UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

November 29, 2007

EPA-CASAC-08-002

Honorable Stephen L. Johnson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Clean Air Scientific Advisory Committee's (CASAC) Peer Review of EPA's Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria (First External Review Draft, August 2007)

Dear Administrator Johnson:

The Clean Air Scientific Advisory Committee (CASAC or Committee), augmented by subject-matter-experts to form the CASAC Oxides of Nitrogen Primary NAAQS Review Panel (hereafter referred to as the panel) completed its review of EPA's *Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria* (First External Review Draft, August 2007, EPA/600/R-07/093) on October 24-25, 2007. The ISA for oxides of nitrogen (NO_x) is the first ISA produced for EPA's new process for reviewing and revising National Ambient Air Quality Standards (NAAQS). Done properly, the ISA should be an informative, succinct, and useful summary of the evidence for consideration of the NAAQS. Overall, the panel found that the first draft ISA did not fully meet its objective. CASAC panel members have provided individual recommendations to strengthen the next draft (Attachment B) and the panel responded to charge questions submitted to CASAC by EPA's National Center for Environmental Assessment. While there is some redundancy in the responses to different charge questions (because the charge questions overlap in their areas of concern), the responses to the different charge questions are consistent with each other. Finally, the CASAC offers general comments related to a multiple-pollutant approach for air quality management.

Charge Question 1. 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 panel advises EPA to expand its discussion of sources and atmospheric chemistry in Chapter 2, Source to Tissue Dose (and later in Chapter 5, the Findings and Conclusions), and

throughout the document to relate assessment of information to the review of the NAAQS. There needs to be more quantitative information provided on the sources of oxides of nitrogen (NOx) and the speciation of NOx, both indoors and out. These findings should be related to where the monitors tend to be, including their vertical elevation and the co-pollutants being emitted and monitored. How these findings relate to exposure and health studies need to be addressed later in the discussion of atmospheric processing and exposure.

CASAC recognizes that the current monitors are susceptible to interferences and may include oxidized nitrogen species other than nitrogen dioxide (NO_2) in the signal, leading to a potentially high bias. As such, it is important to provide quantitative information on the extent or level of likely bias in specific metrics of ambient NO_2 levels/air concentrations, e.g., the expected uncertainty/bias in annual averages, daily maximum(s), etc., and how they vary by time of day and season. The ISA should be careful to provide a balanced assessment of possible issues involved in use of monitoring data, taking into account the likely relevance of these issues to monitors across the United States and the likely impact of those issues on human health assessment.

Given that the health literature suggests that NO_2 is at least likely to be the pollutant of concern [*vis à vis*, e.g. nitric acid, peroxyacyl nitrate (PAN), nitrous acid (HONO), or other oxides of nitrogen], developing a method that has less interference would be preferred over a method that captures all oxidized nitrogen species without identifying the concentrations of specific species. The monitoring method used, however, should be consistent with the method used in key epidemiological studies or an appropriate correction factor used (see response to Charge Question 2).

The panel advises EPA to present a series of maps that show spatial trends as well as figures or tables that show temporal trends in ambient concentrations in various parts of the country, ideally from some time before the establishment of the existing health standard in 1971. It would be helpful to relate trends to major economic, transportation, technological, or other historical events that may have some relevancy to emissions of oxides of nitrogen events since 1971. Information is needed about the location of NO_2, NO_x, and NO_y [the sum of all oxydized nitrogen compounds including those listed in Section 108(c) of the Clean Air Act] monitors. The ISA or its appendices should include information about monitor location in terms of proximity to roadways, size of roadways. The ISA should provide a list of NO_x, particulate matter (PM), ozone, and other pollutants measured at these same monitoring sites.

Charge Question 2. Are the properties of ambient oxides of nitrogen appropriately characterized, including policy-relevant background, spatial and temporal patterns, and relationships between ambient oxides of nitrogen and human exposure?

The discussion of nitrogen oxides species needs to be made clearer and more complete. For example, the relative importance of the various nitrogen oxides [NO, NO_2, nitric acid (HNO_3), PAN, etc.] as a function of location and time should be discussed. In addition, a more accurate depiction of PM nitrate species (both inorganic and organic) is needed in Figure 2.2.1.

A better description of the spatial and temporal variability of NO_2 and other nitrogen oxides is needed. In particular, the ISA should discuss the spatial variability of nitrogen oxides near roadways since spatial variability is directly relevant to the discussion of high-exposure individuals in Chapter 4 (Susceptible and Vulnerable Populations).

The discussion of the ambient monitoring needs to be more focused, keeping in mind that the objective of the monitoring network should be consistent with the NAAQS. If the NAAQS is based in part on epidemiological studies that used a certain monitoring technique for ambient NO_2 concentrations, the designation of attainment or non-attainment should be based on the same or a similar monitoring technique. If a significantly different technique were to be used, then some correction may be needed.

The panel advises that NO, as well as NO_2, should be reported by the states since the measurement is available from current monitoring. If NO were reported, scientists could better understand the atmospheric chemistry and spatial and temporal patterns of the related nitrogen species.

The siting of monitors will be critical for future attainment designations and exposure assessments because of the strong horizontal and vertical gradients in nitrogen oxides concentrations near roadways, and their effects on human exposure. The difference in NO_2 concentrations between measurements made near the ground and those made at 10 m above ground level should be taken into account in exposure and health effects studies.

Charge Question 3. 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?

The panel finds that information in Chapter 2 is insufficiently integrated for purposes of evaluating human health effects and lacks key information. The ISA would be improved if it were revised to incorporate changes identified by the panel. The ISA should integrate information about the current standard in order to give perspective to the ambient exposure data cited in graphs and tables.

The emissions of NO_2 and related species from both indoor and outdoor sources need to be discussed both in general and specifically in the context of the correlation of ambient NO_2 levels with other co-pollutants, including ultrafine and carbon-containing particles. The relationships between personal, indoor, and outdoor levels of NO_2 deserve more discussion, particularly with respect to the parameter "alpha" (the ratio of ambient exposure to ambient concentration) and in the context of specific epidemiological study designs.

The ISA should address the complex nature of spatial variability of NO_2 within urban areas in more detail. Important topics to address include potential exposure misclassification due to siting of monitors away from busy roads, the presence or absence of street canyons, in-vehicle exposures, and the effect of atmospheric dilution with height above ground. The panel recognizes, however, that many of these issues cannot be addressed in detail, given the current state of information.

The panel advises EPA to revise the ISA to include some discussion of the biological activity of inhaled NO, particularly with respect to cardiovascular function. The ISA should also include some discussion of the dosimetry associated with that activity.

Charge Question 4. To what extent is the discussion and integration of evidence from the animal toxicology and controlled-exposure human experimental studies and epidemiologic studies, technically sound, appropriately balanced, and clearly communicated?

Chapter 3 was a multi-author effort and, for balance, the inconsistencies in integration and level of discussion across the sections should be rectified. The chapter is quite long and should be greatly reduced in size. Ideally, only the key studies that support a NAAQS should be discussed in detail. In addition, the document should identify the relevant chemical species of concern and clearly discuss how the processes involved in NO_x production result in additional air pollutants that confound study findings. For communication purposes, it is important to have an integrated analysis that draws key conclusions from the available data sets and includes the magnitude of the concentration response for the different health endpoints. Providing the concentration response information is not only the key to Chapter 3, Health Effects, but also to the overall quality of the ISA. The ISA would be improved if a plan or process for integration and study selection was clearly laid out and followed throughout the document. Such an approach would facilitate integration across the three study types of epidemiology, clinical, and animal toxicology. In particular, the toxicological studies should be evaluated with respect to their support or inconsistency with the biological plausibility of health effects related to NOx exposures.

Charge Question 5. To what extent does the integration of health evidence focus on the most policy-relevant studies or health findings?

The panel advises EPA to revise Chapter 3 to explicitly relate discussion of the health evidence to a detailed explanation early in the document concerning the search strategy for identifying literature, the criteria for selecting studies for the ISA, and the criteria for evaluating studies for health effect. Adding discussion of such a comprehensive framework for the assessment of studies at the start of the document would allow a more consistent evaluation of the various study evidences for relevance and help with integration across chapters.

The panel also called for more integrated assessment of the health evidence presented in Chapter 3. The panel advises the ISA to be revised to evaluate the interaction between animal toxicology studies, dosimetry studies, and epidemiological investigations. In particular, there is a need to cross-compare the separate evidence (e.g., toxicology vs. epidemiology) in order to see which health results are coherent or inconsistent with each other. The panel also advises EPA to ensure a balance in reporting both negative and positive studies and to take steps to avoid publication bias. Panel members noted at the October 25th consultation that several studies with negative findings that merited inclusion were missing from the ISA (see list below for examples of studies discussed[1]). The panel advises EPA to review panel members' written comments in

[1] Partial list of studies with negative findings that were missing from the ISA and merited inclusion (see Appendix B comments for additional references below):

detail for additional discussion of studies that should be examined for the ISA. Finally, examining the epidemiology results as a function of exposure concentration, the consideration of study environment (indoor/outdoor, near/way from roadway), and the consideration of other pollutants would help future decisions related to the NAAQS. The panel noted that the emphasis given to the indoor and intervention studies in Chapter 5 was generally felt to be appropriate. A more comprehensive and consistent evaluation of possible PM-NO_x interactions is needed throughout the ISA.

Charge Question 6. 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?

Since the 1993 Air Quality Criteria Document for Oxides of Nitrogen, a substantial body of evidence has been developed that documents adverse health effects associated with exposures to ambient or near ambient levels of NO_2 and its oxidative reaction products. These include epidemiologic studies demonstrating relationships between oxides of nitrogen and hospital admissions, emergency department visits, and mortality. There is evidence of adverse health responses in sensitive populations such as children, asthmatics, and those living and working near roadways. Field and panel studies have demonstrated relationships between NO_2 exposure and both respiratory symptoms and pulmonary function impairment. The relationships between these health responses and NO_x exposure appear to be robust and to maintain significance when corrected for confounding variables.

In spite of the robust relationships with NO_x levels, CASAC recognizes that the primary associations are between products of combustion and adverse health impacts. NOx levels may partly be a surrogate for combustion product exposures. However, the consistent finding of strong associations with NO_x levels across studies of diverse designs, including indoor exposures, suggests that NO_x can be a significant factor in the causation of the observed adverse health impacts. Epidemiological findings discussed in the draft ISA indicate that current ambient NO_2 exposures are associated with adverse impacts to the public health. CASAC advises EPA to revise the ISA to better document that these findings are plausible, consistent and coherent. In revising Chapter 3, the Agency should explicitly relate discussion of the health evidence to a detailed explanation early in the document of the search strategy for identifying literature and an exposition of the criteria for selecting studies for health effect, based on A. B. Hill's criteria (Hill 1965).

In addition, the panel notes that the ISA strongly benefits from the creation of tables that integrate the complex data from studies of multiple designs. If possible, tables should also

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Witten A, et al. (2005) Effects of nitrogen dioxide on allergic airway responses in subjects with asthma. J Occup Environ Med. Dec;47(12):1250-9

Aris R, et al. (1993) Effects of nitric acid gas alone or in combination with ozone on healthy volunteers. Am Rev Respir Dis Oct;148(4 Pt 1):965-73

Metzger et al. (2007) Ambient Air Pollution and Ventricular Tachyarrhythmic Events in Patients with Implantable Cardioverter Defibrillators. Epidemiology. Sep;18(5):585-92

Sinclair and Tolsma (2004) "Associations and Lags between Air Pollution and Acute Respiratory Visits in an Ambulatory Care Setting: 25-Month Results from the Aerosol Research and Inhalation Epidemiological Study", J. Air & Waste Manage. Assoc., 54:1212.

consider co-pollutant effects and confounding. The Agency should choose a reliable method in the tables to standardize the metric used for comparison between studies.

Charge Question 7. What are the views of the Panel on the appropriateness of public health impact and the characterization of groups likely to be susceptible or vulnerable to NO_2?

The panel advises EPA to revise the ISA to define "susceptible" populations with regard to the extent of response relative to the general population. It would be helpful to reorganize the discussion of susceptible populations under the umbrellas of biological susceptibility, socioeconomic susceptibility, and susceptibility related to geographic locale. The ISA treatment of susceptibility would be strengthened by: 1) including discussions of potential mechanisms of action that relate specifics of NO_2 biology to pathobiological perturbations; and 2) defining susceptible populations more clearly and systematically examining how different toxicological, clinical, and epidemiological data relate to these populations, reporting results as a function of concentration, and considering both relative risks and absolute attributable risks in such at-risk sub-populations. With these changes, the ISA discussion of susceptibility will better address biological plausibility with regard to specific populations and allow attribution of health outcomes to direct causal actions of NO_2.

The panel notes that the lung growth studies from the California Children's Health Study are particularly important in identifying children as a distinctive and probably susceptible population with respect to NO_2 exposure. Children offer the opportunity to observe the whole spectrum of injury, growth, and repair in response to NO_2 exposure, if it occurs. Some discussion of dosimetric differences between adults and children would be useful and the panel notes that there are at least two peer-reviewed papers related to this subject.[2]

Charge Question 8. What are the Panel's views on the adequacy of this first external review draft ISA to provide support for future risk, exposure and policy assessments?

While Charge Question 8 calls for a consideration of whether the entire ISA document provides adequate support for "future risk, exposure and policy assessments," the panel considers it essential that Chapter 5 summarize all of this support succinctly and rigorously so readers can understand how EPA is drawing scientifically sound conclusions from the previous chapters. Chapter 5 does not currently meet this goal. The most significant problems are that: 1) the bulleted conclusions in Chapter 5 are not always the most relevant findings from the earlier chapters; 2) most of these items provide little quantitative support for the kinds of risk assessment and policy decisions that will eventually need to be made on population risk, form of the standard, dose-response, etc.; 3) the authors have not applied - or at least have not specified clearly - a transparent set of criteria in drawing the conclusions presented in the face of at times conflicting data (for more insight into this, see the criteria supplied by Dr. Ellis Cowling in his individual comments); and 4) the conclusions drawn do not adequately address the uncertainties

[2] See: Sarangapani et al. (2003) Evaluation of the potential impact of age- and gender-specific lung morphology and ventilation rate on the dosimetry of vapors. Inhal Toxicol. 2003 Sep; 15(10):987-1016. and Ginsberg et al. (2005) Review and analysis of inhalation dosimetry methods for application to children's risk assessment. J. Toxicology Environ Health-Part A. 68:573-615.

in slope factors, the judgment on causal associations, and the efficacy of control measures targeting NO_2 introduced by confounding exposures in the epidemiological studies that play such a strong role in the assessment. This Chapter needs significant work before it will provide a good synthesis for the updated science assessment of NO_x.

Summary

In summary, the CASAC review of this first draft ISA raises concerns about the approach used by the Agency for this important assessment, which will serve as a template for future assessments within EPA's new NAAQS process. The draft NO_x ISA inadequately describes the NAAQS review process, including EPA's approach to literature identification and evidence evaluation. The ISA does not appear to have been developed by a process that approaches the current "state-of-the-art" around the development of systematic reviews for decision-making purposes. A replicable approach is needed that presents a clear statement of principles for evidence evaluation and that presents standardized language for characterizing the strength of evidence. Additionally, CASAC found that a clear framework was not established in the draft ISA for considering potential causal effects and non-causal associations of NOx with human health effects.

General Comments Related to a Multiple-Pollutant Approach for Air Quality Management

In addition to the responses provided above to the charge questions, the panel felt strongly that a major issue that needs to be addressed more fully is the multiple pollutant aspect of the ISA for oxides of nitrogen. The August 2007 draft *Integrated Science Assessment* for oxides of nitrogen contains many references to:

1) the role of gaseous NO and NO_2 in the formation and accumulation of ozone and other photochemical oxidants,
2) the role of NO and NO_2 in the formation of nitrate-containing secondary aerosols,
3) the co-occurrence of any two or all three of these pollutants in the same air parcel near the ground,
4) the possibility that the respiratory functions of many susceptible populations of people will be affected differently when their lungs are exposed to mixture of these pollutants than when exposed to any one of these pollutant when occurring alone; and
5) the possible interaction of NO_x and PM in association with health effects.

These five possibilities are part of the reasons why the National Research Council's recent report on *Management of Air Quality in the United States* recommended that the EPA consider development of a multiple-pollutant approach in air quality management – this as an addition or alternative to the Agency's long-established tradition of dealing with one pollutant at a time by establishing separate National Ambient Air Quality Standards for CO, ozone, sulfur dioxide, oxides of nitrogen, PM, and lead. The EPA is currently considering a multiple-pollutant approach to air quality management in addition to the present "one-pollutant-at-a-time" approach. CASAC strongly recommends that EPA seriously consider developing a multiple-pollutant, multiple-effects approach to air quality management.

In closing, the CASAC Oxides of Nitrogen Primary NAAQS Review Panel was pleased to review the first draft of the ISA for oxides of nitrogen. We look forward to review of the second draft and wish you well in this important endeavor.

Sincerely,

/Signed/

Dr. Rogene Henderson, Chair
Clean Air Scientific Advisory Committee

Attachments

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

Attachment B: Compilation of Individual Panel Member Comments on EPA's *Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria* (First External Review Draft, August 2007, EPA/600/R-07/093)

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

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

CHAIR

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Attachment B: Comments from CASAC Oxides of Nitrogen Primary NAAQS Review Panel on EPA's *Integrated Science Assessment for Oxides of Nitrogen – Health Criteria* (First External Review Draft) (EPA/600/R-07/093, August 2007)

Comments Received:

Comments from Professor Ed Avol

Integrated Science Assessment for Oxides of Nitrogen: Health Criteria
EPA/600/R-07/093, August 30, 2007
First External Review Draft

Comments By Ed Avol

General Comments:
This document represents a heroic compendium of information, and Staff are to be congratulated for pulling this substantial set of diverse information together. It is clear from the assembled document that a great deal of additional information has become available since the previous document review (which last occurred almost 15 years ago). The current compilation will be useful and critical in deliberations concerning possible revisions to the standards.

That said, I have several concerns with the layout and presentation of the document. The logic behind the organizational layout eludes me. Although it presumably is focused on published relevant research since the previous NO2 review document (ca. 1993), there are numerous references, discussions about, and consideration of data from 1965-1992. It seems that Staff could have summarized this previous data more efficiently, provided some summary tables in a chapter essentially describing how we got to this level of understanding NO2, or referred to the previous document, and moved on. There is too much discussion, review, and emphasis on pre-1993 research.

Within the health chapter, the order of topical presentations seemed to circle and re-circle around topics presented again and again in the chapter, in a sort of ever-decreasing (downward) spiral, re-visiting (at least two or three times) each topic under a slightly different heading in a slightly different manner. The document is unduly repetitive and could be significantly re-compiled and shortened. The chapter that is entitled "Integrated Health Effects of NO2 Exposure", for example, is over 150 pages long and often re-visits and re-visits more than it integrates.

In the Health Chapter, I found the separation of US research from research performed in other countries to be unwarranted, inconsistent, and counter-productive. Quality research does not have borders; the relevance of well-performed research should dictate the weight given in determining the value of each contribution. The separation of research by country in the text seemed to be inferring some diminution in quality, consideration, or relevance, which (for the most part is not warranted).

Organizationally, the document is inconsistent (possibly reflecting multiple chapter contributions from different authors). Sometimes there are summaries following major sections reporting the research data, sometimes sections are completed by an integration section, and sometimes one or both are missing (for example, see P3-94 [no integration], P3-118 [no summary], or P4.13 [missing both]). Summary and integration in this document is critical (isn't that supposed to be one of the benchmarks of the "new"

process?), but the document seems to reflect a transitional state between the former compendium-of-complete-results approach and a more-streamlined distillation of recent research with an emphasis on integration.

The Chapter 3 summary figures and tables are especially well-constructed, very useful, and much appreciated. Document staff are to be commended for the practical utility of the summary figures, allowing readers to visually review a number of study results easily and effectively. Similarly, the provided tables contain a large amount of concentrated information that were useful to review, and will be useful as summary reference material.

Specific Comments:
CHAPTER 3
P3-4, Sec 3.2.1.1 Lung Host Defenses and Immunity, line 1 – the word "new" should be replaced with "recent"

P3-4, Sec 3.2.1.1 Lung Host Defenses and Immunity, lines 8 & 9 – This section is ostensibly about human research data, but these references all cite animal work.

P3-5, Sec 3.2.1.1 Lung Host Defenses and Immunity, lines 7 & 8 – "…mucociliary clearance is not affected by NO2 exposure as low as 3ppm…" is an awkward way to phrase this; recommend re-wording, such as "…mucociliary clearance effects have not been reported below 3ppm…"

P3-5, Sec 3.2.1.1 Lung Host Defenses and Immunity, line 29 – should be "…body *of* evidence…"

P3-6, Sec 3.2.1.1 Lung Host Defenses and Immunity, line 6 – "…confounding with ultrafine emissions remains a concern…" comes unsupported and out of nowhere in the discussion. This should be supported by a sentence or removed.

P3-11, Sec 3.2.1.1 Lung Host Defenses and Immunity, line 1 – Reference to a study involving an exposure of 29ppm NO2 is unnecessary, given the unrealistic level of the exposure and the general guidelines to only refer to relevant study concentrations (in the less than 5ppm range).

P3-14, Sec 3.2.1.2 Effects of Short-Term NO2 Exposure on Lung Function, lines 26 & 27 – "…spirometry…is not generally used for large-scale studies…" This is incorrect and should be removed; the document itself contains numerous references to "large-scale" studies utilizing spirometry.

Additionally, why are the California Children Health Study citations (Gauderman, Peters, McConnell, Avol) not in this section?

P3-19, Sec 3.2.1.2 Effects of Short-Term NO2 Exposure on Lung Function, lines 20 thru 22 – Most of these references precede the previous NO2 review document and were already previously discussed in the earlier document. This approach (reviewing earlier work that has already been reported in the previous document, is repeated *ad nauseum* throughout this chapter.

P3-44, Sec 3.2.1.6 Hospital Admissions and Emergency Department…, lines 30 thru 32 – This discussion of morbidities that can result in Emergency Department visits is all true and completely irrelevant.

P3-45, Sec 3.2.1.6 Hospital Admissions and Emergency Department…, line 5 – "Asthma visits typically dominate the daily incidence counts…" *(in the Emergency Department and hospital admissions for respiratory disease)* may be true, but still is not especially germane (unless an argument is going to be made that most asthma admissions are somehow related to NO2 exposure).

P3-45, Sec 3.2.1.6 Hospital Admissions and Emergency Department…, line 6 thru 8 – "…Chronic bronchitis…is a prominent diagnosis among older adults…" is another true statement that is irrelevant to the discussion.

P3-46, Sec 3.3.1.6.1 All Respiratory Outcomes…, line 4 – A calculate relative risk of 1.0027 is really pushing the edges of credulity; this may indeed be statistically significant, but as a practical matter, is it likely to be important?

