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WASHINGTON D.C. 20460

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June 8, 2010

EPA-CASAC-10-013

The Honorable Lisa P. Jackson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Review of the *Policy Assessment for the Review of the Carbon Monoxide National Ambient Air Quality Standards (NAAQS): External Review Draft*

Dear Administrator Jackson:

The Clean Air Scientific Advisory Committee (CASAC or Committee) Carbon Monoxide (CO) NAAQS Review Panel met on March 22-23, 2010, to review EPA's *Policy Assessment for the Review of the Carbon Monoxide National Ambient Air Quality Standards (NAAQS): External Review Draft*. The chartered CASAC held a public teleconference on April 19, 2010, to review and approve the report. This letter provides CASAC's overall comments and evaluation. We highlight the most important issues which need to be addressed as the draft Policy Assessment (PA) is revised and finalized.

CASAC expresses appreciation to EPA staff in regard to the draft PA document. We recognize that limited time was available for its development, given the court ordered deadline. In this letter, we offer the main suggestions and concerns identified by the Carbon Monoxide Panel and approved by CASAC. The PA needs to be clearer about how the three main sources of carbon monoxide that contribute to the carbon monoxide dose in the body combine and interact. These three primary sources are endogenous production of carbon monoxide, exposure to indoor sources, and ambient outdoor CO exposure. Ambient CO exposure needs to be considered in the context of these other two sources of the biologically effective dose.

The Panel found that there was too much dependence on the now classic clinical study conducted by Allred et al. (1989) and funded by the Health Effects Institute (HEI). While agreeing that this seminal study provided important evidence, its findings should not be so emphasized as to ignore more contemporary epidemiologic studies, especially those directed at coronary artery disease (CAD) and at cardiovascular disease (CVD) more generally. The epidemiologic studies are important because other cardiovascular conditions affect a large number of people who are at risk from CO exposure. We support the high level of attention to populations at risk, but continue to be concerned that the Agency is underestimating CO exposure among some vulnerable groups, especially persons with low income status. This is one

rationale for placing greater emphasis on the findings of the epidemiologic studies versus the controlled clinical studies. As with other criteria pollutants, the existence of these populations and the extent of their increased susceptibility are essential to promulgating NAAQS that protect the public health. We recommend this greater emphasis of the epidemiologic data across all of the CO documents, beginning with the Integrated Science Assessment and extending through the PA. There needs to be greater balance in treating the various lines of evidence.

The chartered CASAC feels that, in general, an ideal PA should be far shorter and more focused. Staff and the Administrator can turn to the REA and the ISA for more background regarding CO as necessary. The PA could be reduced in length to present a more concise summary of the evidence and how the evidence relates to alternative CO standards. A concise description of how the form of the standard is important would also be useful.

It is important to acknowledge the decreases in ambient CO levels over time; however, this success should not preclude an objective assessment of the potential health consequences of exposures at the current CO NAAQS. While measured concentrations infrequently reach the current NAAQS, evidence indicates that adverse health effects could occur at these levels. For that reason, CASAC expresses its preference for a lower standard.

We understand there will not be a subsequent draft before the release of the final PA. After EPA incorporates our major comments and recommendations, the PA will be adequate for rulemaking. We look forward to the Agency's response and the successful completion of the CO NAAQS review. The CASAC and Panel memberships are listed in Enclosure A. The Panel's responses to EPA's charge questions are presented in Enclosure B. Finally, Enclosure C is a compilation of individual panel member comments.

Sincerely,

/Signed/

Dr. Joseph D. Brain, Chair
CASAC CO Review Panel

/Signed/

Dr. Jonathan M. Samet, Chair
Clean Air Scientific Advisory Committee

Enclosures

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Enclosure A

Rosters of the CASAC CO Panel and CASAC

U.S. Environmental Protection Agency
Clean Air Scientific Advisory Committee
Carbon Monoxide Review Panel

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Enclosure B

CASAC's Consensus Responses to EPA's Charge Questions

1. Does the Panel find the introductory and background material, including that pertaining to previous reviews of the CO standard, the current review and current air quality, to be clearly communicated and appropriately characterized?

Chapter 1 of the PA does a good job providing background information. There is a brief review of the CAA and provisions to establish primary and secondary NAAQS; adequate margins of safety; previous reviews; CO sources in ambient air; the monitoring network; low dose levels; new monitors/NCore network; recent ambient and steady-state decreases in ambient CO; and finally, the "staff's evaluation of policy implications of scientific evidence in the ISA and results of quantitative analyses based on that evidence." The PA focuses on the four basic elements of a NAAQS: indicator, averaging time, form and level. None of these elements have been clearly defined in the PA. The Panel recommends including clear definitions of these four elements, consistent with previous CASAC recommendations in the review of other criteria pollutants.

2. Consistent with the revised NAAQS process which includes development of this draft Policy Assessment (PA) document, considerations with regard to the primary standard for CO have been organized around a set of policy-relevant questions for the review.

a. Does the Panel find the question posed to appropriately reflect the policy relevant questions in the review?

The questions posed raise the major issues, and the information provided in response to these questions provides the essential evidence required for making policy decisions. It is difficult to make a judgment on the adequacy of protection because there is no estimate of the total population exposed to benchmark CO concentrations. Only numbers for test cases in Denver and Los Angeles are provided and additional information is needed on the application of the two case studies' findings to the whole country.

The increase in scientific evidence on the effects of environmental CO since the last evaluation of CO standards, as documented in the ISA, comes primarily from epidemiology based studies. A combined consideration of the findings of epidemiological studies and controlled human exposure studies leads to the conclusion that substantial numbers of persons experience ambient CO concentrations resulting in lower effective CO doses than the doses used in the controlled human exposures. The document does not appear to give the epidemiologic studies sufficient standing relative to the controlled human exposure data, even though they may be more realistic.

One question that was not adequately posed is: what are the confounding effects of non-traffic sources of CO (e.g., indoor air)? Numerous studies have shown that we spend 80-90% of time indoors. For healthy elderly and people with CVD, the time they spend indoors may be even greater. The non-traffic sources of CO are at times substantial and may override the ambient CO

levels in contributing to dose. It is suggested that information from the 2000 criteria document on indoor sources be included.

b. Does the Panel consider the document to provide the appropriate level of detail in addressing these policy-relevant questions?

For the controlled human studies, the Panel found the level of detail appropriate. However, the opposite is true for the epidemiological studies.

3. The discussion of the health effects evidence (e.g., section 2.2.1) draws from the most recent information contained in the final ISA for CO and information from the previous review described in previous Air Quality Criteria Documents.

a. Does the draft PA accurately reflect the currently available health effects evidence for CO as characterized in the final ISA and the extent to which it differs from that available at the time of the last review?
b. Does the Pane find the presentation to be technically sound, clearly communicated and appropriately balanced?

The description of the data considered by the previous EPA reviews is basically sound but too focused on the Allred et al. study. There should be a way to mention key elements of other controlled human studies in this document. The document continues to emphasize the use of %COHb as the optimal dose metric for assessing risk associated with CO exposure and its health consequences. However, the discussion of the epidemiological data should also consider non-hypoxia mechanisms. Increased COHb is important, but may not be the only mechanism for CO health effects.

The last review of CO was halted for several years due to the pending study of the effects of CO at high altitude and extreme cold environments and its subsequent report. The PA should very briefly acknowledge the findings of this report. Without that information, it is difficult to determine to what extent there are changes from the last review that commenced in 1999.

In order to facilitate better understanding of the cardiovascular effects, particularly myocardial ischemia, we suggest adding to the reported values of changes in % time to angina on page 2-11 (top paragraph), including the actual changes in seconds with the confidence intervals (CI). Moreover, regarding time to angina endpoint, are there any long-term consequences on repeated exposures, duration of angina, and frequency of occurrence without CO exposure? EPA should address these questions. If data are not available, the PA should state this to be the case. This information would seem to be important for the more complete understanding of the uncertainties associated with using these data to support the standards.

4. The discussion of the quantitative analysis of exposure and dose (e.g., section 2.2.2) draws from the analyses described in the second draft Risk and Exposure Assessment (REA).

a. Does this discussion accurately reflect the analyses contained in the draft REA?

The Panel largely agreed that the discussion in the PA accurately reflects the analyses contained in the second draft REA. We continue to be concerned with whether increased emphasis could be placed on the increment that ambient CO contributes to COHb or whether the emphasis should be on the final resulting %COHb concentration itself. We have a related interest in modeling indoor source contribution to COHb to better understand the total COHB concentrations.

