4/7/2008 Preliminary Comments from CASAC CO Primary NAAQS Review Panel on EPA's *Draft Plan for Review of the Primary NAAQS for Carbon Monoxide* **(March 2008)**

Comments received:

Dr. Douglas Crawford-Brown

Review of EPA's Draft Plan for Review of the Primary NAAQS for Carbon Monoxide

The document is intended solely to provide the general structure of a review, rather than details as to how this will be carried out. As a result, the following comments are general in nature and may change as the actual plan is formalized.

My most general comment is that the draft plan contains all of the relevant sections that must be completed to produce a full review. The authors have therefore not left out any major considerations. However, throughout the document, the authors raise a series of questions that will be addressed in each section without providing a succinct statement as to the role the answers to these questions will play in specific policy considerations. As a result, the reader is left unclear as to how any specific answer to any specific question might push the discussion of a NAAQS decision in any particular direction. Perhaps this was intentional on the part of the authors: trying not to judge how a particular answer might inform a final decision. But it leaves the reader unclear as to the intent behind specific questions, other than providing a scientific base on which any manner of decision might be based.

The authors raise the issue of co-pollutants, which will be important in using epidemiological studies. It is not clear, however, how these co-pollutants will be analyzed. Is the plan to treat them as confounders and then work to extract this confounding from any slope factors developed? Is the intent to examine the effect of CO exposures on the sensitivity of individuals to the co-pollutants, and the effect of the co-pollutants on the sensitivity of individuals to CO? The document doesn't give much of a hint as to how this issue will be treated. There is a sense at several points in the document that clinical, controlled studies might form the basis for any effects measures, which could avoid this issue, but this sense is never made fully concrete. There also is a hint that the assessment might stop at exposure or at blood levels, which again would avoid this issue (much as in the case of the early Pb standards). It would be good if some clarity on this issue could be provided.

On Page 3-2, the authors ask whether new data might indicate that effects occur at exposures lower than those previously found to induce effects. This question is too one-sided. It presumes that the only thing new data can do is push the assumed threshold for effects to lower values. New data might suggest that previous data suggesting a lower threshold were incorrect, and that the threshold is in fact higher than thought.

On Page 4-1, the authors mention a formal framework for integrating health effects, found in the second draft of the NOx document. The reader should not need to go to that document to at least find a summary of this framework, and in any event that document provides no such summary framework and so readers will come away from it with different conceptions of what the framework might be when applied to CO. More clarity is needed on precisely what this framework consists of.

On Page 4-2, the authors state that welfare effects will be noted if any are found during the search. However, the literature that is mentioned as forming the basis for the search, rooted only in human health sciences, is not the appropriate set of disciplines to locate papers on welfare effects. So I cannot see how the literature review will constitute a “hard look” at the relevant science on welfare effects.

Around Pages 4-7 and 4-8, the authors discuss the need to perform analyses of spatial and temporal variability. There is no description, however, of the role of these analyses in any specific decision on exposure, exposure-response, risk, etc. I certainly agree that analysis of variability is needed, but without a clear statement as to the purpose of the analyses, and the questions they are intended to support, it will not be possible to determine whether appropriate statistical methods and databases are being used.

The same problem arises on Page 4-8 when the authors discuss uncertainty analyses. They mention, for example, uncertainty in extrapolating between area monitors and personal exposures. However, no insight is provided as to why this uncertainty would be important for specific questions to be addressed (I agree it IS important, but the document doesn’t give a hint as to why).

On Page 4-9, at the bottom, the authors list a series of effects that will be considered. While I agree with this list, no hint is given as to how it was compiled based on past studies. Clarity is needed here.

On Page 4-12, developmental and birth outcomes are mentioned as chronic effects. Why are they only considered chronic effects? Surely such effects might occur with shorter-term exposures during critical developmental periods.

On Page 4-12, the authors raise the issue as to whether CO might stand as a surrogate for exposure to the mixture of pollutants from vehicles. I could not find any explanation as to why they might want to know this. The CO NAAQS doesn’t stand as a surrogate for control on exposures to these other pollutants.

On that same page, the authors mention the exposure-response curve for CO. They formulate the question as one of determining the shape of that curve. But they don’t formulate it as an issue of uncertainty ABOUT the shape of that curve, or how different curves would produce different NAAQS results. That bullet needs to be rethought.

At the bottom of Page 4-14, the authors ask for any medical conditions or medications that make an individual susceptible. I suspect that there might also be activities (e.g. running near roadways) that make them susceptible.

On Page 4-15, the authors ask about the extent to which the elderly and fetuses are more susceptible. This seems to me to beg the question, which should be about the extent to which they DIFFER in susceptibility one way or the other. If the authors want to restrict the question to increased susceptibility, they need to include a justification for this (perhaps in past literature suggesting increased susceptibility in these groups).

On Page 5-3, the authors first introduce the idea of using 2.1 % COHb as an effects threshold. But no justification is given for this. I realize it is analogous to the approach in Pb exposures, and that the figure of 2.1 % is based on past decisions at the EPA, but this needs to be explained so the reader has some context for the decision here.

On Page 5-4, it would be good to know why the CO NAAQS review in 1999 was put on hold and never completed.

Some material is missing in the incomplete bullet at the top of Page 5-6.