P3-49, Sec 3.2.1.6.2 Asthma…, line 19 – in two places, the wrong reference appears; it should be Lin, not Linn.

P3-49, Sec 3.2.1.6.2 Asthma…, line 30 – The differences in study results could also be related to the analytical power of the respective studies (differing subject population sizes).

P3-51, Sec 3.2.1.6.2 Asthma…, lines 18 and 19 – should be replace to read "…models show*ed* that the addition *of* O3, smoke, or SO2 into the model result*ed* in…"

P3-67, Sec 3.2.2.1 Studies of Hospital Admissions…, line 5 – delete the word "been".

P3-68 and 3-69, Sec 3.2.2.1 Studies of Hospital Admissions…, Figures 3.2-15 and 3.2-16 – Check relationships, units, and conversions between what is stated in the text reports of percent changes and what appears as relative risk plots in the figures; for ease of reading and following the discussion, these should be consistent.

P3-79, Sec 3.2.2.3 Integration for Effects of Short-Term NO2…, line 15 – insert "NO2" between "ambient" and "(Peters…".

P3-82, Sec 3.3.1.2 Canadian Multi-City Studies – Why are these broken out as a separate group for discussion? Why are they not a part of the discussion under multi-city studies? Throughout the previous presentations, studies from Europe and Australia and elsewhere have been cited and discussed, so it is not the case that studies are presented in the text by country of origin?

P3-84, Sec 3.3.1.3 Air Pollution and Health… – similar comment as above; what is this European study set separately presented from the previous data?

P3-88, Sec 3.3.1.5 Other European MultiCity Studies – same comment

P3-89, Sec 3.3.1.6 Australian Four Cities Study – same comment

P3-112, Sec 3.4.1.3 Asthma Prevalence…, line 27 – phrasing of "…reported positive associations for girls to both NO2 and NOx…" is awkward and a bit confusing; change to "…reported associations with both NO2 and NOx for girls…"

P3-130, Sec 3.4.4.1 Integration and Biological Plausibility…, line 31 – insert a space between "Nitrogen" and "deemed".

P3-144, Sec 3.6 Studies of NO, HONO, and HNO3, line 8 and line 13 – As mentioned previously, studies are referred to here with exposure concentrations of 16ppm, 50ppm, and even 80ppm; these are not especially relevant to ambient health concerns, and violate the boundary condition that studies utilizing exposures in the realm of ambient (<5ppm NO2) would be the focus.

P3-152, Table 3.2-2, need to specify the units of Age, ***in years***.

CHAPTER 4

P4-2, Section 4.1.1 Pre-existing Disease as a Potential Risk Factor, line 8 – delete "…and some nonasthmatic individuals do…"; this is assumed in the phrasing of the statement.

P4-13, Sec 4.2.2 Estimation of Potential Numbers of Persons in At-Risk Susceptible Population Groups…- Why is there no summary section on genetic susceptibility? It has been discussed as a risk factor, there are published articles about it, and we do know something about the penetration of certain genes of interest in the general population.

P4-13, Sec4.2.2 Estimation of Potential Numbers of Persons in At-Risk Susceptible Population Groups…- Why is there no summary statement about those subpopulations considered to be susceptible (asthmatics, children, those with certain genetic profiles, cardiovascular disease patients)?

P4-15, Table 4.1 – Re-write the third and fourth sentences in the second paragraph (the ones that refer to the Islam et al work). These are inconsistent with the summary perspective of the table. (Just state the findings, don't introduce the study).

CHAPTER 5
P5.1, Sec 5.1 Introduction, line 8 – delete "this" from "…(1) this introduction…"

P5.1, Sec 5.1 Introduction, lines 10 thru 12 – delete this first sentence; it is unnecessary.

P5-3, Sec 5.2 Atmospheric Sciences, line 3 – "…motor vehicles are a large source of urban NO2…" – more correctly, aren't motor vehicles a large source of NO, which is quickly converted (in the presence of oxygen) to NO2?

P5-3, Sec 5.2 Atmospheric Sciences, line 13 – replace the words "a few" with "some", since across the country, there will be more than "a few".

P5-11, Sec 5.5.2.4 Morbidity and Long-Term Exposure…, line 20 – Why is it necessary to specify that two studies were from Europe? If the studies are valid, they should be discussed on their merits.

P5-12, Sec 5.5.2.6 Concentration-Response Relationships…, lines 29 thru 32 – what are these studies being referenced and discussed here? This chapter is supposed to be a summary of findings presented in the previous chapters, in an integrated presentation.

P5-14, Sec 5.5.2.7 Susceptible and Vulnerable Populations, line14 – Why is there not a section on Genetic Susceptibility?

P5-17 onward… - What are all these tables doing here? They should be in Chapter 3, where the data is presented.

Comments from Dr. John Balmes

Charge 4 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?

GENERAL COMMENTS

Chapter 3 on Health Effects is long (over 150 pages) and overly detailed in certain parts. There should be less detail about experimental design and specific results in the chapter text; these details are best left to the annex. By trimming this detail and endeavoring to present the information in a more thematically clear manner, a revised chapter will better support whatever recommendations for an air quality standard emerge from the review process. The chapter as currently written reads too much like a mini-criteria document rather than an integrated synthesis.

In general, the presentation of the results of the animal toxicologic, controlled human exposure, and epidemiologic studies that have been reviewed is technically sound, although I am concerned about the selection of studies based on the observation that two relevant but negative studies from my own lab are not included (see specific comments below). The criteria for selection of specific studies in all three categories should be clearly stated. In addition, the criteria for judging the strength of findings from specific studies as well as those used to assess aggregate findings of studies on a relevant research question should also be clearly stated.

In my view, the epidemiologic data are relatively consistent and coherent with regard to the association of daily ambient NO2 and exacerbations of asthma. In addition, the data from a single well-designed and conducted study, the Children's Health Study, that show an association between annual average NO2 and decreased rate of growth of lung function provide strong evidence of a chronic effect on lung development in children. The toxicologic evidence in Chapter 3 is not presented in a way that convincingly supports potential mechanisms for either of these two health outcomes.

The toxicologic data that are best presented in the chapter are those which indicate that NO2 exposure increases risk of bacterial and viral respiratory infection in experimental animal models. While these data do provide some plausibility for the epidemiologic studies that find an association between ambient NO2 and total respiratory hospitalizations or emergency department visits, they do not illuminate how NO2 exposure might induce exacerbations of asthma not related to respiratory infections. The controlled human exposure data on NO2 and non-specific airway responsiveness in asthmatic subjects are mixed and on aggregate do not show an exposure-response relationship. The animal toxicologic data show an effect of sub-chronic but not acute exposure on non-specific airway responsiveness. Enhancement by NO2 of airway responses to specific allergen challenge is perhaps the potential mechanism of asthma exacerbation best supported by the combined controlled human exposure and animal toxicologic data. While these data are presented well in Chapter 3, they are not included

in either the integration of evidence and biological plausibility for respiratory effects in Chapter 3 or the summary of respiratory health effects and short-term exposure in Chapter 5.

There are really no controlled human exposure data that support a mechanism for the decreased rate of growth of lung function in children observed in the Children's Health Study. Because the animal toxicologic studies that have demonstrated lung structural changes with chronic NO2 exposures used much higher than ambient concentrations, these studies also do not really provide much support for the effect observed in the Children's Health Study. In my view, the relative lack of both human and animal toxicologic data to support the strong epidemiologic evidence that ambient NO2 is associated with asthma exacerbations and decreased growth of lung function in children should be clearly stated in the ISA. The issue of dose-response in comparison of animal toxicologic data with those from human studies also should be addressed directly in Chapter 3. Rodents are likely less sensitive to the effects of a given concentration of NO2, but no quantitative discussion of this issue is included in the current draft.

Regarding the question of appropriate balance, this can be best handled by the provision of clear criteria for the inclusion of studies and rating of quality of the evidence as noted above.

In terms of clear communication, Chapter 3 as currently drafted falls short. The text in Chapter 3 needs to be tighter, less redundant, and more thematically organized (i.e., each section should have a story line). In particular, the summary/integration subsections should provide an overview of the quantity and quality of the evidence for the health outcome(s) of interest as well as evaluation of how well the toxicologic data support the epidemiologic findings.

SPECIFIC COMMENTS

Chapter 3 would be easier for the reader to follow if the NO2 exposure metric noted for each study discussed was the same (i.e., either all μg/m3 or ppb or ppm). Although the point is mentioned here and there, it would probably also be easier for the reader if there was a discussion early in the chapter about NO2 often being correlated with CO and PM in epidemiologic studies, suggesting a common origin from combustion sources.

p. 3-5, line 29 …the body <u>of</u> evidence…

p. 3-6, line 29 The experimental protocol used in the Solomon et al. study actually involved three consecutive days of exposure, not four.

p. 3-21, lines 10-22 Two recent controlled human exposure studies provide relevant data for this paragraph. The paper of Barck et al. (2002) cited later in the chapter reported the results of a study of 13 asthmatic subjects exposed to 0.26 ppm for 30 min. A second paper by Witten A, et al. (J Occup Environ Med 2005; 47:1250-9) reported the results of a study of 15 asthmatic subjects exposed for 3 h to filtered air or 0.4 ppm NO_2

with intermittent exercise. No effect of NO2 on FEV1 was noted in either of these papers. Brief discussion of these papers in this paragraph would strengthen basis for the subsequent statement on p. 3-22 that "For asthmatics, the effects of NO2 on pulmonary function have also been inconsistent at exposure concentrations of less than 1 ppm NO2."

p. 3-33 The Solomon et al. study (2000) cited earlier in the chapter also showed increased PMNs in the bronchial fraction of BAL 18 h after the third consecutive day of exposure to 2.0 ppm NO2 for 4 h with intermittent exercise and could be easily cited here as well.

p. 3-35 , lines 22-25 The first sentence of this paragraph appears to refer to the studies in rats and mice mentioned in the previous paragraph. If that is the case, then the second sentence of the paragraph is superfluous.

p. 3-41, line 1 The study by Witten et al. noted above is a study that did not confirm the findings of Barck et al. and thus should be discussed here. In the Witten et al. study inflammatory cells and molecules were measured in sputum induced at 6h and 26h post-house dust mite allergen challenge after both NO2 and filtered air exposures. After NO2 exposure, eosinophil concentration decreased significantly in the 6-h post-allergen sputum. No significant NO2-related difference was observed for other variables. In this study, multi-hour exposure to a high ambient concentration of NO2 did not enhance the inflammatory response to subsequent inhaled allergen as assessed by cell distribution in induced sputum.

p. 3-43, line 17 Should be airways responsiveness here, not hyperresponsiveness.

p. 3-45, lines 21-27 As written these two sentences are confusing because the first sentence states that there were no significant associations between NO2 and hospital admissions found for children 1 to 4 years, and then the next sentence notes a 2.8% increase in respiratory admissions for a 9-ppb increment in the daily maximum 1-h concentration of NO2 was observed. That this increase was not statistically significant needs to be made more clear.

p. 3-49, line 19 Should be Lin et al., not Linn et al. for both citations.

p. 3-50, line 3 Both the mean 24-h and maximum daily 1-h concentrations of NO2 in this study should be given here.

p. 3-51, line 19 …addition <u>of</u> O3, smoke or SO2…

p. 3-51, line 23 …working day<u>s</u> shows…

p. 3-54, lines 5-6 This sentence would be clearer if it read as follows: "…showed increased risks in each quartile <u>for the summer months</u>, although the increase was not monotonic." Figure 3.2-11 does not show increased risks in each quartile for the winter months.

p. 3-57, line 15 "there" should be deleted from this line.

p. 3-57, lines 16-17 It might be better to state "In many of these studies, there was evidence of correlations between NO2 and CO or PM measures."

p. 3-58, lines 12-13 Ibid.

p. 3-62, lines 11-19 This paragraph in the "Integration with a Focus on Asthma" section should include some discussion of the effect of NO2 to enhance the airways responses to inhaled allergen because this could be a mechanism by which asthmatic individuals develop exacerbations after exposure to high ambient levels.

p. 3-63, lines 28-29 I would delete the first sentence of this paragraph; it is an unnecessary distraction here. Cerebrovascular disease is discussed later.

p. 3-67, line 3 …a 4.2-ppb increase in NO2…

p. 3-67, lines 16-17 For clarity, I would modify this sentence as follows: "An effect of NO2 on hospitalization for IHD was observed only during the cold season (Jalaludin et al., 2006)."

p. 3-70, line 32 Should it be PAH here rather than PIH?

p. 3-72, line 5 …Barnett et al. (1997a) reported robust estimates…

p. 3-76, line 1 The citation here should be Rich et al., 2006b).

p. 3-76, line 7 There are two separate papers by the same team of investigators, but I do not think it is correct to say that this represents two separate analyses.

p. 3-76, lines 14-17 For clarity, this sentence should be revised as follows: "Rich et al. (2005, 2006b) examined associations between ambient pollution levels and PAF episodes as well as ventricular arrythmias." In addition, the Rich et al. (2006a) study of ventricular arrythmias in St. Louis is not actually discussed as the paragraph is currently written.

p. 3-79, lines 13-14 It is inappropriate to cite a German paper as a secondary reference regarding the leading causes of hospital admissions for CVD in the U.S in a U.S. federal agency document. Primary U.S. data should be cited.

p. 3-79, line 15 …ambient NO2 (Peters…

p. 3-79, line 18 I suggest this sentence be revised as follows: "A study of repolarization changes and air pollution in Germany…"

p. 3-86, Figure 3.3-2 I suggest that the figure legend be revised as follows: "Shape of the association of total mortality with NO2 over 6 days (lags 0 through 5) in the APHEA2 study summarized…"

p. 3-92, lines 13-14 For clarity, I suggest this sentence be revised as follows: "The combined estimate for total mortality was 0.8% (95% CI: 0.2, 1.5) per 20-ppb increase in the 24-h average NO2 from the single-pollutant models, and 0.4% (95% CI: -0.2, 1.1) per 20-ppb increase in the 24-h average from the multipollutant models."

p. 3-95, lines 5-6 I suggest this sentence be revised as follows: "Risk estimates for specific causes of death are useful in evaluating consistency of the association for causal inference."

p. 3-104, line 17 …new cells in the bronchioli are derived…

p. 3-111, line 19 In each community studied, NO2 was…

p. 3-112, lines 1-4 There is insufficient information in Figure 3.2-4 for the reader to understand how these graphs show a protective effects from better lung function regarding risk of new-onset asthma.

p. 3-113, Figure 3.4-2 The figure legend needs to include a better explanation of what the graphs actually show (i.e., that HR = hazard ratio for new-onset asthma and that the two letter abbreviations are for the 12 communities of the Children's Health Study and that these communities are arrayed by annual average of the pollutant shown on the X axis of each graph).

p. 3-116, Figure 3.4-3 I would add the following words to the figure legend: "…for two-pollutant models for the 12 communities of the Children's Health Study."

pp. 3-118-119 This integration section is problematic. The first paragraph discusses both respiratory illness in children associated with long-term exposure to NO2 in children and the decreased rate of growth in lung function observed in the Children's Health Study. The next six paragraphs then discuss the human and animal toxicological data on altered immune responses and lung defenses. The section then concludes with a paragraph on possible mechanisms by which chronic exposure to NO2 might affect lung growth. For greater clarity, I would suggest that the discussion of the epidemiologic and toxicologic evidence be treated separately for each of the two health outcomes (i.e., epi-tox for respiratory illness followed by epi-tox for decreased growth of lung function).

p. 3-118, lines 17-19 Because the Children's Health Study was a prospective study, multiple papers reporting the results of the longitudinal analysis of lung function at various time points during the course of the study were published. However, it is not correct to describe these results as "recent evidence from cohort *studies* from California." There was really only one cohort studied, albeit for a long follow-up period.

p. 3-120, line 29 Ibid.

p. 3-120, lines 12-16 This is a confusing sentence as written and needs to be revised for clarity.

pp. 3-149-150 This section on Nitric Acid does not include discussion of a relevant controlled human exposure study (Aris R, et al. Am Rev Respir Dis 1993; 148:965-973).

3-151, Table 3.2-1 I would add the following to the first proposed mechanism under the Lower Airways, Allergens category: "…and ↑ epithelial permeability"

p. 3-156, Tables 3.4-1 and 3.4-2 The Titles for both of these tables should include "in the Children's Health Study"

Comments from Dr. Ellis Cowling

Very General Comments on these NAAQS Review Processes

Before dealing with the details of my specific assignment during the September 24, 2007 Peer Review of the *Integrated Science Assessment for Oxides of Nitrogen*, I would like to offer the following very general comments about these periodic NAQQS Review processes – and thus our responsibilities during Peer Reviews of *Integrated Science Assessment documents* in general.

In a May 12 2006 summary letter to Administrator Johnson, CASAC Chair, Dr. Rogene Henderson, provided the following statement of purpose for these periodic NAAQS review processes.

> "CASAC understands the goal of the NAAQS review process is to answer a critical scientific question: *"What evidence has been developed since the last review to indicate if the current primary and/or secondary NAAQS need to be revised or if an alternative level or form of these standards is needed to protect public health and/or public welfare?"*

During the past 18 months, CASAC has participated in reviews of three of the existing six criteria pollutants – particulate matter, ozone, and lead. CASAC has also joined with senior EPA administrators in a "top-to-bottom review" and the resulting recently-completed revision of the NAAQS review processes. These two experiences have led to a seemingly slight but important need for rephrasing and refocusing of this very important "critical scientific question:"

> *"What scientific evidence and/or scientific insights have been developed since the last review to indicate if the current public-health based and/or the current public-welfare based NAAQS need to be revised or if alternative levels, indicators, statistical forms, or averaging times of these standards are needed to protect public health with an adequate margin of safety and to protect public welfare?"*

With this rephrasing held carefully in mind, I offer the following general comment with regard to one very important part of my assigned Charge Question on Air Quality aspects of the ISA for Oxides of Nitrogen:

What is the major "pollutant of concern" in the case of the public-health-based standard for "oxides of nitrogen?"

It appears (but is not stated clearly anywhere that I can find in Chapter 2 or any other part of this ISA) why nitrogen dioxide (NO_2) was chosen by the USEPA as the "indicator" of choice in the case of the NAAQS for "oxides of nitrogen." Much attention is given in both Chapters 1 and 2, as well as other chapters in this ISA, to the many different oxidized forms of nitrogen (including nitric and nitrous acids, nitrites, nitrates,

nitrosamines and other carcinogenic and potentially carcinogenic derivatives of oxides of nitrogen, as well as NO, NOx, NOy, and NOz) that have been shown to have significant effects on public health. But the specific rational for choosing NO_2 among all these different oxides of nitrogen as the "indicator" of choice for a National Ambient Air Quality Standard is not described in this *Integrated Science Assessment for Oxides of Nitrogen*. The present ISA does include some discussion of using NO_y rather than NO_2 as the "indicator" for oxides of nitrogen -- See especially the "Key Fingings" statements on lines 17 and 18 on page 5-3 and lines 9-16 on page 5-4.

My Assignment in this Peer Review for Oxides of Nitrogen

My specific assignment in preparation for the October 24, 2007 CASAC Peer Review of EPA's First (August 2007) External Review Draft of the *Integrated Science Assessment for Oxides of Nitrogen* is the first Charge Question asked by Mary Ross in her transmittal note to Fred Butterfield on August 31, 2007:

> 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?

These topics are covered in detail mainly in Chapter 2 and in summary form in the "Atmospheric Sciences" part (section 5.2) in Chapter 5. I found the brief summary in chapter 5 much more clear and relevant to the existing primary standard than the much more detailed information contained in Chapter 2.

Chapter 2 is filled with detailed analyses of specific topics that are relevant to indoor and outdoor exposures, to personal vs community exposures, to the strengths and limitations of monitoring instruments for oxides of nitrogen, and analyses of the strengths and limitations of specific health-effects research studies on nitrogen oxides in this country and abroad. But there is not a single place in all 67 pages of Chapter 2 where this large body of information is discussed in the context of the existing primary NAAQS standard for oxides of nitrogen!

In fact, I could find only eight places in this ISA document where the existing primary standard is mentioned – in the Preface on pages iv and v, on line 17 on page 1-2 of the Introduction, and on lines 11 and 12 on page 5.3, lines 7-9 on page 5.8, lines 10-12 on page 5-11, lines 17-18 on page 5-12, and lines 21-24 on page 5-14 in Chapter 5.

I was pleased, however, to find a carefully annotated presentation of the "*History of Review of the Primary NAAQS for* NO2" on pages iv and v of the Preface. But even here there was no discussion of the rational behind the original (1971) selection of NO_2 as the "indicator" of choice for "oxides of nitrogen."

It was also surprising to find that the last sentence in the Preface is the only place in this ISA document in which all four essential parts of a National Ambient Air Quality Standard – level, indicator, statistical form, and averaging time – are discussed – and then

only in the context of the identical primary (public health based) and secondary (public welfare based) standards that were established in 1971 and have never been changed since that time. The staff and administrator of the USEPA in 1971 must have been very wise indeed to have created identical primary and secondary standards for oxides of nitrogen that did not require any science-based or other modification during the past 36 years!

More specific Comments and Suggestions for Improvement of Chapter 2

Title of the Chapter:
"Chapter 2 highlights key concepts or issues relevant to understanding the atmospheric chemistry, sources, exposure and dosimetry of oxides of nitrogen, following a "source to dose" paradigm." The idea of dealing with atmospheric chemistry all the way from emissions sources to dosimetry in the lung is a good one; but titling the chapter "Source to Tissue Dose" is a little too "cute" to be taken seriously. In my opinion, "Chemistry and Dosimetry of Nitrogen Oxides" would be better as a title for this important chapter.

Organization within Chapter 2
Distributing all the Figures within the text so that the text descriptions of the figures is near the figures themselves is a good one, but the distributing all the tables to the end of Chapter 2 makes reading and checking back and for the between text descriptions and the important data and information in the tables very tedious, time consuming, and needlessly challenging. I got lost more often than I succeeded in finding my way through the information contained in most parts of chapter 2.

Design and Content of Figure and Table Captions
In my opinion, every figure and table in an Integrated Science Assessment document -- that is clearly to be used for policy purposes -- should "stand alone" to the maximum extent possible and not be any more dependent on descriptions in the text than absolutely necessary for understanding by the reader.

Some specific examples of these difficulties that lead to confusion, lack of clarity, or, worse yet, communication of disinformation include the following:

The caption for Figure 2.2-1 implies incorrectly that the "reactive nitrogen species" in the atmosphere include only oxidized forms of nitrogen and do not include any reduced forms of nitrogen. In fact, the total amount of ammonia emissions from animal agriculture on both a global scale and a national scale are considerably larger than the total emissions of nitrogen oxides from all the power plants on these same scales! See paper by Galloway et al in AMBIO 31(2):63-71.

The caption for Figure 2.4-2 contains no units of measurement for any of the three different panels in this complex figure. The data displayed in this figure are much too important to require that readers must see the "text in Annex Section nAX2.9 for details."