Panel members offered mixed opinion regarding the decision by the EPA not to pursue the 1% COHb benchmark as suggested by the Panel. The staff correctly pointed out that "this level overlaps with the upper part of the range of endogenous levels." One Panel member supported the agency's decision, since this complies with the EPA's task "to establish standards that are neither more nor less stringent than necessary for these purposes", i.e., public health. However, other members considered that a more advanced modeling approach could focus on the increment that ambient CO contributes to %COHb, rather than the final resulting COHb concentration itself. The incremental CO analysis would provide a clear context of the full range of benchmarks for policy analysis. Further, if adverse effects are clearly observed in controlled human exposure studies with a small sample size associated with an increase in the percent COHb of 2%, then it is prudent to consider standards that would use a benchmark of ambient CO-attributable COHb increases as low as 1%. This benchmark would lead to a wider range for a margin of safety, given that a no observable adverse effect level for CO effects among susceptible populations has not been demonstrated.

b. Does the Panel find the presentation to be technically sound, clearly communicated and appropriately balanced?

Most Panel members agreed that the presentation was technically sound and appropriately balanced. However, most of the Panel was concerned that the presentation unnecessarily diminished the value of epidemiological studies in establishing the underpinnings (if not the details) of the quantitative relationship. Despite the fact that the PA may need to be based on a risk assessment drawn primarily from one particularly informative controlled human exposure study (i.e., the multi-center investigation described in Allred, et al.), there would be value in highlighting the supporting role of other studies, in particular the body of epidemiological evidence.

The %COHb module of the APEX model, although the most important, also has weaknesses, given that some physiologic data and the range of values for many variables that enter into the model are not transparent. Despite these limitations, however, there seems to be sufficient information for some variables that can be used to refine the estimates generated (e.g., Hb concentrations stratified by race-ethnicity as should be available from NHANES or other readily accessible sources).

5. Does the document identify and appropriately characterize the important uncertainties associated with the evidence and quantitative analysis of CO exposure and dose, particularly those of particular significance in drawing conclusions as to the adequacy of the current CO standards?

In general, the uncertainties are dealt with appropriately with one exception. Under the pretext of evaluating the uncertainty regarding ST segment changes, the current review suggests that the uncertainty is now greater than in 1991 (p. 2-32). The Allred et al. study used EKG changes in the ST segment to substantiate that the subjective measure of angina was indeed due to ischemia. These two indicators, one subjective and one objective, were very highly correlated and not independent. Therefore, separate analyses of the two indicators should be avoided.

The most thorough clinical studies remain those of Allred et al., Kleinman et al., and Sheps et al. While the effects in these groups are clear, and together these subjects may be "the best characterized population," it is not clear that they represent the "most susceptible population." First, these experiments have not been repeated in the past 20 years, and second, other potential susceptible groups have not been exposed to such controlled clinical conditions. Additionally, the epidemiologic data on cardiovascular (heart) disease, including congestive heart failure (CHF), suggest that those groups might be at least as susceptible to CO-related stress as the coronary artery disease group.

The data available in the PA and the ISA on CO and heart failure are instructive. The statement on page 2-14 (lines 16-19) that there are only "…small or no associations between hospital admissions" and stroke is inaccurate (see next paragraph). Of the five studies listed in the footnote at the bottom of that page, four of the five reported increased hospital admissions for CHF. A close look at Figures 5-2, 5-3, and 5-4 in the ISA support the association of CO with CHF and stroke more than for CAD. If all the studies for stroke, CHF and CAD were placed on the same x-axis, it could very well demonstrate the heightened uncertainty in statements of CAD patients being the most susceptible to CO effects.

Another possible uncertainty regards the question of whether CO is a surrogate and whether its effects at low concentrations can be separated from those of co-pollutants (p. 2-34, lines 24-34). There are analytical and methodological challenges in disentangling the effects of CO from those of co-pollutants, although the problem does not exist in the controlled clinical studies of CO alone.

6. This document has integrated health evidence from the final ISA and risk and exposure information from the second draft REA as it relates to reaching conclusions about the adequacy of the current standard and potential alternative standards for consideration.

a. Does the Panel view this integration to be technically sound, clearly communicated, and appropriately characterized?

Although it may be a challenging task, it is important to integrate the evidence from the epidemiological studies with clinical studies (p. 2-25). Some of the conclusions are not well supported. In particular, the estimation of population exposures (p. 2-5, lines 27-34, and p. 2-6, lines 1-8) may underestimate exposures of those in lower socioeconomic status populations because of their higher likelihood of residing in heavily trafficked areas and an increased probability of exposure to secondhand tobacco smoke. Inclusion of population prevalence of low income status and smoking prevalence in the simulated populations might shift the distribution of estimated CO exposures towards higher levels.

The conclusion that the current evidence supports a primary focus on those with cardiovascular disease is justifiably based on observations from clinical studies. However, the best characterized and most extensively studied population does not necessarily coincide with the most highly susceptible population. Since the last review, there are additional studies with positive findings that assess effects on the fetuses. There is also strong toxicological evidence relevant to the association of prenatal CO exposure with adverse pregnancy outcomes, such as premature birth and low birth weight. A stronger commentary on exposure during pregnancy and reproductive outcomes is needed.

b. Does the document appropriately characterize the results of the draft REA, including their significance from a public health perspective?

The conclusion that the current evidence supports a primary focus on individuals with cardiovascular disease is justified by current clinical research. Discussion should be added, however, that the best characterized and most extensively studied population does not necessarily identify the most highly susceptible population. In particular, commentary on the fetus as an at-risk group should be added because of newer data describing the effects of CO on the fetus coupled with toxicological evidence for risks associated with prenatal CO exposure.

If the PA is going to use %COHb as the dose metric, then there has to be a better rationale provided for interpretation of the epidemiological data using this metric.

7. *What are the views of the Panel regarding the staff's discussion of considerations related to the adequacy of the current and potential alternative standards?*

The staff has provided an extensive analysis of the adequacy of the current and potential alternative primary CO standards. The current standards set the levels for 1-hr average and 8-hr average at 35 ppm and 9 ppm, respectively. The form of the standard is that those levels are not to be exceeded more than once per year. In reviewing the recent literature, staff has documented that the "much expanded epidemiological evidence … provides support for previous conclusions regarding cardiovascular disease-related susceptibility and indications of air quality conditions that may be associated with ambient CO-related risk" and concluded that a causal relationship is likely to exist between relevant short term exposures to CO and cardiovascular morbidity.

Staff also concludes that the currently available evidence provides limited but suggestive epidemiologic evidence for CO-induced effects on preterm births, birth defects, and developmental outcomes. Individuals with conditions limiting their ability to deliver oxygen to target tissues represent groups susceptible to the adverse effects of CO, in addition to those with coronary artery disease. Based on the analyses of epidemiological studies presented in the PA, there is consensus in the Panel that the current standards may not protect public health with an adequate margin of safety, and therefore revisions that result in lowering the standards should be considered.

While the epidemiologic studies provide evidence that is coherent with the controlled exposure studies, the Staff determined that four of the studies cited in Table 2.1 included years in which

the ambient CO concentrations exceeded the 8-hr standard. However, Table 2.1 includes three studies of hospitalizations for ischemic heart disease and/or congestive heart failure from Atlanta for which this was not the case (Tolbert 2007, Peel 2007, Metzger 2007). An additional study of CHF (Wellenius, 2005) also did not include data from years in which either the 1-hr or the 8-hr standards were exceeded.

The PA suggests that CHF could have multiple causes, and for that reason it would be problematic to use it as a health effect indicator. The three studies of ischemic heart disease were consistent, but only the Tolbert et al. study had clear statistically significant results. It should be recognized that new controlled exposure studies of some of the sensitive groups (e.g., infants, fetuses, individuals with CHF or MI's) would be nearly impossible to justify ethically. Therefore more reliance needs to be placed on the epidemiologic studies and assessing whether there are causal relationships. Pooling methods, such as quantitative meta-analyses, may also be useful for developing exposure-response relationships. The available studies cover periods during which the current NAAQS was exceeded as well as studies covering lower ranges. This coverage of a wide range of CO concentrations makes possible a relatively robust estimation of exposure-response relationships. The emphasis should be on studies that used a multipollutant model approach to control for potential confounding of CO effects by those of other co-varying pollutants.

While there have been no new controlled human exposures designed to examine effects of CO at COHb levels below 2%, there have been numerous improvements to the exposure and COHb dosimetry models employed to provide exposure and risk estimates. The Staff analysis indicates that some of the uncertainties identified in previous reviews of the standard have been reduced. Based on their overall analysis, they conclude that the body of evidence and the quantitative exposure and dose estimates provide support for a standard at least as protective as the current standards. I.e. the data provide support for retaining or revising the current 8-hr standard.

Overall the Panel agrees with this conclusion. If the epidemiological evidence is given additional weight, the conclusion could be drawn that health effects are occurring at levels below the current standard, which would support the tightening of the current standard. The PA should include an analysis the number of exceedances that would have occurred if the standard had been based on the epidemiological data.

