UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL CENTER FOR ENVIRONMENTAL ASSESSMENT
OFFICE OF
RESEARCH AND DEVELOPMENT

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MEMORANDUM

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

FROM: John Vandenberg, Ph.D.
Director
National Center for Environmental Assessment
Research Triangle Park Division (B243-01)

TO: Aaron Yeow, M.P.H.
Designated Federal Officer
Clean Air Scientific Advisory Committee
EPA Science Advisory Board Staff Office (1400R)

The Second External Review Draft *Integrated Science Assessment for Oxides of Nitrogen – Health Criteria* (second draft ISA for Oxides of Nitrogen) 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 for nitrogen dioxide (NO_2) was released on January 30, 2015.

The second draft ISA will be reviewed by the Clean Air Scientific Advisory Committee Oxides of Nitrogen NAAQS Review Panel (CASAC Oxides of Nitrogen Panel) at a public meeting on June 2-3, 2015. Electronic copies of the second draft ISA are available for download at http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=288043. We have distributed the draft ISA to the CASAC Oxides of Nitrogen Panel. I am requesting that you forward our charge to the Panel.

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 the ambient air" (Clean Air Act, Section 108; 42 U.S.C. 7408). The second draft ISA for Oxides of Nitrogen integrates the scientific evidence and provides draft findings, conclusions, and judgments of the strength, sources of bias, and uncertainties in the evidence base for relationships between NO_2 exposure and health effects.

Following the review of the second draft ISA, NCEA-RTP staff will produce a final ISA, projected for release in Fall 2015, which will addresses comments received from the CASAC

Oxides of Nitrogen Panel and the public. 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 current primary standards for NO_2 to protect human health. We look forward to the CASAC Oxides of Nitrogen Panel review of the second draft ISA at the upcoming meeting. Should you have any questions regarding the second draft ISA for Oxides of Nitrogen, please feel free to contact me (919-541-4527, vandenberg.john@epa.gov) or Dr. Molini Patel (919-541-1492, patel.molini@epa.gov).

Charge to CASAC Oxides of Nitrogen Panel

The second draft ISA includes revisions based on the comments and advice provided by the CASAC Oxides of Nitrogen Panel and comments received from the public on the first external review draft ISA. Specific revisions were described in EPA's response (October 2014) to the CASAC Oxides of Nitrogen Panel's review letter on the first draft ISA (June 2014).1 We have carefully considered all of the comments provided by the CASAC Oxides of Nitrogen Panel and the public in creating this second draft ISA. In addition, we have incorporated information from relevant studies published since the release of the first external review draft ISA through August 2014. The revisions reflected in the second draft ISA for Oxides of Nitrogen focus on several overarching concerns raised by the CASAC Panel:

- Re-organizing information about exposure assessment methods for NO_2 and their potential utility, sources of error, and uncertainties to better inform the evaluation of epidemiologic studies of various designs.
- Improving the transparency of the application of the causal framework in forming causal determinations by:
  - integrating the evidence across scientific disciplines for specific outcome groups (e.g., asthma exacerbation, triggering of myocardial infarction); and
  - more explicitly describing the strength of inference from epidemiologic studies considering the exposure assessment methods used and the examination of potential confounding, in particular by other traffic-related pollutants.

Major changes to the content and structure of the draft ISA are broadly summarized below, and charge questions are provided for this review by the CASAC Oxides of Nitrogen Panel. These charge questions are not intended to limit the scope of the Panel's review but rather are intended to assist the Panel by highlighting specific areas where the Agency has responded to prior comments of the Panel or where the Agency raises issues to be addressed by the Panel.

Executive Summary and Chapter 1 – Integrative Summary

The Executive Summary and Chapter 1 provide overviews of the ISA. The Executive Summary is intended to be a concise synopsis of key findings targeted to the broadest audience, whereas

1The CASAC Oxides of Nitrogen Panel's review letter is available at: http://yosemite.epa.gov/sab/sabproduct.nsf/15E4619D3CD3409A85257CF30069387D/$File/EPA-CASAC-14-002+unsigned.pdf.
EPA's response to the CASAC Oxides of Nitrogen Panel's review letter is available at: http://yosemite.epa.gov/sab/sabproduct.nsf/15E4619D3CD3409A85257CF30069387D/$File/EPA-CASAC-14-002_Response-10-09-14.pdf.

Chapter 1 is a more detailed synthesis of the ISA's most policy-relevant findings. The Executive Summary and Chapter 1 are revised to address the CASAC Oxides of Nitrogen Panel's advice to provide a more cohesive discussion of the array of issues that are considered in evaluating the causality of relationships between NO_2 exposure and health effects. The revised discussions describe the extent to which available scientific information has addressed these issues and the uncertainties that remain.

