UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

June 18, 2013

EPA-CASAC-13-006

The Honorable Bob Perciasepe
Acting Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Consultation on the EPA's *Draft Plan for the Development of the Integrated Science Assessment for Nitrogen Oxides – Health Criteria (May 2013 Draft)*

Dear Acting Administrator Perciasepe:

EPA's Clean Air Scientific Advisory Committee (CASAC) Oxides of Nitrogen (NOx) Primary National Ambient Air Quality Standards (NAAQS) Review Panel held a public meeting on June 5, 2013 to conduct a consultation with EPA staff on the EPA's *Draft Plan for the Development of the Integrated Science Assessment for Nitrogen Oxides – Health Criteria (May 2013 Draft).* The Panel generally found the Draft ISA Plan to be a useful roadmap for the development of the ISA.

The Science Advisory Board Staff Office has developed the consultation as a mechanism to provide individual expert comments for the EPA's consideration early in the implementation of a project or action. A consultation is conducted under the normal requirements of the Federal Advisory Committee Act (FACA), as amended (5 U.S.C., App.), which include advance notice of the public meeting in the Federal Register.

No consensus report is provided to the EPA because no consensus advice is given. The individual CASAC NOx Review Panel members' written comments are provided in Enclosure A.

We thank the EPA for the opportunity to provide advice early in the NAAQS review process. The Committee does not expect a formal response from the EPA.

Sincerely,

/signed/

Dr. H. Christopher Frey, Chair
Clean Air Scientific Advisory Committee

Enclosure

NOTICE

This report has been written as part of the activities of the EPA's Clean Air Scientific Advisory Committee (CASAC), a federal advisory committee independently chartered to provide extramural scientific information and advice to the Administrator and other officials of the EPA. The CASAC provides balanced, expert assessment of scientific matters related to issues and problems facing the agency. This report has not been reviewed for approval by the agency and, hence, the contents of this report do not necessarily represent the views and policies of the EPA, nor of other agencies within the Executive Branch of the federal government. In addition, any mention of trade names or commercial products does not constitute a recommendation for use. The CASAC reports are posted on the EPA website at: http://www.epa.gov/casac.

U.S. Environmental Protection Agency
Clean Air Scientific Advisory Committee
CASAC Oxides of Nitrogen Primary NAAQS Review Panel (2013-2016)

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Enclosure A

Compendium of Individual Comments by CASAC NOx Review Panel Members on EPA's *Draft Plan for the Development of the Integrated Science Assessment for Nitrogen Oxides –Health Criteria (May 2013 Draft)*

Mr. George A. Allen

Chapters 1 and 2 - The process overview and the history of reviews for the primary NAAQS for NO2 are useful and well written. It is helpful to have the target dates for major milestones of the ISA development.

Chapter 3, development of the ISA, is well organized and provides appropriate information on the process, including the literature search and study quality evaluations - two key early steps in the ISA development. Page 9 lines 25-27 and page 10 lines 3-6 note the issue of confounding co-pollutant interactions, an important issue for health effect studies since NO2 often serves as a surrogate indicator of a wide range of mobile-source pollutants that to a large degree co-vary with NO2 or NOx. This theme is carried forward in subsequent sections of this draft, which is appropriate. It is discussed very clearly and in more detail on page 16, part F (Uncertainties),

Page 12, lines 5-6 note measurement method issues with the existing Federal Reference Method (FRM) for NO2. New methods are now available that use a photolytic (UV) NO2 to NO converter (instead of the classic moly-based converter) that is specific to NO2. One instrument manufacturer sells a photolytic NO2 instrument that is an EPA Federal Equivalent Method. Presumably the photolytic converter method will be considered as a replacement for the current NO2 FRM in this review cycle.

Page 12, Lines 10-13 and elsewhere on this page note the issue of near-road exposures. At present, there are limited long-term data for the near-road environment, especially in a multi-pollutant context. The new EPA near-road monitoring network that is just now [and over the rest of 2013] becoming operational should provide very useful data, including other relevant near-road pollutants, but data will not be available in time for the August 2013 first draft. By the time the second draft is expected (April 2014), there should be one-half to one year of data available from at least 25 near-road sites to inform these exposures.