8. *Staff believes that the evidence presented in the final ISA and the exposure and risk information presented in the second draft REA supports a range of policy options for the CO standards.*

The Staff have proposed a range of policy options based on the quantitative risk analyses performed. As a starting point, the Staff indicates that the evidence is consistent with maintaining standards that are at least as protective as the current levels. However, given new evidence, primarily epidemiological, that there are many individuals potentially at risk in addition to those with coronary artery disease (e.g., fetuses, pregnant women, people with congestive heart disease, and people with anemia of various types), there is reason to consider reducing the standard below the current level(s).

The Panel suggests describing example policy options such as:

- 8 hr – retain the 8-hr averaging time with consideration given to levels within the range of 3 to 6 ppm, with no more than a single exceedance or revise the form of the standard to 99th percentile with a concentration range of 3-5 ppm. See also Figure 1 which shows the linear relationship between the 99th percentile and the design value measured for epidemiologic studies summarized in PA Table 2-1.
- 1 hr – retain the current standard to provide protection against infrequent acute exposures. Consider a range of concentrations from 5 ppm to 15 ppm, combined with a 99th percentile or fourth-highest daily maximum. The panel does not concur with revoking the 1 hr standard.

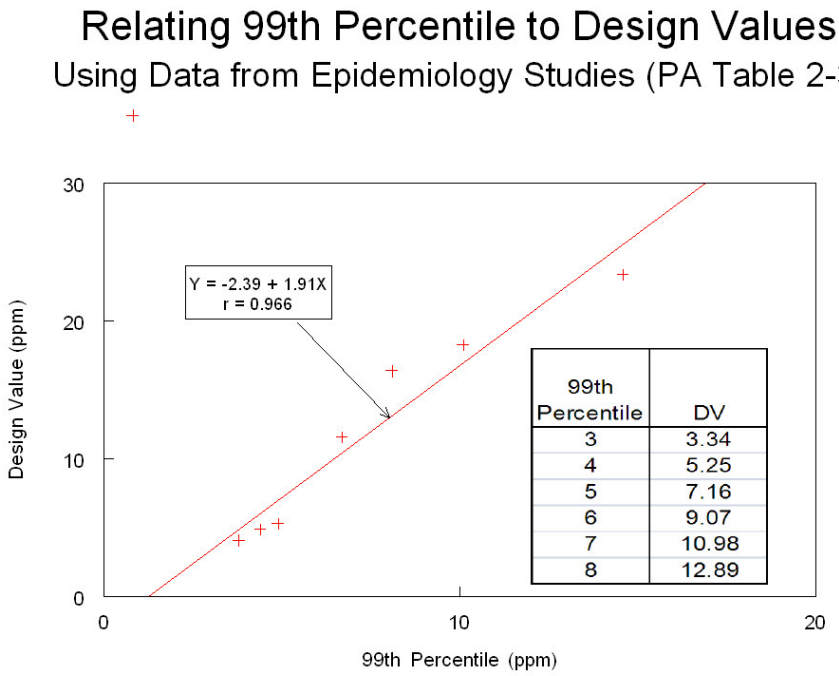

Figure 1

a. *To what extent does the document provide sufficient rationale to justify this range of options?*

The risk models were based on effects in people with coronary artery disease. They were used to estimate the percentages of individuals in LA and Denver that would reach benchmark levels of COHb ranging from <1.5% COHb to <2% COHb. These were summarized in Tables 2-6 and 2-7 in the PA. The overall guidance for the policy was not clearly described and the wide range of options needs better definition. It might be useful to present a table of options with the pros and cons of each respectively. The information is embedded in the RA and PA documents, but the options and their respective advantages or disadvantages need to be more clearly summarized.

The Panel concurs with the staff that the 1-hr standard might provide protection independent of the type of protection provided by the 8-hr standard (page 2-54, line 14); however, the discussion supporting this statement should be more clearly documented.

b. Does the Panel have any recommendations regarding additional considerations which should inform characterization of these options for both the 8-hour and 1-hour standards?

In choosing a more stable form of the standard, such as the 99th percentile, which would allow more days on which the standard can be exceeded in a given year, the level of the standard must be reduced to insure that the degree of health protection is sufficient. EPA should consider conducting an evaluation of the representativeness of the risk analysis to the entire US. Currently, the PA is based on two very different cities. Spatial heterogeneity of CO exposures that increase exposures near major sources, i.e. near and on roadways, should be given more weight since these might drive some of the adverse health effects.

9. What are the Panel's views regarding the level of detail presented in this chapter?

The PA concludes that there is insufficient information at this time to support the consideration of a secondary standard for CO. In general, the level of discussion detail is appropriate; however, some additional detail could be added at the end of chapter 3 on what information is missing in order to make a determination regarding a secondary standard.

10. The discussion of the CO-related welfare effects draws from the most recent information contained in the final ISA for CO.

a. Does the draft PA accurately reflect the currently available evidence as characterized in the final ISA?

The Panel agrees that the Policy Assessment appropriately characterizes the evidence as presented in the ISA.

b. Does this discussion effectively summarize the information on climate-related effects of CO?

Yes, but there should be a clear statement, to match a similar assertion in the ISA, that there is some evidence that CO has effects on climate. It addition, it would be appropriate in the last paragraph of this chapter to summarize what information is missing and thus needed, such as more accurate U.S. and global emissions inventory, monitoring specifically for climate rather than just for standards and exposure, and improvements in localized chemical reactions between CO, CH_4, and O_3 within global models.

11. What are the Panel's views regarding the appropriateness of staff's initial conclusions related to considering a secondary standard for CO?

The PA concludes that there is insufficient information at this time to support consideration of a secondary NAAQS. Nonetheless, there is substantial evidence that CO has adverse effects on climate. It would be appropriate in the last paragraph of this chapter to summarize what information is missing.

Enclosure C

Review Comments from CASAC CO Panel Members on the *Policy Assessment for the Review of the Carbon Monoxide National Ambient Air Quality Standards: External Review Draft*

Dr. Paul Blanc

4. The discussion of the quantitative analysis of exposure and dose (e.g., section 2.2.2) draws from the analyses described in the second draft Risk and Exposure Assessment (REA).
a. Does this discussion accurately reflect the analyses contained in the draft REA?
b. Does the Panel find the presentation to be technically sound, clearly communicated and appropriately balanced?

The Policy Assessment perpetuates and to a degree magnifies the fundamental misunderstanding of the REA in relation to susceptibility based to narrowly on CAD alone (i.e., past MI or angina) rather than on cardiovascular disease as a group. In both cases this is a misread of the ISA and marks a failure to grasp what the accumulated epidemiological evidence shows. Thus this presentation is unbalanced, in interpreting the ISA through the flawed "lens" of the REA.

6. This document has integrated health evidence from the final ISA and risk and exposure information from the second draft REA as it relates to reaching conclusions about the adequacy of the current standard and potential alternative standards for consideration.
a. Does the Panel view this integration to be technically sound, clearly communicated, and appropriately characterized?
b. Does the document appropriately characterize the results of the draft REA, including their significance from a public health perspective

It is very difficult to decipher the conclusions of Policy Assessment beyond an unequivocal position that what ever is done the current standards should not be *weakened*. I would characterize the conclusion as clearly communicating a sense of not wishing to communicate something definitive, at this point at least. The rationale for not considering how many at risk persons are pushed over a threshold of body burden of COHb because they have baseline exposures form non-ambient sources seems ill-judged and counter-intuitive in terms of public health protection. Perhaps there are parallels in considerations of ambient lead exposure limits?

Dr. Thomas Dahms

Charge Question 2. Consistent with the revised NAAQS process which includes development of this draft Policy Assessment (PA) document, considerations with regard to the primary standard for CO have been organized around a set of policy-relevant questions for the review.

a. Does the Panel find the question posed to appropriately reflect the policy relevant questions in the review?

I believe that the questions posed raise the major issues and the information provided in response to these questions provides the essential data required for making policy decisions. These questions regarding 1. the adequacy of protection by the current standards; 2.does new information alter previous conclusions regarding health effects; 3. should COHb continue to be the dose indicator for CO exposure; 4. the health effects of ambient CO levels; and 5. any reduction in the uncertainties regarding CO.

Regarding the adequacy of protection: it is difficult to make a judgement in this area for two reasons.

1. There is no definition presented of what is considered to be an acceptable risk and 2. The number of persons in the at risk groups exposed to criteria levels of CO is not defined for the country. The only description of numbers exposed is for two cities: Los Angeles and Denver with no guidance provided for extrapolation to the whole country. For example, if the document is to discuss the numbers of persons in the U.S. with CAD, then the reader needs to have some estimate of how many of these persons would reach criteria levels of COHb on an annual basis given the current standards. Therefore it is difficult to judge the effectiveness of the current standards in protecting the population

2. The new information in this area all comes from epidemiological studies that are crucial to the interpretation of the meaning of the controlled human exposures. The adverse health effect of limiting the amount of work a person with CAD can perform with doses of CO near the current standard has been clearly established. However it is not clear that the extent of limitation has any further impact on the health of this at risk group. This concern is implied in the discussion regarding the uncertainty about the significance of ST segment changes on page 2-32. The epidemiological studies are designed to provide one means of determine if low CO doses have measureable impacts on health by correlating CO exposure with hospital based treatment for CV related events. This link between the two types of studies is clear in my mind but I'm not sure that the connection is clearly stated in this document.

