

**Summary Minutes of the
U.S. Environmental Protection Agency (EPA)
U.S. Environmental Protection Agency – Science Advisory Board (SAB) Staff Office
Clean Air Scientific Advisory Committee (CASAC)
Oxides of Nitrogen Primary NAAQS Review Panel
Public Meeting
October 24-25, 2007**

Committee Members: (See Roster – Appendix A)

Scheduled Date and Time: From 8:30 a.m. to 5:30 p.m. (Eastern Time) on October 24, 2007;
and from 8:30 a.m. to 3:00 p.m. (Eastern Time) on October 25, 2007. (See
Federal Register Notice, Appendix B)

Location: Marriott at Research Triangle Park, 4700 Guardian Drive, Durham, NC,
27703

Purpose: To conduct a peer review of EPA’s Integrated Science Assessment (ISA)
for Oxides of Nitrogen – Health Criteria (First External Review Draft,
August 2007) and to conduct a consultation on the EPA’s Nitrogen
Dioxide Health Assessment Plan: Scope and Methods for Exposure and
Risk Assessment (September 2007 Draft).

Attendees: Chair: Dr. Rogene Henderson.

Panel Members: Dr. Ed Avol
Dr. John R. Balmes (by phone)
Dr. Ellis B. Cowling
Dr. James Crapo
Dr. Douglas Crawford-Brown
Dr. Terry Gordon
Dr. Dale Hattis
Dr. Donna Kenski
Dr. Steven Kleeberger (October 24th only)
Dr. Timothy Larson (by phone)
Dr. Kent Pinkerton
Dr. Edward Postlethwait
Dr. Armistead (Ted) Russell
Dr. Jonathan Samet (by phone)
Dr. Christian Seigneur
Dr. Elizabeth A. (Lianne) Sheppard (by phone)
Dr. George Thurston
Dr. James Ultman, (by phone)
Dr. Ronald Wyzga

SAB Staff Office: Dr. Angela Nugent, EPA SAB Staff Office,
Designated Federal Officer (DFO)

Dr. Vanessa Vu, Director of the EPA SAB Staff
Office

EPA Participants Listed on the Agenda

Dr. Ila Cote, EPA Office of Research and
Development (ORD)
Dr. Mary Ross, EPA ORD
Ms. Lydia Wegman, EPA Office of Air Quality
Planning and Standards (OAQPS)
Dr. Karen Martin, EPA OAQPS
Dr. Scott Jenkins, EPA OAQPS
Dr. Stephen Graham, EPA OAQPS
Mr. Harvey Richmond, EPA OAQPS

Meeting Summary – October 24, 2007

The discussion addressed the topics included in the Proposed Meeting Agenda (See Meeting Agenda - Appendix C) and roughly followed the sequence summarized below.

Opening of Public Meeting

Dr. Angela Nugent, Designated Federal Officer (DFO) for the CASAC Oxides of Nitrogen Primary NAAQS Review Panel, opened the public meeting at 8:35 a.m. on October 24, 2007. She noted three requests for oral public comment and one written public comment received before the meeting. She also pointed out that the agenda showed that the panel planned to summarize major review comments and recommendations related to the ISA at the end of the day. She invited interested members of the public to provide public comment on those recommendations on October 25, 2007 before the chartered CASAC members approved those substantive points for the report.

Dr. Vanessa Vu welcomed panel members and recognized the service of outgoing CASAC members Dr. Frank Speizer and Dr. Richard Poirot. She welcomed new CASAC members, Dr. Donna Kenski and Dr. Jonathan Samet. She thanked Dr. Rogene Henderson for her ongoing work as Chair of the CASAC and the panel.

Dr. Rogene Henderson welcomed members and Dr. Nugent as DFO for the Panel. She noted that Mr. Fred Butterfield would continue as DFO for the chartered CASAC and that Dr. Holly Stallworth would be serving as DFO for the CASAC Sulphur Dioxide Primary NAAQS review Panel.

Review of Agenda

Dr. Rogene Henderson noted that the meeting was important because it provided a review of the first Integrated Science Assessment (ISA) document drafted to implement EPA's new National Ambient Air Quality Standards (NAAQS) review process as a replacement for the Criteria Document previously generated by EPA. She thanked members for their written comments (Attachment D) provided to strengthen the ISA. She also noted the passing of Dr. Henry Gong, a member of the panel, and gave a tribute to his research and science advisory contributions.

Highlights of Draft ISA and Agency Charge Questions

Dr. Ila Cote, Division Director for EPA's National Center for Environmental Assessment – Research Triangle Park (RTP) (NCEA) presented an introduction to the ISA (Attachment E) and related charge questions and introduced Dr. Mary Ross who provided detail on the assessment.

First Public Comment Period)

Dr. Angela Nugent introduced three members of the public who requested the opportunity to provide public comment. Dr. Christopher Long from Gradient Corporation presented comments on behalf of the Utility Air Regulatory Group (UARG). His major comments are provided in Attachment F. Dr. Howard Feldman presented public comments on behalf of the American Petroleum Institute (Attachment G). Dr. Jon Heuss from Air Improvement Resource, Inc. spoke on behalf of the Alliance of Automobile Manufacturers. He noted that his organization planned to provide detailed comments on the ISA to EPA and CASAC. He noted that the ISA should: 1) increase attention to control studies; 2) deal with confounding interactions with other chemicals; 3) include discussion of a recent study in Fresno; 4) address double and triple counting and not only focus on single pollutant results; 4) eliminate publication bias. .

Discussion and Response to Charge Questions: Agency 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 NO₂ NAAQS?

Dr. Armistead Russell, the lead discussant, began by commending the Agency for condensing information in the ISA, compared to past Criteria Documents. He recommended that Chapter 1 be structured more clearly and include a section on sources. The section he envisioned would evaluate sources that are relatively important and would evaluate the contributions to exposure of the following categories: outdoor vs. indoor sources; local vs. distant sources; and ground vs. elevated sources. He advised the Agency to present information on the fraction of chemicals present and then to discuss atmospheric processing for outdoor exposures, indoor exposures, and outdoor and indoor exposures combined. He recommended including a table of source emissions and emission estimates that would include available information about the fraction of oxides of nitrogen that is Nitrogen Dioxide (NO₂) or other species, because the current text does not provide consistent information about emission of different oxides of nitrogen. He also recommended that the Agency show what is known about how NO₂ varies with Particulate Matter (PM) 2.5, elemental carbon, and sulfate, so EPA can deal

with confounding issues related to exposure to multiple chemicals. He also recommended including a map showing placement of monitors for oxides of nitrogen and NO₂ and density functions showing emissions to inform Agency decisions about possible long and short-term standards. Dr Russell also noted a concern that European control technologies are converting more oxides of nitrogen to NO₂ potentially increasing exposure to NO₂, and that future exposures in the United States may be similar. Dr. Russell closed his comment by noting that the findings chapter did not reflect the conclusions of chapter 2 conclusions.

Dr. Ellis B. Cowling, the second lead discussant for Charge Question 1 began with the observation that the purpose of the ISA was to summarize available information that is needed to reexamine the standard for oxides of nitrogen, for which the last standard was set in 1971: He noted that the ISA, therefore, should contain information to help inform decisions about the level of air concentration, indicator of choice, statistical form, and averaging time. He noted that those issues were explicitly discussed only in the preface of the ISA where those are discussed and that the ISA did not explain why NO₂ had been chosen as the indicator in 1971 for oxides of nitrogen. He noted that the summary points in Chapter 5 did not relate consistently to the topics and conclusions described in Chapter 2. He advised the Agency to provide a map that showed geographical variability in exposure to oxides of nitrogen and a graph that shows trends over time for each of the exposures to oxides of nitrogen exposure for which there are evidence of health effects over time.

Members of the panel followed with additional comments. A member recommended that the EPA clarify recommendations concerning measurement of oxides of nitrogen. He also asked for more information on fractionation of oxides of nitrogen in summer and winter. Another member (Dr. Christian Seigneur) noted the complicated relationship of NO₂ to nitric oxide (NO) and agreed with Dr. Russell that the NO/ NO₂ ratio was likely to change. He also noted the importance of Figure 2.2-1, which provides a schematic diagram of the cycle of reactive nitrogen species in the atmosphere. He noted the need to clarify several interactions noted in his written comments, including the relationship between PM and nitrate. Other members asked about EPA's current monitoring of oxides of nitrogen (NO_x) vs. NO_y. Agency staff responded that none of the states report NO, and that only a few monitors record exposures to NO₂ specifically. Several members of the panel then noted the desirability of asking or requiring states to provide emission data for NO.

Agency 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?

Agency 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 Chair asked lead discussants to respond to charge questions 2 and 3 together. Dr. Christian Seigneur advised the Agency not to switch measurement methods for NO₂ for purposes of deriving NO_y because health effects' reporting was based on historical methods for measuring

NO₂. He noted that Section 2.3 of the ISA switched from a discussion of NO_y exposures to a discussion of NO₂ health effects. He called for more consistency in discussions of species exposures and effects. He called for more in-depth discussion of near-roadway exposures for NO_x and NO₂ and discussion in the ISA of the tool plans to use for exposure to pollutants of concern.

Dr. Donna Kenski responded that the ISA did not adequately address the properties of oxides of nitrogens. She advised EPA to synthesize information from the annex in the ISA in several ways. She advised EPA to include a map or maps of spatial concentrations across the country, showing spatial gradients within cities and gradients around roadways. She advised EPA to include a map showing monitors that depicts the sparse nature of NO_x monitoring networks in use. She noted that is unrealistic to believe that current monitors capture the exposures experienced by people, especially for short-term peak concentrations that may occur at small scale. She also advised that a revised ISA include more information on temporal variations, so that readers can understand when high concentrations are occurring. She advised that the document clarify the oxides of nitrogen that should be measured from the perspective of protecting public health and then summarize the spatial and temporal dimensions of the monitors available to characterize the species of interest. She also advised that the ISA address how monitoring for oxides of nitrogen is confounded by various species, including ultrafine and fine PM. She noted that the draft ISA touches on this issue in several places but does not address it comprehensively.

Dr. Timothy Larson responded to Charge Question 3. He noted that this broad question related to several issues previously discussed: the need to provide clear and consistent information about the species of chemicals measured; the correlations between personal and ambient exposures; the strength of correlations; the effects of different pollutants generated along with oxides of nitrogen; and clarifying the sources of different oxides. He advised EPA to discuss the siting criteria for NO₂ monitors in terms of their distance from roads and to compare the location of monitors with population densities. He noted that people who live near roads get systematically higher exposures. He also advised EPA to address the issue of vertical integration and exposures to oxides of nitrogen in street canyons, and indoor exposures, given inlets to building. He noted that some European cities site NO₂ monitors next to road in canyons and collect urban background data for comparison.

Dr. Larson advised that the draft ISA discuss the “surrogacy issue,” explicitly how and whether NO₂ serves as a surrogate for other combustion products that have similar health effects, such as PM. He noted several sources of helpful information, such as Canadian studies comparing NO₂ and ultrafine particles.

Dr. James Ultman, the second lead discussant for charge question 2, advised EPA to clarify the ISA discussions to indicate how measurements and effects relate to EPA’s current standards. He recommended EPA to clarify its discussion of personal exposure and integrate equations presented into the text. He emphasized that the ISA should explain how “microenvironments,” relationships between microenvironments, and people’s activities within and moving between microenvironments affect personal exposures (e.g., explain the infiltration of outdoor environments into indoor spaces, including inside cars). He advised EPA to clarify the factors

that relate to key exposures with one or more figures.

He also advised EPA to include a discussion of endogenous nitric acid for treatment of lung disease for people with pre-existing conditions. He noted that with low ventilation, nitric acid can build up in the atmosphere and he asked EPA to discuss the likely effect on physiological function that would occur. He noted that the document did not include much discussion of dosimetry because relatively little research had been conducted on this topic and asked, given the dearth of information available, whether Chapter 2 should be titled "Source to Tissue Dose." Other members responded that the intent of the title was helpful and should not be changed. A panel member suggested that the ISA discuss animal to human extrapolation concerning dose, similar to the Agency's discussion for PM.

Panel members then provided several comments. The chair advised EPA to discuss the Australian study both in chapter 2 and chapter 3 and in each discussion to make the relevant conclusions (about exposure and health effects) clear. Another member emphasized the importance of focusing the discussion of exposure data to prepare EPA to decide the kind of standard needed. He argued that evidence suggests the importance of short-term effects, peak effects. He called for the ISA to evaluate data that would illuminate whether lowering national standard to 15 ppm, would lower exposures. Several members emphasized the importance of providing information in tables that compare relationships between NO₂ and other pollutants, separating annual average vs. peak exposures, outdoor exposures and indoor exposures. A member noted that studies from Southern California show that children closer to roadways are demonstrating low lung functions. Several members emphasized the importance of interpretation of monitoring data that specifies the height of monitors related to people's locations. Although data are sparse, quantitative analysis is important.

The chair noted the importance of CASAC panel advice on monitoring for oxides of nitrogen. Interpreting monitoring results is important for determination of whether an area is in attainment and in understanding the relationship between epidemiological research and monitoring results. A member called for the ISA to provide a more thorough assessment of uncertainties of measurement metrics for NO₂. Such an assessment should help other researchers and decision makers understand the limits and proper use of monitoring data. The panel agreed on the importance of characterizing uncertainties fully for these exposure issues and in the document overall.

A member asked whether the panel had a consensus view about whether NO₂ was the indicator of choice for oxides of nitrogen. Another member responded and stated that the relevant health effects that should be the focus of the ISA should drive monitoring decisions. An Agency representative noted that EPA had considered using NO_y. A speaker from the audience, Dr. Mark Frampton, University of Rochester, spoke and noted that there were direct adverse cellular and respiratory effects for NO₂ at concentration where nitric oxide is therapeutic. A panel member asked a related question concerning the choice of indicator. He asked whether EPA should deal with oxidant pollutants together. Members agreed that the panel's letter should address the multi-pollutant issue. A member noted that the draft document already addresses the issue of multiple pollutants in several places and that multi-pollutant analysis could be a theme in the document. The discussion of susceptible populations would be an important place to

develop this theme. The discussion of asthma, children, and older people could discuss their relative exposures to different oxides of nitrogen, PM, and other products of combustion. Agency staff noted that they were not aware of published studies comparing exposures to these different chemical species for these groups. The panel generally agreed that there was not substantial evidence to move away from NO₂ as an indicator for oxides of nitrogen but that there was concern that multi-pollutant effects needed to be discussed more systematically in the ISA. Multi-pollutant health effects were of great concern, and monitoring and exposure information related to them should be included in the document.

Agency 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?

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

Agency 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 NO₂-related health effects?

Agency 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 NO₂?

Dr. Henderson suggested that lead discussants address charge questions 4, 5, 6, and 7 together. Dr. Terry Gordon noted that chapters 3 and 4 presented health-relevant studies. He advised EPA to eliminate redundancies in the text and discuss only the key studies that illuminate whether the current standard is acceptable or not. All other information should be moved to the Annex. He noted that the epidemiology studies were central and suggested that discussion of susceptible and vulnerable populations in chapter 4 should be moved to a separate section in chapter 3. He also advised EPA to include the magnitude and concentration relations for key endpoints.

Dr. Jonathan Samet noted that he had provided fairly lengthy written general comments relate largely to this charge question. In general, he stated that the document was not sufficiently integrative and that EPA should review other existing models for systematic integrated reviews for designing the ISA. He observed that the document used such terms as plausibility and coherence without definition or systematization reference.

He noted that chapter 3 should integrate information more fully. The chapter contains "mini-reviews" that do not reach a conclusion. He expressed concern that apportioning NO₂ and NO_x is difficult because of their complex chemistry, the role of ozone, and the relationship of NO₂ and NO_x with PM. He noted that his written comments provide figures that suggest how EPA can communicate why NO₂ is the right indicator and that provide a causal model showing

how reduction of NO₂ is related to health benefits. He advised EPA revise the draft ISA to provide more integration of science related to key NAAQS policy questions.

Dr. John Balmes committed to providing written comments. He also noted the need for EPA to articulate clearly the criteria for selecting and evaluating epidemiology studies. He expressed concern that the ISA may not be appropriately balanced, especially given that two negative studies concerning nitric acid vapor that he co-authored did not appear and an additional 2005 study with negative findings concerning NO₂ allergic effects. He also advised that the chapter be revised to communicate information more clearly and eliminate repetition. He also noted that information on mechanism was not well integrated into the text and that tables and figures be edited to check that reference units (e.g., ppm, micrograms per meter cubed) were represented accurately.

Dr. Ronald Wyzga also expressed concern that negative studies were not reported. He called for the chapter to evaluate NO₂ effects in light of exposures to multiple pollutants so that decision makers could consider whether NO₂ served as a surrogate for other chemicals. He advised EPA to consider clinical, epidemiological, and toxicology studies carefully looking at effects regarding co-pollutants. He also advised EPA to provide more consistent analysis of the time lags associated with epidemiology studies discussed in the ISA. Dr. Wyzga committed to providing references for studies relating to co-pollutants.

EPA representative Dr. Mary Ross welcomed references from Dr. Balmes and Wyzga and committed to conducting an additional literature search.

Dr. Jonathan Samet observed that EPA should communicate its strategy for conducting the literature search more transparently. He expressed a caution that interpretation of multi-variable model is complex because of multiple pathways (i.e., direct pathways and indirect pathways) and confounding effects among chemicals. He urged great caution in analyzing multi-pollutant models and advised EPA to build a better framework for interpreting evidence regarding multiple pollutants.

Dr. Edward Postlethwait noted that humans produced NO₂ endogenously whenever they have an inflammatory response. He advised EPA to discuss biological action of the chemical and to automatically equate disease causality with 10 or 20 ppb exposures. Dr. Ed Avol advised EPA to coordinate the work of its writers on sources, exposures, effects and multi-pollutant models. Dr. Kent Pinkerton focused his comments on the toxicology data. He noted that toxicology data are usually 2-to-3 orders of magnitude greater than clinical data, and that clinical exposures are usually 2-to-3 orders of magnitude higher than epidemiological data. He noted that this information could help inform EPA's use of toxicology data. He noted that since the criteria were set in 1973, there have been rare exceedances of the EPA standard. Given that information, he noted the importance of the children's health data: health effects appear in children at 10-20 ppb levels. He viewed this information as critical for the integration of the document and noted that NO₂ health effects attributed may always be confounded with other co-pollutants.

Dr. John Balmes compared NO₂ data with ozone. In contrast to ozone, there are no good clinical and toxicology data at levels close to ambient levels for NO₂. Integration of the epidemiology and toxicology literature on NO₂, therefore, is very important. He advised EPA to devote more attention to that integration and evaluate the direct effects of NO₂ as compared to co-pollutants, especially in light of relatively limited toxicology data related to epidemiological effects.

Dr. James Crapo observed that the draft ISA finds a clear impact occurring on morbidity, but noted that it was unclear whether NO₂ was acting directly, as a surrogate for another chemical, or acting along with a co-pollutant. He noted a gap in knowledge and advised EPA to report findings accordingly. He also expressed some concern about EPA's not reporting negative studies. He noted a positive study from Sweden and Norway not reported relating to the incidence of cancer and air pollution. Although the study reported profound NO₂ effects, he expressed belief that the study overlooked the effects of other air pollutants. Dr. Crapo noted that Table 5.5-3 made a "laudable effort to integrate information about risks" but questioned whether techniques used to standardize metrics (e.g., standardization of excess risks at 95% confidence intervals, excess risk attributable to NO₂ in 20 ppb increments) were appropriate. Other panel members agreed that the table should not imply causality and require a background discussion concerning uncertainties in the data, with distortions likely in both directions (e.g., causality might go away in multi-pollutant model, if NO₂ is poorly measured; NO₂ could be the causal agent, but appear to go away given some multi-pollutant data).

