UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

June 25, 2008

EPA-CASAC-08-015

The Honorable Stephen L. Johnson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Clean Air Scientific Advisory Committee's (CASAC) Peer Review of EPA's Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria (Second External Review Draft)

Dear Administrator Johnson:

The Clean Air Scientific Advisory Committee (CASAC), augmented by subject-matter-experts to form the CASAC Oxides of Nitrogen Primary National Ambient Air Quality Standards (NAAQS) Review Panel (hereafter referred to as the panel, roster contained in Enclosure A) held a public meeting on May 1-2, 2008 to review EPA's *Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (Second External Review Draft) (EPA/600/R-07/093aB, March 2008).* The Chartered CASAC held a public teleconference on June 11, 2008 to review and approve this report.

The *Integrated Science Assessment* (ISA) states (Page 1-1) that its purpose is to present a "concise review, synthesis, and evaluation of the most policy-relevant science" and to communicate the "critical science judgments relevant to the review of national ambient air quality standards for review of the primary standard for oxides of nitrogen (NO_x)." Although the CASAC finds that the second draft ISA was much improved compared to the first draft reviewed in November 2007, the document in its current state does not provide adequate guidance as to what would be expected at current ambient concentrations. CASAC finds that scientific data exist with which to answer this question, albeit with some level of uncertainty, so that the document can provide an adequate scientific basis for the exposure and policy assessments during the next stage of the NAAQS review. Perhaps the most important consideration in improving the document is a much better discussion of the significance of the epidemiology data for a potential risk assessment, despite the uncertainties associated with those data. Incorporating an analysis of the available epidemiology data will allow estimation of the potential uncertainties that need to be fully described and quantified in the risk and exposure assessment. The ISA discussion should consider the effect of co-exposures to

other pollutants, the relationship between ambient and personal exposures, and how the problems associated with the available epidemiology studies limit their use for risk assessment. Because of EPA's accelerated NAAQS schedule for NO_x, CASAC may not have an opportunity to provide additional input for revising the ISA and so underscores its advice that the document be further strengthened to support the NAAQS review.

Panel consensus comments on how the ISA might be further strengthened are given below in the form of responses to the Agency's charge questions. Individual comments from CASAC panel members are enclosed in Enclosure B.

Charge Question 1. What are the views of the Panel on the characterization of the search strategy for identifying literature, criteria for study selection, the framework for scientific evaluation of studies and causality determination?

Substantial improvements have been made based on prior comments. The process for review of recent literature is reasonable and the results appear to be accurately reported. In regard to the Agency's approach to synthesis of the evidence and causal inference, an extensive Annex has been prepared that reviews a number of relevant frameworks. The background is a useful foundation for informing the selected approach for assessing available evidence and should be extended to justify the adopted framework. Based on this Annex, the Agency has made changes in Chapter 1 that are responsive to prior critiques. In particular, there is a description of literature selection; an approach to evaluating evidence for inferring causality is provided; and a reasonable set of descriptors of strength of evidence for causation is offered.

EPA has improved the second draft ISA by having a better prepared first chapter that includes the framework for the document. However, the sections that synthesize the evidence are still somewhat loosely written, and do not systematically apply the guidelines offered by Bradford Hill and adopted by the Agency. (Note, these should not be renamed as "decisive factors," a misnomer). Too often, sections that are offering judgments as to the strength of evidence use such language as "taken together" or "integrating" without a more specific application of the criteria offered by Hill. Nonetheless, the revised Chapter 1 and the approach set out represents an advance over the earlier draft.

Additional issues that are not considered are publication and model selection biases, a concern given that many studies address the health effects of air pollution and employ multivariable models to attempt to isolate the effects of particular pollutants at specific temporal or spatial scales. There may have been some tendency on the part of investigators to report positive associations or not to reflect the full health effect from such factors as multiple lags.

A further issue in integrating the evidence is the substantial difference in the doses and mixtures of pollutants and their interactions given to animals or human volunteers in toxicology and clinical studies versus those experienced by the populations in epidemiology studies. Specific consideration needs to be given to the relevance of mechanisms identified in toxicology studies to effects observed in the epidemiology studies.

Charge Question 2. To what extent are the atmospheric chemistry and air quality characterizations clearly communicated, appropriately characterized, and relevant to the review of the primary NO_2 NAAQS? Are the properties of ambient oxides of nitrogen appropriately characterized, including spatial and temporal patterns and relationships between ambient oxides of nitrogen and human exposure? Does the information in Chapter 2 provide a sufficient atmospheric science and exposure basis for the evaluation of human health effects presented in later chapters?

Overall, the description of the atmospheric dynamics, measurement techniques and ambient concentrations is adequate, though aspects are still wanting. The document would benefit greatly by having summaries at the end of each section with the points most key to providing information that will be used in technical documents supporting the rulemaking for NO_2, in particular those that inform the rest of the ISA and the risk/exposure assessment (REA) and delineate what matters. The Panel still views that a quantitative summary of sources would be beneficial. The REA relies heavily on the application of various modeling techniques, including AERMOD and an empirical approach for estimating on-road NO_2 concentrations. Consequently, the needed background information on their scientific fundamentals, and their ability to reproduce observed concentrations, should be covered in the ISA. Along those lines, given the importance of on-road concentrations, that section of the ISA should be enhanced, with additional attention given to street canyon concentrations. Siting characteristics of monitors should be incorporated into all analyses of monitoring data.

The Panel found that the section on measurement interferences continues to give a somewhat distorted picture of the importance of interferences. The implications of the interferences should be made explicit (i.e., by quantifying how much the interferences impact the peak NO_2 levels and annual averages and identifying whether the interferences pose an important issue for exposure and epidemiology studies). Given the potential that the REA may depend more heavily on the epidemiology results, the ISA should more comprehensively assess how NO_2 levels correlate with air quality variables besides particulate matter (PM) mass (either PM_{10} or $PM_{2.5}$), ozone and sulfur dioxide, e.g., addressing the correlations with elemental carbon, organic carbon and other combustion products. It is known that carbon particles will adsorb $NO_2$when they are exposed to high concentrations of the gas in the lab. EPA should consider the extent to which this may occur in the atmosphere..

In the last section on dosimetry, there is little progress to report on extrapolation modeling since the 1993 Criteria Document. Nevertheless, the established dosimetry models could be applied to the many of the key studies in the ISA, particularly to put response data collected from animals and humans on a comparative footing with each other and with the exposure conditions in the epidemiological studies.

Charge Question 3. To what extent is the discussion and integration of evidence from the animal toxicology and controlled human exposure studies and epidemiologic studies technically sound, appropriately balanced, and clearly communicated? What are the views of the Panel on the conclusions drawn in the

draft ISA regarding the strength, consistency, coherence and plausibility of NO_2-related health effects?

The second draft ISA is substantially improved in organization and content compared to the first draft. The revised document has addressed a number of the concerns expressed by CASAC. New publications from the scientific literature since 1993 have been appropriately incorporated into this ISA draft. Substantial new findings have occurred since 1993 that are relevant to the issue of health risks related to oxides of nitrogen. These include animal toxicology studies, human clinical studies and epidemiology studies. Although the exposure concentrations in animal toxicology studies are typically well above ambient conditions, they do provide biological plausibility for adverse health effects that can be attributed to NO_2.

Panel members concur with the primary conclusions reached in the ISA with regard to health risks that are associated with NO_2 exposure. In particular, the Panel agrees with the conclusion that the current scientific evidence is "sufficient to infer a likely causal relationship between short term NO_2 exposure and adverse effects on the respiratory system." The strongest evidence in support of this conclusion comes from epidemiology studies that show generally positive associations between NO_2 and respiratory symptoms, hospitalizations or emergency department visits, as summarized in Figure 5.3.1. Furthermore, we would conclude that the epidemiology studies show significant effects related to NO_2 exposure that are robust in some cases, even when adjusted for co-pollutants. One limitation of the available epidemiology studies, however, is an inability to establish a definitive NO_2 exposure level that can be specifically associated with the observed adverse health effects. Consequently dose-response relationships are difficult to establish for NO_2, however best estimates and their uncertainties should be discussed. Separately and for future consideration, there is a recognized need to consider regulatory approaches to complex mixtures of air pollutants rather than considering each pollutant individually.

The human clinical studies reviewed in the ISA need to be interpreted with caution. The lowest reported effect of NO_2 exposure was found in three Swedish studies of airway responses to antigen challenge in allergic asthmatics. However, other human clinical studies have shown mixed results with some studies failing to find biologically significant health effects at similar or higher levels of NO_2 exposure alone. In addition, although airway responses to antigen challenge can be considered an adverse health effect, admission to a hospital or a visit to an emergency department for an exacerbation of asthma can be considered a clearer adverse effect. Epidemiology studies more directly address these adverse health effects and provide evidence identifying health risks related to ambient NO_2 exposures. In summary, the new scientific literature reviewed in the second draft of this ISA document provides a number of strong indications of possible NO_2 health effects, but confounding or exacerbating co-pollutants and variable findings in human clinical studies remain problematic. Of special concern are potential interactions with particulate matter, potentially increasing lung NO_2 dosages above what would occur with NO_2 alone. These aspects should be addressed in considering a revised criteria standard for NO_2.

Charge Question 4. What are the views of the Panel on the characterization of groups likely to be susceptible or vulnerable to NO_2 and the potential public health impact of NO_2 exposure?

Overall, the draft ISA does an adequate job of discussing the public health significance of exposure to ambient NO_2. The chapter 4 summary indicates that persons with preexisting respiratory disease (especially asthma), children, and older adults may be more susceptible to the effects of NO_2 exposure. While the panel agrees with this assessment, other subpopulations may also be at increased risk of adverse health effects from exposure to ambient NO_2. Specifically, there is evidence in the ozone and PM health effects literature that individuals who have poor dietary intake of antioxidants, are obese, or have certain genetic variants, as well as premature or low-birth-weight infants, may be more susceptible to these pollutants. Since NO_2 is thought to cause health effects by a similar oxidant injury pathway to ozone and fine PM, these subpopulations should be considered in this chapter. We suggest that a table or figure be included in the document to more clearly identify subpopulations that are likely susceptible to adverse effects of exposure to NO_2 and to identify the research that indicates that susceptibility.

The panel recommends that the draft ISA more clearly communicate the distinction between "susceptibility" and "vulnerability." Susceptibility as used in the latest draft ISA appears to describe those factors that may be considered "host" or "intrinsic" while vulnerability appears to be related to an interaction between susceptibility (risk-based on intrinsic risk factor) and increased risk of exposure. As currently used in the document, these terms have overlapping meanings that could lead to unnecessary confusion.

Charge Question 5. What are the Panel's views on the adequacy of this second external review draft ISA to provide support for future exposure and policy assessments?

The Panel has several comments on the adequacy of the draft ISA as a basis for exposure and policy assessments. First, Chapter 5 satisfactorily summarizes the information and judgments from earlier chapters that are relevant to exposure and policy assessments. The authors of the draft have both accurately reflected that earlier material and chosen the material most relevant for further assessments.

The charge question, however, asks not only about the fidelity of Chapter 5 in presenting results from earlier chapters, but also whether the draft provides an adequate basis for exposure and policy assessments. The CASAC Panel is not convinced that the chapter, as currently written, has met this goal, but the Panel believes that the chapter and the draft can be improved to that point through the improvements we have suggested in our review. Chapter 5 does indicate directions that are important for exposure and policy assessments: towards sensitive subpopulations that should be considered; towards specific health effects that should be considered; and towards the difficulties in estimating exposure due to uncertainties in the relationship between ambient monitoring results and personal exposures. In each of these categories more details need to be

provided so that a risk assessor can find useful summary information to inform how an exposure/risk assessment should be structured and how the residual uncertainties should be characterized.

At present, the draft provides an inadequate basis for performing exposure and policy assessments quantitatively, or even summarizing the information that will be used in such assessments. The draft is uninformative as to what the levels of exposure are for any specific population in any specific geographic location. The authors should have summarized at least the ambient exposure information available (alluded to in the previous chapters) and then drawn judgments as to the validity of using that information in specific kinds of exposure assessments (e.g., the spatial scale on which variability can be determined and how to correct for indoor exposures). This summary and its interpretation can be offered without moving into the policy domain or even unduly specifying the tasks of further exposure assessors. There also should be a succinct statement as to whether an exposure-response curve can be developed, so that the risk assessor is not left solely with the option of using methods akin to hazard quotients.