1. Please comment on how clearly the Executive Summary communicates the major findings of the ISA for a non-technical audience.

2. How well does Chapter 1 link together information about the distribution of NO_2 in the atmosphere, exposure assessment, dosimetry, modes of action, and health effects to convey the major issues that need to be considered in evaluating scientific information on NO_2 exposure and health effects? To what extent does Section 1.4.3 address potential confounding factors?

3. What are the Panel's views on how well Chapter 1 provides an integrated analysis of the weight of evidence for NO_2-health effect relationships? For example, information on exposure assessment, dosimetry, modes of action, and health effects is incorporated into individual health effect discussions in Section 1.5 (e.g., respiratory effects, cardiovascular and related metabolic effects). Also, the section from the first draft ISA on confounding was removed and incorporated into each health effect discussion. To what extent is the causal framework transparently applied and the rationale for changes made (or not made) to causal determinations from the 2008 ISA for Oxides of Nitrogen clearly articulated in the Executive Summary, Chapter 1 and Table 1-1?

<u>Chapter 2 – Atmospheric Chemistry and Ambient Concentrations of Oxides of Nitrogen</u>
Revisions to Chapter 2 aim to address the CASAC Oxides of Nitrogen Panel's recommendation to describe in more detail spatial and temporal patterns in ambient NO_2 concentrations and aim to clearly identify factors that may influence variation in exposure within the population and potential uncertainties in exposure estimates.

1. Chapter 2 expands characterization of the spatial variability in NO_2 concentrations within several U.S. cities (Section 2.5.2) and near-road gradients (Section 2.5.3) using information from U.S. monitoring networks and/or published studies. Please comment on the appropriateness of the content, interpretation, and scope of the material. How useful is the content and organization of Table 2-6, which synthesizes results from published studies of near-road gradients?

2. Data from the U.S. near-road monitoring network became available after the first draft ISA, and the second draft ISA presents preliminary data for a small group of U.S. cities that had at least one full year of measurements. Please comment on utility to the review of the primary NO_2 NAAQS of the presentation, interpretation, and scope of the discussion of the near-road network measurements.

3. Section 2.5.3 further characterizes near-road NO_2 concentrations with data that are available from networks outside the U.S. Data on near-road NO_2 were publicly available for several sites and years in London, U.K. but not Canada. To what extent are the statistics presented in Table 2-9 and the discussion of the London data useful and adequate for describing how monitor siting can affect characterization of the spatial and temporal patterns in NO_2 concentrations? Are the potential limitations (e.g., lack of traffic count data for roadside sites) of the London monitoring data appropriately described?

Chapter 3 – Exposure to Oxides of Nitrogen

As suggested by the CASAC Oxides of Nitrogen Panel, the discussion of exposure is separated into its own chapter and is considerably revised in response to the Panel's comments on the need for the discussion to better inform the interpretation of epidemiologic studies of various designs and exposure durations.

1. The exposure discussion is re-organized to clarify: a) the connection between particular exposure assessment methods and epidemiologic study designs, and b) the influence of exposure error on health effect associations from epidemiologic studies of specific designs. How explicitly and accurately is epidemiologic study design considered in the discussion of the utility and uncertainties of various exposure assessment methods, the nature of exposure measurement error, and the impact of exposure measurement error on NO_2-health effect associations? How effective is the discussion in facilitating the evaluation of the strength of inference from epidemiologic studies in Chapters 5 and 6?

2. Section 3.4.4 expands discussion of the relationships of NO_2 with copollutants and traffic noise for various short-term and long-term time periods as well as various exposure parameters (e.g., ambient, personal, indoor). To what extent is this information appropriately characterized and useful for the evaluation of potential confounding in epidemiologic studies in Chapters 5 and 6?

Chapter 4 – Dosimetry and Modes of Action for Oxides of Nitrogen

Chapter 4 is revised to address the CASAC Panel's advice to improve characterization of the NO_2 transport within the respiratory tract, existing dosimetric models, as well as mode of action for specific health outcome groups such as asthma exacerbation.

1. The dosimetry section (Section 4.2) expands on the description of the epithelial lining fluid in the tracheobronchial and alveolar regions. Further, the deficiencies and uncertainties associated with the lack of a validated NO_2 dosimetry model are more explicitly described. Please comment on the adequacy and clarity of these expanded discussions. To what extent does Section 4.2 address the reactive nature of NO_2 and its ability to pass beyond the epithelial lining fluid?

2. Section 4.3 discusses mode of action for specific outcome groups and also includes new figures that describe what scientific information is available on the key events and endpoints that make up the pathophysiological changes that lead to particular health effects. What are the Panel's views on the effectiveness of the organization around the outcomes of interest?

To what extent do the new figures facilitate integration with the health effects evidence in Chapters 5 and 6?