Dr. Stephen Kleeburger echoed other panelists' advice that EPA communicate more effectively the strength of evidence categories and their criteria. He advised that EPA start with A.P. Hill's criteria, discuss different levels of uncertainty, and carry this discussion throughout the document. He advised EPA to synthesize conclusions across disciplines. He suggested that the Agency consider whether effects on clearance and immune function consistent with epidemiological evidence and determine whether there is coherence presented by the data. He advised EPA to relate discussions throughout the document to susceptibility. The document should define susceptible populations more clearly and systematically examine how different toxicological, clinical, and epidemiological data relate to these populations, reporting results as a function of concentration. He advised EPA to consider a tabular format for conveying this information, grouping results in terms of concentrations and exposures. If there is missing information, EPA might consider information available (e.g., sometimes studies report the 98th percentile; sometimes they report maximum or minimum rates or ambient data) and develop a way to characterize by concentration range to inform future decisions about standard setting. He emphasized that ISA conclusions should focus results on susceptible populations, the groups EPA must protect through the NAAQS. He noted that EPA did not necessarily need studies at ambient levels. The Agency can consider available data and evaluate them for biological plausibility. He noted, for example, on pages 4-12 and 4-13, EPA presents a discussion of at-risk susceptible populations and heart disease. He questioned the value of that section. Although there are large and growing populations in those categories, those groups are not necessarily susceptible to NO₂ or heart disease.

Dr. Ed Avol advised EPA to revise the ISA to identify more clearly the conclusions reached about health effects and to provide a decision tree relating to strength, consistency,

coherence and plausibility of evidence that explains how the conclusions were reached. He noted that his written comments provided specific advice and noted that the major issue is the role of NO₂ and other pollutants, especially particulates. He advised EPA to tease out those relationships in the draft so that the Agency can make decisions to protect public health,

He advised the Agency to describe the coherence among toxicological studies, epidemiological studies, field studies, hospital and emergency room reports, looking at multiple endpoints [i.e., asthma, Chronic Obstructive Pulmonary Disorder (COPD), exacerbation of cough, asthma systems and lung growth] and examining confounding issues with PM. He noted that better epidemiological and clinical analyses are finding a profound effect. EPA needs to determine, in light of imperfect evidence, if the effect can be attributable to NO_x. He and other panel members advised EPA to discuss whether there is a threshold for NO_x effects. This information would help inform future decisions about the possible form and averaging time for the standard.

Dr. Jonathan Samet responded to Charge Question 6 and 7 by noting that the draft ISA, as a document, does not establish a plausible case for health conclusions. He advised EPA to look to a Surgeon General's report as a model for assessment and noted that references to strength, consistency, coherence and plausibility were not sufficient. He noted that he did not have "a personal bottom line" regarding conclusions about health effects. He noted that toxicology studies show most effects occur at levels greater than 100 ppb and up. He noted that NO₂ is present at different levels in indoor and outdoor environment. Although there have been many NO₂ studies, the relationship of NO₂ to PM is difficult to interpret. He noted that the OSA overall seemed to show more than expected positive effects, especially in its discussion of epidemiology studies.

The Chair asked Dr. Karen Martin of EPA's Office of Air Quality Planning and Standards to review the purpose of the ISA within the overall process of NAAQS review. Dr. Martin underscored the importance of the science assessment and also noted that EPA considers additional factors in determining the NAAQS level including policy considerations related to the interpretation of "adequate margin of safety," and different forms of the standard. She asked the panel to focus its attention in reviewing the ISA on the science bases for preliminary causal inferences about health effects, so that EPA can proceed to develop its exposure and risk assessments for the effects of greatest concern

Dr. Edward Postlethwait then addressed Charge Question 7. He characterized the ISA discussion as "intuitive but not quantifiable." He advised EPA to consider using American Thoracic Society criteria in its discussion of genetic factors. He advised EPA to include discussion and analysis of the site of disease and to provide a structured discussion of the biology related to different effects, the mechanism of action, the definition of subgroups, exposure of subgroups, and health effects observed within particular subgroups that justify designation as susceptible populations.

Dr. James Ultman also noted that chapter 4 should provide a more structured discussion of susceptible populations. He advised EPA to provide additional information about lung growth studies, especially the California children's health studies. He noted that the chapter should

discuss exposure levels and exposure history, compared to the current standard. He advised EPA to devote more attention to dosimetry and to discuss whether the dose received by a child will be equivalent to the NO₂ dose received by an adult and discuss the implication that children should not be considered as “little adults.” He advised EPA to review the literature and refer to ozone analysis as a model.

Another member suggesting grouping susceptible populations in categories, such as biological susceptibility (e.g., prior disease, age, children); socio- economic susceptibility (lower income populations, exposure to stress and violence); and location (e.g., in vehicle exposures, living close to roadways) to provide a framework for discussion of susceptibility. Other members responded that discussion of high or unusual exposures properly belonged in the exposure chapter. One member called for discussion of populations that fell into multiple susceptible subpopulation categories. Yet another member emphasized the importance of the section on susceptibility and genetics. He noted great potential for linking genetics and genomics to NO and NO_x and encouraged EPA to take a more systematic, open approach to evaluating available literature.

Agency 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?

Dr. Douglas Crawford-Brown focused his initial comments on chapter 5, noting that the chapter did not integrate conclusions from all the chapters effectively. He advised EPA to integrate the conclusions of the ISA within the context of the regulatory decisions to be informed by the ISA and to consider such questions as the incidence of disease at different levels and exposure rates relative to forms a new NAAQS standard might take. .

Dr. Dale Hattis noted that chapter 5 synthesizes information from different study types, but does not communicate the uncertainties weighted by inference. He advised the Agency to consult his written comments and consider ways to replot the data to consider data sets best designed to address the regulatory questions to be informed by the ISA.

Other committee members echoed the call for conclusions about the science that would provide information needed for policy decisions. Dr. Ellis Cowling recommended that EPA consider the guidelines prepared by the National Acid Precipitation Assessment Program Oversight Review Board for developing policy-relevant scientific findings and referred EPA to his written comments for specifics.

Dr. Mary Ross of EPA asked the panel for feedback on the key conclusions on health effects in the draft ISA, as presented in her slides showing short-term and long-term exposures (Appendix E, slides 15 and 16). Panel members individually provided the following comments:

- There was lack of transparency regarding the characterization of short term exposures for respiratory morbidity as likely causal.
- The conclusions generally require a clearer algorithm for determining health effects.

- Likely causal determination for respiratory effects acceptable given indoor epidemiological studies.
- Ranking was acceptable for short-term exposures, with respiratory morbidity having the strongest evidence, but discomfort with labels used by EPA.
- Clinical studies support respiratory effects after several hours' exposure
- If NO₂ were controlled with lower standards, EPA would control co-pollutants and reduce effects listed on slide. Likely net impacts consistent with slide.
- Decreasing NO₂ might increase PM.
- Key issue is whether NO₂ has an independent effect.
- Disagreement with slide showing long-term exposures and indicating "suggestive evidence" for lung cancer.
- Agreement with long-term exposure slide relative rankings
- Evidence for lung cancer is limited.
- Do not list lung cancer incidence in two places (e.g., lung cancer morbidity and mortality including lung cancer).

Summary of Major Review Comments and Recommendations Related to the ISA

Dr. Henderson asked lead discussants whose names were underlined in the agenda to prepare draft written responses to their charge questions that reflected the panel's overall response and to send them to the DFO by 10 p.m. She also listed major themes she had heard during the day's discussion:

1. Multipollutant confounding, is NO₂ a surrogate for air pollution in general?
2. Need balance of negative and positive studies, consider publication bias.
3. Need better integration throughout document.
4. Discuss the uncertainties associated with monitoring:
 - Uncertainties related to measuring technique
 - Criteria for siting monitors
 - Personal exposures versus area monitors
 - Indoor and outdoor exposures
 - Spatial distribution of NO_x
5. Justify causality and plausibility in a systematic manner; discuss dose/response data in toxicology, clinical and epidemiology studies.
6. Proved health effects from short and long-term exposures (this may already be in the report)
7. Condense Chapter 3.
8. Give a framework for evaluations with cross references to annexes for details (could combine this with # 5)
9. Consider that NO_x may be reduced in the future?
10. States should report NO if they monitor it.
11. Add more quantitative data when it is available.

At the chair's request, the Designated Federal Officer adjourned the meeting at 5:15 p.m.

The DFO opened the meeting at 8:30 and noted that one written public comment had been received related to the Agency's draft *Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment*. She noted that the panel had made its draft responses to charge questions discussed on October 25th available and that there had been no formal requests for public comment. Dr. Jon Heuss asked to make a brief public comment. He stated that he would be submitting written public comments on the ISA from the Alliance of Automobile Manufacturers by October 31, 2007 and asked CASAC to consider those comments as they plan to review the next draft of the ISA.

Discussion of Chartered CASAC Acceptance of Major Points Related to the ISA and Next Steps Related to the ISA

The panel then discussed the draft responses to charge questions prepared by designated lead discussants and decided on changes in language as indicated in bold in Appendix H.

In the course of discussions, panel members discussed additional issues:

- the relative importance of placement of vertical monitoring vs. horizontal to capture distribution of NO₂ in confined urban areas to provide health scientists with accurate information about high exposure levels
- The importance of both long term and short-term exposures. Long-term exposures may relate to adverse effects on children's lung development; short-term exposures may be responsible for other adverse effects.

In response to a question from the chair, the panel indicated that they were comfortable with text in Appendix B appearing as the substance of the letter. The chair announced that since a quorum of CASAC members was present, the chartered CASAC had approved the report. The chair said she would work with the DFO to draft the report for panel review before the letter is sent to the Administrator.

Review of Agenda for Consultation on the Draft Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment

The chair then introduced the consultation and emphasized the importance of panel members' written comments to assist EPA in revising the Draft *Nitrogen Dioxide Health Assessment Plan*. Ms. Lydia Wegman of EPA's OAQPS thanked CASAC for its review and introduced Dr. Karen Martin and three OAQPS staff (Dr. Scott Jenkins, Dr. Stephen Graham, and Mr. Harvey Richmond) to introduce the draft plan (see Presentation, Appendix I). Ms. Wegman specifically asked CASAC to identify the most important aspects of the exposure and risk assessment for EPA to identify as priority activities, given time and resource constraints. Dr. Martin noted that ISAs focus on individual pollutant effects and interactions with other pollutants as part of the NAAQS development process. She noted that OAQPS is separately pursuing strategies for controlling multiple pollutants. She viewed these two activities as complementary, not competing, and noted that in the case of PM, where multiple species are involved, the focus of activity is on teasing out the relative toxicity of different species of chemicals within the PM mix.

Members' Discussion – Air Quality

Members individually provided the following observations and questions:

- The plan appears reasonable but is it “do-able” within the 5-month time limit.
- The charge question regarding use of historic data is important and EPA’s proposed approach appears logical.
- Panelist asked whether EPA is seeking alternative ways to model expected exceedances, other than the historical model. EPA responded that it is looking at exponential models and use of logistic regressions that would provide a probability-based analysis. Panelist responded that it appears reasonable to evaluate those other alternatives.
- Panelist called for a realistic scenario that includes a future reasonable growth in traffic causing deteriorating air quality enough to reach or exceed the standard.
- Importance of evaluating data provided by existing monitoring sites for short-term levels. For example, evaluating effects derived from epidemiological data requires information about short-term exposures derived from sites where exposures occur (e.g., 1-hour peak exposure measurements while commuting may be important). EPA responded that EPA would enhance assessment information to try to match exposures with exposure responses and will seek information that is a surrogate for exposure or distribution of exposures. If epidemiology leads to a likely causal conclusion, EPA would try to use ambient fixed sites monitors. If urban clinical results lead to a causal conclusion, EPA would seek the best modeling for the appropriate urban area that replicates effects that are more complicated.
- The proposed approach works for single-family residential exposures but is otherwise questionable. The panel agreed that NO₂ exposure analysis is more challenging than ozone assessment. Drs. Larson and Sheppard committed to provide examples of how to conduct exposure assessments to reflect the complexity presented by NO₂ in an urban street canyon exposure scenario related to likely NO₂ health effects.
- Given the accelerated schedule for NAAQS assessments, there is a need for efficient methods for exposure and risk assessments.
- There is a need for a national assessment, rather than information on individual cities, so EPA should consider developing a national assessment, with estimates of likely peak and long-term exposures, along with a description of the uncertainties and assumptions involved in the modeling.
- Panel members interested in plans to provide ambient vs. total exposure estimates, using co-modeling, reporting total ambient outdoor and indoor measures, with and without indoor sources.
- The AERMOD model appears to have useful capabilities for estimating exposure to roadways but was not developed for that purpose. Recommendation from panelist that the model be specifically evaluated and recommended for that purpose.
- The complexity of air quality modeling is challenging with the street canyon issue, especially given resource and time limitations. Simplification is possible,

but strategies depend on the purpose of the analysis. Air quality modeling has many purposes (e.g., evaluating exceedances, long-term exposures, short-term exposures) and modeling must necessarily be complex. In addition, spatial and temporal variations are not likely to be separable. EPA should think carefully about which monitors are representative for the purpose of a particular analysis before beginning the analysis. EPA should simplify its work to show how much each tier is conditional on a previous tier, and determine those modeling requirements that can be removed in some tier and conducted in only one tier.

Members' Discussion – Exposure

Members individually provided the following observations and questions:

- Plans for the exposure assessment are consistent with a wide range of other assessments.
- Clarify whether plan moves from tier to tier based on outcome of previous tier or based on data availability. Clarify whether the design of Tier 1 is more conservative than other tiers.
- Uncertainty characterization should combine both qualitative and quantitative information. Scenario specification is very important. Do not reduce the discussion entirely to a quantitative probability density functions. Discussion of expert judgment used will be important.
- Uncertainty assessments should identify key assumptions and involve a sensitivity analysis looking at a range of assumptions.
- Do not stop at Tier 1.
- Groundtruth exposure analysis through "tighter mapping" in terms of road designations.

Members' Discussion – Health Risk Assessment

Members individually provided the following observations and questions:

- Retain risk assessment for both 1 hour and long-term exposures. Long-term lung function effects are also important.
- Clarify for each risk assessment tier the populations and outcomes to be addressed and the criteria for choosing them
- In the uncertainty assessment, go beyond sensitivity assessment to look at multiple different assumptions. Discuss different weights for linear and logistic functions that can accommodate multiple assumptions. Dr. Sheppard committed to providing additional detail.
- Panelist liked risk assessment model, choice of health endpoints, and focus on short-term exposures and averaging times.
- Need to go beyond Tier 1 to conduct Tier 2 and 3 assessments, since there are many reports of significant health effects with ambient concentrations of NO₂ below current standard.
- Plan appears thorough; implementation with time and resource constraints is the challenge.

- Be careful to communicate results of Tier 3 assessment based on current epidemiology studies that may use linear models that suggests no threshold. Results may overestimate risk for a particular area.
- Address the issue of possible double counting effects of NO_x, PM, and ozone. Review assessments for all chemicals to check that the total is reasonable.

Summary and Next Steps

1. Dr. John Balmes will provide written comments including negative studies not addressed in the ISA.
2. Dr. Ronald Wyzga will provide references to assist EPA in evaluating NO₂. and co-pollutant effects.
3. Drs. Larson and Sheppard will provide examples of how to conduct exposure assessments to reflect the complexity presented by NO₂ in an urban street canyon exposure scenario related to likely NO₂ health effects.
4. Members who have not provided written comments on the draft ISA and Methods documents will provide them to the DFO.
5. The Chair will work with the DFO to develop a draft peer review letter for the ISA for comment by the Panel.
6. The Chair will work with the DFO to send consultative comments on the method document to the Administrator.

Respectfully Submitted:

/s/

Angela Nugent
Designated Federal Officer

Certified as True:

/s/

Rogene Henderson
Chair

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by committee members during the course of deliberations within the meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice from the panel members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final advisories, letters, or reports prepared and transmitted to the EPA Administrator following the public meetings.

Appendices

Appendix A	Roster
Appendix B	Federal Register Notice
Appendix C	Meeting Agenda
Appendix D	Panel Pre-meeting Written Comments on EPA's Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (First External Review Draft) (EPA/600/R-07/093, August 2007)
Appendix E	Integrated Science Assessment Oxides of Nitrogen Presentation by NCEA/RTP
Appendix F	Public Comment Presentation from Dr. Christopher Long from Gradient Corporation presented comments on behalf of the Utility Air Regulatory Group (UARG)
Appendix G:	Public Comments Presented by Dr. Howard Feldman on behalf of the American Petroleum Institute
Appendix H:	Major Points Related to the Peer Review of EPA's Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria (First External Review Draft, August 2007). Draft Text Generated by CASAC Panel Members for Consideration by CASAC Oxides of Nitrogen Primary NAAQS Review Panel – on 10/25/07 -
Appendix I	Overview of the Scope and Methods Plan Supporting the Review of the Primary NO ₂ NAAQS; Presentation to CASAC October 25, 2007
Appendix J:	Panel Member's Comments

Appendix A: Roster

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

CHAIR

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

CASAC MEMBERS

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

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

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

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

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

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

CONSULTANTS

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

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

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

Dr. Dale Hattis, Research Professor, Center for Technology, Environment, and Development,

George Perkins Marsh Institute, Clark University, Worcester, MA

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

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

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

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

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

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

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

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

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

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

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

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

SCIENCE ADVISORY BOARD STAFF

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

Appendix B: Federal Register Notice

Science Advisory Board Staff Office; Clean Air Scientific Advisory Committee (CASAC);
Notification of a Public Advisory Committee Meeting of the CASAC Oxides of Nitrogen (NOX)
and Sulfur Oxides (SOx) Primary NAAQS Review Panel

[Federal Register: October 9, 2007 (Volume 72, Number 194)]

[Notices]

[Page 57333]

From the Federal Register Online via GPO Access [wais.access.gpo.gov]

[DOCID:fr09oc07-80]

ENVIRONMENTAL PROTECTION AGENCY

[FRL-8480-1]

Science Advisory Board Staff Office; Clean Air Scientific
Advisory Committee (CASAC); Notification of a Public Advisory Committee
Meeting of the CASAC Oxides of Nitrogen (NOX) and Sulfur
Oxides (SOx) Primary NAAQS Review Panel

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The Environmental Protection Agency (EPA) Science Advisory Board (SAB) Staff Office announces a public meeting of the Clean Air Scientific Advisory Committee's (CASAC) Oxides of Nitrogen (NOX) and Sulfur Oxides (SOx) Primary NAAQS Review Panel (Panel) to conduct a peer review of EPA's Integrated Science Assessment for Oxides of Nitrogen--Health Criteria (First External Review Draft) (EPA/600/R-07/093, August 2007) and to conduct a consultation on the EPA's Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment.

DATES: The meeting will be held from 8:30 a.m. (Eastern Standard Time) on Wednesday, October 24, 2007 through 4 p.m. (Eastern Standard Time) on Thursday, October 25, 2007.

Location: The meeting will take place at the Marriott at Research Triangle Park, 4700 Guardian Drive, Durham, NC, 27703, telephone: (919) 941-6200.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes to submit a written or brief oral statement (five minutes or less) or

wants further information concerning this meeting must contact Dr. Angela Nugent, Designated Federal Officer (DFO), EPA Science Advisory Board (1400F), U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, NW., Washington, DC 20460; via telephone/voice mail: (202) 343-9981; fax: (202) 233-0643; or e-mail at: nugent.angela@epa.gov. General information concerning the CASAC or the EPA Science Advisory Board can be found on the EPA Web site at: <http://www.epa.gov/sab>.

SUPPLEMENTARY INFORMATION:

Background

EPA is in the process of reviewing the primary National Ambient Air Quality Standards (NAAQS) for nitrogen oxides (NOX). Under the Clean Air Act, EPA is required to carry out a periodic review and revision, as appropriate, of the air quality criteria and the NAAQS for six criteria air pollutants, which include NOX. Primary standards set limits to protect public health, including the health of "sensitive" populations such as asthmatics, children, and the elderly.

As part of that process, EPA's Office of Research and Development (ORD) has completed a draft document, Integrated Science Assessment for Oxides of Nitrogen--Health Criteria (First External Review Draft) (EPA/600/R-07/093, August 2007, 72 FR 50107) and has requested that CASAC peer review the document. EPA's Office of Air and Radiation (OAR) has also completed a document entitled Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment and has requested that the CASAC provide consultative advice to assist the Agency in developing human exposure and health risk assessments for nitrogen dioxide (NO₂). EPA has released an integrated plan for all aspects of this review of the primary NO₂ standard, Integrated Review Plan for the Primary National Ambient Air Quality Standard for Nitrogen Dioxide (August 2007), which reflects advice provided by the CASAC panel through a consultation on a draft of that document, Draft Plan for Review of the Primary National Ambient Air Quality Standard for Nitrogen Dioxide (February 2007). Background information about the CASAC NOX review activities and about formation of the CASAC Panel was published in the Federal Register on August 7, 2006 (71 FR 44695-44696).

