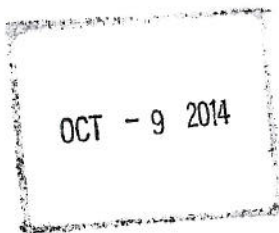




UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460



OFFICE OF
RESEARCH AND DEVELOPMENT

H. Christopher Frey, Ph.D.
Chairman
Clean Air Scientific Advisory Committee
Science Advisory Board
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Dear Dr. Frey:

Thank you for your June 10, 2014, letter providing the Clean Air Scientific Advisory Committee Oxides of Nitrogen Review Panel's comments on the U.S. Environmental Protection Agency's "Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria, First External Review Draft – November 2013." We at the EPA greatly appreciate the panel's thorough review.

My staff is carefully considering your comments and recommendations as well as the comments we received from the public. We are making revisions to address both consensus and individual CASAC comments. Enclosed is an overview of the major revisions we are incorporating into the "Second External Review Draft of the ISA for Oxides of Nitrogen – Health Criteria." Highlighted in my letter are some of the key changes we are making in response to the advisory committee's comments.

We are paying particular attention to several important points raised by the CASAC panel, including the need to:

- increase synthesis and integration of the scientific evidence to support the causal determinations made for the evaluated health effects;
- reorganize and clarify the discussion of human exposure to oxides of nitrogen to better inform the evaluation of epidemiologic studies of varying designs;
- more explicitly evaluate potential confounding of the associations observed between nitrogen dioxide and health effects by copollutants and other factors; and
- expand discussion of the near-road environment, including the spatial and temporal distributions of oxides of nitrogen and characterization of populations living or spending time near major roadways.

To address the CASAC panel's recommendation for increased synthesis and integration of scientific evidence, we are revising Chapter 1's Integrative Summary so the second external review draft will better link discussion among various topics, providing a more complete picture of the array of issues

considered in evaluating the causality for health effects. The integration will be carried through in subsequent chapters. For example, the spatial and temporal distributions of oxides of nitrogen, including those near major roads as presented in Chapter 2, has important implications on exposure. This is being incorporated more explicitly into the discussion of various exposure-assessment methods (separated into a new Chapter 3). This discussion, in turn, is being used to evaluate the strength of inference from epidemiologic findings in Chapters 5 and 6. Also, in the second external review draft we are increasing integration of dosimetry and modes of action in Chapter 4, with health effects in Chapters 5 and 6 based on short-term and long-term exposure and specific health effect categories to characterize more transparently the weight of evidence for effects related to oxides-of-nitrogen exposure.

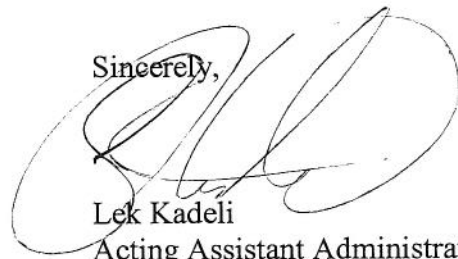
In the second external review draft we are paying particular attention to comments from the CASAC panel about a need to revise the discussion of human exposure to oxides of nitrogen. As noted previously, the exposure discussion is being separated into its own chapter, now Chapter 3, and organized to better inform the interpretation of epidemiologic study results. Chapter 3 will include a summary of the strengths and limitations of various exposure parameters, such as ambient and total personal, and exposure-assessment methods applicable to particular epidemiologic study designs and exposure durations. The discussion of exposure-measurement error and impact on inference from epidemiologic findings is being organized similarly with respect to epidemiologic study design.

In response to the CASAC panel's advice on the assessment of health effects related to short-term and long-term exposure to oxides of nitrogen, we are revising Chapters 5 and 6 to improve the description of the strength of inference drawn from the lines of evidence across various topic areas and disciplines. This will allow us to more clearly articulate the rationale for the causal determinations. The changes include reorganizing the evaluations around specific health-effect categories, such as asthma exacerbations, and more critically evaluating exposure measurement error and potential confounding by other traffic-related pollutants in epidemiologic studies.

The CASAC panel also offered advice on characterizing lifestages and populations potentially at risk of health effects related to exposure to oxides of nitrogen. We are revising Chapter 7 to increase synthesis among study results to better communicate the overall weight of evidence for the evaluated lifestages and populations. We are also expanding discussion of populations living or spending time near major roads and evaluating the potential for at-risk populations to be characterized by multiple co-occurring factors.

As you know, our work to protect public health and the environment can only be as good as the science upon which it is based. Your independent critical reviews help to ensure that we use the best science in our decision making, and I thank you once more for all your hard work.

Sincerely,

A handwritten signature in black ink, appearing to read 'Lek Kadeli', is written over a large, faint circular stamp or watermark.

