UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

February 12, 2010

EPA-CASAC-10-006

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

Subject: Review of *Risk and Exposure Assessment to Support the Review of the Carbon Monoxide (CO) Primary National Ambient Air Quality Standards: First External Review Draft*

Dear Administrator Jackson:

The Clean Air Scientific Advisory Committee (CASAC) Carbon Monoxide (CO) Review Panel met on November 16-17, 2009 to review the *Risk and Exposure Assessment (REA) to Support the Review of the Carbon Monoxide (CO) Primary National Ambient Air Quality Standards: First External Review Draft* (October 2009). The Panel's report was reviewed and approved by the chartered CASAC on a December 22, 2009 public teleconference. This letter begins with CASAC's overall comments and evaluation. We highlight the most important issues which need to be addressed as the first draft is revised. The Panel and CASAC membership is 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 comments from individual panel members.

The Panel recognizes the time constraints under which this first draft REA was prepared. However, we found the document will need further development and refinement based on the strength of scientific evidence presented in the CO ISA, which was finalized January 2010. Fundamental concerns with the current CO monitoring strategy and the limited amount of data at realistic CO concentrations further constrain the analyses that can be carried out in the REA. We view this first draft REA as a reasonable exercise in risk characterization, but look forward to more fully-developed assessments and analyses in the second draft. Our major comments and suggestions to strengthen the document follow.

- We concur with the document's conclusion that the available CO data is a limitation of the REA. However, CASAC finds that a more robust risk and exposure assessment could have been produced with better utilization of the existing data and modeling tools. The

existing monitoring network is limited and most monitors do not have the sensitivity needed to describe current ambient CO concentrations. These challenges are accentuated by decades of success in reducing ambient CO emissions and concentrations. The limited accuracy of measurements at lower concentrations has rendered many of the current CO monitors obsolete. Moreover, in order to obtain adequate temporal and spatial information, a more extensive monitoring network is needed. These deficiencies reduce our confidence in the numerically simulated CO concentrations in the REA.

- The Agency needs to be more transparent in its selection of the urban centers for case studies and in its specification of exposure parameters for modeling, as well in addressing the implications of these choices. Nonetheless, CASAC supports the aspects of the modeling that incorporate a public health protective strategy, such as modeling that attempts to capture worst-case exposure scenarios.

- EPA should improve the analysis of CO concentrations to better capture spatial- and temporal-variability and the ratio of in-vehicle to ambient-air concentrations. Uncertainty in the model predictions of CO levels translates into uncertainty in COHb estimates, further limiting the REA's utility. The next draft REA should include a prioritization of the key sources of variability and discussions of the degree of confidence with which they are characterized, as well as additional ambient concentration scenarios.

- EPA has selected adults with coronary artery disease (CAD) who experience myocardial ischemia to represent sensitive subpopulations in the REA. EPA should expand its consideration of susceptible populations to include others who are at elevated risk of CO-induced adverse effects. CASAC finds the broader definition of cardiovascular disease (CVD) that includes populations with peripheral cardiovascular disease or stroke to be a more appropriate representation of susceptible population. Other at-risk groups should also be accounted for in the REA, such as, pregnant women, fetuses, and people with anemias and sickle cell anemia, specifically.

- CASAC strongly recommends inclusion of a final summary chapter in the next draft REA.

- We are concerned with the last line in Chapter 6, "staff finds the utility of this assessment for the purpose of considering the adequacy of the current standards to be limited." Deficiencies in the current REA demonstrate the critical need forr enhanced utilization of the available data, models and approaches to improve the next draft REA. Strengthening the current assessment can only further improve future CO reviews, which we anticipate will have better emissions data and air quality and exposure models.

CASAC repeats its expectation that the revised REA will be returned with a commentary pointing to key changes. This will enhance the efficiency of our subsequent review and will provide a transparent public record of the evolution of the document.

Sincerely,

/Signed/

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

/Signed/

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

Enclosures

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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*Dr. Weathers did not participate in CASAC's December 22, 2009 call to approve the draft report.

NOTICE

This report has been written as part of the activities of the EPA's Clean Air Scientific Advisory Committee (CASAC), a federal advisory committee independently chartered to provide extramural scientific information and advice to the Administrator and other officials of the EPA. CASAC provides balanced, expert assessment of scientific matters related to issues and problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the EPA, nor of other agencies within the Executive Branch of the federal government. In addition, any mention of trade names of commercial products does not constitute a recommendation for use. CASAC reports are posted on the EPA website at http://www.epa.gov/CASAC.

Enclosure B

CASAC's Consensus Responses to EPA's Charge Questions

Air Quality Considerations (Chapter 3)

1. Does the Panel find the considerations of current ambient carbon monoxide monitoring data and the discussion of the extent to which near roadway concentrations are represented to be technically sound, clearly communicated, and appropriately characterized?