Technical Contact: Any questions concerning EPA's Integrated Science Assessment for Oxides of Nitrogen--Health Criteria (First External Review Draft) should be directed to Dr. Dennis Kotchmar, ORD (by telephone: 919-541-4158, or e-mail: kotchmar.dennis@epa.gov). Any questions concerning EPA's Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment should be directed to Dr. Scott Jenkins, OAR (by telephone: 919-541-1167, or e-mail:

jenkins.scott@epa.gov).

Availability of Meeting Materials: EPA-ORD's Integrated Science Assessment for Oxides of Nitrogen--Health Criteria (First External Review Draft) can be accessed on EPA's National Center for Environmental Assessment Web site at:

<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=181712>.

EPA-OAR's Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment will be accessible via the Agency's Office of Air Quality Planning and Standards Web site at: http://www.epa.gov/ttn/naaqs/standards/nox/s_nox_cr_pd.html. Agendas and materials in support of meeting will be placed on the SAB Web site at: <http://www.epa.gov/sab> in advance of the meeting.

Procedures for Providing Public Input: Interested members of the public may submit relevant written or oral information for the CASAC Panel to consider during the advisory process. Oral Statements: In general, individuals or groups requesting an oral presentation at a public meeting will be limited to five minutes per speaker, with no more than a total of one hour for all speakers. Interested parties should contact Dr. Nugent, DFO, in writing (preferably via e-mail) by October 19, 2007 at the contact information noted above, to be placed on the public speaker list for this meeting. Written Statements: Written statements should be received in the SAB Staff Office by October 19, 2007, so that the information may be made available to the Panel for their consideration prior to this meeting. Written statements should be supplied to the DFO in the following formats: one hard copy with original signature (optional), and one electronic copy via e-mail (acceptable file format: Adobe Acrobat PDF, WordPerfect, MS Word, MS PowerPoint, or Rich Text files in IBM-PC/Windows 98/2000/XP format).

Accessibility: For information on access or services for individuals with disabilities, please contact Dr. Nugent at the phone number or e-mail address noted above, preferably at least ten days prior to the meeting, to give EPA as much time as possible to process your request.

Dated: September 28, 2007.
Anthony F. Maciorowski,
Deputy Director, EPA Science Advisory Board Staff Office.

Appendix C: Agenda

**U.S. Environmental Protection Agency – Science Advisory Board (SAB) Staff Office
Clean Air Scientific Advisory Committee (CASAC)
Oxides of Nitrogen Primary NAAQS Review Panel
Public Meeting
October 24-25, 2007
Marriott at Research Triangle Park, 4700 Guardian Drive, Durham, NC, 27703**

Meeting Agenda

Purpose: to conduct a peer review of EPA’s Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria (First External Review Draft, August 2007) and to conduct a consultation on the EPA’s Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment (September 2007 Draft).

October 24, 2007

8:30 a.m.	Welcome	Dr. Angela Nugent, EPA SAB Staff Office, Designated Federal Officer Dr. Vanessa Vu, EPA, SAB Staff Office
8:40 a.m.	Introduction of Members, Review of October 24th Agenda	Dr. Rogene Henderson, Chair
8:50 a.m.	Highlights of Draft ISA and Agency Charge Questions (Attachment A)	Dr. Ila Cote, EPA, National Center for Environmental Assessment-RTP
9:20 a.m.	First Public Comment Period Discussion and Response to Charge Questions	To be announced
9:35 a.m.	Agency Charge Question 1	Lead Discussants: <u>Dr. Armistead Russell</u> Dr. Ellis B. Cowling
10:15 a.m	Agency Charge Question 2	Lead Discussants: <u>Dr. Christian Seigneur</u> Dr. Donna Kenski
10:55 a.m	BREAK	
11:15 a.m	Agency Charge Question 3	Lead Discussants: <u>Dr. Timothy Larson (by phone)</u> Dr. James Ultman (by phone)

12:00 p.m.	LUNCH	
1:00 p.m	Agency Charge Question 4	Lead Discussants: <u>Dr. Terry Gordon</u> Dr. Jonathan Samet (by phone) Dr. John Balmes (by phone) Dr. Ronald Wyzga
1:40 p.m	Agency Charge Question 5	Lead Discussants: <u>Dr. George Thurston</u> Dr. Jonathan Samet (by phone) Dr. Steven Kleeburger
2:20 p.m	Agency Charge Question 6	Lead Discussants: <u>Dr. James Crapo</u> Dr. Jonathan Samet (by phone) Dr. Ed Avol
3:00 p.m	BREAK	
3:20 p.m	Agency Charge Question 7	Lead Discussants: <u>Dr. Edward Postlethwait</u> Dr. James Ultman
4:00 p.m.	Agency Charge Question 8	Lead Discussants: <u>Dr. Douglas Crawford-Brown</u> Dr. Dale Hattis
4:40 p.m.	Summary of Major Review Comments and Recommendations Related to the ISA	Dr. Rogene Henderson
5:30 p.m.	Adjourn Meeting	Dr. Angela Nugent
October 25, 2007		
8:30 a.m.	Reconvene the Panel Meeting	Dr. Angela Nugent
8:35 a.m.	Second Public Comment Period*	To be Announced
9:15 a.m.	Discussion of Chartered CASAC Acceptance of Major Points Related to the ISA	Chartered CASAC Members
9:45 a.m.	Next Steps Related to the ISA	Dr. Rogene Henderson
9:55 a.m.	Review of Agenda for Consultation on the	Dr. Rogene Henderson

* Members of the public wishing to provide short oral statement on the major review comments and recommendations related to the ISA during the October 25th public session are asked to contact the DFO in person or by email (nugent.angela@epa.gov) before 8 a.m. October 25th

Draft Nitrogen Dioxide Health Assessment
Plan: Scope and Methods for Exposure and
Risk Assessment

10:00 a.m.	Highlights of the Draft Nitrogen Dioxide Health Assessment Plan	Ms. Lydia Wegman Dr. Scott Jenkins Dr. Stephen Graham Mr. Harvey Richmond EPA Office of Air Quality Planning and Standards
10:30 a.m.	BREAK	
11:00 a.m.	Members' Discussion and Deliberation – Air Quality	<u>Lead Discussants:</u> Dr. Ellis Cowling Dr. Donna Kenski Dr. Timothy Larson (by phone) Dr. Armistead Russell Dr. Christian Seigneur
11:45 a.m.	Members' Discussion and Deliberation – Exposure	<u>Lead Discussants:</u> Dr. Douglas Crawford-Brown Dr. Terry Gordon Dr. Lianne Sheppard (by phone) Dr. James Ultman (by phone)
12:30 P.M.	LUNCH	
1:30 p.m.	Members' Continued Discussion and Deliberation – Exposure	
2:15 p.m.	Members' Discussion and Deliberation – Health Risk Assessment	<u>Lead Discussants:</u> Dr. Ed Avol Dr. John R. Balmes (by phone) Dr. James Crapo Dr. Dale Hattis Dr. Steven Kleeburger Dr. Kent Pinkerton Dr. Jonathan Samet (by phone) Dr. George Thurston Dr. Ronald Wyzga
3:30 p.m.	Summary and Next Steps	Dr. Rogene Henderson
3:30 p.m.	Adjourn the Meeting	Dr. Angela Nugent

Attachment Agency ISA Charge Questions

1. To what extent are the atmospheric chemistry and air quality characterizations clearly communicated, appropriately characterized, and relevant to the review of the primary NO₂ NAAQS?
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?
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?
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?
5. To what extent does the integration of health evidence focus on the most policy-relevant studies or health findings?
6. What are the views of the Panel on the conclusions drawn in the draft ISA regarding the strength, consistency, coherence and plausibility of NO₂-related health effects?
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 NO₂?
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?



**Appendix D Panel Pre-meeting Written Comments on EPA’s
Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (First
External Review Draft) (EPA/600/R-07/093, August 2007)**

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 Dr. Ed Avol.....	28
Comments from Dr. John Balmes.....	32
Comments from Dr. Ellis Cowling.....	36
Comments from Dr. Douglas Crawford Brown.....	41
Comments from Dr. Terry Gordon.....	43
Comments from Dr. Dale Hattis.....	45
Comments from Dr. Donna Kenski.....	49
Comments from Dr. Steven Kleeberger.....	52
Comments from Dr. Timothy Larson.....	54
Comments from Dr. Kent Pinkerton.....	56
Comments from Dr. Edward Postlethwait.....	60
Comments from Dr. Armistead Russell.....	61
Comments from Dr. Jonathan Samet.....	64
Comments from Dr. Richard Schlesinger.....	73
Comments from Dr. Christian Seigneur.....	76
Preliminary comments from Dr. ‘Lianne’ Elizabeth Sheppard.....	78
Comments from Dr. Frank Speizer.....	81
Comments from Dr. George Thurston.....	83

Comments from Dr. 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 replaced to read “...models showed that the addition of O₃, smoke, or SO₂ into the model resulted 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 NO_x...” is awkward and a bit confusing; change to “...reported associations with both NO₂ and NO_x 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, Sec 4.2.2 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, line 14 – 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 of 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 NO₂ 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 of O₃, smoke or SO₂...
- p. 3-51, line 23 ...working days shows...
- p. 3-54, lines 5-6 This sentence would be clearer if it read as follows: "...showed increased risks in each quartile for the summer months, 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 arrhythmias." In addition, the Rich et al. (2006a) study of ventricular arrhythmias 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 NAQSS 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 (NO₂) 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, NO_x, NO_y, and NO_z) that have been shown to have significant effects on public health. But the specific rationale for choosing NO₂ 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 NO₂ as the “indicator” for oxides of nitrogen -- See especially the “Key Findings” 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 NO₂

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 rationale behind the original (1971) selection of NO₂ 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 forth 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 October 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 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 NO_x 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 NO_x 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 NO_x 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 NO_x 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 NO_x? Similarly, the rest of the para provided more info on other pollutants than it does on NO_x 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 assessment’.

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 NO_x 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, line 15 – 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 NO_x?

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 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 vertical bias in NO₂ concentrations measured at regulatory monitors, 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 vertical gradients. Ideally there should also be information on the relationship between the slope of the vertical 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. 90th or 99th 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)

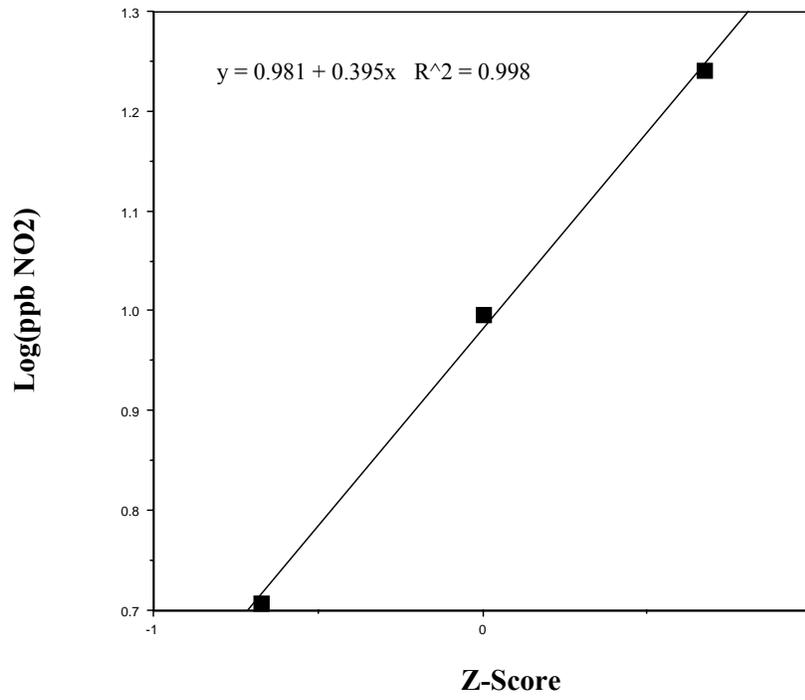
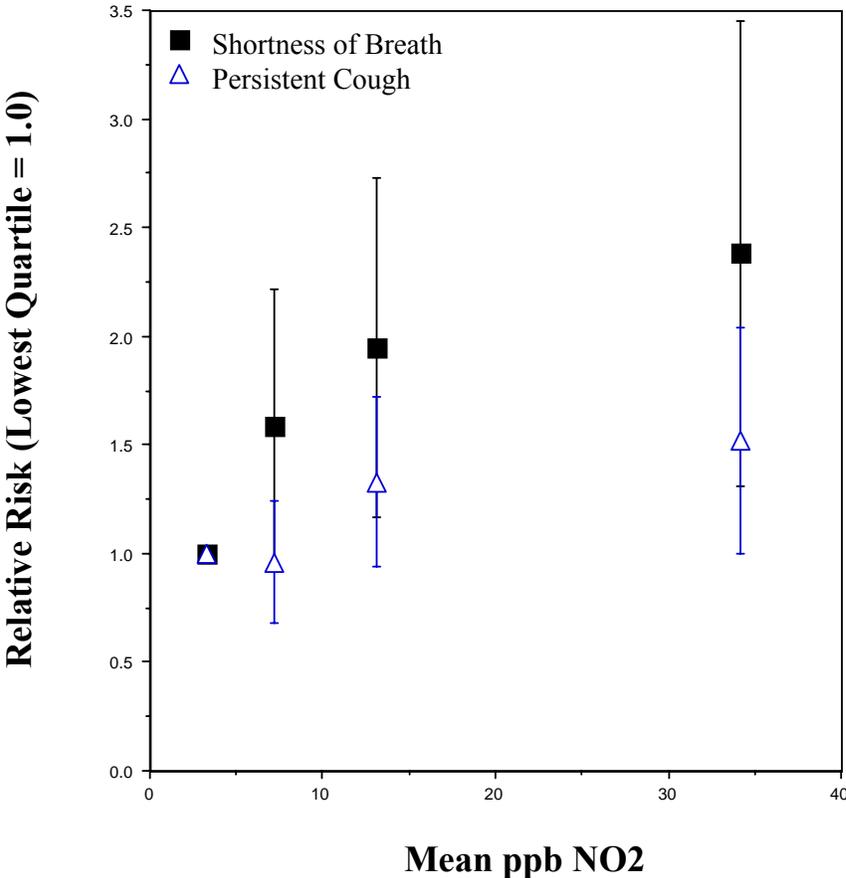
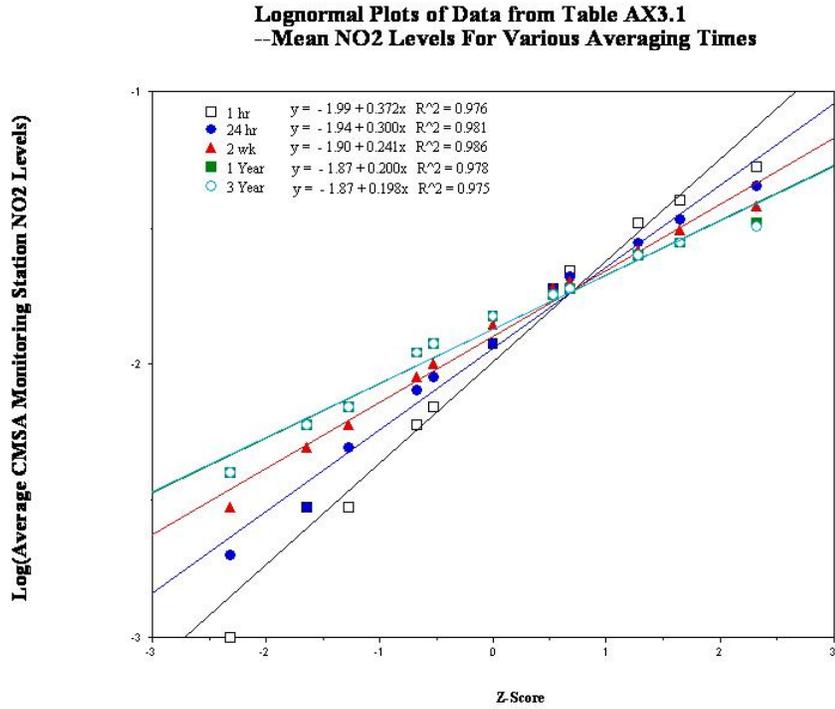


Figure 2
Replot of the Concentration Response Data of van Strien et al (2004) On Linear Axes Based on
Estimates of Mean Concentrations for the Four Quartile Groups



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 NO_z 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 NO_z 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 NO_z 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 NO_y measurements as somehow better than the current NO_x, 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 NO_y 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 NO_x 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 NO_y rather than NO_x. 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 NO_y or NO_y-NO and health effects) must be made explicitly. The last bullet on p. 5-2 is true, existing NO_x monitors can be converted to NO_y monitors fairly easily, but the subsequent calibration, operation, and maintenance of those NO_y 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 <i>not</i> 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 NO ₂ and <i>pollutants other than those</i> presented above.'
		Make lines 13-24 all one paragraph. Rephrase: "Table 2.5-8 shows correlations between NO _x and traffic pollutants measured in ambient air <i>for the Kim 2005 study and several others.</i> " 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 NO ₂ here (i.e., in Sec. 2.4) rather than relegating it to the Annex.
2-38	23	For clarification, add: Motor vehicle emissions <i>of NO_x</i> consist mainly...

2-39	10	Why ‘ <i>still</i> 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 NO ₂ is emitted from power plants, which do have a strong seasonal cycle, there certainly <i>is</i> good reason to suspect seasonal variations in its emissions.
2-42	9	Indoor NO ₂ <i>concentrations</i> or <i>exposures</i> 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 <i>within</i> 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 <i>attacks</i> , not <i>attache</i> ?
4-11	18	Item (2) needs rewording to be meaningful
5-2	25	Measuring NO _y 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.

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 responsiveness to NO_x. 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 responsiveness 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 NO_x. 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 NO₂ it 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 PM_{2.5} 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 NO_x 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 NO_y.

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 NO₂ needed to observe health effects in animals are much higher than those used for NO₂ to observe effects in human studies. To observe toxic effects in animals, most toxicology studies appear to require concentrations of NO₂ well above (by at least an order of magnitude) those implemented in human controlled studies. In a similar manner, are the levels of NO₂ 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 NO₂ standard is justified, while epidemiological studies show clear health (respiratory) effects of NO₂ exposure in both children and adults (particularly in the case of asthma) defined by a 10 to 20 ppb change in NO₂ 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 NO₂. Finally, it is critical to further elucidate if health effects attributed to NO₂ are confounded by co-pollutants or whether NO₂ 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 NO₂ that should be

emphasized in the document.

Page 2-36: The fact that NO₂ behaves similarly to CO and PM_{2.5} as well as the fact that NO₂ may be a surrogate for ultrafine particles emphasizes the potential for confounding effects in the interpretation of health effects due to NO₂. 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 NO₂ 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 NO₂ exposure on morbidity and mortality. The chapter ends with a brief discussion on other chemical derivations of NO₂, namely, NO, HONO and HNO₃.

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 NO₂ exposure at levels well above 1 ppm and 3) the need to further disentangle the confounding effects of NO₂ from that of other co-pollutants, especially PM. It will also be important to further address the potential for NO₂ to simply be a surrogate for ultrafine particles.

Pages 3-2 to 3-6: Excellent recent studies to demonstrate NO₂ 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 NO₂ exposure on systemic effects of immune function should be further elaborated. The primary target of NO₂ 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 NO₂ 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 NO₂ exposure. A concern is the use of quite high levels of NO₂ 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 NO₂ 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 NO₂. 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 NO₂ exposure on childhood asthma management seems to indicate mixed results. How should this material be interpreted relative to previously mentioned studies suggesting strong NO₂ 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) NO₂ levels. Toxicology studies in animals use even higher levels of NO₂ exposure. Since none of these levels of NO₂ 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 NO₂ 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 NO₂ 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 NO₂ directly or whether NO₂ 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 NO₂ exposure. A summary for this section would be helpful. From this section, it would be concluded that NO₂ exposure has minimal cardiovascular impact.

Pages 3-80 to 3-98: The literature on mortality effects of NO₂ exposure are nicely reviewed with excellent summary and integration sections. The conclusions made suggest a consistent increased risk of mortality risk associated with NO₂ exposure. These significant effects associated with small incremental increases in NO₂ 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 NO₂ review on new data in lung function growth from the Southern California Children's Health Study. This study is particularly compelling, but must separate NO₂ 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 NO₂ exposure. Again, many of these studies were conducted using very high levels of NO₂ 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 NO₂ 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 NO₂ exposure based on case control studies is a fascinating observation. However, it is important to assess whether this is a NO₂ 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 NO₂.