The data in Table 2.5-1 is simply impossible to understand without reading and rereading lines 25-32 on page 2-17 and lines 1-31 on page 2-18.

Neither the text on lines 10-22 on page 2-19 nor the caption for Figure 2.5-2 make clear whether the data displayed in this figure are from the South Bronx, New York City, or a wide variety of urban areas throughout the state of New York. It also would be very helpful to know for sure what averaging time was used in calculating and plotting the data shown in this figure and to show the present NAAQS standard in this same figure.

I recommend that essentially every figure and table (and the corresponding text descriptions) in Chapter 2 be revised to conform to the principal that all figures and tables should "stand alone" to the maximum extent possible. This principal will greatly facilitate comprehension by readers and facilitate the accumulation of carefully crafted statements of scientific findings as was accomplished to a very useful extent in Chapter 5 of this ISA for oxides of nitrogen.

Inclusion of carefully crafted Statements of Findings and Conclusion in Chapter 2

My understanding of much of the useful information contained in Chapter 2 was increased substantially after reading the nine "Key Findings" listed on lines 10 through 31 on page 5-2 and on lines 1-18 on page 5-3.

In reading these nine "Key Findings" statements listed in the Atmospheric Chemistry part (section 5.2) in Chapter 5, however, I was surprised and disappointed to recognize that all nine of these "Key Findings" were relevant to "measuring nitrogen oxides" and that there were no statements of "Key Findings" that were relevant to the other major topics covered in Chapter 2: including indoor and outdoor exposures, personal vs community exposures, and analyses of the strengths and limitations of specific health-effects research studies on nitrogen oxides in this country and abroad.

Please note that the "Key Findings" outlined on lines 11-13 on page 5-3, lines 7-9 on page 5-8, lines 10-12 on page 5-11, lines 17-18 on page 5-12, and lines 21-14 on page 5-14 are the only places I can find in this ISA where conclusions are reached that are relevant to the adequacy or inadequacy of the existing primary standard for health effects of oxides of nitrogen. Maybe these six statements are sufficient to provide a scientific foundation for evaluation of the adequacy or inadequacy of the existing health-based standard for oxides of nitrogen. It is not clear to me, however, if these relatively few conclusionary statements cover all the bases that base that are necessary for final decisions by Administrator Johnson. Thus I look forward to the further discussions we will have on Octiber 24 and 25 during this peer review of the First External Review Draft Integrated Science Assessment for the health-based NAAQS for oxides of nitrogen.

For this reason and many others, I call attention once again to the attached "*Guideline for Formulation of Statements of Scientific Findings to be Used for Policy Purposes.*" These guidelines were developed and published in 1991 by the Oversight Review Board for the National Acid Precipitation Assessment Program. These guidelines will also be very useful as we examine all 47 of the "Key Findings" statements presented in Chapter 5.

GUIDELINES FOR FORMULATION OF SCIENTIFIC FINDINGS TO BE USED FOR POLICY PURPOSES

The following guidelines in the form of checklist questions were developed by the NAPAP Oversight Review Board to assist scientists in formulating presentations of research results to be used in policy decision processes.

1) **IS THE STATEMENT SOUND?** Have the central issues been clearly identified? Does each statement contain the distilled essence of present scientific and technical understanding of the phenomenon or process to which it applies? Is the statement consistent with all relevant evidence – evidence developed either through NAPAP research or through analysis of research conducted outside of NAPAP? Is the statement contradicted by any important evidence developed through research inside or outside of NAPAP? Have apparent contradictions or interpretations of available evidence been considered in formulating the statement of principal findings?

2) **IS THE STATEMENT DIRECTIONAL AND, WHERE APPROPRIATE, QUANTITATIVE?** Does the statement correctly quantify both the direction and magnitude of trends and relationships in the phenomenon or process to which the statement is relevant? When possible, is a range of uncertainty given for each quantitative result? Have various sources of uncertainty been identified and quantified, for example, does the statement include or acknowledge errors in actual measurements, standard errors of estimate, possible biases in the availability of data, extrapolation of results beyond the mathematical, geographical, or temporal relevancy of available information, etc. In short, are there numbers in the statement? Are the numbers correct? Are the numbers relevant to the general meaning of the statement?

3) **IS THE DEGREE OF CERTAINTY OR UNCERTAINTY OF THE STATEMENT INDICATED CLEARLY?** Have appropriate statistical tests been applied to the data used in drawing the conclusion set forth in the statement? If the statement is based on a mathematical or novel conceptual model, has the model or concept been validated? Does the statement describe the model or concept on which it is based and the degree of validity of that model or concept?

4) **IS THE STATEMENT CORRECT WITHOUT QUALIFICATION?** Are there limitations of time, space, or other special circumstances in which the statement is true? If the statement is true only in some circumstances, are these limitations described adequately and briefly?

5) **IS THE STATEMENT CLEAR AND UNAMBIGUOUS?** Are the words and phrases used in the statement understandable by the decision makers of our society? Is the statement free of specialized jargon? Will too many people misunderstand its meaning?

6) **IS THE STATEMENT AS CONCISE AS IT CAN BE MADE WITHOUT RISK OF MISUNDERSTANDING?** Are there any excess words, phrases, or ideas in the statement which are not necessary to communicate the meaning of the statement? Are there so many caveats in the statement that the statement itself is trivial, confusing, or ambiguous?

7) **IS THE STATEMENT FREE OF SCIENTIFIC OR OTHER BIASES OR IMPLICATIONS OF SOCIETAL VALUE JUDGMENTS?** Is the statement free of influence by specific schools of scientific thought? Is the statement also free of words, phrases, or concepts that have political, economic, ideological, religious, moral, or other personal-, agency-, or organization-specific values, overtones, or implications? Does the choice of how the statement is expressed rather than its specific words suggest underlying biases or value judgments? Is the tone impartial and free of special pleading? If societal value judgments have been discussed, have these judgments been identified as such and described both clearly and objectively?

8) **HAVE SOCIETAL IMPLICATIONS BEEN DESCRIBED OBJECTIVELY?** Consideration of alternative courses of action and their consequences inherently involves judgments of their feasibility and the importance of effects. For this reason, it is important to ask if a reasonable range of alternative policies or courses of action have been evaluated? Have societal implications of alternative courses of action been stated in the following general form?:

"If this [particular option] were adopted then that [particular outcome] would be expected."

9) **HAVE THE PROFESSIONAL BIASES OF AUTHORS AND REVIEWERS BEEN DESCRIBED OPENLY?** Acknowledgment of potential sources of bias is important so that readers can judge for themselves the credibility of reports and assessments.

Two Additional General Concerns

As an ecologist, who is aware of the many different and important adverse public-welfare effects of both oxidized and reduced forms of reactive nitrogen, I was pleased to find that Annex 2 is described on page 1-6 of the Introduction to this ISA as containing "evidence related to the physical and chemical processes controlling the production, destruction, and levels of reactive nitrogen compounds in the atmosphere, including both oxidized and reduced species."

When I looked through Annex 2, however, I was glad to see that this Annex does indeed deal with both gaseous and particulate matter forms of ammonia and ammonium ion and their short and long-distance transport.

But it was also disappointing to find that there was little or no discussion in Annex 2 about the important adverse effects of both reduced and oxidized forms of reactive nitrogen on visibility in urban, rural, and wilderness areas, on the productivity and stability of aquatic and terrestrial ecosystems in lakes, streams, fields, forests, and coastal regions of this country.

Many of us in the ecological community continue to believe that the US and other developed countries of the world need to consider the establishment of an integrated total reactive nitrogen approach in air-quality management. Such an integrated total nitrogen idea was considered in a 1997 EPA report titled "Nitrogen Oxides: Impacts on Public Health and the Environment." This document was prepared by a team of scientists and engineers led by Doug Grano in EPA's Office of Air and Radiation. Such an integrated approach was also recommended in a more recent review paper titled "Optimizing air quality management in Europe and North America: Justification for integrated management of both oxidized and reduced forms of nitrogen" by Cowling et al (Environmental Pollution 102 S1 (1998) 599-608).

Such an Integrated Total Reactive Nitrogen approach in air quality management ideally will include both reduced and organic as well as oxidized forms of reactive nitrogen and would be aimed at decreasing adverse effects on both public welfare and public health. These ideas are also currently under study by an Integrated Nitrogen Committee established within EPA's Science Advisory Board in 2006 under the leadership of Dr. James Galloway of the University of Virginia and with additional advice and counsel from me as a CASAC-liaison representative.

Comments from Dr. Douglas Crawford Brown

Comments on Chapter 5: The Integrated Science Assessment for Oxides of Nitrogen: Health Criteria

Doug Crawford-Brown

My comments here focus largely on Chapter 5: Findings and Conclusions, although material from other chapters used to form the conclusions in Chapter 5 will be mentioned as needed. These comments should be paired with those of Dale Hattis, who is charged with reviewing the same chapter.

The charge question concerns the "adequacy of this first external review draft ISA to provide support for future risk, exposure and policy assessments". As a broad statement, I will begin by noting that Chapter 5 could not be used as the basis for a risk assessment on oxides of nitrogen. It is a largely qualitative discussion of, and summary of, the findings in the earlier chapters. It does draw the conclusions that U.S. populations are currently exposed to NOx concentrations both above and below the existing NAAQS; that there are adverse health effects associated with short term exposures both above and below the existing NAAQS, and adverse health effects associated with long term exposures at levels slightly above the existing NAAQS; that the exposure-response relationship is approximately linear with no evident threshold for effect; and that NOx produces both direct adverse effects and probably makes individuals susceptible to the effects of other pollutants and to exposure to microbes such as viruses. In each of these conclusions, Chapter 5 represents an accurate summary of the information provided in the earlier chapters.

The authors have adopted a scale of causality from "inconclusive" to "suggestive" to "likely causal". This was helpful throughout the chapter. It was a good way to summarize the strength of the conclusions for both short and long term exposures. The one caveat I would place on my support for this system is the curious omission of the judgment "demonstrates (weakly or strongly) that there is NO adverse effect". This is a problem throughout the chapter, and remains a weakness of EPA risk assessment methodologies (especially the Hazard Identification stage). The current chapter follows an EPA tendency to present the evidence as if one were building a legal case in which evidence FOR a belief is what matters most. Throughout the chapter, and throughout the report, there is a focus on the studies that are suggestive of an adverse effect, with the conflicting studies providing a kind of counter-evidence that lowers a judgment from "likely causal" down to "suggestive" or down to "inconclusive". What is needed instead is a methodology that examines ALL studies, supportive and counter-supportive; considers the potentially conflicting findings from these studies; weighs these findings systematically by trying to determine why there are conflicting results; and then yields a final judgment of causality that reflects this full range. I realize the authors probably feel they did that, but it is not evident in the report. If this were done, there would naturally be the fourth category of judgment I mentioned: the judgment that existing evidence suggests that there is in fact no adverse effect (and yes, I do realize the issue of proving a negative!).

To be useful in a quantitative risk assessment, the EPA needs to develop some sort of system of describing – for epidemiological, clinical and animal studies – the Minimum Detection Limit and Minimum Quantitation Limit for a study. This could be based on some sort of power calculation. If the chapter is intended only as a kind of Hazard Identification, then it is useful to know whether a study that finds no effect would have detected any effects at some level of odds ratio (i.e. could it have found an effect with an odds ratio of 2 if one had been present?). But if Chapter 5 is to be used for quantitative risk assessment, one needs information on the minimal effects level (minimal odds ratio) that could be quantified from the study. This MQL is always above the MDL, and often quite far above the MDL.

There are some places in the chapter in which the terminology is poor, or perhaps some part of the text is missing. Instances are:

- On page 5-10, line 15, the statement is that effects estimates ranged from "0.5 to 3.6% excess risk". More context is needed here. The statement should be that this level of excess risk is the difference between exposure at X and Y, but X and Y are not provided. And it is not clear whether this is a relative or absolute risk model (i.e. whether a person has a 0.5 to 3.6% risk of developing the effect above and beyond the background probability of effect - an absolute risk model -, or whether this percentage is to be multiplied by the natural incidence to obtain the probability of effect - a relative risk model.

- On page 5-20, the final bullet needs to be reworked. There is something missing on line 27. In addition, the authors state that the "range of mortality risk estimates is smaller", but no insight is given as to what is meant by a "mortality risk estimate". Is this referring to some sort of slope factor?

- On page 5-11, line 6, the authors state that "results were similar for boys compared to girls" without stating WHICH results (perhaps they mean ALL results?).

- On page 5-12, line 25, the authors are considering the issue of linearity in exposure-response, and include a reason based in the "additivity of pollutant-induced effects to the naturally occurring background disease processes". Even if the pollutant-induced effects are additive, this does not imply that the curve will be linear. It is possible for the effect to be additive and yet non-linear if the modes of action are not the same.

- On page 5-13, line 2, the authors state that "effects are weaker at low concentrations". They don't state what they mean by "weaker". Weaker in the sense that the effect in a diseased individual is not as pronounced? Weaker in the sense of a more shallow exposure-response curve?

- On page 5-14, lines 10-12, the authors suggest there is an adverse effect related to a shift towards greater sensitivity to illness. While I agree that the data on NOx make this a reasonable possibility, this chapter provides no evidence to support that claim.

This raises for a me a more general critique of the chapter. All conclusions drawn in the chapter should reference the findings in earlier chapters, and explain why the BODY of evidence (both supporting and counter to the conclusion) presented in those chapters leads on balance to the claim being made. As currently written, readers are left to their own devices to determine which results from previous chapters are being invoked, and to determine how the often conflicting results are being reconciled or weighted. A typically vague example is on page 5-14, lines 24-25, in which the authors state "These conclusions are supported by evidence from toxicological and controlled human exposure studies". This is a much too subjective approach to forming conclusions, especially because there is no way for a reader to determine the basis for the claim and, therefore, to find any points around which a discussion might begin. The reader is left with nothing other than a claim rooted in some unknown reasoning process, or emotive process, in the writer, and some unknown body of actual data presented in earlier chapters.

This then brings me to the largest issue with the chapter, which is related to the charge question. This chapter is intended to "provide support for future risk, exposure and policy assessments". I can see no way in which it can serve in that role. The conclusions drawn in the chapter are too qualitative to form the basis for a risk assessment. The chapter doesn't provide any guidance or insights into the existing ambient levels of NOx for the exposed populations. It does not provide a summary exposure-response relationship, other than to suggest it is linear. It correctly identifies the sensitive subpopulations, but does not express this increased sensitivity quantitatively. It would not be possible to use this chapter as a basis for any sort of quantitative risk assessments or benefits assessment.

And even if the goal is only to assist in setting a safe exposure limit, or establishing the form, etc for a NAAQS, rather than calculating actual risks and benefits, the chapter falls short. There is no way to use the results in the chapter to determine where there is a NOAEL or LOAEL, or where the probability of adverse effect drops below any target level of risk. The authors conclude (on page 5-15) with the statement that "it is plausible, consistent and coherent that current ambient NO2 exposures directly result in adverse impacts to public health below the current NAAQS for NO2", but there is no systematic support for even this qualitative claim (although I personally agree with the claim).

Overall, I don't feel this chapter is adequate "to provide support for future risk, exposure and policy assessments".

Comments from Dr. Terry Gordon

Comments from Terry Gordon

Major Comments:

There is a chapter-to-chapter difference in the level of detail and integration provided to the reader. For example, the title of Chapter 3 states "Integrated" but there are several sections, particularly in the animal toxicology studies, where the text does not integrate the science but reports on individual studies in too much detail. This is a key chapter and should have better balance between providing the details of essential data/studies and the overall integration.

Minor Comments:

Chapter 2

Figure 2.2-2 – ppbv or pptv?
page 2-17 – Why are tables at the end of each chapter and the figures are inserted where appropriate in the text?
page 2-23, line 10-12 – Does this sentence apply to NOx? Similarly, the rest of the para provided more info on other pollutants than it does on NOx without integrating how these confounding pollutants should be considered.
page 2-24, lines 11-12 – Because all of this data on NO3 is modeling data (i.e., not real data), does the conclusion that NO3, in ppt, "may be meaningful confounders"?
pages 2-24, lines 23 and on – This entire section presents a lot of chemistry w/o much 'scientific assessement'.
page 2-30, lines 6-18 – After stating that more weight would be given to North American studies, and referencing a ton of literature in the previous para, why was this one European study discussed in detail? The same comment applies to the second para on page 2-31.
page 2-38 – Why is this a separate subtitle when it's almost identical to 2.5.3.2? Also, lines 18-32 and some of the next page don't appear to provide correlations as stated in the subtitle.

Chapter 3

page 3-1, line 11 – Is the discussion of studies at 5 ppm NOx warranted?
page 3-4, lines 15-30 – This section is redundant and described again on pages 3-7 and 3-8.
page 3-5, lines 28-29 – These first 2 sentences are confusing. First it states the evidence is "coherent" and then it states it "lacks consistency and robustness".
page 3-6, line 1 – The Pilotto study (2004) is referenced but no description of it is given previous to this mention.
page 3-6, line 8 – Why is this subtitle different or even used? The same words are used in the sentence in line 10, page 3-4. Combine?

page 3-6, lines 10-17 – The authors should consider cutting the Goings study in a final 'integrated science assessment' if the findings were "inconclusive"?
page 3-6, lines 21 and on – As mentioned above in the Major Comments, this paragraph provides too much detail for an 'integrated' chapter. Maybe it should be cut and summarized/referenced as is nicely done in the following paragraph.
page 3-7, lines 21 and on – Some of this work was already described (same comment for top of page 3-8).
page 3-8 – Starting here, there are too many study details and not enough integration. Also, many pre-1993 studies are described rather than referencing the 1993 CD as done in other sections/chapters.
page 3-14, line 9 – 20 ppm NO2?
page 3-16, lines 20-28 – As in the animal tox section, there is too much detail in describing this study, whereas the last couple sentences give an excellent assessment.
Figure 3.2-1 – Is this figure important enough for inclusion?
Figure 3.2-2 – Possible typo: should it be ppb on the Y-axis?
page 3-19, lines 1-5 – Too much detail for a study for which "quantitative results not provided".
page 3-20, lines 11-13 – Unclear: No change in spirometry but a change in airway resistance? Some labs measure airway resistance by what they consider 'spirometry'.
page 3-21, lines 5-7 – Redundant
page 3-21, lines 10 and on – Integrate and shorten?
page 3-22 – The summary is very good and more of this integration should be used in this chapter.
Figure 3.2-5 – The legend need to be rewritten to clarify the figure.
Figure 3.2-7 – The boxed legend in the graph (giving ages) is not described in the legend text.
page 3-32, line 8 – Unclear as to how a significant association could exist if the 95% CI of ln(CC16) was 0.1 to 18.3.
page 3-38 – Here is an example of the kind of excellent level of integrated text that should be used throughout this Chapter.
page 3-51, line 19 – Add 'of' after addition?
Figure 3.2-9 – Describe gray boxes in this and the following figure.
Figure 3.2-11 – The boxed legend doesn't match the legend text (authors vs. city/country).
page 3-61, line 2 – what is 'attache'?
page 3-61, line 16 – Are the NO2 effects on macrophages 'especially relevant' at 1 ppm?
page 3-61, line 26 – Cut 'strong' as the animal effects are typically at much higher concentrations.
page 3-62, lines 12-15 – Slightly confusing to say airway responsiveness is most sensitive response at 0.2 to 0.5 ppm and then say other studies found nothing up to 4 ppm.
page 3-62, line15 – Be more specific on what is meant by lung function – in some ways airway responsiveness describes the function of the lung.
page 3-67, line 5 – delete 'been'.
page 3-70, line 2 – 95% CI for the OR of 1.08?
page 3-75, lines 14-26 – condense
page 3-78, line 7 – Please reference these 'subsequent studies'.

page 3-79, line 15 – ‘exposure to ambient’…. what?
page 3-80, lines 28-32 – Switch the order of the first 2 sentences?
page 3-97 – Why the different sub-headings (e.g., Confounding)?
Figure 3.4-1 – Figure legend text: ‘average’ is daily or hourly or yearly?
page 3-106, line 29 – 10 to 20 ppm data? too much detail; same goes for Barth studies on next page.
page 3-108, lines 3-26 – Why not summarize from 1993 CD? same for page 3-110.
page 3-121, line 17 – 2.0 plus or minus?
page 3-124 – If 0.05 ppm was a LOAEL for NO2 in this unreferenced study (lines 23-31), this should be described more clearly here and elsewhere as to its importance. Similarly, an increase in post-implantation lethality at 0.5 ppm should be discussed. Neither of these findings are mentioned in the Integration section on pages 3-125-126.
page 3-145, lines 23-27 – An ‘older’ 10 ppm study like this could be cut unless this is a relevant concentration for NO.

Chapter 4

page 4-9, line 4-5 – PCR and time are too much detail.
page 4-9, line 25 – typo: suggestive?
page 4-11 – This is a good summary but why are the next 2 or 3 subheadings included yet not related directly to interpreting the data for NOx?

Chapter 5

page 5-4, lines 14-15 – Is this sentence comparing ambient to ambient?
page 5-6, lines 4-5 – Unclear.
page 5-8, lines 19-28 – These 2 paragraphs/bullets seem to contradict each other. The first says “Few recent epidemiological evaluations…” and the second section says “provide key support…”
page 5-14, lines 10-12 – I understand what this is saying if I read it enough times, but it should be made more clear.

Comments from Dr. Dale Hattis

Comments on the ISA

Charge Question 2: Ref p. 2-19, lines 15-22. It is important for eventual risk assessments that may be based on absolute measurement data (e.g. the data from the Australian intervention study) to characterize not just that there is a verticle bias in NO2 concentrations measured at regulatory montiors, and how large it is on average with height, but the distributional aspects of how much correction is needed to convert the distribution of concentrations measured at existing monitor heights to concentrations that would approximate breathing level concentrations. This can only be done by combining information about how many sampling stations are at what height with data on the verticle gradients. Ideally there should also be information on the relationship between the slope of the verticle gradient in concentrations and the absolute level of NO2 measured at the monitoring station.

In cases where the health concentration-response data are implicitly based on measurements at monitoring stations with the same height distribution as those used for exposure analysis, such a correction may not be needed, as a general matter, but it is still important to keep track of the biases that may exist in the determination of exposures in different studies used for the concentration-response analysis and ultimate projection of the likely incidences of different types of adverse health effects.

Charge Question 3: Ref p. 2-22, lines 9-10. It is not technically correct that "shorter term average concentrations tend to be much higher than longer-term averages". Real averages—arithmetic means—must be the same independent of averaging time. What is true is that higher percentile values—e.g. 90^{th} or 99^{th} percentiles, will tend to be higher for shorter averaging times because of regression to the mean effects.

Charge Question 4: As a general matter the integrated analyses do a reasonable job of bringing together relevant data sets of the same kind, but do not do enough to draw key conclusions from the available data on the forms and magnitude of concentration response for different endpoints, associated uncertainties, and the need for correction of individual data sets for the vertical bias in between regulatory monitors and breathing zone concentrations in assessing exposure levels.