Lek Kadeli
Acting Assistant Administrator

Enclosure

ATTACHMENT

Overview of Revisions to the First Draft ISA for Oxides of Nitrogen – Health Criteria in Response to CASAC Peer Review Comments dated June 10, 2014

Executive Summary

Both the Executive Summary and Chapter 1 are being revised to reflect changes made to the subsequent chapters. The language is being simplified for a non-technical audience by removing scientific jargon. Rather than presenting a sequential summary of the ISA, the revised Executive Summary is focusing on integrating the lines of evidence across topic areas that inform the causal determinations (e.g., air quality characterization, exposure assessment, dosimetry, modes of action, health effects) and on more clearly articulating the basis for changing causal determinations from the 2008 ISA for Oxides of Nitrogen.

Chapter 1 – Integrative Summary

Chapter 1 is being revised to improve synthesis and integration among topic areas and scientific disciplines to more clearly articulate the overall weight of evidence contributing to the causal determinations for the evaluated health effects. The revised chapter and Table 1-1 will more transparently describe the specific line(s) of evidence that form(s) the basis for changing causal determinations from those made in the 2008 ISA.

Information is being integrated among emissions sources, spatial and temporal patterns in ambient oxides of nitrogen and other pollutants, and exposure assessment. Revisions also are increasing linkages between information on modes of action and health effects examined in epidemiologic, controlled human exposure, and animal toxicological studies (in text and as a figure). This improved integration is serving to: (1) better communicate judgments about the implications of epidemiologic evidence and potential uncertainties regarding copollutant confounding and exposure measurement error; and (2) more explicitly identify health effects for which evidence characterizes biological pathways linking nitrogen dioxide (NO₂) exposure to health effects and health effects for which there is uncertainty.

Chapter 2 – Source to Concentrations of Oxides of Nitrogen

Revisions to Chapter 2 are aimed at improving characterization of the spatial and temporal distributions of oxides of nitrogen at various scales and the chemical and physical processes that influence the dispersion of oxides of nitrogen. Staff also is reviewing the availability of data that may improve characterization of emissions sources in large U.S. cities and their geographic variation.

Chapter 2 is expanding the description of the distribution of oxides of nitrogen near major roadways as well as gradients that occur with increasing distance from roadways. To the extent that data are available, Chapter 2 will summarize ambient NO₂ concentrations from the first set of sites from the new U.S. near-road monitoring network. Staff also is assessing the availability of data from networks outside of the U.S. to improve characterization of the spatial variability in ambient NO₂ concentrations.

Chapter 3 – Exposure to Ambient Oxides of Nitrogen

Separated into a new Chapter 3, the exposure discussion is being re-organized and clarified in order to better inform judgments about the strength of inference from epidemiologic studies. One focus of revisions is more explicit discussion of the role of the various exposure parameters (e.g., ambient concentrations, total personal exposure, indoor concentrations) examined in epidemiologic studies in informing judgments about relationships between NO₂ and health effects.

Another focus of revisions is communicating more clearly how the method for assessing ambient exposure may influence epidemiologic inference. To describe the important considerations for characterizing human exposure to oxides of nitrogen, Chapter 3 is drawing more explicitly from discussion in Chapter 2 of the spatial and temporal variability in ambient concentrations of oxides of nitrogen at various scales and of the design of the ambient monitoring network. Further, Chapter 3 is discussing the strengths and limitations of various exposure assessment methods used to assess relationships with health effects. For example, Chapter 3 is being more explicit about the need to consider the extent to which the monitoring network or exposure model adequately represents the variability in ambient NO₂ concentrations, including that near major roads, in the study area.

The discussion in Chapter 3 of exposure assessment methods is being organized around the various epidemiologic study designs and exposure durations evaluated in the health effects chapters (Chapters 5 and 6). Chapter 3 is describing personal-ambient relationships, exposure measurement error components, factors contributing to exposure error, and the potential impact on the magnitude and precision of health effect estimates in the context of particular epidemiologic study designs (e.g., time-series, panel, cross-sectional, longitudinal cohort), exposure durations (i.e., short-term, long-term), and exposure parameters (e.g., ambient concentrations, total personal exposure). Additional recent publications are being incorporated and where applicable, uncertainties in the scientific information are more explicitly noted. The revised exposure discussion is being used to better inform judgments about health effects observed in association with oxides of nitrogen in epidemiologic studies.

Revisions to Chapter 3 also are more clearly describing relationships between oxides of nitrogen and other pollutants. The discussion is distinguishing copollutant relationships for particular exposure parameters (e.g., personal, ambient, indoor) as well as particular geographic and time scales. This information is being used to more critically evaluate the potential for copollutant confounding, interactions, or joint effects in epidemiologic studies of health effects related to short-term exposure (Chapter 5) and long-term exposure (Chapter 6) to oxides of nitrogen.