The final bullet on that page considers the relationship between the 1 and 8 hour exposures. But no explanation is given as to why this is of interest (I agree it is, but the document should state the reason).

On Page 5-8, it is not clear whether temporal variability will be used to estimate a rolling average for exposures, or whether the timeline will be discretized and averages calculated only in the discrete intervals. These generally give slightly different results with differing degrees of variability.

On the bottom of Page 5-10, the authors ask whether a given factor contributes to uncertainty in a way that over-or-under-states the risk/exposure. But a given factor could be neutral on average, neither systematically under-or-over-stating the risk/exposure.

On Page 5-11, the authors state that the ideal way to assess uncertainty due to model formulation is to compare model results against data. No further clarification of this comment is given. I note first that such an approach requires assumptions as to the validity of the data, especially in geographic areas with high degrees of spatial variability. And I can see how this can be used to assess the quality of one model, but don't see how it is to be used to compare the degrees of belief in competing models in characterizing uncertainty due to model formulation.

In that same paragraph, the authors speak of partitioning uncertainty into model components. Is some form of contribution to variance intended here? I assume it is, but this is not stated.

Section 6 is too generic to justify any further statements here. It would be of interest only if the reader were provided a succinct statement of the policy questions to be addressed and how these are related to the answers to specific questions asked in the previous sections.

The Morgan and Henrion 1990 reference appears to be missing from the References section even though it is called out in the text.

Dr. Ellis Cowling

Individual Comments on the March 2008 Draft Plan for Review of the Primary National Ambient Air Quality Standard for Carbon Monoxide

Very General Comments on these NAAQS Review Processes

Before dealing with the details of my specific assignment during the April 8, 2008 CASAC Consultation on the Primary (public-welfare based) NAAQS for Carbon Monoxide (CO), I would like to offer a few general comments about these periodic NAQQS Review processes and the changes that are being made in both the organization and focus of these reviews.

As described on pages 1-2 of the "Draft Plan" for review of the primary NAAQS for CO, the Clean Air Act of 1970 established two general goals for management of air quality in the United States -- protection of human health and protection of public welfare. Section 108 of the CAA directs the Administrator of EPA to identify and list "air pollutants" that "in his judgment may reasonably be anticipated to endanger public health and welfare" and to issue air quality criteria for those that are listed – hence the term "Criteria Pollutants."

Section 109 of the CAA further directs the Administrator of EPA to propose and promulgate "Primary" National Ambient Air Quality Standards to protect public health and "Secondary" National Ambient Air Quality Standards to protect public welfare.

A secondary standard, as defined in Section 109, must "specify a level of air quality the attainment and maintenance of which, in the judgment of the Administrator, based on such criteria, is required to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air …" The welfare effects of concern include, but are 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."

So far, the several Administrators of EPA since 1970 have:

1) Identified six specific "Criteria Pollutants" – carbon monoxide, ozone and other photochemical oxidants, sulfur dioxide, oxides of nitrogen, particulate matter, and lead – which have thus been designated officially as requiring development and implementation of National Ambient Air Quality Standards;

2) Emphasized protection of public health as the principal (and overwhelmingly important) *de facto* focus of concern within the Agency, and public welfare as a (rarely openly acknowledged) but distinctly less important *de facto* focus of concern;

3) Established Secondary (public-welfare-based) NAAQS standards for all six criteria pollutants that almost always were identical in form (including level, indicator, statistical

form, and averaging time) to the Primary (public- health based) NAAQS standards for each of these six criteria pollutants;

4) Developed a long-standing tradition of dealing with these six specific air pollutants mainly on a "one-at-a-time" basis rather than collectively – i.e., without strong attention to the frequent interactions and simultaneous occurrence of some of these pollutants as mixtures within the air in various parts of our country;

5) Maintained a reluctant attitude about the concepts of ecologically based "Critical Loads and Critical Levels" developed in Europe as possible alternative or additional approaches to air-quality management in the US; and

6) Maintained a long-standing general focus on the related concepts of:

   a) "attainment counties and non-attainment counties,"
   b) "attainment demonstrations" based on mathematical modeling of a limited number of exceedance events under extreme weather conditions, and
   c) "local anthropogenic sources" as opposed to "both local and regional biogenic and anthropogenic sources of emissions."

In recent years, in contrast to several of the six ideas listed above, EPA has shown increased willingness to think more holistically – and in more fully integrated ways – about both the policy-relevant science and the practical arts of air quality management aimed at protection of both public welfare and public health. These shifts in both emphasis and approach have included:

1) Participation with other federal agencies and international bodies in discussions about the "One Atmosphere," "Critical Loads–Critical Levels," and "Multiple-Pollutant–Multiple Effects" concepts;

2) Adoption of the "NOx SIP Call" in 1999 and both the "Clean Air Interstate Rule" (CAIR) and the "Clean Air Mercury Rule" (CAMR) in 2005 with their more balanced perspectives about both regional (interstate) and local sources of emissions and interactions among NOx, SOx, VOCs, "air toxics," and mercury in the formation, accumulation, and biological effects of "ozone and other photochemical oxidants," and fine, coarse, thoracic, and secondary aerosol particles;

