

06-03-13 Preliminary Draft Comments from Clean Air Scientific Advisory Committee (CASAC) NOx Review Panel. These preliminary pre-meeting comments are from individual members of the Panel and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

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

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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 NO_x. 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 for NO₂. New methods are now commercially available that are more specific to NO₂ and presumably will be considered as replacements for the current FRM in this review cycle. 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.

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Dr. Ronald C. Cohen

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

What spatial and temporal patterns can be seen in air quality data for NO_x? 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, NO_x concentrations and exposures. What new information is available to characterize the influence of meteorological parameters and exposures?

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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 NO_x or other air pollution exposure data. What is their role in the NO_x 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 NO_x 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 NO_x ISA Development plan highlights many of the issues with NO_x 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 NO_x 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. Panos G. 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 NO_x EMISSIONS AND CONCENTRATIONS

- a. Advancements (including significant methodological) in developing emission inventories for NO_x, that have taken place since the 2008 ISA, should be identified and assessed explicitly. Quantifying emission levels and patterns in time and space for urban and rural regions as well as for specific, both outdoor and indoor, microenvironments, 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. NO_x-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. Spatiotemporal patterns and trends 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 NO_x ISA and

should consider multiple temporal and spatial scales not only for NO_x but for co-occurring air pollutants as well.

- d. Assessment of the impacts of climatic change and of potential future changes in energy production and usage on NO_x emission levels and patterns should be explicitly considered in the ISA.

2. ASSESSMENT OF MODELING CAPABILITIES FOR NO_x 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 NO_x should be explicitly assessed in the ISA and included in the plan. In fact, transport and dispersive/diffusive mixing of emitted NO_x species with ambient air is intricately coupled with atmospheric chemistry, as steep gradients as well as random (turbulent) fluctuations in NO_x 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 NO_x 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.

4. ASSESSMENT OF (MECHANISTIC) MODELING CAPABILITIES WITH RESPECT TO CHARACTERIZING DOSIMETRY AND MODES OF ACTION FOR NO_x, 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. This evaluation should then be extended from respiratory to whole body toxicokinetics.
- b. The draft plan includes consideration of qualitative comparison of NO_x (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

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- 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 NO_x.
- 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 NO_x 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. 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 these variabilities are not independent), but will eventually be required for more thorough characterizations of environmental health risk issues.

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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

Here are a few initial thoughts:

1. There is no mention that I could see from my quick read on a large literature on indoor exposures to NO_x and particularly NO₂. This could be important for establishing causality based on the criteria mentioned in the document. It would also be a factor potentially influencing susceptibility to other ambient exposures.
2. I did not see noise specifically mentioned as a potential confounder or modifier. Because noise and NO_x often have similar emission sources and dispersion parameters (not exactly the same but highly correlated), this could be an important issue.
3. To what extent can we consider NO_x as a marker for a mixture of pollutants (I'm thinking mostly of mobile sources) where ultrafine particles, organic carbon, transition metals, and numerous other pollutants could be in the mixture and contributing to potential health effects?
4. One other factor that is mentioned is outdoor activity is being important, but we probably need to consider the physical activity levels of the subjects who are exposed while in traffic (for example bicyclists inhale about 4-7 times more than a person sitting in a car) - which would affect their dose.

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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 than 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 NO_x 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 No_x distributions. There is also increasing evidence of increased health effects near roadways where NO_x 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 NO_x control beyond the direct effects of the gaseous species on health, the role of NO_x in O₃ formation and the formation of secondary inorganic nitrates.
2. Assessment Approach – The role of NO_x 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.
3. 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 NO_x, on-road NO_x, and in-vehicle exposures to NO_x? Given the concern over short term exposures at or even less than one hour in duration, are the directly emitted NO₂/NO_x 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 NO_x exposures based upon measurements at locations susceptible to interferences from other nitrogen compounds (e.g. downwind sites with relatively low NO_x)?
3. How well do the current and proposed near-road NO₂ monitoring sites represent exposures to populations living near major roads?

Dr. Jeremy Sarnat

I apologize in advance if any of my comments or suggestions contradict previously accepted CASAC norms or protocols. I'll try to get up to speed quickly during this process. I don't have too many comments on this draft. Looks like a really interesting process. Below are several minor comments/questions.

- To avoid confusion especially among non-CASAC readers, consider using either ppb or ppm consistently in discussing the NO_x 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 NO_x 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 NO_x 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 NO_x *health criteria*, but the differences among the sections are fairly pronounced.

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Dr. Richard B. 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 NO_x 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. Lianne Sheppard

Overall I found the *Draft Plan for Development of the ISA for NO_x – 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. Where will these appear in the ISA?
2. P 12: Consider adding this exposure-related question, perhaps in addition to the questions starting on line 32: *To what extent is NO_x 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.

Dr. Ronald E. 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 NO_x. 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 NO_x species and about averaging times.

p. 12, lines 1-16: It would also be important to indicate how different NO_x species are related; what is the role of atmospheric chemistry in this relationship? What are the correlations between ambient concentrations of the various NO_x 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 one 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 NO_x due to NO_x per se or due to other pollutant mixtures that NO_x 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.