On the summarization of health effects, this chapter is greatly improved from the previous draft. t identifies health effects associated with exposure to nitrogen oxides and the strength of evidence supporting causality of associations. On the issue of whether effects would be expected at current ambient concentrations, however, the chapter does not provide adequate guidance. This is one of the weakest aspects of the current draft, even though this is one of the most important conclusions to be drawn from the document. Some statement with regard to the degree of certainty in the occurrence of effects at ambient levels is needed, no matter how difficult it may be to characterize uncertainty. The chapter also should summarize evidence on, and draw summary conclusions for, the issue of whether associations between NO_2 and health responses in epidemiology studies result from NO_2 exposures per se or whether NO_2 is a surrogate for other exposures associated with common-cause sources. The information to support such a conclusion is scattered throughout the document, but an explicit and articulate consideration of this issue would greatly improve the draft.

Finally, to meet that goal, the draft ISA should be improved through a better discussion of the significance of the epidemiology data for a potential risk assessment despite the uncertainties associated with those data. Incorporating an analysis of the available epidemiology data into the risk assessment will allow estimation of the potential uncertainties that need to be fully described and quantified in the risk and exposure assessment. The ISA discussion should consider the effect of co-exposures to other pollutants, the relationship between ambient and personal exposures, and how the limitations of the epidemiology studies impact their use for risk assessment.

In closing, the CASAC was pleased to review this second draft of the ISA for the primary NO_x standard and looks forward to continued interactions with the Agency in this important task.

Sincerely,

/Signed/

Dr. Rogene Henderson, Chair
Clean Air Scientific Advisory Committee

Enclosures

Enclosure A: Roster of CASAC Oxides of Nitrogen Primary NAAQS Review Panel

Enclosure B: Compilation of Individual Panel Member Comments on EPA's Integrated Science Assessment (ISA) for Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (Second External Review Draft)

Enclosure A

U.S. Environmental Protection Agency
Clean Air Scientific Advisory Committee
Oxides of Nitrogen Primary NAAQS Review Panel

CHAIR

Dr. Rogene Henderson, Scientist Emeritus, Lovelace Respiratory Research Institute, Albuquerque, NM

CASAC MEMBERS

Dr. Ellis B. Cowling, * University Distinguished Professor At-Large, Emeritus, Colleges of Natural Resources and Agriculture and Life Sciences, North Carolina State University, Raleigh, NC

Dr. James Crapo, Professor of Medicine, Department of Medicine, National Jewish Medical and Research Center, Denver, CO

Dr. Douglas Crawford-Brown, Professor and Director, Department of Environmental Sciences and Engineering, Carolina Environmental Program, University of North Carolina at Chapel Hill, Chapel Hill, NC

Dr. Donna Kenski, Data Analyst, Lake Michigan Air Directors Consortium, Des Plaines, IL

Dr. Armistead (Ted) Russell, Professor, Department of Civil and Environmental Engineering , Georgia Institute of Technology, Atlanta, GA

Dr. Jonathan M. Samet, Professor and Chair of the Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

CONSULTANTS

Mr. Ed Avol, Professor, Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA

Dr. John R. Balmes, Professor, Department of Medicine, Division of Occupational and Environmental Medicine, University of California, San Francisco, CA

Dr. Terry Gordon, Professor, Environmental Medicine, NYU School of Medicine, Tuxedo, NY

Dr. Dale Hattis, Research Professor, Center for Technology, Environment, and Development, George Perkins Marsh Institute, Clark University, Worcester, MA

Dr. Patrick Kinney, Associate Professor, Department of Environmental Health Sciences, Mailman School of Public Health , Columbia University, New York, NY

*Unable to participate in the May 1-2, 2008 CASAC Panel Meeting

Dr. Steven Kleeberger, Professor, Lab Chief, Laboratory of Respiratory Biology, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC

Dr. Timothy V. Larson, Professor, Department of Civil and Environmental Engineering, University of Washington, Seattle, WA, USA

Dr. Kent Pinkerton, Professor, Regents of the University of California, Center for Health and the Environment, University of California, Davis, CA

Dr. Edward Postlethwait, Professor and Chair, Department of Environmental Health Sciences, School of Public Health, University of Alabama at Birmingham, Birmingham, AL

Dr. Richard Schlesinger, Associate Dean, Department of Biology, Dyson College, Pace University, New York, NY

Dr. Christian Seigneur, Vice President, Atmospheric & Environmental Research, Inc., San Ramon, CA

Dr. Elizabeth A. (Lianne) Sheppard, Research Professor, Biostatistics and Environmental & Occupational Health Sciences, Public Health and Community Medicine, University of Washington, Seattle, WA

Dr. Frank Speizer, Edward Kass Professor of Medicine, Channing Laboratory, Harvard Medical School, Boston, MA

Dr. George Thurston, Professor, Environmental Medicine, NYU School of Medicine, New York University, Tuxedo, NY

Dr. James Ultman, Professor, Chemical Engineering, Bioengineering Program, Pennsylvania State University, University Park, PA

Dr. Ronald Wyzga, Technical Executive, Air Quality Health and Risk, Electric Power Research Institute, Palo Alto, CA

SCIENCE ADVISORY BOARD STAFF

Dr. Angela Nugent, Designated Federal Officer, 1200 Pennsylvania Avenue, NW 1400F, Washington, DC, Phone: 202-343-9981, Fax: 202-233-0643, (nugent.angela@epa.gov)

Attachment B: Compilation of Individual Panel Member Comments on EPA's Integrated Science Assessment (ISA) for Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (Second External Review Draft

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General Document Comments

This is an impressive compilation of a great deal of work that reflects the large amount of effort put into it. It is generally well-written and with sufficient detail and reference to provide readers with useful guidance and documentation, as needed. There is a great deal of important and useful information in each of the several chapters, although the respective chapters have a slightly different architecture to them. Several important points are made in some chapters (such as Chapter 2), but not always emphasized at a section or chapter conclusion (as they are, for example, in Chapter 3). Although an excellent summary of the chapters appears as Chapter 5, is it worth considering having a conclusion, summary, or results section at the close of each chapter to re-emphasize or focus on the critical points raised?

Agency ISA Charge Questions

1. What are the views of the Panel on the characterization of the search strategy for identifying literature, criteria for study selection, the framework for scientific evaluation of studies and causality determination?

Everything seems appropriate and well –described, except for the operational assignments for causality (P1-16, lines 22-23). I agree with the utility of a gradation of confidence in conclusive statements, but it's a bit confusing as to the clear distinction between "sufficient to infer a causal relationship" and "sufficient to infer a likely causal relationship". Isn't the clarification currently present ("more likely than not") the definition for the next lower level of confidence ("suggestive but not sufficient to infer a causal relationship")?

2. To what extent are the atmospheric chemistry and air quality characterizations clearly communicated, appropriately characterized, and relevant to the review of the primaryNO2 NAAQS? Are the properties of ambient oxides of nitrogen appropriately characterized, including spatial and temporal patterns and relationships between ambient oxides of nitrogen and human exposure? Does the information in Chapter 2 provide a sufficient atmospheric science and exposure basis for the evaluation of human health effects presented in later chapters?

In general, yes…However, P2-7 through P2-10, Section 2.3 provides useful (and much appreciated) information regarding the various approaches to measurement of ambient levels of nitrogen-containing species, but does not provide any succinct conclusions or directed message for the reader. Perhaps a closing paragraph or bullet to provide a "take-home" message would be valuable? What discrete message(s) are you are trying to convey in this section?

3. To what extent is the discussion and integration of evidence from the animal toxicology and controlled human exposure studies and epidemiologic studies technically sound, appropriately balanced, and clearly communicated? What are the views of the Panel on the conclusions drawn in the draft ISA regarding the strength, consistency, coherence and plausibility of NO2-related health effects?

This portion is generally excellent - well-written, thoughtfully presented, and meticulously designed. The summary figures, visually presenting the results of numerous studies to gauge consistency of response for a given outcome, is a noteworthy accomplishment that adds to the accessibility of the document. The summary of evidence sections at the close of each section are invaluable and much-appreciated.

(P3-4, line 24) – A comment made here that "Relatively few new clinical and animal (NO2) toxicologic studies have been published since 1993…" seems inconsistent with a review of the literature. A PubMed search reveals over 200 publications reporting on NO2 health outcomes, animal studies, etc…? Please clarify or correct this sentence.

4. What are the views of the Panel on the characterization of groups likely to be susceptible or vulnerable to NO2 and the potential public health impact of NO2 exposure?

(P4-9, Section 4.3 and elsewhere) A brief but clear delineation of the operational differences between susceptibility and vulnerability in this document would be useful; this is likely to otherwise create some confusion. Is vulnerable being used to describe "a lack of defenses against" or something more? Is susceptible being used to describe being "prone to a certain response" or something more? This section discusses children and older adults as being "…particularly susceptible to air pollution…", but aren't they more vulnerable? If they were missing a specific gene (in the oxidant stress pathway) or had pre-existing disease (such as emphysema, asthma, or possibly diabetes), then they would be susceptible.

5. What are the Panel's views on the adequacy of this second external review draft ISA to provide support for future exposure and policy assessments?

Overall, this document provides sufficient support for future exposure and policy assessments.

Specific Comments

Chapter I - IntroductionP1-13, Fig 1.6-2 – shouldn't "Mediated Effect" arrows from PM to NOx to O3 go in both directions? NOX can affect PM formation which can then have an effect on observed outcomes, and O3 can affect NOx levels which will affect the entire chain of events. Similarly, shouldn't there be a "Surrogate" arrow from NOx to Other Pollutants?

Chapter 2 – Source to Tissue Dose
P2-18, line 1 – (spelling error in San Bernardino, and I don't think I have ever heard this region referred to as the San Bernardino "Valley"…??)
P2-21, Figure 2.5-1 (spelling error, "In a residence"(68.7%)

Chapter 3 - Integrated Health Effects of NO2 Exposure
(No additional specific comments other than those above)

Chapter 4 – Public Health Significance

(No additional specific comments other than those above)

Chapter 5 – Integrative Summary and Conclusions
This chapter is an excellent compilation of the assembled data.

Comments from Dr. John Balmes

Agency Charge Question 3. To what extent is the discussion and integration of evidence from the animal toxicology and controlled human exposure studies and epidemiologic studies technically sound, appropriately balanced, and clearly communicated? What are the views of the Panel on the conclusions drawn in the draft ISA regarding the strength, consistency, coherence and plausibility of NO_2-related health effects?

GENERAL COMMENTS

The second external review draft of the NOx ISA is much improved. In particular, the discussion in Chapter 1 on the "EPA Framework for Causal Determinations" provides an integrative approach to how the agency will assess the evidence presented in the subsequent chapters. Given that this is the first ISA to be produced under the agency's new process for reviewing a "criteria" pollutant NAAQS, it is important to provide such an integrative approach as a precedent. My major concern about this draft of the NOx ISA is that in certain summaries of sections of Chapter 3, the framework described in Chapter 1 is insufficiently applied. I will provide specific examples below.

In my opinion, the discussion of healthy effects of short-term exposure to NO2 in Chapter 3 is appropriate and fairly well integrated. My major concern with this discussion involves a statement is made on p. 3-14 and repeated on p. 3-15, 3-61, and p. 5-12 that "the onset of inflammatory responses in healthy subjects appears to be between 100 and 200 ppm-min, i.e., 1 ppm for 2 to 3 h." Figure 3.1-1 is presented to demonstrate this threshold graphically, but appears to be the wrong figure, perhaps an alternative version of Figure 3.1-2. In any event, Figure 3.1-1 presents studies of the effect of NO2 on allergen-induced lung function and inflammatory responses not the studies of the airway inflammatory effect of NO2 alone that are described on pp. 3-12 to 3-14. This figure needs to be replaced with one that actually supports this important statement.

