EPA

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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
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1. INTRODUCTION

1.1 OVERVIEW OF THE PROCESS

The U.S. Environmental Protection Agency (EPA) is conducting a review of the air quality criteria for the health effects of nitrogen oxides (NO_X) and the primary (health-based) national ambient air quality standards (NAAQS) for nitrogen dioxide (NO_2). Figure 1.1 illustrates the four major phases of the NAAQS review process: (1) planning, (2) science assessment, (3) risk/exposure assessment, as warranted[1], and (4) policy assessment and rulemaking. An Integrated Review Plan (IRP) is being developed for this NAAQS review, and a draft IRP will be released for review by the Clean Air Scientific Advisory Committee (CASAC) and the public later in 2013. The IRP will characterize the review of the primary NAAQS for NO_2, including discussion of the four major phases listed above, the schedule for the entire review, the process for conducting the review, and the key policy-relevant science issues that will guide the review.

The purpose of this document is to communicate the draft plan for the development of the Integrated Science Assessment (ISA) for NO_X health criteria which will comprise the science assessment phase for the review of the primary NAAQS for NO_2. An ISA is intended to provide a concise review, synthesis, and assessment of the most policy-relevant science, including key science judgments that are important to the design and scope of exposure and risk assessments, as well as other aspects of the NAAQS reviews. An ISA is intended to provide a comprehensive assessment of the current scientific literature pertaining to known and anticipated effects on public health and welfare associated with the presence of the pollutant in the ambient air, emphasizing information that has become available since the last air quality criteria review in order to reflect the current state of knowledge. As such, an ISA provides the scientific foundation for each NAAQS review and is intended to provide information useful in forming judgments about the air quality indicator(s), form(s), averaging time(s) and level(s) for the NAAQS. The current review process generally includes production of a first and second draft ISA, both of which undergo CASAC and public review prior to completion of the final ISA.

The plan for development of an ISA usually is included as part of the IRP. However, a separate draft plan for ISA development is being released for CASAC and public consultation prior to completion of the draft IRP so that EPA may benefit from advice and comments as the first draft ISA is developed. EPA intends to release the first draft NO_X health effects ISA for CASAC and public review in August

[1]EPA staff will consider the extent to which information and conclusions presented in the ISA support the development of quantitative estimates of NO_2 risks and/or exposures for the current review.

2013. This draft plan for ISA development includes discussion of the history of the primary NAAQS for NO_2 and relevant legislative requirements as background material.