Chapter 4 – Dosimetry and Modes of Action

Revisions are being made to the dosimetry section to improve characterization of NO₂ transport within the respiratory tract. Specifically, Chapter 4 is noting the heterogeneity in composition and thickness in the epithelial lining fluid (ELF). Information regarding known products of reactions between NO₂ and ELF constituents is being added. References provided by the CASAC panel are being considered for inclusion.

The discussion of modes of action is focusing more on the health effects examined in Chapters 5 and 6 by grouping key events that lead to particular health effects (e.g., asthma exacerbations). These revisions are aimed at better communicating the underlying pathophysiologic changes that lead to particular health effects. Further, the spectrum of health effects (e.g., cardiovascular effects, cancer) covered under the broad category extrapulmonary effects is being more explicitly described, as is the extent to which the evidence base characterizes modes of action underlying particular extrapulmonary effects.

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

Revisions are being made to Chapters 5 and 6 to articulate more clearly how the various lines of scientific information are evaluated and integrated to form causal determinations for relationships between NO₂ and health effects. Broadly, these revisions include:

- (1) grouping material by health effect category (e.g., group asthma emergency department visits, airway hyperresponsiveness in people with asthma under asthma exacerbations) rather than design of study (e.g., emergency department visits for all respiratory causes);
- (2) providing a more consistent critical evaluation of exposure assessment in epidemiologic studies and the impact of potential measurement error on study findings;
- (3) providing a more consistent critical evaluation of NO₂ as a constituent within an air pollution mixture and the extent to which epidemiologic studies have evaluated potential confounding, pollutant interactions, and joint effects.

The health effects discussion is being re-organized not only around health effect category, but also clinical events (e.g. asthma emergency department visits) versus subclinical effects (e.g., changes in inflammatory cytokines), with greater emphasis placed on clinical events. With this re-organization and improved integration with mode of action evidence (Chapter 4) to inform biological plausibility, Chapters 5 and 6 are more clearly communicating differences in weight of evidence among various health effect categories and identifying the lines of evidence contributing more heavily to causal determinations.

Chapters 5 and 6 are improving integration with exposure assessment by examining the adequacy of the exposure assessment method in the epidemiologic studies based on the study design used and information reported on the spatial and/or temporal variability in the study area and distribution of subjects in the study area. Drawing upon information presented in Chapter 3 about potential exposure measurement error, Chapters 5 and 6 are more explicitly weighing the strength of inference about NO₂-related health effects among the epidemiologic studies evaluated.

Integrating information from earlier chapters on common sources, spatial and temporal distributions, and modes of action, the health effects assessments are more critically evaluating potential copollutant confounding, effect modification, and/or joint effects. This evaluation is including description of the methods used to examine copollutant influences and their strengths and limitations, which is being moved from Chapter 1 to the health effects chapters. The evaluation of copollutant confounding and interactions also are more consistently identifying which copollutants are examined. Emphasis is being placed on other highly correlated traffic-related pollutants such as carbon monoxide, fine particulate matter, black/elemental carbon, and certain organic and inorganic particle components. The discussions also are noting uncertainties that remain for certain copollutants and health effects. The health effects assessments also are discussing in more detail what other potential confounding factors (e.g., socioeconomic status, stress) are important to consider.

With improved integration among various lines of evidence and more explicit description of the strengths of various studies and sources of bias and uncertainty, the revised Chapters 5 and 6 are more clearly identifying the most informative studies in the evidence base and increasing the transparency of Staff's application of the causal framework and rationale for the current causal determinations as well as changes made from the 2008 ISA.

Revisions are being made to the meta-analysis of controlled human exposure studies of airway hyperresponsiveness to provide more detailed discussion of the methodology used. To evaluate the robustness of findings and inform the clinical relevance of changes, sensitivity analyses are being performed and additional outcomes such as the fraction of individuals experiencing a doubling reduction in provocative dose in response to NO₂ exposure relative to air exposure are being evaluated.

Chapter 7 – Populations Potentially at Increased Risk for Health Effects Related to Oxides of Nitrogen Exposure

The evaluation of potential at-risk lifestages and populations is being revised to focus more on synthesizing findings across studies rather than describing individual studies. Study details are being summarized in tables, similar to the one for genetic variants, and include study strengths and limitations that specifically inform interpretation of results for effect measure modification. In order to improve understanding of the many factors that may characterize potential at-risk lifestages and populations, Chapter 7 is evaluating the potential for multiple co-occurring population characteristics (e.g., asthma in children, low SES, nonwhite race) to influence risk of health effects related to exposure to oxides of nitrogen.

Chapter 7 also is expanding discussion of populations living, working, engaging in activity, and commuting near or on major roads, characterizing their sociodemographic characteristics, and examining the extent to which scientific information indicates that these populations have increased exposures to oxides of nitrogen and/or related health effects.