The Panel found the discussions in Chapter 3 to be satisfactory. The REA makes it clear that many current monitors lack the sensitivity to provide accurate measurements of ambient concentrations (although page 3-3, line 8 should be "below 1 ppm" not "near 1 ppm"). Accurate measurements would be useful for estimating exposure at high concentrations and showing long-term trends. The difficulties in estimating actual exposure from point monitors' data that have been usually set up to demonstrate compliance with the NAASQ are clearly and thoroughly presented. The added discussion of the NCore multi-pollutant monitoring network strengthens the document. The actual concentrations to which people are exposed will have to be estimated with a combination of measurements and models. There is one point made explicitly in the ISA but not in the REA: some published comparisons of emissions inventories and ambient measurements reveal substantial disagreements, potentially leading to major uncertainties in numerically simulated CO concentrations. The chapter needs a final statement regarding uncertainties in emissions and/or measurements. The Panel notes that the quality and quantity of CO monitors must be improved in order to reduce uncertainties in exposure, emissions, and distributions in the future.

Although the REA discusses the monitoring network, there is an unresolved issue related to the combined use of models and measurements to estimate exposure. This point is addressed in the Panel's response to charge questions related to Chapters 5 and 6, on the need for measurements and models to go hand in hand. They are complementary. Neither alone can provide the information needed to estimate concentrations accurately in each microenvironment, such as in vehicle and near roadways. The exposure modeling was judged to be oversimplified. Meteorological models like the Weather Research and Forecasting model,WRF-URBAN, have progressed to realistically represent wind fields and thermodynamic variables on scales of hundreds of m over an urban domain[1]. Without better estimates of exposure – from a combination of better models and measurements – the COHb estimates remain highly uncertain.

Selection and use of Health Endpoint, Target Population and Risk Metric (Chapters 2 and 4, Sections 5.3.7 and 6.2)

To characterize CO risks, the risk/exposure assessment estimates the distribution of COHb levels

[1] D. L. Zhang, Y. X. Shou, and R. R. Dickerson, Upstream Urbanization Exacerbates Urban Heat Island Effects, *Geophys. Res. Lett.*, in press, 2009.

in the adult population with coronary heart disease that are exposed to ambient CO.
1. Does the Panel find the description and selection of health endpoint, target population and risk metric (Chapters 2 and 4) to be technically sound, clearly communicated, and appropriately characterized?

Health Endpoints: The selection of health endpoints for effects of COHb in patients with ischemic heart disease (IHD, CAD) is justified. The Panel members agree that the controlled exposure studies in subjects with CAD currently provides the results with the highest degree of exposure and outcome certainty in the scientific data base. In addition, the IHD endpoint is coherent with a significant number of epidemiologic publications that need to viewed as supportive of this endpoint. However, the discussion of levels relevant to current NAAQS (e.g. page 2-3 line 19 and page 2-5, lines 10-11) creates confusion. By stating that COHb levels of 3-6% produced most of the results in patients with CAD, the document unintentionally implies that the levels of interest should be 3-6%. Yet the projections of numbers at risk are based on the lower numbers. Clarification needs to be provided regarding this issue throughout the document. This strategy is appropriate and consistent with an apparent lack of a threshold for CO effect but this is not stated explicitly.

Target Population: A target population including individuals with coronary artery disease (CAD) is appropriate for the reasons noted in the ISA regarding the nature of their disease. Their diminished ability to compensate for the loss of oxygen being carried in the blood due to increased carboxyhemoglobin makes them highly likely to be at risk when exposed to CO. The epidemiological studies show increased hospital admissions in this population. This provides support for this target population but indicates that the CAD target categorization is likely to be too restrictive relative to a broader group of cardiovascular disease. The populations of other likely targeted individuals are indicated by the epidemiology studies and include: congestive heart failure, ischemic heart disease and general cardiovascular disease (for example, with risk of stoke) (Summary Section 5.2.3).

The subset of the susceptible population with CAD/IHD that has been studied needs to be placed in the context of a larger population with varied cardiovascular diseases. This section should also acknowledge that many susceptible people have not been diagnosed. Reconcile the descriptions in section 2.5, p.2-5 line 12 with section 4.1, p.4-2, lines 18-22. This becomes important in attempting to understand the numbers of susceptible persons in the population.

The Risk Metric: Limiting of the analysis to the benchmarks of 1.5, 2.0, 2.5 and 3.0% COHb appears to be based on the assumption that no human clinical studies were carried out at levels below 2.0% COHb. Based on the information presented in the ISA (section 2.6.2. page 2-18 lines 32-34) and the body of epidemiologic data, the Panel recommends that 1.0 % COHb be added as a benchmark. The dose response curves cited in ISA section 2.6.2 include many data points below 2.0% COHb. Should the staff choose to not consider the above-mentioned dose response information in the REA, justification needs to be provided.

2. Based on conclusions in the draft ISA regarding exacerbation of preexisting coronary heart disease in exercising individuals following CO exposures, we have selected

potential health effect benchmark values of 1.5, 2.0, 2.5 and 3.0 % COHb. To what extent does this range of benchmark values appropriately reflect the controlled human exposure studies health effects evidence related to CO exposures evaluated in the draft ISA?