Pages 3-143 to 3-150: The discussion of oxides of nitrogen other than NO₂ 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 NO₂.

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 NO₂.

Chapter 5

This chapter on findings and conclusions is a good start. The question of how nitrogen oxides should be defined is relevant. Is NO₂ 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 NO₂ 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 NO₂.

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, i.e., 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 NO₂ 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 NO₂. 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 NO₂ (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 NO_x 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 NO_x comes out as NO, and is then transformed to NO₂ by O₃ and other odd-oxygen species. Thus, after much transport, most of the NO_x 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 NO_y 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 NO_x 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 NO_x. 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 NO_x 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 Restrepo 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 NO_x, and the two must be reconciled and both discussed given the possible rapid conversion.) Much of the discussion of indoor NO_x 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 NO_x 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 NO_x?
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: 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, NO₂ represents an ideal starting point for carrying out an integrated assessment of the literature. There are multiple ways by which sources of NO₂ 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 O₃; 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 NO₂ and adverse health effects, by the actions of one or more other exposures, themselves associated with NO₂ 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 NO₂.

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 NO₂, 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.

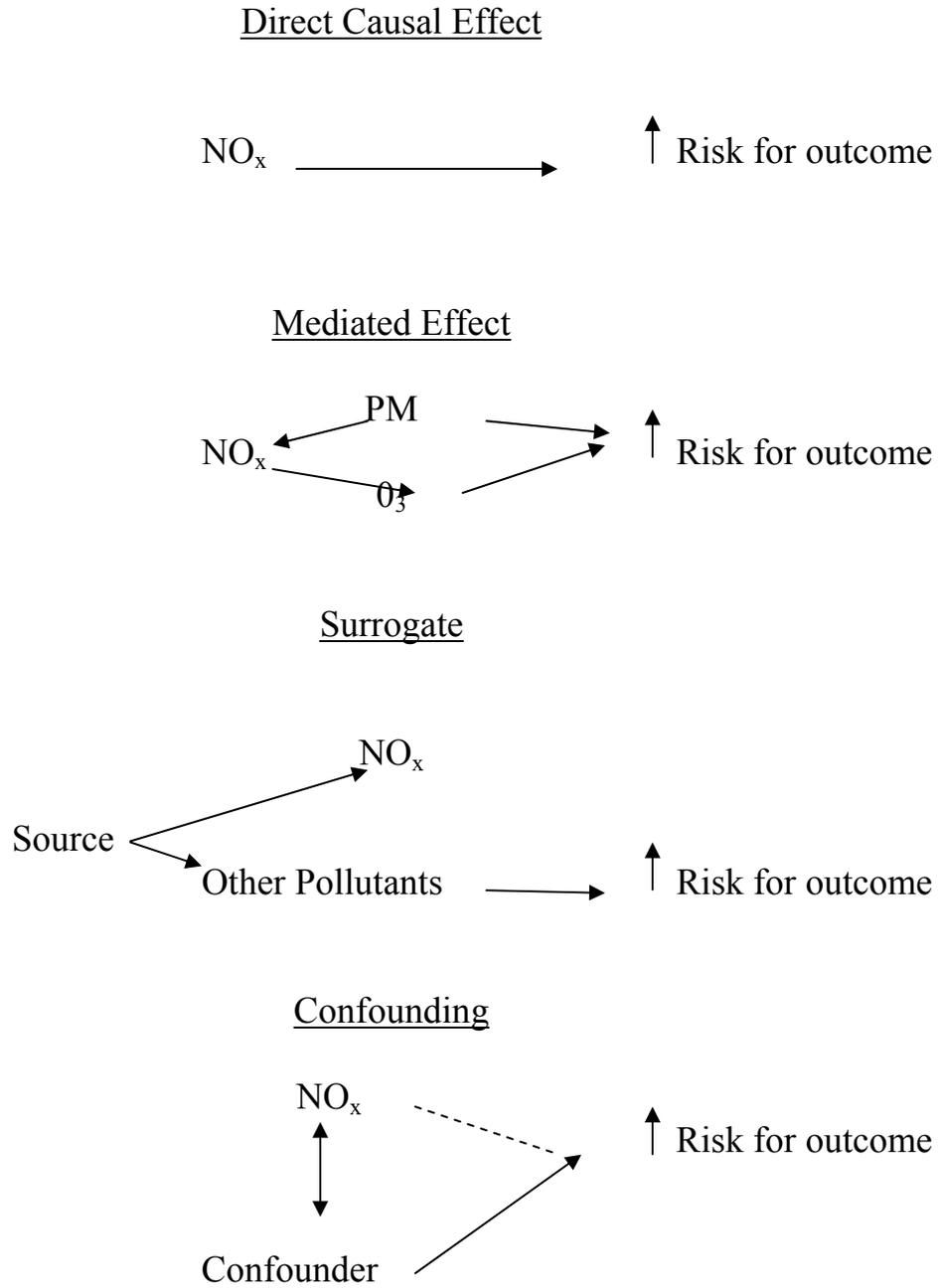
Chapter 4

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 NO₂. 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 NO₂ 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, NO_x 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 NO_x?

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 NO_x.

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 NO_x; 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 NO_x.

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 contradict 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 overstatement.

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 NO_x 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 susceptible 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 NO_x. 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 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 N₂O) and in atmospheric chemistry (only NO and NO₂). 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 NO₂ 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 “NO₂ 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 NO₂ that are less than 5% of NO. Also, diesel vehicles equipped with particulate emission control now have NO₂ 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/NO₂ 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 NO₂ from HNO₃). The arrow leading to NO₃⁻ from NH₄⁺ 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 NH₄⁺. 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 NO₂. 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 HNO₃ by aqueous particles (rather than aerosols) will not remove HNO₃ from the atmosphere very rapidly unless it rains; similarly, uptake by cloud droplets will not remove HNO₃ 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 NO₂ 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 NO₂ concentrations. A major issue with NO₂ 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 NO₂ exposure

Charge question 4: This chapter discusses the results of clinical, toxicological and epidemiological studies related to NO₂ exposure. In the case of epidemiological studies, the uncertainty in the NO₂ ambient concentration measurement is of interest (I assume that the use of higher NO₂ concentrations in clinical studies minimizes the measurement uncertainty). It is likely that the NO₂ 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 NO₂ measurement. However, the health effects discussion of Chapter 3 addresses predominantly NO₂. How would EPA use a NO_y monitoring network to determine the attainment status of a NO₂ standard?

Charge question 2: Section 5.3, pp 5-3 and 5-4: The strong NO₂ 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. NO₂ 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 O₃ ISA rather than for a NO_x ISA. For example, the discussion of CMAQ model performance evaluation focuses on ozone (rather than NO₂) and does not reflect in any case the most recent performance evaluation studies.

Preliminary comments from Dr. 'Lianne' Elizabeth Sheppard

Comments on the ISA

The overall organization of the ISA successfully provides a shorter document with a more integrated perspective. Chapter 2 is successful from an organizational perspective, but I had difficulty with many details. Chapter 3 ideally will be simplified and shortened. However, there are so many subtle differences between studies and effect estimates so I am concerned that the effort to condense will make such distinctions even more opaque. The integrated synthesis of Chapter 5 gives about the right level of detail. 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.

2-15 | 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 and cohort studies target different aspects of exposure and thus different measurement features will dominate.

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

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

2-17 | 30: Insert annual? “mean annual concentration”?

2-17 | 31: Modify to “between daily measurements at individual site pairs”.

2-18 | 1: Insert “daily average” before concentrations. How is COD calculated?

2-18 | 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 | 26-28: Why would sheer number of monitors be a reason for representativeness of community or personal exposures?

2-25 | 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.

2-29 | 17: F_{inf}

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

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

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

2-32 | 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 | 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 | 8-9: While the statement that indoor sources could affect ambient levels is certainly true, how often would this influence be a large contribution enough to matter practically?

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

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

2-35 | 23: Clarify the phrase “in moving away from the urban core”.

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

2-36 | 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 | 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 | 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 suggest 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 | 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 | 4: Can’t the figure also show the wheeze results?

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

2-49 caption: Note SD

2-50 | 11: Give the reader more context. For instance, begin the sentence with “Among the _____ outcomes evaluated, ...”

2-51 | 11-14: 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: The term “significant” or “statistically significant” appears to be used as synonymous with scientifically important. If a result is worth mentioning I think the estimate and 95% CI should also be given, regardless of the statistical significance. (e.g. 3-15 | 10)

3-23 | 13: There were no NO₂ data in Seattle, so this city should be dropped from the list.

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

3-24 | 6, 7: Given the prevalence of cough, 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 | 5-22: More information is needed about the universe of studies being compared before these conclusions can be drawn.

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

Chapter 5:

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

**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 NO_x 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 least 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 findings 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 NO_x-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 NO_x associations with health separately discussed across all the document aspects (e.g., in Toxicology: is NO_x affecting macrophage ability to handle particles?, or in Epidemiology: is NO_x 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 SO_x and NO_x documents. Overall, while there are smatterings of references (here and there) to PM-NO_x interactions as a 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 SO_x 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 word “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..."

Page 3-36, 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 criteria? 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 NO_2 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 NO_2 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, lines 1,2. 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 line 15-16. 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.).

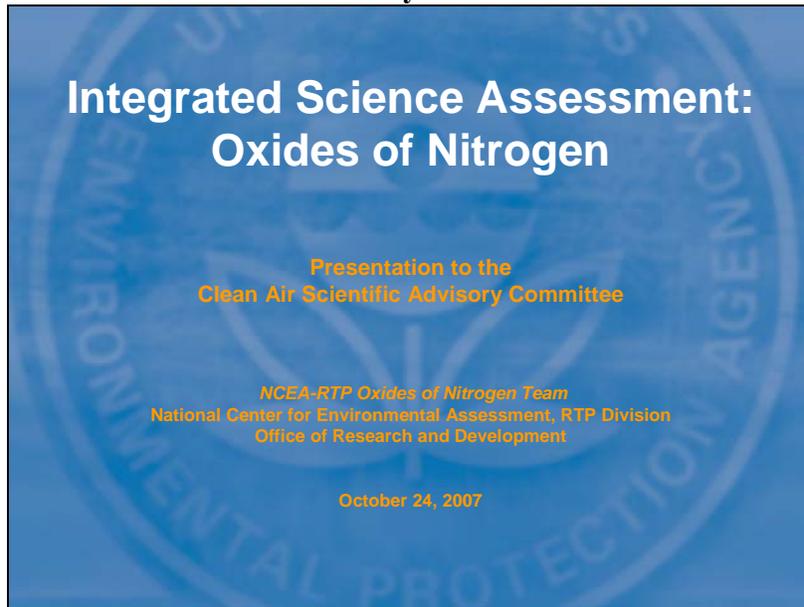
Page 3-149. Consider the potential implications, if any, of gaseous acidity on the bio-availability of transition metals in particles in the same aerosol.

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"?

Slide 1



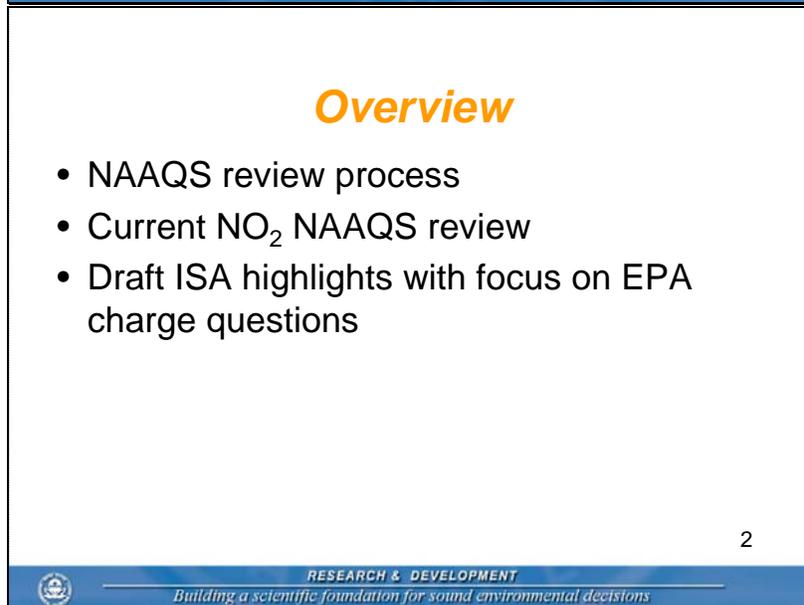
**Integrated Science Assessment:
Oxides of Nitrogen**

Presentation to the
Clean Air Scientific Advisory Committee

NCEA-RTP Oxides of Nitrogen Team
National Center for Environmental Assessment, RTP Division
Office of Research and Development

October 24, 2007

Slide 2



Overview

- NAAQS review process
- Current NO₂ NAAQS review
- Draft ISA highlights with focus on EPA charge questions

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 **RESEARCH & DEVELOPMENT**
Building a scientific foundation for sound environmental decisions

Slide 3

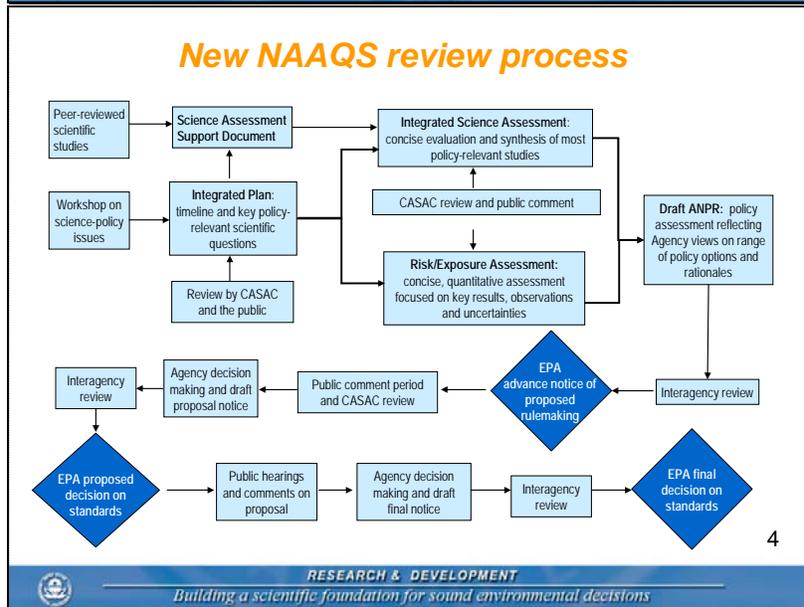
New NAAQS review process: Key steps

- **Planning:** Early in the process, NCEA/OAQPS will develop one integrated plan to guide the entire review
 - Plan will outline schedule, process, and key policy-relevant science issues
- **Science Assessment:** The Criteria Document will be replaced by a more concise evaluation and synthesis of the most policy-relevant science
 - Integrated Science Assessment (ISA): Drawing from detailed Annex chapters, provides concise evaluation and synthesis of the most policy-relevant science
 - ORD working to develop and implement process (state-of-the-art electronic database) to identify, compile, characterize, and prioritize new studies
- **Risk/Exposure Assessment:** OAQPS will develop a more concise document, informed by the ISA, that focuses on key results, observations and uncertainties
- **Policy Assessment/Rulemaking:** The Staff Paper will be replaced with an advance notice of proposed rulemaking (ANPR) containing a policy assessment that reflects Agency views, rather than staff views
 - ANPR will present a range of policy options for standard setting, and will include a description of the underlying interpretation of the scientific evidence and risk/exposure information that might support each option

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Slide 4



Slide 5

Integrated Science Assessment Preparation

- Initial preparation of ISA annex to provide more comprehensive, detailed review of recent studies
 - Discipline-specific focus
 - Chapters on atmospheric science, exposure, toxicology, controlled human exposure studies, epidemiology with more detailed summaries of study findings
 - Workshop held in February 2007 for peer review of initial draft annex chapter materials and discussion of focus for integration of evidence
- ISA draws from annex chapters to evaluate and synthesize evidence
 - Health outcome focus
 - Evidence from different disciplines integrated and assessed
 - Strength and robustness of evidence from specific disciplines
 - Coherence and plausibility of evidence for various health outcomes
 - Recommendations and conclusions provide scientific support for future risk and exposure analyses, policy assessment

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Slide 6

History of the NO₂ NAAQS

- **1971:** EPA promulgated first NAAQS for NO₂
 - Primary and secondary NAAQS set at 0.053 parts per million (ppm), annual average
- **1985 and 1996:** NAAQS for NO₂ reviewed and existing standards retained
- **September 2005:** Complaint filed by the Center for Biological Diversity (and others) on 5 year deadline for review of the NO₂ standards
 - February 2006: Complaint was amended to add SO₂
- **Spring 2006:** Both parties file motions for summary judgment with proposed schedules for completing reviews of NO₂ and SO₂ NAAQS
- **Fall 2006:** Briefing on motions for summary judgment completed
- **Present:** We are waiting for the judge's decision on the schedule

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Slide 7

Schedule for the Current Review

Major Milestones		Projected Completion Date	Projected CASAC Review Date
Integrated Science Assessment	First Draft	August 2007 (completed)	October 2007
	Second Draft	February 2008	May 2008
	Final	July 2008	
Risk/Exposure Assessment	Plan	September 2007 (complete)	October 2007
	First Draft	March 2008	May 2008
	Second Draft	August 2008	September 2008
	Final	November 2008	
Policy Assessment/Rulemaking	ANPR	December 2008	January 2009
	Proposed	May 2009	
	Final	December 2009	

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Slide 8

NCEA-RTP NO_x TEAM

ISA IN SUPPORT OF THE PRIMARY STANDARD

Dr. Ila Cote – Acting Division Director
Dr. Mary Ross – Branch Chief

Dr. Dennis Kotchmar - NO_x Team Leader

Dr. Jeff Arnold
Dr. James Brown
Dr. Jee Young Kim
Dr. Ellen Kirrane
Dr. Thomas Long
Dr. Thomas Luben
Dr. Qingyu Meng
Dr. Joseph Pinto
Dr. Paul Reinhart
Dr. David Svendsgaard
Dr. Lori White
Dr. William Wilson

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Slide 9

ISA organization

- Integrated science assessment
 - Introduction
 - Source to dose
 - Integration of health evidence
 - Public health impact
 - Conclusions
- Annexes: more detailed summaries of evidence
 - Atmospheric chemistry, physics
 - Measurements, sources, etc.
 - Toxicology and dosimetry
 - Controlled human exposure studies
 - Epidemiology

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Slide 10

Charge Questions 1-3

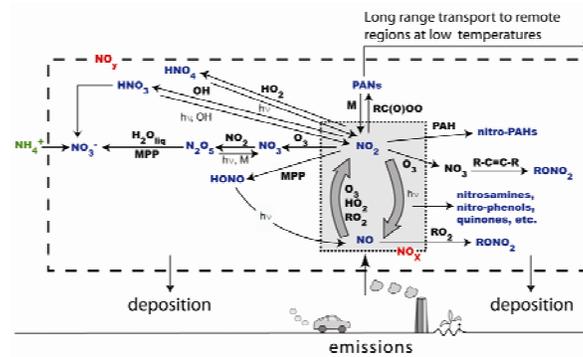
- To what extent are the atmospheric chemistry and air quality characterizations clearly communicated, appropriately characterized, and relevant to the review of the primary NO₂ NAAQS?
- Are the properties of ambient oxides of nitrogen appropriately characterized, including policy-relevant background,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

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Slide 11

Cycle of Reactive Nitrogen Species in the Atmosphere



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Slide 12

Oxides of Nitrogen: Definition, Measurements, Concentrations

- Atmospheric chemistry: processes involving NO_2 result in the formation of photochemical oxidants such as O_3 and PAN and the strong acid, HNO_3 , as well as compounds such as nitro-PAHs
- It has long been known that measurements of NO_2 in ambient air are subject to interference by NO_z compounds, chiefly HNO_3 and PAN
 - Measurement of NO_y (the sum of NO_x and NO_z) is a more precise measurement of oxides of nitrogen and captures more of the total mix of oxides of nitrogen than does NO_x
- Annual average concentrations of NO_2 (~15 ppb) are well beneath the level of the current NAAQS (~53 ppb). However, daily maximum 1-h average concentrations can be greater than 100 ppb in a few locations that are heavily influenced by traffic.