3) Recognition of both fine and coarse PM as complex and geographically variable mixtures of sulfate-, nitrate-, and ammonium-dominated aerosols; natural biogenic and anthropogenic organic substances; heavy metals including cadmium, copper, zinc, lead, and mercury; and some other miscellaneous substances;

4) More frequent discussion about of the occurrence and both ecologically-important and public-health impacts of mixtures of air pollutants; and, most recently

5) Making the unprecedented decisions (at least in the case of the NAAQS reviews for oxides of nitrogen and sulfur) to:

   A) Separate the preparation and review of documentation, the required CASAC and public reviews, and the final decision-making processes for the Secondary (public-

welfare-based) National Ambient Air Quality Standards from the (previously always dominating) Primary (public-health-based) NAAQS review processes, and

B) Prepare and publish a single draft plan for integrated [simultaneous] of two different criteria pollutants (NOx and SOx), and

6) Identify in advance a set of Key Policy-Relevant Questions that will be the primary focus of attention in the design and completion of all four major components of the new NAAQS review processes:

A) An Integrated Review Plan (IRP),

B) An Integrated Science Assessment (ISA),

B) A Risk/Explosure Assessment (REA), and

C) A Policy Assessment/Rulemaking document developed in the form of an Advanced Notice of Proposed Rule Making (ANPR).

All six of these adjustments in focus of attention, documentation requirements, and sequential procedures are being undertaken with the intention to:"

> "… improve the efficiency of the process while ensuring that the Agency's decisions are informed by the best available science and timely advice from CASA and the public" … and
>
> "… help the agency meet the goal of reviewing each NAAQS on a 5-year cycles as required by the Clean Air Act without compromising the scientific integrity of the process."

Need for Policy Relevancy as the Dominant Concern in NAAQS 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 that either support or call into question the current public-health based and/or the***

current public-welfare based NAAQS, 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."

Thus, a second very critical scientific question that needs to be answered for CO as well as the other 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 CO, NOx, SOx, PM, ozone, and lead.

We now have the considerable advantage that a much more complete focus can be achieved in the Integrated Science Assessment than has historically been achieved in the encyclopedic Criteria Documents that have been prepared during the years since 1970.

Thus, I recommend that every chapter of the soon to be completed Integrated Science Assessment, the Risk/Exposure Assessment, and the Policy Assessment/Rule Making documents for CO **contain a summary section composed almost entirely of a series of very carefully crafted statements of Conclusions and Scientific Findings that:**

1) **Contain the distilled essence of the most important topics covered in each chapter, and**

2) **Are as directly relevant as possible to the two Critically Important Scientific Questions written in bold italic type above**.

In this connection, I call attention once again to the attached "*Guideline for Formulation of Statements of Scientific Findings to be Used for Policy Purposes.*" These guidelines were developed and published in 1991 by the Oversight Review Board for the National Acid Precipitation Assessment Program. They are the best guides that I know of for formulation of scientific findings to be used for policy purposes.

GUIDELINES FOR FORMULATION OF SCIENTIFIC FINDINGS

TO BE USED FOR POLICY PURPOSES

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

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

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

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

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

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

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

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

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

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

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

My Assignment in this CASAC Consultation on the Draft Plan for Review of the NAAQS Primary Standard for Carbon Monoxide

My specific assignment in preparation for the April 8, 2008 CASAC Consultation on the Draft Plan for review of the NAAQS for CO, as outlined in Chairman Rogene Henderson's memo of 7 March 2008, is -- *Key Policy-Relevant Issues*. Rogene also asked Jim Crapo to deal with these same issues. Thus, I am very much looking forward to comparing notes with Jim during our Consultation on April 8 – especially since he knows so much more than I do about public health effects of CO and other Criteria Pollutants.

These Key Policy-Relevant Questions are summarized on pages 3-1 through 3-3 in Section 3.2 and are presented as a series of thirteen major policy-focused "Issues to be considered in the current review". In addition, several other detailed questions are presented in the several Sub-sections of Chapter 4. In most cases, however, these more detailed questions are focused mainly on scientific issues rather than policy issues and, I presume, will be dealt with adequately by other members of our CASAC Carbon Monoxides Panel.

I see the decision to develop "Key Policy-Relevant Policy Questions" as a part of these Draft Plans for NAAQS reviews as a major step forward. I am also very satisfied with the particular set of 13 such questions listed in Chapter 3 of this Draft Plan. Of course they all relate to the effects of CO on public health – which is the principal focus of this NAAQS review.

In addition, however, I also note that Section 1.3 – History of Reviews of the NAAQS for CO -- indicates that identical primary and secondary NAAQS standards for CO were promulgated in 1971 and that the decision was made in 1985 to revoke the secondary standard. The rationale for this decision was not included in this "History" section,

But Section 1.4 – Scope of the Review – also indicates that

> " … relevant scientific information on human exposures and health effects associated with exposures to ambient concentrations of CO will be assessed. The possible influence of other atmospheric pollutants on the interpretation of the role of CO in health effects studies will e considered. This will include other pollutants with the potential to co-occur in the environment (e.g., NO_2, SO_2, O_3, and PM). The review will also assess any relevant scientific information associated with known or anticipated public welfare effects that may be identified."

