ – Robert Wood Johnson Medical School, Piscataway, NJ

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Dr. Helen Suh, Northeastern University, Boston, MA

Dr. Ronald Wyzga, Electric Power Research Institute, Palo Alto, CA

Dr. Junfeng (Jim) Zhang, University of Southern California, Los Angeles, CA

**SCIENCE ADVISORY BOARD STAFF**

Mr. Aaron Yeow, Designated Federal Officer, U.S. Environmental Protection Agency, Science Advisory Board (1400R), 1200 Pennsylvania Avenue, NW, Washington, D.C. 20460-0001, Phone: 202-564-2050, Fax: 202-565-2098, (yeow.aaron@epa.gov)

# DRAFT OUTLINE FOR INTEGRATED SCIENCE ASSESSMENT FOR NITROGEN OXIDES – HEALTH CRITERIA

<b>ISA Section</b>	<b>Section Title</b>
<b>Preamble</b>	Process of ISA Development
<b>(will be available online)</b>	EPA Framework for Causal Determination
	Public Health Impact
	Concepts in Evaluating Adversity of Health Effects
<b>Preface</b>	Legislative Requirements for the NAAQS Review
	History of the Primary NAAQS for Nitrogen Dioxide
<b>Executive Summary</b>	
<b>Chapter 1</b>	<b>Integrative Summary</b>
<b>Section 1.1</b>	Policy-relevant Questions for Nitrogen Dioxide NAAQS Review
<b>Section 1.2</b>	ISA Development and Scope
<b>Section 1.3</b>	Nitrogen Oxides Sources, Ambient Concentrations, Exposure
<b>Section 1.4</b>	Health Effects Evidence
	Exposure, Dosimetry, and Modes of Action
	Comparison of 2008 ISA and Current Conclusions
	Key Evidence for Evaluated Health Effects
<b>Section 1.5</b>	Policy-Relevant Considerations
	Concentration-Response and Thresholds
	Exposure Averaging Times and Lags
	At-risk Populations
	Adverse Health Effects, Public Health Significance
<b>Section 1.6</b>	Summary
<b>Chapter 2</b>	<b>Atmospheric Chemistry and Exposure to Nitrogen Oxides</b>
<b>Section 2.1</b>	Introduction
<b>Section 2.2</b>	Atmospheric Chemistry and Fate
<b>Section 2.3</b>	Sources
<b>Section 2.4</b>	Measurement Methods
<b>Section 2.5</b>	Atmospheric Concentrations of Nitrogen Oxides
<b>Section 2.6</b>	Spatial Modeling
<b>Section 2.7</b>	Exposure Assessment
<b>Section 2.8</b>	Summary and Conclusions

<b>ISA Section</b>	<b>Section Title</b>
<b>Chapter 3</b>	<b>Dosimetry and Modes of Action of Inhaled Nitrogen Oxides</b>
<b>Section 3.1</b>	Dosimetry of Inhaled Nitrogen Oxides Dosimetry of Inhaled Nitric Oxide Reaction with Epithelial Lining Fluid Water Mechanisms of Absorption of Nitrogen Dioxide Epithelial Lining Fluid Interactions with Nitrogen Dioxide Regional and Total Respiratory Absorption of Nitrogen Dioxide Experimental Studies of Nitrogen Dioxide Uptake Endogenous Generation, Metabolism, Distribution, and Elimination of Nitrogen Dioxide
<b>Section 3.2</b>	Modes of Action for Exposure to Nitrogen Oxides Introduction Formation of Secondary Oxidation Products or Reactive Nitrogen Species Activation of Neural Reflexes Initiation of Inflammation Alteration of Epithelial Barrier Function Sensitization of Bronchial Smooth Muscle Modification of Innate/Adaptive Immunity Remodeling of Airways and Alveoli Extrapulmonary Effects Nitric Oxide Nitric Oxide and Nitrogen Dioxide Metabolites Interindividual Variability in Response
<b>Chapter 4</b>	<b>Integrated Health Effects of Short-term Exposure to Nitrogen Oxides</b>
<b>Section 4.1</b>	Introduction
<b>Section 4.2</b>	Respiratory Effects
<b>Section 4.3</b>	Cardiovascular Effects
<b>Section 4.4</b>	Mortality
<b>Section 4.5</b>	Other Health Effects Related to Short-term Exposure

<b>ISA Section</b>	<b>Section Title</b>
<b>Chapter 5</b>	<b>Integrated Health Effects of Long-term Exposure to Nitrogen Oxides</b>
<b>Section 5.1</b>	Introduction
<b>Section 5.2</b>	Respiratory Effects
<b>Section 5.3</b>	Cardiovascular Effects
<b>Section 5.4</b>	Reproductive and Developmental Effects
<b>Section 5.5</b>	Mortality
<b>Section 5.6</b>	Central Nervous System Effects
<b>Section 5.7</b>	Other Noncancer Health Effects Related to Long-term Exposure
<b>Section 5.8</b>	Cancer
<b>Chapter 6</b>	<b>Potential At-risk Lifestages and Populations</b>
	Introduction and Summary of 2008 ISA Key Findings
	Review of Evidence for Specific Lifestages or Factors
	Influencing Health Effects of Nitrogen Oxides such as:
	Children, Older Adults, Socioeconomic Status, Diet, Sex,
	Pre-existing Disease, Genetic Variants
	Summary and Conclusions