Benchmarks: The Panel agrees with the document regarding the strength of the evidence about the effects of low levels of COHb on cardiovascular morbidity in the controlled human exposure studies. There is justification for continued use of these data as one of the primary health endpoints even though the evidence for these doses from environmental exposure and comparable cardiovascular events has not been made. Increasing epidemiological evidence on CHD makes the case for the use of these data even stronger. The controlled human exposure studies provide sufficient data to demonstrate dose-response relationships. Concern was voiced by the Panel that the draft document implies that the data from the controlled human studies do not support the development of a quantitative risk assessment that can characterize the dose-response relationship within the range of interest. It is the view of the Panel reviewers that there is no convincing evidence supporting a threshold for key CO-mediated health effects relevant to at risk populations. Therefore, CASAC has recommended adding a 1.0% COHb benchmark to provide a lower level of COHb in the risk assessment.

3. Does the Panel find the derivation and presentation of COHb estimates (sections 5.3.7 and 6.2) to be technically sound, clearly communicated, and appropriately characterized?

The Agricultural Policy EXtender (APEX) model utilizes the non-linear form of the Coburn-Forster-Kane (CFK) equation to estimate COHb. Several improved predictive models of COHb were discussed in Chapter 4 of the ISA (Smith et al, 1994; Bruce and Bruce, 2008, Gosselin et al, 2009) that lack some of the limitations of CFK. For example, they are more responsive to transient changes in ambient CO concentrations. These approaches might be better suited for use in APEX for future analyses. In light of the improved models available, justification should be given for using the non-linear CFK. In addition, if no transient environmental data were used to coincide with activity patterns, this should be made clear.

The input variables for different susceptible populations need to be spelled out for APEX as well as for CFK. Perhaps this could be accomplished with an appendix that identified the major variables for different at risk groups used in the modeling. If there were no substantive differences in the estimated outcomes among several models despite varying parameters, this needs to be stated and justified.

The exposure scenarios appear to be based on single monitoring stations in LA and Denver. Given the non-uniformity of CO distribution described in the ISA, these 'worst-case' scenarios may not adequately describe representative exposures. The manner in which data from the selected sites are adjusted for distance from the site and from local sources needs to be better explained. The selection of numbers for the at risk population being exposed to the levels of CO close to the high reading monitors may not be realistic. The extension of these monitoring sites to persons up to 20 km away is suspect.

Characterization of Exposure (Chapters 5 and 6)

In recognition of key limitations in available data with regard to spatial detail of ambient concentrations, this draft REA employs a simplified approach to exposure assessment in the Denver and Los Angeles study areas. We are interested in eliciting the views of the Panel on the usefulness of this approach in informing our review the NAAQS for CO and we are also interested in the Panel's view on the relative merits of alternatives or modifications to this approach, in light of the characterization of uncertainty as well as the limitations of the current data and time constraints on this review.

1. *Does the Panel find the summary of CO exposure and discussion of the relationship between in-vehicle and ambient concentrations to be technically sound, clearly communicated, and appropriately characterized?*
2. *What are the views of the Panel on the approach taken?*

There is limited data available characterizing the relationship between in-vehicle CO and corresponding levels measured at fixed site monitors. From limited data, the REA chooses a single multiplier, 2, to relate in-vehicle CO levels to those observed at fixed site monitors. The studies cited here and the work on the NO_2 REA show that this ratio is likely highly variable. The NO_2 REA captured this variability in the modeling used in that document. The distribution of in-vehicle to fixed site monitors should be presented and compared to what was found for NO_2, recognizing that there are differences in the sources and chemistry. This distribution should guide how the exposure modeling is carried out.

3. *Does the Panel view the results of the exposure analyses to be technically sound, clearly communicated, and appropriately characterized?*

While the assumptions made for the exposure modeling are clear, the model used may be too simple. The Panel previously noted that the CO monitoring network was limited and did not fully capture the range of ambient CO levels as might be desired for conducting an exposure analysis. But it presumed that instead of simplifying the analysis further, the EPA would use tools to capture better the spatial variability involved. There are a number of approaches that could have been employed to conduct the modeling that would have addressed greater spatial resolution. This includes using more monitors (as done in the prior assessment) with an approach to interpolating between monitors. This might still miss many important microenvironments. Using results from a microscale dispersion model (as done in the NO_2 REA), land use regression or fusing larger scale model results with observations should be considered. Though this might also miss higher levels in some of the important microenvironments. If possible, one of these more advanced approaches should be conducted. A range of in-vehicle vs. monitored levels could be utilized. Adding a third compartment, near road, should be explored. Given the presentation of the prior exposure modeling, the REA should be more clear as to the relevant strengths and weaknesses between the prior and current analyses and how the prior assessment is informative *vis a vis* the current one. There should be an assessment of how the differences between the prior and current versions of APEX impact results, quantitatively, if possible. The REA should be more transparent as to the reasons behind

the approaches chosen for how the exposure modeling was conducted. It should also discuss what needs to be done to make the analysis less limited for future use.