3. Carbon monoxide is unique among the regulated air pollutants because it has a clear marker of dose, %COHb. The document indicates that the well established effects of COHb are related to the reduction in oxygen delivery to the tissues. This is in the face of the immerging evidence of effects of the partial pressure of CO, P_{CO}, as a messenger molecule, which could result in various patho-physiological conditions in combination with CO exposure. What is missing from the REA and carried through to the PA is a brief description of the relationship between P_{CO} and %COHb. This could possibly provide some prospective for the reader as to the importance of the physiological tensions of carbon monoxide in

tissues of interest. This would not distract from the current understanding that the dose indicator of %COHb is currently the primary focus for policy assessment.

4. The decreasing ambient levels of CO in the United States makes it ever more difficult to demonstrate health effects of CO based on the concept of sufficient exogenous dose to result in %COHb levels that have been shown to have pathophysiological effects. It would appear that the epidemiological effects of CO occur at such low levels of exposure as to result in very little increases in %COHb. Accepting the premise that the epidemiological results attributed primarily to CO exposure implies that adverse health effects occur at levels of %COHb considerably below those shown to have statistically significant effects in controlled human exposures. For these effects to be consistent with the controlled human exposure data, one would have to accept the statement that the effects of CO are without threshold (page2-11, Line 9; 2-12, L4; 2-15, L24; 2-16, L26; 2-40, L2). Are we to assume that the reason that the epidemiological studies can show significant effects of very low levels of exposure (very small increases in %COHb) is due to the large number of subjects being studied. Or is there another hypothesis regarding how these effects are mediated?

5. The uncertainties related to CO exposure have not been lessened.

b. Does the Panel consider the document to provide the appropriate level of detail in addressing these policy-relevant questions?

Yes but brief verbiage linking concepts as noted above would be helpful in creating transitions between the types of information.

Charge question 3. The discussion of the health effects evidence (e.g., section 2.2.1) draws from the most recent information contained in the final ISA for CO and information from the previous review described in previous Air Quality Criteria Documents.

a. Does the draft PA accurately reflect the currently available health effects evidence for CO as characterized in the final ISA and the extent to which it differs from that available at the time of the last review?

b. Does the Pane find the presentation to be technically sound, clearly communicated and appropriately balanced?

The description of the current state of knowledge includes suggestive information regarding cellular processes that can result in regional increases in endogenous levels of CO that could be altered by exogenous exposure. Given the considerable amount of current research in this area, mention of this data should exist in this document. The last review of CO was halted for several years due to the pending study and report on the effects of CO at altitude and at extreme cold environments. The document should very briefly acknowledge the findings of this report. Without that information in the current document it is difficult to determine how this report should differ from the last review started in 1999.

Charge Question 4. The discussion of the quantitative analysis of exposure and dose (e.g.,section 2.2.2) draws from the analyses described n the second draft Risk and exposure Assessment (REA).

a. Does this discussion accurately reflect the analyses contained in the draft REA?

The discussion focuses on the detail of one multicenter study following brief mention of the supporting studies. I believe that this information could be strengthened by working in the information that the CO exposures in the other studies was very similar with confirming evidence regarding time to angina. This would address the current concern of imbalance in the discussion of the studies in this area.

b. Does the panel find the presentation to be technically sound, clearly communicated and appropriately balanced?

There are some concerns regarding the technical soundness of the descriptions given which do make physiological sense.

i. Inaccuracy: page 2-8, line 26. The statement "This binding to reduced iron…" is very misleading. It has been transferred from the REA description of CO binding to hemoglobin. In particular it comes from the mathematical fiddle noted in Appendix B of the REA on page B-5 which states: "In working with the CFK model it is convenient to express COHb as a percent of $[RHb]_0$." This false concept should not be repeated in the text of the document. The fundamental relationship as described by Haldane clearly indicates that the much higher affinity of hemoglobin for CO vs Oxygen results in CO displacing O2 from oxygenated hemoglobin. The implication that CO binds preferentially to only reduced Hb is incorrect and needs to be corrected.

ii. Page 2-9, line 1. The statement "…or increased cardiac output) is not clear. The preceding sentence is discussing cardiovascular disease in the context of CAD. Therefore the normal compensatory mechanism that exist in healthy individuals is increased myocardial blood flow through vasodilatation, not vasodilatation and increased cardiac output. The current verbiage does not make sense and needs to be changed.

Charge Question 5. Does the document identify and appropriately characterize the important uncertainties associated with the evidence and quantitative analysis of CO exposure and dose, particularly those of particular significance in drawing conclusions as to the adequacy of the current CO standards?

Generally the uncertainties are dealt with appropriately with the exception of the item mentioned below.

The current review on page 2-32 under the guise of evaluating the uncertainty regarding ST segment changes suggests that the uncertainty is now greater than it was in 1991. The policy assessment is based on the adverse health effects of 2% COHb resulting in reducing the amount of work a person with CAD can perform before chest pain develops with is due to myocardial ischemia. The Allred et al study used EKG changes in the ST segment to substantiate that the

subject measure of angina was indeed due to ischemia. These two indicators, one subjective and one objective, were very highly correlated and not independent. Therefore the separation of the two indicators (page 2-32, line 25-28) is a reflection of the reviewers not understanding the study design. (This should have been corrected throughout the ISA, REA and the PA. The statement attributed to the ISA, p.48 –assumed to be 5-48—on page 2-32 needs to have a line reference otherwise it is difficult to locate this conclusion in the ISA.) In fact the ever increasing amount of epidemiological data on the effects of CO probably reduces the uncertainty of the effects of CO exposure in individuals with cardiovascular disease.

Exposure/Risk-based Considerations

Page 2-40 lines 3-10. The rationale for not using the benchmark of 1% COHb is flawed. In the version of the ISA dated January 2010, I cannot find a reference to the range of endogenous levels of %COHb: the source needs to be better documented. There is a list of rates of endogenous product provided in the Appendix but there are multiple studies listed. If one of these studies is the source it should be identified. The rationale for requesting the inclusion of this benchmark was the sense that 'the effects of CO are without threshold (page2-11, Line 9; 2-12, L4; 2-15, L24; 2-16, L26; 2-40, L2).' The %COHb data that is being used is that of Allred et al cited on page 2-11, line 1 as showing %COHb levels for exposure to 0-2 ppm CO as being 0.6%. The benchmark of 1% does not appreciably overlap 0.6% any more than one would expect there to be overlap between 1.5% and 2.0%. What is not stated is that the Apex model may overestimate the range of values resulting from no exposure to exogenous CO.

Without the 1% COHb benchmark how are the epidemiologic studies to be interpreted? Are these effects due to the effects of a pollutant that is not measured but very highly correlated to atmospheric CO? If the Policy Assessment is going to use %COHb as the dose metric, then there has to be a rationale provided for interpretation of the epidemiological data using this metric. If the result is a very high number of individuals with CAD having doses of 1%COHb and very few appearing in the ER or being admitted, this point should be discussed.

Dr. Russell Dickerson

The Policy Assessment in Chapter 3 addresses the issue of a secondary standard.

9. What are the Panel's views regarding the level of detail?

The detail is a little light as indicated below.

10. a. *Does the draft PA accurately reflect the currently available evidence?*

Within the limits of what is written yes.

b. *Does this discussion effectively summarize the information on climate related effects of CO?*

See below.

11. What are the Panel's views regarding the appropriateness of the initial conclusions?

The PA concludes that there is insufficient information at this time to support the consideration of a secondary NAAQS. None-the-less, there is evidence that CO has adverse effects on climate. It would be appropriate in the last paragraph of this chapter to summarize what information is missing. For example, U.S. and global emissions inventories must achieve a certain level of accuracy before a secondary standard is established. Is the level of uncertainty sufficient and if not what would it take? Monitoring was being phased out – should this policy be reconsidered? Representative monitoring to evaluate emissions inventories or models may look different from monitoring to access exposure. The basic question of what form is needed for regulations or standards should be addressed. A concentration-based standard would probably be inappropriate. Emissions standards such as are being considered for CO_2 would be more applicable to the issue of how to control CO emissions. The ISA (Figure 3.8) shows nicely how CO is low hanging fruit with respect to short term (20-year) climate forcing. The PA may be an appropriate forum to provide guidance to how these environmental benefits may be realized.