Appendix A is a helpful summary of the legislative requirements behind the NO2 NAAQS, including references to actions since the 1990 Clean Air Act that clarify the Act’s intent, including the 2001 ruling that EPA can not consider the cost of implementing the standard.

Dr. Matthew Campen

It would be good to provide a review of known reactions of NO2 in the airway surfactant / epitheilail lining fluid. In the ISA Development document the following question was raised:

> What NOx reaction products can be found in the respiratory tract cells, tissues, or fluids that may serve as markers of NOx exposure and effect?

This question is appropriate but possibly underemphasized, as emerging science suggests that the initial pollutant-lung microenvironment interactions may be essential to driving systemic effects, and some consideration to per-2008 studies on this topic (William Pryor, Ed Postlethwaite, others) may be valuable for NOx immediately, but also for the next round of reviews of O3 and PM. There is a new paradigm emerging that degradation by-products, rather than circulating cytokines or neurally-mediated events, may be central to the systemic effects of inhaled pollutants, and recent studies with NO2 in humans is consistent with this idea. Thus, review of the NOx reactions with surfactant proteins and phospholipids in the airways will be very important.

Dr. Ronald C. Cohen

Suggested revision pg 12, 3rd bullet: Changes in itlaics.

What spatial and temporal patterns can be seen in air quality data for NOx? In particular, what patterns can be seen on a micro-scale near sources including *major roadways, power plants and wood-burning stoves? What patterns can be seen on urban, regional and national scales based on satellite data?*

For item B on the same page, I suggest adding a question that would require discussion of the interaction of meteorology with concentration and exposures. For example:

What are the relationships between diurnal variations in the boundary layer height, NOx concentrations and exposures. What new information is available to characterize the influence of meteorological parameters and exposures?

Dr. Douglas Dockery

There have been a substantial number of epidemiologic studies since 2008 reporting health effects associated with proximity to roads. Most of these lack any NOx or other air pollution exposure data. What is their role in the NOx ISA?

Especially strong associations are reported with acute cardiovascular events. In this case, given other observational and experimental evidence for CVD associations, roadway proximity studies would appear to provide supporting evidence for causality.

Roadway proximity studies are also reporting associations with other unexpected health outcomes. In these cases, the evidence is suggesting new areas for investigating rather than suggesting causality.

These roadway proximity and traffic studies are consistent with associations with NOx exposures, but also could be explained by other traffic air pollutant emissions, or factors associated with traffic such as noise. Noise has recently remarkably little attention as a potential alternative exposure in this country, although there are a substantial number of observational studies from Europe.

The Draft NOx ISA Development plan highlights many of the issues with NOx exposure misclassification related to personal versus ambient fixed site, relative errors compared to co-pollutants, and indoor versus ambient outdoor exposures. There is suggestion that remote satellite sensing may provide usable data in the future. More attention needs to be given to exposure modeling based on land-use regression and neighborhood modeling.

The health effects of NOx have received much more attention in Europe and other countries than in the United States. The statement that more weight will be given to US or Canadian studies than European studies because of more comparable sociodemographic characteristics is narrow-minded and undervalues potentially superior observational science.

Dr. Philip Fine

There is a focus on near-road NO2 exposures, commensurate with recent monitoring regulations. First, any recently collected near-road NO2 data should be part of the air quality and exposure analysis. Second, other near-source NO2 exposures should also be considered. Point source modeling has suggested that large non-road or stationary sources, such as rail yards, may lead to localized NO2 levels at least as high as near road locations.

Newer engine control technology has effectively lowered tailpipe NOx emission overall. But the ratio of emitted NO2 to NO may be increasing. While this has little impact on regional NO2, ozone, and PM, local NO2 exposure may not necessarily be decreasing at the same rate as overall tailpipe NOx emissions.