Charge Question 8: I think the authors of the ISA have generally done a good job in analyzing information within specific data types and showing the comparisons and contrasts between studies of the same endpoints. What they have not generally done is to provide overall uncertainty weighted quantitative conclusions that reflect the combined implications of all reasonably decent studies for specific adverse effects. They have not come to definite quantitative conclusions about the extent of interindividual variability in susceptibility among different people within and among different putatively susceptible subgroups, and they have not done quantitative evaluations of the uncertainty in overall measures of relative potency for causing effects of different types and severities. Shapes

of dose response relationships have generally not been subject to critical statistical analyses informed by mechanistic theories of likely relevant causal mechanisms.

In my reading of the ISA I came across one example of an apparent missed opportunity to do the kind of reanalysis that can shed light on implications for the forms of dose response relationships. Figure 2.7-3 on page 2-47 shows plots of data of van Strien et al. (2004) on confounder-adjusted relative risks of persistent cough and shortness of breath in relation to quartiles of NO2 concentrations for a large number of infants (762) in the first year of life. Plotting by quartiles where, as is usual, exposures are approximately lognormally distributed, implicitly introduces a log transformation into the dose scale that is known to give rise to an impression of threshold like behavior, even for dose response relationships that are in fact linear when plotted with an untransformed x-axis. I therefore first did a lognormal probability plot of the quartile data and found that, as is usual, the exposures appear to be reasonably well described as lognormal, as indicated by the adherence of the points in Figure 1 (next page) to the straight regression line. Using the lognormal distribution of individual exposures derived in Figure 1, I then calculated mean levels of NO2 within each of the quartile groups and replotted the relationships with a linear x axes (Figure 2). It can be seen that, viewed in this way, the suggested form of the relationship for shortness of breath appears to have a saturation-like convex shape; and the relationship for persistent cough may well be similar.

Figure 1

Lognormal Plot of the Distribution of Exposures of First Year Infants in the Study of van Strien et al. (2004)

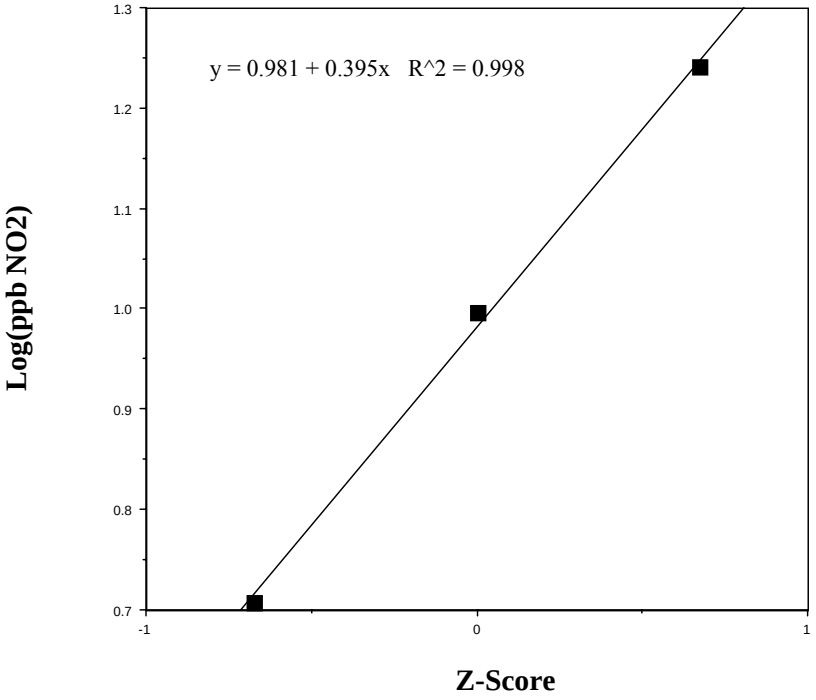
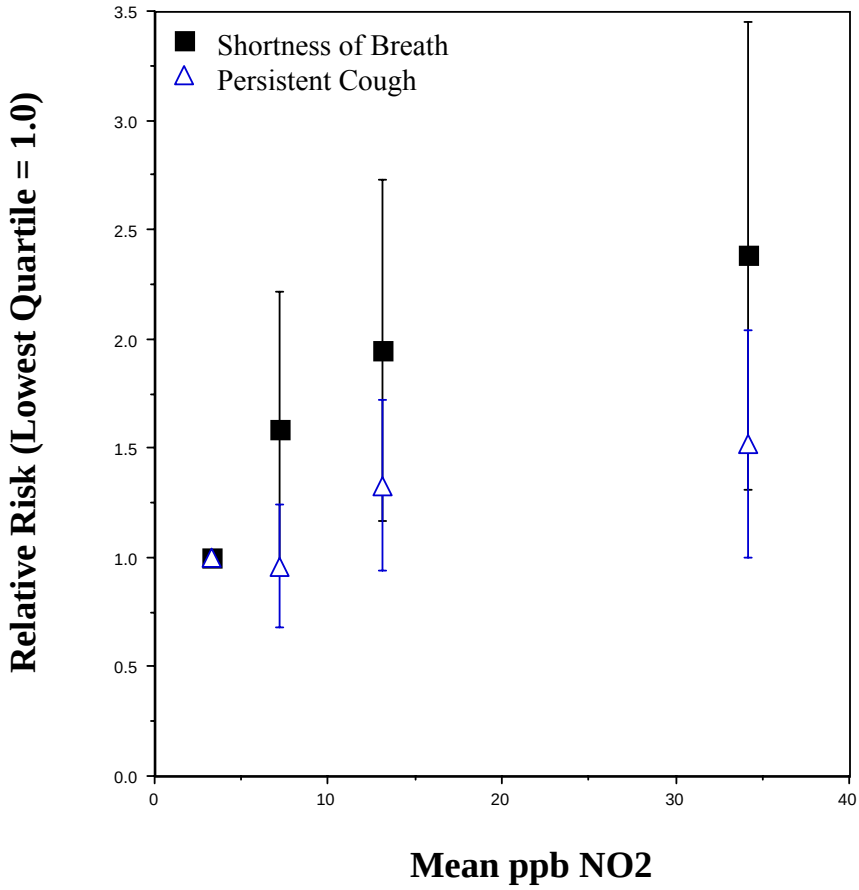
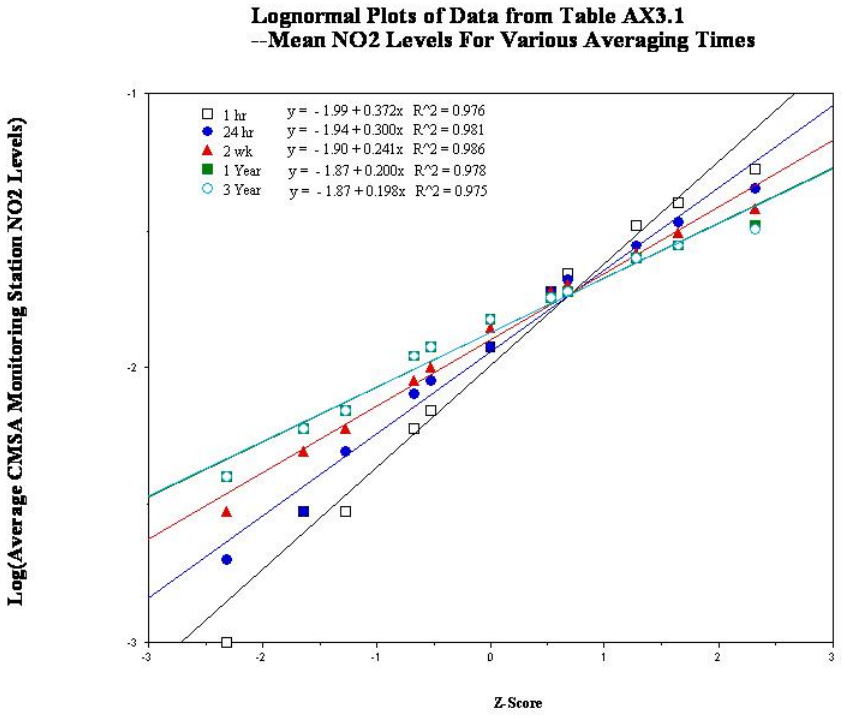


Figure 2
Replot of the Concentration Response Data of van Strien et al (2004) On Linear Axes Based on Estimates of Mean Concentrations for the Four Quartile Groups



I have done log probability plots (see Figure 3) analyzing the amount of lognormal variability for different averaging times, based on the data from a particular table in Annex 3.

Figure 3



Comments from Dr. Donna Kenski

Review of Integrated Science Assessment for Oxides of Nitrogen – Health Criteria
Donna Kenski
October 19, 2007

Charge question 2: *Are the properties of ambient oxides of nitrogen appropriately characterized, including policy-relevant background, spatial and temporal patterns, and relationships between ambient oxides of nitrogen and human exposure? (Sec. 2.5)*

One overarching observation: A huge amount of research is gathered and described in this document and that is commendable. But the integration of that research is sorely lacking synthesis. It seems that no significant attempt has been made to summarize and pull common threads from the many studies. Rather, the authors have been much too careful to keep any semblance of interpretation out of this document, especially in Chapter 2, making it difficult for readers/reviewers to pull all the pieces together into a coherent picture.

Section 2.2: Needs to discuss the relative importance of the various NOz species, at least by giving average concentration data where available. More discussion of the formation of particle nitrate and removal mechanisms would be helpful. The information on NOz species concentrations given in AX3.2 should be summarized in a table or figure and included here.

Sections 2.3-2.4: Since our ability to find health effects due to NO2 depends partly on accurate measurements, this section should be much more comprehensive in describing and quantifying the accuracy of the FRM and the degree of interference from various NOz species. The single paragraph on interference on p.2-8 is not adequate. Again, it could be more useful if this information were summarized graphically, including the diurnal differences in interferences. The document seems to be of two minds on measurements – in some instances leaning toward NOy measurements as somehow better than the current NOx, and in some instances implying that more specific NO2 measurements are to be preferred. At some point the two should be explicitly compared to the FRM and the merits of each measurement approach noted for various applications (epi studies, atmospheric chemistry, etc.). Both NOy and 'true' NO2 are useful measurements in certain situations, but it is not clear to me whether a change in the FRM is being encouraged, or whether there is any need for such a change. In addition, the challenges of making both of these measurements are significantly underestimated in this document, particularly in the context of a state or local agency being asked to undertake them.

Section 2.4.1 is woefully lacking adequate information on US NO2 concentrations. At the very least this section needs to include a map of the distribution of sites (instead of stashing it in the Annex) and visually make the point that there just aren't very many NO2 sites providing data for health studies or NAAQS comparisons. A brief discussion and enumeration of the number of sites by type (i.e., roadside monitors, population-

oriented, point-source-oriented, suburban, urban, etc) should be here. Figure 2.4-1 is helpful, but it should be accompanied by similar figures showing diurnal, day-of-week, and seasonal variation in NO2. Most of these are already in the Annex AX3.2 and in Section 2.5.3.2. The discussion of spatial variability from Sec. 2.5.2.2 should be moved here, and expanded to include a discussion of the extreme gradients in NOx found near roadways. The vertical variability section 2.5.2.2.2 should include some information about the monitoring probe heights in the current network – how many are at 4 m vs 15 m? How significant might the bias be when estimating human exposures?

Section 2.4.2 is generally adequate in describing background concentrations. The caption for Fig. 2.4-2 should be concentrations in pptv, rather than ppbv.

Section 2.5 needs some reorganizing, as mentioned above. The variables in Eqns 2.5-1 thru 2.5-5 need to be defined immediately, not as they are now, 13 pages later in section 2.5.2.3.3.

Section 2.5.2.3 needs a summary. Throughout Chapter 2, summaries were used only sporadically. At least each major subsection should incorporate a 1-2 paragraph summary. On page 2-30, the summary paragraph (together with the one that follows) seem like they were written for the section 2.5.2 as a whole, and should be moved to the end.

The description of diurnal cycles of NO2 and its link to motor vehicle emissions belongs in Sec. 2.4.

The ISA needs a section devoted to a discussion of confounding. I'm not sure where this should go – probably in Chapter 2. Section 2.5.3 seems like it was intended to cover this but doesn't quite accomplish that goal. Similarly, Annex section AX3.6 ostensibly discusses confounding but almost exclusively by describing correlations among copollutants. Rather than just summarizing these correlations, a more thoughtful discussion of the impacts of confounding would be useful. Implications and estimates of impacts from confounding are mentioned in Chapter 3 in part of the discussion of individual summaries, but again not treated comprehensively.

Chapter 3; Much better presentation and summarization of studies than Chap 2. Figures are very helpful. Summaries at the end of each subsection were careful, fair, and thoughtful. This chapter was impressively comprehensive – perhaps a bit too long or too comprehensive? More reliance on figures and less discussion of individual studies would make it more manageable.

Chapter 4: The last half of this chapter had a lot of typos and grammatical errors and needs a careful proofreading. The section on traffic exposure seems more suited to discussion in Chapter 2.

Chapter 5: Conclusions in section 5.2 seem to be advocating a move to NOy rather than NOx. While the previous chapters did demonstrate that this is preferable in terms of

understanding atmospheric chemistry, there was no supporting information given to show that this would be a better measurement in terms of understanding the health effects of NO2 or supporting epidemiological studies. That link (between ambient NOy or NOy-NO and health effects) must be made explicitly. The last bullet on p. 5-2 is true, existing NOx monitors can be converted to NOy monitors fairly easily, but the subsequent calibration, operation, and maintenance of those NOy monitors is considerably more complex and must not be ignored. Finally, the last paragraph is odd. Yes, NO2 is an indicator of traffic pollutants. But since estimates of its health effect are confounded by other traffic pollutants, wouldn't it be more reasonable to state that the health effects we attribute to NO2 may be partly due to other pollutants? In any event, the abrupt introduction of multipollutant mixtures as the last point of this conclusion seems out of place and inappropriate without more supporting information.

The following were typos or minor wording changes:

Page no.	Line no.	
2-5	2	Nitro-patts should be nitro-PAHs
2-17	4	"...tube measurements were *not* likely to be..." ?? Doesn't seem right as written.
2-31	17	An r_s of 1 seems extraordinary – typo?
2-36	13-14	Rephrase: '...between ambient NO2 and *pollutants other than those* presented above.'
		Make lines 13-24 all one paragraph. Rephrase: "Table 2.5-8 shows correlations between NOx and traffic pollutants measured in ambient air *for the Kim 2005 study and several others.*" Move this sentence to follow the one beginning 'Leaded gasoline...'
2-38	18+	This description of diurnal concentration variations belongs in Sec. 2.4 rather than here.
		There certainly needs to be a description of seasonal variability in NO2 here (i.e., in Sec. 2.4) rather than relegating it to the Annex.
2-38	23	For clarification, add: Motor vehicle emissions

		of NOx consist mainly...
2-39	10	Why '*still* show positive correlation with CO'? Since both pollutants tend to peak during the winter in most places, isn't this the expected relationship?
2-40	1-2	Since ~50% of NO2 is emitted from power plants, which do have a strong seasonal cycle, there certainly *is* good reason to suspect seasonal variations in its emissions.
2-42	9	Indoor NO2 *concentrations* or *exposures* are not likely confounded, rather than sources
2-42	18+	Isn't the Pilotto 2004 study still subject to possible confounding from other pollutants emitted from the heaters? I.e., ultrafines?
2-46	Fig. caption	between children *within* classrooms
2-51	11-14	It seems more accurate to say that these studies did not measure other pollutants that could have confounding effects.
	25	What exactly is meant by "evidence of coherence for respiratory effects"? That the evidence is consistent? Not clear. But unlike most of the previous sections, which desperately need a summary, this was a nice summary.
2-52		This table would benefit from some explanatory information (mostly for P90) in a footnote.
3-61	2	Triggering asthma *attacks,* not attache?
4-11	18	Item (2) needs rewording to be meaningful
5-2	25	Measuring NOy would perhaps be more meaningful in terms of atmospheric chemistry,

		but the implications of that measurement for health studies aren't at all clear. It may just lead to further confounding.
AX3-88	30-31	Sentence beginning 'Stronger correlations..' needs rewording
AX3-93-94		These pages have a number of typos and grammar problems that need to be fixed.

Comments from Dr. Steven Kleeberger

Chapter 4 Comments.

The document focuses on susceptibility factors that include preexisting disease (e.g. asthma, COPD, cardiovascular disease), age (e.g. neonates, children, and the elderly), high exposure occupational groups, and genetic background. IS GENDER CONSIDERED SUFFICIENTLY?

The document adequately discussed the existing literature regarding differential responsivity to NOx. My overall impression of the chapter is that, while some studies do address susceptibility factors, the critical issue is the relative dearth of systematic investigations that sufficiently evaluate each of the potential modulators of response. Therefore, it will be difficult to come to hard conclusions regarding the relative risk due to the susceptibility risk factors described above.

Specific comments:

Page 4-5. It is not clear to me that new evidence since 1993 "raises concerns" for increased severity and frequency of respiratory infections, decreased lung function growth, increased onset of asthma and allergy, etc. Does the new evidence truly raise concern or simply indicate that these questions are now being pursued and suggest that these factors could be important? The lack of consistent findings within investigations, and between investigations, suggests that additional investigations need to be performed before attributing risk of exposure to NO2 among the susceptible subgroups.

Page 4-10. In particular, the lack of investigations on the role of genetic background on susceptibility to NO2 exposure is evident. The studies performed to date are focused on candidate genes (e.g. GSTM1, GSTP1) which, while defensible, are "looking under the lightpost". Multiple genes could be examined in this manner without obtaining a clear understanding of the role of genetic background on responsivity to NO2. Investigations that systematically approach the importance of genetic variation in experimental models with translational or extrapolation potential are clearly necessary. This information could lead to explanations regarding the inter-individual variation observed in many of the clinical investigations in healthy individuals and those with pre-existing disease.

It is not clear that "understanding a basis for susceptibility to asthma, will facilitate/improve the precision of future studies of air pollution and health". In fact, it is probable that understanding the basis of susceptibility to environmental exposures (such as NO2) and interaction between asthma susceptibility genes will facilitate understanding asthma and other chronic diseases. It is understood that we are not making recommendations regarding the research that should be done, but the literature available currently does not inform adequately on genetic susceptibility to enable firm conclusions.

Page 4-12. It is not clear that section 4.2.2 is informative. Documentation of estimates of the number of individuals with asthma and/or heart disease does not seem meaningful if

there are no clear indications that these diseases are predisposing to the effects of exposure to NOx. Furthermore, it is also not clear that all individuals with asthma (or other chronic lung disease) will respond similarly to exposures to air pollutants. The variation in responses to pollutants among diseased individuals may be as great as that found among healthy individuals.

GENERAL COMMENT

With respect to Question 5: "to what extent does the integration of health evidence focus on the most policy-relevant studies or health findings".

"integration of health evidence" was not as clearly delineated as probably should have been to enable evaluation of its focus on policy-relevant studies or health findings. To enable this interaction, we must have a more comprehensive evaluation of the integration between animal toxicology studies, dosimetry studies, and epidemiological investigations. This leads to question whether integration is possible with the existing literature or whether the studies do not exist and should be proposed as recommendations.

Comments from Dr. Timothy Larson

General Comments

Charge Question 3: I would agree with the conclusion on p. 5-14 that epidemiological studies are potentially confounded by other traffic related pollutants, although I would qualify this to say that the evidence suggests that CO is not one of these. The ISA relies more heavily on the intervention study of Pilotto to argue for the independent effects of NO2 in real world exposures. However, as mentioned in Chapter 2, this study is also potentially confounded by other combustion related products (c.f. page 2-42). This issue deserves more elaboration if possible. For instance, the recent survey of Canadian homes by Weichenthal et al (JESEE 17(3) 288-297, 2007) indicates that heating sources including natural gas are not significant sources of ultrafine particles, but cooking is. Given that indoor heating by natural gas is an important source of NO2it may be possible to argue more persuasively that indoor ultrafine particle exposures are not correlated with NO2 exposures. I have had a hard time finding any direct studies on this topic. At a minimum I would suggest more research in this area.

Charge Question 1: In Chapter 2, the discussion about the spatial variability of NO2 concentrations needs to be prefaced by a brief discussion of the EPA siting criteria for NO2 monitors. These siting criteria include proximity to traffic and are an important determinant of the observed spatial variability as summarized in Table 2-5-1 and related tables. One could also show the distribution of distance to major roads for both the EPA NO2 monitors and the population in general, and the relationship between NO2 levels at monitors less than xx meters from major roads vs all others.

Charge Question 1: The decision to exclude the European data in Chapter 2 is understandable, but misses the opportunity to compare networks based on near road monitoring of NO2 with the U.S. networks sited away from roads. Some European networks have at least one NO2 monitor at an 'urban background' location for contrast. This location would be comparable to the majority of U.S. locations. The importance of street canyons in many is also worth discussing in more detail, given that this is a very important determinant of spatial variability in urban areas. Again, most of this work has been done in the European context and clearly shows this effect. However, it is generally applicable to parts of many U.S. cities.

Specific Comments

p. 2-14 As presented, its not clear how the physical factors determining exposure are in turn determined by the exposure factors. Some are obvious, but others are not. How do the indoor sources affect a person's exposure to the ambient component of a given pollutant? If this were generally true, then the assumption that these are independent (which I think is generally true) is brought into question.

p. 2-16 line 26 For clarity, add "tube-type TEA passive sampler.." Presumably it is the this type of sampler that has demonstrated significant artifacts.

p. 2-17 line 19 The fact that passive samplers cannot currently provide hourly information should be stated at the beginning of this section. The statements about health effects should be put in Chapter 3.

p. 2-52 Table 2-5-1 might also include the NO2 data from Vancouver, B.C., a relatively dense regulatory monitoring network with similar siting criteria to the U.S. (c.f. Henderson et al Environmental Science & Technology 41 (7): 2422-2428 Apr 1 2007).

p. 2-21 line 9 A reference is needed for the statement about the importance of indoor sources on outdoor NO2 levels. I am not aware of this literature.

p. 2-33 line 22 Although it may be true that susceptible populations have different levels of protection, a reference is needed. I am aware of the work sponsored by the EPA PM Centers that showed no differences in PM2.5 as a function of susceptibility.

p. 2-34 line 11 The error here would probably not be a fixed difference, but rather proportional to the average level. This would be consistent with spatial variations during a given sampling period being proportional to the spatial distribution of emissions and spatially averaged levels over the sampling period being determined by meteorology.

p. 2-34 line 22 Is this true even if there is significant spatio-temporal interaction?

