UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

June 8, 2007

EPA-CASAC-07-005

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

Subject: Clean Air Scientific Advisory Committee's (CASAC) Consultation on the Draft Integrated Plans for Review of the Primary NAAQS for NO_2 and SO_2

Dear Administrator Johnson:

The Clean Air Scientific Advisory Committee (CASAC or Committee) Oxides of Nitrogen (NO_X) and Sulfur Oxides (SO_X) Primary National Ambient Air Quality Standards (NAAQS) Review Panel (Panel) met on May 11, 2007, via a public teleconference to conduct a consultation on EPA's *Draft Plan for Review of the Primary National Ambient Air Quality Standard for Nitrogen Dioxide* (Draft Integrated Plan for Review of the Primary NAAQS for NO_2, February 2007) and *Draft Integrated Plan for Review of the Primary National Ambient Air Quality Standards for Sulfur Dioxide* (Draft Integrated Plan for Review of the Primary NAAQS for SO_2, April 2007). The CASAC roster is attached as Appendix A of this letter, the NO_X & SO_X Primary NAAQS Review Panel roster is contained in Appendix B, and Panel members' individual written comments are provided in Appendix C.

The SAB Staff Office has developed the consultation as a mechanism to advise EPA on technical issues that should be considered in the development of regulations, guidelines, or technical guidance before the Agency has taken a position. 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*. Although there per our customary practice will be no consensus report from the CASAC as a result of this consultation, the Committee would nonetheless like to underscore several key points that arose in the conduct of its consultation on the draft integrated plans for review of the primary NAAQS for NO_2 and SO_2. These are provided as follows, along with the names of those Panel members whose individual written comments expand on these points or issues:

- The existing NO_2 and SO_2 primary (and secondary) standards as well as the current draft integrated plans for review of primary NO_2 and SO_2 standards are narrowly focused on considerations of *direct* exposure effects from these gaseous pollutants alone. The plans appear to specifically exclude any consideration of the combined influences of the many secondary transformation products (gaseous, aerosol and deposition) which inevitably result from, and coexist with, these precursor pollutants. EPA may eventually conclude in the associated Policy Assessments for primary NO_X and SO_X (to be published in the form of ANPRs) that there are more efficient alternative mechanisms (such as through $PM_{2.5}$ standards or the Clean Air Interstate Rule) for mitigating adverse health or welfare impacts of SO_X and NO_X transformation products. However, it would seem useful to include some consideration of the health and welfare effects of S and N transformation products (or other pollutant mixtures) in the ISAs and the risk/exposure assessments for both the primary and secondary NAAQS for NO_2 and SO_2. (Mr. Poirot and Dr. Cowling)

- It is not clear how the Agency will select the most relevant literature to include in its Integrated Science Assessments (ISAs) for primary NO_X and SO_X, nor how any new information would be managed that might come available between the CASAC's review of the 2nd Draft ISAs for primary NO_X and SO_X in April and July 2008, respectively, and the release of the corresponding Advance Notices of Proposed Rulemaking (ANPRs) in April and June 2009. (Dr. Larson and Dr. Speizer)

- There is apparent confusion over the use of SO_2 versus SO_X and NO_2 versus NO_X in the documents. These terms should be carefully and consistently employed. Also, the SO_X plan states in one place that particulate sulfates will not be considered, yet the ambient level of SO_2 is of concern because it contributes to sulfate formation. In addition, the NO_X document does not say whether nitrate particles will be considered. Furthermore, multi-pollutants and their influence on the toxicity of NO_X and SO_X should be considered in the integrated plans. This is particularly true for particles and ozone. (Mr. Avol, Dr. Gong, Dr. Hattis, Dr. Kleeberger, Dr. Russell, Dr. Sheppard, Dr. Speizer, Dr. Thurston and Dr. Ultman)

- Risk assessment cannot be excluded from the risk/exposure document. Both quantitative and qualitative evidence are necessary for the integrated assessment of risk leading to NAAQS policy recommendations. Semi-quantitative risk assessment information, such as estimates of risk bounds, should be incorporated where quantitative assessment is not possible. It is also not clear how the information on uncertainty and variability (*i.e.*, the results of the uncertainty analysis) will be used. Additionally, rural as well as urban areas should be evaluated for potential NO_X and SO_X exposures. (Dr. Henderson, Mr. Avol, Dr. Crawford-Brown, Dr. Hattis, Dr. Kinney, Dr. Russell, Dr. Seigneur and Dr. Sheppard)

Finally, several members remarked on how the review of the primary NAAQS for NO_X and SO_X will be conducted, noting in particular that the process by which EPA's positions are developed and presented in the ANPRs needs to be clear and transparent. (See, in particular, the individual written comments from Mr. Avol, Dr. Gong, Dr. Sheppard and myself.)

The CASAC was pleased to consult with the Agency on these draft integrated plans for review of the primary NAAQS for NO_2 and SO_2 and would appreciate a formal response from EPA indicating how Agency staff intents to incorporate these comments into the final planning documents. In addition, the Committee looks forward to conducting a peer review of EPA's first draft ISAs and risk/exposure methodologies for the review of the primary NAAQS for NO_X and SO_X later this calendar year. As always, we wish EPA staff well in this important task.

Sincerely,

/Signed/

Dr. Rogene Henderson, Chair
Clean Air Scientific Advisory Committee

cc: Marcus Peacock, Deputy Administrator
George Gray, Assistant Administrator, ORD
Robert Meyers, Acting Assistant Administrator, OAR

Appendix A – Roster of the Clean Air Scientific Advisory Committee

Appendix B – Roster of the CASAC NO_X & SO_X Primary NAAQS Review Panel

Appendix C – Comments from Individual Panel Members

NOTICE

This report has been written as part of the activities of the U.S. Environmental Protection Agency's (EPA) Clean Air Scientific Advisory Committee (CASAC), a Federal advisory committee administratively located under the EPA Science Advisory Board (SAB) Staff Office that is chartered to provide extramural scientific information and advice to the Administrator and other officials of the EPA. The CASAC is structured to provide balanced, expert assessment of scientific matters related to issue 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 in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use. CASAC reports are posted on the SAB Web site at: http://www.epa.gov/sab.

Appendix A – Roster of the Clean Air Scientific Advisory Committee

U.S. Environmental Protection Agency
Science Advisory Board (SAB) Staff Office
Clean Air Scientific Advisory Committee (CASAC)

CHAIR

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

MEMBERS

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

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

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

Mr. Richard L. Poirot, Environmental Analyst, Air Pollution Control Division, Department of Environmental Conservation, Vermont Agency of Natural Resources, Waterbury, VT

Dr. Armistead (Ted) Russell, Georgia Power Distinguished Professor of Environmental Engineering, Environmental Engineering Group, School of Civil and Environmental Engineering, Georgia Institute of Technology, Atlanta, GA

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

SCIENCE ADVISORY BOARD STAFF

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Appendix B – Roster of the CASAC NO_X & SO_X Primary NAAQS Review Panel

U.S. Environmental Protection Agency
Science Advisory Board (SAB) Staff Office
Clean Air Scientific Advisory Committee (CASAC)
CASAC NO_X & SO_X Primary NAAQS Review Panel

CHAIR

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

MEMBERS

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

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

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

Dr. James D. Crapo [M.D.]*, Professor, Department of Medicine, National Jewish Medical and Research Center, Denver, CO

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

Dr. Henry Gong, Professor of Medicine and Preventive Medicine, Medicine and Preventive Medicine, Keck School of Medicine, University of Southern California, Environmental Health Service, Downey, 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, NIH/NIEHS, Research Triangle Park, NC

Dr Timothy 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

Mr. Richard L. Poirot*, Environmental Analyst, Air Pollution Control Division, Department of Environmental Conservation, Vermont Agency of Natural Resources, Waterbury, VT

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

Dr. Armistead (Ted) Russell*, Georgia Power Distinguished Professor of Environmental Engineering, Environmental Engineering Group, School of Civil and Environmental Engineering, Georgia Institute of Technology, Atlanta, GA

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 [M.D.]*, 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, P.O. Box 10412, Palo Alto, CA

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* Members of the statutory Clean Air Scientific Advisory Committee (CASAC) appointed by the EPA Administrator

Appendix C – Comments from Individual Panel Members

This appendix contains the preliminary and/or final written comments of the individual members of the Clean Air Scientific Advisory Committee (CASAC) Oxides of Nitrogen (NOx) and Sulfur Oxides (SOx) Primary National Ambient Air Quality Standards (NAAQS) Review Panel who submitted such comments electronically. The comments are included here to provide both a full perspective and a range of individual views expressed by Panel members during the review process. These comments do not represent the views of the CASAC, the EPA Science Advisory Board, or the EPA itself. Panelists providing review comments are listed on the next page, and their individual comments follow.

Panelist **Page #**

Mr. Ed Avol

Comments on the Draft Plan for Review of the
Primary National Ambient Air Quality Standard for Nitrogen Dioxide

Ed Avol, NOx-SOx Primary Review Panel Member

P1-2, line 5 – Ambient NOx chemistry is intimately bound between gaseous NOx emissions and particle NO3 formation. How will this be addressed, considered, and weighted in the "Integrated Science Assessment" or "Science Assessment Support Document"? Comments in the Plan (P4-3, line 12, for example) suggest that particulate nitrate information is relevant to the proposed discussion. If the plan is to only consider gas-phase processes, how can this be scientifically justified in terms of air quality and public health?

P1-2, line 19 – Who will prepare the policy assessment, and how can the public be assured that the best science, and not political policy, has a substantive role in the process?

P4-6, lines 21 and 22 – why is this question limited specifically to traffic, and not to any combustion source (home fireplaces, industrial stationary sources, etc.) affecting ambient NO_2?

P4-6, line 25 – add "…or indoor space/water heating sources…" after "…gas stoves…"

P4-7, line 7 – why are other health effects related to NOx exposure relegated to the status of "may be evaluated"? Isn't the purpose do the ISA to identify and compile the recent science and observed health outcomes, without *a priori* censure or determination of which health outcomes might be of interest?