Dr. Panos Georgopoulos

The "Draft Plan for the Development of the Integrated Science Assessment for Nitrogen Oxides – Health Criteria" (Draft - May 2013) is a thoughtful and well-prepared document that builds upon the experience accumulated through developing the series of Integrated Science Assessments, that USEPA has completed in recent years. These assessments have been of great value in the field of air quality, representing substantial contributions to the effort of transforming and synthesizing large amounts of information from disparate sources into issue-related knowledge. The proposed plan provides a solid foundation for updating and even improving the 2008 *Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria* (EPA/600/R-08/071), that been an excellent resource for scientists and regulators.

The following comprise a brief series of suggestions that could enhance certain aspects of the plan for the new ISA; in some cases they may essentially be requests for explicitly identifying in the plan issues that could in fact be implicitly addressed in the new ISA, however they are of sufficient significance to justify explicit consideration.

1. ASSESSMENT OF DATA PATTERNS AND TRENDS FOR NOx EMISSIONS AND CONCENTRATIONS

    a. Advancements (including significant methodological) in developing emission inventories for NOx, that have taken place since the 2008 ISA, should be identified and assessed explicitly. Quantifying emission levels and patterns in time and space <u>for urban and rural regions as well as for specific, both outdoor and indoor, microenvironments</u>, under a variety of conditions, is critical not only for exposure and risk characterization but also for rational management and mitigation. Therefore the identification of progress - as well as of remaining uncertainties and challenges - in this area is important.

    b. NOx-related issues are inherently multiscale and appropriate consideration of this fact should be explicit in the ISA plan. Identifying attributes of both short- and long-term emission and concentration patterns and trends (and, subsequently, of associated exposures) requires systematic consideration of temporal variability across multiple time scales. Also, different physical processes dominate different spatial scales, whether the scales are defined from the perspective of emission sources or from the perspective of (human) receptors. These scales vary from local and near-field (from the source perspective) and from personal and residential (from the receptor perspective), to neighborhood, urban, inter-urban, regional, national, continental, and global scales. The draft plan explicitly identifies consideration of near-road and national scales (page 12, lines 12-13), but the consideration should be expanded to other scales as well.

    c. <u>Spatiotemporal patterns and trends</u> in both emissions (anthropogenic and biogenic) and ambient concentrations should be developed for the new ISA through synthesis of

available data. The plan of analysis should expand upon that of the 2008 NOx ISA and should consider multiple temporal and spatial scales not only for NOx but for co-occurring air pollutants as well.

d. Assessment of the potential impacts of climatic change patterns, and of potential future changes in energy production and usage, on the levels and patterns of NOx emissions should be explicitly considered in the ISA. Changes in regional, anthropogenic and non-anthropogenic, emissions may affect base/background concentrations in relation to human population exposures.

2. ASSESSMENT OF MODELING CAPABILITIES FOR NOx TRANSPORT AND CHEMISTRY ACROSS MULTIPLE SCALES IN BOTH OUTDOOR AND INDOOR SETTINGS

a. Advancements (and remaining challenges and limitations) in modeling the multiscale ambient transport and chemistry of NOx should be explicitly assessed in the ISA and included in the plan. In fact, transport and dispersive/diffusive mixing of emitted NOx species with ambient air is intricately coupled with atmospheric chemistry, as steep gradients as well as random (turbulent) fluctuations in NOx concentrations (associated with "localized" - point and line – emission sources) will impact the effective rates of nonlinear reactions involving these species and other atmospheric constituents. Advances in modeling these gradients and their effects, such as “plume-in-grid” (PiG) models, adaptive grid models, higher order chemical closure models, etc., should be identified and evaluated as part of the new ISA.

b. Evaluation of advancements in modeling NOx emissions, transport/mixing, and chemistry in indoor environments is also very important from the perspective of exposure characterization.

3. ASSESSMENT OF MODELING CAPABILITIES WITH RESPECT TO CHARACTERIZING ESSENTIAL ATTRIBUTES OF POPULATION EXPOSURES

a. The status of population exposure characterization should be evaluated in the context of metrics that account explicitly for different population-relevant attributes of short and long-term exposures, such as pervasiveness, persistence, severity, and efficacy of exposures. The current ability of available data and models to quantify the relative contribution of "far-field" emissions (e.g., from power plants) versus "nearby" emissions (e.g., from a gas stove indoors) to human exposures, should be evaluated and assessed for a wide range of conditions. Advancements (as well as remaining “data gaps”) in databases that link human activities to time and location (microenvironment), employing relational and spatiotemporal data management systems, are critical for the improvement

and reliability of modeled exposure estimates and should be assessed as part of the new ISA.