Thus, because of my keen scientific interest in the welfare effects of criteria pollutants, I believe it is essential that both current and past scientific literature be examined closely to determine if:

A) There are significant public-welfare effects that are caused by ambient concentrations of CO acting alone or in combination with other criteria pollutants. – and thus, in essence to determine if the 1985 decision to revoke the secondary NAAQS standard for CO is valid in the context of current scientific knowledge --especially about the effects of CO on the health of both domestic and wild animals, and perhaps also on crop, forest, and ornamental plants, insects, and microorganisms as well.

B) There are significant interactions of ambient concentrations of CO with other co-occurring Criteria Pollutants in terms of their potential to cause either additive, competitive, or no significant interactions with regard to the effects of CO on both public health and public welfare, and

C) Since CO is a chemical precursor of ozone in ambient air, to determined if there are significant contributions of ambient concentrations of CO from both locally occurring, regional, and even far distant wild fires that contribute to the accumulation of ozone near the ground in urban, suburban, rural, and even remote regions of our country.

I suggest this last issue for inclusion in the First Draft Integrated Science Assessment for CO as a result of the discovery by Wotawa and Trainer during the 1994 and 1995 Nashville-Middle Tennessee Ozone Study by the Southern Oxidants Study -- where a coherent plume containing extraordinarily high concentrations of CO were observed for several days about 50 miles east of Nashville and could be traced to wild fires in the Northwest Territories of Canada that persisted over a six-week period.

Wotawa, G. and M. Trainer. 2000. The influence of Canadian forest fires on pollutant concentrations in the United States. Science 288:324-328.

Dr. Thomas Dahms

Section 3. Key policy-relevant Issues

3.2 Issues to be considered in the current review

- Better understanding of effects on subpopulations

It is my understanding that previous documents were unable to establish any non-toxicological effects of CO on the respiratory system unlike 4 other regulated pollutants. In the 2000 AQC for CO lungs were implicated as being involved in the decrease in exercise performance with CO exposure in healthy individuals with no evidence that this was due to an effect on the lungs. (Table 6-12 page 6-50). There needs to be a determination as to whether or not CO effects the lungs. If there is no effect of CO on the lungs, this area of investigation should be dropped as it is only distracting to the users of this document.

- Alternate dose indicators other than COHb

Is there insight to be gained from data on mechanism by which CO has metabolic effects on tissues? Are there long lived markers of exposure that could be used to support the use of COHb? The suggested use of %O2Hb would merely be a mathematical manipulation
A supposition was made in the 2000 that the hypoxia from altitude and the hypoxia resulting from CO would be additive. Evidence for this should be evaluated as it could place a significant number of residents who reside at altitude at risk when exposed to CO.

3.2.2. Evidence needed for revision of standard

a. evidence of effects at levels lower than current standard

- Q: do exposure estimates suggest that exposures of concern occur?

This statement implies that if sufficient exposures do not occur that the current level is not supported. If this is the case how does EPA set standards that allow a reasonable margin of safety?

- Q: do health effects evidence and air quality/exposure assessment provide support for considering different exposure indices or averaging times?

This would have to be based on modeling of real time exposures. Is there data available to support such a change?

- Q: what range of levels is supported?

What guidance is provided for the data necessary to support recommending a range of levels?

- Q: what is the range of forms supported

How does this statement pertain to atmospheric CO?

Section 4. Science Assessment

4.2.2 Literature Search

Will only peer reviewed material be included in the database? [The previous AQC documents in this field have unreferenced material in them. It is not clear how this material should be used by the authors of the ISA.]

It is not clear how this data base will be made available to the authors of the ISA. Will articles not referred to by the authors be in this literature data base? This is implied by the way it is written.

Specific Comments

Page 4-1, line 29. "Emphasis will be placed on studies conducted at or near CO concentrations found in ambient air". [Given the uncertainty in CO dosimetry and the falling atmospheric levels of CO, should this statement provide better guidance?]

Page 4-2, line 1. Multiple studies have been carried out in the most sensitive population for CO. Therefore this language does not provide the ISA authors clear direction.

Page 4-5. line 1. This statement implies that if the data is unique that the paper(s) should be included even though they do meet the other stringent criteria? It also implies that confirmatory data is of less importance which is clearly not the case.

Page 4-6. lines 4-10. The toxicology experiments and the health effects experiments often used exposures that result in relatively rapid increases in concentrations of COHb. Hardly any of these experimental exposures would meet the guidelines as written in the draft. Alternate guidance should be provided..

Page 4-6. line 25. How does the inclusion of non-peer reviewed material provide any assurance of quality?

Page 4-7. line 21. What do current atmospheric levels of CO have to do with setting levels of acceptable human exposure? It should not matter if atmospheric levels have decreased, there should remain a level(s) that should not be exceeded. If atmospheric levels are decreasing, the issue becomes one of how to alter enforcement not alter criteria setting. If atmospheric levels are decreasing it will become more difficult to demonstrate epidemiological effects of CO in the US and Canada.

Page 4-8. line 5… This section clearly identifies key questions that the ISA needs to attempt to answer.

Page 4-9. line 14. The original CFK model includes endogenously produced CO in the factors considered for predicting increments in COHb.