Chapters 5 and 6 – Integrated Health Effects of Short-term and Long-term Exposure to Oxides of Nitrogen

In response to the CASAC Oxides of Nitrogen Panel's recommendations, the health effect evaluations in the second draft ISA more explicitly integrate various lines of scientific information and describe the strengths, sources of bias, and uncertainties in the evidence base. The revisions aim to address the Panel's comments on the need to more transparently apply the causal framework and clearly articulate the rationale for the causal determinations.

1. To more transparently characterize the weight of evidence for health effects, discussions are organized by specific outcome groups. For example, outcome groups under respiratory effects include asthma exacerbation and respiratory infection (versus respiratory-related hospital admissions). Within specific outcome groups, clinical outcomes and events are emphasized over subclinical effects that may be more relevant to characterizing the mode of action. Please comment on the extent to which individual endpoints are appropriately placed into specific outcome groups. For example, how well does the discussion of asthma exacerbation integrate the evidence for relevant health endpoints across disciplines, including mode of action information? How clearly do the causal determinations identify the specific outcome groups that contribute most heavily to the conclusions?

2. Section 5.2.2.1 expands discussion of an EPA meta-analysis of controlled human exposure studies of airway responsiveness in individuals with asthma. The methods for this meta-analysis are described in more detail, and additional analyses of individual-level data assess the magnitude and clinical relevance of effects. Further, sensitivity analyses are presented that demonstrate that the statistical significance, distribution of responses, and determination of clinical relevance are robust to the exclusion of full studies and the removal of repeated measurements. These analyses were recently published in *Inhalation Toxicology* in Brown (2015). Please comment on the extent to which the results from the meta-analysis, including the new analyses, are clearly described, appropriately interpreted, and informative to the evaluation of NO_2-induced increases in airway responsiveness. Given that the results are now published in a peer-reviewed journal, what material that is presented in the manuscript could be removed from the ISA and referenced to the manuscript?

3. Drawing from Chapter 3, the health effect evaluations more critically evaluate the exposure assessment methods used in epidemiologic studies. Please comment on the adequacy and consistency with which exposure assessment, including the utility and uncertainties of the methods used and potential impact of exposure measurement error, is considered in describing the strength of inference from epidemiologic results. To what extent is available information on health effects related to personal and indoor NO_2 adequately considered in conclusions?

4. Chapters 5 and 6 provide a more consistent critical evaluation of potential confounding by traffic-related exposures in epidemiologic studies. The potential for various copollutants,

stress, and noise to confound NO_2 associations with particular health effects is identified based on correlations with NO_2 and similar health effects and mode of action (Section 1.4.3 and Table 5-1). Further, the strength of inference from copollutant models is assessed by considering the correlations reported between pollutants and potential for differential exposure measurement error. What are the Panel's views on the extent to which confounding by traffic-related copollutants and other exposures are appropriately and consistently evaluated?

5. The health effect evaluations describe in more detail judgments of the strength and limitations of the evidence, drawing upon information about study quality and evidence integration to form causal determinations (Section 5.1.2, Table 5-1). To what extent are the strengths, sources of bias, and uncertainties in the integrated evidence base adequately considered in forming causal determinations? How transparently is the causal framework applied to the evidence for each of the broad health effect categories in communicating the rationale for the causal determinations?

<u>Chapter 7 – Populations and Lifestages Potentially at Increased Risk for Health Effects Related to Nitrogen Dioxide Exposure</u>

Chapter 7 is revised to address the CASAC Oxides of Nitrogen Panel's recommendation to provide a more integrated analysis of the weight of evidence for potential at-risk populations and lifestages and to expand the discussion of populations with proximity to roadways and risk of NO_2-related health effects due to multiple co-occurring factors.

1. The enhanced integrated analysis of at-risk populations and lifestages includes moving individual study results to tables and focusing the discussion on the synthesis of the health effects evidence as well as available information on exposure and dosimetry. Please comment on the effectiveness of the integrated analysis and the extent to which the strengths and limitations of the evidence are explicitly and consistently described in communicating the rationale for conclusions about at-risk populations and lifestages.

2. A new section (Section 7.5.6) describes what information is available on differences in NO_2 exposure or risk of NO_2-related health effects for populations with proximity to roadways. To what extent does the added discussion accurately reflect the available information?

cc: Lynn Flowers, ORD/NCEA
Scott Jenkins, OAR/OAQPS
Ellen Kirrane, ORD/NCEA
Kenneth Olden, ORD/NCEA
Molini Patel, ORD/NCEA
Erika Sasser, OAR/OAQPS
Debra Walsh, ORD/NCEA
Karen Wesson, OAR/OAQPS
Aaron Yeow, SAB, OA