P4-7, line 16 – "…add "…or pre-existing susceptibility (i.e., genetic, biochemical)…"; the identified group of "pre-existing disease state" is arbitrary and limiting, and the current literature should at least be reviewed for susceptible groups.

P4-7, line 25 – As in the previous comment, other susceptible groups (i.e., genetically susceptible) may be relevant here as well, and the available literature should be canvassed with the widest possible initial filter.

P4-8, line 29 – add "…or other identified susceptibility (i.e., genetic)…"

P4-10, line 15 – replace "animal-to-man" with "animal-to-human"

P4-10, line 20 – add "genetic susceptibility" to the list for consideration

P4-10, lines 25 and 26 – the issue is not whether children and asthmatics are more sensitive than the general population to NOx exposure, but rather, whether there is supporting evidence that

there are (a) susceptible sub-groups of the population with increased sensitivity to NOx, and if there are, (b) what we know or can surmise about the characteristics of that sub-population.

P5-2, line 24 – It would seem potentially more useful to review ambient data made available since the previous NAAQS review, so the window of reviewable data should be the last decade, not the last three or four years.

P5-3, lines 1 and 2 – Major locations to be evaluated should include both urban areas impacted by traffic (Los Angeles, Houston, New York, Phoenix) and rural areas. Metropolitan areas in rapid growth, as well as those with a long history of minimal change, should be considered.

P5-3, lines 7 and 8 – Isn't this potentially going to be related to location (urban vs. rural, or roadside vs. regional)? If this is potentially going to be an important confounder/adjustment/covariate, should this be modified to include the notion of location?

P5-4, line 7 – Why is this necessarily limited to urban areas across the US?

P6-1, lines 2 and 3 – Which section/department of the EPA will be charged with development of the ANPR?

P6-1, line 12 – why is it assumed there is "…a gap between the Agency's scientific assessments and the judgments required of the Administrator…"?

Dr. Ellis Cowling

Dr. Ellis Cowling
North Carolina State University
May 17, 2007

Individual Post-Consultation Comments on the
Draft Plan for Review of the Primary National Ambient Air Quality Standards for Sulfur Dioxide and the
Draft Plan for Review of the Primary National Ambient Air Quality Standard for Nitrogen Dioxide

My colleagues on CASAC have offered a number of very constructive comments on specific details of these two very similar draft plans. My preference instead is to focus attention on the most general rather than more specific aspects of these two plans – that is, the fundamental reason for conducting these periodic reviews of NAAQS for all six criteria pollutants, and, of course, also, these two specific criteria pollutants – sulfur dioxide and nitrogen dioxide.

I am well aware that these two "Draft Plans for Review" refer only to reviews of the primary (public-health based) standards for SO_2 and the single primary standard for NO_2, and thus do not deal directly with reviews of the secondary (public-welfare based) standards for these two criteria pollutants. I am also aware that a second set of "Draft Plans for Review" probably will be developed for the secondary (public-welfare based) standards for these two pollutants. Especially since the decision has been made to conduct separate reviews for the primary and secondary standards for each of these two criteria pollutants, it is desirable that an appropriate relationship be maintained between these two review processes.

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 regard to the important distinction in purpose of the primary (public health) and secondary (public welfare) NAAQS standards, it is noteworthy that in all five cases in which a secondary NAAQS standard has been established, the secondary standard has been set "Same as Primary."

In this connection it is also important to recognize that "public welfare effects" are defined in the Clean Air Act to include, but are not limited to: "effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility, climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being, whether caused by transformation, conversion, or combination with other air pollutants."

The Clean Air Act also specifies that "Any national secondary ambient air quality standard … shall specify a level of air quality the attainment and maintenance of which in the judgment of the Administrator … is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of such air pollutant in the ambient air."

Thus, a second very critical question that needs to be answered with regard to all six criteria air pollutants is:

"What scientific evidence and/or scientific insights have been developed since the last review to indicate whether, and if so, what particular ecosystem components or other air-quality-related public welfare values, are more or less sensitive than the populations of humans for which primary standards are established and for this reason may require a different level, indicator, statistical form, or averaging time of a secondary standard in order to protect public welfare."

I hope these two "critical scientific questions" will be borne in mind carefully as CASAC joins with the various relevant parts of the Environmental Protection Agency in completing the upcoming reviews of both the primary and secondary National Ambient Air Quality Standards for these two criteria pollutants and the four other criteria pollutants that will follow under the guidance of the new NAAQS review processes.

Dr. Douglas Crawford-Brown

Review of Draft IP for Nitrogen Dioxide

Doug Crawford-Brown

Given that this is a draft IP, there is not a lot that can be said at this stage since the real issues will revolve around how these plans are implemented in the actual assessments. Still, there are a few initial issues I want to raise. The issues raised here are largely identical with those raised in my review of the Nitrogen Dioxide IP, as the two documents are almost identical.

1. On page 3-2, the question is raised as to whether there is evidence of effects at exposure levels lower than those found in the previous studies. I believe this should refer to lower levels and/or shorter periods of time (i.e. exposure duration), although the latter issue is hinted at later in the questions.

2. On page 4-1, the issue is raised of the new studies being integrated into the older ones. I would like to have seen a sentence or two as to how that will be done. There are always two approaches to this: either treat the older conclusions as a form of prior and then ask whether the new data cause you to change these prior conclusions, or re-do the older assessment entirely with the new data folded into the pool of data to be considered. The authors are not clear which is to be done here, but the results can differ between the two approaches since the former sets up a kind of epistemic barrier the new data must possess to move the assessor off previously established positions. The latter approach is, of course, also more time intensive.

3. The approach for locating new data, starting on page 4-2, is well developed, so I have no suggestions there. While I appreciate the desire to use only peer reviewed literature, this requirement is getting less germane as internet publishing expands, and at some point the EPA will need to confront this issue.

4. The material on Exposure beginning with page 4-6 is a bit sketchy, and I understand the need to be so at this stage. However, I have some significant issues to raise as to how activity patterns of individuals, including movement through geographically inhomogeneous fields of concentration, will be treated. The most fundamental issue is whether the assessment is intended to reflect, in the greatest detail possible, the actual exposures to actual individuals in the population, or the exposures that would occur if an individual were to adopt some activity pattern that puts them at greatest risk. There certainly is merit in the argument that one wants the former, as it best reflects the actual risks being experienced by the population given their current distribution of activity patterns. But there is equal merit in the argument that the job of the EPA is to create environments within which individuals could move in whatever activity patterns they choose without sacrificing their rights to protection against significant health risks. In the latter case, one would model scenarios that are designed to be reasonable expectations of what people might choose to do in the environment, rather than trying to model these activities probabilistically. This will be an issue we can discuss more when in session.

5. On page 4-7, second bullet, the authors raise the issue of whether there are effects on lung functions changes or development. It is important here to also consider whether these effects are to be determined adverse. I realize this is in part the intention of the phrase "potential clinical relevance" in the next bullet, but the effects in that third bullet are not identical with those in the second.

6. On pages 4-7 and 4-8, the authors begin to confront the idea that past exposures at low but chronic levels might affect an individual's sensitivity to shorter term but higher concentration exposures, and to infection. This issue seems to me important, since the chronic exposures could either sensitize or de-sensitize people.

7. On page 4-9, third bullet under Biological Mechanisms of Action, the authors might consider adding something like "…and what are the implications…" to the end of the bullet.

8. On page 4-10, second bullet under Susceptible Populations, the presumption is that children and asthmatics are more sensitive. I realize this is the predominant case, but I would be inclined at this stage to not stack the deck in the question, but rather to ask the extent to which these groups are more or less sensitive.

9. On page 5-1, the authors state that they anticipate an inability to produce a quantitative health risk assessment. Do they really mean no quantitative health risk assessment can be conducted, or do they mean it will need to be an assessment that ends with something like a hazard quotient rather than a probability and/or severity of effect? And will it be driven by the HQ in the most sensitive subpopulation? This sentence just leaves me wondering what the assessment WILL end up producing that is useful in setting a NAAQS if there is insufficient exposure-response information to estimate risks. Perhaps the problem here is that I consider an HQ value to be a legitimate result of a risk estimation procedure while perhaps the authors do not? I am particularly unclear as to how the screening assessment results will be used to determine whether a more refined assessment is warranted. There should be at least some rudimentary decision criterion, pre-specified, to guide this process. I suppose the bullets on page 5-5 are intended to in some way specify criteria for this decision, but they are too generic to play that role.

10. In section 5, the authors are beginning to consider the issue of the spatial resolution that will be needed to estimate exposures. I agree that greater spatial resolution might be good to have, but there are two caveats to this. First, I am not convinced that the quality of predictions of exposure at fine spatial resolution are accurate below some level of resolution. Second, the spatial resolution should not be any better than the spatial resolution of the activity patterns for individuals. There comes a point at which increased spatial resolution in ambient air concentration or microenvironment concentration is more than washed out by uncertainties in activity patterns.

11. On page 5-6, there is also some discussion of uncertainty due to model formulation. The description of how this will be treated is too cursory for me to feel very comfortable. There is some hint that subjective confidence measures will be applied, but also some hint that these will be driven solely by some sort of relative likelihood measure obtained from a fit to data. This raises huge questions as to WHICH data will be the primary data on which the likelihoods will

be developed, and whether model fit is the sole criterion for judging the validity and strength of a model. I think the authors have some significant issues to consider here.

15. Finally, the assessment will be based in part on case studies in different cities. The authors describe this choice as being rooted in an assessment of variability, giving some idea of the upper and lower bounds of the variability. However, it is not clear how the choice of cities will produce recognizable percentiles of the variability distribution. Is there any way in which the EPA intends to relate specific individuals, or scenarios, in specific case studies to specific percentiles? Absent this, it is not clear how such an assessment of variability will be related to specific regulatory bases for setting a NAAQS.