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Slide 13

Personal – Ambient Exposure Relationships

- The evidence relating ambient levels of NO₂ to personal exposures is mixed
 - Many of the studies examined found that ambient levels of NO₂ were significant proxies of personal exposures to NO₂.
 - However, a number of studies did not find significant associations between ambient and personal levels of NO₂.
 - A number of factors contribute to these results.
- Epidemiologic studies often use measurements at central sites to estimate population exposures
 - Measurement error often results in underestimated risk estimates and increased standard errors

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Slide 14

Charge Questions 4-6

- 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?
- To what extent does the integration of health evidence focus on the most policy-relevant studies or health findings?
- What are the views of the Panel on the conclusions drawn in the draft ISA regarding the strength, consistency, coherence and plausibility of NO₂-related health effects?

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Slide 15

Key Conclusions: Short-term Exposures

Respiratory morbidity: likely causal

- Strongest new evidence from epidemiologic studies of ED visits and hospitalization
- Confirm previous findings of associations with increased respiratory symptoms (cough, wheeze) especially in children and asthmatics; particularly new multicity studies with ambient NO₂ exposures, and studies of indoor/personal exposures
- Evidence of airways hyperresponsiveness and inflammation from controlled human exposure and toxicologic studies, especially in susceptible groups
- Limited new evidence on lung function decrements and loss of lung capacity in children from epidemiologic studies

- **Cardiovascular morbidity: inconclusive**
- **All Cause Mortality: suggestive evidence**

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 **RESEARCH & DEVELOPMENT**
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Slide 16

Key Conclusions: Long-term Exposures

- **Respiratory morbidity: suggestive evidence**
 - Decreased lung function growth
 - Increased asthma prevalence
- **Lung cancer incidence: suggestive evidence**
 - Associations reported with NO₂ in two epidemiologic studies, but no support from animal tox studies for carcinogenicity of NO₂
 - Atmospheric reaction products of NO₂, such as nitro-PAH's, may be carcinogenic
- **Adverse birth outcomes: limited evidence**
- **Cardiovascular effects: no evidence available**
- **Mortality (including lung cancer): inconclusive evidence**

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Charge Questions 7-8

- 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 NO₂?
- 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?

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Slide 18

Potentially Susceptible and Vulnerable Subpopulations

- Preexisting disease status
 - Respiratory diseases, especially asthma
 - Viral infections
- Age
 - Children
 - Older adults
- High exposure populations
- Genetic susceptibility

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**Appendix F Public Comment Presentation from Dr. Christopher Long
from Gradient Corporation presented comments on behalf of the Utility Air
Regulatory Group (UARG)**

Slide 1

Gradient
CORPORATION

Comments on the Integrated Science
Assessment (ISA) for Oxides of Nitrogen-
Health Criteria (August 2007 Draft)

On Behalf of the Utility Air Regulatory Group
(UARG)

Christopher M. Long, Sc.D.
Peter A. Valberg, Ph.D.
October 24, 2007

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Slide 2

Gradient
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EPA Paradigm for Assessing the
Strength of the Evidence

- On p. 5-7, EPA proposes a decision paradigm
*“to draw conclusions regarding the overall strength of the
evidence and the extent to which causal inference may be made.”*
- EPA identifies several essential characteristics
of scientific data bearing on the health effects of
ambient NO_x:
 - Strength
 - Consistency
 - Coherence
 - Plausibility (*i.e.*, showing dose-response)

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Slide 3

Summary of EPA Decision Paradigm

Level of Inference ↓	Required Level of Findings				
	Epidemiology	Clinical	Experimental		
<i>“likely causal”</i>	strong / consistent / coherent / plausible	AND	strong / consistent / coherent / plausible	AND	strong / consistent / coherent / plausible
<i>“suggestive”</i>	strong / consistent / coherent / plausible	OR	strong / consistent / coherent / plausible	AND	limited
<i>“inconclusive”</i>	limited	AND	limited	AND	limited

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Slide 4

- ### EPA’s Application of Its Paradigm
- Several examples where evidence is described as “weak,” “inconsistent,” “with no clear pattern,” “confounded,” and/or “limited” and EPA makes overall determination that evidence is *“inconclusive”*
 - Short-term NO₂ exposure and CV effects
 - Long-term NO₂ exposure and mortality
 - However, quantitative (or even methodical) criteria as to what constitutes “strong,” “consistent,” “coherent,” and “plausible” evidence are not clearly outlined, and in some cases, the text does not seem to reflect rigorous application of EPA’s paradigm
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Slide 5

Examples of Inconsistencies in EPA's Application of Its Paradigm

- On p. 5-8, in its conclusion that there exists a "likely causal" relationship between short-term NO₂ exposure and adverse respiratory effects, EPA appears to heavily rely upon "strong" new epidemiological data of associations between ambient NO₂ and increased ED visits and hospital admissions for respiratory causes
 - However, nowhere is the "strength," "consistency," "coherence," and "plausibility" of these epidemiological data systematically assessed, despite observations in Chapter 5 that these studies typically showed high correlations between a number of co-pollutants (e.g., NO₂, CO, and PM), and that there remains uncertainty as to whether NO₂ is the causal agent or is instead a marker for the effects of another traffic-related pollutant or mix of pollutants.
- The first sentence of the "Mortality and Short-Term Exposure" section (p. 5-10) identifies the epidemiological associations as "suggestive" and later in the section, clinical and experimental evidence are characterized as "limited."
 - This would support an overall conclusion of "inconclusive," but in the Conclusions section (p. 5-16), mortality evidence is inexplicably characterized as "suggestive."

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Slide 6

Recommendations for EPA

- Overall, the ISA document would be strengthened if the EPA evidence-evaluation paradigm was consistently implemented.
- That is, "strength," "consistency," "coherence," and "plausibility" require more quantitative definition. Often, the positive attributes of data are merely given as "significant evidence," "numerous studies," "new insights," "robust effects," and "high correlations."
- The supportive (or non-supportive) role of clinical and experimental studies at the specific ambient concentrations in question is not fully presented.

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**Appendix G: Public Comments Presented by Dr. Howard Feldman on
behalf of the American Petroleum Institute**
**October 24, 2007 API Comments before the Clean Air Scientific Advisory
Committee Oxides of Nitrogen and Sulfur Oxides Primary NAAQS Review Panel
during its Peer Review of the EPA Integrated Science Assessment (ISA) for
Oxides of Nitrogen (NO_x)—Health Criteria (First External Review Draft)
(EPA/600/ R-07/093, August 2007)**

Good morning, my name is Howard Feldman and I am here on behalf of the American Petroleum Institute. API represents almost 400 member companies involved in all aspects of the petroleum industry. We appreciate the opportunity to comment on the initial draft NO_x ISA being considered today by the Clean Air Scientific Advisory Committee NO_x/SO_x Panel.

Overall, our preliminary review indicates that significant changes need to be made to the draft ISA before it can be considered to accurately reflect the current state of the science. The draft ISA conclusion that NO₂ concentrations below the current standard are causing health effects is based primarily on observational epidemiology. The inherent limitations of these studies do not permit such a conclusion. The reasons for our view and the key changes we recommend to the draft ISA are provided as follows.

- 1. We disagree with the crucial ISA conclusion that NO₂ measurements on regulatory ambient monitors provide a good correlation with personal NO₂ exposure from ambient sources and that NO₂ measurements on ambient monitors are a good surrogate of personal exposure for use in observational epidemiology studies.** These ISA conclusions contradict those in the final PM Criteria Document and Staff Paper. In the PM review, EPA concluded that monitored gaseous ambient concentrations, including NO₂, were *poorly* correlated with personal gaseous pollutant exposures and better correlated with personal PM. Nor are ambient-personal exposure conclusions in the draft ISA supported by results of recent studies in Baltimore, Boston, and Steubenville (Sarnet et al. 2001, 2005, 2006; Koutrakis et al., 2005) that confirm the poor correlation of ambient and personal NO₂ exposures. Furthermore, the ISA acknowledges that the federal reference method for NO₂ fails to provide reliable measures of NO₂ but rather of NO_y, a signal derived from the conversion of a number of additional nitrogen-, sulfur-, and chlorine-containing species that varies in response to the composition of the ambient mixture (e.g., olefins sensitize sulfur compound responses) and humidity (ASTM, 2006).

We recommend that the draft ISA be revised to conclude that (1) ambient NO₂ levels are poorly correlated with personal NO₂ exposures from ambient sources; that (2) ambient NO₂ measurements are a poor surrogate for personal NO₂ exposure in observational studies; and that (3) observational studies reporting effects of NO₂ are confounded by ambient PM.

- 2. We disagree with ISA conclusions that there is *strong evidence* that ambient NO₂ levels below the current standard are causing decreased lung function, respiratory symptoms, and increased emergency department visits and hospital admissions. We also disagree that there is *suggestive evidence* that current ambient levels of NO₂ are causing acute cardiopulmonary mortality.**

Pulmonary Function - The ISA cites a number of observational epidemiology studies as evidence of lung function effects from acute exposure. No association of peak expiratory flow rate (PEFR) with NO₂ exposure is reported in 9 of 9 (9/9) studies using self reported PEFR measurements. The ISA (3-18) discounts these negative results concluding that such PEFR results are notoriously unreliable. This conclusion contradicts EPA use of PEFR studies in the draft ozone NAAQS rule (e.g., Mortimer et al., 2002, Neas et al., 1995, Naeher et al., 1999; Ross et al., 2002). In 2/3

studies performed using spirometry (e.g., FVC, FEV₁), small associations were reported using single pollutant models (Linn et al., 1996; Timonen et al., 2002). Since similar responses were observed for other highly correlated air pollutants, it is not possible to attribute the effects to NO₂ alone in these studies. In the third study (Hoek and Brunekreef 1994), no association was reported using spirometric measures. The ISA proceeds to inappropriately discount results from human clinical studies, including studies of potential susceptible groups such as the elderly or those with chronic obstructive pulmonary disease, which fail to report pulmonary function effects at ambient concentrations (e.g., Table 5.5-1 indicates inconsistent effects for FVC and FEV₁ in COPD patients, citing Gong et al., 2005, Morrow, et al., 1992, and Vagaggini et al., 1996) *We recommend that the draft ISA be revised to conclude that there is inconclusive evidence, rather than strong or suggestive evidence, of acute pulmonary function effects at current ambient NO₂ level.*

Respiratory Symptoms -Schildcrout et al. 2006 is cited by the ISA as *strong evidence* of respiratory symptoms in child asthmatics. We commend EPA for considering this study, which was ignored during the ozone review, possibly because it reported no positive associations for ozone. However, Schildcrout et al. do not provide clear much less strong evidence for an independent effect of NO₂. In 3/4 results, the risks attributed to NO₂ were not statistically significant when PM₁₀ was included in a multi-pollutant analysis.

We recommend that the draft ISA be revised to conclude that there is inconclusive evidence, rather than strong or suggestive evidence, of respiratory symptoms at current ambient NO₂ levels.

Emergency Department (ED) Visits and Hospital Admissions from Acute Exposure - EPA cites selected results from observational studies as evidence of independent effects of NO₂ on ED visits and hospital admissions. However, (1) the results of the studies are mixed with some reporting positive statistically significant associations while others do not; (2) in many of the studies reporting positive associations, only single pollutant models were used (and if - as EPA has concluded - ambient NO₂ levels are better surrogates for personal PM exposure than for NO₂ then single pollutant models have *no* weight in determining NO₂ causality); (3) in many studies that the ISA considers “positive”, only one of multiple model results presented was statistically significant; and (4) the NO₂ risks were not generally robust to inclusion of other pollutants. Rather, in many of these studies, the risks attributed to NO₂ were markedly reduced in multi-pollutant models (e.g., Linn et al., 2000; Peel et al., 2005; Yang et al., 2005).

We recommend that the draft ISA be revised to conclude that there is inconclusive, rather than strong, evidence for an independent causal NO₂ association with increased ED visits and hospital admissions.

Acute Cardiopulmonary Mortality – The ISA concludes that multi-city studies, particularly the National Morbidity and Mortality Study (NMMAPS), provide the most useful information for determining whether ambient NO₂ is associated with acute mortality. Although this study provided the primary basis for earlier mortality effect evaluations for both PM and ozone, the authors (Dominici et al., 2003) report *no association* between NO₂ and total mortality. The ISA apparently revises conclusions of the NMMAPS authors without performing published or reviewable independent reanalysis. The ISA also reinterprets the Canadian 8-city study (Burnett et al., 2000) assuming little PM confounding although the authors report that inclusion of PM_{2.5} markedly reduced the risk estimates for NO₂ particularly when every day PM data were available.

We recommend that the draft ISA be revised to conclude that multi-city and mechanistic studies provide no convincing evidence, rather than suggestive evidence, that current levels of ambient NO₂ are causing acute cardiopulmonary mortality.

I thank you for your consideration.

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Appendix H: Major Points Related to the Peer Review of EPA's Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria (First External Review Draft, August 2007). Draft Text Generated by CASAC Panel Members for Consideration by CASAC Oxides of Nitrogen Primary NAAQS Review Panel – on 10/25/07 -

1. To what extent are the atmospheric chemistry and air quality characterizations clearly communicated, appropriately characterized, and relevant to the review of the primary NO₂ NAAQS?

Some tune-up is required in the discussion of sources and atmospheric chemistry in Chapter 2 (and later the Conclusions and Summary), and how the pertinent sections relate to reviewing the standard. First, one needs more quantitative information on the sources of NO_x, and the speciation of NO_x, both indoors and out. These should be put in perspective of where the sources tend to be (including their elevation: this discussion does come up later) and co-pollutants being emitted. How these factors 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 being used are susceptible to interferences as to the reported NO₂ levels in that other oxidized nitrogenous species are included in the signal, leading to a potentially high bias. As such, it is important to provide quantitative information on the extent/level of potential bias in specific metrics of ambient NO₂ levels/air concentrations, e.g., the expected uncertainty/bias in annual averages, daily maximum(s), etc., and how they vary by time of day, season, and altitude. Given that the health literature suggests that NO₂ is at least as likely to be the pollutant of concern (vis a vis, e.g. nitric acid, PAN, HONO, etc. 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. Given that the current method does measure both NO and something that approximates NO₂, both should be regularly provided to EPA and made available. The uncertainties associated with the current method should be described.

It would be very helpful to have in the ISA 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 and through any of the major economic, transportation, military, and political events that may have some relevancy to emissions of oxides of nitrogen events since 1971. Information is needed about the location of NO₂, NO_x, NO_y, or other monitors– location in terms of proximity to roadways, size of roadways, and the list of NO_x, PM, O₃, and other pollutants measured at these same monitoring sites.

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?

Speciate NO_x wherever available
Include known information about temporal paradigms for personal monitoring
Need more information about peak exposures
Importance of temporal and spatial variability

Nitrogen oxides species:

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, NO₂, HNO₃, PAN, etc.) as a function of location and time should be discussed. Also, a more accurate depiction of PM nitrate species (both inorganic and organic) is needed in Figure 2.2.1.

Spatial and temporal variability:

A better description of the spatial and temporal variability of nitrogen oxides (NO₂, but also other nitrogen oxides as well) is needed. In particular, the spatial variability of nitrogen oxides near roadways should be discussed since it is directly relevant to the discussion of high-exposure individuals in Chapter 4.

Ambient monitoring:

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, i.e., if the NAAQS is based in part on epidemiological studies that used a certain monitoring technique for ambient NO₂ concentrations, the designation of attainment or non-attainment should be based on the same or a similar monitoring technique. If a significantly new technique were to be used, then some correction may be needed.

A map of the current NO₂ monitoring network and concentrations would be useful.

NO should be reported by the states since the measurement is available from the current monitoring method (which measures NO and NO_x = NO + NO₂ + some fraction of other N species; NO₂ is obtained by difference of NO_x and NO).

The siting of monitors will be critical for future attainment designations and exposure assessments because of the strong gradients in nitrogen oxides concentrations near roadways.

The difference in NO₂ 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.

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 emissions of NO₂ 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 NO₂ levels with other co-pollutants, including ultrafine particles.
- The relationships between indoor and outdoor levels of NO₂ deserve more discussion, particularly the relevance of the parameter, α , relating ambient levels to personal exposures.
- The spatial variability of NO₂ within urban areas is very complex. There is inadequate discussion of potential exposure misclassification due to the effect of the 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.
- Integrate information about the current standard in order to give perspective to the ambient exposure data cited in graphs and tables.
- Add some discussion of the biological activity of inhaled NO, particularly with respect to cardiovascular function.
- Include some discussion of extrapolation modeling in the dosimetry section, and its relevance to determining equivalent exposures in animals.
- Important features of monitoring data, exposure, and their relationship depend upon the intended epidemiological study design.

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 ideally only the key studies that support a NAAQS should be included (**CLARIFY WHAT KEY STUDIES MEAN**). In addition, the document has to identify the relevant chemical species of concern and clearly discuss how the processes involved in NO_x production result in additional air pollutants which confound study findings. For communication purposes, it's 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 – this latter is the key to Chapter 3 but also the overall quality of the ISA. In regard to the integration across the 3 study types of epidemiology, clinical, and animal toxicology, the ISA would be improved if a plan or process for integration and study selection was clearly laid out **SO IT WOULD BE CLEAR TO READER WHY STUDIES WERE INCLUDED**.

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

Discussants felt that this needs improvement in the document. The emphasis given to the indoor and intervention studies in Chapter 5 was generally felt to be appropriate. One important comment from several reviewers was that providing a more comprehensive framework for the assessment of studies at the start of the document would allow a more consistent evaluation the various study evidence for its relevance. In addition, several reviewers noted a need for greater attention to integration across chapters. To enable this, we must have a more comprehensive evaluation of 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., from toxicology vs. epidemiology) in order to see which health results are coherent or inconsistent with each other. Members (**Ron Wyzga, John Balmes**) also **pointed out that several of the several recent epi and toxicological studies that examined relationships between NO_x and health effects were either not included or not cited correctly**. Finally, examining the epidemiology results across outcomes as a function of exposure concentration would help clarify whether there is a dose-dependence to any associations or effects noted.

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

Since the 1993 AQCD a substantial body of evidence has been developed that documents adverse health effects associated with exposures to ambient or near ambient levels of NO₂ 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 effects in sensitive populations such as children, asthmatics and those living and working near roadways, **GENETIC POLYMORPHISMS SHOULD ALSO BE EXPLORED**. Field and panel studies have demonstrated relationships between NO₂ exposure and both respiratory symptoms and pulmonary function impairment. The relationships between these adverse health effects 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. NO_x levels may, in part, 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. CASAC concurs that the **epidemiologic findings indicate** that current ambient NO₂ exposures **is** associated with adverse impacts to the public health, **but that the ISA better document that these findings are plausible, consistent and coherent**.

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 NO₂?

- Define “susceptible” populations with regard to the extent of response relative to the general population.
- Reorganize susceptible populations under the umbrellas of biological, socioeconomic, and geographic locale.
- This topical area would be strengthened by including integration among disease states, measured outcomes, exposure, and potential mechanisms of action that related specifics of NO₂ biology to pathobiological perturbations. The chapter did not address biological plausibility with regard to specific populations and thus it is difficult to attribute health outcomes to direct causal actions of NO₂.
- 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 NO₂ exposure. **Explain rationale relating to injury, growth, repair**
- Some discussion of dosimetric differences between adults and children would be useful; 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)

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 asks us to consider whether the entire ISA document provides adequate support for "future risk, exposure and policy assessments", we consider it essential that Chapter 5 summarize all of this support succinctly and rigorously so readers can understand how NCEA is drawing scientifically sound conclusions from the previous chapters. As it stands currently, this goal is not met by Chapter 5. The most significant problems are that: (i) the bulleted conclusions in Chapter 5 are not always the most relevant findings from the earlier chapters; (ii) 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, (iii) 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. Cowling in his individual comments), and (iv) the conclusions drawn do not adequately address the uncertainties in slope factors, causal claims and the efficacy of control measures targeting NO₂ 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 the kind of support called for in this Charge Question.

Multiple Pollutant Aspects of the ISA for Oxides of Nitrogen

The present (August 2007) Integrated Science Assessment document for oxides of nitrogen contains many references to:

- 1) the role of gaseous NO and NO₂ in the formation and accumulation of ozone and other photochemical oxidants,
- 2) the role of NO and NO₂ 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, and
- 4) the likelihood that the respiratory functions of 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.

