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)**

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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. 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. 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. 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).