Page 2-38 What information is there on the correlation of NO2 with the ultrafine fraction?

p. 2-42 line 7 This caveat is not mentioned much in other discussions in Chapter 3 about the importance of the intervention studies (e.g. Pilotto et al.) in elucidating the effects of NO2 alone. The conclusion in the following sentence is not clear, i.e., isn't CO a combustion product of unflued gas heaters? (c.f. the summary statement on page 51, line 11)

p. 3-1 line 27 I think it is better to say that these estimates represent the exposure to other oxidized species rather than the effects.

p. 3-4 line 4 Although these concentrations are lower, the CxT may not be.

p. 3-6 line 6 If confounding with ultrafine particles is a concern, why wasn't it discussed in Chapter 2? I suggest expanding the discussion of this potential confounding in the exposure section. This qualifying statement is not included later in Chapter 3. On page 3-58 line 28 the Chauhan et al study is interpreted without mention of potential confounding, as are the short term mortality studies on page 3-97, line 10.

p. 5-2 line 15 "roughly 20 to 25%" overestimate implies a relative amount of certainty whereas the previous sentence implies a lot of uncertainty.

p. 5-2 line 27 suggest wording as " total oxidized nitrogen" to be more consistent with "physically meaningful"

p. 5-3 line 18 why is this by itself an additional benefit? It might be if we also were to measure NO and NO2 as this would provide information on NOz that may have different effects.

p. 5-4 line 8 The biases are a function of sampler type and some are better than others as discussed in chapter 2.

p. 5-5 line 11 Or one could suggest doing both, i.e., pursue better NO2 measurement methods and also measure NOy.

p. 5-6 line 5 The findings refer to studies that looked at the daily 1-hr max, not the actual relevant 1 hr values with comparable health outcomes on this time scale. Therefore the conclusion should more precisely state that "differences between daily 1-h max and 24-h exposures…."

Comments from Dr. Kent Pinkerton

Review comments for the draft Integrated Science Assessment (ISA) for Oxides of Nitrogen: Health Criteria

Kent E. Pinkerton, Ph.D.
University of California, Davis
Center for Health and the Environment

Charge #4: To what extent is the discussion and integration of evidence from the animal toxicology and controlled-exposure human experimental studies and epidemiologic studies, technically sound, appropriately balanced and clearly communicated?

REPLY: Outstanding work has been done to address this charge in Chapters 3 and 4. However, the integration of animal toxicology, controlled-exposure human experimental studies and epidemiologic findings would benefit from further efforts to address disparities. For example, the levels of NO_2 needed to observe health effects in animals are much higher than those used for NO_2 to observe effects in human studies. To observe toxic effects in animals, most toxicology studies appear to require concentrations of NO_2 well above (by at least an order of magnitude) those implemented in human controlled studies. In a similar manner, are the levels of NO_2 used in human experimental studies an appropriate reflection of ambient levels under which epidemiologic studies are observed. It is also critical to address whether the current standard (set 36 years ago) which is associated with only a rare occurrence of exceeding or violating the current NO_2 standard is justified, while epidemiological studies show clear health (respiratory) effects of NO_2 exposure in both children and adults (particularly in the case of asthma) defined by a 10 to 20 ppb change in NO_2 levels. The document certainly does a reasonable job to review the new literature, but does not provide for a clear interpretation of what data we should be used as relevant and important in the decision-making process to determine if a change should be made for the next NAAQS standard for NO_2. Finally, it is critical to further elucidate if health effects attributed to NO_2 are confounded by co-pollutants or whether NO_2 is simply serving as a surrogate for other pollutants.

Chapter 1

This introductory chapter does a nice job to identify the purpose of the ISA with a series of questions to be addressed. Perhaps these bullet points could be better implemented by referring to given sections found in each chapter where they will be addressed using page numbers and/or the section location in the document. Efforts to further revise the document will be critical in order to reach the goal stated in the first sentence of the chapter to formulate “a concise synthesis and evaluation of the most policy-relevant science”. Although some chapter sections are approaching this goal, others appear to be plagued with excessive findings presented in a somewhat rambling fashion. Some sections also deal with the dilemma of being forced to discuss literature that is quite dated.

Chapter 2

This chapter is excellent with up-to-date studies that are nicely discussed. The vast majority of the references for this chapter are new since the publication of the last criteria document. The figures throughout the chapter and tables at the end of the chapter are extremely useful in providing a nice summary of the most salient points for this portion of the document.

Page 2-3: This figure (2.2-1) provides a nice summary of the cycle of reactive nitrogen species.

Page 2-13: This figure (2.5-1) is an excellent reminder of the time spent in different environments in the U.S. This is an important issue to consider in evaluating the potential for exposure to NO_2 that should be emphasized in the document.

Page 2-36: The fact that NO_2 behaves similarly to CO and $PM_{2.5}$ as well as the fact that NO_2 may be a surrogate for ultrafine particles emphasizes the potential for confounding effects in the interpretation of health effects due to NO_2. This is a fact that needs to be clearly stated throughout the document.

Chapter 3

This chapter makes a heroic effort to bring together all the available information on the health effects of NO_2 exposure. The chapter is organized into sections to cover potential mechanisms of injury, morbidity and mortality associated with short-term exposure driven in large measure by impacts on the respiratory system, followed by short-term effects on the cardiovascular system and finally the long-term effects of NO_2 exposure on morbidity and mortality. The chapter ends with a brief discussion on other chemical derivations of NO_2, namely, NO, HONO and HNO_3.

Although all the appropriate points are covered in this chapter, there remain concerns regarding some of the contents. This includes 1) repetition of the data, 2) data that describes health effects of NO_2 exposure at levels well above 1 ppm and 3) the need to further disentangle the confounding effects of NO_2 from that of other co-pollutants, especially PM. It will also be important to further address the potential for NO_2 to simply be a surrogate for ultrafine particles.

Pages 3-2 to 3-6: Excellent recent studies to demonstrate NO_2 exposures at or below the current NAAQS lead to increases in respiratory symptoms and exacerbation of asthma. The issue of confounding with ultrafine particles needs to be addressed.

Pages 3-6 to 3-8: The impact of NO_2 exposure on systemic effects of immune function should be further elaborated. The primary target of NO_2 effects resides in the respiratory tract. However, it is unclear how much evidence exists for systemic effects as well.

Pages 3-8 to 3-14: This is the section of the current document that provides some degree of concern. Many of the studies quoted were done well before the last criteria document was published. Why are these studies still present in this document? A second concern are the levels of NO_2 used in many of these studies which clearly exceed the 1 ppm level originally stated would represent the maximal level for consideration. Some justification for the inclusion of these older studies needs to be made.

Pages 3-12 to 3-13: Infectivity models add credibility to susceptibility to NO_2 exposure. A concern is the use of quite high levels of NO_2 exposure well above ambient levels to document toxic infective effects in publications that are fairly dated.

Pages 3-14 to 3-31: Lung function measures in children in this section appear to provide excellent data to demonstrate significant effects of NO_2 exposure. How do we interpret unsupervised peak flow measurements in children? Spirometric studies in adults also suggest decrements in lung function with exposure to ambient levels of NO_2. However, a critical question is whether studies (SAPALDIA and Lagario et al, 2006) controlled for the co-pollutant PM?

Page 3-21, lines 5 to 7 were also discussed on page 3-20, lines 14-16. Is this redundancy necessary?

Page 3-26: The impact of NO_2 exposure on childhood asthma management seems to indicate mixed results. How should this material be interpreted relative to previously mentioned studies suggesting strong NO_2 exposure effects in children with a history of asthma?

Pages 3-31 to 3-36: Measurements of airways inflammation have made dramatic advances since the approval of the current NAAQS. New studies in controlled human clinical experiments (Frampton et al., 2002) suggest effects, but only at high (1.5 ppm) NO_2 levels. Toxicology studies in animals use even higher levels of NO_2 exposure. Since none of these levels of NO_2 exposure represent levels to simulate ambient concentrations, how should we interpret these findings? Do these represent plausible mechanisms that may play a role in airway effects of exposure to NO_2 at lower, more relevant ambient concentrations? In this respect, it would seem the existing controlled human clinical studies are more relevant than the toxicity studies in animals for interpretation in risk assessment evaluations.

Pages 3-31 and 3-44: The summary provided for each of these sections is a nice idea. It is important in the document to take the next step to integrate or synthesize this summary into what information can be used to help better evaluate the current NAAQS standard for NO_2 and whether a change in the standard is needed.

Pages 3-45 to 3-57: Recurring evidence for small, but significant health impacts on respiratory outcomes is presented in a number of new studies reviewed. Emergency department admissions also show mixed findings that may be based on location (US versus Europe). However, a recurring concern remains the question of whether these findings are based on the effects of NO_2 directly or whether NO_2 simply serves as a surrogate for other pollutants. It is critical to disentangle these confounding factors.

Pages 3-60 to 3-62: The section on integration with a focus on asthma is a nice summary of the literature to date. The section provides a nice amalgamation of the literature to provide greater credibility for these in terms of biologic plausibility. This type of integration greatly facilitates interpretation of the existing literature.

Pages 3-62 to 3-80: The section on cardiovascular effects is a nice summary of possible short-term effects of NO_2 exposure. A summary for this section would be helpful. From this section, it would be concluded that NO_2 exposure has minimal cardiovascular impact.

Pages 3-80 to 3-98: The literature on mortality effects of NO_2 exposure are nicely reviewed with excellent summary and integration sections. The conclusions made suggest a consistent increased risk of mortality risk associated with NO_2 exposure. These significant effects associated with small incremental increases in NO_2 levels provide strong arguments for a change in the current NO_X standard. However, again it is critical that the influence for potential confounding due to co-pollutants must be considered and discussed to place this in the proper perspective.

Pages 3-99 to 3-102: Morbidity associated with long-term exposure to NO_2 review on new data in lung function growth from the Southern California Children's Health Study. This study is particularly compelling, but must separate NO_2 effects from PM. Figure 3.4-1 is very helpful as it appears in this draft.

Pages 3-104 to 3-107: Animal toxicology studies provide a summary of morphological effects of NO_2 exposure. Again, many of these studies were conducted using very high levels of NO_2 that are one to two orders of magnitude above ambient levels. How should these findings be interpreted for this document?

Pages 3-111 to 3-120: This section seems to be repetitious on asthma prevalence and incidence in children. Although it may be important to distinguish between acute and chronic effects of NO_2 exposure, perhaps the presentation of issues regarding asthma could be better addressed in a single location for the document.

Pages 3-126 to 3-131: The positive relationship of cancer incidence to chronic NO_2 exposure based on case control studies is a fascinating observation. However, it is important to assess whether this is a NO_2 effect or more an air pollution effect. The recent study of the American Cancer Society cohort study based in New York City demonstrates a small, but significant increased risk for cancer, but the air pollutant implicated is PM rather than NO_2.

Pages 3-143 to 3-150: The discussion of oxides of nitrogen other than NO_2 is good.

Final thoughts for chapter 3: Based on the current measured annual level of NO_X today that is well below the current NAAQS, yet health effects have been noted in children and adults with ambient exposures to NO_X, it is absolutely critical to explain why such health outcomes can be justified without changing the current NAAQS for NO_2.

Chapter 4

I like the format for this chapter to discuss susceptible and vulnerable populations. The writing is well done and stresses key points such as pre-existing respiratory disease, children, the elderly, folks who live in proximity to high volume traffic, as well as genetic factors related to susceptibility (oxidant and inflammatory damage). However, it is not clear how we should consider the findings in susceptible and vulnerable populations in addressing the current NAAQ for NO_2.

Chapter 5

This chapter on findings and conclusions is a good start. The question of how nitrogen oxides should be defined is relevant. Is NO_2 a reasonable measure (reflection) for the presence of other forms of nitrogen oxides? Toxicology and controlled human clinical studies clearly demonstrate a health effect associated with only NO_2 to provide justification for this part of the NO_X. To emphasize conclusions based on new findings since 1993 should be a critical part of this chapter.

Comments from Dr. Edward Postlethwait

Comments on Chapter 4: Appropriateness of public health impact and the characterization of groups likely to be susceptible or vulnerable to NO_2.

To form a more solid basis for the subsequent discussions, it is suggested to first open the chapter by defining "susceptibility" and making note that while all populations may be susceptible, the objectives are to help identify those populations that may be especially susceptible, ie., it's a matter of degree and range of biological responses. Subsequently, the paragraphs (section 4.2) on public health impacts and the definitions of adverse health effects should be moved up before addressing the individual factors and populations. In general, the selection of sensitive populations appeared to be more intuitive rather than quantifiable. It may also be useful to categorize susceptible populations under the general headings of biological (e.g., genetic, age, underlying disease, etc), socioeconomic, and geographic (including proximity to traffic zones). It would also be useful to estimate the magnitude of especially susceptible population responses relative to the population at large to demonstrate the extent of enhanced responses. As with other aspects of the ISA, this topical area would be strengthened by including integration among disease states, measured outcomes, exposure, and potential mechanisms of action that related specifics of NO_2 biology to pathobiological perturbations. The chapter did not address biological plausibility with regard to specific populations and thus it is a challenge to attribute health outcomes to direct causal actions of NO_2. On page 4-8 were very specific criteria for characterizing causal associations between genetics and health outcomes that appeared to be significantly more robust conditions than the evaluation criteria applied to other portions of the document. Consideration should be given regarding the correlations between the intrapulmonary distribution of inhaled NO_2 (dosimetry) relative to the anatomic sites of the specific disease processes. Finally, some overlap among the identified groups (e.g., children and asthma) may serve to amplify responsiveness and may categorize specific individuals into multiple susceptible groups.

Comments from Dr. Armistead Russell

Review of NOx Primary ISA
Armistead Russell

First, some kudos to the team putting this together on a few fronts:

1. Having a greatly trimmed down report was great.
2. The title of Chapter 2 was spot on, as well as the approach to condensing what used to be multiple chapters in to one nice, more concise chapter providing just what was needed.

That being said, there are a number of areas that need to be strengthened and refocused, both in the chapters and then again in the summary.

Chapter 1: Good introduction.
Page 1-4, line 2 (1-4:2), include studies showing a lack of effect as well.
1-5: 25, Add a comma between epidemiologic and controlled.

Chapter 2: Again, I like the title and the idea that the report should quickly move to discussing when the pollutants get to where some effect will be found. However, at present, the road it has taken could be straightened.

If I might, I would recommend the following outline for Chapter 2:

2.1 Introduction
2.2 Sources (provide magnitudes in a table)
2.2.1 Outdoor
2.2.1.1 Note that industrial and EGU emissions are often elevated and usually distant so their impact on exposure is usually reduced and there is a change in speciation.
2.2.2 Indoor
2.2.2.1 Note that while smaller, this is where people are, and there is drastically less dispersion.
2.3 Atmospheric and indoor processing
2.3.1 Dispersion
2.3.2 Chemistry (or the other way around… don't care)
2.4 Measurement methods
2.5 Ambient and Indoor concentrations
2.5.1 Ambient
2.5.1.1 PRB
2.5.2 Indoor
2.6 Exposure (this section is broken apart pretty well… no changes suggested)

It is not radically different, but adds a few key pieces in areas that provide needed information and in a way that such can be compared to other relevant pieces of information.

In regards to their discussion of sources, it is a bit short and also (I think) misleads the reader. The Annex also is light on detail. There should be a table of sources emissions, with emission estimates. This should include indoor sources as well. Also, it should include estimates of the fraction that is NO2. Some in Europe are making a big deal out of how changing technologies will change the fraction of NO2 in emissions, hence changing NO2 exposure. In this section, one should note that the location of source is quite important and why, noting that indoor sources will have a greatly enhanced impact on exposure, while upper level, distant sources may have a relatively minor impact, and that speciation will be different. The inventory used should be for 2008, and it would be good to have a forecast inventory for, say, 2020 to show how the relative source makeup will change. Having the actual numbers will negate the need to have much commentary about the relative size of sources.

The section on chemistry was sufficient, and about the right length. I might add more emphasis on that most of the NOx comes out as NO, and is then transformed to NO2 by O3 and other odd-oxygen species. Thus, after much transport, most of the NOx is NO2, but in the near field, exposure can be dominated by NO, and that the transformation of NO to NO2 is dependent on the amount of ozone running around.

In the section on measurement techniques, measurement uncertainty should be addressed quantitatively. The piece on the following page on interferences in Mexico City should be brought up here and removed from the next section, AND significantly de-emphasized, and studies conducted in the US given. Mexico City results are not overly relevant to the conditions here, and that was one study. If one considers the total amount of interfering species in a typical US urban atmosphere, one comes to the conclusion that the interferences will not be that large. It is interesting that in the conclusions the document suggests (maybe even rails on about) getting an NOy monitor as that might be more appropriate, but the current monitor sort of does that, though with some uncertainty. My view is that it would be good to have a pure NO2 monitor, but we can live with the level of uncertainty we currently have, and if we want to better understand other oxides, we should measure them specifically. This section should also discuss how indoor measurements and personal exposure is also done. When this is done, the section on 2-16 needs to be made more clear, and the sentence starting on 2-16:9 ("Briefly, …") needs to be cleaned up.

The ambient measurement section should be expanded to include indoor and other related species for comparison. Further, they quickly focus on NO2, though really should keep NOx and NO2 more together as an NO molecule is just an NO2 molecule waiting for an ozone to come along. Yes, they have different effects, but when one looks at controls, and considers spatial variabilities, one can not understand NO2 without understanding NOx. This whole section should give more of an overall oxidized nitrogen understanding followed by speciation. A figure with observed NO2 at monitors throughout the US should be presented as a PDF, showing both the mean as well as the maximum levels, and how the former compares to the current NAAQS. This section should also discuss how NOx species correlate to related species that have health effects, e.g., ultrafine particles and Primary OC/EC.

The first part of the General Concepts part of the Exposure section is a bit scattered, and also is not very exacting in presenting EQ's 2.5-2 and 2.5-4. All variables should be provided either before, or immediately after, the equation is presented.
The section on Spatial Variability does something that just adds bulk, A whole paragraph is devoted to saying what is in a Table, then the following paragraphs discuss each topic. The first paragraph is not needed. Also, I was baffled by the whole section on vertical variability. It was overly long, a bit biased, and when one got done, you wondered why it was even provided as it is not really used, and further, one can not say how representative it might be. Further, vertical variability is going to be very location and time dependent. One also needs to expound on what Restrapo et al., says, in that one has to be specific about exposure to ambient NO2 and monitor location. It is quite easy to envision cases when using ambient NO2 measurements near a road would lead to over estimates of exposure to ambient NO2.

The two paragraphs starting at the bottom of 2-20 (2-20:7) and going over to the next page are scattered and repeat some earlier discussion. Breathing should be included as a source in the table discussed above. (Note, this section also talks about emitting NO2, not NOx, and the two must be reconciled and both discussed given the possible rapid conversion.) Much of the discussion of indoor NOx species being converted to other things comes on 2-23. This should go up in the chemistry part.

Chapter 2 Specific Comments:

2-1:8: NRC, 1998 not in reference list
2-1:19: Should be (VOCs: anthro…
2-4:6: add HNO3 to list
2-5:2: nitro-patts ?
2-5:9: Very weak sentence
Fig. 2.4-1: Clarify figure caption and add detail as to what is being shown.
2-8:12…: The SEARCH monitoring network is probably more complete.
2-9: 9 NOx in **non-surface level** unpolluted air.
2-10:1 Sentence is awkward, try: "Contributors to PRB concentrations include natural emissions of …"
Fig. 2.4-2: Add units ON THE FIGURES themselves. Also, I think the figure caption is wrong in that regard. How did they treat lightening NOx?
2-12: Again, define all variables immediately upon use.
2-16:9 This sentence is awkward, and it is not just Fician diffusion at work. The last part of that paragraph is awkward.
2-16: 26 Remove "cost-effective"
2-17:1 Appears to contradict prior paragraph.
2-17: 18 Awkward.
2-18: 1 COD… provide the mathematical definition somewhere.
2-20: 7 Probably use "Penetration of outdoor NO**x** and **indoor** combustion in …"
2-21: top paragraph is awkward and repetitive.

2-21: 19. Remove length of monitoring period as a cause. (This paragraph is also quite awkward).
2-22:9: They need to be more precise in the working of this sentence. It makes no sense as currently given.
2-22:21: "… of **indoor** NO2…"
Fig. 2.5-3: Add the range of slopes as well.
2-27:10. Obvious…
2-30, last paragraph: Doesn't this repeat 2-25 a bit much.
2-36: 25. This reminds me, discuss the co-occurrence of NO2 and particles in both the source and ambient concentration sections, and how this confounds epidemiologic analyses.

The Findings and Conclusions Chapter is still rather rough, and appears to have picked up some pieces from the prior parts without consideration of balance and importance. Interestingly, this Chapter, at the beginning of the second paragraph, has the phrase "at the outset". Chapter 5/Conclusions is no longer the outset. This Chapter might have one section on sources, long. In the summary on Atmospheric Sciences, I thought it was unbalanced and did not adequately characterize what was said. I was immediately put off by the first bullet being on interferences. This, I doubt, is a major issue in terms of policy making, and they need to do a better job of figuring out how important this is in a typical US urban atmosphere. Taking results from one study in the Mexico City area is a bit extreme. They also bring up an issue that really is not well explored beforehand, e.g., monitoring total oxides. Why? How different would this be in practice? How can you criticize the current method when, in essence, that is almost what it does? One gets the feeling this is a pet issue. Indeed, the "Atmospheric Science" part of the Conclusion has four separate bullets related to the monitoring device when my guess is that that issue will have little impact on standard setting. The conclusions section should look back and consider the important pieces in a balanced fashion.

Comments from Dr. Jonathan Samet

Comments: NO_x Integrated Science Assessment (ISA)
Jonathan M. Samet, M.D., M.S.
General Comments

As the first of the Integrated Science Assessment's (ISA) of the Agency, the general approach and form of the NO_x ISA merits careful and thorough evaluation. Done properly, the ISA should be an informative, succinct, and useful summary of the evidence for consideration of the NAAQS. I have long advocated for more critical synthesis of the evidence in evaluation of the need for NAAQS revision; the limitations of prior documents, including the Criteria Document and Staff Paper, have long been evident. Unfortunately, this draft ISA has not accomplished the anticipated and needed level of synthesis.

Inadequate development of the review process: On reading the draft, there is no clear statement of the methodology; the ISA does not meet the widely applied standards for evidence-based reviews that at a minimum include a clear and replicable strategy for evidence evaluation, criteria for evidence evaluation, and agreed to and uniform language for specifying conclusions. There are abundant models: reports of the Surgeon General and reviews of the Agency for Health Care Research and Quality and the Cochrane Collaboration, for example. In reviewing the draft ISA, the following can be identified:

- Only a general approach is described for literature identification. How do the Agency and authors move from literature identification to inclusion of specific studies?
- The criteria for inclusion of epidemiological studies are vague and not replicable.
- Terms for evidence evaluation are introduced but without clear definition or uniform application. There is no clear statement of how strength of evidence is evaluated and there is a patchwork of discussion of this critical issue across the ISA.
- In considering the epidemiological information, no consideration is given to the possibility of publication bias, a serious concern, given the number of epidemiological studies that have been carried out and the high potential for selective reporting of positive findings.