If the choice is made to consider COHb levels down to 1.5% or 1.0%, this has implications for the interpretation of the exposure modeling results and how it was conducted. At 1%, the current analysis shows that 100% of the individuals would experience that level under the "just meeting" conditions assumption. Further, the prior results suggest that the percent of total population exceeding 1% increases by about 25% if indoor conditions are simulated. This suggests that the indoor exposures are of increasing importance at the lower ambient levels. Like prior REAs, the fraction of exposure in the different microenvironments should be delineated.

4. What are the views of the Panel regarding the adequacy of the assessment of uncertainty and variability? To what extent have sources of uncertainty been identified and the implications for the risk characterization been addressed? To what extent has variability adequately been taken into account? Does the Panel have any recommendations for sensitivity analyses that they feel would improve this assessment?

Variability: Table 6-24 is very useful. The key sources of variability have been well-characterized. However, there should be more discussion to help identify which sources of variability lead to more variation in adverse health effects compared to others.

EPA should, to the extent possible, provide information on additional susceptible populations beyond cardiovascular disease. CVD is overly narrow in definition, and asthmatics and pregnant women need to be considered. At a minimum, EPA can quantify the exposures to such groups, if not health effect indicators such as percent COHb in the blood. EPA should also comment more on the effect of incremental exposures to CO and their implications for those persons who may already have elevated levels of COHb because of exogenous sources of CO, such as use of leaf blowers.

Uncertainty: The document has an extensive discussion of the qualitative assessment of uncertainty. The methodology for treatment of these topics is consistent with that in other ISAs, such as for PM. EPA has done a reasonable job of qualitatively identifying the key sources of uncertainty. Major sources of uncertainty are:

- Spatial and temporal variability of CO concentrations
- In-vehicle CO concentrations
- Historical data used for the analysis of "just meeting" the standard
- Commuting data
- Activity pattern data
- Longitudinal profile data

Including uncertainties in commuting data, activity pattern data, and longitudinal profile data will be difficult given the limited time available for finalizing the REA. Furthermore, these sources of data are not specific to CO. Most are important for exposure assessment for many pollutants. However, there are opportunities to significantly improve the characterization of the first three and thereby to address the implications of their uncertainties more fully in the 2nd draft REA.

We are concerned with the last line in Chapter 6, "staff finds the utility of this assessment for the purpose of considering the adequacy of the current standards to be limited." This statement implies that the REA is not useful as an input to decision making regarding whether to retain or revise the NAAQS for CO. This raises the question of what can be done to improve the quality of the REA. How can it become a more useful basis for informing decision making? The Panel has identified several promising opportunities for improvement, which are presented below.

With regard to spatial and temporal variability in CO concentrations, there are several possibilities for improvement (listed in order from simplest to more complex):

- Rather than base the analyses on only one monitor per city, use all of the monitors in the city, and restrict the geographic domain to that associated with the nearest monitor.
- Use a spatial interpolation technique to create a concentration field based on monitoring data, to enable use of multiple monitors as input to an exposure assessment.
- Use air quality model output, such as from the Community Multiscale Air Quality modeling system (CMAQ), to characterize spatial and temporal variability in CO concentration for each urban area, taking into account some model evaluations compared to the local monitoring data.
- Use CMAQ predicted CO concentrations combined with monitoring data, such as in Bayesian framework, to create a "fused" model-monitor based estimate of spatial and temporal variability in CO concentrations.

With regard to the ratio of in-vehicle to ambient concentrations, this can be addressed via more extensive sensitivity analysis (i.e. vary this ratio over a plausible range). The central tendency of this ratio should be based on a best estimate from the available data.

Regarding the analysis of "just meeting" the standard, there are several fairly straightforward improvements that could be made:

- Rather than focus on one scenario, try multiple scenarios.
- Rather than base the assessment on an older scenario, also consider scaling from a more recent scenario. In this case, one might need to scale upward rather than downward to "just meet" the standard.

In the 2nd draft REA, EPA should point out that they conducted a preliminary uncertainty assessment in the 1st draft REA, and used the results to target efforts to improve the REA as recommended above. Furthermore, the results of Table 6-25 should be revised if/as appropriate. This will be a good example of an iterative approach to both uncertainty analysis and model refinement, leading to an improved REA.

To support future exposure assessments that would quantify both inter-individual variability in exposure and uncertainty in exposure, EPA should continue to develop input data needed for microenvironmental population-based stochastic simulation models for exposure, as well as continue to develop and improve the models themselves.

5. To what extent does the simplified approach taken in the document help to characterize the public health implications of the current standard.

The rationale for focusing on Denver and Los Angeles based on limited monitoring sites was cogently presented, as was the rationale for focusing upon health effects at low level benchmarks.

A key aspect of the approach used was limiting the monitoring data input to the single most appropriate monitoring site in each city. The basis of selection for the sites whose data was used was their relevance to (but still underestimating) the microenvironment of prime interest – roadways. Simplifying the REA approach is justified when monitored or modeled exposure input data for the more complex model are unavailable. For example, it is reasonable when we lack spatially well-defined CO data, or when it can be shown that one of the key steps in the more complex APEX model is not likely to impact the overall results.