Page 4-10. line 4-6. Endogenous formation of CO in all mammals is not new information. What is potentially new is that there exists the potential for regional/tissue differences in partial pressure of CO due to local endogenous production, i.e., non-heterogenous distribution of CO. The task should be to determine the tissue levels of CO (partial pressure of CO) that would exist when hemoxygenase is activated. These local endogenous levels of CO in addition to increased exogenously derived levels could generate local levels of COHb that would produce health effects in sensitive tissue not predicted by the current methods of assessing effective exposure.

Page 4-14. lines 7-8 and line 22. Based on what is well documented in the structural changes in coronary vessels of patients with ischemic disease, the document fails to request such a brief description of the pathophysiology. Without this information the reader will not be able to understand how any mechanism identified in response to lines 7-8 fails to function in those subjects with ischemic heart disease.

Dr. Russell Dickerson

Comments EPA's *Draft Plan for Review of the Primary National Ambient Air Quality Standard for Carbon Monoxide* for the teleconference on April 8, 2008

Three noteworthy topics: The current monitoring program is inadequate but could easily be improved; CO plays an major role in the budgets of other criteria pollutants and other environmental problems and thus a secondary standard warrants serious consideration; the process by which the scientific judgment of the CASAC and its focus groups is used in forming policy needs careful consideration - especially in light of the recent problems with PM2.5 and ozone standards.

On page 4-7, we may be asking the wrong questions. It might be better to ask "how can current monitoring methods for CO be modified to provide information adequate to determine CO exposure, statistics of ambient concentrations, to evaluate models, etc?" CO, even at concentrations well below the NAAQS, is responsible for a large fraction of the OH reactivity and thus production of HO_2, H_2O_2, and O_3 over the US, but emissions inventories and monitoring methods are inadequate. Direct investigation of HOx chemistry has quantified the role of CO as responsible for 10's of percents of the total OH reactivity (e.g., Ren et al., 2005; Ren et al., 2008). The ratio of emissions of CO/NOx (based on road-side research grade measurements) has decreased dramatically, but MOBILE6 CO/NOx emission ratios have not followed this trend - they are too high now. MOBILE6 indicates a ratio of 15:1 while current measurements show 5-8 (Bishop and Stedman, 2008; Parrish, 2006). In other words, current CO monitors as employed can not determine the concentration of CO much of the time, but with relatively minor modifications, these monitors can be improved such that the detections limits are essentially always sufficient for ambient CO mixing ratios [*Dickerson and Delany*, 1988; Parrish et al. 2000). The Maryland Dept. of the Environment operates one at Piney Run, MD. The manufactures of CO analyzers have indicated a willingness to improve the instruments for commercial sales.

The atmospheric chemistry and physics of CO are relatively simple and well understood, making it enormously useful as a tracer. Improved monitors would provide data useful to

- evaluate emissions inventories
- investigate the epidemiology of CO
- evaluate chemical transport models (such as CMAQ) for ozone and PM2.5
- determine the impact of CO emissions on the large scale composition of the atmosphere and climate.

Although the EPA did not complete the review which started in 1997, a revised CD was prepared and reviewed. That CO CD recommended changes in monitoring technique to provide data

useful to models. Ambient concentrations are typically below 300 ppb and commercial CO analyzers can be easily modified to improve the resolution from 200 to 20 ppb. While current monitors are adequate to demonstrate compliance with the NAAQS, ambient concentrations are frequently below detection limits.

Global atmospheric composition, the oxidizing capacity of the troposphere, and climate forcing should be considered in formulating a secondary standard for CO to protect public welfare. In addition to its direct health effects, the environmental effects of CO include:

- A core precursor to ozone.
- As a precursor to the oxidants that form PM2.5.
- An impact on the large-scale composition, and oxidizing capacity of the atmosphere.
- A role in global radiative balance and climate.

I am not clear on the new review procedures, but the comment by Dr. Henderson "The CASAC is a science advisory body and we cannot give the EPA our advice if the scientific analyses of the EPA staff are obscured from us," needs substantial discussion.

References

Parrish, D.D., Critical evaluation of US on-road vehicle emission inventories, *Atmospheric Environment*, 40, 2288-2300, 2006.

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Ren, X.R., et al., HOx chemistry during INTEX-A 2004: Observation, model calculation, and comparison with previous studies, *J. Geophys. Res.*, 2008.

Dr. Milan Hazucha

The Plan for Review (Plan) is structured around a series of critical activities/tasks clustered into four key components that have to be accomplished in developing the ISA and Annexes for CO. Generally, the ISA and supporting ANNEX documents approach has been successfully used in the development of recent NAAQS documents. The Plan review schedule as proposed is reasonable.

One of the changes from the previous approaches to NAAQS reviews is the proposed elimination of a staff paper. The staff paper served as a compendium, an extended summary of the ISA, generally incorporating answers to questions raised in a respective review plan. In the absence of staff paper the ISA should include a Chapter where each of the questions raised in the Plan will be briefly, in a couple of sentences or a short paragraph, answered. This will help to quickly identify the areas which may have not been addressed or overlooked as well as identify the gaps in the current scientific knowledge and database(s).

Apart from eliminating the staff paper, I think that only minor adjustments, most likely specific in nature, will be required to the proposed Plan. My suggestions for changes/modifications in Chapter 4 are listed below.

Page 4-4, line 5: Include ISI Web of Knowledge database in the search list. Of all mentioned databases, ISI is the most comprehensive database and includes publications not found in other databases.