Review of Draft IP for Sulfur Dioxide

Doug Crawford-Brown

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10. On page 5-3, the authors approach the issue of ambient exposures and exposures in microenvironments. From the writing, it appeared to me that they will convert ambient levels to those in microenvironments solely through models. This seems to me to leave out increasingly detailed studies of the empirical relationships between these quantities, many of which have been funded by the EPA. I may be wrong that these are being ignored, but the wording in this section does emphasize modeling rather than data.

11. On page 5-4, the authors are beginning to consider the issue of the spatial resolution that will be needed to estimate exposures. I agree that greater spatial resolution might be good to have, but there are two caveats to this. First, I am not convinced that the quality of predictions of exposure at fine spatial resolution are accurate below some level of resolution. Second, the spatial resolution should not be any better than the spatial resolution of the activity patterns for individuals. There comes a point at which increased spatial resolution in ambient air concentration or microenvironment concentration is more than washed out by uncertainties in activity patterns.

12. On page 5-5, under Uncertainty and variability, the authors state that they will determine "…the relative degree of confidence in the results…". I have no idea what is meant by this. Relative with respect to what? And what is the measure of confidence? Is it frequentist, subjective, Bayesian?

13. On page 5-6, I worry about the phrase "…information is often not available to estimate uncertainty separately from variability". Not only do I disagree that this is true, I can see no way around separating these two. They are two different concepts, existing in different places in the world (variability exists solely outside our minds, uncertainty exists solely within them – a distinction that seems to me pretty fundamental). I have little doubt that CASAC would have significant concerns with the final product if uncertainty and variability are NOT separated.

14. On page 5-6, there is also some discussion of uncertainty due to model formulation. The description of how this will be treated is too cursory for me to feel very comfortable. There is some hint that subjective confidence measures will be applied, but also some hint that these will be driven solely by some sort of relative likelihood measure obtained from a fit to data. This raises huge questions as to WHICH data will be the primary data on which the likelihoods will be developed, and whether model fit is the sole criterion for judging the validity and strength of a model. I think the authors have some significant issues to consider here.

15. Finally, the assessment will be based in part on case studies in different cities. The authors describe this choice as being rooted in an assessment of variability, giving some idea of the upper and lower bounds of the variability. However, it is not clear how the choice of cities will produce recognizable percentiles of the variability distribution. Is there any way in which the EPA intends to relate specific individuals, or scenarios, in specific case studies to specific percentiles? Absent this, it is not clear how such an assessment of variability will be related to specific regulatory bases for setting a NAAQS.

Dr. Henry Gong

Post-Conference Comments on Draft Plan for Review of the Primary National Ambient Air Quality Standards for NO2 (February 2007) and SO2 (April 2007)
Henry Gong
May 19, 2007

Although I was unable to participate in the teleconference on May 11, I wish to submit some impressions based on my review of the documents and comments by the CASAC panelists. I apologize if I am repeating any discussion held during the recent conference call.

I offer these general comments that pertain to both draft plans:

1. I appreciate (and support) the interesting and perceptive comments and perspectives raised by my fellow colleagues on the Panel. They raise important general and specific issues related to the administration and process of the review, as well as to science and public health.
2. NO2 vs. NOx? SO2 vs. SOx? Each plan may confuse the reader at times since it is unclear whether the text is actually (or should be) referring to either or both NO2 vs. NOx or SO2 vs. SOx, in the respective plans. Even the titles ("Draft Plans…") refer only to NO2 or SO2 and not to other related chemical species. I read the NO2 Plan before the SO2 Plan and noted that the explanation for addressing only NO2 was missing, but an explanation was present for SO2 (Section 1.4. Scope of Review, page 1-6)). However, even the SO2 rationale is somewhat confusing in that I came away with the perception that sulfuric acid, sulfates, etc., may or may not (?) be addressed. The occurrence/ interactions of gas-particulate mixtures is not referred to. Thus, I recommend that careful consistency of terms and stronger explanations for inclusion and exclusion be used.
3. The series of questions about air quality, exposure, health effects, etc., to be addressed (if possible) in the ISA of both Plans are excellent.
4. Does the possible lack of a full or proper quantitative risk assessment impair a good estimate of the "margin of safety"?
5. What is the role of CASAC (if any) in the draft of the ANPR? My reading of the Plans suggests that the ANPR is an independently developed document published in the Federal Register. This presentation may, in effect, give it an "authoritative" scientific-policy representation and almost law-like quality. I would appreciate more information about the development and vetting of the ANPR.

Dr. Terry Gordon

Gordon – General Comments on NOx and SOx Draft Plans for Review

In general, the comments I've read reflect my opinions. Rather than repeat things, my 2 additional comments are:

1. More consistent wording should be used in directing the emphasis on the quality and inclusion of studies in the Assessment document. At one point in the Plan, miniscule detail is given in terms of studies must include filtered air control groups, yet Section 4-1 states that exceptions to peer-reviewed and published studies can be made depending upon rather vague terms. This point may be moot, however, if all relevant studies will be included in a supporting table and only key studies discussed in the text of the documents themselves.

2. If concentration exposure levels in controlled studies must be relevant to ambient concentrations, what will those levels be and who and when will they be decided upon? This point may also be partially moot, as the draft chapters have already been submitted and discussed. Also, if all studies are included in the supplemental/annex tables, then only the studies with relevant concentrations can be discussed in the text.

Dr. Dale Hattis

Comments on the Draft Integrated Plans for Reassessment of the SOx and NOx National Ambient Air Quality Standards

Dale Hattis, Clark University

SO_2

I have one overarching comment/suggestion that stems from the first two bullets representing "uncertainties" on the bottom of page 4-8. These bullets are:

- How do confounding by co-exposure to other pollutants and by meteorological factors influence the uncertainty of the evidence base for both short- and long-term exposures?

- To what extent are the observed health effects associations attributable to SO_2 versus the pollutant mixtures that SO_2 may be representing? For example ambient SO2 concentrations may be serving as a surrogate measure for long range transport of particles.

I think these are both such excellent and potentially important questions that EPA should consider moving them from a rather peripheral discussion of uncertainties to main lines of analysis. As I believe was discussed in the February meeting I attended, my recollection is that from the earliest days of Mary Amdur's fine and extensive series of experimental observations in guinea pigs, mixtures of sulfur oxide gases and particles may have greater effects than either component administered separately. One possible interpretation of this is that the particles are acting as a kind of vector for the sulfur oxide gases—facilitating the delivery of larger amounts of the gases in adsorbed form farther down into the respiratory tract than would otherwise occur. If this turns out to be the case on full review of the older and newer literature, then perhaps we should be asking, "Are the concentrations/exposure times of SO_2 that are 'requisite to protect public health" *different* depending on typical local co-exposures to particulates and/or different meteorological conditions such as humidity? If so, I think two kinds of policy responses could be considered:

- Locations with relevant monitoring data could be classified into a number of categories based on interacting particle and/or meteorological conditions, in order to provide the basis for application of a graded series of NAAQS SO_2 criteria taking into account the likely greater SO_2 effects in some places rather than others.

- The SO_2 NAAQS could be modified to take the form of an index modified to take into account the contributions of particles and meteorological conditions on the SO_2 -dependent response. Such an index would have some technical advantages in that the particle and meteorological influences could be represented in continuous functional form, rather than as categorical variables.

Both of these options would respond to EPA's evident concern that the purpose of the present review is to modify the SO_2 /SOx gas standard, not revisit the particulate standard

itself. An implication for the EPA work is that the plan for exposure data collection and analysis/modeling (Section 5.3) will need to be appreciably changed to keep track of the co-exposures of particles of various size ranges and meteorological information so that they can be analyzed to see the effects of potential standards reformulated in these ways.

Another comment that pertains to section 5.4, is that I would like to urge EPA to attempt a full probabilistic risk assessment—treating both variability and uncertainty of both exposures and health effects. This kind of high profile national-level review and analysis is just the kind of enterprise that should be expected to utilize the most sophisticated treatment of the very different concepts of variability and uncertainty. This would afford the EPA an opportunity to quantitatively define its "margin of protection" goal in setting NAAQS in terms of assuring that there is Z% confidence that the incidence of effects of a defined level of severity is less than some specific value. Without such definition, the policy goals of the Clean Air Act will remain in their present vague and non-evaluatable state.

NOx

I have no specific comments on the NOx plan. However the last comment in the previous section applies equally to both the NOx and SO_2 analyses.

Dr. Rogene Henderson

Comments on the draft plans for review of the primary NAAQS for NO_x and SO_x

Submitted by Rogene Henderson

Major general comment:
I have a comment that applies to both draft plans in regard to the third component of the review process, i.e., the risk/exposure assessment. In both the section on Overview of the Review Process (Section 1.1), and the section on Risk/Exposure Assessment (Section 5), the "risk" part of the title seems to have been left out. Only the exposure assessment is discussed. In a memo dated April 17, 2007, Marcus Peacock describes the latest version of the new review process and states that, "I am modifying the process to enable CASAC to review and provide advice to the Agency on the second draft risk/exposure assessment report, which will include estimated risk/ exposures associated with potential alternative standards, prior to issuance of the ANPR " Thus the plan needs to provide for inclusion of a listing of potential alternative standards and the estimated risks/exposures associated with those standards in the risk/exposure assessment documents .

Minor specific comment:
SO_x document, page 4-8 lines 9-10: Should insert "SO_2 –induced" before "lung inflammation"

Dr. Patrick Kinney

Draft Plans for Review of the Primary National Ambient Air Quality Standards for NO2 and SO2
Comments of Patrick L. Kinney, May 18, 2007

I was very impressed by the quality of both documents. Overall, the proposed process for review of the NAAQS looks to be reasonable.

My main substantive comment is on Section 5.1 of both documents, where the risk assessment methodology is discussed. EPA should provide an expanded rationale for their initial decision not to conduct a quantitative risk assessment (QRA) for either pollutant. What is missing, and what kind and quantity of data would EPA need in order to proceed with a QRA?