These four 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 USEPA consider development of a

multiple-pollutant approach in air quality management – this as an alternative or addition 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, particulate matter, and lead.

In addition to the present “one-pollutant-at-a-time” approach to air quality management, CASAC recommends that EPA give serious consideration to developing a multiple-pollutant–multiple-effects approach to air quality management in this country. The approach EPA may choose could be very similar to- (or very different from-) the multiple-pollutant–multiple-effects approach currently being implemented by the European Union through its 2003 (?) adoption of the Gothenburg Protocol.

Appendix I Overview of the Scope and Methods Plan Supporting the Review of the Primary NO₂ NAAQS; Presentation to CASAC October 25, 2007

Slide 1

**Overview of the Scope and Methods
Plan Supporting the Review of the
Primary NO₂ NAAQS**

Presentation to CASAC
October 25, 2007

Slide 2

Purpose of this Meeting

- Solicit feedback on EPA's planned approach to assessing risks and exposures associated with NO₂

2

Slide 3

Overview

- Background
 - Schedule
 - Conclusions from previous review
 - Scope of the Planned risk and exposure assessment
- Exposure Assessment
 - Tier I
 - Tier II
 - Tier III
- Risk Assessment
 - Tier I
 - Tier II
- Charge Questions for CASAC

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Slide 4

Background: Schedule

Major Milestones		Completion Date	CASAC Review Date
Integrated Review Plan	Draft	April 2007 (complete)	May 2007
	Final	August 2007 (complete)	
Integrated Science Assessment	First Draft	August 2007 (complete)	October 2007
	Second Draft	February 2008	May 2008
	Final	July 2008	
Risk/Exposure Assessment	Plan	September 2007 (complete)	October 2007
	First Draft	March 2008	May 2008
	Second Draft	August 2008	September 2008
	Final	November 2008	
Policy Assessment/Rulemaking	ANPR	December 2008	January 2009
	Proposed	May 2009	
	Final	December 2009	

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Slide 5

Background: Overview of Conclusions from Previous Review

- In the previous review of the NO₂ NAAQS, the Administrator concluded that the existing annual standard will...
 - Maintain annual NO₂ concentrations considerably below the long-term levels for which serious chronic effects have been observed in animals
 - Provide protection against short-term peak NO₂ concentrations associated with mild changes in controlled human studies
- Basis for conclusions regarding short-term exposures
 - Air quality assessment evaluated the relationship between annual average NO₂ levels and short-term (1-hour average) NO₂ levels
 - Number of exceedances of various short-term benchmark values was estimated with the assumption of just meeting the current standard
 - Short-term benchmarks evaluated ranged from 0.15 ppm to 0.3 ppm
 - Result: If the existing annual standard is attained, short-term NO₂ levels of potential concern would be unlikely in most parts of the country

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Slide 6

Background: Scope of the Planned Risk and Exposure Assessment

- NO₂ will be considered as the surrogate for the gaseous nitrogen oxides
 - Little health data available for other gaseous species
 - Particulate nitrogen oxides are addressed by current NAAQS for particulate matter
 - Most recent review concluded that size-fractionated particle mass, rather than particle composition, remains the most appropriate approach for addressing ambient PM
 - This conclusion will be re-assessed in the next review
 - However, at present it would be redundant to also use the NO₂ NAAQS to protect against the health effects of particulate nitrogen oxides
- Assessment will evaluate the risks and exposures associated with...
 - Recent ambient levels of NO₂
 - Ambient levels of NO₂ associated with just meeting the current standard
 - Ambient levels of NO₂ associated with just meeting potential alternative standards
- Assessment will focus on both short- and long-term exposures/risks

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Slide 7

Exposure Assessment: Overview

- Goals of the exposure assessment:
 - Estimate short- and long-term exposures associated with current levels of ambient NO₂ and assuming alternative levels of ambient NO₂
 - Develop quantitative relationships between long-term average and short-term peak concentrations of NO₂
- Approach
 - Tier I: air quality characterization
 - Tier II: screening-level exposure assessment
 - Tier III: refined exposure assessment
- Populations Considered
 - general population
 - susceptible/vulnerable populations (as identified in ISA): children (birth to 18), asthmatic children (birth to 18), asthmatic adults (>19), and the elderly (>65)
- Assessment of uncertainty
 - At each analysis Tier, will progress from qualitative to quantitative depending on availability of data and anticipated magnitude of the uncertainty

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Slide 8

Exposure Assessment: Tier I

- Purpose: To estimate potential exposures using
 - historic and current ambient monitoring data (1995-2006) as a surrogate for exposure
 - enhancement factors to estimate on-road NO₂ from ambient monitoring data
 - available concentration data for outdoor (e.g., utilities) and indoor (e.g., gas stoves) sources
- Locations Considered
 - based on air quality trends, data availability, population demographics, location of NO₂ epidemiologic studies, and inclusion of a range of geographic areas
 - Los Angeles, Houston, Atlanta, Philadelphia, Chicago, and aggregation of others
- Expected output
 - Descriptive statistics for NO₂ concentrations in selected locations
 - Relationships of short-term peak levels to long-term average levels
 - Identification of additional areas to be modeled in Tier II and/or III, if needed
- Uncertainty
 - Assessment of uncertainty and variability will be primarily qualitative
- Tier I exposure assessment will provide input to a tier I risk assessment to identify exposures of concern (i.e., exposures that exceed identified health benchmarks)

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Slide 9

Exposure Assessment: Tier II

- Purpose: To improve characterization of the relationship between ambient concentrations, local sources, and exposure considering
 - on- and near-roadway concentrations using dispersion model and/or enhancement factors
 - modeled concentrations for other outdoor and indoor sources, if any, identified in Tier I
 - influential factors
 - e.g., time spent in broad microenvironments, decay of NO₂ indoors, population
- Locations Selected
 - Individual locations identified in the Tier I air quality characterization
- Expected output
 - Short-term Exposure Outcome
 - Temporally and spatially resolved ambient levels of NO₂ accounting for local sources
 - Estimates of the number of individuals who may experience exposures of concern
 - Long-term Exposure Outcome
 - Annual average exposure levels for each census tract
 - Ratios of exposure to ambient for assessing exposures in other locations not modeled
- Uncertainty
 - Model to measured comparisons for near-road and microenvironmental concentrations
 - Limited sensitivity analyses on model input data/distributions

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Slide 10

Exposure Assessment: Tier III

- Purpose: Refine the approach for addressing personal human attributes (e.g., time-location-activity patterns, human physiology) using
 - on- and near-roadway concentrations using dispersion model and/or enhancement factors
 - EPA's Air Pollutants Exposure Model (APEX)
 - Monte Carlo approach where individuals in a population are simulated as they move through time and space
 - Also used to estimate concentration contribution of indoor sources
- Locations Selected
 - Individual locations used in the Tier II exposure analysis
- Expected Output
 - Counts of people exposed one or more times to several NO₂ levels based on evaluation of the ISA
 - Counts of person occurrences of a particular exposure
- Uncertainty
 - Model inputs
 - assessed with a Monte Carlo approach using specified distributions for each input
 - e.g., air exchange rate, NO₂ decay rate, physiological parameters
 - Model formulation
 - assessed by comparing model predictions to measured values (where data are available), or
 - qualitatively evaluating plausible uncertainties for sub-models

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Slide 11

Risk Assessment: Overview

- **Goals of risk assessment**
 - To estimate number of occurrences of short-term air quality events and number of people exposed at or above various potential health effect benchmarks associated with alternative NO₂ scenarios
 - To provide health risk estimates for NO₂-related health endpoints associated with alternative NO₂ scenarios (if a Tier II assessment is conducted)
 - Identify and characterize key assumptions, variability, and uncertainty associated with the assessments
- **Scenarios evaluated**
 - Recent air quality levels, air quality levels just meeting the current standard, and air quality levels just meeting potential alternative standards
- **Two-tiered approach**
 - Tier I: Potential Health effects benchmark levels (based on review of ISA) compared to air quality and/or exposure estimates
 - Tier II: Combine concentration-response or exposure-response data with exposure estimates to generate population risk estimates (if judged feasible and of sufficient utility)

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Slide 12

Risk Assessment: Tier I

- Air quality levels (from the tier I exposure assessment) or estimated exposure levels (from a tier II or III exposure assessment) will be compared to potential health benchmark levels for several example urban areas
- Health effect benchmarks will be identified from the 2nd draft ISA
 - Tentative benchmarks: 0.2 to 0.3 ppm (1-hour averaging time) in asthmatics (children and adults)
 - Based on controlled human exposure studies
 - Uncertainty about health effect benchmarks will be qualitatively addressed
 - Will use alternative benchmark levels to illustrate impact of alternative choices about lowest exposure level of concern
 - Variability:
 - Geographic variability addressed by conducting analysis for several example urban areas
 - Population variability in response addressed qualitatively
- Projected outcomes:
 - Number of occurrences of air quality levels at or above several benchmarks
 - Number of times in a given year that a population or individual experiences various exposure levels of concern

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Slide 13

Risk Assessment: Tier II

- If conducted, would estimate number of individuals in selected populations for several example urban areas expected to experience specified health effects
- Would be based on epidemiologic literature
 - Preliminary judgment that controlled human exposure studies do not provide enough information to identify credible exposure-response relationships
 - Still evaluating whether or not epidemiological evidence adequate to conduct credible quantitative risk assessment
- Criteria for determining if Tier II assessment conducted
 - Outcome of Tier I assessment
 - Availability of info and data required to conduct a Tier II assessment (e.g., adequate C-R functions, baseline incidence data for urban areas)
 - Utility or value-added to decision process, beyond insights provided by Tier I assessment
 - Feasibility of conducting a Tier II assessment within consent decree schedule and resources

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Risk Assessment: Tier II (Continued)

Based on our analysis of the first draft of the ISA...

- A tier II risk assessment, if conducted, would focus on short-term (1- and 24-hour) ambient levels and respiratory-related effects
 - Respiratory-related hospital admissions, especially for asthmatics
 - Respiratory-related emergency department visits, especially for asthmatic children
 - Respiratory symptoms (e.g., cough and wheeze), particularly in children and asthmatics
- Risk estimates based on both single- and multi-pollutant models would be reported
- Uncertainty associated with the NO_x coefficient in the concentration-response function would be addressed by providing confidence intervals around point estimates of risk and by presenting a range of results based on different epidemiological studies from different cities
- Expected outputs (in each case central tendency and 95% confidence interval estimates would be provided)
 - Estimated incidence (number of cases)
 - Incidence per 100,000 relevant population for each health endpoint
 - Hypothetical change in incidence associated with moving from just meeting current standard to just meeting potential alternative standards

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Broader Risk Characterization

- Summary of U.S. air quality information and discussion of various health effects from the ISA
 - Provide context for quantitative risk estimates
 - Will include air quality statistics for all areas of U.S. with NO₂ monitoring data
- National-scale information on size of potentially susceptible populations will be presented

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Slide 16

Charge Questions for CASAC

- Does the Panel have comments on the way we propose to use air quality data?
 - Approaches to simulating just meeting current and potential alternative standards
 - Using annual average air quality levels to estimate expected exceedances of short-term health benchmarks
 - Approach to estimating on- and near-roadway NO₂ concentrations
 - Approach to addressing uncertainty and variability
- Does the Panel have comments on the way we propose to assess exposures?
 - Proposed choice of models
 - Identification of groups of interest (children, asthmatics, elderly)
 - Developing individual exposure profiles through the use of APEX
 - Approach to addressing uncertainty and variability
- Does the Panel have comments on the way we plan to assess health risks?
 - Proposed choice of health endpoints
 - The proposed approaches for conducting risk assessments
 - Approach to addressing uncertainty and variability
- Does the Panel have comments on the proposed criteria for deciding whether to proceed to a more sophisticated analysis (i.e., higher tier) for assessing exposures and/or risks?

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**Attachment J: Comments from CASAC Oxides of Nitrogen Primary NAAQS
Review Panel on EPA’s
Draft Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure
and Risk Assessment (September 2007 Draft)**

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Comments from Dr. Ed Avol

Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment (Draft September 2007)

General Comments:

The document provides a useful road map for how the Agency will proceed on the Risk Assessment. If the plan is to only provide a Tier I assessment (air quality characterization) and attempt to argue that insufficient information exists to assess exposure, I believe the Agency will find its own credibility and level of commitment questioned. The annexes provide a wealth of information about the current state of knowledge regarding NO₂, and most reasonable and objective reviewers will conclude, I believe, that sufficient information exists to perform the Tier II assessment, and to seriously consider the Tier III assessment. The modeling approaches can provide us with guidance if they are applied appropriately, and we should move forward. Continuing to vacillate and wait for complete and perfect information before deciding that there is sufficient data to proceed (which will ultimately end with an estimate and range, anyway) does not serve the public health or the public's interest.

It would be helpful to have a listing of Abbreviations and Acronyms in this document, to which the reader could refer for clarification.

Specific Comments:

P6, Sec 3.1, para2, line 1 – “Several tools would...” should be “Several tools will...”

P6, Sec 3.1, last paragraph discussing evaluation of uncertainties: This discussion is well-intentioned but not well-constructed. What are the objective criteria by which the exposure assessment will be determined to be worthy of a qualitative or quantitative assessment? How will the magnitude of uncertainty (minimal/moderate/maximal) be assigned? Does a rating of “minimal” (which I would think would be the starting point for every evaluation) lead to qualitative or quantitative determinations? How about two “minimals” and one “moderate” in the matrix of uncertainties, or other possible combinations? And what about over and under-estimates – are over-estimates going to be viewed as more conservative and therefore less uncertain, or vice versa? It is difficult to see how this proposed process will lead to a logical, credible determination, based on what is provided here. Staff may well have a clear understanding and process in mind, but that procedural clarity has not been effectively communicated in writing in the document.

P7, Sec 3.2, para2, last sentence – How will “...those commuting on roadways and persons who reside near major roadways...” be incorporated into the modeled population?

P8, Sec3.3, para 1, first sentence – “All available ambient monitoring data collected since...1995...will be used as is.” Presumably what is meant is that all *quality-assured* ambient air monitoring data collected since 1995 will be used?

P8, Sec 3.3.1, para1 (regarding the selection of CMSAs for evaluation) - Presumably some tabular summary will validate this selection of cities, but why Atlanta, Philadelphia, and Chicago over New York, Phoenix, and Denver? Some additional and transparent justification for CMSA selection should be provided.

P13, Sec 3.3.1.3, para 1, last sentence – This summary claim of “...insignificant to limited contribution...” of biomass combustion and ETS to NO₂ personal exposure is an over-simplification and over-interpretation of what is presented in the referenced Chapter of the ISA. Please review the referenced chapter and re-evaluate the accuracy of this summation.

P.15, Sec 3.3.3, para 1 (Ambient NO₂ measurement), last sentence – In areas like Los Angeles, where significant reductions in NO₂ in the past decade have only recently resulted in achievement of NAAQS compliance, the assumption that sources present in the past are the sources present now is almost certainly

a poor one; some sources are no longer present, and engine/boiler/source emission reduction controls have changed substantially to achieve emission reductions. How will this be addressed or handled?

P15, Sec 3.3.3, para 3 (Spatial Representativeness), line 6 – Low spatial correlations could be the result of several circumstances other than the presence of local sources (for example, topographical intrusions such as canyons, hills, or slopes between sampling locations leading to local variations in wind direction or wind speed).

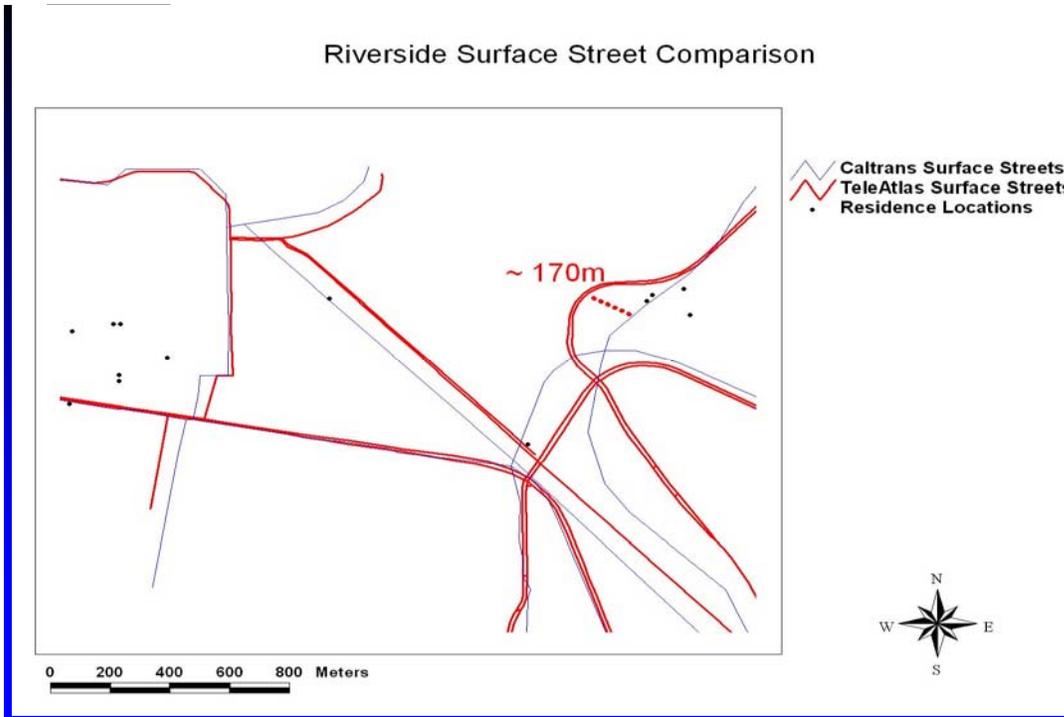
P16, Sec 3.3.3, para 1 (Roadway to Ambient Monitor Relationship), lines 14-19 – Is the implication here that NO₂ is a “...reactive pollutant...” and will tend to have a lower I/O ratio? This assertion should be compared to more recent information about in-vehicle measurements. It is my understanding that based on the available information, NO is higher in the passenger compartment (due to the fresh emissions from combustion exhaust being drawn into the vehicle compartment), and that NO₂ is somewhat elevated over ambient (reflecting on-roadway conditions), but that NO₂ is not as high as near off-roadway (because there has been insufficient time for NO to oxidize to NO₂).

P16, Sec 3.3.3, para 1 (Roadway to Ambient Monitor Relationship), last sentence) – Some qualifier must be missing from this statement, because this seems to directly contradict the earlier explanation made in the justification of Equation 3.

P17, Sec3.4 Tier II Screening-Level Exposure..., para 1, bullet 3 – “...factors that contribute to lessened personal exposures to ambient NO₂...including time spent indoors and indoor vehicles...” – Doesn’t the recent in-vehicle measurements suggest in-vehicle NO₂ is somewhat elevated?

P17, Sec3.4 Tier II Screening-Level Exposure..., para 2, lines 6 thru 8 – Is there some protocol for when to apply one of these approaches or the other? Presumably one or two hourly gaps could be filled in using interpolation between valid values at the ends of the missing gap, but this approach would lead to incorrect values if gaps included morning or afternoon traffic hour peaks (since it would not capture or re-construct the peak structure).

P17, Sec 3.4.1 Short-Term Exposure Approach, para1, “...TIGER ROAD network...” If this refers to the road structures based from the highway transportation files, there may be some issues with road placement accuracy, compared to commercially available Tele-Atlas road files. In working with the road files in Southern California to locate streets and residents’ homes for Children’s Health Study-related research, the transportation files were demonstrated to be occasionally mis-located by 100 meters or more compared to the Tele-Atlas files and the actual location of the roadways. This variation can be critical when considering near-road pollutant exposure (see figure below), given the decay of pollutants with distance from roadways.



P31, Sec 4.1 Risk Assessment Scope Overview..., para2, last sentence – Failing to assign some risk estimate to long-term NO₂ exposures runs the risk of not protecting public health from the more potentially more serious and persistent health effects (from long-term, low-level exposures). This sounds akin to ignoring the quantification of the impact because we don't yet fully understand it. At the very least, a statement or discussion should be included discussing this.

P33, Sec 4.3 Tier II Risk... - "health responses reported to be related to NO₂ include..." lists several health outcomes, but does not include low lung function (from the Children's Health Study).