The discussion of respiratory effects associated with long-term exposure to NO2 is important since several prospective cohort epidemiological studies have been published since the 1993 NOx NAAQS review that reported adverse effects on growth of lung function. There is a subsection on "Toxicological Studies" on p. 3-89 and 3-90 that is apparently intended to provide mechanistic support for the results of the epidemiological studies. However, the discussion on pp. 3-95 and 3-96 of "Animal Studies of Long-Term Morphological Effects to the Respiratory System" is both more comprehensive and concise. I would delete the subsection on p.3-89.

On p. 3-90, the concluding paragraph for section 3.4.1 on "Lung Function Growth" provides no assessment of the strength of the association between long-term exposure to NO2 and decreased rate of growth of lung function among children. This paragraph merely states that the epidemiological studies og long-term exposure to NO2 aqre likely confounded by other ambient pollutants. Unfortunately, section 3.4.5, which is supposed to be the summary and integration of evidence on "Long-Term NO2 Exposure and Respiratory Illness and Lung Function Decrements" also does not provide an assessment of the strength of the association. This is a critical deficiency given the relative importance of the issue of potential respiratory effects of long-term NO2 exposure. The

section also does not directly assess the strength of the association for either "Asthma Prevalence and Incidence" or "Respiratory Symptoms". It is not until Chapter 5 that the strength of the association for long-term exposure to NO2 and respiratory morbidity is assessed.

Another concern that I have regarding section 3.4.5 is the long discussion on animal toxicological studies that have found effects of NO2 on host defense against respiratory infections on pp. 3-98 to 3-100. While I believe that this discussion is technically accurate, I find that it is unnecessary and distracting given the relative lack of discussion of the strength of the epidemiological evidence on long-term exposure to NO2 and asthma and the total absence of such discussion regarding respiratory symptoms.

Agency Charge Question 4. What are the views of the Panel on the characterization of groups likely to be susceptible or vulnerable to NO_2 and the potential public health impact of NO_2 exposure?

Chapter 4 does an adequate job of discussing the public health significance of exposure to ambient NO2. The chapter Summary (4.5) indicates that persons with preexisting respiratory disease (especially asthma), children, and older adults may be more susceptible to the effects of NO2 exposure. I agree with this assessment of the evidence. There is one statement in section 4.5, however, with which I am uncomfortable. The final sentence on p. 4-16 states that "evidence, albeit inconsistent, exists for a gender-age-based difference in susceptibility" regarding the effects of NO2 on children with asthma. I find this statement to be too strong. While I agree that there is evidence that the incidence of asthma differs between boys and girls with age, the evidence for a gender-age-based difference in susceptibility to effects of NO2 exposure in asthmatic children is too limited to draw any conclusions. I would delete this sentence.

The major problem I have with Chapter 5 is that the relatively strong evidence for an effect of long-term exposure to NO2 on growth of lung function in children reported by both the Sothern California Children's Health Study and the Mexico City study (Rojas-Martinez et al.) is diluted by combining discussion of these studies with those on asthma and respiratory symptoms. In my opinion, the issue of the strength of evidence for a long-term effect of NO2 on growth of lung function needs to be dealt with more directly in the document, in both Chapters 3 and 5.

SPECIFIC COMMENTS

3-11, line 5	"…increases inflammation in children with asthma."
3-14, line 8	This statement would better reflect the studies discussed on the previous pages if it were worded "…NO2 concentrations ≤2.0 ppm in healthy adults."
Figure 3.1-1	wrong figure
3-16, line 3	"Challenge with "specific allergens" can be performed in allergic asthmatics."

3-20, line 28	delete second "of" in this line
3-22, line 7	"By 72 h, bronchopulmonary hyperreactivity was comparable."
3-37, line 19	delete "from a meta-analysis" in this line
3-61, lines 7-10	This statement would better reflect the data summarized if worded as follows: "Controlled human exposure studies provide consistent evidence for airways inflammation at a NO2 concentration of 2.0 ppm (one study found airway inflammation at a concentration of 1.5 ppm); the onset of the inflammatory response…"
3-75, line 12	"…mortality in 28 of the same cities…"
Figure 3.4-1	The x axis in the lower graph should be labeled "FEV1".
Figure 3.4-4	Use decimals rather than commas for the y axes. Explain "study phase" in the legend.
3-88, line 4	"The association between long-term exposure to NO2 and decreased PEF was comparable to that found in the CHS, but associations with forced volumes were considerably weaker."
3-89 and 3-90, Toxicological Studies	I would eliminate these three paragraphs. The summary of the toxicological literature on 3-95 and 3-96 is better.
3-90, lines 8-16	There is a lack of assessment of the strength of association in this summary.
3-95, line 1	"The association of NO2 with dry cough at night observed in the German study…"
3-98, line 25	"…major cohort studies, the CHS in southern California and a birth cohort study in the Netherlands,…"
3-98, line 29 to 3-100, line 2	I would eliminate this discussion on potential mechanisms of NO2 effects respiratory illness because the first sentence on p. 3-98 (lines 29-30) is at odds with the summary of the epidemiological evidence for respiratory symptoms on p. 3-95 (lines 23-26). The information discussed here also does not relate to long-term NO2 exposure and asthma prevalence which was the subject of the preceding paragraph on p. 3-98.
3-100, line 23	"…an OR of 1.10 for lung cancer…"

3-100, lines 28-31	"Exposure to 10 μg/m^3 (5.2 ppb) of NO2 was associated with an OR of 1.08 for lung cancer (95% CI: 1.02, 1.15); exposure to ≥30 μg/m^3 (15.7 ppb) was associated with an OR of 1.36 (95% CI: 1.01, 1.83). However,…"
3-104, line 13	"…with other NO_2^- sources…"
3-106, line 29	"…exposed to 2.0 and 1.0 ppm…"
3-112, line 8	"…examined associations between…"
3-113, line 18	"are suggestive of a traffic-related air pollution effect on mortality, but…"
4-7, line26	"limitation of this experimental animal work…"
4-11, line 8	"Several glutathione S-transferase (GST) genes have common…"
4-13, line17	delete "biologically" from this sentence
4-16, lines 30-32	This statement is a bit of a stretch based on the evidence presented.

Comments from Dr. Douglas Crawford-Brown

The primary question addressed in this review is in reference to Chapter 5, Integrative Summary and Conclusions, and focuses on the adequacy of the ISA (especially Chapter 5) to provide support for future exposure and policy assessments. I begin by noting that this second draft is a significant improvement on the first. The authors have dealt with the majority of my comments on the first draft, and have responded to the majority of comments made by the committee as a whole in our earlier review. There is beginning to emerge a vision for what the ISAs in general are intended to accomplish, so this is a positive step forward for the EPA staff.

On the primary issue of adequacy as a basis for exposure and policy assessments, my comments are of two kinds. First, Chapter 5 does indeed summarize the information from earlier chapters that would be relevant to exposure and policy assessments. The authors have done a good job of both accurately reflecting that earlier material and choosing the material that is most relevant. They have drawn appropriate conclusions from that earlier material, including assessments of the strengths and limitations of the conclusions. While I might still have some quibbles over the lack of formal assessment of the epistemic strength of conclusions, I fully agree with the judgments they have made as to whether the evidence for each category of effect is conclusive, supportive, inconclusive, etc. I don't think I could trace the judgments of the authors back to any specific reasoning they have done, because the only reference to that reasoning is a vague citation of the Hill criteria (criteria that seem to me woefully inadequate as a philosophical basis for rigorous assessments of epistemic status). But the judgments of the authors nonetheless appear to be the correct ones based on the available evidence.

The second issue is whether Chapter 5 not only summarizes accurately the information in earlier chapters (which it does) but also provides an adequate basis for exposure and policy assessments. Here I am less comfortable the chapter, or even the entire document, has met the target. It is certainly the case that both the document and the chapter point the reader in directions that will be important for exposure and policy assessments. The reader is guided to judgments on the appropriate sensitive subpopulations that should be considered; on the specific effects that should be considered; on issues related to the

relationship between ambient monitoring results and personal exposures; and on the issue of whether epidemiological studies are confounded by exposures to the mix of air pollutants that normally accompany exposure to oxides of nitrogen. An assessor will, therefore, find much useful information in the document and in Chapter 5.

However, neither the chapter nor the document provides an adequate basis for performing exposure and policy assessments quantitatively. It is not possible from the document alone to see what the levels of exposure will actually be to any specific population in any specific geographic location. I realize this level of detail may not be what is intended by an ISA, but then I am left wondering what could be meant by asking whether the document provides an adequate basis for exposure assessment. The only way it could do that, in my mind, is to summarize the actual exposure information available, guiding the reader to understanding how well that information will allow accurate estimates of exposure to specific subpopulations in specific geographic areas. The ISA does not summarize exposure information, or even monitoring information, but instead summarizes the strengths and limitations of that information. The latter is an important goal, as it will place caveats on the use of more detailed information in later exposure assessments. But it leaves the task of assembling the information on concentrations, and converting these to estimates of exposure, to a later step in the assessment process. ***As a result, I am not comfortable that the ISA provides an adequate basis for subsequent exposure and policy assessments, but rather provides an adequate basis for these subsequent steps to understand the strengths and limitations of the available data. Having said that, this may be all that the ISAs are intended to accomplish, in which case the current document would be judged adequate.***

I also was looking for some sort of scientific statement as to how the information available ought to be used in conducting an exposure or policy assessment. This can be done without wandering into policy decisions. Are the authors suggesting that no exposure-response curve can be developed, and hence the assessments must be conducted in ways similar to non-cancer risk assessments (with a presumed threshold of effect)? Should an uncertainty factor be applied? Would the goal of an assessment be to estimate the number of people in the U.S. population exposed at levels above the threshold (or

with a hazard quotient above 1)? Should there exposure be averaged over an hour, or 4 hours or a day or year? These are questions that will crucial in a future assessment and can be answered scientifically without getting into the policy realm, so I expected to see them here if the document is to provide an adequate basis for exposure and policy assessments.

I then have a series of specific issues to raise.

1. I continue to be less than convinced by the epistemic assessments performed, or at least the formal descriptions of the assessments. The reference on page 5-1 is to the Hill criteria (which are completely inadequate philosophically in my view) and to "other pertinent frameworks". No reference is provided to these other frameworks, so I have no idea what they are. I realize the ISA is not a philosophical document, but some better guidance as to how the specific judgments of the quality of conclusions are developed is needed. There is no problem in stating that they are informed judgments based on some set of criteria (and then stating these criteria). Having said that, I do agree with the conclusions drawn and so will not push this point too strongly.

2. The fourth bullet on Page 5-1 asks whether new data affect the plausibility of judgments about oxides of nitrogen causing adverse health effects. I had expected to see some further qualification such as "adverse health effects at levels of exposure of at levels found in the environment".

3. On Page 5-3, the bullets don't seem to follow at all from the opening sentences of the paragraphs. I agree with what is contained in the bullets, but they seem to me unconnected to the sentences that presumably introduce them. I have read this paragraph several times and just don't see the link.

4. In that same list of bullets, 6th bullet, the authors talk about artefacts. There is no explanation as to what an artefact means, how it affects exposure or policy assessments, what a positive artefact would be (presumably in contrast to a negative one), etc.

5. The listing of issues in section 5.2.2 is a good one, and is certainly useful to anyone conducting an exposure assessment. But I point back to my earlier comment that even if the issues raised here are the correct ones, it is not possible to take this and form a basis for an exposure assessment because specific data are not provided and summarized. I also expected a bullet suggesting how exposures SHOULD be estimated, rather than simply listing the limitations in any exposure measures. I would expect a recommendation as to the ratio of personal to ambient levels in specific settings, the time period over which exposure should be averaged, etc. I also expected some conclusion as to whether it is even valid to use ambient monitoring results, from the network set up for regulatory monitoring, as a starting point for estimating exposures.

6. The last paragraph in section 5.2.2 cautions against strict conclusions being drawn based on the epidemiological studies due to a lack of conclusive evidence that ambient and personal exposures are completely correlated. The implications of a lack of complete correlation depend on the differences in exposure levels between the different exposure categories in the study. The implications become more significant as the exposure groupings are closer together in exposure, in which case there can be significant misclassification and therefore bias towards the null (generally at least). I think a more nuanced conclusion here is needed.