Failure to develop an underlying set of conceptual models: In many ways, NO_2 represents an ideal starting point for carrying out an integrated assessment of the literature. There are multiple ways by which sources of NO_2 might cause or be associated with adverse health effects: 1) a direct causal effect; 2) an indirect causal effect mediated by secondary pollutants, including PM and O_3; and 3) by standing in as a surrogate for emissions from the same sources that are actually responsible for the adverse health effects observed (see figure). These possibilities are not necessarily exclusive. Confounding, as usually defined, would refer to the production of association between NO_2 and adverse health effects, by the actions of one or more other exposures, themselves associated with NO_2 in a particular study. Multipollutant approaches are the mostly widely used strategy to address confounding in epidemiological studies, but such

models are not readily interpreted when the potential "confounders", e.g., PM, are potentially mediating effects attributable to NO_2.
These complexities speak to the need for a far more thoughtful approach to the development of the ISA and particularly to far more specificity in considering the indicators used in the epidemiological studies. The ISA nicely lays out a foundation on the complex atmospheric chemistry related to NO_x but this information is largely ignored in the remainder of the document. Similarly issues of dosimetry are largely overlooked. At the least, the document needs to bring far greater specificity to the types of exposures considered.
A fundamental issue for the NAAQS is the causal attribution of effects to NO_x. Implicit in the specification of the NAAQS is the assumption that achieving the specified level(s) brings health benefits; the risk assessment also implicitly assumes causation.
Overall, the ISA does not meet the standards used elsewhere for a systematic review of evidence that has the purpose of reaching judgments on a body of evidence in a clear, replicable and transparent process.

Charge Questions

1. In general, the ISA does an adequate job on covering atmospheric chemistry (extensively covered elsewhere) and air quality.
2. Chapter 2 succeeds to an extent in addressing the issues in this question. It does not adequately consider, however, the relationships of NO_2, as measured at ambient sites, and the various species that may be relevant to health. It needs to set a better context for interpreting the epidemiological evidence particularly in view of considering the alternative models of causation that were set out above.
3. See above.
4. The integrated discussions only partially succeed. One problem with the present approach is replicative discussion of pathogenetic issues. Since the focus is largely on respiratory outcomes, with lesser concern with cardiovascular effects, there should be one in-depth discussion. The issue of dose in the toxicological studies needs greater discussion; there is no attempt to consider doses to key target sites at ambient concentrations and the relationship of such doses to those in the experimental research.
5. The health effects considered are encyclopedic, rather than focused on those most relevant to the NAAQS. For example, literature on reproductive effects is only emerging now, and not readily interpreted. The studies on cancer are problematic in their interpretation. A review process that offered criteria for selecting the most relevant outcomes would have avoided a chapter as unfocused as Chapter 3.
6. See general comments above.
7. See comments above. Chapter 4 is satisfactory.

8. My general concerns are set out above. The ISA does not adequately establish the causal relationships that should underlie the risk assessment.

Comments on Specific Chapters

Chapter 2

This should be a critical chapter but it does not achieve the goal implied by its title: "Source to tissue dose". The material reviewed in the chapter's first portion nicely establishes that ambient NO_x contributes to the generation of a heterogeneous group of gaseous and particulate compounds. There is the potential for effects associated with ambient NO_x to be consequent to either exposure to NO_x itself or to be mediated by the many potentially toxic compounds generated through chemical and physical transformations of the combustion-generated NO_x. The paths from source to dose(s) may well be different and sites of deposition in the respiratory track differ for the different compounds. Unfortunately, the chapter fails almost entirely in the needed integrative function. Additionally some of the material seems out of place: should the studies of indoor NO_x be in Chapter 3? Some of the discussion of exposure measurement error and misclassification might also be better placed in Chapter 3.

Chapter 3

This chapter is lengthy, difficult to read, and reminiscent of the style of the Criteria Documents. Its sections offer lengthy descriptions of individual studies, generally only brief and non-informative summaries of the evidence, and duplication of mechanistic discussions. In part, the chapter fails because an adequate framework was not provided; there is clear variation in approach across its segments.

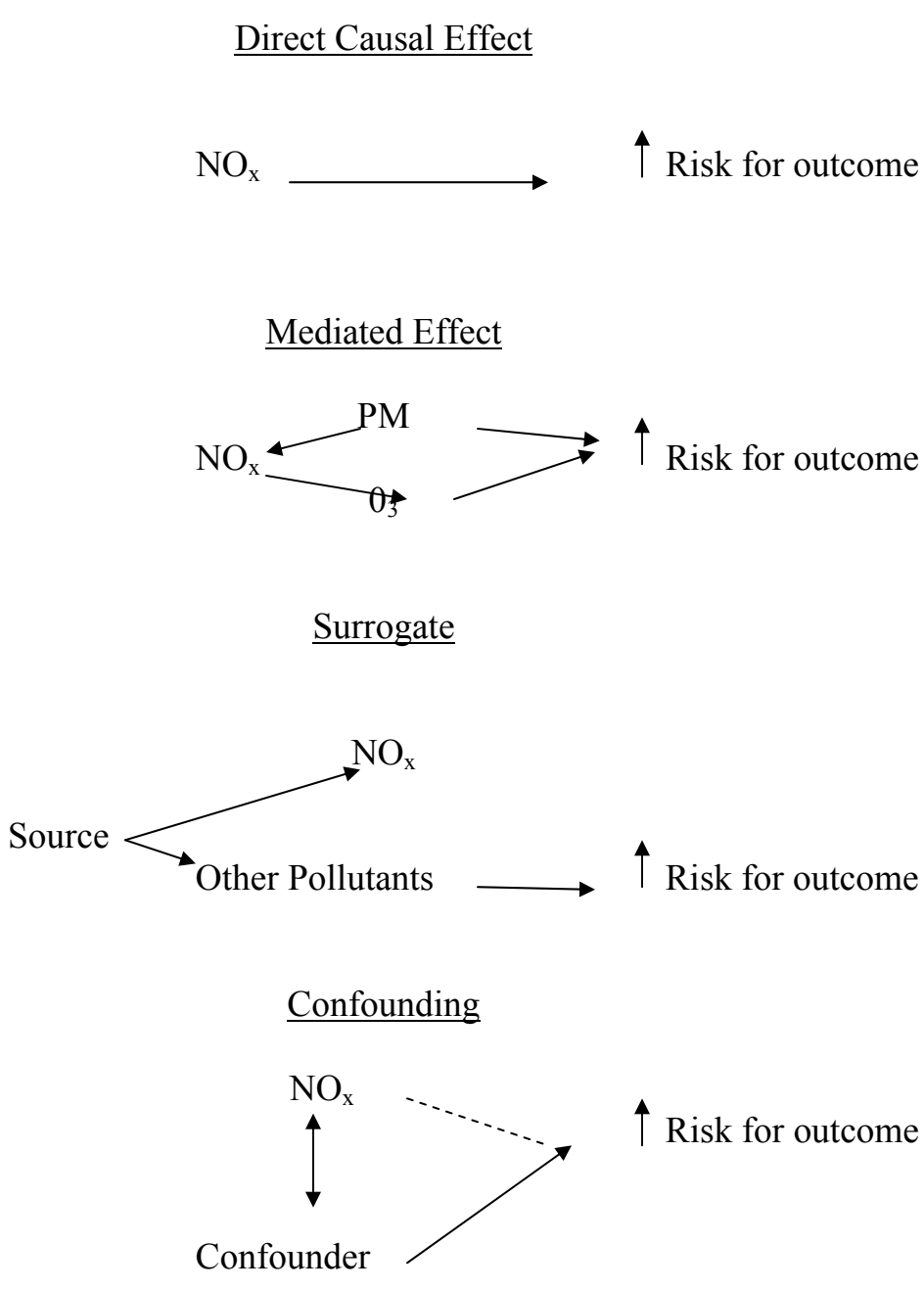
Chapter 4

This is a "pro-forma" discussion of the issue of susceptibility that offers a relatively "standard" review of the various populations that might be susceptible to NO_2. It is not well linked to Chapter 3.

Chapter 5

My expectations for this chapter were much higher than what I found, which is largely a set of bulleted findings of prior chapters with limited integration.

Figure
Potential Relationships of NO_2 With Adverse Health Effects



Summary of Comments on 1

Page: 1-1
Author: JSAMET
Subject: Sticky Note
Date: 10/20/2007 8:59:43 AM
This is not a matter of definition for the research committee, but what has actually been studied, whether in the laboratory or the community.

Page: 1-2
Date: 10/16/2007 11:36:35 PM
There needs to be a sharp discussion of use of terms such as "interaction" which has multiple definitions and meanings depending on the domain. Here for example, NOx is a contributor to PM, not the same as "interaction".

Page: 1-3
Date: 10/16/2007 11:40:03 PM
What does this mean? Is this a documented process?
Date: 10/16/2007 11:42:09 PM

Date: 10/16/2007 11:42:05 PM
What does this mean? Accurate?

Date: 10/16/2007 11:43:55 PM
What does credible mean? accurate? and meaningful?

Page: 1-4
Date: 10/16/2007 11:45:37 PM
This is very ambiguous. Ambient levels where and when?

Page: 2-15
Date: 10/16/2007 11:58:34 PM
NO2 or NOx?
Isn't another issue whether NO2 measured by an ambient monitor is an adequate surrogate for the various compounds produced from NO2?

Page: 2-19
Date: 10/20/2007 9:14:56 AM
This paragraph seems off the mark in the comparison to PM and O3.

Page: 2-20
Date: 10/20/2007 9:16:42 AM
Not clear what is meant by alter. Indoor sources contribute to total exposure but why modify?

Page: 2-21
Date: 10/20/2007 9:18:23 AM
These variables are not confounders but exposure determinants or determinants of concentration. The document needs to be precise in its use of language.

Page: 2-22
Date: 10/20/2007 9:21:53 AM
Not in reference list. Are these European data?

Page: 2-25
Date: 10/20/2007 9:25:04 AM
How does this discussion relate to outdoor NOx? What is its relevance to interpreting the evidence on health related to outdoor NOx?

Page: 2-27
Date: 10/20/2007 9:27:32 AM
speculation—

Page: 2-32
Date: 10/20/2007 9:30:43 AM
Undoubtedly, ambient monitors do not capture personal exposure to NO2 with complete accuracy.

Page: 2-33
Date: 10/17/2007 12:09:13 AM
A very confused paragraph

Page: 2-35
Date: 10/17/2007 12:13:45 AM
Confounding by what? It is critical for this document to carefully specify the relationship of NOX and NO2 with other pollutants.

Page: 2-47
Date: 10/20/2007 9:38:06 AM
In what way? are they studying the same pollutant mix as is associated with ambient NOx?

Page: 3-1

Date: 10/20/2007 9:58:16 AM
What do these terms mean? Presumably, "strength" means strength of association? What about consistency? How do coherence
and plausibility differ?

Page: 3-3
Author: JSAMET
Date: 10/20/2007 10:01:02 AM
This discussion would benefit by clear linkages to a stronger Chapter 2 that gave greater specificity to discussion of "doses" of various compounds.

Page: 3-5
Date: 10/20/2007 10:03:11 AM
Is this where bacteria and viruses deposit? what is the reference for this?

Page: 3-6
Date: 10/20/2007 10:05:29 AM
The issue of dose and dose-response needs to be addressed. Some of the studies involve quite high doses.

Date: 10/20/2007 10:06:36 AM
This is not clear at all. Confounding under what circumstances? for what health effects?

Page: 3-14
Date: 10/20/2007 10:24:40 AM
reliable means repeatable

Page: 3-27
Date: 10/20/2007 10:30:06 AM
Not a correct statement about the advantage of GEE

Date: 10/20/2007 10:31:07 AM
plausibility?

Page: 3-38
Date: 10/20/2007 10:34:53 AM
Would be careful to not include research recommendations

Page: 3-43
Date: 10/20/2007 6:32:16 PM
Tachypnea is very nonspecific.

Page: 3-44
Date: 10/20/2007 6:33:29 PM
A comment is needed here on the dose range in these studies.

Page: 3-45
Date: 10/20/2007 6:34:48 PM
The problem of interpreting multivariable models with NO2 needs far deeper discussion.

Page: 3-57
Date: 10/20/2007 6:40:19 PM
This paragraph is illustrative of the need to have some unifying approach to sorting out potential causal, from mediating, from confounding effects.

Date: 10/20/2007 6:40:51 PM
same problem here

Page: 3-58
Date: 10/20/2007 6:43:19 PM
What are the criteria for coherence applied here?

Date: 10/20/2007 6:42:38 PM
The issue of publication bias needs to be addressed. This is a major concern in interpreting the time-series results as there is a high likelihood that positive responses were selectively reported.

Date: 10/20/2007 6:44:24 PM
More "frank effects"? What is intended here?

Page: 3-60
Date: 10/20/2007 6:45:21 PM
Plausibility of this lag structure?

Page: 3-61
Date: 10/20/2007 6:46:27 PM

This paragraph offers a very weak discussion of plausibility.

Page: 3-62
Date: 10/20/2007 6:47:32 PM
In what way are these strong associations?

Page: 3-72
Date: 10/20/2007 6:51:43 PM
And what is the view of the ISA's authors on this critical issue?

Page: 3-78
Date: 10/20/2007 7:16:34 PM
support for this comment?

Page: 3-87
Date: 10/20/2007 7:21:36 PM
Another example of an inadequate conceptual framework.

Page: 3-91
Date: 10/20/2007 7:23:50 PM
Interpretation is far more than a matter of addressing confounding.

Page: 3-95
Date: 10/20/2007 7:26:27 PM
very poorly phrased and indicative of the lack of an underlying, unifying approach. Presumably, the authors refer to disease specific associations that would be consistent with an underlying causal effect.

Page: 3-97
Date: 10/20/2007 7:27:37 PM
A far deeper discussion of this sort is needed up front.

Page: 3-112
Date: 10/20/2007 7:40:07 PM
Needs more careful explanation.

Page: 3-115
Date: 10/20/2007 7:42:30 PM
A poorly phrased and somewhat erroneous set of statements. Chronic symptoms, core to many respiratory questionnaires, are presumed to reflect chronic exposures. Symptoms are an outcome by themselves, as well as possibly being indicators of the presence of a disease.

Page: 3-118
Date: 10/20/2007 7:46:19 PM
This section has yet another discussion of underlying mechanisms of respiratory effects. Emphasis and interpretation differ across these sections. One thoughtful discussion is needed. Not multiple reviews of the same range of evidence. This one, for example, does not carefully consider dose range.

Page: 3-119
Date: 10/20/2007 7:47:17 PM
Isn't this statement overly confident, given the concentrations of most of the toxicological work?

Page: 3-127
Date: 10/20/2007 7:51:10 PM
A further example of failure to link the atmospheric chemistry discussion to the health effects.

Page: 3-139
Date: 10/20/2007 7:55:10 PM
By no means is this a correct characterization of the origins of these studies.

Page: 3-141

Date: 10/20/2007 7:56:57 PM
Needs more complete discussion.

Page: 4-1
Date: 10/20/2007 7:59:42 PM
Not a very useful or informed discussion of this key issue.

Page: 5-1

Date: 10/20/2007 8:09:54 PM
This is a mis-characterization. Much of the reviewed material is extraneous to the policy objective.

Page: 5-5
Date: 10/20/2007 8:11:09 PM
Far too sweeping. What is a reasonable proxy?

Page: 5-7
Date: 10/20/2007 8:12:42 PM
The ISA has never set up a framework for application of the criteria offered in this paragraph.

Comments from Dr. Richard Schlesinger

CHAPTER 2

GENERAL COMMENT: Overall, the document needs to be reorganized as indicated in a number of comments below. There is much repetition in different sections that often make it difficult for the reader to determine what is new material or what has already been discussed but within a different context. More summaries within certain sections are also needed so as to clearly indicate the conclusions from each of these sections regarding health outcomes from NOx.

CHAPTER 2

Section 2.7 is misplaced in the draft document. It should be integrated earlier in the chapter where ambient outdoor exposures are discussed. Also, discussion of health outcomes in this section should be avoided. The real purpose of the chapter is to provide the reader with a perspective on the relative exposure levels of NOx; this information will then be evaluated in light of the exposure atmospheres used in the health effects studies discussed in Chapter 3.

CHAPTER 3

This chapter is not very well organized. There are sections that are separate that should be integrated, which would make it easier to evaluate the significance of the health outcomes from NOx.

This document is supposed to discuss material since the previous AQCD, yet it seems to also discuss studies that were included in that prior document but does not do so in a manner which will allow the reader to understand why some early studies were selected for inclusions and others were not. Perhaps each section should have a brief summary of the conclusions from the previous document and then go into the newer data followed by a summary to indicate whether these new studies change or support the earlier conclusions or make some that were not possible due to a sparse dataset in the earlier document.

p.3-1, line 11. Here it is noted that the document concentrates on NO2 levels at or below 5 ppm. This appears to contadict the statement on page 1-5, line 9 that limits evaluation of studies to those using levels < 1 ppm. In fact, some of the sections in the document discuss studies at levels > 5ppm.

Section 3.2 There is no consistency in the integration of health data in the different sections. Some provide a summary of the effects on the outcomes while others are merely a description of a number of studies.

p.3-5, lines 28-31. It is confusing to be told that the evidence for altered defense is coherent and plausible, and then be told that the evidence for such effects is not consistent and not robust. How can it be plausible if it is not consistent or robust?

p.3-22, lines 20-21. High variability does not necessarily mean increased susceptibility. One subgroup could be more variable than another, yet be within the normal range. Thus, this seems to be an overstatment.

p.3-32, line 20. Clinical Studies of Airway Inflammation. This section provides an example of the need to better integrate related material. The topic discussed here is also discussed in the host defense section and could be incorporated there.

p.3-34, lines 19-21. On page 3-2, lines 16-18, it is noted that effects seem to be dependent upon the concentration, duration and exposure profile rather than simply the product of C x T. However, both here on page 3-34 and in other places in the document, a simple C x T value is given to indicate some threshold of response. This seems to conflict with the earlier comment.

p.3-37, lines 7-11. The degree of increased airway responsiveness is not always a good marker of the severity of asthma. Furthermore, it is stated on p. 4-2, lines 7-9, that not all asthmatic show increased airway responsivity. Therefore, the comments about responsiveness and asthma need to be corrected and made consistent in the various sections of the document.

p.3-39, line 5-7. This last sentence should be deleted. It really does not add anything to the previous discussion.

p.3-39, line 11. Remove "allergic" from airways inflammation.

p.3-44, Summary. This is a summary of clinical studies but does not integrate them with the animal toxicology studies.

p.3-59, line 3. The sentence should read "…evidence for airways HYPERresponsiveness…"

p.3-61, line 15. It is not clear how alterations in mucociliary clearance can be a mechanisms underlying asthma exacerbation in children. It is most likely that NOx induced changes in mucociliary clearance may be an independent effect that is not causally related to any effect on asthma.

p.3-80, lines 13-14. What is the biological rationale for the comment that changes in hemoglobin and hematocrit could account for the cardiovascular effects in certain groups of people? One does not seem to be the cause of the other, except perhaps for changes in blood viscosity.

p.3-99, lines 1-2. Expand this sentence to indicate time frame for the cellular changes in relation to the lag times.

p.3-105, line 4. Perhaps the lesser sensitivity of rats is due to their ability to produce ascorbic acid.

p.3-108, line 28. Factors affecting susceptibility… This section should be in Chapter 4 or wherever the main discussion of suspectible populations is eventually located.

p.3-119, line 18. Insert "may be" after systems and delete "is."

p.3-119, lines 23-25. This supports the earlier comment that it is not just C x T that is responsible for effects.

p.3-125, line 22. Wording error here.

p.3-125, lines 29-30. The sentence should be reworded as follows, "The small body of toxicological literature examining the effects of NO2 on birth outcomes is inconclusive as to whether NO2 is a reproductive toxicant." The rest of the original sentence should be left out since it makes a summary statement without adequate supporting evidence.

p.3-126, line 7-11. The comment made here that there is a weak association between NO2 exposure and adverse birth outcomes contradicts the statement on page 3-125, line 30 that NO2 is not a reproductive toxicant.

p.3-129, line 22. If statistics were inappropriate, then why discuss the study. Alternatively, indicate why they were inappropriate.

p.3-130, line 24. Reword as follows: "…the main source of NO2- in the body is endogenously formed NO2-…"

p.3-131, line 1. The statement that NO2 is a tumor promoter at the site of contact is too strong.

p.3-131, line 19. Parallel to what?

p.3-144, lines 13-14. NO is a bronchodilator, so the comment that NO2 is a bronchoconstrictor is not needed.

p.3-144, line 19. A study from 1995 is not recent.

p.3-146, line 27. Effects of short term exposure. It is not clear whether this section is a summary of presented material or is presenting new material. It should be integrated in another section, perhaps that beginning on p.3-144 line 6.

p.3-149. Nitric Acid. Since this section discusses a number of early studies, then the ones below should be included.

Schlesinger, RB, HAN El-Fawal, JT Zelikoff, JE Gorczynski, T McGovern, CE Nadziejko and LC Chen. Pulmonary effects of repeated episodic exposures to nitric acid vapor alone and in combination with ozone. Inhalation Toxicology. 6: 21-41 (1994)

Chen, LC and RB Schlesinger. Considerations for the respiratory tract dosimetry of inhaled nitric acid vapor. Inhalation Toxicology 8: 639-654 (1996)

CHAPTER 4

This is a weak chapter in its present iteration. It would be better to integrate the material within Chapter 3 since it would make a more coherent picture of the effects of NOx. The repeating of material is especially evident in Section 4.1.2.

The public health impacts section should also be in Chapter 3.

This chapter discussed drivers as potentially susceptible populations but does not seem to include general population living near major freeways.

p.4-3, line 13. The sentence should be changed to read, "…and have higher minute ventilation compared to adults…"

p.4-3, line 18. Add "and/or to a decline in immune system surveillance or response."

Section 4.1.3. The description of exposure levels should be in Chapter 2. This section should just have the relevant toxicology and epidemiology that shows that such exposure levels as may occur result in increased mortality/morbidity.

p.4-8, line 20. Change"respiratory" to "health". This makes it more general.

p.4-10, lines 19-21. The logic behind this sentence is not clear.

p.4-13, line 16. West Virginia reported the highest prevalence of heart disease is what comparison?

CHAPTER 5

The title should be changed to SUMMARY AND CONCLUSIONS.

Comments from Dr. Christian Seigneur

Comments on the Integrated Science Assessment for Oxides of Nitrogen: Health Criteria – First External Review Draft, EPA/600/R-07/093, August 30, 2007.

