

**19 March 2010 Preliminary Review Comments from the CASAC CO Panel
on the *Policy Assessment for the Review of the Carbon Monoxide National
Ambient Air Quality Standards: First External Review Draft***

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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 (page 2-11, 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 Panel 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 in 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 not 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 (page 2-11, 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. 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.

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 NO₂ 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, 1.31). 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 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? I agree with the staff leaning towards retaining the current 8-hour standard.

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.

Consideration of a Secondary Standard (Chapter 3)

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. 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. 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 levelsimportant 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 rationale 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 O₃ precursor and there is a localized chemical interdependency of the CO-CH₄-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 99th 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.