Also, current CO monitors – even the micro-scale ones – would not be able to represent exposures in a micro-environment of great concern, i.e., homes in close proximity to roadways. While the density of the current CO monitoring network and the sensitivity of instruments are not adequate to produce reliable, small scale exposure surfaces for CO even in the cities with the largest numbers of monitors (such as LA), we nonetheless recommend exploring how exposure modeling based on traffic density and related factors could be used to better inform the APEX model in future risk assessments.

The simplified approach used can be justified for public health purposes. It is likely to be more public health protective than the area-wide averaging techniques that have been used previously. But that still leaves much room for future improvement. For example, it is very difficult to intuit how simply changing some of the input values (or weights) for on-road and near-road exposures would influence the modeled REA estimates. However, the 2.0 multiplication factor for in-vehicle exposures is not acceptable and should be changed to 2.4 based on the data provided; we also request a simulation based on the mean winter values derived from LA data and results from models with a probabilistic set of several values to better gage the influence of changing these parameters. Finally, these models should be applied down to 1.5 ppm or even 1.0 ppm, rather than cutting analyses off at 2.0 ppm, based on the absence of an apparent threshold for cardiovascular endpoints.

As mentioned earlier, the Panel is concerned with using only narrowly-defined and poorly-estimated adult CAD as one of the simulated outcomes. This ignores concern for many different outcomes including impacts on fetuses and children or on the elderly and clear linkages for causal inferences. We recommend strongly that the current modeling of those at risk on the basis of cardiac ischemia be extended to include a more broadly defined category of cardiovascular disease (including congestive failure and stroke) rather than narrowly restricting the modeling to coronary artery disease (based on NHIS 2007 checklist responses). Even with such changes, it is important to acknowledge that this REA exercise does not allow us to gauge in a quantitative or even qualitative manner how possible health effects from even low levels of CO exposure in large populations affect the growing number of elderly and very elderly individuals living in the US or the more than 4 million children born in the US each year. There are other susceptible subgroups (such as those with diabetes or non-CAD cardiovascular disease within the brackets of youth and old age).

6. Does the Panel have any recommendations regarding how the approach might be modified to better characterize the public health implications of the current standards, in light of the uncertainty associated with the simplified approach, the current data and time constraints on this review?

It would have been helpful if the evaluation of uncertainties had not just been done qualitatively. We need to know how modeling specifications would change the estimates. It would have been helpful to have at least some quantitative data for one or two of the strongest and weakest factors. This would help calibrate our judgments, understand the magnitude of their impacts, and support the qualitative judgments presented.

Chapter 6 lacks a conclusion and leaves the reader to question what should be made of the difference in outcome between the current approach and the more thorough approach used in previous reviews. What are we to make of this difference? What practical significance does it have? Section 6.4.2 lacks sufficient direction and "punch." Further, the Panel is not convinced that a simple score-card rating of low, medium, and high-impact uncertainty factors was adequate. A more rigorous and focused description of this should be achievable in the subsequent draft.

The Panel recommends EPA add a table similar to Table 6-24 that lists all capacities of the APEX model for all 7 steps in one column. The second column could list steps employed and assumptions made to help guide the reader. This would clarify why certain steps were omitted due to lack of detailed input data or because modeling was not productive.

Exposures for residents very close to roadways may be higher in winter during stagnant air conditions. It is not clear whether and how this type of weather has been taken into account in the REA (for example, in Denver).

For the two monitoring sites selected, data was chosen from the year 2006. In Denver, at the site in question, there was a marked upward trend from 2006 to 2007 and 2008 for the monitor in question for 1 hour (2nd highest) average and to a lesser degree for 8 hours (data Figure 3-1). Baring other issues, it would seem that greater public health protection would result with the use of 2008 data or at a minimum to combine 2006-2008 for Denver. Although Los Angeles overall was flat in these years, the monitor in question did fall during 2007-2008 (opposite to the Denver pattern). Nonetheless it is not clear why 3 years of data are not used (Figure 3-2).

Enclosure C

Compendium of Review Comments from CASAC Carbon Monoxide Review Panel on EPA's *Risk and Exposure Assessment to Support the Review of the CO Primary National Ambient Air Quality Standards: First External Review Draft (October 2009)*

Comments received:

Dr. Paul Blanc 17
Dr. Thomas Dahms 19
Dr. Russell Dickerson 23
Dr. Laurence Fechter 25
Dr. H. Christopher Frey 26
Dr. Milan Hazucha 30
Dr. Michael Kleinman 32
Dr. Beate Ritz 35
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Dr. Armistead (Ted) Russell 43
Dr. Anne Sweeney 46
Dr. Stephen Thom 47

Dr. Paul Blanc

CO: EPA Review Risk and Exposure Assessment, Draft Comments

Characterization of Exposure (Chapters 5 and 6)

Question 5. To what extent does the simplified approach taken in the document help to characterize the public health implications of the current standard.