Page 4-4, line 19: Delete “pertinent”. We do not know yet how pertinent those studies are.

Page 4-4: Will EPA consider potentially pertinent studies published in a foreign language? Will they be translated by EPA?

Page 4-5 line 4: List of conditions should be expanded to add “Sufficient statistical power”

Page 4-5, line 9: Insert after the word “issues “ the following text “fully discussed in Annexes” .

Page 4-5. Change the subtitle to read “Criteria for Selecting Pertinent Field and Epidemiological Studies.”

Page 4-5, line 24-27: Suggest to change the sentence to read:” Certain findings of the studies conducted in the U.S. may be generally discussed .....”.

Page 4-6, line 4: Change subtitle to “Criteria for Selecting Human Laboratory, Clinical and Animal Toxicological Studies.”

Page 4-6, 2nd para: There is no discussion about selection criteria for animal studies.

Page 4-6, line 8-10: It is highly unlikely that any of the mechanisms can be elucidated under atmospherically relevant conditions. The sentence should be deleted or reworded.

Page 4-7, l. 24: Insert “and temporal “ between the words spatial and variability.

Page 4-8: One of the questions that should be included in this section is: “What is the effect of averaging time on health risk assessment?”

Page 4-10, l. 28: Reword. The time to onset of angina is not an endpoint for healthy individuals.

Page 4-11, lines 1-6: The, this aim is identical to the preceding one. Delete.

Page 4-11, line 7-9. The answer is none to inconsequential at relevant ambient exposure conditions. . Delete this question/aim.

Page 4-13, line 10: Insert “human laboratory and” between “with “ and “toxicologic”.

Page 4-15, line 28-29. The first goal should be “to comprehensively and critically review the literature and subsequently identify.....” as stated on p.1-2, line 11-13.

I also suggest adding a Chapter at the end of the ISA discussing commonalities and differences, if any, of key factors and studies that have led to and determined the current WHO, EU and the NAAQS for CO.

Dr. Rogene Henderson

Comments on Section 6. Policy Assessment/Rulemaking of the US EPA Draft Plan for Review of the Primary NAAQS for Carbon Monoxide.

In a letter to the Administrator dated January 23, 2008, the CASAC expressed their opposition to the use of an ANPR as a Policy Assessment document at the end of the NAAQS review process and that opposition still exists. As pointed out in that letter, the ANPR is a document that belongs at the beginning of the review process, not at the end, because the ANPR (Advance Notice of Proposed Rulemaking) is meant to describe every possible choice that might be considered.

In a memo from Assistant Administrator Marcus Peacock of December 7, 2006, the ANPR/Policy Assessment Document was described as containing essentially the analyses that had been in the former staff paper plus modifications related to EPA management concerns. The ANPR that was presented to CASAC at the end of the lead review process was NOT such a document, but was the standard ANPR with all options described but with no scientific justification for the options. It is **not acceptable** to CASAC to remove from the review process the scientific analyses of the data that was formerly provided in the Staff Paper and substitute an ANPR that provides little or no scientific justifications.

The CASAC is a science advisory body and we cannot give the EPA our advice if the scientific analyses of the EPA staff is obscured from us.

Dr. Michael T. Kleinman

Chapter 3

A policy relevant issue that is not explicitly addressed is the non-uniformity of CO exposures in various environments. This has a profound effect on the adequacy of our ability to judge health effects as a function high local exposures, i.e. near heavily trafficked roads. Monitoring plans for CO should take this into account.

Perhaps this could be folded into the question: What do recent studies focused on the near-roadway environment tell us about high-exposure subpopulations and the health effects of CO?

Alternatively, it might be advisable to raise the issue of whether the current network of air sampling monitors adequately represents population exposures to CO as an explicit charge question.

Chapter 4

4.1 Scope and Organization

Vis-à-vis the issue stated above, if ”emphasis will be placed on studies conducted at or near CO concentrations found in ambient air.” Some guidance should be provided with respect to ranges of exposures measured near areas of unusually high concentration that are not always represented by the placement of monitors for other criteria pollutants.

4.2 Assessment Approach

Literature Search

The suggested search terms are rather limited. An important aspect of the current literature relates to long-term sequelae which include neurological as well as cardiovascular endpoints. While this may be subsumed in the guidance to look at specific health outcomes, it might be useful to state this explicitly.

General Criteria for Study Selection

The criteria are well thought out. In keeping with my previous comments I suggest that we discuss the following criterion.

- To what extent are the aerometric data, exposure, or dose metrics of adequate quality and sufficiently representative to serve as indicators of exposure to ambient CO?

This should be placed into a context of the exposure range for populations with exceptional exposures since this criteria might be interpreted to exclude some studies near CO sources that use measured values that are in excess of those seen at central site monitoring stations.

Criteria for Selecting Animal and Human Toxicological Studies
"Criteria for the selection of research evaluating animal toxicological or controlled exposure studies will focus primarily on those studies conducted within about an order of magnitude of ambient CO concentrations and those studies that approximate expected human exposure conditions in terms of concentration and duration."

There are seasonal and site-specific factors that contribute to the non-homogeneity of CO exposures. The order of magnitude requirement may be too restrictive.