On a more philosophical level: if a) there is an insufficient health database to support risk assessment for NO2 and SO2, and b) both NO2 and SO2 are precursors for PM2.5 formulation, and c) there IS a sufficient health database to support PM2.5 risk assessment, what is EPA's rationale for continuing to regulate NO2 and SO2 as criteria pollutants? Wouldn't it be more rational to simply set NO2 and SO2 emissions limits based on PM2.5 risk assessment?

Dr. Steven Kleeberger

Steven R. Kleeberger
Laboratory of Respiratory Biology
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Comments

NO_X Document

I have only a few comments in addition to those already raised by other reviewers. In particular, I wonder whether greater emphasis or detail regarding phenotypes of response to NO_x (and SO_x) exposures should be written. In the Science Assessment (Section 4), pages 4-7 and 4-8 of the NO_x document, discussion of responses to short-term and long-term exposures is largely limited to adults and, to a lesser extent, children in epidemiologic and clinical studies. I would suggest that an unexplored, or not very well considered, aspect of air pollution relates to *in utero* or epigenetic effects, and reproductive effects. Epigenetic effects of NO_x and SO_x may have important implications in development of childhood and adult diseases. Effects of pollutant on reproductive characteristics including fecundity, prematurity, and sex ratio have not been well studied but could be important outcomes of exposure to pregnant women.

Susceptible populations are mentioned in many sections of the NO_x and SO_x documents. However, the susceptibility factors generally considered include pre-existing disease (e.g. COPD and asthma) or age (e.g. children). Some mention of genetic background is made in the two documents, but inasmuch as genetic background is increasingly recognized as an important susceptibility factor for responsivity to pollutant exposure, I suggest that greater emphasis be placed on this intrinsic host factor. Mention of inter-species differences in sensitivity on page 4-10 of the NO_x document could also include inter-strain differences.

I would re-emphasize the point made by one of the reviewers that effects of mixtures should perhaps receive greater emphasis in both documents. I recognize that mixtures are covered by other CASAC committees, but additional emphasis in the NO_x and SO_x documents is warranted.

Dr. Timothy Larson

Comments on Draft IPs for Review of the Primary SO_2 and NO_2 NAAQS
Timothy Larson
University of Washington

General Comments

In general, it is reasonable to have a review schedule that results in a timely assessment of the science and a promulgation of a revised standard. However, if events as outlined do not keep on schedule, one simple question is whether we as a committee will have a chance to review a revised schedule that contains all the elements of the currently proposed schedule. One would assume so. Another question is how are 'important' late breaking studies considered? By 'important' I mean those studies that are published between the final review of the ISA (July 2008) and the final review of the ANPR (June 2009), and that the committee as a whole (or in part?) deem sufficient to change the basis of a risk assessment. This is a bit trickier and probably deserves discussion.

Some of the questions listed in both documents in section 3.2 seem redundant. Regarding evaluation of the newly available evidence, five of the questions are variations of the same general question, i.e., the extent to which newly available information reinforces or calls into question evidence for the occurrence of health effects at ambient levels. The two other questions in this group are qualitatively different, dealing with the levels of exposure where health effects occur (the dose response relationship) and the aerometric relationships. I would shorten the list and add a specific question about our current understanding of the mechanisms of effect (the plausibility question). Regarding the identification of alternative standards, the first question, strictly speaking, excludes the possibility of effects at different averaging times. The effect could occur at a higher (rather than lower) concentration than those observed previously because of a shorter exposure time than previously considered.

I agree with Professor Speizer's suggestion that we should have access to a list of studies that will be considered for inclusion in the SASD.

NO_2 Document:

In section 4 of the document, there are explicit criteria listed for study selection, including an upper limit on NO_2 exposures in controlled human studies. I would suggest considering an upper limit on NOx as well, as many of the diluted combustion exhaust studies report both NO_2 and NO and can have fairly high levels of NO (above 1 ppm). This consideration may not be relevant for all endpoints, but could be for some given that NO is used as a therapeutic agent.

Page 4-5 line 26: emissions of NOx? Most NO_2 is initially emitted as NO.

Page 4-5 line 28: the notion of an additive background may not hold for NO_2, given the concept of a photochemical steady state for NO_2 and O_3.

Page 4-6 lines 10 and 23: these seem like a health questions, not exposure questions

Page 4-8 line 7: Do you mean NO_2 rather than NOx?

Page 4-9 line 1: What are the criteria for there being a causal relationship?

Page 4-9 line 24: In this and the following section, are you considering only NOx or also NO_2 and NO separately?

Page 5-4 line 12: I would also suggest that the exposure assessment take into account any personal exposure data sets that exist and can be reliably compared with model predictions.

SO_2 Document

Page 4-3 line 8: What is the rationale for down-weighting studies from other than the US or Canada? I would think that the criteria should be the relative mix of sources of SO_2 and other pollutants, not the geography per se.

Page 4-3 line 26: what about double blinding as a requirement?

Page 5-4 line 28: Most if not all current air quality dispersion models do not predict 5-minute average concentrations with much skill. It's not clear that this is a viable alternative.

Dr. Kent Pinkerton

May 10, 2007

Comments on the Science Assessment of the "Draft Plan for Review of the Primary National Ambient Air Quality Standard for Nitrogen Dioxide"

Kent E. Pinkerton, University of California, Davis

(The comments listed below, in general, are also relevant to the Sulfur Dioxide Document)

1) The organizers and writers for the Science Assessment portion of the document are to be commended for their clear and logical explanation of the scope and organization of the science assessment to be implemented for this criteria document.

2) The approach to be taken to conduct the assessment of what is new since the last writing on this criteria pollutant, as well as input from the public of this scientific review are excellent and based on both integrated science assessment (ISA) and the creation of a science assessment support document (SASD). The purpose, content, and interpretation of this assessment approach, as well as the creation of the document are clearly outlined in the scope and organization of this integrated draft document.

3) The primary focus of the ISA and SASD is to present literature published since the previous review of the air quality criteria for NO_x. Key findings and conclusions will be briefly summarized from the previous document dated in 1993. More recent studies will be integrated into previous findings. In addition, important older studies will be specifically discussed and opened to reinterpretation based on more recent data. I think this approach is highly logical and clearly responsive to the mandate for scientific rigor and completeness in reassessing the NO_x criteria standard.

4) I am in complete agreement with the importance to emphasize studies conducted at or near NO_x concentrations found in the ambient air. However, I would also emphasize the critical importance to also examine unique conditions in which NO_x concentrations may be unusually high due to specific occupational conditions or conditions that may exist within certain dwellings or settings that may be unintentional but do occur. Such an understanding of the potential health effects associated with likely short-term exposures to very high levels of NO_x is as important as those to evaluate ambient concentrations of NO_x.

5) The need to include studies that may deal with NO_x concentrations above ambient levels is simply based on the fact that people could accidentally be exposed to NO_x concentration far above ambient levels that may have persistent or lingering effects following such events.

6) The authors of the current draft of the NO_x document from both the EPA staff, as well as extramural scientists contracted to the EPA should be commended for their excellent and thorough evaluation of the more recent data of NO_x findings. I find no serious deficiency or omission in the approach taken to conduct a complete and thorough literature search. Key words, as identified by the NCEA-RTP team, are highly appropriate. It is assumed that

nitrogen-containing compounds that are based in ammonia or ammonium constituents would not be appropriate for this document? If not, I think it is important that the absence of other nitrogen-containing compounds (associated with other criteria pollutants such as particulate matter) be stated as not relevant (or exempt) for this criteria document.

7) The thorough review proposed of the draft document by EPA staff, as well as comments on draft chapters by outside reviewers are superb ways to provide a more polished and finished product to the members of CASAC for their review. This is very much appreciated by all of us serving on this Committee!

8) The criteria used for study (publication) selection for the next NO_x document seems to be highly appropriate for epidemiological studies using both short- and long-term exposures at near ambient concentrations of NO_x. The selection of such studies is logical and appropriate. To examine the health effects of specific NO_x species or indicators related to NO_x sources is also an excellent idea. Inclusion of populations not previously involved in extensive research is critical. Multiple pollutant analysis is also important to undertake as part of the new criteria document.

9) Methodology applied in published studies is highly relevant for consideration, but it is not clear whether this is an area of concern that will present a serious issue in the reassessment of the next NO_x document. Never-the-less, the evaluation of methodological issues will provide greater credibility for the next NO_x document.

10) A continuing concern is the preferential selection of research which evaluate human exposures of NO_x that are limited to those studies where subjects were exposed to NO_2 at concentrations less than 1ppm. Such criteria may be scientifically sound and logically based on what typically the public and/or individuals in this country encounter. However, do these selection criteria miss an important group, i.e., workers in an occupational setting where NO_2 and other species of NO_x may be higher than 1ppm levels or there may be transient conditions in which NO_2 or NO_x may be evident? Although I admit not being familiar with the literature to be aware if such conditions exist, I would assume under specific conditions for space heater or gas stove use (die to faulty maintenance) that such conditions may exist in which NO_2 levels may exceed 1ppm. This may also be true of cases in which diesel or car emissions through testing may lead to higher exposure levels of NO_2 or NO_x than this designated concentration of 1ppm.

11) The organization and content of the SASD will focus on two goals. First, to identify scientific research that is relevant to informing policy issues; second, to produce a base of evidence containing all of the publication relevant to the NO_x review. These goals are appropriate and important to the preparation of this document.

12) Since the number of publications could be rather extensive, it is critical the preparation of this document use an approach to distill these studies into something that can easily understood. It is anticipated the organization of the document will categorize studies in such a way that will make them easy to follow. I am confident such a plan is already in the works. The most obvious confirmation of this approach is the division of the draft document into chapters that cover key issues, such as the chemistry of NO_x, environmental concentrations in

human exposure, dosimetry, toxicological studies, human clinical studies, laboratory animals, etc.

13) I would recommend that some sense of the scientific rigor and relevance of each study be assigned with a priority score to better interpret which studies provide the most reliable and relevant information for setting a possible new standard for the NO_x criteria.