4. ASSESSMENT OF (MECHANISTIC) MODELING CAPABILITIES WITH RESPECT TO CHARACTERIZING DOSIMETRY AND MODES OF ACTION FOR NOx, INCLUDING INTER-SPECIES EXTRAPOLATIONS

    a. The status of interspecies extrapolation for inhalation dosimetry should be evaluated and assessed in a quantitative rather than in a qualitative context; in particular, existing data gaps that currently limit the ability of dosimetric models for NOx to incorporate quantitatively effects of reactivity etc. should be characterized, and research needs for filling these data gaps should be identified. This evaluation should then be extended from respiratory to whole body toxicokinetics.

    b. The draft plan includes consideration of qualitative comparison of NOx (toxicity or in general biological response) mechanisms across species (page 13, line 18). It is recommended that the comparison is in fact extended to any relevant biological pathways/networks for which information may be available at different biological scales (from molecular signaling to histological response). Consideration of such information may provide components for the development of quantitative mechanistic toxicodynamic models for NOx.

    c. Availability of information for adding considerations of intraindividual variability (in biological response) to those of interindividual variability (p. A-6), should be evaluated.

5. CLARIFICATION OF SYSTEMATIC CONSIDERATIONS OF VARIABILITY WITH RESPECT TO CHARACTERIZING NOx EFFECTS AND RISKS FOR INDIVIDUALS AND POPULATIONS

    a. Though the draft plan demonstrates a substantial focus on identifying uncertainty and variability issues relevant to risk characterization, the discussion of “intrinsic” and “extrinsic” factors affecting risk, “and/or factors affecting dose or exposure” on page 17 (lines 3-27) under “G. At-risk Lifestages and Populations,” can be further improved. Though it is noted that “some factors (e.g., age) may influence risk through multiple mechanisms,” it does not fully recognize the relevance of multiscale networks that link “exposure biology” and “behavioral biology” with health effects. As an example, socioeconomic status, activities, diet, and biology (physiology and biochemistry) for an individual are dynamically interdependent, with the dependencies forming “influence networks,” that potentially include both negative and positive feedback loops of various “strengths”. Explicit considerations of age and gender in conjunction with genetic

variability, physiological variability, behavioral variability, etc. within populations of concern present substantial challenges in relevant information analyses (especially since both the above listed attributes and their variabilities are not independent), but will eventually be required for more thorough characterizations of environmental health risk issues.

Dr. Jack Harkema

I have read over the documents you have provided. I have no preliminary written comments at this time, other than to say that the current draft plan for the development of the ISA for Nitrogen Oxides - Health Criteria is adequately developed and includes a process that appropriately resembles that recently adopted for the most recent Ozone ISA.

Dr. Michael Jerrett

The section dealing with exposure appears underdeveloped compared to other central parts of the report. I recommend that the EPA examine the conceptual model put forward by the National Academy of Science in the report entitled, "Exposure Science in the 21st Century: A Vision and a Strategy." The report carefully documents the elements of exposure science that are important for understanding all aspects of exposure, and the CASAC would benefit from such a systematic approach to the ISA.

The section on how to establish causality is not clearly laid out and needs to be articulated in a way that gives readers an understanding of how, for example, the review will weight potentially conflicting evidence supporting different aspects of causality (e.g., coherence between epidemiology and toxicology vs. consistency among epidemiological findings).

Reviews of the evidence should give similar weight to studies from Europe as those from the US or Canada. Similarly there should be a thorough review of studies from Latin American and Asia. In all instances, the differences in underlying population characteristics, health behaviors, co-exposures, levels of economic development, and pollution mixtures as sources of heterogeneity in the findings, which may limit applicability to the U.S. population.

Dr. Patrick Kinney

The Draft ISA Plan is in very good shape. I have just a few very minor comments.

Page 9, top: this section would be more appropriately titled "Evaluation of Individual Study Quality and Relevance". Much of the section focuses on relevance rather that quality.