Many toxicological studies are limited with respect to time. Perhaps a criteria of whether the study was performed to assess subjects with reasonable levels of biomarker
One important factor that should be considered for assessing the acceptability of human toxicological studies is whether the study was appropriately blinded.

Dr. Beate Ritz

Chapter 4:

page 4-4 "Emphasis in the text will be placed on discussion of (1) new, multi-city studies that employ standardized methodological analyses for evaluating CO effects and that provide overall estimates for effects based on combined analyses of information pooled across multiple cities; "

The emphasis on pooled results from multi-city studies that use standardized methods might be misplaced i.e. it is not clear that such approaches will be informative. The problem with CO is its intra-community heterogeneity due to local sources, heterogeneity may not be reflected in ambient monitoring station measurement data. Depending on how ambient monitoring is used to derive exposure estimates in different communities, this could lead to differences in measurement errors depending on how dense the network is. Concerning standardized exposure modeling approaches, if different sources contribute to high CO in different cities, a 'standardized model' for different cities might not work or be appropriate e.g. in some cities CO may depend more on vehicular traffic and in others on power plant emissions etc.

Similarly questionable is the emphasis on "studies that consider CO as a component of a complex mixture of air pollutants." It is unclear whether this means only multi-pollutant models will be taken into consideration and how the expected (and possibly strong) correlational pattern with particles and NO2 will be dealt with in such models. It might be impossible to adjust for (highly) correlated pollutants in the model, and it is not clear how this may be addressed and/or evaluated in the report.

Furthermore, it is unclear what the emphasis on "new studies that provide quantitative effect estimates for populations of interest" means. For pregnancy outcomes, the issue of scaling according to a (susceptible) time period is essential and it is not clear that 1ppm exposure on average during a trimester is comparable to a 1ppm average exposure during a month or week of pregnancy.

Chapter 5, page 5-4

"For this current review, EPA staff will build upon the 1999 work and subsequent improvements to the exposure model (now called APEX) in developing its plan for CO exposure assessment. " It is unclear what this work will be i.e. what kind of data will be used to develop these models and whether the data already exist and/or will be retrieved from existing research (e.g. the LA RIOPA study that monitored CO).

Given that the highest CO exposures might occur inside cars during commute, it is unclear how this will be integrated into the stated goals for CO exposure assessment (page 5-5), even though the Apex model uses in-vehicle microenvironments and this is also mentioned on page 5-10.

Dr. Paul Roberts

Comments on the "Draft Plan for Review of the Primary National Ambient Air Quality Standard for Carbon Monoxide" before the CASAC CO NAAQS Review Panel conference call on April 8, 2008

Note that this document outlines a plan for the several year review process for the CO NAAQS and thus includes little or no technical detail. In general, this plan is well-written, is adequate to meet its objectives, and (presumably) matches the review process currently ongoing for sulfur dioxide and nitrogen oxides, which are both further along than the process for CO. Overall, I am concerned about the elimination of the EPA staff paper from the process, since I am not sure how the summary and integrative aspects of the staff paper will be handled in the new process (within the ISA and the Scope and Methods Plan). Maybe this should be addressed directly in the "Plan".

In Section 1.3, I think that there should be some discussion of why the previous 1997-2000 CO NAAQS review process was not completed (see page 1-6, lines 23-24).

Table 2-1 seems to have a duplicate listing for the first draft of the risk and/or exposure assessments in January 2010 (see 3rd and last entry under Risk/Exposure Assessment in the table).

Specific comments on Sections 4 and 5:

- The introduction to Section 4 mentions that a formal framework for the integration of health effects evidence was developed in the NOx ISA (see page 4-1, lines 13-16); I think this should be summarized here in the draft plan.
- As far as I can tell, the WHO guidelines referenced on page 5-5, lines 3-4 do not include CO; information on CO was not updated from the earlier WHO Air Quality Guidelines for Europe, 2nd edition published 2000.
- I do think that a comparison and explanation of the different standards (and studies supporting them) published by WHO and others for CO should be discussed in summary form in this plan and in more detail in the ISA and/or the Scope and Methods Plan. This specifically could help on the short-term issues discussed on pages 4-10 to 4-12 etc., since short-term standards is one major area of difference.
- Text is missing from the bullet that begins on page 5-5 and continues onto the top of page 5-6.
- There are several potential CO ambient exposure environments which are not mentioned in this document, but should be mentioned here and information for them explored during the development of the ISA and the Scope and Methods Plan. Existing study data may be useful for determining levels and averaging times, as well as relevant to future exposure environments. These exposure environments include other near-source environments such as near ship loading and unloading ports (potential exposure from trucks and other vehicles plus potential exposure from the ships themselves) and exposures near

recreational boats. Recreational boat engines, including both 2-stroke and 4-stroke engines, do not have exhaust controls and several potential environments can result in very high CO concentrations in the near-source environment. Even with coming emissions controls on new boats, fleet turnover is extremely slow and such exposures will likely persist for 10-20 years. Places in the draft plan where these additional environments might be mentioned include: page 3-2, lines 1-2; page 4-8, lines 3 and 28-29; page 4-10 subsection on short-term exposure; and page 5-3, lines 23-26.