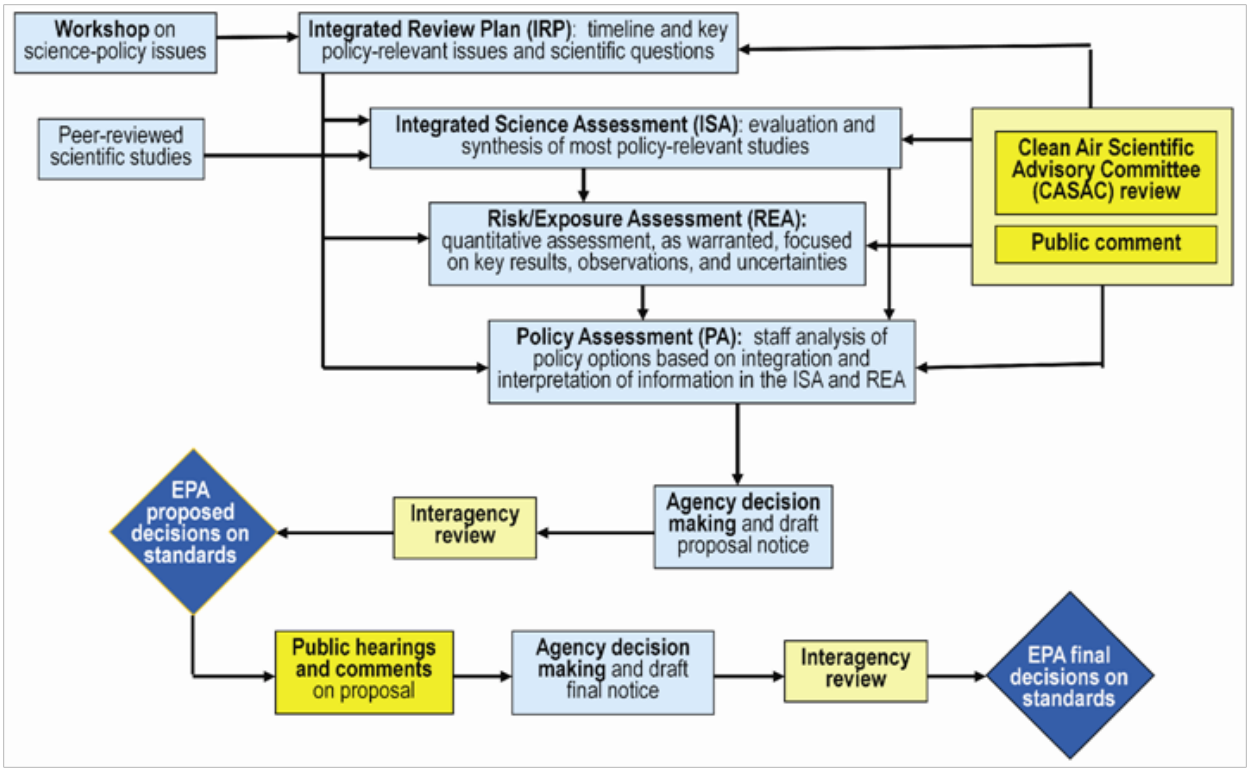

Figure 1.1 Overview of Process for Reviewing the NAAQS

1.2 HISTORY OF REVIEWS OF THE PRIMARY NAAQS FOR NO_2

The establishment and revision of the NAAQS is governed by two sections of the Clean Air Act, as described in more detail in the Appendix. On April 30, 1971, EPA promulgated identical primary and secondary NAAQS for NO_2, under section 109 of the Act, set at 0.053 parts per million (ppm), annual average (36 FR 8186). EPA concluded the first review of the NAAQS with a final decision to retain these standards published on June 19, 1985 (50 FR 25532). The next review was initiated in 1987 and culminated October 8, 1996 in a final determination by the Administrator not to revise the NAAQS for NO_2 (61 FR 52852).

EPA initiated the most recent review of the air quality criteria for the health effects of NO_X and the NO_2 primary NAAQS on December 9, 2005 (70 FR 73236) with a general call for information. Upon completion of the Integrated Science Assessment for Oxides of Nitrogen-Health Criteria and the Risk and Exposure Assessment to Support the Review of the NO_2 Primary National Ambient Air Quality Standard (Risk and Exposure Assessment), EPA proposed to supplement the existing annual primary standard for

NO_2 by establishing a new short-term standard on July 15, 2009 (74 FR 34404). On February 9, 2010, EPA finalized a new short-term primary NO_2 standard with a level of 100 parts per billion (ppb), based on the 3-year average of the 98th percentile of the yearly distribution of 1-hour daily maximum concentrations. In that rulemaking, EPA also retained the existing annual primary standard, with a level of 53 ppb[2] (75 FR 6474). The Administrator signed a notice of final rulemaking on January 22, 2010.

1.3 SCOPE OF THE CURRENT REVIEW

As noted above, in reviewing the NO_2 NAAQS, EPA has historically focused its review of relevant scientific information on a broad category of nitrogen oxides, while finding it appropriate to specify the indicator of the standard specifically in terms of NO_2. As specified in Section 108(c) of the Clean Air Act, EPA considers the term nitrogen oxides to refer to all forms of oxidized nitrogen including multiple gaseous (e.g., NO_2, nitric oxide [NO]) and particulate (e.g., nitrate) species. 42 U.S.C. 21 7408(c). EPA has evaluated the atmospheric chemistry, exposure, and health effects associated with nitrogen compounds present as particulate matter within the context of ambient particles in the Agency's review of the NAAQS for particulate matter. Thus, the current review of the NO_2 NAAQS will focus on the gaseous species of nitrogen oxides, which in this document are abbreviated as NO_X[3].

Although it is likely that the majority of the information available to inform the current review, particularly with regard to human exposures and health effects, will be specifically for NO_2, evidence on the other gaseous nitrogen oxides will be considered to the extent that information is available and relevant to the review of the NO_2 NAAQS. In addition, evidence will be considered on the possible influence of atmospheric pollutants other than the NO_X (e.g., sulfur oxides, carbon monoxide, ozone, particulate matter) on the role of the NO_X in health effects.

[2]At standard temperature (25ºC) and pressure (1 atm), 53 ppb NO_2 is equivalent to 100 micrograms per cubic meter of air (µg/m^3), and 100 ppb NO_2 is equivalent to 188 µg/m^3.
[3]In the fields of air pollution research and control, the term NO_X can refer more narrowly to the sum of NO and NO_2.