P37, Sec 4.4 Criteria for Determining Approach, last bullet- This undertaking is supposed to lead to the Agency's best efforts to assess the current information regarding NO₂ health effects. The suggestion that there might not be enough time (after allowing 14 years to pass since the previous document release) or insufficient resources to accomplish what the Agency is charged to do is simply not credible; this bullet should either be revised or removed.

Comments from Dr. Ellis Cowling

**Individual Comments on the Nitrogen Dioxide Health Assessment Plan:
Scope and Methods for Exposure and Risk Assessment**

My comments are organized below in response to each of the several Charge Questions posed in Karen Martin's September 2007 transmittal letter to Angela Nugent.

Air Quality Considerations

1. Do the Panel members generally agree with using historic air quality data (e.g., pre2000) in certain analyses as a reasonable approach to simulating air quality scenarios with higher NO₂ concentrations, given that current ambient air quality concentrations are lower than the current standard?

Yes, I agree that historical data is a reasonable approach even though some of the historical air concentration measurements may be higher than current ambient air concentrations.

2. Based on the low estimated contribution of policy-relevant background NO₂ to overall ambient NO₂ levels, staff is considering a proportional (i.e., linear) approach to adjusting air quality to simulate just meeting potential alternative NO₂ standards that are lower than current air quality concentrations. Do the Panel members have comments on adopting a proportional approach to simulate just meeting more stringent alternative air quality standards?

Although I am surprised that the contribution of policy-relevant background is as low as it is currently estimated to be, I see no great problem in using a proportional method of adjustment. I have no additional comments to add.

Exposure Analysis

1. In considering the exposure analysis broadly:

a. Do Panel members have any comments on the general structure and overall three-tier approach that staff plans to use for the exposure analysis? Are the criteria that staff plans to use for deciding whether to conduct a Tier II or Tier III analysis clear and appropriate?

The three tier approach seems reasonable to me and the criteria suggested by staff also seem reasonable.

b. Have the most important factors influencing exposure to NO₂ been clearly accounted for and described?

My only major concern is to know whether, and if so, how indoor exposures will be considered and evaluated.

c. The draft plan describes the basis for and selection of population groups of interest (i.e., children, asthmatics (children and adults), and the elderly) for which NO₂ exposure estimates are to be developed. Do Panel members generally agree with the groups of interest identified in the draft plan?

The suggested population groups seem very reasonable to me.

2. In considering the Tier I exposure assessment:

a. Do Panel members agree that an exponential model is appropriate for estimating expected exceedances of short-term health effect benchmarks based on long-term annual average air quality?

I have no experience on which to base an informed judgment in response to this question.

b. Do Panel members agree with the approach to enhance NO₂ air quality data by accounting for the influence of roadway emissions?

Yes, this approach seems reasonable to me.

3. In considering a potential Tier II exposure assessment:

a. Do Panel members agree with the combined emissions/dispersion modeling approach to estimate short-term (hourly) on- and near-roadway NO₂ concentrations?

I have no experience on which to base an informed judgment in response to this question.

b. Is the proposed use of time-location-activity diary data reasonable for estimating short-term exposures for population cohorts?

I have no experience on which to base an informed judgment in response to this question.

c. Do Panel members agree with the use of HAPEM6 to estimate long-term exposures (annual average) and the approach to account for on- and near-roadway NO₂ concentrations?

I have no experience on which to base an informed judgment in response to this question.

4. In considering a potential Tier III exposure assessment:

Do Panel members generally agree that developing individual exposure profiles through the use of APEX is reasonable and appropriate to estimate both short- and long-term NO₂ exposures?

I have no experience on which to base an informed judgment in response to this question.

5. Do Panel members have any comments or advice regarding the general approach to addressing uncertainty and variability in each Tier of the exposure assessment as described in the draft plan?

I have no experience on which to base an informed judgment in response to this question.

Health Risk Assessment

I have no experience on which to base an informed judgment in response to any of these several Health Risk Assessment questions.

Comments from Dr. Douglas Crawford Brown

Review of the Draft Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment

Doug Crawford-Brown

This review follows the Charge Questions for the chapter on Exposure. A general comment is that I approve of the overall methodology to the extent it is specified in the document. The outline of the methodology comports with past Agency practice and has the potential to generate the kinds of variability and uncertainty characterizations of risk needed for a rigorous setting of a NAAQS for NO₂. However, the devil is in the details, and this document does not lay out very clearly how the detailed computational steps will be performed. It mentions the kinds of models and databases that will be considered, and I generally agree with these, but the real question is how they will be employed. This is especially true for the uncertainty analysis, where I think there is a lot of work still needed (not necessarily in this plan) to determine how the more qualitative and quantitative uncertainty results will be combined into an overall measure of uncertainty that can also serve to guide future research. Still, as a plan, this one is reasonable so long as the Agency can decide how to treat the on-going evolution of sources when depicting future exposures and risks..

One other general comment is that the Agency should consider how to balance an assessment based on individual rights, which would focus on setting a NAAQS that protects some upper percentile of the distribution of risk, with one based on cost-benefit analysis, which would focus on the entire variability distribution. The former might be easier to do, and could be a back-stop approach should the complete variability distribution (Tier III) prove infeasible.

1a. Is the three-tier approach appropriate, and are the criteria for deciding whether a given tier is needed clear and appropriate? Yes, I like the three tiered approach. I would just caution that Tier I, while providing some useful insights, is unlikely to yield a scientifically rigorous basis for setting a NAAQS. I would instead view Tier I as producing only a decision as to whether a new NAAQS is needed at all. If the answer is yes, then Tiers II or III would be required to actually generate that NAAQS. And I am confident that the methodologies and databases exist to allow at least Tier II. I did not find the criteria well specified, and kept wondering throughout how a decision would be made to move to Tier II or III. After several readings, I am not certain what the Agency would need to see in Tier I to motivate it to move to Tier II, and from II to III. There are qualitative criteria given, but I don't know how these would relate to any specific quantitative results.

1b. Have the most important factors influencing exposure been accounted for? For the most part, yes. The largest problem remains in determining how the activity patterns, and mode choice for travel, will be used to relate ambient air levels to personal exposures. These methods have been employed for other pollutants, however, and so I am confident the Agency staff can obtain at least a first approximation to these issues. On this one point, it will be important not to get too caught up in trying to characterize intersubject variability of risk too exactly, because human movement in an exposure field is an inexact modeling effort at best.

1c. Is the selection of population groups of interest correct? Yes, with the caveat that there should be special focus on groups that intersect these criteria.

2a. Is the exponential model in Tier I justified? I think any model here is only a rough approximation, and the exponential one is as good as any other. As I mentioned previously, it is important not to get caught up in too much detail here, since individuals will tend to average out this spatial curve as they move about.

2b. Is the approach to enhance roadside NO₂ concentrations appropriate? I don't know much about this topic, and so cannot comment on it. But it is clear to me that something does need to be done to produce

this enhancement, and also to consider in-vehicle exposures.

3a. Is the combined emissions/dispersion modeling approach in Tier II justified? As a general approach, the answer is yes. I am, however, skeptical of the ability to perform such calculations at a refined spatial scale. This will be especially true in road canyons. It will be necessary, therefore, to use the modeling results only as averages over significant geographic areas (not below a census tract or block group).

3b. Is the proposed time-location-activity diary approach correct? This will be a state of the art approach, although it will be difficult to get the kind of spatially accurate estimates of ambient air concentration needed to make a refined diary approach really worth the effort. There will, however, need to be some thought given as to the level of effort put into the diary approach, and not put in more effort than is justified by the spatial resolution of the ambient air field.

3c. Is HAPEM6 the correct approach? Yes, this is the model I would have selected. It has been employed successfully by Agency staff in the past, although the weaknesses noted during the NATA process should be reviewed.

4. In Tier III, is APEX reasonable? My answer here is the same as in 3c. APEX is a good approach, and one with which Agency staff have some experience, but just be sure to match the effort to the level of spatial resolution of the ambient air field.

5. What is our advice on uncertainty and variability in each Tier? Here there is a lot of work still to be done. I agree with the approach of having both qualitative and quantitative aspects. I would not try to force everything into a quantitative framework. The best one can do is a series of conditional uncertainty and variability statements: that conditional upon a certain set of scenarios, or modeling approaches, or databases, or corrections to the data, the following quantitative uncertainty and variability distributions are obtained. These U and V distributions can be generated for each combination of scenario, modeling approach, etc, and then an overall judgment of uncertainty and variability developed from expert judgment based on these quantitative distributions. But I recommend this for Tiers II and III, not Tier I (where the uncertainty should be more qualitative and where variability should be treated by examining reasonably maximally exposed individuals rather than producing an actual variability distribution.

On a related note, the plan does not yet specify very well how model validation will be performed. This is an important step required by the uncertainty analysis, and so needs to be rounded out a bit.

Comments from Dr. Dale Hattis**Comments on the Risk Assessment Plan**

The overall approach for the risk assessment is described as follows:

“health risk will initially be assessed through the identification of concentration levels associated with adverse health effects, termed potential health effect benchmarks. These.. will then be used to determine how often air quality concentrations or estimated exposures exceed concentrations associated with adverse health effects....”

This seems a rather indirect approach that needlessly economizes on helpful theoretical model-building. I think EPA should essentially discard the evident hope that only a “Tier 1” analysis will be sufficient. What is needed are a set of estimates of the entire population distribution of likely exposures¹ and corresponding distributions of population sensitivity to various health effects. These two distributional inputs could then be used to develop estimates of the current burden of adverse health associated with the current exposure distribution, and the capability to estimate how the burden would change with hypothetical changes in the exposure distribution or with possible changes in the NAAQS or other regulatory standards or feasible non-NAAQS technical measures (e.g. standards for auto emissions). The paragraph goes on to say that “an additional characterization of risk may involve use of concentration-response functions...” In my view it is not a question of whether this level of analysis will be needed. It is certainly needed to support the technical and policy choices that EPA needs to make in seriously considering the effects of various options to revise and restructure the NO_x NAAQS. The EPA authors need to immediately start their analysis by going about the business of constructing these exposure/response functions, with due cognizance of the need to quantitatively represent uncertainties in the functions used to estimate health endpoints of various types from the various sources of available scientific information.

p. 9, equation 1.

This exponential equation is not discussed in terms of theoretical mechanisms. I am prepared to believe that distributions of concentrations by exposure time are likely lognormal, but it is not clear that this is the basis of equation 1 or how equation 1 is in fact derived from this basis. Equation 1 is simple enough to use, but there should be some comparative testing with data to show it really works for existing NO₂ data in the sense of being free of systematic distortions in the incidence of exceedances out to levels that are very far from the mean.

p. 10, Table 2. The occurrence of zero’s in this table, rather than fractional values below 1, seems unwise and potentially misleading. (As an aside—the assertion that there are absolutely zero places in the U.S. that exceed the current standard of 0.53 ppm annual average also seems dubious.) The equation provided cannot yield true zero incidences.

In general I question the whole “exceedance” basis of the key calculations that seem to be aimed at. This framework is probably derived from an implicit threshold theory of the incidence of effects as a function of concentration, and threshold theories seem to have little support in the existing epidemiological data. Another presumption seem to be that long term effects, if any, depend on short term episodes of relatively high concentration. This assumption does not appear to be supported by either empirical observations or theoretical analysis. Rather, I think what would be more useful is a distributional expression of the total fraction of time spent at various levels of exposure for the population as a whole and for various at groups that are at risk because of either unusual susceptibility or residence in locations with various levels of annual average concentrations. Many of the exposure-response observations seem equally well analyzed

¹ This does not necessarily correspond to the distribution of concentrations/”exposures” at regulatory monitoring sites, as people may live in locations that are differentially represented by the monitoring sites, in addition to the distortion discussed in the document between ground level locations of people and the elevated locations of the air monitors.

Comments from Dr. Timothy Larson

Comments on NO2 Health Assessment Plan

I have several general comments on the exposure assessment portion of this plan. The multi-tiered approach is a reasonable one, moving from more general to more specific in the exposure assessment. The Tier I approach will provide a reasonable ranking of urban areas for further consideration. However, I have concerns about the Tier II approach. In particular, the use of near road gradient algorithms and Gaussian plume models from line sources will not capture the actual traffic related gradients in many urban areas. The reason for this is the presence of buildings and associated street canyons. There are many urban areas where this is an important factor. It would be useful to identify the presence of canyons as part of this screening procedure prior to using 'flat world' gradients and models. The Danish AirGIS system has this capability if information is available on building footprints and approximate building heights. It would also be useful to develop information on the vertical distribution of personal residences in these same urban areas, given the importance of this parameter. Inclusion of the above factors in a Tier III SHEDS type model seems promising, but only if the Tier II screening is done properly.

Comments from Dr. Donna Kenski

Comments on Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment

Donna Kenski

October 22, 2007

Air Quality Considerations: Using historic data to simulate scenarios with higher concentrations seems reasonable, as does the proposed choice of a linear approach to adjusting data to lower concentrations. The proposed list of CMSAs did not include New York, which the ISA indicated had the highest mean NO₂ concentrations of selected urban areas with multiple monitors (Table 2.5-1). Presumably it will show up in the identification of additional locations of interest?

Exposure Analysis: The 3-tier approach is satisfactory. The important factors influencing exposure have been accounted for. This plan emphasized traffic exposures far more than they were discussed in the ISA, which I thought somewhat neglected this source, so that's a definite improvement. The groups of interest are appropriate.

The choice of exponential model is probably okay, although it would be helpful to see what other approaches were considered and to have some comparative assessment—the McCurdy report is not readily available. Was survival regression considered? How does the change in variance over time (apparent from Fig. 1) affect this model? It is not clear from the text why the predictive equation for each location is lumping all monitors together when, in some locations, significant siting differences exist that will impact the number of exceedances. Why not include a site variable in the model? As above, a comparison of various models or additional rationale for this particular one would be helpful.

Health Risk Assessment: The approach outlined here seems fine. In particular the proposed method of characterizing uncertainty and variability is conceptually appealing. The actual implementation of the Tier I/Tier II risk assessment may uncover issues not dealt with in this document, but it seems like a reasonable approach that can be modified as needed and especially as the data require.

Comments from Dr. Kent Pinkerton

Review comments for the Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment

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

To assess risks and exposures using a tiered assessment approach for the level of analysis required and the anticipated utility of the results is a highly logical process, especially in the face of possible future limited resources and budget constraints.

Exposure estimates to compare to potential health effect benchmarks to 1) estimate the number of individuals experiencing exposures of concern and to 2) estimate the range of exposures above levels of concern are appropriate and laudable. Since epidemiologic data appears to be the major driver to establish health effects, it is also important to better define whether uncertainties in the degree of health effects observed are due to NO₂ or an associated co-pollutant.

Since at the present time rare excursions of NO₂ above the current NAAQS occur in the nation, yet numerous health effects due to NO₂ exposure have been reported in the literature, it is highly likely this tiered assessment approach will need to be applied well beyond Tier I assessment. Tier II is a critical and needed parameter, especially for NO₂ exposures to allow for screening-level exposure assessments to establish the relationship between ambient concentrations, local sources and human exposure.

It is my opinion and recommendation that exposure assessment for NO₂ include both short and long-term measurements of ambient concentrations through routine air quality monitoring and modeling analysis. The identification of uncertainties in exposure estimates is also essential to determine.

The populations to be modeled which include children (normal and asthmatic), asthmatic adults and the elderly are the proper groups. It may become essential in the future to further determine the influence of gender and genetic predisposition to respiratory disease as well.

In the Tier I air quality characterization, how were the 5 cities of Los Angeles, Houston, Atlanta, Philadelphia and Chicago chosen? Some justification for city selection would be good. Although it is understood motor vehicles, electric utilities and industrial combustion processes represent the major sources of total NO₂ emissions, why totally exclude rural and areas of high agricultural activity? For example, in figure 2 of the document what is the contribution of agriculture to off-highway emissions of NO₂?

A nice example is provided for Tier I air quality characterization in Table 2. However, it appears Los Angeles would be the only city to experience exceedances in NO₂ levels, based on the current standard. Therefore, how useful would this model be for other portions of the country to explain potential health effects associated with NO₂ exposure? Perhaps it is important to clarify this model can be adjusted to deal with lower NO₂ levels should the air quality standard be changed to provide greater health protection.

A clear explanation of both short-term and long-term exposure approaches to be implemented in Tier I and II exposure assessment is provided in the document. The Decision Flow diagram for Tier II screening, as well as the basic data required to estimate the numbers of person occurrences of short-term exposures in Tier II exposure assessments are provided and extremely helpful.

Again, the explanation provided for Tier III refined exposure assessments is very helpful to better understand the approach to be used, generated outcomes, as well as variability and uncertainty factors that may be encountered and handled.

Figure 5 is excellent in providing an overview of the entire tiered assessment process. Using a tiered approach as outlined seems very reasonable and highly appropriate to insure the proper assessment of exposure levels to NO_x.

Under the overview (4.1) for risk assessment scope and methods, one of the goals of the NO₂ risk assessment is to estimate the number of people exposed at or above potential health effect benchmarks associated with NO₂ exposures at levels just meeting the current standard. This goal could be more specific by estimating subgroups such as children, those with asthma, the elderly and socioeconomic classes.

It is important to clearly indicate what constitutes sufficient scientific data to develop population-based health risks for health effect endpoints in at-risk population groups.

Under the overview (4.1) it is not clear why the EPA would not develop risk estimates for NO₂-related effects associated with long-term NO₂ exposures. Although the evidence is not strong, it has been described as “suggestive” for long-term health effects associated with NO₂ exposure. Mobile, stationary and indoor sources of exposure can clearly be long-term.

Under Tier I health effect benchmarks, susceptible populations composed of asthmatics and allergen-sensitive individuals also factor in children and gender-based differences.

The inclusion of baseline data for emergency department visits and respiratory-related hospital admissions for candidate US locations in Tier II risk assessment to enhance risk assessment seems logical and desirable.

Comments from Dr. Armistead RussellReview of EPA NO₂ Scope and Methods

I am generally pleased with the scope and methods as laid out. It appears, and I hope this to be the case, that it is building upon and building further, EPA's other exposure and risk assessments for reviewing the NAAQS. At the end of one or two more pollutant reviews, it should be almost a well oiled machine (though one that continually improves and considers the unique aspects of the pollutant under consideration).

In regards to its application to nitrogen dioxide, one of the first question that arises is that the ISA considers more than just NO₂, but nitrogen oxides in the broad sense (not just NO and NO₂). Does the Scope and Methods also have to consider such (e.g., at least consider what the response might be if the determination is that one should look at other components or a sum of components)?

While I generally find that their approaches for assessing the distributions of NO₂ exposures are viable and at the level that is appropriate. One could always do a better job, but it is not apparent that for the task at hand it is necessary, with one exception at present. They use an exponential decrease in NO₂ going away from a road. They should use the exponential decrease in NO_x going away from the road, and then use an appropriate method to split NO_x between NO and NO₂. In an oxidant limited situation, this could be significant. Also, this will allow them to more explicitly account for changing NO₂:NO ratios in the emissions, and assess the overall sensitivity to that split.

Another comment is to try to identify up front the broad levels at which the standard might be set and do some exploratory analyses to show how EOC will vary, and the primary sensitivities. While, in the end, the panel will be interested in uncertainties and variabilities, some assessment early on about the sensitivities will be quite useful.

Some other specifics:

In eq (3), the m should be found using linear regression, not as a ratio.

k in eq (2) is not a rate constant. One could call it a dispersion constant, or the like.

Carrying on my comments from the ISA: The monitor uncertainty is overemphasized, and I do believe, mischaracterized. Further, if one is using epidemiologic study results, that bias is built in.

Fairly early on in the process, the results from the exposures and risks in the five cities should be put in perspective of the broader population.

In replying to the given questions:

1. Do the Panel members generally agree with using historic air quality data (e.g., pre2000) in certain analyses as a reasonable approach to simulating air quality scenarios with higher NO₂ concentrations, given that current ambient air quality concentrations are lower than the current standard?
 - a. **Answer:** It is necessary to know exactly when and how this would be used, but is probably fine. A specific concern is that the older data may have a different NO:NO₂ split due to different ozone levels and a different NO:NO₂ split in the emissions. The data should be corrected for this if older data is used, and should also be corrected for this when considering future scenarios (this may be a small difference, and if they can show this, great, and then move on).