Page 9, lines 1-3: move this sentence to the previous section.

Page 16, lines 10-16: Sentence is too long. Break up.

Dr. Michael T. Kleinman

1. Scope of the Current Review – The atmospheric chemistry of NOx leading to the formation of toxic reaction products such as nitroaromatics and nitropyrenes should be part of the discussion, especially as we begin to develop more information on multipollutant health effects even if these are thought to have been subsumed in the discussion of PM. There has been increasing discussion of the inhomogeneity of ambient Nox distributions. There is also increasing evidence of increased health effects near roadways where NOx concentrations are often highest and the potential for chemical interactions is also high. Some of these aspects are mentioned in the discussion of Exposures (p12) but it might be useful to express the rationale in the section on Scope. I think that consideration of these aspects could help inform discussions of the adequacy of current monitoring approaches as well as providing additional factors when considering the potential benefits of NOx control beyond the direct effects of the gaseous species on health, the role of NOx in O_3 formation and the formation of secondary inorganic nitrates.

2. Exposure – p12 – It would be appropriate to include the topics of Receptor Modeling and also Time-Activity assessments with respect to the roles these play in understanding individual exposures.

3. The section on Dosimetry (p 13) should take notice that the level of physical activity in individuals will influence respirations rates which will alter NOx penetration and uptake in the respiratory tract and will also change regional deposition patterns in the lung. This can have profound effects on potential health effects.

4. Assessment Approach – The role of NOx in cancer should be included in the questions to be addressed (p 14 and 15). This is a 'sticky' problem but there is increasing evidence of associations with cancer and especially metastatic disease. The interrelationship to immunosuppression and metastatic disease may be important.

5. Although it is mentioned in passing in the Section on At Risk populations (pg 17) it would be appropriate to discuss the role that genetic variations and polymorphisms moderate individual susceptibility and may influence the variance of data about the concentration-response or dose-response relationships. So-called susceptibility genes can have a regional characteristic because of population and immigration specificities which can influence the outcomes of epidemiological studies and increase uncertainties of exposure-related health effects.

6. Literature search selection (O3 preamble) – Figure II shows articles being screened by title. The screening level might be expanded to Title and Abstract (which may already be the way the review begins).

Dr. Timothy V. Larson

My comments are directed to the exposure assessment section. The questions in this section are well conceived and relevant. Several additional questions that could be also addressed pertain to on-road exposures, measurement artifacts, and the siting of monitors near roads. Specifically:

1. What studies are available to examine the relationship between near-road NOx , on-road NOx, and in-vehicle exposures to NOx? Given the concern over short term exposures at or even less than one hour in duration, are the directly emitted NO2/NOx ratios sufficiently high such that on-road NO2 exposure is a significant component of total NO2 exposure?

2. What are the implications to epidemiology for assessing chronic NOx exposures based upon measurements at locations susceptible to interferences from other nitrogen compounds (e.g. downwind sites with relatively low NOx)?

3. How well do the current and proposed near-road NO2 monitoring sites represent exposures to populations living near major roads?

Dr. Jeremy Sarnat

Below are several, minor comments/questions.

- To avoid confusion especially among non-CASAC readers, consider using either ppb or ppm consistently in discussing the NOx NAAQS standards (pps. 2 and 3)

- This is a naïve question, but it's not clear to me how, specifically, the Final Plan for the ISA will inform the first draft of the NOx ISA. Both the final draft of the draft plan and the first draft of the ISA are scheduled for August 2013. Shouldn't the Final Plan for the development of the ISA precede the first draft? Again, sorry for my lack of understanding on the process.

- Page 10. Line 6. The suggestion that epi studies with results from copollutant analyses will be given greater emphasis in the ISA is a bit problematic. I recognize the importance of viewing NOx within a complex mix, but copollutant modeling is only one approach for doing this. I'd avoid ascribing preferential language regarding mixtures characterization, or include other approaches that are being used as well (i.e., Bayesian modeling, various factor analytical approaches). Maybe it's just a question of including 'such as' before mention of copollutant analyses.