2. REVIEW SCHEDULE

On February 10, 2012, EPA's National Center for Environmental Assessment in Research Triangle Park, NC (NCEA-RTP) announced the initiation of the current periodic review of the air quality criteria for the health effects of NO_X and the primary NO_2 NAAQS and issued a call for information in the Federal Register (77 FR 7149). EPA held a workshop February 29 to March 1, 2012, to discuss with invited scientific experts, key science and policy issues relevant to the review of the health effects of NO_X (77 FR 7149). Table 2-1 outlines the anticipated schedule for development of the ISA. The anticipated schedule for the remainder of the review of the primary NO_2 NAAQS will be included in the draft IRP, which will be released later in 2013.

Table 2-1. Anticipated Schedule for the Development of the Integrated Science Assessment for NO_X – Health Criteria

Major Milestone	Projected Target Dates
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

The ISA comprises the science assessment phase of the NO_2 NAAQS review. The ISA may be supplemented with additional materials if additional documentation is required to support information contained within the ISA. These supplementary materials may include more detailed and comprehensive coverage of relevant publications and may accompany the ISA or be available in electronic form as output from the Health and Environmental Research Online (HERO) database developed by EPA (http://hero.epa.gov/). Supplementary information available in the HERO database will be presented as electronic links in the ISA.

The ISA will critically evaluate and integrate the scientific information on exposure and health effects associated with NO_X in ambient air in the discipline areas of atmospheric science, human exposure, epidemiology, controlled human exposure, toxicology, and dosimetry.[4] The purpose of the discussions within the ISA is not to provide a detailed literature review but to draw upon the existing body of evidence to synthesize the current state of knowledge on the most relevant issues pertinent to the review of the NAAQS for NO_2. The ISA discussions will be designed to focus on the key policy-relevant questions described in Section 3.2.

The focus of the ISA will be on literature published since the 2008 NO_X ISA. Key findings and conclusions from the 2008 ISA for NO_X will be briefly summarized at the beginning of the ISA and of individual sections. The results of recent studies will be integrated with previous findings. Important studies reviewed in previous assessments will be discussed in greater detail if they are open to reinterpretation in light of newer data or if they provide the most informative evidence in the available literature. Generally, only information that has undergone scientific peer review and that has been published (or accepted for publication) in the open literature will be considered. In evaluation of controlled human exposure and animal toxicological studies, emphasis will be placed on studies conducted at or near NO_X concentrations that represent the range of human exposures in the ambient environment across various microenvironments. However, in recognition of the fact that controlled human exposure and animal toxicological studies do not necessarily reflect effects in the most sensitive

[4]Note that evidence related to environmental effects of NO_X will be considered separately in the science assessment conducted as part of the review of the secondary NAAQS for NO_2 and SO_2.

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

3.2 ASSESSMENT APPROACH

Introduction

The NCEA-RTP is responsible for preparing the ISA for NO_X health criteria. In each NAAQS review, development of the science assessment begins with a "Call for Information" published in the Federal Register. This notice announces EPA's initiation of activities in the preparation of the ISA for the specific NAAQS review and invites the public to assist through the submission of research studies in the identified subject areas. This and subsequent key components of the process currently followed for the development of an ISA (i.e., the development process) are presented in Figure 3.1 and are described in greater detail in the Preamble to the ISA for Ozone and Related Photochemical Oxidants (U.S. EPA, 2013). How the ISA fits into the larger NAAQS review process is briefly described in Section 1.1, the Overview of the Review Process.