2. Based on the low estimated contribution of policy-relevant background NO₂ to overall ambient NO₂ levels, staff is considering a proportional (i.e., linear) approach to adjusting air quality to simulate just meeting potential alternative NO₂ standards that are lower than current air quality concentrations. Do the Panel members have comments on adopting a proportional approach to simulate just meeting more stringent alternative air quality standards?
 - a. **Answer:** Do you mean proportional or linear? I would prefer linear, though it is recognized there is little difference in this case.

Exposure Analysis:

1. In considering the exposure analysis broadly:
 - a. Do Panel members have any comments on the general structure and overall three-tier approach that staff plans to use for the exposure analysis? Are the criteria that staff plans to use for deciding whether to conduct a Tier II or Tier III analysis clear and appropriate?

Answer: Yes. (The approach is fine.) EPA should compare and contrast their approach to that used for other pollutants, and document why different methods are used. Again, use each review to make the exposure and risk assessment a more systematic, documented and turn-key. One could see that in about three years (a couple more pollutants) that a system much like that used for air quality modeling is used such that with relatively little effort exposures, risks, variabilities, sensitivities and uncertainties can be calculated, and the system as a whole has been intensely reviewed such that staff need not spend such effort, and the community is more comfortable with the results.

- b. Have the most important factors influencing exposure to NO₂ been clearly accounted for and described?

Answer: Not totally... The large role of indoor sources on NO_x, and how that gets converted to NO₂, needs a bit more work. This issue probably should be picked up more in the ISA as well. Also, the role of NO_x in forming and destroying ozone feeds back in to converting NO_x to NO₂. Further, the discussion here should also deal with the co-occurrence of other pollutants of concern.

- c. The draft plan describes the basis for and selection of population groups of interest (i.e., children, asthmatics (children and adults), and the elderly) for which NO₂ exposure estimates are to be developed. Do Panel members generally agree with the groups of interest identified in the draft plan?

Answer: Yes.

2. In considering the Tier I exposure assessment:
 - a. Do Panel members agree that an exponential model is appropriate for estimating expected exceedances of short-term health effect benchmarks based on long-term annual average air quality?

Answer: This is fine as long as the model is tested and the appropriate measures of performance are given.

- b. Do Panel members agree with the approach to enhance NO₂ air quality data by accounting for the influence of roadway emissions?

Answer: See discussion above.

3. In considering a potential Tier II exposure assessment:

- a. Do Panel members agree with the combined emissions/dispersion modeling approach to estimate short-term (hourly) on- and near-roadway NO₂ concentrations?

Answer: Yes, as long as the model is evaluated and performance documented.

- b. Is the proposed use of time-location-activity diary data reasonable for estimating short-term exposures for population cohorts?

Answer: Yes, as long as the model is evaluated and performance documented.

- c. Do Panel members agree with the use of HAPEM6 to estimate long-term exposures (annual average) and the approach to account for on- and near-roadway NO₂ concentrations?

Answer: See discussion above (in regards to NO:NO₂ splits).

4. In considering a potential Tier III exposure assessment:

- a. Do Panel members generally agree that developing individual exposure profiles through the use of APEX is reasonable and appropriate to estimate both short- and long-term NO₂ exposures?

Answer: Yes, as long as the model is evaluated and performance documented.

- 5. Do Panel members have any comments or advice regarding the general approach to addressing uncertainty and variability in each Tier of the exposure assessment as described in the draft plan?

Answer: Provide, early on, results of some sensitivity analyses. Do not overestimate uncertainties going in.

Comments from Dr. Christian Seigneur**Comments on the Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment- Draft - September 2007.**

Christian Seigneur
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The three-tier approach for exposure assessment and the two-tier approach for risk assessment appear to be logical ways to proceed. The various steps of each approach are described with sufficient detail for the reader to understand the technical approach and the sources of the data to be used.

QA/QC: One aspect which is not articulated in the document is the Quality Assurance/ Quality Control (QA/QC) procedures that will be followed by EPA. As the assessments proceed to the higher tiers, there will be some very large amounts of data being treated and one must ensure that the proper QA/QC procedures are in place to avoid input or calculation errors.

NO₂/NO_x speciation – Equations 2 and 3 on pp. 11 and 12: The use of particulate emission control devices on diesel vehicles typically leads to a greater fraction of NO₂ in the NO_x emissions. Such a change in the NO_x speciation for mobile sources could lead to stronger NO₂ spatial gradients near roadways as the NO₂/NO_x ratio will increase at the roadway but the NO₂/NO_x ratio at background sites, which is driven mostly by atmospheric chemistry, may not change. The implication is that the spatial gradient obtained from historical data may not apply (see Equation 2 on p. 11 and associated text). How will EPA address this possible change in the relationship as the vehicle fleet evolves over time?

Estimates of NO₂ concentrations, p. 18: EPA proposes to use the steady-state Gaussian dispersion model AERMOD to calculate the NO₂ concentrations near roadways. AERMOD is a dispersion model that was designed for point sources (Cimorelli et al., “AERMOD: An dispersion model for industrial source applications – Part 1”, *J. Appl. Meteorol.*, **44**, 682-693, 2005) and which has been evaluated with data from point sources (Perry et al., “AERMOD: An dispersion model for industrial source applications – Part 2”, *J. Appl. Meteorol.*, **44**, 694-708, 2005). Emissions from roadways differ from those from point sources as vehicle traffic induces some additional turbulence. The use of a simple chemical scheme to account for the rapid titration of NO by ozone to form NO₂ appears appropriate here (although it is not clear what is meant in footnote 8 on p. 18 by “simple reaction rate constant”). However, it is unclear why EPA would want to use a point source dispersion model that is not designed for roadway emissions when roadway dispersion models (such as CALINE4) are available. CALINE4 has been subjected to performance evaluation with measurements made near roadways (Benson, “A review of the development and application of the CALINE3 and CALINE4 models”, *Atmos. Environ.*, **26B**, 379-390, 1992) and would seem more appropriate for use here, particularly if AERMOD has not been evaluated for near-roadway estimates.

Example calculation of Table 4: It is not clear how the in-vehicle concentrations are calculated. One person appears to be in a vehicle at more than 75 m from the road but the concentration within the vehicle does not appear to be a function of the distance from the road. Is the NO₂ concentration within the vehicle assumed to be constant regardless of the location of the vehicle?

Preliminary comments from Dr. 'Lianne' Elizabeth Sheppard

Comments on the Scope and Methods Plan for the Exposure and Risk Assessment

Summary comments:

- Overall the tiered approach to exposure and risk assessment seems to be generally reasonable. *However*, modifications to the risk assessment tier structure and additional detail are necessary.
- To the extent feasible, *all* criteria should be specifically stated in advance.
- Throughout the document the word “would” is used when “will” is more correct. This is after all a plan, not a hypothetical plan.
- In order to help assure the process is open and transparent, all tiers of the exposure and risk assessment need to be covered in the risk and exposure assessment document. This policy should be followed even if the final judgment is that the data are insufficient to conduct a specific tier of the assessment. This policy should be stated in the introduction.

Section 2: Shouldn't this section be folded into Section 3? It seems premature to be discussing simulated air quality data when the purpose of the simulation hasn't been stated.

Section 3: The general improvements for this section are to clearly state criteria and to make equations more explicit by adding indices.

Section 3.1: Clearly define each tier in the overview section. Add the tier numbers to Table 1. Clarify whether the information used in each tier is conditional on the data, information, or choices made in the previous tier.

Section 3.2: Why are no population groups defined based on exposure? I suggest adding people living or working near roads.

Section 3.3:

- Clearly state the intended use of the air quality characterization. Without the intended use stated, it is difficult to evaluate the objectives of the analysis (paragraph 2). For instance, why would the analysis be limited to areas of potential concern, and what are the criteria for “potential concern”. As another example, a statistical model (objective 3) is only useful if it meets a specific purpose, but the purpose is not stated.
- It is also necessary to distinguish long-term from short-term metric objectives. This distinction needs to be revisited *throughout* the section.

Section 3.3.1:

- The first sentence is good, but now this summary statement needs to be made clear.
- The second sentence appears to be missing a word at the end.
- As an example of clarifying “aggregating data”, it should be stated that the objective is to create a single daily (hourly?) time series over space of monitors that are similar. Note that criteria are needed for “similar”.
- The criteria for the selected cities are generally listed, but the reader is not informed why those cities were selected.
- Shouldn't site characteristics be included in the list of criteria used to identify additional locations? This is alluded to with the motor vehicle traffic density criterion, although the reference to “by location, not monitor” is cryptic.
- State how the aggregation will be done and what are the criteria for including monitors in the aggregation. Make it clear whether this is temporal or spatial aggregation, or both. I don't understand the purpose of all the statistical tests that are planned and what criteria will be used to determine if additional aggregation is appropriate. (p 8-9).
- p 9: The first full paragraph confuses me. What are the purpose and the outcome of the comparisons within and between locations? What data are to be used?

- p 9: Please add indices to all variables in all equations and define these indices!! Are these data indexed in time by year, day, or hour? What are the spatial indices – site within location?
- p 10: This document is very short on specifics. For instance, *how* will “regression models, parameters, and respective concentration exceedance estimates” be compared?
- p 10: I don’t understand how the two parts of the sentence fit together: “The regression model is highly dependent on the prevalence of concentration exceedances, justifying the aggregation of particular (and similar) locations.”
- Footnote 4 suggests a valid year could have an entire season missing.

Section 3.3.1.1:

- Equation (2) is a general equation. None of the parameters have values. Will they be estimated from data? What time scale is being considered? Add indices.
- Are C_v and C_b data or predictions? How are they obtained?
- How will the equation (2) result be used to derive (3)? Add indices.
- The entire plan for this section is wide open and subject to many interpretations.
- Why is the goal to obtain on-road estimates of NO_2 instead of characterizing NO_2 as a function of distance from road?
- Note that “on-road NO_2 concentrations” are *predictions*, not data.

Section 3.2: Descriptive statistics should include measures of spread as well as central tendency.

Section 3.3:

- Paragraph 2: Restate sentence to say the tiered approach uncertainty assessment is done with the goal of identifying the best supported quantitative analysis.
- Paragraph 2: Presumably the “identified components are, in a broad sense, also relevant to subsequent exposure analyses” because this tier I analysis is the input to the tier II analysis. Correct? Please state clearly.
- Add “Choice of NO_2 as the index compound” as one of the components of uncertainty.
- Temporal representativeness: State what the “temporal profiles” are. Are these estimated hourly average air quality over a multi-year period for a given spatially aggregated location with specific spatial features?
- Spatial representativeness: The purpose of the predictions really matters when deciding how to proceed with limited spatial data. State the purpose. What prediction equations are being referred to? What kind of correlations will be evaluated?
- Monitor to exposure representativeness: Why is personal exposure even being mentioned in the Tier I estimates? Isn’t it more important that the AQ characterization is done in locations that are representative of population exposure to ambient concentration?

Section 3.4:

- p 17 line 2 – add “ambient-source” to describe the possible lower bound estimate.
- Gas stoves are an important factor in greater personal exposure and should be listed in the example to indicate home characteristics will also be considered.
- In doing spatial interpolation of exposure, it will be important to only include monitors that are representative of usual population ambient source exposure (as opposed to those highly influenced by local sources that won’t apply to the entire census tract or adjacent tracts). I am concerned that some factors could be counted twice if the local source monitors aren’t removed first, since local sources will be added in with the planned adjustment.
- Following the previous comment, I suggest discussing locations represented by ambient monitors as a function of monitor siting criteria and/or GIS covariates.
- Insert the word “predicted” to clarify the complete set of concentrations won’t necessarily be data.

Section 3.4.1:

- Organizationally, why not define the on-road concentrations as the 0 m road proximity class?

- Why do indoor sources need to be identified as important contributors to ambient air concentrations to be considered?
- Figure 4: Why can there be significant on-road concentration but little elevated concentration at <75m? (see the first site)

Table 4: While it is clear that the total column is a weighted average, it is completely unclear what the average concentration total row means (particularly given the numbers provided).

Section 3.4.1.2:

- There is an assumption that the spatial and temporal contributions to NO₂ are relatively simply related, i.e. temporal estimates from one location can be linearly transformed to get estimates at a new spatial location. Ideally this assumption should be checked. At least it should be discussed.
- I think uncertainty in model structure can be evaluated with sensitivity analyses.

Section 3.4.2:

- Does the term “long-term exposure” mean “annual average exposure”?
- Add an introductory paragraph and start a new section subheading for the material already at the beginning of this section.
- Equation (4) needs indices for time, space, and microenvironment type. Clarify the range and units of the indices.
- Note a different approach to roadway contribution is being used here.

Section 3.4.2.1:

- Give an equation to show the relationship described in the first sentence.
- On what time scale will the additional exposure metric be calculated? (p 24 top)

Section 3.5.1:

- p 26 first sentence first full paragraph: The approach to predicting hourly NO₂ from monitoring data and dispersion models is a major research topic in itself. The approach taken here is quite simple, and thus it should be mentioned as a limitation and source of uncertainty.
- Should in-vehicle estimates be separated by road type?

Section 3.5.3: Instead of relying solely on informed judgment, why not compare estimates from plausible models formulated differently?

Section 3:6: Define number of peak concentrations. Discuss Figure 5 in more detail, and possibly move it to the beginning of Section 3.

Section 4:

- I think the risk assessment needs to be reorganized to have 3 tiers. The first tier should be a qualitative assessment of the health evidence. This will list and consider all important health effects based on human and animal studies. Not all of these can be used for benchmark calculations or quantitative risk assessment, but it will be important to review them all first and get a sense of the scope of the risk qualitatively. Then a narrower list will be used for the second and third tier assessments. Not only does this proposed new tier structure allow for better progression in the treatment of the health results, but it also elevates the importance of the qualitative risk assessment in the document and protects against it being treated as an afterthought.
- Criteria for acceptable outcomes to use in the risk assessment (as well as other aspects of the RA such as choice of city for the analysis) needs to be specified in advance for each tier.
- Criteria for even conducting a quantitative risk assessment (my third tier, the written second tier) need to be specified in this document in advance of the risk assessment.

Section 4.2: State the criteria for selecting health effects to be used for the benchmark analysis.

Section 4.2.1: State the planned health effect benchmark levels or criteria for selecting these levels.

Section 4.2.3: Third paragraph: In addition, a distribution of benchmarks could be applied rather than sensitivity analyses of a set of single values. I'm confused by the end of this paragraph (starting "From a directional perspective..."). My understanding suggests either the wording is backwards or I am confused. Perhaps an example will help the reader's comprehension.

Section 4.3: The criteria for what is sufficient information to develop credible exposure-response relationships *must* be stated. I note there is information about such criteria in later subsections. Restating the criteria in another form, such as a list, may be helpful.

Section 4.3.1.1 (and 4.4): I believe that the last two additional factors (2: availability if sufficient C-R data in locations relevant to the US and 3: availability of baseline incidence data) should be given less weight in the decision to proceed. Both can be evaluated with sensitivity analyses.

Section 4.5: Restating an earlier comment: Summary of the health effect data should precede the quantitative risk assessment as the first tier risk assessment. The qualitative risk assessment should do more than just provide the "broad context for the quantitative risk estimates". It should be the foundation.

Comments from Dr. Frank Speizer

**Nitrogen Dioxide Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment
(September 2007 draft)**

Answers to Charge Questions (paraphrased)

Submitted by Frank E. Speizer

Date: October 17, 2007

Air Quality Considerations

1. Use of historic air quality data pre 2000.

This is not an unreasonable use of historical data. Figure 1 on page 5 suggest a marginally significant decline in the annual average NO₂, but the variation seems to have changed substantially with a marked drop in the 90%tile level starting around 1997. In table 2.5-1 in ISA on page 2-52 spatial variations are wide in some cities. Thus, for the last 10 years may want to inflate the variance to better take into account the individual city variation.

2. Use of a proportional approach to modeling alternative air quality standards.

I think the same observation made above applies to the use of proportional adjustments. Somehow the drop in the 90%tile values along with the variation across regions (cities) needs to be dealt with. If proportional models works that is fine.

Exposure Analysis

1. Broad considerations.

General Structure. This seems reasonable but I would be disappointed if Staff concluded that they could not get past Tier I. For factors influencing exposure perhaps there needs to be some discussion on how the interaction with Ozone will be handled. In some of the regions there are likely to be competing interaction, with quenching affecting what is being measured and difficulties attributing risk. (This may all come up later). In addition, it might be indicated as to how, at least in a general sense indoor exposure, will be considered. Population groups of interest. If possible I think it would be useful to consider children broken down somewhat differently. The text in section 3.2, page 7, suggests birth to age 18. I think it would be better to consider birth- preschool (near home); 4 or 5 to 9 (local community); and 10-18 (active outdoor physical activity). I recognize that the data may not exist but at least the breakdowns for exposure might be considered. The other grouping seem appropriate, except might want to consider those adults carrying a cardiovascular disease diagnosis as a separate (potentially more susceptible) group.

2. Tier I exposure assessment

For exponential model and accounting for emissions this seems to be appropriate, however, what will need to be discussed later is how this model deals with the time-varying patterns of exposure that might occur as people “move through” their approximate exposures. This forms the basis of the discussion of uncertainties in section 3.3.3. Although the potential issues that might vary exposure and uncertainties are well described, it is not made clear just how these will be handled. (Perhaps there will not be a variable added to Equation 3 and residential time within x number of meters of a roadway value will only be discussed qualitatively at this level of analysis but such should be stated. Alternatively, if there would be a way to incorporate residential time (or other modifiers of exposure) in the equations that would be useful.

3. Tier II. This is a exceeding well written description of what needs to be done, and if accomplished should satisfy the numbers needed for any risk assessment. As I read through this I am wondering if all the comments above on Tier I are irrelevant as many of the comments above are answered in this section. Therefore should consideration be given to combining the two Tiers into a more expanded discussion, since much of the uncertainty in Tier I and specified again on page 17 are dealt with here . (Leaving it own uncertainties.) In picking the distance to roadways (<75 m, 75-200 m, >200 m) some justification needs to be added on page 18. Particularly since on page 11 the spatial drop off exposure levels gives a range of 200-500m to get to ambient. Note also the footnote on page 18 on age distributions is more in line with my comments above on age groups.

What is not clear in the discussion of uncertainty is the how the nature of the monitoring station (residential, commercial, industrial) as well as nature of residence near roadway (single family houses,

large apartment blocks) get taken into account, for example in table 4. Will sites that are used for regulatory control at the edge of a factory be excluded? What if all the people in the tract live more than 200m from the monitor? In addition I assume that “fraction of the population in each location” somehow gets factored in when census tract is used (as total population, and age distribution within in each census tract, are not all the same). Again, many of these issues are discussed in the Tier III section, and again it makes me question whether the separation into separate Tiers in imposing more criticism than is necessary. Figure 3 on page 29 outlines the criteria needed, it seems likely that sufficient data are available to proceed, so no more than a descriptive discussion of how staff gets to Tier 3 is needed and they should get on with doing the assessment as proposed.

Risk Assessment Scope and Methods

On page 33 section 4.3 I would recommend to staff that they reverse the order of discussion on the credible exposure response relationships for controlled human exposure studies and the epidemiological studies, particularly sine the section title is Risk Based on Epidemiological Studies. Clear most if not all of the controlled studies have been carried out in normal healthy volunteers; whereas the epidemiological studies are in general observations on free-living population groups that obviously contain people with vary levels of risk. Judgment on risk assessment should be made on the latter group with the controlled human exposures experiments mostly designed to assess and understand potential mechanisms for the risk observed in free-living populations.

The plan as outlined a two Tier effort, like for the exposure assessment seems somewhat arbitrary as to whether it is called a two tier effort or a logical progression in gathering the data necessary (and I believe from the draft ISA) available to do all that is proposed. The short term exposure assessment is well documented to move forward, particularly for the respiratory outcomes described. With regard to the long term assessment particularly for hospitalizations and mortality by sub-regions, this may have to await the assessment of the draft ISA.

With regard to the criteria for determining the approach to tier ii on page 37, I accept that the thinking of these steps are necessary to get to the data but as indicated above I believe there are sufficient evidence, particularly for the short term effects, that doing the risk assessment for respiratory outcomes should be straight forward. However, I totally reject the placement of the last bullet on page 37, in section 4.4 as a criteria for doing what is needed. If there are insufficient resources to accomplish this in the next 15 months than the Administrator deserves to go to jail for not meeting the consent decree!!