A key aspect of the approach used is to limit the monitoring data input to the single most appropriate monitoring site in each of 2 cities (Denver and Los Angeles). The basis of selection for the sites whose data was used was their citing as relevant to (but still underestimating) the microenvironment of prime interest – roadways. Consistency and other sampling characteristics were also taken into account in this selection. In principal, this "simplification" is logical and is indeed likely to be more public health protective than the area-wide averaging techniques that have been used previously.

A second driver to the model was testing of a second exposure scenario taking into account commuting time with higher exposure, calculated a 2 x the monitoring site value. Once again this approach of a commuter higher exposure scenario is reasonable.

The third assumption of the model is that the key outcome to be modeled is acute-exposure related adverse cardiovascular events. Once again, in principal this is a reasonable endpoint to choose as being the most sensitive, based on the revised ISA.

Question 6. Does the Panel have any recommendations regarding how the approach might be modified….

For the two monitoring sites data was chosen from the year 2006. In Denver, at the site in question, there was marked upward trend from 2006 to 2007 and 2008 for the monitor in question for 1 hour (2^{nd} highest) average and to a lesser degree for 8 hours data Figure 3-1). Baring other issues it would seem more public health protection to use 2008 data or at a minimum to combine 2006-2008 for Denver.

Although Los Angeles overall was flat in these years, the monitor in question did fall 2007-2008 (opposite to the Denver pattern) - nonetheless it is not clear why 3 years of data are not used.(Figure 3-2)

The Los Angeles site seems less optimal for the microenvironment but this does not seem to have been taken into account with an upward adjustment. This may need to be considered.

The factor used to go from best-as-possible fixed site to roadways was 2x as noted above, but based on table 5-3 this values is actually 2.4. The text may simply not be clear and 2.4 was used but if not it should be. Moreover, the winter ratio (based on LA data; Table 5-3) was actually 2.7. Given the more extreme winter conditions in Denver, should a higher ratio be used?

The population at risk for the risk calculations is estimated overly narrowly by defining this as persons with coronary artery disease (based on NHIS 2007). This may reflect the omission in Chapter 4 (Health Effects Benchmark) of any of the epidemiological data in the draft ISA, and in particular, the 2009 pivotal Bell study. That study, for example, makes clear that the risk is for cumulative cardiovascular disease endpoints, not all of which reflect baseline known coronary artery disease as would be defined in the NHIS. A clear example of this is the risk of CVA (stroke) in that analysis.

The modeling output cuts off at CO concentrations of 3 before going down to zero. Modeling person days at 2 PPM and 1 PPM would also appear to be relevant (e.g., based on Bell)

Dr. Thomas Dahms

Selection and use of Health Endpoint, Target Population and Risk Metric (Chapters 2 and 4, Sections 5.3.7 and 6.2)

To characterize CO risks, the risk/exposure assessment estimates the distribution of COHb levels in the adult population with coronary heart disease that are exposure to ambient CO.

Questions:

1. Does the panel find the description and selection of health endpoint, target population and risk metric (Chapters 2 and 4) to be technically sound, clearly communicated, and appropriately characterized?

A. Section 2.3, page 2-3, line 19. I believe that the characterization of the level of COHb at which angina and ST-segment changes occur is improperly characterized as being 3-6% COHb. The levels emphasized by placement in text in this document are those levels produced by CO-oximeter readings. The presentation of findings using CO-ox data needs to be justified in light of the information in the 2000 CO NAQC (Section 2.6.1) based on Vreman's findings that co-oximeters that are not designed to provide accurate information in this range of COHb. The effect of emphasizing the 3-6% COHb findings is problematic when numbers of at risk patients is determined for 1.5, 2.0 etc levels of COHb.

The presentation of CO-Ox data with the implication that it is equivalent to data collected by many other methods is not justifiable. Several other more sensitive methods have been shown to be accurate for measuring COHb levels near baseline and these data need to be denoted somehow so the reader is not mislead. The sensitivity of different methods for measuring COHb has been known for at least 30 years and the misinformation should not be promulgated in this document.(see Table 5.2 on page 5-36 in the 1979 AQC for CO published by the EPA).

B. Section 2.3, page 2-3, lines 20-22. The studies using controlled human exposures mostly used one level of CO exposure resulting in a limited range of COHb levels (effective dose). Review of this information apparently leads to assessment of effects of CO pertaining to the mean COHb levels. However as noted in the ISA in section 2.6.2. page 2-18 lines 32-34, the 63 subjects reported by Allred et al demonstrated a dose-response curve for COHb and angina and for ST-segment changes in subjects with CAD. There is a suggestion the the Allred et al (1991) publication that there was no obvious threshold of effects of COHb. This is information conflicts with the statement in this section and needs to clarified, discussed or changed.

C. Section 2.5, page 2-5, lines 10-11. There is only uncertainty about the COHb levels measured with the CO-oximeters (see item A above). All of the studies cited on page 4-2 line 8 either used the same exposure conditions or obtained similar increases in COHb.

The levels of COHb of interest should be concordant with the values used in the uptake models in the document.