7. I found the summary tables quite useful, so the authors are to be applauded for developing them in this coherent fashion.

8. In the sections on effects, it would be useful if the authors were to provide information as to whether an increase in exposure changes the fraction of people with effect, the frequency with which a subset of people develop the effect, the severity of the effect, etc. I realize that this distinction may not be so important in a regulatory decision (where one person getting the effect N times counts the same as N people getting the effect once), and that the available exposure-response information may not allow development of exposure-response curves, but some comment on this issue would be useful.

9. In the last paragraph (Page 5-22), the authors correctly conclude that it is plausible to believe that effects are occurring at levels of exposure below the current NAAQS. But the question here is “how far below?”. I should think that the science assessment (this document) would be the place where the EPA states clearly the answer to this crucial scientific issue – an issue that will greatly affect the policy assessment.

Comments from Dr. Terry Gordon

Charge Question 3. To what extent is the discussion and integration of evidence from the animal toxicology
and controlled human exposure studies and epidemiologic studies technically sound, appropriately balanced, and clearly communicated?

The ISA document is a tremendous improvement over the first draft. There are appropriate-length discussions of key studies and the overall message of the ISA is clearly communicated. There are, perhaps, sections of the animal toxicology data that have too much detail given the high(er) concentrations of NO2 used in some studies. As mentioned in past discussions by the Panel, animal toxicology studies should be included in the ISA only when they are of relevant concentrations.

What are the views of the Panel on the conclusions drawn in the draft ISA regarding the strength, consistency, coherence and plausibility of NO-related health effects?

The development of the guidelines to evaluate the strength, consistency, coherence, and plausibility of NOx-related health effects is critically important to the ISA. In a similar fashion, the use of structured language to describe relationships between exposure to NOx and adverse health effects is an important improvement to the ISA. The 5 descriptor categories appear well thought out and appropriate, but discourse on these categories may bring modifications to future ISAs if not this one.

Minor Comments:

Disclaimer page
Page ii – first line – First or second external draft?
Page ii, para 2 – typo for (4) before "to set…."?

Page 1-17, para 2 – Why would tox and cancer have a linear response? Many researchers say otherwise. What does dose-transitional mean?

Page 2-4, last line – 'at low temperature' is imprecise; does this mean ambient temperatures?
Page 2-21, figure 2.5-1 – Label for largest part of pie chart should be 'In a residence'.

Page 3-6, table 3.1-1 – Under peripheral blood, 'Total macrophages' should be (re)moved as they are in the lower airways.
Page 3-8, para 3 – The 3 to 9 ppm 2 week study has little relevance to the toxicity of exposure to peak ambient levels of 0.05 or 0.1 ppm NO2. Also, it is unbalanced to give the details and results of this high dose study and then say that alveolar macrophages are a sensitive target for NOx's effects and give no refs on macrophages and just refer the reader to the Annex.
Page 3-12, figure 3.1-1 – The figure legend needs more details (e.g., what are the + and – on the Y-axis for; what does the * mean?; what do the 3h and 6h mean? Some of this is explained later in the legend of figure 3.1-2.
Page 3-22, first and second line – Needs a ref.

Page 3-22 – There is a lot of detail here for high dose (5 ppm and 20 ppm NO2) animal studies. Please consider cutting the long paragraph and summarizing in a couple of sentences.
Page 3-24 – Add 'Nonspecific' before 'Airways' in the title for consistency with the last 2 subtitles.
Page 3-25, para 2 – Delete 'of' before 'as low as….'. Having stated that effects can occur at 0.26 ppm, why include the 1-sentence results of a 5 ppm study?
Page 3-44, para 4 – Elsewhere the Gong study had 18 subjects.
Page 3-47 – I may be reading this all wrong but some of the bars on the figure make no sense: on the preceding page, it says the Tolbert study had a 2% increase with a 95% CI of 0.5, 3.3. The figure shows a significant box with error bars totally dissimilar the reported 95% CI. The same goes for the Barnett (2005) study which says something different in the text (page 3-47) than is in the figure. Should all data be re-checked?
Page 3-59, second line – insert 'for asthma' after '…. or ED visits'.
Page 3-59, line 7 – Adding 'other' before 'diseases' would make this sentence clearer.
Page 3-62, lines 4, 5 – I'm not sure what is meant by '….NO2 effects to be mediated by other pollutants or exposures;'
Pages 3-62, 63 – Although the physiology descriptions are good, the text has 15 lines describing HRV and then 5 lines to say there have been mixed results. The same goes for the repolarization section – 5 lines to describe what it is and then 1 line to say there was no effect. Condense?
Page 3-79, 2nd para – The statement regarding animal studies and mortality as an endpoint in acute studies is not correct. Several studies have looked at LC50 values for NO2 in different species.
Page 3-90, para 3 – This paragraph on epidemiology appears to be misplaced in this tox section.
Page 3-96, para 1 – A mention of the higher doses used in animal tox studies could be added to qualify the last sentence.
Page 3-111, para 3 – Add 'a' before 'sensitivity'.
Page 3-118, para 2 – Should the last line of this para read, 1.0 to 2.8, or 0 to 1.28?
Page 4-4, first line – Has this really been recapitulated in preceding sections of this chapter?
Page 4-8, para 1 – Adding a conclusion sentence for this section on asthma would be appropriate. The same goes for the other susceptibility sections.
Page 4-12, para 1 – The sentence states that in-vehicle concentrations are 2 to 3 times 'ambient'. Does this mean that it's higher in the vehicle than just outside the car? Or does it mean compared to non-traffic ambient levels?
Page 4-13, first line – Ponce 2003 or 2005?
Page 4-16, para 2 – This is a strange intro sentence for the Summary section.

Page 5-26 – The title for the table is unclear – Legend of Figure 5.3-1??

Comments from Dr. Dale Hattis

1. What are the views of the Panel on the characterization of the search strategy for identifying literature, criteria for study selection, the framework for scientific evaluation of studies and causality determination?

I used a few different methods to evaluate the results of the literature search. First I read through all of the references cited at the end, noting the frequency of 2006-2008 references, and selecting in particular titles that appeared highly relevant to the analysis of health hazards. From the large numbers of 2007 references and the occasional 2008 citation, it is clear that the authors have brought their literature searches up to date as of the present. I then retrieved the abstracts for about a dozen interesting recent references and checked how the revised ISA reported on them in the main text or tables. In every case I found that the description in the text or tables corresponded reasonably to the abstract.

Comments from Dr. Donna Kenski

Charge Question 2: To what extent are the air quality characterizations and analyses clearly communicated, appropriately characterized, and relevant to the review of the primary NO2 NAAQS? Are the properties of ambient oxides of nitrogen appropriately characterized, including spatial and temporal patterns and relationships between ambient oxides of nitrogen and human exposure? Does the information in Chapter 2 provide a sufficient atmospheric science and exposure basis for the evaluation of human health effects presented in later chapters?

This second draft ISA is much improved from the first draft ISA and it was gratifying to see the panel's suggestions from the last review incorporated to a large extent. The discussions of measurement interference and its spatial and temporal variability were much better, as was the discussion of ambient concentrations of NO2. The paragraph on NO2 increases in other countries was somewhat irrelevant (p. 2-13, lines 25-30) and could be deleted or moved to the section on policy-relevant background concentrations. Sec. 2.4.5 on concentrations of NOz species is still quite limited and I think more information on these various species and their interrelationships would be helpful. Data are admittedly sparse but there are more papers that could be usefully summarized. Two that I know of are:

Continuous wet denuder measurements of atmospheric nitric and nitrous acids during the 1999 Atlanta Supersite, Atmospheric Environment, Volume 37, Issues 9-10, March 2003, Pages 1351-1364
Zhang Genfa, Sjaak Slanina, C. Brad Boring, Piet A. C. Jongejan, Purnendu K. Dasgupta

Measurements of gaseous HONO, HNO3, SO2, HCl, NH3, particulate sulfate and PM2.5 in New York, NY, Atmospheric Environment, Volume 37, Issue 20, June 2003, Pages 2825-2835,
Abdul Bari, Vincent Ferraro, Lloyd R. Wilson, Dan Luttinger, Liaquat Husain

Section 2.2.1 on sources of NOx still needs to be augmented with a *shortened* version of Annex Table AX2.6-1 (the old AX2-3) giving quantitative data on emissions contributions from major source categories. Fig. 2.2.1 is nice but just doesn't convey any quantitative sense of emissions.

The reorganized Sec. 2.5 on exposure is a much better integration of the relevant information.

In the previous CASAC review, we requested that chapter 2 in particular include section summaries, as was done so effectively in later chapters. It doesn't seem like this has been accomplished, but it would help tie up this chapter and make the conclusions drawn from it in Chapter 5 more obviously connected to the relevant sections.
Aside from these fairly minor tweaks, I found this section of the ISA satisfactory and I think (together with the supporting documentation in the annexes) that it provides a suitable basis for the Risk and Exposure Assessment.

Other comments:

Chapter 5 is great; it gave a fair and balanced presentation of the studies reviewed and the conclusions drawn. Very helpful.
In our review of the first draft ISA, we requested that EPA consider multipollutant approaches to managing air quality. While acknowledging that changing the traditional one-pollutant-at-a-time approach is likely to take considerable time and effort to implement, I'd like to encourage EPA to move in that direction with the ISA process.
The inclusion of data for multiple N species as well as some sulfate and oxidant chemistry was a step forward.
p. 2-17, Fig. 2.4-6d, title of figure should be Weekend, rather than Weekday

Comments from Dr. Steven Kleeberger

The document reads very well. I have very few comments that would not be considered only editorial- or style-related. However, I found the Figures 3.1-1 and 3.1-2 to be somewhat confusing. While the information presented is very useful, I would suggest that the data would be better presented in tabular form rather than figures. At first glance, the +/- on the y-axis suggests a degree or quantitation of positive or negative finding. It would be simpler simply to list the studies in a table with negative and positive categories.

Comments from Dr. Timothy Larson

General Comments:

I am limiting my comments to the exposure issues covered in Chapter 2 and parts of Chapter 6. In general, this document is much improved on the first draft and the authors should be commended. The issues raised by the committee upon review of the first draft have been addressed for the most part. I think the Chapter 6 summary of the topics in Chapter 2 is reasonable and consistent. The discussion of NO2 infiltration seems a little long.

However, I disagree with the statement beginning on page 2-31 about street canyons being complicated and modeling their effects to be "highly problematic". In fact, recent work has shown that both CFD and much simpler integral models provide reasonable predictions (c.f. Di Sabatino S, Buccolieri R, Pulvirenti B, et al. (2008) *Atmos. Environ.* 41 **(**37) **,** 8316-8329). In addition, there are a number of recent studies showing good prediction skill with these simpler models (c.f. Mensink C, Cosemans G (2008) *Env. Modeling & Software.* 23 **(**3) **,** 288-295; Berkowicz R, Ketzel M, Jensen SS, et al. (2008) *Env. Modeling & Software.* 23 **(**3)**,** 296-303; Ghenu A, Rosant JM, Sini JF (2008) *Env. Modeling & Software.* 23 **(**3)**,** 314-321). This seemingly minor point is in fact rather important to the interpretation of the spatial heterogeneity of NO2 in built up urban areas. These studies and others (e.g. Vardoulakis S, Gonzalez-Flesca N, Fisher BEA, et al. (2005) *Atmos. Environ.* 39 **(**15) **,** 2725-2736) indicate that street canyons are similar in NO2 concentrations to on-road values in otherwise open areas, i.e., enriched by about a factor of 2 above measurements taken away from the road in more open areas. Including a discussion of the skill level of these models in similar applications and a multiscale approach that includes street canyons seems appropriate (c.f. the Danish forecast system at http://www2.dmu.dk/1_viden/2_Miljoe-tilstand/3_luft/4_spredningsmodeller/5_Thor/default_en.asp). This adds another dimension to the exposure assessment, namely the fact that pedestrians spend time walking in these canyons and having windows opening onto these canyons and can therefore experience exposures for equal or greater times than they do on roads in transit (they may not even own cars in dense urban areas).

Specific comments:

Page 2-25 line 26 and page 2-26 line 6: Text seems to arrive at different conclusions about passive samplers without comment.