14) The organization and content of the ISA in its current form is highly relevant, clearly responsive, and covers all the critical elements to be able to competently evaluate and interpret key issues involved in this criteria pollutant and relevant health implications.

15) The specific questions to be addressed in each section are well thought out. It will be critical that the ISA as well as the resultant document clearly identify the answer (or the lack of an answer!) to each of these questions in air quality, atmospheric chemistry, and short- and long-term health effects in both animals and humans.

16) The importance of causality is perhaps the ultimate goal such a document can provide in reassessing this criteria pollutant standard. To identify scientific uncertainties that continue to exist is also critical to help redirect efforts to better understand the potential impacts of NO_x on human health.

17) The interaction of NO_x with other atmospheric components is essential to provide the proper insights of how NO_x under certain conditions may influence the formation or concentrations of other criteria pollutants.

18) Biological mechanisms of action are clearly important in better understanding health implications. It is important that age, gender, and pre-existing diseases are brought into account to explain for some of these conditions. Such actions will help us to better understand susceptible populations and help exposure to NO_x may impact on the quality of life and their well-being.

19) Plans for public and scientific review of the document prepared for NO_2 take a logical and clear path designed to produce the best product possible in the proper review of this criteria document.

20) To have the draft essay SD undergo peer-review by external reviewers with the appropriate scientific expertise is fabulous. The guidelines provided to these external reviewers are clear and important for them to follow. If these actions are indeed taken and satisfied by the reviewers, then the work and review requested by members of CASAC will be greatly facilitated to be able to identify, hopefully, any key elements that they may be missing from the final draft document.

21) It is our hope that CASAC's contribution to the evaluation of the NO_x document will be one to provide the most sound and rigorous scientific review of what has been observed since the last publication of the NO_x document. I think EPA's Draft Integrated Plan for review will clearly facilitate this process. Thanks!

Mr. Rich Poirot

EPA Draft Plans for Review of Primary Sulfur Dioxide and Nitrogen Dioxide Standards: Key Policy-Relevant Issues

R. Poirot VT DEC

Following are some general comments that apply to the draft plans for both NO_2 and SO_2.

1. What are the current functions of the primary (& secondary) NO_2 and SO_2 standards?

The current primary NO_2 and SO_2 standards were both established in 1971 and have not been revised in the past 36 years. While there were a large number of non-attainment areas for these pollutants in the 1970s, there are currently no areas that fail to attain the primary and secondary standards for NO_2 and only a few (8) designated non-attainment areas for SO_2. From EPA's AirData website (http://www.epa.gov/air/data/geosel.html), it appears that (with the exception of 2 monitoring sites in Hawaii Volcanoes National Park) there has been only 1 measured violation of the 24-hour primary SO_2 standard and no violations of the annual primary or 3-hour secondary SO_2 standards over the past 5 years. Since there are no areas which attain the primary standards but not the secondary standards, these secondary standards currently serve no useful function. Given the absence of recent primary violations, the primary NO_2 and SO_2 standards may help guard against future emissions increases (unlikely), but are not resulting in currently active reductions in NO_x or SO_2 emissions. Rather, current emissions reductions of these pollutants are driven by other regulatory programs, including the CAA Title IV Acid Rain Control Program, the Regional Haze Rule, and NAAQS attainment for $PM_{2.5}$ and ozone – for which SO_2 and NO_x are the most important precursors.

Future SO_2 and NO_x emission reductions are required under the EPA Clean Air Interstate Rule (CAIR), which is essentially an expansion of the market-based Title IV cap and trade program. In describing the benefits of the CAIR rule (which will apply to only 28 Eastern states) the Agency estimates that the future reductions in SO_2 and NO_x emissions "will result in $85 to $100 billion in health benefits and nearly $2 billion in visibility benefits per year by 2015 and will substantially reduce premature mortality in the eastern United States. The benefits will continue to grow each year with further implementation." (http://www.epa.gov/interstateairquality/).

Conceivably, the same (or greater) degree of these well-justified, long-overdue emissions reductions could have been achieved (in a shorter time period) through a tightening of the SO_2 and NO_2 NAAQS. But the Agency has made a clear policy choice in favor of market based controls which would essentially conflict with a NAAQS approach, since the former assumes all emissions have equal effects, while the latter would require reductions in specific emission sources. For these reasons, I suspect we are basically going through the motions of symbolic NAAQS review with a predetermined policy decision that lowering the SO_2 and NO_2 NAAQS is not the best way to reduce the adverse health effects resulting from these pollutants.

Perhaps the NAAQS Review Plans should clearly state this policy perspective up front. It would also seem useful to include a detailed evaluation of future CAIR controls (and timing) in the

risk/exposure assessment, as well as an evaluation of benefits of further tightening of CAIR allowances and/or accelerating the time schedule. It would also seem useful to include some specific focus on effects of SO_2 and NO_2 sources or regions (the West) which will not be subject to future CAIR emission controls, or to consider ways in which the SO_2 and NO_2 primary (and/or secondary) NAAQS might be used in ways that are seen as complimentary to rather than in conflict with a market-based approach.

2. Should revisions to NO_2 and SO_2 standards include consideration of their secondary transformation products?

Current standards are based on considerations of direct health effects from these gases only, and do not appear to consider the combined influences of the many various secondary transformation products which result from these precursor pollutants. In the draft SO_2 Review Plan, the authors indicate (page 1-6) that the principal transformation products of SO_2 (sulfuric acid and sulfates) will be addressed in the PM review and not considered here, except as possible confounders for which (co-varying) SO_2 may act as an indicator in epidemiological analyses. The draft NO_2 Review Plan does not specifically exclude consideration of effects of transformation products, but it appears that the intent is to consider only health effects from gaseous NO_2, although the draft plan frequently mixes the terms NO_2 and NO_x in an inconsistent manner, leaving the intended meaning unclear.

In the final policy assessment, a separation of precursor and secondary pollutants and effects may be a reasonable policy alternative, but in the beginning I think it would seem short-sighted to intentionally exclude any consideration in the science assessment of transformation products and pollutant mixtures. I think he Clean Air Act allows for and in several cases specifically requires such considerations. For example, Section 108 (c) of the 1977 (and current) CAA Amendments specifically directed the Administrator to:

> "revise and reissue criteria relating to concentrations of NO_2 over such period (not more than three hours) as he deems appropriate. Such criteria shall include a discussion of nitric and nitrous acids, nitrites, nitrates, nitrosamines, and other carcinogenic and potentially carcinogenic derivatives of oxides of nitrogen."

It is noteworthy that the current NO_2 standard remains as an annual average only, and that the draft review plan makes no mention of the above secondary transformation products. It is also noteworthy that the Section 302 (h) definition of welfare effects in the 1977 Amendments originally stated that:

> "All language referring to effects on welfare includes, but is not limited to, effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility, and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being."

This section 302 (h) was specifically revised in the 1990 CAA Amendments by adding the phrase: **"…, whether caused by transformation, conversion, or combination with other air**

pollutants" to the end of this definition (emphasis added). So the Agency is clearly required to consider transformation products and other pollutant mixtures in proposing and revising secondary standards, and has been specifically directed to consider transformation products in developing criteria for primary NO_2 standards. I think both SO_2 and NO_2 plans for review of the primary NAAQS should be revised to include assessments of combined effects of the gaseous criteria pollutants and their various gaseous & particulate transformation products. Possibly also some consideration should be given to evaluating mixtures of these gasses and PM which is not a direct transformation product (i.e., NO_2 + Diesel exhaust).

One possible approach to considering transformation products in standard setting would be to retain the current indicators – SO_2 and NO_2 – but adjust the levels or forms downward to reflect the combined influence of secondary products. The current SO_2 plan proposes consideration of secondary products only as they may be the actual causal factors for apparent health effects which are statistically associated with SO_2 as an indicator of correlated aerosols. However, SO_2 is not merely correlated, it is the cause of the associated aerosols, and if SO_2 concentrations were reduced by lower NAAQS, the associated secondary aerosols would also be reduced. This was the logic recently employed in substantial downward revisions (to 0.008 ppm, 24-hour) of the World Health Organization guidelines for SO_2 (for which our colleagues Mort Lippmann and Kaz Ito were principal authors). They wrote that:

> "…assuming that reduction in exposure to a causal and correlated substance is achieved by reducing sulfur dioxide concentrations, there is a basis for revising the 24-hour guideline for sulfur dioxide downwards, adopting a prudent precautionary approach." (WHO Air Quality Guidelines, Global Update 2005, Particulate matter, ozone, nitrogen dioxide and sulfur dioxide).

An alternative approach to considering secondary transformation products might be through revisions to the indicator(s). For example, a new NAAQS for "total oxidized sulfur" might be defined the sum of S from SO_2 and various sulfate compounds. The NO_2 indicator might be revised to include nitric acid, aerosol nitrate, etc. For secondary standards, deposition-based indicators and/or critical loads for total sulfur and nitrogen deposition might be effective alternatives to ambient air indicators of only the individual precursor gases.

Dr. Armistead (Ted) Russell

Review of the Draft Integrated Plans for Reassessment of the NOx and SOx National Ambient Air Quality Standards

Ted Russell

NOx

My first comment on the Draft Integrated Plan (IP) is that it would have been nice to have, even at this point, a bit more of what we know about NOx and SOx (e.g., levels in the environment, levels of possible health concern) in the IP just to get an idea of what might/might not be important. Something in the introductory parts would be good.

A second thought is that the IP should lay out more of a plan to address confounders in the health studies, and how laboratory exposures related to ambient exposures, recognizing that the latter exposure is more complex. In regards to the greater complexity of ambient exposures, like ozone, one wonders if there might be other pollutants that are very closely tied to NOx, but would not be present in the laboratory, that have significant health effects. Given that it is an NO_2 standard, how this might be treated in a standard is unclear. However, the IP should lay out a plan to address this case. For example, HONO is formed from NO_2 heterogeneously. HONO rapidly photolyzes, forming HO radical, a strong oxidant. In regards to confounders, NO_2 will correlate with diesel vehicle emissions, thus, diesel particulate matter (DPM). (Though, controlling diesel NOx will not necessarily reduce DPM or vice versa, so saying that addressing one will work for both, as is sometimes assumed, can be wrong in this case.)