- There's imbalance in the specificity of the questions from the Health Effects sections (p. 13) compared to the other sections. The other sections are much broader and more conceptual than the Health Effects section. I'm assuming different people wrote the questions for the various sections. I understand that this is an ISA for NOx *health criteria*, but the differences among the sections are fairly pronounced.

Dr. Richard Schlesinger

I just have a few comments on the Draft Plan so far:

P. 10. The animal studies should also potentially include those in which exposure may be to N0x in combination with other pollutants similar to what is proposed for the controlled clinical studies on lines 26-27.

P.13. Lines 11-12. One may also indicate reaction products in systemic circulation.

P. 14. There is much redundancy in issues on this page so perhaps a more concise version can be developed. Also, in the bullet starting on line 21, some of the changes noted are really quite overt so what is meant by use of that term?

Dr. Elizabeth A. (Lianne) Sheppard

Overall I found the *Draft Plan for Development of the ISA for NOx – Health Criteria* to be appropriate and clearly written. I appreciated the background material that was incorporated, including the legislative requirements summary in Appendix A, the overview of the process in the introduction, and the references to the preamble of the Ozone ISA. I have a few specific questions and/or suggestions:

1. The draft outline for the ISA (pages A-5 to A-7) does not cover all content areas described on pages 16-17 : E. Causality, F. Uncertainties, and H. Public Health Impacts. Based on the discussion, I understand these are integrated into the health effects and at-risk lifestages and populations sections.

2. P 12: Consider adding this exposure-related question, perhaps in addition to the questions starting on line 32: *To what extent is NOx a marker of the complex traffic-related pollution mixture?*

3. P 13, line 23 (section D. Health Effects): Should cognitive and aging effects be added?

4. There are several references to exposure measurement error including on line 30 of p. 14, and line 1 of page 17. Consider rewording or expanding the questions about measurement error to include concepts of data, study design and models. For instance, in addition to the question on line 1 of page 17, we could add: *How do features of the data, study design, and models affect the conclusions?* A similar idea could be integrated into the point on page 14.

5. P 10 line 19: Is point (3) really about power or appropriateness of study design? Consider rewording (3) to say "appropriateness of the study design to determine responses to relevant exposures". A similar point applies to (6) on line 28.

6. Incorporate a bullet point in <u>B. Exposure</u> addressing the role of exposure prediction on health effect estimates. This topic has both methodological and practical aspects. From a methodological perspective we now know that an essential assumption for using exposure predictions for inference about health is that the underlying distribution of locations of monitors used to develop predictive models is the same as the distribution of locations of subjects. From an applied perspective, exposure data and predictions from specific studies should be evaluated in the context of the health effect target of inference.

7. Another exposure topic brought up in our consultation call was the importance of time-activity of people while they are in the exposure field.

Dr. Helen Suh

General Comments

The plan for the development of the NOx ISA is well presented and does a good job of tying the ISA framework and terminology to those used in previous ISAs. As with previous ISAs, it will be important for the NOx ISA to include summary tables within each section that describe key studies and a chapter that integrates findings across the different disciplines (e.g., sources to exposure to health). It was not clear from the plan whether the public health impacts section was intended to serve as this integration chapter.

In addition, the summary of pre-2008 findings within the individual sections should also discuss key data gaps from the 2008 ISA. This added information will help to provide a foundation that can be used to establish whether and how our understanding of NOx has improved since the last ISA and to justify any changes to causality determinations.

The scope of the ISA for NOx may also need to be expanded to include consideration of other traffic pollutant measures, such as black carbon, elemental carbon, source apportionment factors, and distance to road. Since many post-2008 epidemiological studies have used NO_2 as a marker of traffic pollution, it is not clear how results from these studies alone will be used to draw overall conclusions, as consideration of findings from other studies of traffic pollution is likely needed. It is possible that the ISA will need to include some discussion of how findings for NOx relates to other commonly used measures of traffic pollution and health.

Specific Comments

Page 8, line 22-23. The sentence beginning “Publications considered for inclusion…”] is unclear. Are all identified studies included in the HERO database, even if they do not meet the inclusion criteria? It makes sense for all identified studies to be included in the HERO database, with a notation added to each of the non-included studies as to why the study was not included.