Dr. Milan Hazucha

The first external draft of the document provides a comprehensive overview of the legislative requirements and approaches to policy decision making process. The draft presents in a succinct way all aspects of the scientific evidence required for a successful policy assessment. The staff has reviewed and discusses key scientific and technical knowledge with clear understanding of health effects associated with CO presence in the ambient air. Various related issues are presented in sufficient detail and clearly communicated.
Asking specific questions throughout the document and answering them in a succinct manner has been very helpful in focusing on the critical aspect of the policy setting.
Answers to charge questions and specific comments:
Introduction and Background for the Policy Assessment (Chapter 1)

1. Does the Panel find the introductory and background material, including that pertaining to previous reviews of the CO standard, the current review and current air quality, to be clearly communicated and appropriately characterized?

I find the introductory and background material pertaining to the previous and current reviews to be clearly communicated and appropriately characterized. All the important factors needed to make an informed judgment are adequately presented and briefly discussed.

Review of the Primary Standard (Chapter 2)

2. Consistent with the revised NAAQS process which includes development of this draft Policy Assessment (PA) document, considerations with regard to the primary standard for CO have been organized around a set of policy-relevant questions for the review.

a. Does the Panel find the questions posed to appropriately reflect the policy-relevant questions in this review?

Qualified yes in all respects. One question that was not posed is about the confounding effects of no-traffic sources of CO, e.g., indoor air. Numerous studies have shown that we spend~80% of time indoors. For healthy elderly and people with CVD the time spend indoors may be even longer. The non-traffic sources of CO are at times substantial and will override the ambient CO levels.

b. Does the Panel consider the document to provide the appropriate level of detail in addressing these policy-relevant questions?

Yes, in all respects. The PA is well written, providing sufficient details, and highlighting important factors/concerns so that the policy relevant questions can be addressed both quantitatively and qualitatively.

3. The discussion of the health effects evidence (e.g., section 2.2.1) draws from the most recent information contained in the final ISA for CO and information from the previous review described in previous Air Quality Criteria Documents.

a. Does the draft PA accurately reflect the currently available health effects evidence for CO as characterized in the final ISA and the extent to which it differs from that available at the time of the last review?

Yes, in all respects. The currently available scientific evidence is evaluated, characterized and presented in a sufficient detail supporting the adequacy of the protection afforded by the current CO standard. The differences with the last review are clearly presented. There are no new human laboratory studies or exposure/risk-based evidence that would alter the conclusions. The evidence from new epidemiologic studies has been presented in a balanced way. The PA correctly points out to limitations in integrating the evidence from laboratory and epidemiologic studies.

Based on the current scientific evidence and practical considerations (e.g. arterial blood draw) venous blood COHb level is the optimal indicator of "CO health."

b. Does the Panel find the presentation to be technically sound, clearly communicated, and appropriately balanced?

Qualified yes. In order to facilitate better understanding of the cardiovascular effects, particularly myocardial ischemia, I suggest to add to the reported values of % time changes to angina on p.2-11, top paragraph, the actual changes in seconds with the confidence intervals (CI) included as well. For example, the reported 4.2% shorter time to angina from a control ~ 9 min interval amounts to 22 sec, with the CI=8.7%. Since Allred et al. studies are considered the key studies, it would be very helpful to comment briefly on the clinical significance of the shortened time. Moreover, regarding time to angina endpoint, are there any long-term consequences on repeated exposures, on the duration of angina, and frequency of occurrence without CO exposure? EPA should address these questions and if we do not have respective data the PA should state so.
Moreover, the first part of the statement in footnote #12 (p. 2-12) commenting on the difficulty determining association of CO with CVD and as a marker for traffic-related pollutants should, because of its importance, be moved from the footnote to the body of respective paragraph. Recently published HEI Special Report #17 (Jan. 2010) entitled:"Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects" discusses CO as a marker for another traffic-related pollutants such as PM and NO_2 and not as a major health hazard.
The review of the epidemiologic evidence (p.2-14) accurately reflects the difficulties to establish causal relationship between CO and reported effects. Similarly, well reasoned section (p. 2-25) points to difficulties integrating laboratory/clinical findings and epidemiologic observations.

4. The discussion of the quantitative analysis of exposure and dose (e.g., section 2.2.2) draws from the analyses described in the second draft Risk and Exposure Assessment (REA).

a. Does this discussion accurately reflect the analyses contained in the draft REA?

Qualified yes. The COHb module of the APEX model though the most important is also the weakest, since we do not have sufficient physiologic data or the range of values for many variables that enter into the model. However, despite this limitation there seems to be sufficient information for some variables that can be used to tune the estimates, e.g. Hb concentration for whites and blacks.

As far 1% COHb benchmark suggested by the Panel, the staff correctly pointed out that "this level overlaps with the upper part of the range of endogenous levels" and decided not to focus on dose estimates (p.2-40). I support this approach since this complies with the EPA's task "to establish standards that are neither more nor less stringent than necessary for these purposes", .i.e. public health.

b. Does the Panel find the presentation to be technically sound, clearly communicated and appropriately balanced?

Yes, in all respects. Again, because of the importance of the statement, the first sentence of the footnote #25 on the difficulty to determine association between CO and CVD in interpreting epidemiological evidence should be moved to the body of a respective paragraph.

5. Does the document identify and appropriately characterize the important uncertainties associated with the evidence and quantitative analysis of CO exposure and dose, particularly those of particular significance in drawing conclusions as to the adequacy of the current CO standards?

Yes, in all respects; The key uncertainties associated with exposure and dose estimates should, besides traffic, list other sources of CO, such as indoor air, smoking, occupational exposures, to name the main ones (p.2-42, l.31). A succinct discussion of how these sources can override the protection afforded by the current CO standard would be helpful.

6. This document has integrated health evidence from the final ISA and risk and exposure information from the second draft REA as it relates to reaching conclusions about the adequacy of the current standard and potential alternative standards for consideration.

a. Does the Panel view this integration to be technically sound, clearly communicated, and appropriately characterized?

Yes, in all respects

b. Does the document appropriately characterize the results of the draft REA, including their significance from a public health perspective?

Yes, in all respects

7. What are the views of the Panel regarding the staff's discussion of considerations related to the adequacy of the current and potential alternative standards?

I find the initial staff conclusion "for either retaining or revising the current 8-hour standard" (p. 2-46) based on the available estimates of exposure ambivalent. Does this mean that EPA is undecided or that the evidence is split 50/50? It is true, as subsequently stated, that a variety of factors will be considered in judging the adequacy of the current standard. But such adequacy should be based primarily on the evidence from laboratory/clinical studies and not on policy and other considerations. The evidence from the epidemiology studies, as commented on in several previous sections of this document, is difficult to evaluate and integrate with clinical evidence (p. 2-25).
The CO concentrations reported in epidemiology studies will produce COHb levels within a normal range. From reading interpretation of these studies in the latest EPA PM ISA the dominant effects in these studies are due to PM. Since we do not have any measurements of COHb level or other adverse effects that can be specifically associated with CO the studies provide no proof beyond statistics that there is a causal relationship. CO is primarily known for its anti-inflammatory effects. However, CO is highly correlated with PM and other pollutants, therefore, it is very likely that CO acts as a surrogate for PM and other pollutants. Thus based strictly on scientific evidence, I agree with the staff interpretation of epidemiology studies and their leaning towards retaining the current 8-hour standard.
The section 2.3 of the discussion of the averaging time, the form and level of alternative standard and potential alternative levels is succinct and well reasoned. What is not clear what form might the alternative standard have?

8. Staff believes that the evidence presented in the final ISA and the exposure and risk information presented in the second draft REA supports a range of policy options for the CO standards.

a. To what extent does the document provide sufficient rationale to justify this range of options?

Yes, the staff provides sufficient rationale for discussion of the range of options, particularly the policy options.

b. Does the Panel have any recommendations regarding additional considerations which should inform characterization of these options for both the 8-hour and 1-hour standards?

There should be a greater emphasis on the evidence based on laboratory/clinical studies.

<u>Consideration of a Secondary Standard (Chapter 3)</u>

9. What are the Panel's views regarding the level of detail presented in this chapter?

The level of detail presented in this chapter is sufficient.

10. The discussion of the CO-related welfare effects draws from the most recent information contained in the final ISA for CO.

a. Does the draft PA accurately reflect the currently available evidence as characterized in the final ISA?

Yes, in all respects

b. Does this discussion effectively summarize the information on climate-related effects of CO?

Yes, in all respects

11. What are the Panel's views regarding the appropriateness of staff's initial conclusions related to considering a secondary standard for CO?

Fully agree with staff conclusions.

Dr. Michael Kleinman

7. What are the views of the Panel regarding the staff's discussion of considerations related to the adequacy of the current and potential alternative standards?