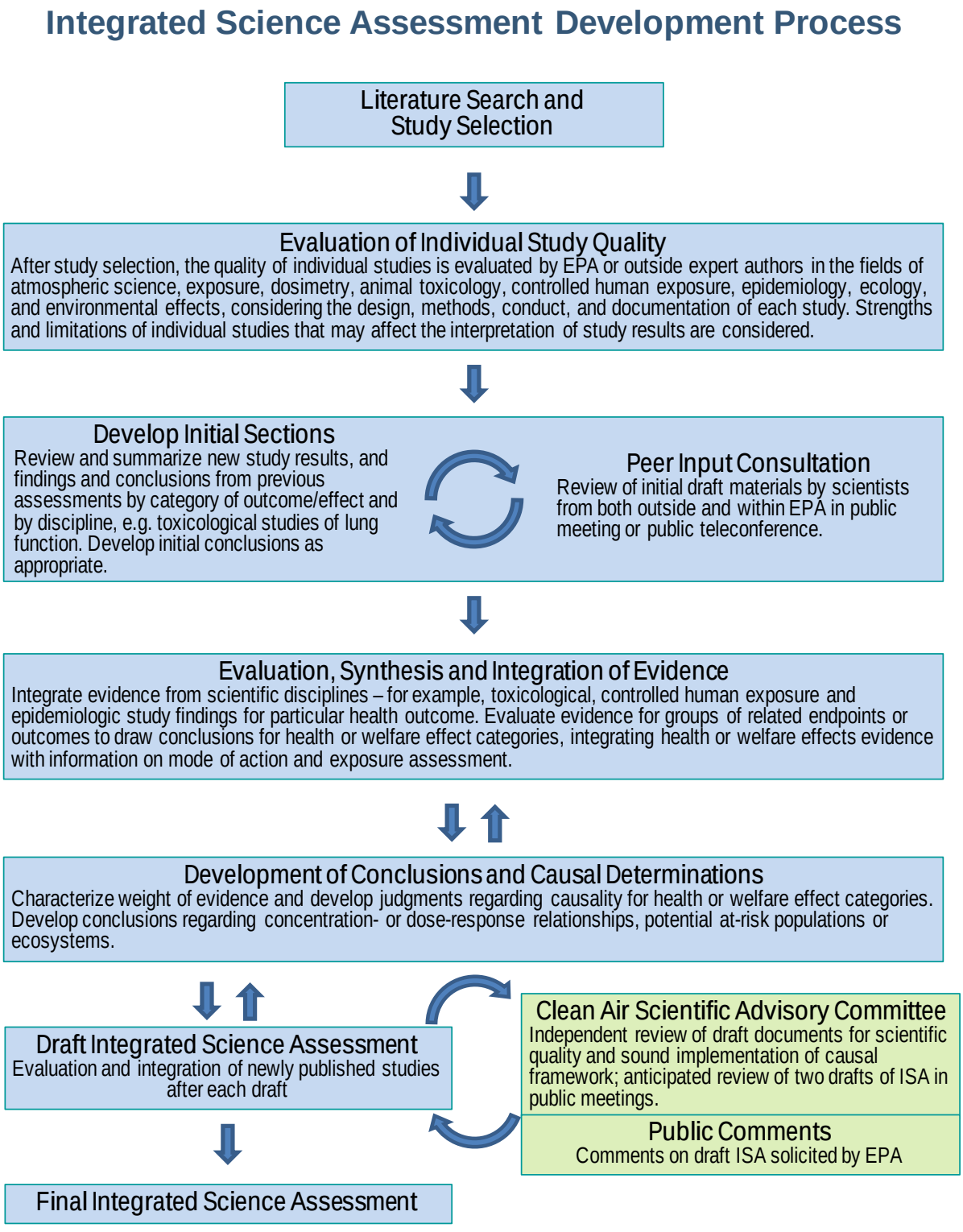

Figure 3.1. General process for development of Integrated Science Assessments (ISAs)

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

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

Literature Search and Identification of Relevant Studies

The NCEA-RTP uses a structured approach to identify relevant studies for consideration and inclusion in the ISA. A Federal Register Notice is published to announce the initiation of a review and request information, including relevant literature, from the public. In addition, publications are identified by EPA through a recurrent multi-tiered literature search process that includes extensive manual and computer-aided citation mining of computer databases on specific topics in a variety of disciplines using as keywords terms such as NO_X, NO_2, NO, nitric acid, peroxyacytyl nitrate, or total reactive nitrogen. The search strategies are iteratively modified to optimize identification of pertinent published papers. Papers are identified for inclusion in several additional ways: searches for recent publications that have cited references included in the previous ISA, independent review of tables of contents for journals in which relevant papers may be published or reference lists from key publications, independent identification of relevant literature by external expert authors, and identification of relevant publications by both the public and CASAC during the external review process. The studies identified will include research published or accepted for publication from January 2008, which was the publication end date for studies reviewed in the 2008 NO_X ISA, through approximately two months before the release of the second external review draft of the ISA (target of February 2014, see Table 2-1). Once identified, studies are reviewed with regard to inclusion criteria described below before including them in the ISA. Publications considered for inclusion in the ISA are added to the HERO database; the references in the ISA include a hyperlink to the database. The combination of approaches described above is intended to produce the comprehensive collection of pertinent studies needed to address the key scientific issues that form the basis of the ISA.