Risk/Exposure Assessment

First, while trivial, I might invert the title of this section to say exposure/risk, as that, to me, is the more logical order, and as noted in the first paragraph, a quantitative risk assessment may not be in the cards.

At first, I liked the tiered approach to figuring out how much detail and effort is required to address this issue. If, indeed, there is little likelihood of significant concerns from exposure, there appears to be little reason to do an APEX-level analysis. However, there may be additional reasons to go to that next level. One of those is that APEX-level analyses (or beyond) are quite appropriate for other pollutants, e.g., ozone and PM, and if the agency continues to do such for each of the pollutants for which it is not scientifically questionable (e.g., SO_2), it will become more routine and problems will be identified sooner. Further, extending APEX to other pollutants can improve its treatment of the pollutants of greatest concern. Thus, it might be appropriate to commit to an APEX-level analysis right off and gear up for it. Also, I fear that if such a commitment is not there, it may not be done even if there might be call to do so. There is always a crunch at the end, and such an effort could just become infeasible because of time and resources if ample foundation is not laid earlier on. On the other hand, if there is really little likelihood of exposures of concern, or that the information that APEX-level analysis can provide is of use in standard setting, it may be true that resources are better spent elsewhere. I am not

sure at this time, and that is where a bit more information up front in terms of likely maximum ambient levels/exposures and levels of concern would be of use.

The air quality analysis, alone, is insufficient as a determinant of whether the agency should go to a screening level assessment. I say this because it is tied to ambient monitors, which are scarce, and there is much more information out there at this time. In this case, I am talking about the studies that are using other techniques to estimate NO_2 exposure using air quality models and, quite importantly, techniques that use information like land-use tied to saturation monitoring of NO_2. For example, see Henderson et al. (2007) and references therein. Such techniques should be consulted up front to suggest if there is a high likelihood of exposures that are significantly higher than found by analysis of ambient monitoring data. This, possibly, would work in to the screening level assessment, but is not explicitly mentioned there.

Criteria for Selection of Assessment Approach.

Here, I would add to the list:

- Analysis of more detailed exposure studies based on non-routine monitoring, including other hot-spot analysis (e.g., railyards, airports) and modeling.
- Associated pollutant exposure

Uncertainty and Variability

Their discussion of uncertainty and variability begins with and focuses on APEX, which is a bit of a concern because they are not committed to going to that level of analysis. However, Uncertainty and variability should be addressed no matter what level of analysis is actually conducted. The form and extent is changed, but it is still an important piece of the exposure and risk assessment.

Let us say that it is decided that APEX-level analysis will not happen. What then? They should have a plan as to how to extend the air quality analysis and screening level assessment to address these two issues. This will, in part, be driven by the tangential information found in conducting the exposure analyses. They should, as part of that work, explicitly identify, and quantify, uncertainties and variabilities (and specify which it is).

In regards to how APEX might be applied (they are quite non-committal, which is not necessarily wrong), things sound fine, though the commitment of resources should be acknowledged. It could turn out that the major reason to embark along this route is to make such practice more standard.

Risk Assessment

While the introduction to this section suggests that a quantitative risk assessment may not be in the card, they really should address how a more qualitative risk assessment will be done if a quantitative one is not.

Henderson SB, Beckerman B, Jerrett M, *et al.*
Application of land use regression to estimate long-term concentrations of traffic-related nitrogen oxides and fine particulate matter
ENVIRONMENTAL SCIENCE & TECHNOLOGY 41 (7): 2422-2428 APR 1 2007

Dr. Richard Schlesinger

NITROGEN DIOXIDE DRAFT INTEGRATED PLAN

P. 1-3, L. 20-22. There is some confusion in this sentence. If the Administrator seeks to prevent pollution levels that have been demonstrated to be harmful, then what is meant by the attempt to prevent lower levels that may pose an unacceptable risk of harm. The levels that will be proposed should be low enough to prevent any unacceptable risk.

P. 3-1. L. 29-30. This bullet and the two that follow are redundant. Perhaps they can be condensed.

P. 3-2. L. 9. Is this issue referring to short or long term exposure?

P. 3-2. L.12. What is meant by air quality issue relationships between short and long term exposures?

P. 4-1, L. 26. After "Emphasis" add the following: "…in controlled exposure studies will be placed…." The comment does not apply to community epi studies.

P. 4-3, L. 26. Add the word "adequately" after "power to …."

P. 4-5, L. 23. Add the word "reaction" after "Are there….."

P. 4-6, L. 16. Add the word "centralized" after "the use of…"

P. 4-6, L. 118-22. This paragraph is not clear.

P. 4-7, L. 15. After "concern" add the following: "…including nature and time course" and delete the fragment following "e.g.". There is no reason to provide these examples as it seems to limit the extent of inquiry.

P. 4-7, L. 24-25. This bullet should be incorporated into the first bullet on the page.

P. 4-8, L. 23. Add the word "other" after "asthma."

P. 4-8, L, 26-27. Doesn't this apply to short term effects as well?

P. 4-9, L. 14. Add "various other" after "including"

P. 4-10, L. 1-4. Rewrite as "What are the potential biological mechanisms underlying response to NOx with a focus on physicochemical characteristics, …."

P. 4-10. L. 7-8. Rewrite as "What NOx reaction products can be found in the respiratory tract cells, tissues or fluids that may serve as markers of NOx exposure"

P. 4-10, L. 9-10. This bullet is redundant with the first bullet on the page.

P. 4-10, L. 11-12. Add “host factors such as” after “effects”

P. 4-10, L. 15. Change “man” to “human”

P. 4-10, L. 27-28. Rephrase bullet as, “What is the relationship, if any, between susceptibility to short and long term exposure to NOx”

P. 4-11, L. 11-20. What about review of experimental studies in the literature. This is not indicated in this paragraph in terms of approach for the SASD.

SULFUR DIOXIDE DRAFT INTEGRATED PLAN

NOTE: I have indicated here specific concerns with the SOx document. Some of the comments related to the NOx document will also apply here since the template wording in many sections is the same. Thus, please look over some of the NOx suggestions in relation to the SOx document.

P. 4-6, L. 3. Why is the term “ambient” needed here.

P. 4-6, L. 4. Change “of” to “at.”

P. 4-6, L. 10-13. This bullet is redundant with the first two bullets on the page.

P. 4-6, L. 14. Give an example of what is meant by “pattern”

P. 4-7, L. 9-10. Small airway resistance is not a good term and, in fact, small airway resistance is not the general measure when airway resistance is used to monitor pollution effects. Furthermore, gas-exchange surface is not a function.

P. 4-7, L. 18-19. This bullet is redundant with others above.

P. 4-8, L. 4. Add “other” following asthma.

P. 4-8, L. 9-10. This bullet is redundant with others that preceded it.

P. 4-8, L. 22. Change “do” to “does.”

P. 4-9. L. 5. What is meant by community risks in the context of this bullet.

P. 4-9., L. 22. Add “host factors” after “of”

P. 4-9, L. 26. Change “man” to “human.”

P. 4-10, L. 4. Change wording to” Is preexisting respiratory or cardiovascular disease an important factor in susceptibility to mortality associated with exposure to SOx and does age also play a role in this relationship.

Dr. Christian Seigneur

Comments on the Draft Plans for Review of the SO_x and NO_x NAAQS

Christian Seigneur
Atmospheric & Environmental Research, Inc.

I have two general comments that apply to both documents.

Data fusion:

The last bullet item of the content of the "Air Quality and Atmospheric Chemistry" section of the ISA in the NO_x document addresses the possibility of performing some data fusion to augment the information available from monitoring sites with satellite retrievals and model outputs. This is an excellent idea although its feasibility may be limited by the fact that one is mostly interested in NO_2 concentrations near sources in urban areas; satellite retrievals and model outputs may not provide sufficient spatial resolution to be helpful here. Nevertheless, the feasibility of this approach deserves to be investigated.

It seems that the same data fusion approach could also apply to SO_2, but it is not mentioned in the SO_x document. I suggest including it for consistency or explaining why it would not apply to SO_2.

Uncertainty and Variability (Section 5.5 in both documents):

This section provides a good overview of the planned approach for the uncertainty analysis of the exposure assessment. The proposed approach distinguishes very nicely between the epistemic uncertainties (referred to as uncertainty) and aleatory uncertainties (referred to as variability), which is the proper way to conduct an uncertainty analysis. However, it is not clear how the results will be used. As currently written in the draft plans, the uncertainty/variability analyses appear to be disconnected from the rest of the assessment because it is not explained how their results will be reflected in the overall assessment. Will the uncertainty analysis results be used in a qualitative manner when discussing the exposure assessment or will there be a quantitative use of those results? It would be useful to add a sentence or two at the end of these sections to clarify that the results of the uncertainty analysis will be part of the body of technical information used to develop the policy options.

Specific comment:

NO_x document, p. 4-5, line 26: NO_x instead of NO_2.

Dr. Elizabeth A. (Lianne) Sheppard

Comments on Draft IPs for Review of the Primary SO_2 and NO_2 NAAQS

Submitted by Lianne Sheppard
Final comments May 18, 2007

General Comments

I believe further clarification is needed regarding the views to be presented in the ANPR. How will the views be selected? How much information will be given to ensure their credibility and to document their source? Based on the conference call of May 11, 2007 I understand the views incorporated into the ANPR will be broader than those previously included in the Staff Paper and include political views. I believe that any views included in the ANPR will acquire credibility just by virtue of being included in the document. In order to ensure transparency, there needs to be a clear and transparent process for how views are selected, a discussion of the scientific justification of each view included in the ANPR, and full disclosure in the ANPR of the sources (including funding) of each view presented.

