



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
NATIONAL CENTER FOR ENVIRONMENTAL ASSESSMENT  
WASHINGTON, DC 20460

December 6, 2013

**MEMORANDUM**

OFFICE OF  
RESEARCH AND DEVELOPMENT

**SUBJECT:** CASAC Review of First External Review Draft Integrated Science Assessment for Oxides of Nitrogen – Health Criteria

**FROM:** John Vandenberg, Ph.D. /s/  
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**TO:** Aaron Yeow, M.P.H.  
Designated Federal Officer  
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EPA Science Advisory Board Staff Office (1400R)

The First *External Review Draft Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria* prepared by the Environmental Protection Agency's (EPA) National Center for Environmental Assessment – Research Triangle Park Division (NCEA-RTP) as part of EPA's ongoing review of the primary (health-based) national ambient air quality standards (NAAQS) for nitrogen dioxide (NO<sub>2</sub>) was released on November 22, 2013. Electronic copies are available for download at <http://www.epa.gov/ncea>. The draft ISA will be reviewed by the Clean Air Scientific Advisory Committee (CASAC) NO<sub>2</sub> Primary NAAQS Review Panel at a public meeting to be held March 12-13, 2014. We are in the process of distributing the draft ISA for Oxides of Nitrogen to the CASAC Oxides of Nitrogen Panel. I am requesting that you forward our charge to the CASAC Oxides of Nitrogen Panel.

The purpose of the draft ISA is to identify, evaluate, and summarize scientific information on the health effects associated with gaseous oxides of nitrogen. The ISA is intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health which may be expected from the presence of [a] pollutant in ambient air" (Clean Air Act, Section 108; 42 U.S.C. 7408). This first external review draft ISA integrates the scientific evidence for review of the primary (health-based) NAAQS for NO<sub>2</sub> and provides draft findings, conclusions, and judgments on the strength, coherence, and plausibility of the evidence. The Preamble presents the process for ISA development, including aspects considered in judging the overall weight of evidence and framework for causal determination. Criteria used to identify relevant studies for inclusion in the ISA are also described in the Preamble. Chapter 1 provides an integrative summary and conclusions of this assessment. This chapter is supported by detailed information on the relevant evidence available from the multiple disciplines and approaches related to the causal framework (Preamble to the ISA); atmospheric chemistry, ambient concentrations, and exposure to oxides of nitrogen (Chapter 2); dosimetry and modes of action (Chapter 3); health effects of short-term exposure to oxides of nitrogen (Chapter 4); health effects of long-term exposure to oxides of nitrogen (Chapter 5); and lifestages and populations potentially at increased risk for health effects related to oxides of nitrogen (Chapter 6). The final ISA for Oxides of Nitrogen, in conjunction with additional technical assessments, will provide the scientific basis for EPA's decision regarding the adequacy of the primary NAAQS for NO<sub>2</sub> to protect human health.

The purpose of this memo is to provide charge questions related to a number of important topics addressed in the ISA. Following the CASAC and public review of the draft ISA, NCEA-RTP will produce a second draft ISA, which will be released the summer of 2014.

### **Charge to the CASAC Oxides of Nitrogen Panel**

EPA has aimed to succinctly present and integrate the policy-relevant scientific evidence for the review of the NO<sub>2</sub> NAAQS while also sufficiently describing how scientific information was evaluated in forming the conclusions presented. Previous panels have emphasized the importance of older studies and concluded that if older studies are open to reinterpretation in light of newer data and/or they remain the definitive works available in the literature, they should be discussed in detail to reinforce key concepts and conclusions. In considering subsequent charge questions and recognizing an overall goal of producing a clear and concise document, are there topics that should be added or receive additional discussion? Similarly, are there topics for which discussion should be shortened or removed? Does the Panel have opinions on how the document can be shortened without eliminating important and necessary content?

In addition, we ask the Panel to focus on the following specific questions in their review:

1. The Executive Summary is intended to provide a concise synopsis of the key findings and conclusions of the ISA for a broad range of audiences. Please comment on the clarity with which the Executive Summary communicates the key information from the ISA. Please provide recommendation on information that should be added or information that should be left for discussion in the subsequent chapters of the ISA.
2. Chapter 1 summarizes key information from the Preamble about the process for developing an ISA. Chapter 1 also presents the integrative summary and conclusions from the subsequent detailed chapters of the ISA for Oxides of Nitrogen and characterizes available scientific information on policy-relevant issues.
  - a. Please comment on the usefulness and effectiveness of the summary presentation. Please provide recommendations on approaches that may improve the communication of key ISA findings to varied audiences and the synthesis of available information across subject areas.
  - b. What are the Panel's thoughts on the application of the Health and Environmental Research Online (HERO) system to support a more transparent assessment process?
  - c. To what extent does Chapter 1 communicate the key scientific information on sources, atmospheric chemistry, ambient concentrations, exposure, and health effects of oxides of nitrogen as well as at-risk lifestages and populations? What information should be added or is more appropriate to leave for discussion in the subsequent detailed chapters?
  - d. What are the Panel's thoughts on the rationale presented for forming causal determinations for NO<sub>2</sub> exposure only and considering epidemiologic results for associations between NO<sub>x</sub> and health effects in causal determinations for NO<sub>2</sub> (Sections 1.4.1 and 1.4.3)?