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

Evaluation of Individual Study Quality

The ISA will emphasize studies published since the 2008 NO_X ISA; however, evidence from previous studies will be included to integrate with results from recent studies, and in some cases, characterize the key policy-relevant evidence in a particular subject area. Several general benchmarks are used to evaluate the quality and policy-relevance of studies included in the ISA. Policy-relevant and informative studies include those that provide a basis for or describe the relationship between the criteria pollutant and effects, such as studies that offer innovation in method or design and studies that reduce uncertainty on critical issues, for example, analyses of potential confounding or effect modification by copollutants or other variables, analyses of concentration-response or dose-response relationships, or analyses related to time between exposure and response. In assessing the scientific quality and relevance of studies, the following parameters are considered:

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

In evaluating epidemiologic studies for the present assessment, EPA also will consider whether a given study contains information on (1) short- or long-term exposures that represent ambient concentrations of NO_X across various microenvironments; (2) health effects of specific NO_X species; (3) lifestages or populations that potentially are at increased risk of NO_X-related health effects; (4) potential copollutant interactions (e.g., are there synergistic effects of NO_X with other pollutants) or confounding (e.g., are associations observed between NO_X and health endpoints biased by the effects of copollutants); and/or (5) important methodological issues (e.g., lag or time period between exposure and effects, model specifications, thresholds, mortality displacement) related to the health effects of NO_X exposure. Among the epidemiologic studies, particular emphasis will be given to those relevant to standard setting in the U.S. Specifically, studies conducted in the U.S. or Canada generally will be accorded more text discussion than those from other geographic regions because of the greater relevance of the population sociodemographic characteristics and air pollution mixture. In addition, emphasis will be placed on

discussion of (1) multicity studies that employ standard methodological analyses for evaluating NO_X effects, provide overall estimates for effects based on combined analyses of information pooled across cities, and examine results for consistency across cities; (2) studies that provide quantitative effect estimates for populations of interest; and (3) studies that regard NO_X as a component of a complex mixture of air pollutants by considering the concentrations of copollutants, correlations of NO_X with these copollutants, and results of copollutant analyses.

A set of additional explicit criteria also will be used to evaluate the quality and relevance of experimental studies included in the ISA. The discussion of research evaluating controlled exposures of laboratory animals will focus primarily on those studies conducted with NO_X exposures representative of exposure concentrations and durations that humans experience across various ambient microenvironments. In animal models, relevant exposures will depend on the toxicokinetics and biological sensitivity of the particular laboratory animal examined. With respect to the mechanisms of NO_X toxicity, studies conducted under environmentally-relevant conditions will be emphasized, but studies at higher concentrations also will be considered, because of species-to-species differences and potential differences in sensitivity between humans or animals included in experimental studies and at-risk human lifestages and populations. Other considerations for the evaluation of animal toxicological studies include: (1) investigation of animal models of disease that can provide information on human lifestages and populations potentially at increased risk of NO_X-related health effects; (2) examination of concentration-response or time-course of responses; and (3) demonstration of sufficient statistical power to assess responses to exposures. Results from in vitro studies also may be included if they provide mechanistic insight or further inform effects demonstrated in vivo. For research evaluating controlled human exposures to NO_X, emphasis will be placed on studies that (1) examine NO_X exposures that approximate the range of human exposure concentrations and durations across various ambient microenvironments; (2) compare responses following NO_X exposure and control or filtered air exposure and thus have subjects serve as their own controls; (3) investigate effects in potential at-risk populations such as people with asthma and compare to responses in age-matched healthy subjects; (4) address issues such as concentration-response or time-course of responses; (5) investigate exposure to NO_X separately and in combination with other pollutants such as ozone and sulfur dioxide; and (6) have sufficient statistical power to adequately assess responses to NO_X exposures.

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

being employed for the current NO_X review, including the development of the ISA for NO_X health criteria. The NCEA QA staff is responsible for the review and approval of quality-related documentation. NCEA scientists are responsible for the evaluation of all inputs to the ISA, including primary (new) and secondary (existing) data, to ensure their quality is appropriate for their intended purpose. NCEA adheres to Data Quality Objectives, which identify the most appropriate inputs to the science assessment and provide QA instruction for researchers citing secondary information. The approaches utilized to search the literature and criteria for study selection and evaluation were detailed in the two preceding subsections. Generally, NCEA scientists rely on scientific information found in peer-reviewed journal articles, books, and government reports. Where information is integrated or reduced from multiple sources to create new figures, tables, or summation, the data generated are considered to be new and subject to rigorous quality assurance measures to ensure their accuracy.