Risk/exposure assessment: It is essential that every risk and exposure assessment document have four "assessment" sections. These are 1) the air quality analysis, 2) the exposure assessment (screening and refined, as appropriate), 3) a qualitative risk assessment, and 4) a quantitative risk assessment. Risk assessment cannot be excluded from the Risk/exposure assessment document. The quantitative and qualitative risk assessment sections need to be distinct because there is a great deal of evidence about risk that is not easily incorporated into a quantitative risk assessment but that enters into a final scientific judgment of risk. Semi-quantitative risk assessment information, such as estimates of risk bounds, should also be incorporated where quantitative assessment is not possible. Furthermore, it is important to recognize that both quantitative and qualitative evidence are necessary for integrated assessment of risk leading to policy recommendations. It is too easy for the quantitative risk assessment to receive disproportionate weight in the integrated assessment of risk and this is particularly likely when the qualitative risk assessment is omitted. Finally, all "assessment" sections should be present in the document even if not all assessments can be supported (e.g. note the anticipated plan regarding the quantitative risk assessment, see p. 5-1 of both documents). In that case the section in question should state the reason(s) that the assessment is not done.

Comparison between documents: I suggest the staff compare similar sections of these two documents to ensure both are as complete and comprehensive as possible. For instance the detailed questions to be addressed in the various sections of the ISA, listed under the "Content and Organization of the ISA" subsection of 4 differ somewhat by pollutant. To the degree that these differences are scientifically motivated, this is appropriate, but verification is needed.

NOx

- The whole document should discuss NOx. Some parts only discuss NO_2 and ignore other oxides of nitrogen.
- How will the process allow consideration of regulation of other oxides of nitrogen?
- 4-6 line 1: data are *spatially* sparse
- 4-6 Section B, particularly lines 13-17: The question of uncertainty about the relationship between ambient concentration from stationary monitor measurements and personal exposure must be framed in the context of the epidemiological study design that is of interest. The issues are different for time series and cohort study designs because the former relies on temporal variation in exposure/concentration while the latter relies on spatial variability.
- 4-11 lines 13-15: how is (1) distinct from (2)? Why is review of the epidemiologic literature distinguished from review of the text and tables/figures.
- 5-1 – 5-7: A subsection needs to be added following section 5.3 to address the approach to risk assessment.
- 5-2 section beginning line 18: Will this analysis be based only on data obtained from AQS monitoring locations? How will monitor siting criteria influence the possible conclusions? Where will considerations of monitor siting be considered? Epidemiological studies that incorporate spatially-varying exposure information are much more sensitive to siting considerations.
- 5-3 lines 7-10: What is the purpose of these analyses? How will their results affect understanding of exposure?
- 5-4 line 1: Complexity of models relates to the bias-variance trade-off. Simpler models tend to be more biased and less variable while more complex models are less biased and more variable.
- 5-4 lines 14-17: Also it would be beneficial to determine the distribution of multiple exposures per person.
- 5-4 lines 26-28: It is very good that now there is a plan to explicitly address individual longitudinal behavior patterns. This improves upon previous exposure assessment models.
- 5-5 line 13: This should be restated to allow for more general relationships, e.g. replace "relative" with "relationship between the".
- 5-6 lines 4-10. Clarify whether this plan implies separate characterization of uncertainty and variability.
- 5-6 paragraph starting line 11: How about proposing a set of sensitivity analyses to compare results using different model formulations? This would be one way to address model uncertainty.
- 6-1 line 5: Presumably the full set of appropriate evidence- and risk-based approaches for reaching policy judgments have already been carefully considered in the risk/exposure assessment document so that the ANPR is not covering new ground at this point in the process. Please clarify or replace "identify" with "review".
- 6-1 line 7: Why not present risk information associated with alternate standards?

SOx

Overall the SOx document is similar enough to the NOx document that all NOx-specific comments should be considered for the SOx process document as well. However in several ways the SOx document appears to be more complete. In particular section 1.4 is missing from the NOx document, Section 6 of the SOx document has more explanation, and only the SOx document lists the NOx and SOx panel members in Appendix A.

Dr. Frank Speizer

Review of Draft IP for NAAQS for Sulfur Dioxide (and NOx)

Submitted by Frank E. Speizer
Pre-meeting comments 5/2/2007

It is clear that there is considerable overlap between the SO_2 document and the NOx document. The comments are likely to apply to both but will be referenced to the SO_2 document. In addition, it is likely that these documents will be substantially revised after our first meeting, as they read now as a tentative expression of the new approach.

Page 1-2, lines 7-11.

It is not clear how the ISA and the SASD will really differ from the old CD and Staff paper except that the plan appears to be that they will appear together. That said it is also not clear how the ISA will determine how the most relevant literature pertinent to the review will be selected. This will need to be discussed at our initial administrative conference call.

Page 3-1.

The fact that the Court of Appeals remanded the decision for further explanation means that this time around will need better documentation of the current state of science on the 5 minute standard and level of effects.

Page 4-1, line 10-11.

CASAC must at least see list of publications being assessed in the SASD, as well as those used in the formulation of the ISA (assuming the latter will have the references in the document).

Page 4-2, lines 25-27

There will need to be an agreed upon cut off date.

Page 4-3, item 3), lines 4-5

Do not believe this is meant to exclude other studies that repeat or extend findings from earlier years, but as presented says that they will be excluded.

Page 4-3, line 19

Not clear that this restriction should apply. Would be worth being more specific of purpose of study. For mechanistic study higher doses may be ok.

Page 4-4, lines 10-14.

How is this going to be different from the old CD?

Page 4-6, line 13-14.

This needs to be extended to indicate which pollutants or mixtures are most implicated.

Page 4-6, line 26-29

Need more guidance on what is meant here. (e.g. Inflammatory evidence –change in CRP), arrhythmias, heart rate variability, endothelial function, or risk of MI, Stroke, hospitalizations, other morbidity or mortality, etc).

Page 4-7, line 18-19

Suggest handle CVD separately form reproductive and other. CVD important enough to have separate categories to consider as is done with respiratory.

Page 4-10, section 4.3

I do not understand this section. Who are the peer reviewers, how are they vetted, how do they differ from the writers of either the SADS or the ISA? What is CASAC's role in evaluating this part of the process?
Page 5-2, end of section.

It seems that the legal judgment of this was that by putting it on a national perspective EPA violated the *de jure* as well as the *de facto* spirit of the law in being required to protect with an adequate margin of safety a sensitive group. Therefore will need to define better than previously what is meant by "national perspective". Surely this must be based on expected numbers of excess exposures.

Post-Conference Call Comments on Draft Plan for Review of the Primary National Ambient Air Quality Standard for Nitrogen Dioxide
Submitted by Frank E. Speizer
May 15, 2007

I am confining my remarks at this point to only the questions raised in the policy relevant chapter. I found it well summarized and as discussed in the conference call was clear and precise. I wanted to add only one point that we discussed briefly but I thought needed greater emphasis. That is, that further discussion will be necessary with regard to the interaction of NO_2(x) at street level with ozone. There is two-way quenching going on, and therefore separating effects may be difficult. Similarly, an alternative source of NOx, and maybe a major source in some restricted areas, may be diesel mobile sources rather than gasoline mobile sources (along with stationary sources) and in these areas may want to consider exploring alternative approaches to utilizing the data. This all speaks to a more modern approach of how we might want to set standards, which may go beyond the current plan, but may need to be discussed in setting a policy approach that is appropriate for 2009 rather than 1989.

Dr. George Thurston

Comments on Draft Integrated Plan (DIP) for Review of the Primary National Ambient Air Quality Standards for NO_2 (Feb., 2007)

The framework of the document is satisfactory, but I had 5 issues with the document. I will summarize them below, along with page citations to the document where they apply.

1) Section 1.4 (as found in the SOx DIP) is missing. It should appear on page 1-5. This section is needed in order to make the point that the document will evaluate the health effects of all Nitrogen Oxides (NOx). Thus, the document will not be limited to assessing the health impacts of NO_2, but will also consider other forms of NOx and mechanisms by which they can have effects on human health.. However, for the purposes of controlling NOx, the EPA will use NO_2 as an index of these pollutants in the setting of the NAAQS.
2) Since the document is about NOx (not NO_2 alone), there are number of places in the document where NO_2 should be changed to NOx, including: Pg. 3-1, line 30; pg. 3-2, lines 2 and 8; pg. 4-3, line18; pg. 4-6, lines 14 and17; pg. 4-8, line20.
3) There is a need to note in this document that the interactions of the gaseous NOx with particles must be assessed. Particles provide a potential vector for gaseous pollutants to reach deeper in the lung than they otherwise would. These gases can also change the nature of the particles they go into solution with (e.g. their pH), so they can also affect human health by increasing the toxicity of particles. Thus, it is important to include these particle interactions in the exposure, health effects, and risk assessment components of this document in order to fully consider the potential toxicity of these gaseous pollutants. This should be discussed in Section 1.4 when it is added. In addition, there is a need to mention the potential for particle-gas interactions throughout the document, including at:
   Pg. 3-2, line 14: Add bullet stating: "What effects are a result of interactions with other criteria pollutants, especially PM?"
   Page 4-3, line 3: Change to read: "potential interactions, confounding, and/or modification of effects"
   Page 4-7, line 3: Add a bullet stating: "How do NO_2 exposures interact with other criteria pollutant exposures, especially PM?
   Page 4-9, line 8: Need a statement for long-term effects similar to that seen at lines 6 and 7 of page 4-8 for short-term effects, such as: "What is the nature of health effects in persons exposed to multi-pollutant mixtures that contain NOx, in comparison to NOx alone."
   Page 4-10, line 17: Add a bullet stating something like: "What interactions with PM occur in the atmosphere that alter the toxic implications of NOx in the environment?"
   Page 4-11, line 3: Add a bullet stating something like: "What interactions with PM occur in the atmosphere that alter the susceptibility of humans to NOx in the environment?"
4) I agree with the written comments by Kent Pinkerton regarding the need to consider evidence from exposure levels much higher than "near ambient" when appropriate. In particular, since we know little about variations in susceptibility across humans and animals on the basis of genetic variability, it is unlikely that the animal and human populations considered in toxicological studies sufficiently represent the most susceptible populations.