Page 12, line 17. The discussion of NOx in a multi-pollutant context could be expanded to include consideration of the relation of NOx to distance to roadway and traffic density and NOx as a surrogate to traffic pollution.

Page 14 and 15. In the health effects section, the plan states that the ISA will present and evaluate data on “studies conducted in environments near roads or other sources”. While this presentation and discussion is valuable, it should be expanded to include discussion of studies using other traffic pollutant measures and how these studies relate to those for NO_2 and health.

Dr. Ronald Wyzga

Overall Comments: The draft plan presents a logical approach to laying out the most relevant science for the eventual development of NAAQS standards for NOx. I would like to see more explicit discussion about the use of human exposure patterns in the choice of indicator species and averaging time.

Specific comments:

p. 9, lines 11-12: what is meant by "sufficiently representative"? One could argue that extreme air quality measures are of greatest concern. I don't know what a "sufficiently representative" dose metric is.

p. 10, lines 1-6: Ideally all 3 criteria should be met, but it should be recognized that a single-city study that satisfies criteria 2 and 3 can be more informative than a multi-city study that does not satisfy these criteria. I would not like to see single-city studies dismissed if they satisfy the last 2 criteria. I would add that single-city studies may be more informative than multi-city studies in the consideration of indicator species and averaging times as I am not aware of any multi-city studies that explore these issues.

lines 7-29: Experimental studies can be particularly informative about the relative toxicity of different NOx species and about averaging times.

p. 12, lines 1-16: It would also be important to indicate how different NOx species are related; what is the role of atmospheric chemistry in this relationship? What are the correlations between ambient concentrations of the various NOx species in different environments (e.g., indoor, near roadways, etc.)?

lines 17-31: I think the 3rd bullet in delineating exposure patterns is particularly important. This could be key in the consideration of averaging times for both the NAAQS and for future studies.

p. 13, line 33: Since we are considering exposures as short as <u>one</u> hour, we may want to change "hours" to "minutes" in this definition.

Pages 13-15: The Uncertainty section raises a key issue in epidemiological studies: to what extent are health effect associations with NOx due to NOx <u>per se</u> or due to other pollutant mixtures that NOx may be representing? Studies of the health effects need to be exploited to help resolve this issue. Given the discussion in the uncertainty section, the ISA clearly is concerned about this issue, but it could be made more explicit in the Health Effects section.

Page 15, line 7: Do we want to have a clear delineation between long-term and short-term studies; e.g., exposures one year or greater could be defined as long-term exposures.

Dr. Junfeng (Jim) Zhang

As a new member of the CASAC NOx Review Panel, I found the draft plan for NOx ISA development very well written. Reading it has given me a clear picture as to what is expected from this Committee and what the final product will look like. I commend the EPA staff who wrote this document. Below are my comments.

1. I understand that indoor NO2 exposure and health effects work has been reviewed and summarized in the 2008 report. I also understand that the current review shall focus on the literature published after 2008. However, given that there might have not been much research done on indoor NO2 since then, it is necessary to repeat in the new ISA. Indoor NO2 research is very helpful in assessing causality, as indoor co-pollutants may be different than outdoor co-pollutants in the air pollution mixture.

2. To support the new 1-hour-based standard, the literature on health effects of short-term exposure may be assessed in two categories (if publications are available): (a) the health effects resulting from single-time or a few repeated short-term exposures most likely done in animal studies and in human chamber studies; and (b) the health effects resulting from constant (routine) short-term exposures such as those experienced in daily commuting or at occupational settings.

3. As a component of the combustion-generated air pollution mixture, NO2 may serve as a surrogate for the mixture or for other pollutants that may be the true causal agents responsible for observed health effects. We all realize the difficulty in sorting out whether a NO2-health outcome association reflects the true NO2 effect or an effect of something else correlated to NO2. To help addressing this issue, I suggest that we evaluate epidemiologic studies conducted in different parts of the world. Because pollutant mixtures vary in different parts of the world in terms of relative abundance of NO2 (e.g., NO2 to PM ratio), comparing the NO2 effects in relation to different pollutant mixtures helps address the causality issue.