Page 2-35 line 13: This sentence needs a reference that indoor pollution affects outdoor levels.

Page 2-49 line 6: Reference to Table 2.5-5, but table does not exist nor does Table 2.5-6.

Page 2-51 line 16: The NO2 east-west spatial variation in greater Los Angeles varies broadly with distance from the coast due to well known meteorological and chemical phenomena. NO2 levels in Riverside are determined in large part by pollution transported from upwind urban areas to the west.

Page 2-55 Table 2.5-9 is presented without comment.

Comments from Dr. Kent Pinkerton

Agency Charge Question 3. To what extent is the discussion and integration of evidence from the animal toxicology and controlled human exposure studies and epidemiologic studies technically sound, appropriately balanced, and clearly communicated? What are the views of the Panel on the conclusions drawn in the draft ISA regarding the strength, consistency, coherence and plausibility of NO_2-related health effects?

General Comments:

The organization and improvement of the second draft ISA document for Oxides of Nitrogen – Health Criteria, compared to the original draft are excellent. The revised document has addressed a number of concerns expressed by CASAC for the original draft document. In my opinion, the content, flow, presentation and logic of materials are well done. New publications from the scientific literature since 1993 incorporated into this ISA draft are extensive and impressive. The majority of these papers cited in the document are highly relevant from an environmental perspective. A number of the new toxicology documents provide biologic plausibility, however, exposure concentrations in these studies are typically well above ambient conditions (greater than or equal to 5 ppm). The addition of new epidemiologic and human clinical studies to this second draft of the ISA is highly impressive and far exceeds new animal toxicology studies. However, those new toxicology studies included demonstrate effects as low as 0.4 ppm (in a lung vitamin deficit model in the guinea pig). Airway hyperresponsiveness following repeated NO_2 exposure at 1 and 2 ppm for up to 12 weeks in guinea pigs has also been demonstrated. Each of these studies adds further validity for the biologic plausibility of NO_2 health effects. Human studies also provide strong evidence for health effects at NO_2 levels in the 0.04-0.08 ppm range as 1 hour peaks. New data to demonstrate greater sensitivity to NO_2 in the form of increased airway responsiveness (approximately 10-fold) for asthmatics vs. healthy individuals further emphasizes the importance for consideration of susceptible populations and children in consideration of setting the NO_2 standard recommendation. In summary, the second draft of the ISA document represents an excellent compilation and reasonable interpretation of new research findings that should greatly aid in formulating decisions for setting the next criteria standard for oxides of nitrogen. Summary statements made for many of the sections under Chapter 3 were very helpful. I feel the conclusions made in the ISA document using integrative analysis of epidemiologic, human clinical and animal toxicological evidence provide strength, consistency, coherence and plausibility for NO_2-related health effects.

Minor Comments:

1) P 2-35, line 15 Will increased use of biomass fuels lead to an increase in NO_2 concentration in the future?
2) P2-40: this section provides an excellent detailed description on the relationship of personal exposures to ambient concentrations.
3) P 2-50 Is there a reason for no section labeled as 2.5.7?
4) P 3-6: Excellent table to summarize the proposed mechanisms whereby NO_2 exacerbates airway symptoms.

5) P3-12: Figure 3.1.1: It would be helpful to more completely label the y axis. Perhaps "observed response" could be added. At first examination, the meaning of the symbols + and – is not clear. Does + mean increased or adverse response; does – mean no change from control or a reduction of response from control?
6) P3-18: Figure 3.1.2: Same comments as for Figure 3.1.1., although the text referring to this figure clarifies the meaning of + and – for the y-axis.
7) P3-25: Excellent comparison of NO_2 concentrations leading to increased airway responsiveness in healthy and asthmatic humans and animals.
8) The intervention study of Pilotto et al (2004) provides striking evidence for health effects among asthmatic children for NO_2 concentrations at extremely low levels. The only concern for the interpretation of this study remains the possibility that ultrafine particles, rather than NO_2 may be driving this effect.
9) There appears to be strong evidence of NO_2 effects on physician-diagnosed asthmatic children (Pilotto et al., 2004). Although it may be difficult to completely rule out the effects of ultrafine particles, multi-pollutant models continue to demonstrate robust NO_2 health effects when adjusting for other pollutants such as CO, O3 and PM.
10) P 3-50, line 29: the term "not sensitive" in this sentence is unclear. Does this mean co-pollutant regression analysis does not work or that other co-pollutants do not confound NO_2 effects?
11) Excellent studies are included throughout the document to demonstrate positive associations between ambient NO_2 concentrations and health effects among young children and older adults (65+ years).
12) There continues to be a concern relative to confounding of co-pollutants, as well as NO_2 being a surrogate for other pollutants. However, there appears to be consistent data throughout more recent publications to suggest NO_2 can elicit health effects at current ambient levels.
13) Susceptible populations are clearly an important group to consider for NO_2 health effects. The Southern California Children's Health Study clearly points to NO_2-related changes with reduction in lung growth function in children.
14) Excellent summary and integration of scientific evidence for all aspects of health effects of NO_2 throughout the document.

Comments from Dr. Edward Postlethwait

1. In general the document shows considerable improvement over the initial draft and thus the EPA staff should be commended.

2. The issue of endogenous NO2 generation appears not to have been addressed as a potential contributor to uncertainties with regard to data interpretation, thresholds, and assessing posited mechanisms of action. This is especially important for three of the posed question in section 5.1 regarding has new information altered support for occurrence of health effects, at what levels of NOx do health effects of concern occur, and plausibility of adverse health effects.

3. On page 2-61, the section dealing with modeling NO2 dose should be clarified with regard to NO2 flux. The term "NO2 flux to air-liquid interface" does not accurately describe the net movement of NO2 from the intrapulmonary gas phase into the surface lining layer, or potentially epithelial cells. If NO2 flux occurs as written, there is a disconnect between the sites of focal injury and mass transfer from the intrapulmonary gas phase.

4. To this reader, there is a consistent ambiguity in the way NO2 thresholds are presented. As written, it is not especially clear in the document whether the lack of documented thresholds means that NO2 related effects can be extrapolated to zero [NO2] in a linear fashion or that threshold concentrations have not been identified due to the numerous confounding factors. The document would be strengthened if this issue was revised throughout to unequivocally present a consistent interpretation.

5. It is somewhat curious that the document supports causal relationships between NO2 exposure and acute but not chronic health effects. If NO2 is able to induce short term effects at the denoted concentrations, one would anticipate that individuals residing in the same geographic locale would also experience long term impacts. Thus, it may be useful to consider whether this represents an inconsistency or is due to any number of mitigating factors.

6. Per discussions from the initial review meeting, the document does not extensively link the potential occurrence of short term NO2 spikes and health outcomes. A more thorough discussion in the summary chapter (Chapter 5) of the possible occurrence rates, NO2 spike concentrations and thus exposures relative to the current long term average values, and observed effects would strengthen the document and provide the impetus to help support a shorter term standard if warranted.

Comments from Dr. Armistead Russell

Post-Meeting Amendment

Given the redirection of the REA, I think it is particularly needed that the ISA highlight (further stress and discuss) epidemiologic studies that have included multi-pollutant models with NO_2, particularly those that have included other combustion byproducts like EC, Total Carbon (TC) and CO. In doing so, they need to provide caveats on the interpretation of such studies, but also recognize their importance. They should note that PM2.5 and O3 are poor indicators for exposure to combustion emissions. If there are studies demonstrating how PM might act as a carrier for NO_2 that should also be assessed.

Original

Again, like the first draft, the 2nd Draft ISA is an effective document for providing the information needed to conduct the risk and exposure assessments. It is substantially improved from the last draft. However, I was a bit disappointed that some pieces did not get changed between the 1st and 2nd drafts.

1. I still think there should be a table of sources in Section 2.2.1. There is no Table 2-3 in the Annex: it is Table 2.6-1. Having a table in the ISA might help OAQPS note that their commercial air craft estimate for Philadelphia does not look right. They should also note that being an elevated source also leads to the emissions being more dispersed. Indeed, the highest NO2 levels found in cities are not from EGUs.
2. In the chemistry section, a bit more should be said about NO to NO2 transformation as NO2 is the apparent indicator species.
3. The measurement section is still a bit biased when highlighting the Mexico studies. Mexico City is a unique place, so I tend to downplay those results. Switzerland is more appropriate. There really should be some US-based studies.
4. The section on ambient concentrations presents an appropriate level of information on NO2 levels in the US at the country/urban scales, but should provide more information on NO at the same time. I would treat them together, with much of the transport discussed as transport and decay of NOx. If one looks at the REA, an important issue is roadway levels. This is hardly treated here. This section should discuss roadway levels of NO2 and NO, as opposed to covering it later in 2.5.4. A major missing component of ambient characterization is that of other pollutants. It is important to show the correlation between NO2 and some other species (e.g., EC) and I think it belongs here as opposed to later in 2.5.8. It would seem to fit more naturally here.
5. 2-31. It is not apparent that a 15 m monitor will lead to an underestimate of what people are breathing given that in cities (e.g., NY) air inlets in to homes may be that high. Also, as noted in the REA, very few of the monitors are at 15m. Give a balanced presentation.
6. 2.5.4: This section is fine, but could go deeper to provide the detail that is ultimately needed in the REA. It should discuss the conversion of NO to NO2 with information as to conversion rate and how quickly NO falls off and NO2

rises. The current REA uses little from this section, instead deriving its own fit to the decay. It is also not apparent how the REA used the information about intrusion of the vehicles own exhaust in to the cabin.

7. 2.5.8. This is a very important section, and I think it does a reasonable job of providing the type of information needed to see how NO2 correlates with other important species, including EC. One of the problems with having this section much later in the document is that they then go over points discussed earlier (e.g., diurnal variation).
8. Conclusions:
    a. P5-3, L19. In the body of the ISA, they never use 25%... even though I think the 50% value given earlier is extreme, whatever number chosen here should be supported in the ISA.
    b. P5-3, L21-23. I would not add "are difficult to predict". CMAQ can do so.
    c. 5-3, L30: Precise is not the correct word here. Possibly accurate, but I would say that it may be accurate enough for the job at hand, so I would back off on this statement altogether.
    d. P5-5, L7: While true, we find out in the ISA this is not a real problem since most monitors are not at 15m.

Something to think about for future ISA's: you should have a section discussing the models that might be appropriate for estimating ambient levels and, possibly, exposure. In this case, it would be AERMOD and APEX. This section should provide the model formulation, inputs and an evaluation of its capabilities. Modeling is discussed to some degree in the NOx-SOx SNAAQS ISA, which is good (though the committee wanted more evaluation).

Comments from Dr. Jonathan Samet

General Comments:

The second draft ISA for oxides of nitrogen (NO_x) is improved and responsive in many respects to concerns raised by CASAC members, including myself, at the review of the first external review draft. The Agency's staff has attempted to be responsive in setting out a better framework for evidence identification, evaluation, and synthesis. I am hopeful that continued progress will be made to sharpen this process, in order to address issues that are still unsolved. Additionally, I think that the peer review process would be enhanced generally by the preparation of a note to CASAC that sets out the Agency's responses to major concerns raised by the CASAC reviewers. Such responses would be consistent with usual practice of peer review, and would provide a trail, documenting how comments made by CASAC were taken into account.

My responses to the charge questions from the Agency follow, and the attached table lists specific comments.

Charge Question 1:

In response to comments with regard to the Agency's approach to literature identification, study selection, and synthesis of the evidence, as well as causal inference, an extensive annex has been prepared that reviews a number of relevant frameworks. The background is a useful foundation for justifying the selected approach. The Agency has made a number of changes in Chapter 1 that are responsive to prior critiques. In particular, there is a description of literature selection, an approach to evaluating evidence for inferring causality is provided, and a reasonable set of descriptors of the strength of evidence for causation is offered.