D. Section 2.5, page 2-5, line 12. The statement "that these studies did not include individuals with more severe CHD" is too vague. It is in conflict with the comments in Section 4.1, page 4-2 lines 18-22 which implies that the subjects studied had CHD that was more severe than most with CHD. Neither statement allows the reader to determine what percentage of the population with CHD is at risk based upon the studies that have been carried out.

E. Section 4.3. lines 23-27. How can this observation be reconciled with information in the ISA regarding a dose-response effect noted in sections 2.6.2 and 5.2.4 of the ISA?

F. Given all of the supportive information obtained from the epidemiology studies, why is there no quantitative weight given to all of these studies? How can this mass of information not be accounted for in this phase of the process?

2. Based on conclusions in the draft ISA regarding exacerbation of preexisting coronary heart disease in exercising individuals following CO exposures, we have selected potential health effect benchmark values of 1.5, 2.0, 2.5 and 3.0% COHb. To what extent does this range of benchmark values appropriately reflect the controlled human exposure studies (in) the health effects evidence related to CO exposures evaluated in the draft ISA?

The range is fine if one does not consider the dose-response curve of Allred et al to be valid.

3. Does the Panel find the derivation and presentation of COHb estimates (sections 5.3.7 and 6.2) to be technically sound, clearly communicated, and appropriately characterized?

A. It is not clear how APEX determined exposures and the non-linear CFK deals with the transient exposures that the model of Bruce and Bruce seemed to handle more convincingly. It seems too crude to use only 1 hour averages for exposure to determine dose of CO for the 1 hour standard.
B. Page 5-12 line 24-25, and page 5-13 line 20. What is the evidence that "accurate results for lower levels of COHb" were obtained from this model?
C. Section 6.1.3. Is the resulting number of persons at risk over estimated because of the concerns raised in sections 2.5 and 4.1?
D. Tables 6-8 and 6-9 should include the current 1 hour standard in their CO concentrations. The foot notes should be changed accordingly. Tables 6-8, 6-10 and 6-12 should have the numbers of person days spelled out in thousands rather than using the exponential notation. This would make the visual comparison between these tables and the following tables easier to read.
E. The assumptions regarding activity patterns of patients with CHD relative to the general population need to be reiterated so that using a percentage of the entire population to generate the numbers at risk is justified. Or do I not understand how these numbers were generated?

F. Does any of the epidemiologic data support any of these estimates assuming that the benchmark levels of COHb would trigger cardiovascular events that would result in contact with the healthcare system?

Editorial comments

1. Section 2.3 and beyond. This section (line 22) introduces the terms susceptibility and vulnerability yet after the first paragraph switches to at risk without explaining the link. For a person to be at risk needs to be clearly defined.
2. Section 2.3, page 2-3 line 26. Use of non-specific terms like IHD or CHD can lead to an overestimation of numbers of people at risk when exposed to CO. The distinction between the use of terms in the epidemiology literature and the controlled human exposure experiments needs to be made.

In reviewing the ICD-9 codes the diseases included under IHD includes a variety of conditions not studied in any of the controlled human exposure studies. CAD is a subset of conditions under IHD and (CHD is no longer identifiable). Therefore it is suggested that these terms be clearly identified in the REA since they have been used as being synonymous in previous documents. The ISA is fairly clear in its limiting its discussion in section 5.8 Summary to use of the more limiting term CAD. The reference on line 5 to section 5.8 of the ISA is not clear. Perhaps the terminology adopted in sections 5.7.8 and 5.8 of the ISA should be followed especially if the focus is on the controlled human subject studies.

3. Section 2.4, page 2-4 line 10. suggested editorial change for clarity: …CO levels of concern is tissue hypoxia due to reduced O2 delivery resulting from increased COHb….
4. Section 2.5, page 2-4 line 26. how do these undefined 'short term ambient CO exposures' relate to the standards or to the exposure models that were used to assess risk?
5. Section 4.1. page 4-1, line 13. 'reduced iron' should read iron. CO will competitively compete with oxygen for hemoglobin regardless of the oxygenation status of hemoglobin. Both will compete for iron in the plus 2 state of oxygenation, so to refer to the valence of the iron is only confusing
6. Section 4.2. p4-3. lines 8-17. As mentioned throughout the ISA (but not summarized in this way) all but one of the controlled human studies used nearly the same exposure conditions so one would expect the same CO dose in all these subjects. Yet the variability is in the blood analysis by CO-Ox. It would be helpful if this information was presented as it would help the reader to understand the consistency in the cardiovascular effects and the inconsistency in the COHb levels reported.
7. Section 4.2, p. 4-3 Lines 20-23. The conclusion of the staff regarding dose-response relationships is clearly not supported by the opinion of the panel. If there is a benchmark for establishing whether or not a dose response exists for regulatory purposes it needs to be stated here. Otherwise it appears to be an arbitrary decision.
8. Section 5.5.2 p.5-24 lines 23-26. If such an approach was acceptable for ozone there needs to be more detailed justification for the position of the CASAC_CO panel as summarized by Samet and Brain in this document. Or is this just a difference of opinion?
9. Tables 6-8 through 6-11 should have the one hour CO concentration values shown (35 ppm).