- e. Based on individual Panel member recommendations from June 2013<sup>1</sup> on the *Draft Plan for the Development of the Integrated Science Assessment for Nitrogen Oxides – Health Criteria* (May 2013)<sup>2</sup>, Chapter 1 presents an integrated evaluation of various epidemiologic lines of evidence that inform the independent effects of NO<sub>2</sub> exposure (Section 1.5). This section discusses available information that is not necessarily included in the health effect chapters on potential confounding by copollutants and other factors as well as the potential for NO<sub>2</sub> to serve primarily as an indicator of traffic-related pollutants and traffic proximity. This discussion is in Chapter 1 because it integrates information across Chapters 2, 4, and 5. Please comment on the extent to which this discussion is informative in describing how the evidence of independent effects of NO<sub>2</sub> is evaluated in this ISA. Does the discussion accurately reflect the available evidence? If this discussion is informative, what information could be added or removed to improve the discussion. Should the discussion remain in Chapter 1 or should it be moved to another part of the ISA?
  - f. Please comment on the extent to which the discussion of various policy-relevant considerations is clearly described and integrates relevant information (Section 1.6). Please identify any other relevant information that would be useful to include.
3. Chapter 2 describes scientific information on sources, atmospheric chemistry, air quality characterization, and human exposure of oxides of nitrogen.
    - a. To what extent is the information presented regarding characteristics of sources, chemistry, monitoring concentrations, and human exposure accurate, complete, and relevant to the review of the NO<sub>2</sub> NAAQS?
    - b. To what extent are the analyses of air quality presented clearly conveyed, appropriately characterized, and relevant to the review of the NO<sub>2</sub> NAAQS?
    - c. How effective are the source category groupings and the discussion of source emissions in understanding the importance and impacts of oxides of nitrogen from different sources on both national and local scales?
    - d. Please comment on the extent to which available information on the spatial and temporal trends of ambient oxides of nitrogen at various scales has been adequately and accurately described.
    - e. Please comment on the accuracy, level of detail, and completeness of the discussion regarding exposure assessment and the influence of exposure error on effect estimates in epidemiologic studies of the health effects of NO<sub>2</sub>.
  4. Chapter 3 characterizes scientific evidence on the dosimetry and modes of action for NO<sub>2</sub> and nitric oxide (NO). Dosimetry and modes of action are bridged by reactions of NO<sub>2</sub> with components of the extracellular lining fluid and by reactions of NO with heme proteins, processes that play roles in both uptake and biological responses.
    - a. Given the ubiquity of reactive substrates and reaction rate of NO<sub>2</sub> with these substrates, it appears unlikely NO<sub>2</sub> itself will penetrate through the lung lining fluid to the epithelium (see Table 3-1). Please comment of the adequacy of the discussion of NO<sub>2</sub> uptake and reactivity in the respiratory tract.

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<sup>1</sup> The individual panel member comments are available at [http://yosemite.epa.gov/sab/sabproduct.nsf/08EF0A3789CDB13A85257B8E006A496E/\\$File/EPA-CASAC-13-006+unsigned.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/08EF0A3789CDB13A85257B8E006A496E/$File/EPA-CASAC-13-006+unsigned.pdf)

<sup>2</sup>The draft plan for development of the ISA is available at <http://yosemite.epa.gov/sab/sabproduct.nsf/4620a620d0120f93852572410080d786/bc264e65792e015f85257b4a007128c6!OpenDocument>