On reading the draft ISA, there has been some impact throughout the document of having a better prepared first chapter and this framework. However, the sections that synthesize the evidence are still somewhat loosely written, and do not systematically apply the guidelines offered by Bradford Hill, and adopted by the Agency. (Note, that these should not be renamed as "decisive factors", a misnomer). Too often, sections that are offering judgments as to the strength of evidence use such language as "taken together or "integrating" without a more specific application of the criteria offered by Hill. Nonetheless, the new Chapter 1 and the approach set out represents an advance over the earlier draft. Discussion is needed as to whether the list developed by Hill should be replaced with the shorter set used in the Surgeon General's Report. Perhaps, a comparison could be made with a test case.

One issue that is left unaddressed is publication bias, a reasonable concern given that many studies address the health effects of air pollution and employed multivariable models to attempt to isolate the effects of particular pollutants. There must have been some tendency on the part of investigators to report positive associations. This topic needs to be mentioned, as the existence of publication bias would be difficult to set aside for some of the epidemiological studies.

Charge Question 3:

This charge question relates to the integration of evidence from the various lines of investigation. Of particular concern is the plausibility of effects observed in epidemiological studies in the context of animal and human toxicology. There is no doubt that high levels of NO_x can injure the lung and other organs. For setting the NAAQS, the plausibility of effects at ambient concentrations is particularly relevant. I am concerned that the draft ISA has only partially addressed the plausibility of effects at current ambient concentrations and at those investigated in a number of the epidemiological studies. The ISA appropriately notes that both clinical and animal studies are carried out at doses well above those that are typical for population exposures. The document would be improved if more attention could be given to considering the relevance of mechanisms observed at higher levels to effects at ambient levels.

Charge Question 4:

Chapter 4, "Public Health Significance", provides as overview of populations potentially at increased risk from exposure to NO_x.

The listing of susceptible subgroups covers those of both particular relevance and of general relevance. The various groups identified are appropriate, although I have concern that EPA will follow the same template for all pollutants without giving sufficient consideration to the relevance of particular subgroups for particular pollutants.

Charge Question 5:

The revised document is greatly improved. It identifies health effects associated with exposure to nitrogen oxides and the strength of evidence supporting causality of associations. It makes an attempt to assess whether effects would be expected at current ambient concentrations. This is one of the weakest aspects of the current draft. Consider, for example, the conclusory language from page 5-22: "integrating across the epidemiologic human clinical and animal toxicological evidence presented above, we find that it is plausible that current exposures can result in adverse impacts to public health at ambient concentrations below for current NAAQS for NO_2." This sentence addresses the most critical matter around the need to revise the NAAQS: are there effects being observed at current ambient concentrations? The sentence addresses plausibility. Some statement with regard to the degree of certainty is needed, no matter how difficult it may be to characterize uncertainty.

Specific Comments:

Page #	Line #	Comment
1-7	5	Not certain this is true!
1-10	2	Along with considerations of plausibility
1-10	24	That may lead to confounding.
1-10	28	"…homogeneous groups ~~with~~ of the confounding…"
1-12	22	What does this mean?
1-13	1	Note, the following discussion refers to statistical models. The

Page #	Line #	Comment
		word "model" has many uses.
1-14	23	Should not label as "decisive factors", these are guidelines.
1-18	8	Because of the experimental manipulation of exposure.
1-18	16	There should not be uncertainty about design and execution.
3-1	24	"obscured" What does this mean?
3-2	3	"partitioning the variance" Not the same as estimating an effect.
3-2	13	"effects observed at O-…" On what basis?
3-2	19	"health effects (and markers of injury) that…"
3-3	9	Could be true, but supporting references??
3-7	5	At what concentration?
3-10	1-2	This is a very sweeping claim. What does it mean?
3-17	4-7	Aren't there more informative ways to show the data, e.g., as a forest plot.
3-19	29	In what way are these taken together?
3-20	29	Not the right place for research recommendations.
3-24	17-19	Speculation; should be deleted.
3-26	5	Isn't this inconsistent with an NO_2 effect?
3-40	4	Well-recognized
3-46	6	"pneumonia" is a LRI
3-46	19-22	"Collectively…" a conclusion—out of place
3-62	15-18	Where do the authors stand on this possibility?
3-101	1	Certainly, the possibility that traffic-related carcinogens are the etiologic agent needs to be raised.
3-106	11	Why confounding, implying underlying causation?
3-107	13	"(2000…") and earlier
4-5	29	Be careful not to overinterpret
5-1	28-29	?
5-22	21	"Integrating across the epidemiologic" How? What does this mean?

Comments from Dr. Richard Schlesinger

Overall, this is a very good document that clearly integrates the essential concepts required to make a judgment related to health effects from NO2.

p. 1-16, line 22. It may be better to change the first bullet to "sufficient to infer a definite causal relationship" since this would make it more consistent with the second bullet indicating a "likely" causal relationship. The way it is written, it is not clear what the difference is between "causal relationship" and "likely causal relationship."

p. 5-13, line 15. The 5 ppm exposure is quite high and its relevance to the document is not clear.

p. 5-16, lines 13-14. Does this sentence mean that the effects observed could have been due to NO2 or are most likely due to confounder pollutants?

Table 5.3-1. This is an excellent table.

Comments from Dr. Christian Seigneur

Charge question 2:

To what extent are the atmospheric chemistry and air quality characterizations clearly communicated, appropriately characterized, and relevant to the review of the primary NO_2 NAAQS?

The second external review draft has been considerably improved in that regard. For example, Figure 2.2-1 is more accurate; the variability of the NO_2 fraction of NO_x emissions is now correctly discussed, and the spatial variability of NO_2 concentrations near sources (in particular, roadways) is properly described.

Are the properties of ambient oxides of nitrogen appropriately characterized, including spatial and temporal patterns and relationships between ambient oxides of nitrogen and human exposure?

The spatial and temporal patterns of NO_x and NO_2 are appropriately described. As mentioned above, the strong spatial gradients observed near roadways are discussed. The temporal variability of NO_x and NO_2 concentrations is also well characterized with sufficient detail being provided in the Annex (e.g., diurnal and seasonal variability).

Does the information in Chapter 2 provide a sufficient atmospheric science and exposure basis for the evaluation of human health effects presented in later chapters?

There is one aspect of the link between atmospheric science and exposure/health effects that needs to be better discussed in the ISA. Currently, measurement error is highlighted early on in the document (Section 1, p-1-11) as important when adjusting for spurious associations. The difference between true and measured ambient concentrations is identified as one of the components of measurement error. Such measurement errors are then discussed in detail in Section 2.3 for outdoor measurements and in Section 2.5.2 for indoor measurements using passive samplers. Some estimates of measurement uncertainty are provided. For outdoor measurements with the Federal Reference Method (FRM), an average interference from NO_z compounds of 22% is given for Mexico City data with peak interference of 50%. A comparative study in Switzerland is reported to have shown average errors of 10% in winter and 50% in summer. This section concludes that the interference is likely to be on the order of 10% or less in winter, but much larger in summer. It is also stated that the interference from NO_z compounds is less significant near the emission sources (because there has not been enough time for NO_z species formation). Passive samplers used in individual exposure studies are described in Section 2.5.2 as being within 10% of the FRM.

The epidemiological studies presented in Section 3 have used in most cases NO_2 measurements from FRM instruments or passive samplers. Therefore, one may imply that there may be significant uncertainties associated with the results of those studies because of the FRM interference errors discussed in Section 2. However, this aspect of the health effect uncertainty does not appear to be discussed. In reality, I anticipate that most NO_2 exposure occurs near emission sources where NO_z concentrations are low and,

therefore, interference error is small. Also, the seasonal variability of NO_2 concentration shows that in most cities higher concentrations occur in winter when the interference error is 10% or less. It may, therefore, be possible to consider that the NO_2 measurement error is not a major source of error in health effects studies. However, such a point needs to be made clearly in the ISA. One possibility is to provide a more definitive discussion of the implication of the interference of the FRM at the end of the introduction of Section 2.3 (p. 2-9). The fact that NO_z species concentrations are low when NO_2 concentrations are high (near emission sources, in winter) and the reasons why (not sufficient time for reaction, low photochemical activity) should be explicitly stated. Then, the implications for the health effects studies need to be articulated clearly.

Annex 2.7.1. Chemistry-transport models

This Annex section has been rewritten and a discussion of local-scale dispersion models has been added. This Annex section is overall well written and very useful. There is, however, one part, which requires some revision. On p. AX2-67 (at the end of the discussion of local-dispersion models), it is stated that (1) emissions from roadways are usually not in steady state and (2) that buoyant plume rise differs for point and line sources. The unwritten implication is that AERMOD, the model used in the exposure and risk assessment, would not be appropriate to simulate NO_2 concentrations from roadways because (1) it uses steady-state assumptions and (2) it is a point source model and does not treat, for example, vehicle-induced turbulence. The text then goes on to discuss CALPUFF, a non-steady-state model that can treat dispersion from surface sources. The implication is that CALPUFF is a better model to simulate NO_2 concentrations downwind of line sources such as roadways. This paragraph needs to be rewritten because (1) the limitations mentioned for AERMOD are not entirely correct and (2) the description of CALPUFF as a better model for line source dispersion is incorrect.

In my earlier comments on the Methods document, I raised some concerns regarding the use of AERMOD for line source modeling and asked why a line source model such as CALINE would not be used. EPA replied that CALINE was no longer supported by the developer and that AERMOD was an acceptable model because it could be adapted for line sources. Although further development of AERMOD to become a true roadway dispersion model is warranted, I agreed with EPA that, given the dispersion models currently available, AERMOD was an appropriate choice. The statement made in the Annex regarding the non-steady-state nature of roadway emissions is not relevant because AERMOD is used to calculate downwind concentrations within a few hundred meters from the roadway and the travel time will be less than one hour (i.e., the time typically used for meteorological and emission inputs). The statement regarding the inappropriate treatment of the initial plume dispersion characteristics for a roadway in AERMOD is misleading as CALPUFF does not treat such roadway initial plume dispersion either. Furthermore, one must note that the current CALPUFF versions that are publicly available (e.g., versions 5.8 and 6) include a coding error that leads to incorrect NO_2 concentrations near the source.

Therefore, the last two sentences of that paragraph ("In contrast, there are models that are non-steady-state…") should be deleted and the limitations of AERMOD when applied to line sources such as roadways should be rewritten in a more objective light.

Comments from Dr. Elizabeth "Lianne" Sheppard

Final comments: Generally the document is much improved and the revisions have been responsive to previous CASAC comments.

Charge question 1:

Conceptually the framework outlined in Chapter 1 is on target. However it reads very much like a preliminary incomplete draft. Section 1.6 needs to be thoroughly revised. It has many of the right concepts mentioned, but often briefly, incompletely, or without good justification for the proposed modifications. For instance, Annex AX1 contains a thorough compilation of previous work on evidence classification, but details on the translation into Chapter 1 are absent – there is no evaluation, interpretation, or justification for the modifications proposed on page 1-16 of the ISA. As another example Table 1.6-1 is an adaptation from two previous documents, but the details of and reasons for the adaptation are not discussed in the Chapter or Annex.

Detailed specific comments:

- P 1-8 section on scientific evidence used for identifying causality: There is a brief discussion of features of study designs and a later discussion of details of study designs (p 1-10). These should be combined. Also key points are missing. One is that the challenge with experimental studies is to create conditions that reflect the complexity of the naturally occurring exposures. Another is that observational studies represent conditions experienced by the population but inference from them is limited because of the absence of experimental intervention. Another is to mention cross-species extrapolation.
- P 1-9: The footnote seems out of place in this chapter since the notation and concepts haven't been introduced.
- P 1-10 l 2: Is this what is meant?: "Developing evidence for going beyond association to causation involves integration of multiple sources of information into a coherent paradigm."
- P 1-10 l 10: Revise sentence. What does "Done properly and setting aside randomness" mean?
- P 1-10 l 15: But there are problems – e.g. washout.
- P 1-10 l 18 Experiments are stronger causally than observational studies tub much more limited in the realistic conditions that can feasibly be studied.
- P 1-10 l 21 Confounders are only one consideration of causal inference from observational studies.
- P 1-10 l 25 Study design, e.g. matching is another tool.
- P 1-11 measurement error discussion is derived from the Zeger et al paper (not cited) and applies to the time series study design. It does not apply to all observational studies of air pollution, but the literature as yet does not have similar papers for other designs.
- P 1-11 l 18 Replace "producing the findings" with "biasing the results"
- How much should section 1.6 be a general review vs. specific application to the air pollution context (e.g. table 1.6-1)? It would be safer to directly cite the sources and then comment on features for this application in the text.