Content and Organization of the ISA

The organization of the ISA for NO_X health criteria will be consistent with that used in the recent assessments for other criteria pollutants (e.g., ISA for Ozone and Related Photochemical Oxidants, U.S. EPA, 2013). Development of the ISA will be guided by policy-relevant questions that frame the entire review of the primary NO_2 NAAQS. These policy-relevant questions will be discussed in more detail in the IRP but are related to two overarching issues. The first issue is whether new evidence reinforces or calls into question the evidence presented and evaluated in the last NAAQS review with respect to factors such as the concentrations of NO_X exposure associated with health effects and plausibility of health effects caused by NO_X exposure. The second issue is whether uncertainties from the last review have been reduced and/or whether new uncertainties have emerged. Specific questions that will be addressed in the ISA are listed subsequently by topic area.

A. Air Quality and Atmospheric Chemistry: The ISA will present and evaluate data related to ambient concentrations of NO_X; sources leading to the presence of NO_X in the atmosphere; and chemical reactions that determine the formation, degradation, and lifetime of NO_X in the atmosphere.

- What progress has been made in improving measurements and reducing interference problems in measuring NO_X? What limitations still remain?
- Based on recent air quality and emissions data, what are current concentrations and emissions of NO_X? How have emissions and concentrations of NO_X and of NO_2 changed since the 2008 NO_X ISA? To what extent can satellite data be used to improve the characterization of NO_X concentrations?
- What spatial and temporal patterns can be seen in the air quality data for NO_X? In particular, what patterns can be seen on a micro-scale for near road environments and on a national scale based on satellite data?
- Based on air quality and emissions data on NO_X and atmospheric chemistry models, what are likely policy relevant background concentrations of NO_X in the absence of anthropogenic emissions?

B. Exposure: The ISA will evaluate the factors that influence exposure to ambient NO_X and the uncertainties associated with extrapolation from ambient concentrations to personal exposures to NO_X of ambient origin, particularly in the context of interpreting results from epidemiologic studies. The issues of uncertainty differ by the exposure period of interest as most short-term exposure studies (e.g., population-level studies using time-series analyses, field/panel studies) rely on temporal variation in exposure while long-term exposure studies (e.g., longitudinal cohort studies) rely on spatial variability of exposure.

- What are the relationships between NO_X measured at stationary monitoring sites and personal exposure to NO_X? What evidence is available regarding these relationships in environments near roads or other sources?
- What new information exists regarding characterization of error in NO_X exposure assessment and how it influences personal-ambient exposure relationships?
- What information is available regarding differences in NO_X exposure patterns and personal-ambient exposure relationships among various lifestages and populations?
- What new information exists regarding NO_X measurements in a multipollutant context? To what extent do NO_2 measurements serve as surrogates of exposure to

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

- What new information is available about the interaction of NO_X with organic compounds that may influence human exposure?

C. Dosimetry and Modes of Action: The ISA will evaluate literature focusing on dosimetry and modes of action that may underlie the health outcomes associated with exposure to NO_X. These topic areas will be evaluated using both human and animal data.

- What information is available to discern the relative contributions to internal NO_X compounds of NO_X derived exogenously from ambient exposures and NO_X derived from pathways such as diet or biological processes?
- What NO_X reaction products can be found in the respiratory tract cells, tissues, or fluids that may serve as markers of NO_X exposure and effect?
- What are the potential biological mechanisms underlying responses to NO_X at or near environmentally-relevant exposures, with a focus on response pathway(s) and exposure-dose-response relationships?
- What new information is available related to the modes of action for health effects associated with exposure to NO_X?
- What mechanisms can be qualitatively compared across species?
- Do interactions between inhaled NO_X and other inhal$_e$d pollutants influence the mechanisms underlying the toxic potential of NO_X?
- What are the effects of host factors such as age, sex, pre-existing disease, and genetic background on NO_X uptake and cellular and tissue responses?

D. Health Effects: The ISA will evaluate the literature related to respiratory, cardiovascular, reproductive, and developmental health effects, mortality, and cancer associated with NO_X exposure. Other health effects also may be evaluated, for example, those related to the central nervous system or gastrointestinal system. Health effects that occur following both short- and long-term exposures will be evaluated in epidemiologic, controlled human exposure, and animal toxicological studies. Efforts will be directed at identifying the lower concentrations at which effects are observed, including those in potential at-risk lifestages and populations.

Short-Term Exposure:

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

weeks) exposures to NO_X and health effects of concern (e.g., altered lung function, respiratory symptoms, inflammation, heart rate variability, cardiac arrhythmias, emergency department visits, hospital admissions, mortality), including the nature and time course, in healthy individuals and in those with pre-existing disease states (e.g., people with asthma or cardiovascular disease) or other potential at-risk factors (e.g., lifestage, genetic, nutritional)?