The staff has provided an extensive analysis of the adequacy of the current and potential alternative primary CO standards. The current standards include a 1-hr average and an 8-hr average standard of 35 ppm and 9 ppm, respectively. The form of the standard is that those levels are not to be exceeded more than once per year. In reviewing the recent literature staff has documented that the "much expanded epidemiological evidence … provides support for previous conclusions regarding cardiovascular disease –related susceptibility and indications of air quality conditions that may be associated with ambient CO-related risk" and concluded that a causal relationship is likely to exist between relevant short term exposures to CO and cardiovascular morbidity. Staff also conclude that the currently available evidence provides limited but suggestive epidemiologic evidence for CO-induced effects on pre-term births, birth defects, developmental outcomes and that individuals with conditions limiting their ability to deliver oxygen to target tissues represent groups susceptible to the adverse effects of CO, in addition to those with coronary artery disease. Based on the analyses of epidemiological studies presented in the PA there is a consensus in the panel that the current standards may not adequately protect public health with a reasonable margin of safety and therefore revisions that result in reducing the standards should be considered.

While the epidemiologic studies provide evidence of coherence with the controlled exposure studies, the Staff determined that four of the studies cited in Table 2.1 included years in which the ambient CO concentrations exceeded the 8 hr standard. However Table 2.1 includes 3 studies of hospitalizations for ischemic heart disease and/or congestive heart failure (CGF) from Atlanta for which this was not the case (Tolbert 2007, Peel 2007, Metzger 2007) and one additional study of CGF (Wellenius, 2005) which did not include data from years in which the either the 1 hr or the 8 hr standards were exceeded. The PA suggests that CHF could have multiple causes and for that reason it would be problematic to use as a health effect indicator. The 3 IHD studies were consistent but only the Tolbert study had clearly statistically significant results. It should be recognized new controlled exposure studies of some of the sensitive groups (e.g. infants, fetuses, individuals with CHF or MI's) would be nearly impossible to justify ethically. Therefore more reliance needs to be placed on the epidemiologic studies and uncovering causal relationships may require methods such as meta-analyses to develop exposure-response curves. For this purpose the fact that some studies included periods in which the current standard was exceeded becomes less important because there are also studies at lower levels so that CR relationships can be interpolated (as opposed to extrapolated). The emphasis should be on studies that used a multipollutant model approach to control for potential confounding of CO effects by other co-varying pollutants.

While there have been no new controlled human exposures that were designed to examine effects of CO at COHb levels below 2%, there have been numerous improvements to the exposure and COHb dosimetry models employed to provide exposure and risk estimates. The Staff analysis

indicates that some of the uncertainties identified in previous reviews of the standard have been reduced and that based on their overall analysis conclude that the body of evidence and the quantitative exposure and dose estimates provide support for a standard at least as protective as the current standards, i.e. the data provide support for retaining or revising the current 8-hr standard. Overall the panel agrees with this conclusion, at the bare minimum. If the epidemiological evidence is given additional weight, than one might conclude that health effects are accruing at levels below the current standard and therefore the evidence might be leaning in the direction of revising the current standard. An issue is that some of the epidemiological studies were under conditions in which the current standard was exceeded at least in some part. More complete details of the degree to which the standard was exceeded should be summarized in the PA document, i.e. some studies covered as many as 7 years; would it have been excluded for as little as 1 exceedence in 7 years?

8. Staff believes that the evidence presented in the final ISA and the exposure and risk information presented in the second draft REA supports a range of policy options for the CO standards.

The Staff have proposed a range of policy options based on the quantitative risk analysis performed. As a starting point the Staff indicates that the evidence is consistent with maintaining standards that are at least as protective as the current levels. However, given the new evidence, primarily epidemiologic, that there are many individuals potentially at risk in addition to those with coronary artery disease (e.g. fetuses, pregnant women, people with congestive heart disease, people with anemia of various types) there is reason to consider reducing the standard below the current level(s).

The panel suggests example policy options such as:

8 hr – retain the 8h r averaging time with consideration given to levels within the range of 3 to 6 ppm, with no more than 1 exceedance or revise the form of the standard to 99th percentile with a concentration range of 3-5. Note see Figure 1 which shows the linear relationship between the 99th percentile and the design value measured for epidemiologic studies summarized in PA Table 2-1 that showed significant IHD hospitalizations.

1 hr – retain the current standard to provide protection against infrequent acute exposures. Consider a range of concentrations from 5 ppm to 15 ppm, combined with a 99th percentile or fourth-highest daily maximum. The panel does not concur with revoking the 1 hr standard..

a. To what extent does the document provide sufficient rationale to justify this range of options?

The risk models were based on coronary artery disease effects and were used to estimate the percents of individuals in LA and Denver that would reach benchmark levels of COHb ranging from <1.5% COHb to <2% COHb. These were summarized in Tables 2-6 and 2-7 in the PA document. The overall guidance for the policy was not very clearly described and the wide range of options needs better definition. It might be useful to present the options in a table with the pros and cons laid out. The information is embedded in the RA and PA documents but the options and their respective advantages or disadvantages need to be more clearly summarized.

The panel concurs with the staff that the 1 hr standard might provide protection independent of the type of protection provided by the 8 hr standard (2-54; L 14), however the discussion supporting this statement should be more clearly documented.

b. Does the Panel have any recommendations regarding additional considerations which should inform characterization of these options for both the 8-hour and 1-hour standards?

i. In choosing a more stable form of the standard, such as the 99th percentile, which would allow more days on which the standard can be exceeded in a given year, the level of the standard must be reduced to insure that the degree of health protection is sufficient.

ii. A summary of the options and their pros or cons would be more helpful.

iii. An evaluation of how representative the risk analysis which is based on 2 very different cities is with regard to the entire US.

i. Spatial heterogeneity of CO exposures that increase exposures near major sources i.e. near and on roadways should be given some weight since these might drive a lot of the adverse health effects.

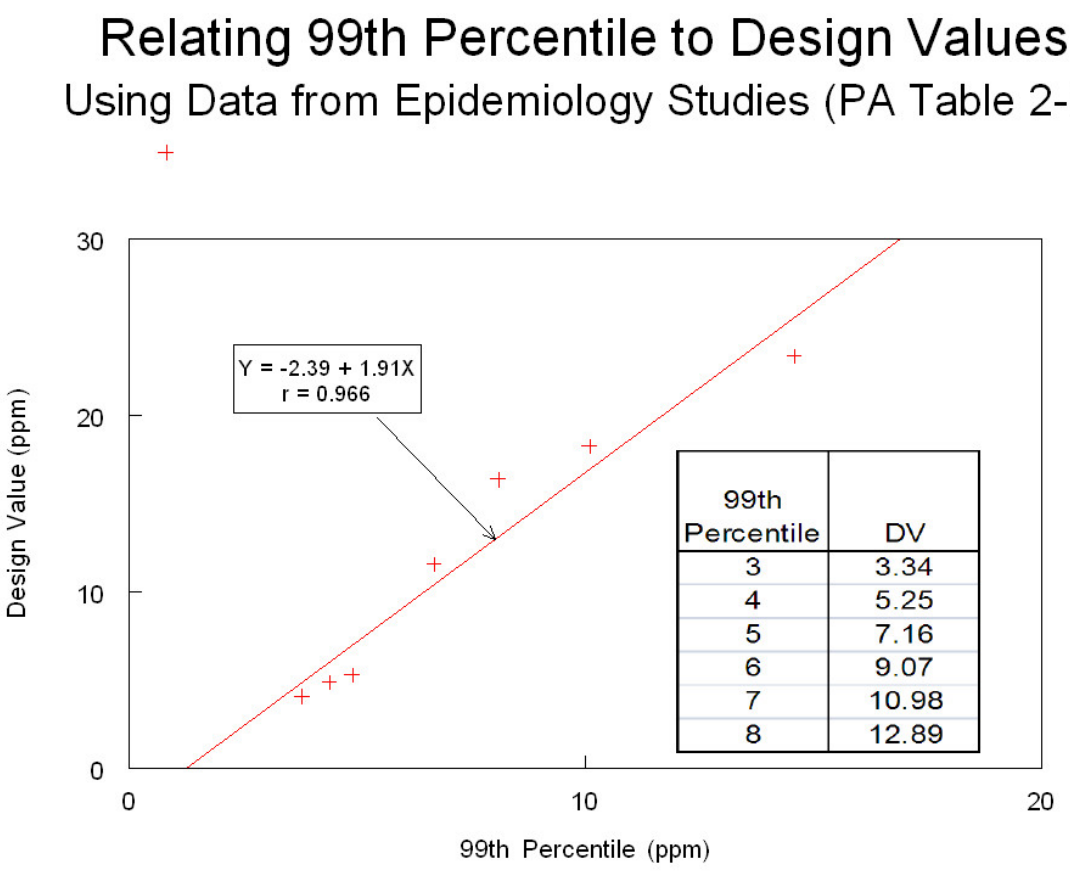

Figure 1

Dr. Francine Laden

2. Consistent with the revised NAAQS process which includes development of this draft Policy Assessment (PA) document, considerations with regard to the primary standard for CO have been organized around a set of policy-relevant questions for the review.
a. Does the Panel find the questions posed to appropriately reflect the policy relevant questions in this review?