- P 1-14 l 8 How about "Model averaging attempts to incorporate model selection uncertainty into the target parameter estimate…"
- P 1-15 l 3-5 None of the criteria are about statistical significance.
- Publication bias should be addressed explicitly. Air pollution studies estimate small effects so some issues become relatively more important in this area: model selection, subgroup analyses, appropriate design and analysis approach (e.g. referent selection in case-crossover studies or panel study approach to analysis).
- Table 1.6-1 Replace "decisive factors" and revise explanations, e.g. #8 drop reference to observational studies.
- AX1-5,1-7 criteria for study selection: All studies are more or less successful on these criteria. Consider how to best address systematically evaluation and discussion of these for individual studies. I suggest moving towards a 1-2 page evaluation for each key study to be included in the annex. This evaluation will be much more detailed than the current appendix tables and addresses study features.
- AX1-8 l 5-6 Is this regardless of analysis and reporting of results? For instance, an analysis that adjusts for measurement error will have wider confidence bands than one that doesn't. Should the study that goes beyond common practice by adjusting for measurement error be given less weight?
- AX1-9 l 21: Stay away from statistical significance as a criterion. Magnitude and precision of estimates should be enough.
- AX1-9 l 26: Do you mean natural experiments?

Charge question 2: Air quality and exposure

The discussion of correlations is much improved although I would like to also see the formulas documented (e.g. in the annex) instead of just described. However, now that the discussion is clearer, it becomes even more questionable in my mind whether the comparisons across studies and study designs are useful. Correlations are standardized quantities that depend on multiple features of the data. In a correlation, not only is the linear "relatedness" (covariance) of the two quantities important, but so is the variability of each. Thus two estimates of correlation could be very different just because one is restricted to a single season (with less variability) while the other captures data from an entire year. Since I expect this feature is extraneous to the interpretation goal, should it be part of the comparison? More work is needed to make the comparisons across studies, populations, pollutants, types of correlation, etc. really useful. This is a difficult task since the literature doesn't give clear guidance on how to summarize these studies. That said, I was surprised to see an apparently reasonable summary of this information in Chapter 5.

Monitor siting is an important and often hidden feature in all of the NO2 data. It could be critically impacting the epidemiological studies and their interpretation. This feature potentially pervades much of the summarized literature and could be affecting conclusions. Any revisions to the document that can be done to directly and openly address monitor siting and its effects on results and interpretation will improve the ISA. Unlike PM, oxides of nitrogen vary dramatically as a function of distance from road and some monitors are sited near roads. Plus much NO2 data are being analyzed at the hourly time scale. Low correlations between monitors could be completely driven by the local sources. For instance, the analysis summarized in Table AX3.2-2 is focused on spatial variability but does not identify the locations or siting features of the monitors. Scatterplot summaries would also be revealing, particularly appropriately included in the

annex. Further analyses of data may suggest features that should be highlighted in these comparisons.

Specific comments:

- Figures 2.5-4: Clarify the meaning of the sampling time (is this duration or averaging time?), the meaning of the information in the Fisher's Z-transform column, and that the reported correlations are shown on the native (not transformed) scale. Consider separating figures by study design or type of correlation reported (including averaging time) rather than location of study. Sorting by high vs. low air ventilation season may be important also.
- Section 2.5.6: Incorporate understanding of monitor siting into this discussion as appropriate.
- 2-45 l 11-13: Is this a better sentence?: "The relationship between personal ambient NO2 exposures and ambient NO2 concentrations found in different types of exposure studies have distinct implications for different types of epidemiologic studies.
- 2-45 l 30: I wouldn't classify the relevant features of exposure to be the same for time series and long-term cohort studies. The cohort studies are mostly relying on spatial variation in a long-term average pollutant while the time series studies are relying on day-to-day variation in daily average.

Charge question 3: Integration of evidence about health effects and conclusions regarding health

I found the integration and presentation of evidence in Chapter 3 to be generally good. However there are a number of details in the presentation I think need to be clarified to support the intent of the chapter. It is also critical that staff continue to refine and improve the information presented in the Annex tables. (I recognize this represents a massive effort.) The organization of these tables has been much improved, but I did not find that they include much more pertinent information. In trying to discern my agreement with the interpretations in Chapter 3 I often found I wanted to evaluate more detail on a particular study but this wasn't available in the annex. I was trying to answer questions such as "did this study properly adjust for confounding", or "what is the seasonal variation in the data". There are also some misleading features in the uniform approach to summarization (such as the change in a 4-point symptom scale in the Chauhan et al (2003) study that appears to be reported as an OR in the appendix and does not include units in Chapter 3 (3-5 lines 21+)). Another important feature of the Chauhan et al study that is discussed in Chapter 3 but completely absent from the Annex summary is that it was conducted over a 13-month period. In looking ahead to future iterations of this ISA process, it is important to consider how to revise the approach. One suggestion is to prepare an annex to the annex with a much more thorough and less constricted summary of each study. Quite likely at least a page or more of abstracted information will be needed for each study, at least for the studies that end up providing the greatest weight of evidence for the inference. Finally, both for the current version and in future versions, better indexing and cross-referencing is needed so the supporting information can be found efficiently.

The conclusions brought forward into chapter 5 and summarized clearly in Table 5.3-1 looked generally appropriate. I ask staff and CASAC to consider whether it is worth also listing health outcomes that have not been studied in this table.

Specific comments:

- Make sure all figures and other summaries include the increment of NO2 (or other pollutant as appropriate) for the RR/OR estimate. This is not done consistently throughout the document.
- Please downplay the apparent use of statistical significance as a criterion for scientific importance throughout. In that vein, change the y-axis for Figure 3.1-2 to not be an evaluation of statistical significance. The new version of Figure 3.1-1 appears to be more informative but I wonder if the graphic misleads in the ordering and scaling of the y-axis.
- P 3-2 l 31: Add a sentence like: "Fourth only a limited number of conditions can be evaluated feasibly.
- P 3-3 paragraph 1: If possible, include a comment on which of the limitations in toxicological studies are most important in this context.
- P 3-4 l 5: This is an example of a natural experiment, not an intervention study. This perspective appears elsewhere in the document(s) as well.
- P 3-4: Is the Shy & Love paper peer-reviewed?
- P 3-5 l 19, 21: Make sure units are included in this reporting and fix AX6-30 where the effect estimate appears to be reported as an OR. Furthermore, the summary information in the Annex fails to mention that this study covers a 13-month period – an important feature to consider in evaluating the results.
- P 3-8 l 3: Why are the findings conflicting? Is this another example of confusing statistical significance with scientific evidence?
- P 3-13: I couldn't find the Delfino et al (2006) paper in the Annex.
- P 3-11 l 4: Here is an example where the increment of NO2 isn't cited but is important for interpretation.
- P 3-11 l 15-16. Here is a case where the differences in correlations may be due to monitor siting. Any way to address that? Also define the correlation w.r.t. time scale, location.

Charge question 4:

This appears to be appropriate. Better distinguish susceptibility and vulnerability.

I like the idea of listing all likely susceptible groups and then determining whether there is any information in the literature about these groups. This can be a new framework that is applied to all pollutants and allows for a very open and transparent evaluation of our focus on particular groups. It also clearly identifies gaps in the literature with respect to this topic.

The concentration-response section 4.2 needs work. Much of the discussion appears to have the time series study design in mind, and if this is the case it should be stated (p 4-4 ll 16-24, l 25). How does the discussion on p 4-5 l 20-29 inform our understanding of the *shape* of the concentration-response function?

- P 4-5 l 16-17: Does this sentence refer to a *nonlinear* concentration response function? Clarify.

Charge question 5:

Generally the integration and summarization of the evidence in Chapter 5 was quite good, even for cases where I quibble with the details in earlier chapters. The new framework for causality supports the goals of the ISA and provides clear-cut criteria for health endpoints to bring forward into the Risk and Exposure assessment. More work should be done in consistent application of the Hill criteria. The CASAC discussion reflects my own concerns about whether this draft provides an adequate foundation for preparation of the ERA, particularly with respect to transparent use of the literature for policy.

Additional points from the discussion that I echo here: Has the document clearly established what we know and what we don't know? Clearly state the goals of chapter 5 in the beginning. Is NO2 *the* pollutant or the index for the effects?

Detailed comments:

- P 5-2 l 7-8: Is the evidence for conclusions only based on the Hill critieria? I would include consideration of the overall quality of the studies that are weighed.
- P 5-3 l 7: I needed an introductory sentence for the list.
- P 5-4 l 28-31 + 1-2 next page: Clarify the details. I want words inserted, e.g. "Intersite temporal correlations for hourly average NO2…" and "…twenty-four hour average concentration…"
- P 5-5 bullet starting l 3: Clarify "epidemiological studies." Not all are the same and I presume this bullet statement refers to time series studies.
- P 5-5 bullet starting l 20: This summary of the difficult to summarize features of personal vs ambient correlation is fairly reasonable. However I don't think statistical significance is the right criterion. Focus instead on the estimates.
- P 5-9 figure: Insert the NO2 increment used. Add a footnote to caution against overinterpretation of this nice summary: "Studies include different lag days and adjustment variables"
- P 5-17 l 15: Revise. Statistical significance is not the key feature, for instance a statistically significant effect could be in the "wrong" direction.

Other general comments:

- There is still overuse of "statistically significant" in this document. This is binary summarization of the data that depends on multiple features including magnitude of the effect, variability, and sample size. It doesn't reflect scientific meaning. To the degree possible replace focus on statistical significance with more meaningful quantities (e.g. effect estimates and confidence intervals).

- There continues to be a need to more thoroughly reference supporting information in the annex and make it easier for readers of the ISA to find this information.

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Comments from Dr. Frank Speizer

Chapter 2

The setting out of the conceptual model in figure 2.1 provides an excellent overall view. The devil is in the details that follow.

Review of Atm. Chemistry and Air Quality:
Page 2.3, line 15: It is probably worth indicating that from elevated sources the dispersion and dilution results in lower levels albeit more widely dispersed.

Page 2.3, Line 28 and Figure 2.21: The text suggests right Side outer box is NO_z but label does not appear in the figure. Needs to be added.

Page 2.6 para beginning line 10: It might be useful in the paragraph to indicate the relative amounts of POM measured.

Spacial and Temporal pattern of ambient NOx and human exposure
Page 2.13, Para beginning line 25: Is it worth either indicating (or speculating) that the increase in NO2 in other countries (could read Western Europe) is related to increase diesel and other mobile source utilization, are there canyon effects, is there a difference in fuels or engines, etc.?

Excellent organized discussion of exposure issues pointing out some of the uncertainty that will have to be taken into account. But certainly providing enough evidence that subsquesnt risk assessment can be done, at least for selective sites, albeit with less data than were available for PM and O3.

Atm. Science and exposure provide basis for evaluation of health effects:
Page 2.24, end of line 4: Suggest adding a table of results from McCurdy et al 2000, giving assessment of 11 different human activity patterns.

Page 2.25, line 4 and line 9: Need to rectify the discrepancy between the two statements although rest of paragraph provides some insight. I do not know what to believe!

Page 2.27, Table 2.51: Needs a footnote. Table ought to be able to stand alone rather then needing text in lines 1-7.

Page 2.28: Surely the important thing here is the paragraph beginning on line 18. The previous paragraph beginning on line 6 is mostly descriptive of what is in Table 2.5.1 and could have been left out.

Page 2.48, para beginning line 7: Needs editing. Discussion of P, K and a mention of twice as not thoroughly investigated..

Page 2.50. Summary: Strengths (and weaknesses) of existing data and what inferences can be drawn are well described.

Chapter 3

Intergrated evidence for Toxicology, human studies, and epidemiology

Table 3.1.1 Need to clarify if Chauhan et al 1998, is speculation or summary of the literature.

Seems to me that a qualitative summary of Hill's criteria might be created in a table for acute effects. Something like: (don't take my +s and –s seriously).