- How do results of recent studies expand current understanding of the relationship between short-term exposure to NO_X and airway hyperresponsiveness or other lung function changes?
- What is the influence of NO_X on host defense against infectious disease?
- What are the effects of NO_X exposure on cardiovascular health in humans (e.g., heart rate variability, arrhythmias, vasomotor function, risk of myocardial infarction)?
- How do results from recent population-level time-series studies expand understanding of relationships between exposure to NO_X and mortality (all-cause, respiratory, cardiovascular), hospital admissions, or emergency department visits?
- To what extent does exposure to NO_X contribute to health effects beyond the respiratory and cardiovascular systems?
- What do results from studies conducted in environments near roads or other sources indicate about the health effects of short-term NO_X exposure?
- How are observed responses such as changes in lung function, airway hyperresponsiveness, heart rate variability, and vasomotor function related to more overt health effects? What other biomarkers of early effect may be used in the assessment of health effects?
- What evidence is available regarding the shape of concentration-response relationships between short-term NO_X exposure and health effects?
- What evidence is available regarding the nature of health effects from interactions between NO_X and other ambient air pollutants in comparison to health effects following exposure to NO_X alone?
- What are the potential effects of exposure measurement error on epidemiologic results?
- To what extent does information on the pattern of NO_X exposure (e.g., peak, repeated peak, average) influence interpretation of the health effects evidence?

- To what extent do data provide information on health effects related to various NO_X exposure indices or averaging times relevant to the 1-hour standard? What data exist comparing associations of health effects among various short-term NO_X exposure metrics (e.g., 1-hour versus 24-hour)?

Long-Term Exposure:

- To what extent does the scientific evidence support the occurrence of health effects from long-term NO_X exposure (e.g., months to years) at ambient concentrations that are lower than those previously observed? If so, what uncertainties are related to these associations and are the health effects in question important from a public health perspective?
- How do results of recent studies expand current understanding of the relationships between long-term exposure to NO_X and chronic respiratory effects manifested as permanent lung tissue damage, a reduction in baseline lung function, or a reduction in lung function development?
- To what extent does long-term NO_X exposure promote exacerbation and development of asthma or other chronic lung diseases, cardiovascular diseases, and other conditions? What is the relationship between long-term NO_X exposure and all-cause mortality and cause-specific mortality?
- To what extent does long-term exposure to NO_X contribute to other health effects, e.g., cognitive, behavioral, reproductive, developmental effects?
- What evidence is available regarding the shape of concentration-response relationships between long-term NO_X exposure and health effects?
- What do results from studies conducted in environments near roads or other sources indicate about the health effects of long-term NO_X exposure?
- What evidence is available regarding the nature of health effects from interactions between NO_X and other ambient air pollutants in comparison to health effects attributable to specifically to exposure to NO_X?
- What information is available regarding the effect of long-term, low-concentration exposure to NO_X on an individual's sensitivity to short-term but higher concentration exposures?
- What evidence is available regarding 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 NO_X exposure metrics (e.g., annual, seasonal, pregnancy average)?

E. Causality: The ISA will evaluate the evidence for and against causal relationships between observed health outcomes and NO_X exposures. EPA has developed a framework to provide a consistent and transparent basis for drawing such conclusions. In the framework, key considerations in drawing conclusions about causality include consistency of findings for an endpoint across studies, biological plausibility, and coherence of the evidence across disciplines and across related endpoints, including those related to modes of action (see Table II in Preamble to the ISA for Ozone and Related Photochemical Oxidants, U.S. EPA, 2013). The ISA will place emphasis on studies conducted with NO_X concentrations representative of those across various ambient microenvironments, with the exception of evidence for biological plausibility and modes of action, which in animal or controlled human exposure study groups with shorter duration (e.g., 2 to 8 hour periods) exposures may be observed with higher exposure concentrations than those (e.g., lower, 24-hour average concentrations) typically associated with the health effects and human populations examined in epidemiologic studies.

- Does the evidence base from recent studies contain new information to support or re-evaluate the causal determinations made for relationships between NO_X exposure and various health effects in the 2008 NO_X ISA?
- What information is available regarding the health impacts of a decrease in ambient concentrations of NO_X?

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

- How does confounding by co-exposure to other ambient pollutants (e.g., ozone, particulate matter, sulfur dioxide, carbon monoxide) or meteorological factors influence relationships observed between health effects and both short- and long-term NO_X exposures? To what extent do other factors serve as potential confounding factors in epidemiologic studies (e.g., demographic and lifestyle attributes)?
- To what extent are the observed health effect associations attributable to ambient NO_X or to the pollutant mixtures that NO_X may be representing? For example, the possibility that ambient concentrations of NO_2 serve as a surrogate for exposure to vehicle exhaust pollutants, including various other gases and particles, will be considered.