Yes – the questions appropriately reflect the policy relevant questions.

b. Does the Panel consider the document to provide the appropriate level of detail in addressing these policy-relevant questions?

Yes – the level of detail is appropriate.

3. The discussion of the health effects evidence (e.g., section 2.2.1) draws from the most recent information contained in the final ISA for CO and information from the previous review described in previous Air Quality Criteria Documents.
a. Does the draft PA accurately reflect the currently available health effects evidence for CO as characterized in the final ISA and the extent to which it differs from that available at the time of the last review?

Yes – the draft PA accurately reflects the currently available health effects evidence for CO. One minor point: On page 2-9, it is stated that "it was concluded that there is not likely to be a causal relationship between relevant long-term CO exposures and mortality." Is EPA confident of this conclusion, or is there not sufficient data to address this relationship?

b. Does the Panel find the presentation to be technically sound, clearly communicated, and appropriately balanced?

Yes – the presentation is technically sound, clearly communicated and appropriately balanced.

Dr. Arthur Penn

1. Does the Panel find the introductory and background material, including that pertaining to previous reviews of the CO standard, the current review and current air quality, to be clearly communicated and appropriately characterized?

Chapter 1 of the PA does a good job, in a limited # of pages, of providing intro/background for the PA. There is a brief review of the CAA and establishment of NAAQS (1^o, 2^o); adequate margins of safety; previous reviews; CO sources in ambient air; the monitoring network; low dose levels; new monitors/NCore network; recent ambient and steady-state decreases in ambient CO; and finally, the "staff's evaluation of policy implications of scientific evidence in the ISA and results of quantitative analyses based on that evidence".

There is one item on p. 1-1 that could benefit from some clarification and possible change of location. Lines 22-25 on that page emphasize that the focus of the PA is on the 4 basic elements of NAAQS: indicator, averaging time, form and level. None of these items is explicitly defined in the first 46 pages of the PA. "Indicator" & "averaging time" both on p. 2-47 are clearly defined. "Level" is not defined explicitly, but its meaning is implicit in Tables 2-6 & 2-7. "Form" (pp. 2-48 & 2-49) is never defined clearly. "Concentration-based form", apparently an area of focus, also is not defined. Lines 15-23 on p. 2-49 suggest that "form" = percentile. Is that correct? Is it ever anything else? If it = percentile, why not say so?

If everything in the PA is based on these 4 elements, perhaps they should be defined on p.1.

5. Does the document identify and appropriately characterize the important uncertainties associated with the evidence and quantitative analysis of CO exposure and dose, particularly those of particular significance in drawing conclusions as to the adequacy of the current CO standards?

2 major uncertainties are listed on pp. 2-26 &2-27. 3 others are listed on pp. 2-4 & 2-5; + 5 on p. 2-53.

There are a couple of other conclusions of the PA that have raised questions for me. Whether they rise to the level of uncertainty depends on how other CASAC CO panelists respond.
p.2-18: The most thorough clinical studies remain those of Allred-Kleinman-Sheps. While the effects in these similar subject groups are clear, and together these subjects may be "the best characterized population" it is not clear that they represent the "most susceptible population". Since a) these experiments have not been repeated in the past 20 years and b) no other groups have been exposed to such controlled clinical conditions, it's difficult to conclude that this is the "most susceptible population". Additionally, the epidemiologic data on congestive heart failure and stroke patients, while minimized in the PA write-up, suggest that those groups might be at least as susceptible to CO-related stress as the coronary heart disease group.

The data available in the PA and the ISA on CO/heart failure are instructive. The statements in the PA, p 2-14, lines 16-19, that there are only "…small or no associations between hospital admissions" and stroke are not accurate (see next paragraph). This tone continues on p. 2-27, lines 8-10, where the document states that "…we did not include studies of associations with CHF… for which the evidence is less clear". Unless I've misread the data, of the 5 studies listed in the footnote at the bottom of that page, 4/5 reported increased hospital admissions for CHF. A close look at Figures 5-2, 5-3 & 5-4 in the ISA supports the CO association with CHF and stroke more than for CHD. In those 3 figures the range of relative risk (RR) values on the x-axis varies widely. In Figure 5-2 the range is from 1.0-1.4, so small changes in RR appear to be larger than they are. On the other hand, the wider ranges of RR values for CHF (1.0-2.20) and for stroke (1.0-4.5) make larger RR values in those figures appear smaller than they really are. In Figure 5-2 (CHD) 27/31 values have a RR< 1.05 and only 4/31 with values between 1.10 &1.18. In Figure 5-3 (stroke) at least 6 studies reported a RR of at least 1.25 and one was as high as 2.8. In Figure 5-4 (CHF), 4/10 studies had RR between 1.2-1.75. If all the studies for stroke, CHF and CHD were placed on the same x-axis, uncertainty could well be heightened about CHD patients being the most susceptible to CO effects. In addition, the mean ambient CO levels (24 hr) reported in 2 of the studies with large increases in RR were ~0.8 ppm, i.e., even lower than the 1 ppm value recommended by the CASAC CO panel at its Nov. 2009 meeting as worthy of attention.

Another possible uncertainty regards the question (PA-p. 2-34, lines 24-34) of whether CO is a surrogate and whether its effects at low concentrations can be untangled from those of co-pollutants. While there may be administrative reasons for focusing on these distinctions, the science justification is not clear. Both CO and organic particles in ambient air are largely products of incomplete combustion (PICs). In real-world (and in most laboratory) situations it is essentially impossible to generate, and therefore to breathe, organic particle PICs without volatiles, including CO. So, disentangling CO effects from those of co-pollutants (not a problem in the Allred-Kleinman-Sheps controlled clinical studies) is not only difficult, but likely also artificial.

Dr. Beate Ritz

7. What are the views of the Panel regarding the staff's discussion of considerations related to the adequacy of the current and potential alternative standards?

In reviewing the recent literature EPA staff has concluded that a causal relationship is likely to exist between relevant short term exposures to CO and cardiovascular morbidity based mainly on the coherence between the results from controlled human chamber studies and the more recent epidemiologic literature. However, the PA makes an argument that epidemiologic studies of IHD and CVD are including some areas with CO concentrations that exceeded the 8-hour standards but also cited and commented on 3 studies from Atlanta for which this was not the case (Tolbert 2007, Peel 2007, Metzger 2007) and stated that 2 of the three studies reported non-statistically significant results.

For the Atlanta studies, first this statement is incorrect, i.e. all 3 studies from Atlanta reported significant results for CVDs (I checked the original papers and this is also not correct according to the ISA table on page C-25), and second the effect estimate sizes are all very comparable (in all three studies) and this is more important than statistically significance testing. Nevertheless, since the 3 Atlanta studies do not use mutually exclusive data and the Tolbert study is the most comprehensive one with regard to the time frame and # of hospitals covered, this largest study can be considered the most informative of the three. Concerning the studies covering areas that exceeded the current standards during the study period, it seems not completely justified to disregard them because of this fact when assessing whether or not to use alternate standards, unless these studies can be shown to be less valid in principle or show some kind of threshold effect rather than a dose response and are very different in the estimated effect sizes reported. Thus, altogether Page 2- 27-28 provide an example of a general tendency of the PA to mis-interpretate and mis-represent epidemiologic study results that is even more evident when it comes to interpreting results for other types of health outcomes.

This is very obvious on page 2-33 in the text addressing the available evidence for CO-induced effects on pre-term births, birth defects, developmental outcomes; the PA states that "the epidemiologic evidence ….has somewhat expanded, although the available evidence is still considered limited with regard to effects .." This, is a misrepresentation of the large expansion of data on these outcomes in the epidemiologic literature in past decade. The category of limited evidence is not attributable to little or conflicting epidemiologic evidence but rather to the lack or impossibility of human chamber studies and valid animal models for many of these outcomes and a general tendency of the EPA staff to not attribute causality solely on the basis of epidemiologic evidence alone.

The EPA staff indicates that some of the uncertainties identified in previous reviews of the standard have been reduced and they provide support for a standard at least as protective as the current standards, i.e. the data provide support for retaining or revising the current 8-hr standard. In fact if the epidemiological evidence was not down-weighted or outright ignored as much as it

currently is in this PA, enough evidence has accrued at levels below the current standard to revise them downwards in the interest of public health in general (not just for CVD outcomes).

8. Staff believes that the evidence presented in the final ISA and the exposure and risk information presented in the second draft REA supports a range of policy options for the CO standards.

a. To what extent does the document provide sufficient rationale to justify this range of options?

Yes, the sufficient rationale for discussion of the range of options is provided

b. Does the Panel have any recommendations regarding additional considerations which should inform characterization of these options for both the 8-hour and 1-hour standards?

Spatial heterogeneity of CO exposures that increase exposures near major sources i.e. near and on roadways should be given some weight since these might drive a lot of the adverse health effects.