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

Chapter 2. Source to tissue dose

Charge question 1: It is important to note in the introduction that the term "oxides of nitrogen" has a different meaning in the NAAQS context (all oxides of nitrogen except N_2O) and in atmospheric chemistry (only NO and NO_2). To that end, the first paragraph of Section 2.1 and Figure 2.2.1 are very helpful. However, more precise definitions of NO_y and NO_z are needed. For example, in the list of abbreviations and acronyms (p. xxix), NO_y is defined as the sum of NO_x and NO_z, whereas NO_z is defined as the difference between NO_y and NO_x, which is an internally consistent but circular set of definitions. I recommend listing the chemical species that constitute NO_y for clarity (as done in the Annex). Also, NO_z does not include all oxides of nitrogen (NO and NO_2 are not included). These definitions could be brought in the third paragraph of Section 2.2 (p. 2-2) as well.

Charge questions 1 and 2: It is stated in the second paragraph of Section 2.2 (third and fourth lines) that "NO_2 typically [is] in the range of 5 to 10% of NO" for combustion sources. First, it would be better to refer to % of NO_x rather than % of NO. Second, this range is misleading because it is incorrect for several sources. For example, some coal-fired power plants have emissions of NO_2 that are less than 5% of NO. Also, diesel vehicles equipped with particulate emission control now have NO_2 emissions that are significantly above 10% of NO_x. This is an issue that will also affect the estimates of future population exposure and a discussion of the evolution of the NO/NO_2 speciation in mobile sources appears warranted.

Charge question 1: Figure 2.2.1 and third paragraph of Section 2.2: The figure is too complicated in some ways and incomplete in other ways. To the extent possible, eliminate minor reaction pathways for simplicity (for example, delete the formation of NO_2 from HNO_3). The arrow leading to NO_3^- from NH_4^+ is incorrect; I assume that the author meant PM formation from those two chemical species. Then, show an arrow originating from these two species and leading to inorganic PM nitrate; add also sea salt and alkaline dust along with NH_4^+. On the other side of the figure, add the formation of organic PM nitrates. On line 20 of p. 2-2, add ozone as an oxidant of NO_2. Delete "As shown in Figure 2.2.1" from the first text line below the figure (p. 2-3). Add a sentence that mentions natural emissions of NO_x from soil, biomass fires and lightning.

Charge question 1: On lines 10-13 of p. 2-4, the sentence needs to be rewritten: the uptake of HNO_3 by aqueous particles (rather than aerosols) will not remove HNO_3 from the atmosphere very rapidly unless it rains; similarly, uptake by cloud droplets will not remove HNO_3 if the cloud evaporates.

Line 16 of p. 2-4: list the precursors of ozone (NO_x and VOC).

Charge question 2: First full paragraph of p. 2-7 (Section 2.3 on measurements): There is a need for a conclusion. Is EPA recommending replacement of the current chemiluminescent measurement technique? Is the luminol reaction technique (used in many atmospheric research programs and discussed in the Annex) a possibility? Also, one should note that NO_2 is not the only criteria pollutant which is poorly measured: ozone and PM measurements also suffer from measurement artifacts. Furthermore, if epidemiological studies have been based on the chemiluminescent technique, would it be wise to change the measurement technique at this time, as consistency between the NAAQS and the measurement technique used to determine attainment should be important?

Charge question 2: Section 2.5.2.2.1: This section discusses the spatial variability of ambient NO_2 concentrations. A major issue with NO_2 concentrations is their strong gradient near roadways (as discussed in Section 4.1.3) but this section only discusses spatial variability at larger scales. It would be useful to bring up the near-roadway spatial variability in this section to set the stage for further discussions pertaining to exposure (such as in Section 4.1.3 and in the Methods document).

Chapter 3. Integrated health effects of NO_2 exposure

Charge question 4: This chapter discusses the results of clinical, toxicological and epidemiological studies related to NO_2 exposure. In the case of epidemiological studies, the uncertainty in the NO_2 ambient concentration measurement is of interest (I assume that the use of higher NO_2 concentrations in clinical studies minimizes the measurement uncertainty). It is likely that the NO_2 concentrations were obtained from routine measurement networks (this is explicitly mentioned for some studies, e.g., Lin et al., 2004, but not for all of them) and that the chemiluminescent method was used. Given the discussion of the uncertainties of this monitoring method in Chapter 2, it seems desirable to explicitly state which measurement method was used for the epidemiological studies reported in Chapter 3. If all those epidemiological studies used routine monitoring network data, this could be stated upfront in the chapter, with a reference to Section 2.3.

Chapter 4. Susceptible and vulnerable populations

Charge question 7: Section 4.1.3 addresses high-exposure groups with a discussion that focuses first on occupational exposure (bus and taxi drivers, highway patrol officers, etc.) and second on geographical exposure (e.g., residences and schools located near roadways). It may help to make the distinction more explicit (e.g., two sub-sections) as those two types of high-exposure groups may be fairly distinct. For example, residences

and schools located near major freeways may relate to an environmental justice concern whereas occupational exposure may fall under occupational health.

Chapter 5. Findings and conclusions.

Charge question 2: Section 5.2, p. 5-2: I do not understand the rationale for having measurements of NO_y. It seems that the NO_y measurement is driven by the fact that there is less artifact than for the NO_2 measurement. However, the health effects discussion of Chapter 3 addresses predominantly NO_2. How would EPA use a NO_y monitoring network to determine the attainment status of a NO_2 standard?

Charge question 2: Section 5.3, pp 5-3 and 5-4: The strong NO_2 spatial gradients near roadways need to be discussed.

Annex 2.7.1. Chemical transport models

This Annex section needs to be rewritten.

A general comment concerns the fact that only the regional Community Multiscale Air Quality model (CMAQ) is discussed here. NO_2 exposure is to a large extent a near-source issue and CMAQ is not designed to address ambient air pollutant concentrations near their source of emission. Other models such as AERMOD for point sources (e.g., stacks) and CALINE4 for line sources (e.g., roadways) are then more appropriate than CMAQ. Therefore, such local-scale models should be discussed to an extent similar to that of CMAQ in this section.

Furthermore, this section of the Annex looks tailored for an O_3 ISA rather than for a NO_x ISA. For example, the discussion of CMAQ model performance evaluation focuses on ozone (rather than NO_2) and does not reflect in any case the most recent performance evaluation studies.

Comments from Dr. 'Lianne' Elizabeth Sheppard

Comments on the ISA

Overall: I commend the contributors for a good first effort at creating a new integrated document for this new process. The overall organization of the ISA is moving towards the goal of providing a shorter document with a more integrated perspective. There should be thorough cross-referencing with the annexes to keep the ISA short and streamlined yet well supported. Chapter 2 has many good organizational features, but certain topics need to be added and I had difficulty with many details. Chapter 3 ideally will be simplified and shortened, with the goal of less literature review and more integrated assessment. However, there are so many subtle differences between studies and effect estimates that I am concerned that the effort to condense will make important distinctions even more opaque. The integrated synthesis of Chapter 5 gives about the right level of detail. Criteria for judgments need to be stated clearly so the integration is as transparent as possible. For outcomes judged to be "likely causal" I suggest summarizing the set of quantitative estimates that will be brought forward into the risk assessment.

Chapter 2: Generally I think this chapter needs to be reworked to make the discussion clearer, use consistent definitions throughout, give specific definitions for quantities and use the same terminology for them throughout the document (needed for the many correlations in particular), and align the review of exposure with the next chapter's health analysis. Consider adding a glossary or definitions table to this section giving specific formulas for each specific quantity that is referred to so the reader can easily distinguish all the different correlations that are discussed. Consider reorganizing the chapter to review exposure features in the context of specific epidemiological study designs. Add discussions about whether NO_2 is a surrogate for the actual exposure, the role of monitor siting in air quality data, and the relationship of NO2 with other ambient concentration measurements (other oxides of nitrogen measures as well as other pollutants).

2-15 l 16: Section 2.5.2: Different features of exposure are important for different epidemiological study designs. Review of exposure must be done within the context of an epidemiological study design. Epidemiological study design must be integrated into this review. Acute studies with time-varying exposure and cohort studies with long-term average exposure target different aspects of exposure and thus different measurement features will dominate.

2-15 l 21-24: For (3), how does temporal scale of the data contribute to this comparison?

2-17 l 27: Fix the table (2.5-1 p. 2-52) so the time scale of all the measurements is clear.

2-17 l 30: Insert annual? "mean annual concentration"?

2-17 l 31: Modify to "between daily measurements at individual site pairs".

2-18 l 1: Insert “daily average” before concentrations. How is COD calculated? Note: This definition appears in the Annex, so cross-referencing between the ISA and the Annex is needed.

2-18 l 9-10: Where does the proximity information come from? The discussion on this page suggests to me there are features of the monitoring sites that may be as important as the spatial location and that the analysis should be expanded to better describe other important features. How do monitoring siting criteria influence the results of the Table 2.5-1 analyses?

2-19 l 26-28: Why would sheer number of monitors be a reason for representativeness of community or personal exposures?

2-25 l 13-24: In all the tables and figures mentioned (plus others), it is not clear what each correlation measure is and whether the different correlations should even be compared. In a later part of this chapter (p2-27) definitions of three types of correlations are given (though sadly without formulas to make it even clearer), but these definitions aren’t used here or in other parts of the chapter. Before discussing any correlations, define each one clearly and then qualify every use to indicate which is being discussed. Note annex section AX3.5.1 also addresses issues with correlations and clearly states two important points: that different correlations have different meanings for different study designs and that the type of correlation can have a big impact on the resultant estimate.

2-29 l 17: F_{inf}

2-31 l 3: “differences in study results” with respect to what?

2-31 l 12: Insert “time series” before epidemiological. This is a place where the statement depends upon the study design of interest.

2-31 l 17-29: Refer to the definitions on p 2-27 l 17: Insert “daily average correlation” to clarify r_s. l 18: Insert “(longitudinal correlation)”, etc.

2-32 l 14: Replace “do” with “may”. While it is correct that this paper made the argument that community average non-ambient exposures don’t vary across communities, this was not supported by data and it is easy to hypothesize scenarios where the statement would not be true (e.g. because of different prevalence of gas stoves across communities).

2-32 l 22: Insert “in time series studies”. The Sheppard paper made statements *in the context of the time series study design*. They do not apply in general to all epidemiological study designs.

2-33 l 8-9: While the statement that indoor sources could affect ambient levels is certainly true, how often would this influence be a large enough contribution to matter practically?

2-35 section 2.5.3.1: Again, need to factor in study design in this assessment.

2-35 l 19: Now here's a new term for a correlation. A glossary or table of terms is certainly needed.

2-35 l 23: Clarify the phrase "in moving away from the urban core".

2-36 l 2: Certainly the suggested analysis can easily be done from existing AQS data?

2-36 l 13-17: I question whether the description and supporting table are anything close to a good incisive summary of the St Louis data.

2-37 Figure: Also evaluate by distance between sites to determine if a different pattern becomes apparent.

2-37 l 7: Add a qualifier for the correlation. Also lines 12, 15.

2-37-38: I question whether any of the comparisons of correlations on these pages represent any kind of reasonable comparison. There are different periods, seasons, site characteristics, etc., in each of the different estimates, all of which could have an important impact on a measure of correlation. For example, correlation estimates can be dramatically affected by the inherent variability in the data (which will be lower for analyses restricted to a single season than analyses that look at all seasons combined).

2-38 l 18: Why is statistical significance important to mention here?

2-39: I'm not convinced it makes sense to combine the data as is done on this page (including the figure) to present composite diurnal variability. I suspect that with so many other sources of variability at play (e.g. site, city, season), the diurnal patterns get washed out in this composite figure.

2-44 l 29-30: If it is worth mentioning the other analysis, please focus on the estimates and 95% CIs, *not* on the statistical significance of the estimates. The significance statement implies this is a different result, but the estimate and CI may or may not support that conclusion.

2-45 l 4: Can't the figure also show the wheeze results?

2-48 l 28: Figure needs uncertainty estimates (e.g. 95% CI) added.

2-49 caption: Note SD

2-50 l 11: Give the reader more context. For instance, begin the sentence with "Among the ____ outcomes evaluated, …"

2-51 l 11-14: Is it possible to make this sentence clearer, particularly statements on line 12? Add "ambient source" before co-pollutants? Other combustion byproducts are still an issue for indoor exposures.

2-52: Rework this figure to be more informative. Add time period to the title.

2-55-56: In addition to various suggestions about correlations that affect this table, explain what all the numbers in the table mean. What is meant by sample size? What is n? Often there is more information about the "sizes" than is implied, e.g. one can infer there are 12 days for 55 adults in the Laird et al results. Omit p-values. What does "pooled" mean? Justify using R^2 in the same table as the correlation. (Has the square root been taken? Is a simple linear regression model used?) Same comments apply to 2-57-59.

2-65: Add "daily average measures" to the title. Add seasonal representation to all studies or a clarifying footnote. Include the number of days in the estimate. Note the distance between sites, site features and any other important site characteristics. Include the summary statistics such as the number of sites in the mean, the range and SD.

2-66 Table 2.5-8: Add "daily average" in the title. Plot vs. distance and add n's.

2-66 Tables 2.5-9 2.5-10: Add Daily average at a single site" before "ambient" and "subject-specific daily average" before personal. Add n's, days, seasons and type of correlation as relevant.

Chapter 3 summary comments: As I note in my discussion of the Schildcrout et al paper below and other CASAC members pointed out, the reporting of study results is not always correct and thus I suggest statements of study results should be checked throughout this chapter. Some CASAC members suggested some studies have been omitted. The term "significant" or "statistically significant" appears to be used as synonymous with scientifically important. If a specific result is worth mentioning I think the estimate and 95% CI should also be given, regardless of the statistical significance. (e.g. 3-15 l 10)

3-23 l 13: There were no NO_2 data in Seattle, so this city should be dropped from the list.

3-23 l 14: Each subject had an (approximate) average of 2 months of data

3-24 l 6, 7: Given the prevalence of asthma symptoms, the rare disease assumption does not hold and the word "risk" should not be used in place of "odds". The analysis was for asthma symptoms, not specifically cough.

3-27 l 5-22: More information is needed about the universe of studies being compared before these conclusions can be drawn.

3-102 l 6: Another example where the more informative comment would focus on point estimates and CIs, not statistical significance.

Chapter 5:

5-3 l 30: The statement "potentially leading to exposure error…" depends upon the study design. It appears that the time series study design is being assumed here.

5-4 l 1-2: Use forthcoming analyses incorporating geographic covariates and monitor siting information to inform and modify this statement.

5-4 l 21: I think the important scientific criterion should be magnitude of the correlation rather than its statistical significance.

5-5 l 3-4: I think this is an overstatement and depends both on the purpose of the proxy (i.e. the epi study design to which it will be applied) and the definition of "reasonable".

5-10 l 10: Perhaps this statement should not have a bullet?

Comments from Dr. Frank Speizer

INTEGRATED SCIENCE ASSESSMENT FOR OXIDES OF NITROGEN—HEALTH CRITERIA (first external review draft, dated August 2007)

Answers to Charge Questions (paraphrased)

Submitted by Frank E. Speizer, MD

Date: October 18, 2007

Chapter 2. Are atmospheric chemistry and air quality characterized clearly, appropriate, and relevant to the review of NO2 primary NAAQS?

Section 2.2 Atmospheric Chemistry: Quite frankly, I do not find either the Figure 2.2-1 or its description very helpful. What does "different sources emit NOx at different altitudes" mean? The figure suggests that automobiles and smoke stacks are emitting NO into some atmospheric level; not clear where as dashed box doesn't tell me how high up. The text says this is better described in Annex AX2.2 (but should be some indication here). The figure itself is complex and certainly as describe doesn't stand alone. It is also not clear what the relevance of the remaining details of section 2.2 do for consideration of the NAAQS.

Section 2.3-4, Pages 2-6-2-11: Ambient Measurements: This section summarizes well the nature of the data base. It might be worth indicating, since the text suggests a limitation of the number of measurements, something about the distribution of measures across the US. Figure 2.4-2 may have the data (or at least it may be in AX2.9).

Section 2.5 Exposure Issues: Generally well handled. Minor fixes necessary.
Bottom of page 2-30 it would be good to define "…poor to good."
Page 2.31, end of first paragraph. What are the biases introduced by this misclassification? Can they be considered random? This needs further discussion, particularly as it is this measurement that is used in the time-series epi studies. The next page sounds as though it was written by a different person. These two sections need to be tied together better.
Section 2.6 Dosimetry: Probably true but disappointing that there appears to be no new work since 1993 AQCD. The important statement of this section is in lines 10-15 on page 2-41. If this is all there is so be it.

Section 2.7 Indoor and personal exposures: Good summary.

Chapter 3: Integrated Health Effects
My primary concern is the length of this chapter, at something over 150 pages. The chapter starts out by telling us there is not much new and then goes on…and on…and on. The saving grace is the excellent number of figures that clearly are almost self describing

of the state of the science and how it has been gathered since 1993, and the excellent summaries at the end of each section. I believe far too much detail of each study is give in the text, and to be truly integrated I would have expect more of the detail in the Appendix rather than here. For example (and I could have picked several) the section 3.3.1.6.1 is well characterized by the figure and the details with CI for each study is simply not necessary in this document. Would have much rather read an integrating summary on page 3.57 that provided a quantitative statement summarizing the impact across studies. In fact that is what pages 3/57-3.62 does. The authors then do the same thing for cardiovascular diseases and the results seem to be predictable. Another example of this reading more like a CD is found on page 3-144 with details of old work at very high(>5-50ppm) exposures.
What is missing is a truly integrated interpretation of all of the results. What do we now know we did not know in 1993 and how can it inform our judgment in the setting of the components of the standard? The chapter still reads more like a CD than an Integrated Summary, and I am left without the ability to think about "form", "level," "average", and in this case chemical form (at lease to the end of this chapter)..

Section 3.4.4 Cancer incidence and long term exposure: The obvious contrast between the two positive and concordant epidemiological studies described on page 3-127; and the lack of evidence of a positive effect in animals and in vitro for NO2 with positive evidence in same for mixtures of NO2 with other pollutants points to the fact that NO2 as an ambient exposure for human does not occur in isolation. Section 3.4.4.1 that is supposed to be the Integration and biological plausibility simply summarizes the findings and does not discuss this issue. This needs to be expanded, since the conclusion in the summary paragraph in section 3.4.5 essentially dismisses the possibility of cancer, and I would argue this is wrong.

Section 3.5 Mortality and Long-term exposure. Data base well summarized however, there does not really appear to be an integrated section. Section 3.5.4 and figure 3.4-5 summarizes data but what does it mean? The section ends with a sentence on page 3.143 that is really not helpful. Authors should be able to provide a more integrated statement.

Section 3.6 This whole section could be considerably shorter. The details of the experimental data are really not necessary. If one wanted to produce a cartoon that summarized all these finding on mechanisms it might be interesting if there were any human data to back up the potential health effects at reasonable exposure levels.

Chapter 4 Susceptible and Vulnerable populations:
Section 4.1 pages 4.-1 to 4-11 presents an excellent summary of the issues related to vulnerability. This seems to me to be a model of what an ISA chapter should contain. However, table 4.1 is most disappointing in that it is simply a summary of what is in the text. The authors need to take the material in the Appendix 6 tables and summarize one table that breaks out the susceptible and vulnerable population and present that in the main text. This should be relatively easy as the references are in the text and the detail that might be included in each category of risk is in the appendix tables.

Page 4-10, line 5, 6: The suggestion that stronger evidence is based on p values seems inappropriate.

Section 4.2 and concept of Adverse Health Effects. I do not find this section useful at all. Tables 4.1.2 and 4.1.3 are standard reference material and don't seem belong here. Section 4.2.2 reads like a good beginning to a section on population estimates but is quite incomplete. Additional material is needed on COPD and other respiratory diseases. If one considers Age alone we need a paragraph of the age trends in the population. Ditto high exposure groups (occupational work forces data exist and need to be summarized). Other potentially susceptible groups, Urban poor? Newborns? Not clear that oxidative stress polymorphisms exist but if not a statement about this should be made.

Chapter 5
Section 5.2. I would have thought that given a bullet on motor vehicles as a large source of urban NO2 that there should be a similar bullet to put in context the degree to which stationary sources emit NO2. In addition, for completeness sake should there be a bullet for indoor sources (gas stoves)? Rest of the chapter seems to be a reasonable summary.

ISA NOXAug2007chargequestions

Comments from Dr. George Thurston

General comments on Chapters 3 and 4 of the ISA

As discussed at our last meeting, this document should comprehensively consider the NOX-PM interaction, given the importance of PM to the many of the same endpoints and studies considered here. This factor is mentioned here and there, but nowhere is this aspect of NOX associations with health separately discussed across all the document aspects (e.g., in Toxicology: is NOx affecting macrophage ability to handle particles?, or in Epidemiology: is NOX a acting as a marker of traffic PM?). These concerns are touched upon here and there, but need to be organized and brought together, and thereby considered in a "holistic" way. Indeed, these issues need to be handled comprehensively in both the SOX and NOX documents Overall, while there are smatterings of references (here and there) to PM-NOX interactions as an possible confounder in various passages, I see PM as the insufficiently addressed "elephant in the room" of each of these two new gaseous pollutant assessment documents. I recommend that the NO_x and SOx documents both address this issue more directly and comprehensively.

The criteria for the evaluation of the health effects considered are not sufficiently laid out at the start of the health chapter (Chapter 3) and, as a result, the various sections are primarily litanies of studies without consistent evaluations across endpoints. On Pg. 3-1, lines 7-8, it is stated that the experimental evidence is evaluated in the document for strength, consistency, coherence and plausibility. Presumably this is based upon Sir A.B. Hill's treatise, but it should be referenced, and the rationale for the selection of these specific criteria from Hill's longer list, and how they will be applied, needs discussion here. In addition, these criteria not consistently considered across the chapter, which would be a helpful step for each summary discussion in the chapter. (For example, on page 3-6, robustness is instead noted as an evaluation criteria instead, but how it is being defined and applied is not explained). I feel that such a consistent application of the A.B. Hill criteria across the various sections, especially as a function of pollutant averaging time and concentration when possible, would enhance the value and usefulness of the document.

Specific Comments

Chapter 3.

Section 2.7 (Indoor and personal Exposure Health Studies) seems like it is more appropriate for integration in Chapter 3, which deals with health effects. Perhaps the exposure aspects/trends from the studies should be introduced here, but the health effects belongs in Chapter 3.

Pg. 3-1, lines 7-8, It is stated here that the experimental evidence is evaluated in the document for strength, consistency, coherence and plausibility. Such choices in evaluation criteria need to be justified, and then applied across all sections consistently (see above general comment in this regard).

Pg 3-1, lines 27-29. Good point made here, but not clearly enough. Needs sentence restructuring. Also, perhaps this sentence belongs in a separate section on the potential/evidence for PM-NO_x interactions that might account in part or whole for associations found between NO_x and health effects.

Pg. 3-4, lines 29-30. I think "Over all" should be "Overall," I also think a comma after the work "equivocal" would help clarify the sentence's meaning.

Pg 3-5, lines 28-29. Define how the consistency and robustness are being evaluated, and support this statement further.