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

G. At-risk Lifestages and Populations: The ISA will examine exposure and health outcome data to draw conclusions about specific lifestages or populations that potentially are at increased risk of NO_X-related health effects. Potential at-risk lifestages or populations can be characterized by a variety of factors: intrinsic factors (biological factors such as age, pre-existing disease, genetic variants), extrinsic factors (nonbiological factors such as diet, lower socioeconomic status), and/or factors affecting dose or exposure (age, outdoor activity or work, lower socioeconomic status). As noted above, some factors (e.g., age) may influence risk through multiple mechanisms. EPA has developed a framework to provide a consistent and transparent basis for drawing conclusions about at-risk lifestages or populations (see Table 8-1 of ISA for Ozone and Related Photochemical Oxidants, U.S. EPA, 2013). In the framework, key considerations in drawing such conclusions include consistency of findings for a factor within a discipline and coherence of the evidence across disciplines.

- What conclusions can be drawn about at-risk lifestages and populations based on evidence integrated across disciplines regarding factors that may increase risk of NO_X-related health effects?
- How does new information augment that evaluated in the 2008 NO_X ISA regarding people with pre-existing respiratory disease or genetic variants as potential at-risk populations and children or older adults as potential at-risk lifestages?
- What information is available that characterizes whether a factor influences risk of NO_X-related health effects by increasing NO_X exposure or dose or by increasing biological response given a specific dose of NO_X?
- What is the extent of the coherence of evidence regarding potential at-risk lifestages or populations for both short- and long-term exposures to NO_X?

H. Public Health Impact: The ISA will evaluate what conclusions can be drawn about public health impacts related to short- and long-term exposure to NO_X. This will include evaluation of the potential for health effects of NO_X exposure to be considered adverse. Development of these concepts may include, as appropriate, an estimation of the sizes of potential at-risk lifestages and populations and discussion of the public health significance of the magnitude of change in health outcomes characterized to result from ambient air NO_X exposure.

4. SCIENTIFIC AND PUBLIC REVIEW

Drafts of the ISA will be made available for review by the CASAC NO_X primary NAAQS review panel and public as indicated in Figure 3.1 above; availability of draft documents will be announced in the Federal Register. The CASAC panel will review the draft ISA documents and discuss their comments in public meetings that will be announced in the Federal Register. EPA will take into account comments, advice, and recommendations received from the CASAC panel and from the public in revising draft ISA documents. EPA has established a public docket for the development of the ISA. After appropriate revision based on comments received from CASAC and the public, the final document will be made available on an EPA website and in hard copy. A notice announcing the availability of the final ISA will 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;

APPENDIX A.

LEGISLATIVE REQUIREMENTS

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

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

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

[5]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.

[6]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)

[7]EPA will conduct a separate review of the secondary NO_2 NAAQS jointly with a review of the secondary SO_2 NAAQS.

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

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

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

Section 109(d)(1) of the Act requires the Administrator to periodically undertake a thorough review of the air quality criteria published under section 108 and the NAAQS and to revise the criteria and standards as may be appropriate. 42 U.S.C. 7409(d)(1). The Act also requires the Administrator to appoint an independent scientific review committee 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, to review the air quality criteria and NAAQS and to "recommend to the Administrator any new … standards and revisions of existing criteria and standards as may be appropriate under section 108 and subsection (b) of this section." 42 U.S.C. 7409(d)(2). This independent review 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

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

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

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

ISA Section	Section Title
Chapter 3	**Dosimetry and Modes of Action of Inhaled Nitrogen Oxides**
Section 3.1	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
Section 3.2	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
Chapter 4	**Integrated Health Effects of Short-term Exposure to Nitrogen Oxides**
Section 4.1	Introduction
Section 4.2	Respiratory Effects
Section 4.3	Cardiovascular Effects
Section 4.4	Mortality
Section 4.5	Other Health Effects Related to Short-term Exposure

ISA Section	Section Title
Chapter 5	**Integrated Health Effects of Long-term Exposure to Nitrogen Oxides**
Section 5.1	Introduction
Section 5.2	Respiratory Effects
Section 5.3	Cardiovascular Effects
Section 5.4	Reproductive and Developmental Effects
Section 5.5	Mortality
Section 5.6	Central Nervous System Effects
Section 5.7	Other Noncancer Health Effects Related to Long-term Exposure
Section 5.8	Cancer
Chapter 6	**Potential At-risk Lifestages and Populations**
	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