Thus, much higher exposure levels may be needed in those populations to elicit the same impacts and effects that might be seen at much lower levels in a more susceptible population. Therefore, the following lines need to be revised to address this fact:

Page 4-1, line 27: edit to read" "However, in recognition of the fact that toxicological studies do not necessarily reflect effects in the most sensitive populations, studies at higher exposure levels will be included when they provide information relevant to previously unreported effects, evidence of the potential mechanism for an observed effect, or information on exposure-response relationships."
Page 4-3, line 18: Edit to read something like: "In discussing the mechanisms of NOx toxicity, studies conducted under atmospherically relevant conditions will be emphasized, but studies at higher levels will also be considered, due to species-to-species and potential genetic differences between study subjects versus especially susceptible humans."
Page 4-9, lines 2,3: Edit to read: " The ISA will place emphasis on studies conducted at ambient levels, except regarding evidence of biological plausibility and mechanisms, as these may only be observable in animal or human exposure study populations at higher levels than they might be observed in susceptible human populations."

5) Each section of the review document should provide a list of "Key Studies" upon which the section primarily relied in coming to its major overall conclusions.

Comments on Draft Integrated Plan (DIP) for Review of the Primary National Ambient Air Quality Standards for SO_2 (April, 2007)

The framework of the document is satisfactory, but I had 5 issues with the document. I will summarize them below, along with page citations to the document where they apply.

6) Section 1.4 needs to make the point that the document will evaluate the health effects of all Sulfur Oxides (SOx). Thus, the document will not be limited to assessing the health impacts of SO_2, but will also consider other forms of SOx and mechanisms by which they can have effects on human health. However, for the purposes of controlling SOx, the EPA will use SO_2 as an index of these pollutants in the setting of the NAAQS. Also, on page 1-6, line 12 of this section, the word "sulfate" should be replaced with the more general case of "particulate matter (PM)"
7) Since the document is about SOx (not SO_2 alone), there are number of places in the document where SO_2 should be changed to SOx, including: Pg. 3-2, lines 8, 10, 13,15,17, and 21.; pg. 4-1 line 6; pg. 4-2, line 2.pg. 4-3, line21; pg. 4-4, lines 10-14; pg. 4-6, lines 3 to 16 and 28; pg. 4-7, lines 6 and 9, pg. 4-8, lines 1 to 7 and 13-17, pg. 4-9, lines 10-24, pg. 4-10, lines 2 to 11, and page 5-1, line 19.
8) There is a need to note in this document that the interactions of the gaseous SOx with particles must also be assessed. Particles provide a potential vector for gaseous pollutants to reach deeper in the lung than they otherwise would. These gases can also change the nature

of the particles they go into solution with (e.g. their pH), so they can also affect health by increasing the toxicity of particles. Thus, it is important to include these particle interactions in the exposure, health effects, and risk assessment components of this document in order to fully consider the potential toxicity of these gaseous pollutants. This should be discussed in Section 1.4. In addition, there is a need to mention the potential for particle-gas interactions throughout the document, including at:

Pg. 3-2, line 22: Add bullet stating: "What effects are a result of interactions by SOx with other criteria pollutants, especially PM?"

Page 4-3, line 6: Change to read: "potential interactions, confounding, and/or modification of effects"

Page 4-6, line 17: Add a bullet stating: "How do SO_x exposures interact with other criteria pollutant exposures, especially PM?

Page 4-8, line 19: Need a statement for long-term effects similar to that seen at lines 20 to 21of page 4-7 for short-term effects, such as: "What is the nature of health effects in persons exposed to multi-pollutant mixtures that contain SOx, in comparison to SOx alone."

Page 4-9, line 27: Add a bullet stating something like: "What interactions with PM occur in the atmosphere that alter the toxic implications of SOx in the environment?"

Page 4-10, line 12: Add a bullet stating something like: "What interactions with PM occur in the atmosphere that alter the susceptibility of humans to SOx in the environment?"

9) I agree with the written comments by Kent Pinkerton regarding the need to consider evidence from exposure levels much higher than "near ambient" when appropriate. In particular, since we know little about variations in susceptibility across humans and animals on the basis of genetic variability, it is unlikely that the animal and human populations considered in toxicological studies sufficiently represent the most susceptible populations. Thus, much higher exposure levels may be needed in those populations to elicit the same impacts and effects that might be seen at much lower levels in a more susceptible population. Therefore, the following lines need to be revised to address this fact:

   Page 4-2, lines 3 to 5: edit to read" "However, in recognition of the fact that toxicological studies do not necessarily reflect effects in the most sensitive populations, studies at higher exposure levels will be included when they provide information relevant to previously unreported effects, evidence of the potential mechanism for an observed effect, or information on exposure-response relationships."

   Page 4-3, line 21 to 22: edit to read something like: "In discussing the mechanisms of SOx toxicity, studies conducted under atmospherically relevant conditions will be emphasized, but studies at higher levels will also be considered, due to species-to-species and potential genetic differences between study subjects versus especially susceptible humans."

   Page 4-8, lines 13,14: Edit to read: " The ISA will place emphasis on studies conducted at ambient levels, except regarding evidence of biological plausibility and mechanisms, as these may only be observable in animal or human exposure study populations at higher levels than they might be observed in susceptible human populations."

10) Each section of the review document should provide a list of "Key Studies" upon which the section primarily relied in coming to its major overall conclusions.

Dr. James Ultman

May 20, 2007

Comments on the Science Assessment of the "Draft Plan for Review of the Primary National Ambient Air Quality Standard for SOx

James Ultman
Penn State University

(Although the following comments are directed at the SO_x document, the same general comments and most of the detailed comments apply to the NO_x document as well).

The Integrated Review Plans (IRP) for SOx are logically organized and clearly present the overall review process, the timetable, and the steps to be taken to develop the Risk/Exposure assessment.

Critique

First, I want to reinforce the importance of the possible risks associated with co-pollutants, susceptibility factors, and different exposure scenarios that affect the balance between tissue damage and repair/adaptation processes. References to these issues do exist in the document as now written.

Second, I feel it is important to improve the description of exposure-response and animal-to-human extrapolation issues in the final planning document. Based on the exposure-dose-response paradigm used in other EPA documents, the apparent sensitivity of an animal to inhalation exposure depends on: 1) the transformation of exposure conditions to local dose levels; and 2) the inherent biological sensitivity at the cellular and subcellular level. As indicated in my detailed comments below, a more explicit recognition and description of these two complementary factors would clarify how (given appropriate scientific studies in the ISA) dosimetry can inform the biological mode-of-action as well as the extrapolation of health effects from high-to-low exposure levels and from laboratory animals to humans.

Detailed Comments:

Page	Line	
1-2	19	Does not appear to be a full sentence.
1-6	10-13	This sentence appears to be inconsistent with the sentence on lines 5-7 stating that the present review will only consider gaseous SO_x.
3-2	20-21	The meaning of this sentence is not clear.

4-3	17-20	The criterion of exposure level and duration will be used to assess the relevance of animal studies. To the extent that the toxicokinetics and biological sensitivity of a particular lab animal (usually a rat) and a human are the same, these criteria are reasonable. If scientific evidence indicates that this is not true, however, then some adjustment of the criteria might be appropriate.
4-6	14	I believe that this question should be placed under category C, Health Effects.
4-6	25	This section is somewhat confusing because the term "short-term" exposure means different things in different questions. In some cases, the term refers to a "short-term peak exposure" of 5 minutes while in other questions it refers to exposures as long as one day. Particularly on the following lines, please make sure that the meaning of short-term exposure is clear: 6,9,14,18,21.
4-8	4	It would be worthwhile to generalized this question to include both exacerbation as well as development of asthma.
4-9	9-10	The last two questions of this section on lines 24-25 and 26-27 concern extrapolation issues that go beyond mechanisms of action to also include dosimetry issues. Somehow the recognition that animal sensitivity is the result of two factors—dosimetry and intrinsic biological mode of action—should be explicitly recognized in the these introductory lines to section F.

Dr. Ron Wyzga

Comments on Draft Plan for Review of the
Primary National Ambient Air Quality Standard for
Nitrogen Dioxide

Ronald E. Wyzga, Sc. D.

By and large, the plan is reasonable; some portions of it, as noted below, are unclear to me as indicated by my specific comments:

p. 4-3, ll. 2-3: I am unclear of what is meant by "multiple pollutant analyses"; does this mean that methods should consider NOx in conjunction with other pollutants in an effort to understand whether NOx is associated with health because it is possibly noxious or because it co-occurs with other pollutants that may be noxious.

ll. 4-3: similarly I am unclear as to what is meant by point (3). I would also urge that multi-city analyses include and examine results for consistency across the cities. There is value is trying to understand differences as well as in lumping results.

ll. 22-24: depending upon the study design, there is value is having an subject serve as his/her own control but with a different or sham level of exposure. Comparison with age-matched healthy controls may not be the best control for some study designs.

ll. 26-27: what is meant by "sufficient statistical power"? Statistical power is important, but it need be defined in terms the probability of detecting a difference of a given magnitude.

p. 4-8, ll. 6-7: is this meant to address the synergism issue or is there some other intention behind this?

Comments on Draft Integrated Plan for Review of the
Primary National Ambient Air Quality Standards for
Sulfur Dioxide

Ronald E. Wyzga, Sc. D.

Overall the document provides a good roadmap. Specific comments are given below:

p. 4-3, ll. 15-16: Please clarify; does this mean that studies should consider other pollutants as well as SO2, jointly in models?

l. 24: 1 ppm is high; is it relevant for real-world exposures?

ll. 27-28: depending upon the study design, there is value is having an subject serve as his/her own control but with a different or sham level of exposure. Comparison with age-matched healthy controls may not be the best control for some study designs.

p. 4-7, ll. 20-21: is this meant to address the synergism issue or is there some other intention behind this?