- There should be some discussion of the types of CO monitoring sites and how data from all types of sites will be used to characterize CO air quality and exposures (specifically mentioned in Section 5.3, pages 5-5 to 5-7). In particular, there are official CO monitoring sites, "hot-spot" sites, and data from special purpose monitoring sites which all might inform the analysis being undertaken. This section of the plan should discuss these additional data sets and how they might be used to further the objectives of the exposure assessment (note that this is also of importance for the discussions on pages 4-7 and 4-8 regarding spatial and temporal analyses). In addition, the appropriateness of current monitoring sites, relative to their purposes, should be discussed in the ISA and/or the Scope and Methods Plan. Also, existing sites should be evaluated in some consistent manner in order to ensure that the CO data being collected is appropriate for the stated purposes, both for the current review and for future uses relative to the NAAQS.

Dr. Jonathan M. Samet

In anticipation of the teleconference meeting on April 8, 2008, I write to provide comments on Section 4 ("Science") of EPA's *Draft Plan for Review of the Primary National Ambient Air Quality Standard for Carbon Monoxide.* Below, I offer both general and specific comments.

General Comments:

- This *Draft Plan* follows the model that is now coming into place for developing a primary National Ambient Air Quality Standard (NAAQS). As such, the plan draws on approaches taken already over the last several years. The overall plan and approach is appropriate.

- However, the new plan appears to draw little on "lessons learned" to date from dealing with nitrogen oxides and sulfur oxides. The plan suffers from an overall lack of specificity and vagueness of wording that will undoubtedly become a limitation during its implementation. Additionally, there has been little advance in the EPA's formulation of such critical concepts as causality, confounding, effect modification, and susceptibility. On reading over the questions that will guide the review, problems arising from this vagueness are abundant. I highlight a number of examples in my specific comments.

Specific Comments:

Page #	Line #	Comment
4-4	27	"...sufficiently representative" Of what? Representative in what regard?
4-4	29	Not clear at all
4-4	30	"meaningful" From what perspective? Reliable means repeatable. Is the concern about misclassification?
4-5	5	"potential confounders…" Specify criteria for these
4-8	20	This needs greater specificity
4-8	24	Temporal and spatial?
4-9	19	What does variability mean here?
4-10	7-10	Lines 7-10 are sweeping. What is this saying?
4-11	18	All other systems?
4-11	23	"…nature of health effects…" Effect modification?
4-12 4-13	20-22 1-2	What is meant by evidence <u>against</u> a causal association? Could more be said about EPA's approach to causal inference?
4-13	9	"evaluate uncertainty…" Any attempt to quantify?
4-13	17-19	What does this mean? Is this in reference to potential effect modification?
4-15	6	Reference to fetuses not clear.
4-15	10	What results?
4-15	19-21	Not clear in the formulation of attributable risk

Dr. Stephen R. Thom

Approach & format for the integrated science assessment section are well organized and logical.

Specific comments I suggest be included in the EPA document are:

A. Human exposure studies: Environmental pollution causes a variety of disorders, although not all studies have documented CO *per se* as the etiologic agent.

1. Neonates/infants:
a) Preterm labor/delivery - association with environmental CO and also particulates (PM) (as separate risk factors & also in combination)
b) Infant mortality - association with CO plus PM
c) Neonate hospitalizations for respiratory diseases - association with CO
d) Intra-uterine growth retardation/low birth weight (risks with CO, PM and NO_2)
e) No relation between SIDS and CO, but a link has been established with NO_2 and SO_2

2. Children
a) Childhood respiratory symptoms (wheezing) - association with CO and also PM.

3. Adults
a) Correlations between ambient CO and ischemic heart disease ED visits (CO and also NO_2)
b) Cardiovascular mortality (esp. elderly) - associations with CO and CO/PM & O_3
c) Respiratory-related ED visits - association with CO and CO+O_3
d) Depression-related ED visits
e) Pneumonia hospitalizations (CO + O_3)
f) No link between CO and tachyarrhythmias (but + link with ultra-fine particulates)
g) Risk of CVA elevated with CO, PM, NO_x
h) Cardiac irregularity (HR variability) and CO (+ link in some but not all trials)
i) Plasma markers of inflammation - atmospheric CO contamination only linked with altered albumin. PM and O_3 showed additional changes in plasma levels of vWF, Factor VIII, fibrinogen. Higher CO concentrations (& shorter exposure times) linked to elevated plasma myeloperoxidase.

B. Issues of CO dose-response, as well as time-course of responses, are not clear. The weight of the scientific findings probably does not warrant an alteration in EPA CO guidelines (1 hr 35 ppm; 8 hr 9 ppm). Also, the variability among findings in some trials indicates that combinations of CO with co-pollutants can yield disparate results, leaving the issue of pathophysiological mechanisms unclear.

C. Dosimetry questions persist, and there needs to be some focus on mechanisms unrelated to CO-O_2 competition for hemoproteins (e.g. the CFK equation alone is not adequate to 'predict' biological stresses). These include pro-inflammatory processes such as intravascular platelet-

neutrophil interactions, and a growing body of information on oxidative stress/free radical mediated mechanisms (some linked to ‘therapeutic’ pathways such as activation of MAPKs, NFκB inactivation, caspase 8 inactivation). Endogenous CO production impacts mitochondrial respiration but whether environmental CO will compound this effect is unknown (current kinetic modeling suggests this is unlikely).