Dr. Anne Sweeney

CQ. 7. The discussion of considerations related to the adequacy of the current and potential alternative standards was comprehensive and clearly established the context for the ensuing discussions. However, some of the conclusions reached were not well-supported, including:

a. The Estimation of Population Exposures (Page 2-5, lines 27-34, and page 2-6, lines 1-8). The contribution of ambient air CO levels to indoor CO levels would be especially relevant among lower socioeconomic status populations. Given environmental justice concerns rendering lower income individuals more likely to reside in heavily trafficked areas, as well as lower income resulting in lack of air conditioning and extended periods of time with windows opened allowing influx of ambient air, and an increased probability of exposure to tobacco smoke, it seems critical to examine the contribution of indoor CO exposures in the modeling. Inclusion of population prevalence of low income status and smoking prevalence (based on income status) in the simulated populations would greatly enhance the ability to estimate CO exposures.

b. Regarding Evidence-based Considerations (2.2.1): The conclusion that the current evidence supports a primary focus on cardiovascular disease (CVD) is justifiably based on the research examining formation of COHb and related CVDs as the most extensively studied adverse health effect supporting an association with CO. It is stated on Page 2-18, lines 15-18 that "*.. the population with pre-existing cardiovascular disease associated with limitation in oxygen availability continues to be the est characterized population at risk of adverse CO-induced effects*..". However, the best characterized and most extensively studied population does not necessarily identify the most highly susceptible population. The expansion of studies with positive findings evaluating effects on fetuses since the previous review, supported by strong toxicological evidence for the finding of prenatal CO exposure and adverse pregnancy outcomes, warrants more attention to this subpopulation. As stated on Page 2-16, lines 12-18: "*With regard to potential effects of CO on birth outcomes and developmental effects, the currently available evidence includes limited but suggestive epidemiologic evidence for a CO-induced effect on preterm birth, birth defects, decrease in birth weight, other measures of fetal growth, and infant mortality (ISA, section 5.4.3). The available animal toxicological studies provide some support and coherence for these birth and developmental outcomes, although a clear understanding of the mechanisms underlying potential reproductive and developmental effects is still lacking (ISA, section 2.5.3).*" This reviewer agrees that the number of human studies in these areas is limited, however, the strength of the evidence to date supports an association of greater concern than the current evaluation bestows.

CQ. 8.

a. Overall, the range of options recommended by the staff support at minimum the continuation of the current CO standards and possibly a lowering of those standards to provide increased public health protection (Page 2-56, lines 23-27). This position is well-supported chiefly by the review of the effects of ambient CO exposure at levels at or below the current standards and the effects on CVD endpoints.

b. Again, the additive or multiplicative effects of ambient and indoor CO exposures need to be given more consideration. In assessing averaging time (section 2.3.2). the 8-hour averaging time was selected in part because *".. this time-frame represented a good basis for tracking continuous exposures during any 24-hour period, recognizing that most people may be exposed in approximately 8-hour blocks of time (e.g., working or sleeping)."* The comments regarding indoor CO exposures especially among lower income populations are relevant here as well.

Dr. Stephen Thom

1. Background/introduction is clear and appropriate.

2. Chapter 2.1 - the approach taken to review primary standards for CO is well organized.

Section 2.2 discusses the adequacy of the current standard by listing key questions. The format involves reiterating much of the rationale listed in the REA, sometimes stating the same evidence used in conclusions multiple times (*e.g.* the Allred, *et al.* findings – page 2-10 lines 4 – 26; page 2-22, lines 17 – 31; page 2-23, lines 7 – 13; page 2-32, line 36 – 37; page 2-33, line 1 – 5). This seems quite redundant.

Of greater concern, there are instances where questions are posed but not answered. Therefore, this reviewer feels that some sections are poorly communicated. For example, section 2-2 poses the question: "Does the currently available scientific evidence and exposure/risk-based information, as reflected in the ISA and draft REA, support or call into question the adequacy of the protection afforded by the current CO standards?" I cannot find any place in the document where the question is answered. Instead section 2-2 is broken down into other questions in sections 2.2.1 and 2.2.2, some of which are answered and some are not.

3. In section 2.2.1 on page 2-8, line 9 the question "Does the current evidence alter our conclusions from the previous review regarding the health effects associated with exposure to CO" is answered (page 2-16, line 23-27). On page 2-16 the question, "Does the current evidence continue to support a focus on COHb ... or does the current evidence provide support for ... alternate dose indicators ..." is answered (page 2-17, line 29-31). On page 2-18, line 1 the question "Does the current evidence alter our understanding of populations that are particularly susceptible to CO exposures?" is answered (page 2-21, line 17 – 20). Of note, there is also a second question posed on line 2-19 that is redundant with that posed on 2-18. The question on page 2-22, line 1, "Does the current evidence alter our conclusions from the previous review regarding the levels of CO in ambient air associated with health effects?" is not answered. The staff reiterates much of the uncertainty with the current state of CO pathophysiology but never offers a conclusion. Moreover, there are parts of this section that are unnecessarily convoluted (*e.g.* the paragraph on page 2-27, lines 14 – 22). The question posed on page 2-31, line 29, "To what extent have important uncertainties identified in the last review been reduced and/or have new uncertainties emerged?" is answered (page 2-35, line 12-19).

4. In section 2.2.2 the end of the first paragraph has the sentence: "These questions are intended to inform consideration of the following overarching question.", but no question stated. On page 2-40 two questions read, "What is the magnitude of ... COHb levels estimated to occur in areas [that] just meet the current CO standards" and "What proportion of the .... population experience maximum COHb levels above levels of potential health concern?" The answers to these questions are, for the most part, outlined in table 2-5 but there is no written summary. The question on page 2-42, "What are the key uncertainties associated with our exposure and dose estimates ... ?" This question is clearly answered in the ensuing paragraph. The question on page 2-43,"To what extent are the estimates of at-risk population COHb levels ....important from a

public health perspective?" is not answered. Instead, the staff state that the answer depends on public health policy (page 2-44, line 26). This is common sense and does not draw upon the scientific data outlined in the ISA.

To conclude, the section 2.2 starts with a question: "Does the currently available scientific evidence and exposure/risk-based information, as reflected in the ISA and draft REA, support or call into question the adequacy of the protection afforded by the current CO standards?". This is clearly important but it remains unanswered in the current policy assessment.

5. Section 2.2.3 is said to offer conclusions on the adequacy of the current standard. The first two paragraphs clearly outline the rational taken by the staff and why they give weight to the 8-hour standard (versus the 1-hour standard). The first three sentences of the third paragraph state what appear to be truisms and in the fourth sentence the "conclusion" is that the eight hour standard should be either retained or revised. Hence, there is no conclusion.

6. Section 2.3, considerations of alternative standards, is organized by posing a series of questions. The first question (page 2-46) is," To what extent does .... information ... support consideration of alternatives to the current CO standards ... ?" is broken down into sub-headings and more questions. Section 2.3.1 states the indicator for carbon monoxide is carbon monoxide (not sure this is really necessary). Alternatively, you fail to mention the issues outlined in ISA chapter 3. Might it be appropriate to mention that CO is an O_3 precursor and there is a localized chemical interdependency of the CO-CH_4-NO_x system, although these alternative products are not used in estimating local CO production? Section 2.3.2 is said to consider alternatives to the current averaging times of 1- and 8-hour exposures. A question (page 2-47) is then posed, "Do health effects ... assessments provide support for considering different exposure ... times?". It seems to me the answer is stated on page 2-24, line 4 (... retain the 1- and 8- hour averaging times) but then the staff back away from this in later sections. A new question is posed on page 2-48, "What is the range of alternative levels and forms for the standard ... ?" The ensuing paragraphs and sections discuss use of a 99^{th} percentile concentration-based form and the 'exceeded only once per year' form. Much of the discussion in the REA is recapitulated in the following pages and the 'conclusions', summarized in section 2.3.4, are that the standards could be either revised or retained. Hence, the document offers no conclusion. A minor comment on the tables 2-6 and 2-7 is uncertainty over the term 'level' in the second columns. I assume, but am unsure that 'level' refers to ppm of CO.

7. I think discussion of current and potential alternative standards is adequate. I have one last comment pertaining to the uncertainties sections of the staff analysis. This relates to the APEX modeling. The discussion in the REA document includes information that most fixed monitors have a 1 ppm CO lower detectable limit so the modelers added 0.5 ppm CO to all measured values to remove zeros and negative numbers thought to be related to monitor drift. It seems to me that this severely weakens estimates of the at-risk population and threshold COHb levels and thus contradicts consideration of changes from the current standards. However, I defer to other Review Panel members with modeling expertise on whether my concerns are valid.

8. I do not think the options listed by the staff are helpful. They merely state what was obvious before starting the entire review process – that is, the guidelines can be left as they are or they could be changed.

9. Section 3 pertaining to consideration of a secondary standard for CO concludes, I think justifiably, that the science does not support establishing a secondary standard. I think the level of detail presented is adequate.