Hill Criteria	Host Def & Immunity	Inflammation	Short term A.R.	Resp. Symptoms	Lung Function	Hosp.	Mort.
Strength	+	+ (1ppm x2-3hrs)		++	Gen. Neg	--	--
Consistency	+	+	+/-	++	+/-	nul	--
Coherence	++	+/- (in children only)	+/- (few studies)	++	-	--	--
Plausibility	++	+/-	+/-	++	+/-	+/-	NA

Ditto something for chronic effects where respiratory effects range RR=1.1-1.3, consistent, particularly in children and adults >65. Asthma 25% increase. No co-pollutant effect, COPD mortality no coherent picture. Long term for other morbidity concur "inadequate evidence to infer presence or absence of causal relation.

Sections do not contain references.
Public Health Implications
Reasonable brief summary. Potential for some confusion in the use of terms susceptible and vulnerable. Sometimes used interchangeably when really means different thinks. Just be careful how the terms are used.

Integrated summary and conclusions.
Table 5.3.4 might be helped in exposure levels were included.
Chapter does a good summary that will work for the risk assessment.

Comments from Dr. George Thurston

In these pre-meeting comments, I will focus upon responding to my assigned questions for the ISA.

1. What are the views of the Panel on the characterization of the search strategy for identifying literature, criteria for study selection, the framework for scientific evaluation of studies and causality determination?

In reading the NOx ISA document, I found that the epidemiological studies I was aware of were considered, and could see no gaps in the epidemiological literature, which has greatly strengthened the evidence for an association between acute NOx exposure and respiratory health effects. With regard to the toxicological studies, I felt that, considering the potential inter-species differences in vulnerability, that it was very appropriate for the document to include studies that used exposures on the order of 5 ppm (approximately 10 mg/m3) to be very appropriate in this document, as such studies (while not useful for the estimation of human dose-response estimation) may well provide insights into the potential mechanisms of damage that might be caused by NOx.

One area that was lacking was a more intensive consideration of the evidence of potential impact of the co-exposure of particles and NOx, both in the toxicology and epidemiology. While I am not as familiar with the toxicological literature, I note that an informative toxicological study by H.G. Boren ["Carbon as a carrier mechanism for irritant gases" Archives of Environmental Health, 8, 119-124]. In this paper, a short-term exposure to 47 mg/m3 (25ppm) of NO2 or inhalation of fine carbon particles exhibited no gross pathological effects in the mouse lung, but when the mice were exposed to carbon particles that had previously been exposed to NO2, the mice developed local destructive lesions, with loss of cells from the alveolar walls. While just one study with high levels of NO2, this study indicates that the co-presence of particles with NO2 can enhance the effects of NO2. Since particles are always in co-exposure with NO2 in the real world, this may provide an important pathway of effect, but one that is not considered by this document, despite my raising this concern early in the process. My question: are there more published toxicological studies considering this particle-NOx interaction mechanism? This seems well worth another intensive look through the entire literature with that focus in mind.

3a. To what extent is the discussion and integration of evidence from the animal toxicology and controlled human exposure studies and epidemiologic studies technically sound, appropriately balanced, and clearly communicated??
?

This is where my above-noted concern really manifests itself. What we have is a wide gap that needs to be bridged between the controlled exposure studies and the epidemiological study results. The former show respiratory effects of NO2 only down to about 200 ppb, while the latter routinely and robustly document significant NO2-respiratory associations down at ambient levels. How can that be the case? We previously confronted a similar situation in the 1980's, when our NYU-Harvard study's of children at summer camps documented significant lung function decrements among

children to be associated with ozone exposures below 100 ppb, while the controlled exposure studies only showed effects down to 120 ppb. Subsequent more realistic controlled exposure studies (with exercise) later confirmed the epidemiology, and we now have a more protective ozone standard.

With regard to NO2, I suspect that ambient particles, always present in epidemiological studies, but not present in controlled NOx exposure studies, may provide the vector for the apparently enhanced effects of NOx in epidemiology vs. controlled studies, but the evidence for this possible avenue to justify the apparent discrepancy between the epidemiology and the controlled-exposure studies is not sufficiently explored in this report. In some cases it is noted in the ISA already (e.g., the fact noted that the APHEA study found greater PM effects in cities with higher NO2 levels), but needs to be brought together to address this specific issue. Thus, while some of the evidence is already present, and more may be in literature not yet brought to bear (or not yet collected), it is important to identify in the ISA what we do and do not know about this potential mechanism of NOx effects, and about other possible factors that may be responsible for this apparent disparity between the levels of effects (e.g., that the most susceptible subjects may not be considered in controlled-exposure studies, or that exercise may be a factor, both of which are mentioned here and there in the ISA).

The way to bring this about in the document, I suggest, is to add a section to Chapter 5 where the questions asked at the start of the Integrative Summary (on page 5-1) are answered to the best we can at this time, and which identify areas of further needed investigation to answer the question more definitively. In particular, the most important question to be answered is:

- At what levels of nitrogen oxides exposure do health effects of concern occur?

Answering this particular question will expedite the addressing of the gap between the controlled-exposure results and the epidemiology results, as well as a comprehensive consideration as to why that might be (i.e., Particle-NOx interactions? Greater degrees of susceptibility in the general public? Exercise? etc.).

3b. What are the views of the Panel on the conclusions drawn in the draft ISA regarding the strength, consistency, coherence and plausibility of NO2-related health effects

While I generally agree with judgments reached by the EPA regarding the strength of the evidence regarding causality, there is a need to discuss the concentrations where the various effects are applicable, as discussed above.

Comments from Dr. James Ultman

This well-organized and comprehensive document and its appendices provides a critical analysis of the newest literature as well as highlighting conclusions make in the 1993 Criteria Document. The EPA staff and its consultants are to be congratulated for a job well done.

As a second draft of the ISA, the document has effectively incorporated the most important suggestions of the NOx Review Panel including better detailing of the criteria used to judge causality and the means by which studies were selected for inclusion in the document.

Chapter 1.

No comment.

Chapter 2.

The description of emission sources and of the spatial variation of ambient measurements is much improved in this chapter.

I appreciate the inclusion of figure 2-1 that provides basis for organization of the chapter.

The sparseness of monitor sites in Figure 2.4-1 begs the question of how compliance is uniformly enforced in all regions of the country.

Figure 2.4-2 indicates the hourly-average ambient NO2 concentration at current monitoring sites almost never exceeds the lowest benchmark level of 200 ppb used in the Exposure and Risk Assessment. This underscores the importance of on-road and indoor sources that have a small influence on the ambient air measurements but a strong influence on personal exposure.

In figure 2.4-3 and others like it, the image should be coded in gray-scale (rather than color) before it is printed out.

There is an error in the title of figure 2.4-6d. Weekday→Weekend.

In equation 2.5-5, C_{nona} has a subscript that is inconsistent with the subscript on Cna used in the text.

In the dosimetry section on page 2-59, there is not much progress to report since the 1993 Criterion Document. Because the Exposure and Risk Assessment is based directly on observations made in clinical experiments, the need to use such models for dose extrapolation is not necessary for the current ISA.

Chapter 4.

No comment.

Chapter 4.

No comment.

Chapter 4.

This chapter provides an adequate summary of the research that is anticipated to guide the risk assessment.

On page 5-3, the key finding that the NO2 concentration is overpredicted by 25% by current monitoring methods is probably a good thing since the overprediction is due to other NOx and NOy that may also induce a health effect.

In the Conclusions on page 5-20, it would be appropriate to provide direct, succinct answers to the framing questions posed on page 5-1.

Answer to charge question 2.

I believe that the chapter does meet all the objectives outlined in the charge question. I do suggest, however, that material be added that describes and supports the method of extrapolating ambient monitor measurements to on-road concentrations. This is too important an issue to leave for the brief discussion that currently appears in section 6.2.3 of the Exposure and Risk Assessment document.

Comments from Dr. Ronald Wyzga

Overall comments:

This draft is much improved over the previous version. The siting of monitors is discussed, and there is a much better understanding of reported ambient measurements represent. The review of the health literature is comprehensive and makes it easier to achieve a good overall understanding of the health consequences of NOx exposure. The summary of the health effects discussed in Chapter 5 is an excellent organizational tool that facilitates an understanding of the nature and consequences of ambient exposures to oxides of nitrogen. There are a few areas that need further clarification. These are presented below in more detailed comments.

Charge question 2: To what extent are the atmospheric chemistry and air quality characterizations clearly communicated, appropriately characterized, and relevant to the review of the primary NO2 NAAQS? Are the properties of ambient oxides of nitrogen appropriately characterized, including spatial and temporal patterns and relationships between ambient oxides of nitrogen and human exposure? Does the information in Chapter 2 provide a sufficient atmospheric science and exposure basis for the evaluation of human health effects presented in alter chapters?

I have two suggestions here. The document refers to several studies undertaken overseas, several of which focus on distance to roadways as a factor "affecting indoor and outdoor NO2 concentration and personal exposure". To the extent that the overall nature of exposure could be quite different from that in the US given differences between the US and overseas sources in terms of fleet composition and extent of pollution control, there should be some note made about the geographic setting of these studies and whether the setting is typical of those found in the contemporary US. Any information on co-pollutants and concentrations would be particularly helpful.

Since the strength of the health argument for NO2 health effects is tied to the observations that effects are found in studies which consider both indoor and outdoor exposures, it would be particularly interesting for this chapter to provide some additional information to inform this argument. For example, given the typical sources of indoor and outdoor NOx, how does the composition change with respect to the different oxides of nitrogen and are the co-pollutants the same or different in indoor and outdoor settings?

Charge question 3: To what extent is the discussion and integration of evidence from the animal toxicology and controlled human exposure studies and epidemiologic studies technically sound, appropriately balanced, and clearly communicated? What are the views of the Panel on the conclusions drawn in the draft ISA regarding the strength, consistency, coherence, and plausibility of NO2-realted health effects?

One of the difficulties in interpreting the epidemiological study results is that it is often unclear whether health responses are due to traffic or to NOx per se, an ingredient of traffic-generated air pollution. To the extent possible, the document should attempt to indicate those studies where traffic is deemed to have a lesser influence on NOx exposure.

I would like to see a more rigorous examination/discussion of the co-pollutant issue; for example, which co-pollutants were discussed in which study; which were not. Are there any differences in measurement error, etc. I personally share some of the concerns raised by Brook et al. (2007) cited in the document.

In several places studies were not considered because they "did not inform"; this needs to be clarified.

Charge question 5: What are the Panel's views on the adequacy of this external review draft ISA to provide support for future exposure and policy assessments?

The current draft is a helpful document and a great improvement over the previous draft. With the appropriate consideration of the issues raised elsewhere in this review, the document would be an excellent resource for future exposure and policy assessments. I also believe that the document needs to tackle the issue of whether associations between NO2 and health responses in epidemiological studies are a reflection of NO2 exposures per se or is NO2 an index surrogate for some other exposure associated with NO2 sources. I believe the information is scattered throughout the document to help address this question, but an explicit and articulate consideration of this issue would greatly improve the document.

Specific comments:

Page 2-21: Figure 2.5-1 "residence"

Page 2-29, ll 1-3: Does this mean that local sources and near-source concentrations are not to be regulated? I think the wording needs to be changed here.

Page 2-42, ll. 5-6: statistical significance per se in not as informative as R^2; if the sample size is large enough any non-zero correlation will be statistically significant.

Page 2-52, Table 2.5-7: The paper by Brook et al. (2007) cited later in the document should be mentioned here. I find it particularly noteworthy that NO2 is highly associated with several organic compounds.

Page 3-12. Figure 3.1-1: This figure is helpful, but it should also indicate the time and concentrations of exposure of exposure in the subtable. See Figure 3.1-2. This would allow the reader to judge whether the application of Haber's law is appropriate and could facilitate the interpretation of results.

p. 3-26, ll 28- : Are there any co-pollutants associated with these exposures? Are they different from the outdoor studies?

pp. 3-51;3-52, Figures 3.1-10; 3.1-11: Where is Peel et al (cited elsewhere)?

p. 3-57, ll. 9-14: clarify what is meant by "did not inform"; if a study is not considered, it is important to understand why. Similar comments exist elsewhere; e.g., p. 3-58, ll 17-20.