Pg 3-6, line 14. No comma needed after "in part"

Pg 3-8, ,line 14. This seems an appropriate place to discuss NO_x-PM interactions with respect to mucociliary clearance of PM.

Pg 3-9, ,line 13. This seems an appropriate place to discuss NO_x-PM interactions with respect to NO_x effects on macrophage activities in coping with PM.

Pg 3-12, ,line 20. This seems an appropriate place to discuss NO_x-PM interactions with respect to infectious microorganisms.

Pg. 3-17, line 8. Sentence structure unclear: inverse relationship between increases in NO_x and decreases in FVC? Needs rephrasing, as seems to be a double negative.

Page 3-19, line 14. Add reference back to discussion of Wendley and Silverman, 2001 on Pg. 3-16, lines 8,9.

Page 3-22, lines 2-22. Refer back more explicitly to the assessment criteria set out at the start of the chapter.

Page 3-31, lines 5-9. Refer back more explicitly to the assessment criteria set out at the start of the chapter.

Page 3-33, lines 5,6. Sentence too long and convoluted. Needs to be broken into two sentences, something like: "In a study completed by Gavres et al. (1994), the same protocol was applied in a separate group, but assessed immediately after exposure. In this case, no effects were found in…".

Page3-36, lines 10-20. Do the studies meet the criteria set out at the start of the chapter? For what averaging times and concentration levels?

Page 3-44, lines 5-24. Do the studies support/challenge any of the chapter's evaluation critieria? For what NO_x levels and averaging period ranges?

Page 3-49, lines 18-19. Lin or Linn?
Page 3-51, line 20. add "potential" before the word "effect"

Page 3-54, Figure 3.2-11. Are there confidence intervals available that could be plotted around each point? This would enhance the interpretability of the data as to whether the relationship differs significantly from linear, or not.

Page 3-57, lines 6-7. Extreme caution must be taken in interpreting multi-pollutant models, given the potential for inter-correlations of the effect estimates and large uncertainties. This caveat needs to be made here. That said, these results have implications regarding the interaction of PM and NO_x, which also bears discussion here.

Page 3-57, lines 15-16. Need to expand the discussion of NO2 as a possible surrogate for traffic PM here. The evaluation criteria set out at the start of the chapter should be considered here, as well.

Page 3-68, lines 2-3. Add discussion of NO2 as a possible surrogate for traffic pollution.

Page 3-72, line 1. Add "Multi-City" to the section title.

Page 3-79, line 32. How is the term "robust" applied here? That the estimates are unstable when correlated variables are added? This result is not surprising, and may be a reflection of that fact, and not that the effect is real or not. Perhaps this term (robustness of NO_x results to consideration of covariables) should be explicitly defined and added to the list of evaluation criteria at the start of the chapter.

Page 3-80, lines 23-24. Expand discussion of the various evaluation criteria and whether they are met, as a function of concentration and averaging period, where relevant and possible.

Page 3-83, lines 12-13. Note the difference of effect as a function of averaging time in the overall discussion of this section.

Page 3-84, line 8. Add comma after "sources" for clarity.

Page 3-84, lines 21-25. What are the implications of these conclusions with respect to the previously stated evaluation criteria?

Page 3-90, line 10. Add "in Multi-City Studies" to the section title.

Page 3-91, lines 4-7. Note these considerations in an overall discussion of the potential role of PM-NO_x interactions in the reported results.

Page 3-94, lines 26-30 and Page 3-95, lines1,2. Note how these conclusions do or do not satisfy the evaluation criteria set out at the start of the chapter.

Page 3-95, lines 10-13. I don't agree with this statement. Lags could easily vary from cause to cause (and city to city for that matter), and assigning "one-lag-fits-all" is not necessarily optimal. A distributed lag model would be best when daily data are available. Providing a range of effect estimates between: 1) forcing one chosen lag on all outcomes or cities; and, 2) choosing the best fit for each outcome/city, is probably the best way to provide the range of possible results when distributed lag models are not possible.

Page 3-97, Section 3.3.3. Need to expand discussion of the NO_x-PM interaction at line15-16. Also, need to discuss the implications of this discussion to the evaluation criteria noted at the start of the chapter.

Page 3-98, section 3.3.4. This section speaks to the coherence of effects, and the implications to causality should be discussed.

Page 3-111. Lines 18-19. Expand consideration of the traffic hypothesis in this section, considering all endpoints.

Page 3-119, lines 4-10. Discuss implication of these NO_x effects on AM to PM health effects in the lung.

Page 3-128, lines 27-28. Include consideration of these results in separate PM-NO_x interaction discussions.

Page 3-131, lines 6-20. Consider implications of these findings to the evaluation criteria provided at the start of the chapter (consistency, coherence, etc.).

Page 3-136, lines 7,8. Include these conclusions in a separate PM-NO_x interactions discussion.

Page 3-141, Section 3.5.4. Consider implications of these findings to the evaluation criteria provided at the start of the chapter (consistency, coherence, etc.).

Page 3-149. Consider the potential implications, if any, of gaseous acidity on the bio-availability of transition metals in particles in the same aerosol.

Page 4-4, lines 1-26. These comparisons would be more meaningful and interpretable if they were also presented in terms of their absolute attributable risks (e.g., effects/ppb/1000,000 persons) for each sub-population. The same percent increases in risk can have very different absolute impacts in different sub-populations, given that their baseline rates of incidence (that the percents are applied to) can be quite different. This needs to be addressed throughout this chapter.

Page 4-13, line 20. "southern states"?

Comments from Dr. James Ultman

Integrated Science Assessment for Oxides of Nitrogen – Heath Criteria
Comments on First External Review Draft -- James Ultman

To my knowledge, this is the first ISA produced in the revised process for revising the NAAQS for a criterion air pollutant. The ISA is intended to be a streamlined version of the Air Quality Criteria document that provides the basis for a subsequent risk assessment. Compared to the Criteria document, the ISA is intended to place more emphasis on integration and assessment of research published since the previous review rather than on a detailed presentation of these new studies.

The authors had and have much to contend with in developing the ISA for NO_2. There is considerable new information to assimilate in animal, human and particularly epidemiological studies. Unambiguous interpretation and evaluation of these studies is clouded by uncertainties in measurement, exposure pattern and confounding by copollutants. Nevertheless, the document has been successful in summarizing the new studies in a succinct fashion and providing a qualitative argument that NO_2-related respiratory health effects are occurring in spite of the current NAAQS, particularly in children and asthmatics.

General Comments

As in any document of this complexity, there are shortcomings in the draft ISA. I have a few general comments of the document as a whole.

1) First and foremost, if the ISA is the precursor to a risk assessment, it must use the current standard to provide a context for the relevance of the new studies. This is particularly important because of the wide range of exposure concentrations that were imposed in laboratory studies or observed in epidemiological studies. Yet, the current standard was mentioned only in the preface of the document, as far as I can see, never explicitly compared to the conditions in the key scientific studies used to support the conclusions in chapter 5.

2) Related to my first point is the question of the perceived impact of new science on the adequacy of the level, indicator, form and averaging time in the current standard. The document does not explicitly discuss this issue. Naturally, final numbers and conclusions will be better described in the risk assessment that follows the ISA. Still, I believe that the authors can discuss how the new findings regarding exposure pattern, different exposure mixtures and levels of exposure might impact the NAAQS.

3) As it now stands, the ISA summarizes current state of the science but does not consistently assess the soundness and the relevance of the individual studies. In other words, most of the document comes across more as an "Integrated Science Summary than an "Integrated Science Assessment." For example, the final chapter, Chapter 5,

appears to isolate the critical studies on which the conclusions are based, but no rationale as why these studies have been chosen is explicitly stated.

4) Some major editorial work needs to be done to improve the organization within and among the chapters. At a minimum, redundancies within and among different chapters should be identified and removed, and misplacement of material between chapters should be corrected. Also, as pointed out in 1-3, much of the discussion relating to the relative value of the new studies and their impact on the NAAQS should be made more explicit.

Chapter Comments

Chapter 1

It would be useful if the 5 points in lines 21 to 30 reemerged at the end of chapter 5 with explicit answers given there.

Chapter 2

Pg 2-10. Line 1. Add "to" after "Contributions"

Figure 2.4-2. This must have originally been a color-coded graph whose scale has been rendered ambiguous by direct copying. Please transform the figure to true gray-scale.

Eqs. 2-1 to 2-5. Given the fact that these equations are rarely referred to, I am not convinced that they are needed. A schematic figure that illustrates the effects of people moving between different microenvironments (i.e., indoor and outdoor), engaged in different activities, etc. would be more useful. Such a figure would also be helpful in clarifying the writing in sections 2.5.2.3.2 and 2.5.2.3.3 on the relationship between personal exposure and ambient concentration.

Pg. 2-19. Line 16. I don't understand what is meant by "mixing ratios." How is this different from concentration gradients, or does it mean the same thing?

Pg. 2-21. Line 1. Nitric oxide is a mediator that plays many important roles in human physiology. It is relevant that the author's estimated how expiration of endogenous NO would affect environmental levels. But it does raise another, probably more important question. That is, how does inhaled NO originating from combustion sources and reduction of atmospheric NO2 affect the physiological functions that endogeneous NO usually provides. It would be worthwhile to add (either here or in chapter 3) a short discussion on the biology of NO, particularly its effect on the cardiovascular system.

Pg. 2-25. Line 18. The "ambient" concentration and "outdoor" concentration should be defined. The difference between the two terms is not readily apparent, and yet they are important elements of this chapter.

Pp. 2-32 Lines 29-31 & Pg 2-33 Lines 1-23. This material is redundant with the immediately preceeding subsection.

Figure 2.5-5. In the caption, change "Asterisks" to "X's"

Section 2.6 on Pp 2-20 & 2-41. The dosimetry section occupying half the title of this chapter, occupies only two pages of text. I agree that there has not been much new research in NOy dosimetry research since the last review, so I suggest changing the chapter title. The dosimetry section itself could benefit from some discussion of animal-to-human extrapolation modeling. In the rest of the document, animal experiments are treated purely as a means of informing the toxicological mechanisms and plausibility of human health effects. In fact, it may be possible to extrapolate the animal exposures to equivalent human exposures to provide a more meaningful context for the observed exposure-response effects.

Section 2.7 beginning on Pg. 2-41. This section includes a combination of personal exposures and resulting health effects. It might be better to move this material to chapter 3 where health effects are discussed.

Chapter 3

General: Much if not most of the new information on the health effects of NOy comes from epidemiological studies. Since the results of the epi-studies are generally presented in terms of relative risk and odds ratio, the document should include an explicit definition of these terms. More importantly, it is hard for the nonstatistician (i.e., me) to appreciate what constitutes an important value for either of these parameters. In other words, is it possible to state when an OR or RR reach a value that we should worry about 1.01, 1.1, 1.5, 2.0….?

Pg. 3-1 Lines 10-11. The authors appear to be saying that <5ppm is "environmentally relevant." Figure 2.5-5 contradicts this point of view.

Pg. 3-2 Line 26 NO and HNO3 are not vapors.

Pg. 3-3 Lines 27-28. change "range of proposed mechanisms" to "factors"

Figure 3.2-2 In the ordinate, change "oob" to "ppb"

Figure 3.4-1 Two of the ordinates are labeled "PM10." One of them needs to be corrected.

Chapter 4

The lung growth studies from the California Children's Health study are particularly important in identifying children as a unique (and probably susceptible) population with respect to NO2 exposure. Since most laboratory studies have been done on adults, some

discussion of how exposure conditions that produced health effects on adults would extrapolate to children. This could best be done within the context of extrapolation modeling. There is at least two peer-reviewed papers related to this subject (Sarangapani et al., Inhalation Toxicology, 15:987-1016, 2003; Ginsberg et al., J. Toxicology Environ Health-Part A). 68:573-615, 2005)

Comments from Dr. Ronald Wyzga

Comments on "Integrated Science Assessment for Oxides of Nitrogen: Health Criteria

Ronald E. Wyzga, Sc. D.

Questions 1-3: I combined my comments for these questions because the dividing line among these three questions is not always clear.

I have 3 general comments:

- The document could give a much clearer discussion about the spatial and temporal heterogeneity of NOx levels. My understanding is that there are two distinct contributions to ambient NOx levels: a general contribution tied to more distant sources; and peaks near specific sources, e.g., roadways. This can lead to considerable spatial and temporal heterogeneity that is not clearly conveyed in the document. One reason for this is that monitors are often sited away from point sources, and therefore do not capture this lack of homogeneity. The document needs to discuss this in more detail in conjunction with the siting characteristics of monitors. Consideration of measurements from monitors far from specific sources could distort the analyses/discussion in this section.
- There is some confusion about the distribution of species within the NOx definition. In particular, I would like to see more about the relative importance of NO and NO_2 at different sites: near sources, away from sources, winter measurements, summer measurements, indoor measurements, outdoor measurements. Some indication of the relative conversion rates to and lifetimes of different species should also be discussed in more detail. It is also my understanding that most extant monitors also capture NO measures, but that these are not reported by the states. Efforts to publish these data could aid future health analyses as NO can be a vaso-dilator could influence health outcomes, and some toxicological studies suggest that NO can elicit adverse responses directly.
- One of the biggest issues in the interpretation of results from epidemiological studies is whether NO_2 is an agent which elicits health response or a surrogate for another agent. For this reason it is important that the correlations between ambient measures of NO_2 and other pollutants be reported for key environments, including indoor environments, outdoor environments near and away from specific sources. These correlations should be presented for a range of averaging times as health studies have considered different averaging times. Where available correlations should not only be presented for currently regulated pollutants, but for other pollutants, which are under active investigation for potential health concerns. The latter include ultrafine particles and elemental carbon.

More specific comments:

- It would be useful to prominently display the conversion rate from ppb NO_2 to ug/m^3 as studies using these measures are discussed.
- Figure 2.4.1. needs some information about the siting characteristics of the monitoring sites.
- p. 2-18, ll. 26-29: Is this a function of the characteristics of monitoring site locations, etc. Clearly this is not true for indoor/outdoor considerations.
- Chapter 2 presents the results of some health studies. Should these be moved to chapter 3?
- Table 2.5.1 should present some description of the placement of monitors vis-a-vis sources and it should define the averaging times considered to derive the correlations.
- Section 2.5.2.4 presents a very good discussion. One addition could be the possible systematic bias in exposure measurements if those responding were near sources and the monitors were not; hence the exposures of the respondents would be systematically higher than the exposure estimates. This would impact the estimates of dose-response.

Questions 4-6: I combined my comments for these questions because the dividing line among these three questions is not always clear.

I have 3 major comments associated with the issues raised by the above questions.

- The ISA is not comprehensive in its consideration of health studies; in particular, several studies that report negative findings between NO_2 and health are not cited. This could be because other pollutants (which are associated with health endpoints) are more prominently featured in abstracts/literature search results, etc.

The following studies are not mentioned in the text of the ISA; these are studies with which I am familiar:

Metzger et al. (2007) "Ambient Air Pollution and Ventricular Tachyarrhythmic Events in Patients with Implantable Cardioverter Defibrillators", **Epidemiology,** reports non-statistically significant associations between ambient NO_2 levels and tachyarrhythmic events under a wide spectrum of models and analytical approaches. Some associations are negative and none approach statistical significance.

Sinclair and Tolsma (2004) "Associations and Lags between Air Pollution and Acute Respiratory Visits in an Ambulatory Care Setting: 25-Month Results from the Aerosol Research and Inhalation Epidemioloigcal Study", J. Air & Waste Manage. Assoc., **54**:1212. This study notes that it examined the associations between NO_2 (and several other pollutants) and unscheduled physician visits for asthma (children and adults separately), upper respiratory disease, and lower

respiratory disease. The paper only reports the statistically significance results, noting that non-reported quantitative results are not statistically significant. NO_2 is not significantly associated with any of the health endpoints studied.

I also undertook a cursory (but not comprehensive) search on Medline and identified the following studies that are not considered; I would urge the staff to consider these studies. I should note that my brief interpretations need be validated as I did not have the time to thoroughly review all of these papers:

Steinvil A, Kordova-Biezuner L, Shapira I, Berliner S, Rogowski O. Short-term exposure to air pollution and inflammation-sensitive biomarkers. Environ Res. 2007 Oct 1; [Epub ahead of print] Abstract reports negative effects of NO_2.

Magas OK, Gunter JT, Regens JL. Ambient air pollution and daily pediatric hospitalizations for asthma. Environ Sci Pollut Res Int. 2007 Jan;14(1):19-23. Reports small effects of NO_2.

Gouveia N, Bremner SA, Novaes HM. Association between ambient air pollution and birth weight in Sao Paulo, Brazil. J Epidemiol Community Health. 2004 Jan;58(1):11-7. Results are more robust for CO than NO_2; paper suggest traffic is issue.

Petroeschevsky A, Simpson RW, Thalib L, Rutherford S. Associations between outdoor air pollution and hospital admissions in Brisbane, Australia. Arch Environ Health. 2001 Jan-Feb;56(1):37-52. Reports no effects of NO_2

Stieb DM, Beveridge RC, Brook JR, Smith-Doiron M, Burnett RT, Dales RE, Beaulieu S, Judek S, Mamedov A. Air pollution, aeroallergens and cardiorespiratory emergency department visits in Saint John, Canada. J Expo Anal Environ Epidemiol. 2000 Sep-Oct;10(5):461-77. Reports no effects of NO_2, which is negative in multi-pollutant models.

Roemer W, Clench-Aas J, Englert N, Hoek G, Katsouyanni K, Pekkanen J, Brunekreef B. Inhomogeneity in response to air pollution in European children (PEACE project). Occup Environ Med. 1999 56(2):86-92. Reports no association with NO_2.

Chen PC, Lai YM, Chan CC, Hwang JS, Yang CY, Wang JD. Short-term effect of ozone on the pulmonary function of children in primary school. Environ Health Perspect. 1999 Nov;107(11):921-5. Reports no effect of NO_2

Setiani O. Trend of air pollution and its effect on human health in Hiroshima Prefecture--a retrospective study in the cities of Otake, Kure, Mihara, Takehara, Fukuyama and Kaita Town, 1977-1992. Hiroshima J Med Sci. 1996 Jun;45(2):43-50. Reports a negative effect of NO_2.

Hoek G, Brunekreef B. Acute effects of a winter air pollution episode on pulmonary

function and respiratory symptoms of children. Arch Environ Health. 1993 Sep-Oct;48(5):328-35. Reports no effects for NO_2.

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Pattenden S, Hoek G, Braun-Fahrlander C, Forastiere F, Kosheleva A, Neuberger M, Fletcher T. NO2 and children's respiratory symptoms in the PATY study. Occup Environ Med. 2006 Dec; 63(12):828-35. NO_2 appears to be an indicator for traffic-related pollutants.

de Hartog JJ, van Vliet PH, Brunekreef B, Knape MC, Janssen NA, Harssema H. [Relationship between air pollution due to traffic, decreased lung function and airway symptoms in children] Ned Tijdschr Geneeskd. 1997 Sep 20; 141(38):1814-8. Dutch. Effects are associated with truck traffic, not NO_2.

Brunekreef B, Houthuijs D, Dijkstra L, Boleij JS. Indoor nitrogen dioxide exposure and children's pulmonary function. J Air Waste Manage Assoc. 1990 Sep;40(9):1252-6. No relationship with NO_2.

Penard-Morand C, Charpin D, Raherison C, Kopferschmitt C, Caillaud D, Lavaud F, Annesi-Maesano I. Long-term exposure to background air pollution related to respiratory and allergic health in schoolchildren. Clin Exp Allergy. 2005 Oct; 35(10):1279-87. No consistent association with NO_2.

Avol EL, Linn WS, Peng RC, Whynot JD, Shamoo DA, Little DE, Smith MN, Hackney JD. Experimental exposures of young asthmatic volunteers to 0.3ppm nitrogen dioxide and to ambient air pollution. Toxicol. Ind. Health. 1989 Dec:5(6):1025-34. Reports no response to NO_2 at 90ppb.

Slama R, Morgenstern V, Cyrys J, Zutavern A, Herbarth O, Wichmann HE, Heinrich J; LISA Study Group. Traffic-related atmospheric pollutants levels during pregnancy and offspring's term birth weight: a study relying on a land-use regression exposure model. Environ Health Perspect. 2007 Sep; 115(9):1283-92. Reports PM2.5, but no NO2 effects on birthweight.

- The results of other studies are not fully reported in a way that could be potentially misleading to the reader; in particular, analyses that consider the robustness of results after consider of other pollutants, etc. are not discussed as fully as they should be. I am familiar with the following studies:

Peel, JL et al. (2005) "Ambient Air Pollution and Respiratory Emergency Department Visits", Epidemiology, 16: 164-174. The document correctly cites the single pollutant model results from this study, but does not mention the multi-pollutant model results in which NO_2 significance disappears in models with ozone (which remains statistically significant).

Metzger, KB et al. (2004) "Ambient Air Pollution and Cardiovascular Emergency Department Visits", Epidemiology, 15:46-56. The ISA reports the single pollutant results, for which NO_2 is often statistically significant, but it does not report the multi-pollutant results. For the earlier time period, NO_2 is more robust than CO; for the later time period NO_2 is dominated by CO, total carbon-containing particles, and oxygenated hydrocarbons.

Lipfert, FL et al. (2000a). Results are presented for single pollutant models, but the ISA does not indicate that the associations between mortality and NO_2 disappear when ozone is present in a 2-pollutant model. Later analyses (Lipfert, 2006a,b) indicate that a traffic density variables dominates many pollution variables, including NO_2.

Other papers where a cursory review of the paper suggests that more elaboration of the results is warranted:

Delfino et al. (2003a) .The ISA concludes that this study was "supportive of these [NO_2] associations for asthmatics" The paper reports associations between NO_2 and asthma parameters, but concludes that VOCs are particularly important; two pollutant models show no significant associations with NO_2.

Prescott et al. (1998): The document refers to differences in the response of different age groups to NO_2, without discussing the statistical significance of these associations. According to the Annex the resposnses are not statistically significant for either age group.

Schouten et al. (1996). The same comments made for Prescott et al. pertain to this study.

Moseler et al. (1994). Table 4.1 should note that responses were found only at NO_2 concentrations above 21ppb.

- The major difficulty in interpreting the results of epidemiological studies is in its attempt to ascertain whether the associations between health outcomes and NO_2 are due to NO_2 per se or due to the possibility that NO_2 is acting as a surrogate for another factor. This issue need be attacked head on with some discussion of these possible other factors (including traffic, CO, ozone, PM, EC, ultrafines, organics)

and their relationship with NO_2 levels. Results should be summarized from multi-pollutant results (with appropriate caveats for differences in measurement error, etc.) for each of the possible pollutant confounders. Results should also be summarized by environment: indoor, outdoor near source, outdoor away from source and by length of exposure (acute, chronic). I would also like some discussion of the likely interferences in NO_2 measures in the above environments. The organization of results in this manner would help in interpreting the role of NO_2 in these associations.