- b. Since existing dosimetric models for NO<sub>2</sub> do not consider the probability of oxidants/cytotoxic products reaching target sites, it was concluded that these models are inadequate for within or cross species comparisons. Please comment on the validity of this conclusion and identify and comment on the validity of any alternative conclusions.
  - c. Please comment on the adequacy of the discussion of endogenously occurring NO<sub>2</sub> and NO and their reaction products in comparison to that derived from ambient inhalation.
  - d. To what extent are the discussion and integration of the potential modes of action underlying the health effects of exposure to oxides of nitrogen presented accurately and in sufficient detail? Are there additional modes of action that should be included in order to characterize fully the underlying mechanisms of oxides of nitrogen?
5. Chapters 4 and 5 present assessments of the health effects associated with short-term and long-term exposure to oxides of nitrogen, respectively. The discussion is organized by health effect category, outcome, and scientific discipline.
- a. To what extent do the discussions in this chapter accurately reflect the body of evidence from epidemiologic, controlled human exposure and toxicological studies?
  - b. Please comment on the balance of discussion of evidence from previous and recent studies in informing the causal determinations.
  - c. Please comment on the adequacy of the discussion of the strengths and limitations of the evidence in the text and tables within Chapters 4 and 5 and in the evaluation of the evidence in the causal determinations.
  - d. What are the views of the panel on the integration of epidemiologic, controlled human exposure, and toxicological evidence, in particular, on the balance of emphasis placed on each source of evidence? Please comment on the adequacy with which issues related to exposure assessment and mode of action are integrated in the health effects discussion. Please provide recommendations on information in other chapters of the ISA that would be useful to integrate with the health effects discussions in these chapters.
  - e. Please comment on the appropriateness of using experimental and epidemiologic evidence for morbidity effects to inform the biological plausibility of total mortality associated with short-term (Section 4.4) and long-term (Section 5.5) NO<sub>2</sub> exposure and in turn, to inform causal determinations.
  - f. Section 4.2.2 discusses the effect of short-term NO<sub>2</sub> exposure on airways responsiveness. This section focuses primarily on an EPA meta-analysis developed for this ISA of airway responsiveness data for individuals with asthma and secondarily on the potential of various factors to affect airways hyperresponsiveness independently or in conjunction with NO<sub>2</sub> exposure in controlled human exposure studies. This material presently is unpublished and we ask the Panel to provide the peer review for the analysis, in particular, to comment on the appropriateness of the methodology utilized for the meta-analysis, the conclusions reached based this analysis, and its use in the draft ISA. With regard to factors potentially affecting airways responsiveness, please comment on the adequacy of this discussion. Are there other modifying factors that should be considered?

- g. The 2008 ISA for Oxides of Nitrogen stated that one of the largest uncertainties was the potential for health effects observed in association with NO<sub>2</sub> exposure to be confounded by correlated copollutants. To what extent has evidence that informs independent effects of NO<sub>2</sub> been adequately discussed in Chapters 4 and 5 and appropriately interpreted as reducing uncertainty (for example, evaluation of copollutant model results)? Has the current draft ISA appropriately considered recent epidemiologic findings regarding potential copollutant confounding in causal determinations? Please provide comments specifically for respiratory effects, cardiovascular effects, and total mortality of short-term NO<sub>2</sub> exposure.
  - h. To what extent is the causal framework transparently applied to evidence for each of the health effect categories evaluated to form causal determinations? How consistently was the causal framework applied across the health effect categories? Do the text and tables in the summaries and causal determinations clearly communicate how the evidence was considered to form causal determinations?
  - i. What are the views of the panel regarding the clarity and effectiveness of figures and tables in conveying information about the consistency of evidence for a given health endpoint? In particular, was the use of the tables and figures in both the text and online in the HERO database effective in providing additional information on the studies evaluated? Are there tables and figures in the ISA that would be more appropriate to include as a resource in the HERO database?
6. Chapter 6 evaluates scientific information and presents conclusions on factors that may modify exposure to NO<sub>2</sub>, physiological responses to NO<sub>2</sub> exposure, or risk of health effects associated with NO<sub>2</sub> exposure. Consistent with the ISAs for ozone and lead, conclusions on these at-risk factors inform at-risk lifestages and populations.
- a. How effective are the categories of at-risk factors in providing information on potential at-risk lifestages and populations? Is there information available on other key at-risk factors that is not included in the first draft ISA and should be added?
  - b. To what extent do the discussions in this chapter accurately reflect the body of available evidence from epidemiologic, controlled human exposure, and toxicological studies, including the extent to which evidence indicates that the effects of NO<sub>2</sub> exposure are independent of other traffic-related copollutants?
  - c. Please comment on the consistency and transparency with which the framework for drawing conclusions about at-risk factors has been applied in this ISA.
  - d. To what extent is available scientific evidence on factors that modify exposure to NO<sub>2</sub> discussed in the chapter and adequately considered in conclusions for at-risk lifestages or populations?

We look forward to discussing these issues with the CASAC Oxides of Nitrogen Panel at our upcoming meeting. Should you have any questions regarding the draft ISA for Oxides of Nitrogen, please feel free to contact Dr. Steven Dutton (919-541-5035, [dutton.steven@epa.gov](mailto:dutton.steven@epa.gov)) or Dr. Molini Patel (919-541-1492, [patel.molini@epa.gov](mailto:patel.molini@epa.gov)).

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