Dr. Russell Dickerson

Air Quality Considerations (Chapter 3)

Considerations of current ambient CO monitoring data and the discussion of the extent to which near roadway concentrations are technically sound, clearly communicated and appropriately characterized?

The REA makes it clear that many current monitors lack the sensitivity to provide accurate measurements of ambient concentrations (although page 3-3, line 8 should be "below 1 ppm" not "near 1 ppm"), but these observations are useful for estimating exposure at high concentrations and showing long-term trends. The REA further discusses thoroughly and clearly difficulties in extrapolating from point monitors (usually set up to demonstrate compliance with the NAASQ) to actual exposure. The added discussion of NCORE strengthens the document. The actual concentrations to which people are exposed will have to be estimated with a combination of measurements and models. There is one point made explicitly in the ISA but not in the REA. Some published comparisons of emissions inventories and ambient measurements reveal substantial disagreements potentially leading to major uncertainties in numerically simulated CO concentrations.

Response to CQ1: Does the Panel find the considerations of current ambient carbon monoxide monitoring data and the discussion of the extent to which near roadway concentrations are represented to be technically sound, clearly communicated, and appropriately characterized?

Many of the comments made in regard to the ISA apply to the REA as well. It is good to see a discussion of the NCORE network. The chapter needs a final statement regarding uncertainties in emissions and/or measurements. The quality and quantity of CO monitors need to be improved in order to reduce uncertainties in exposure, emissions, and distributions, and the REA reflects these data limitations, so the answer to Charge Question 1 is "yes".

As far as monitoring goes, the REA does a good job – there is an issue related to the combined use of models and measurements to estimate exposure. This point is addressed in an answer to questions related to Chapters 5 & 6, on the need for measurements and models to go hand in hand. They are complementary and neither alone can provide the information needed to estimate accurately concentrations in each microenvironment such as in vehicle and near roadways. The exposure modeling was judged to be oversimplified. Meteorological models such as WRF-URBAN have progressed to realistically represent wind fields and thermodynamic variables on scales of 100's of m over an urban domain (e.g., Zhang et al., 2009). Without better estimates of exposure – from a combination of better models and measurements – the HbCO estimates remain highly uncertain.

D. L. Zhang, Y. X. Shou, and R. R. Dickerson, Upstream Urbanization Exacerbates Urban Heat Island Effects, *Geophys. Res. Lett.*, in press, 2009.

Dr. Laurence Fechter

Comments on Risk and Exposure Assessment document for CO

I found the 1st draft of this document to be a reasonably strong and effective presentation of the new approach to modeling human exposure to carbon monoxide. The rationale for focusing on Denver and Los Angeles was cogently presented as was the rationale for focusing upon the health effect benchmarks between 1.5-3% COHb and specific monitoring sites. Given the enormous detail that is provided in chapters 5 and 6 of this document I confess to feeling seriously let down by the lack of conclusions. It is very interesting that the current approach and the previous one produce significant differences in outcome, but what am I to make of this difference? What practical significance does it have? I found section 6.4.2 to lack sufficient direction and "punch". I kept wondering where we were headed here. Additionally, I was not convinced that a simple score card of low, medium, and high-impact uncertainty factors was adequate. I am certain that a more rigorous and focused description can be achieved in the subsequent draft.

Dr. H. Christopher Frey

Review of Carbon Monoxide First Draft of Risk and Exposure Assessment

Chapters 5 and 6

Charge Question 1: Does the Panel find the summary of CO exposure and discussion of the relationship between in-vehicle and ambient concentrations to be technically sound, clearly communicated, and appropriately characterized?

Response to Charge Question 1: From a qualitative perspective, the REA reasonably characterizes the relationship between in-vehicle concentration, concentration outside the vehicle, near-roadway concentration, and area-wide concentration. It is clear that the CO concentration on the roadway is typically higher than at fixed site monitors (FSMs). It is also appropriate that the CO concentration in the vehicle is very similar to the CO concentration immediately outside the vehicle. Hence, it is appropriate to estimate that the in-vehicle CO concentration is a multiplier greater than the FSM data.

The REA could better describe the "microscale" aspects of vehicle activity and emissions that could lead to substantial variability in exposure. For example, on a portion of roadway with positive road grade, for which a significant portion of vehicles might be operating in fuel enrichment mode, the localized tailpipe emissions of CO can be much higher than elsewhere on the transportation network. Such episodes might last only a few seconds, however, and thus are of an averaging time that may not be commensurate with the available health effects data and models.

Even for longer term averages, there is likely to be substantial variability in in-vehicle exposure depending on factors such as wind speed, atmospheric stability class, vehicle traffic volume, and vehicle tailpipe emission rates.

Charge Question 2: What are the views of the Panel on the approach taken?

Response to Charge Question 2: The use of a multiplier such as 2 might be a reasonable average, but is not likely to take into account variability in onroad conditions that might lead to much higher exposures. Rather than use one number for the multiplier, a range of numbers can be used either as a sensitivity analysis or as a probabilistic analysis using a distribution.

The distribution of windspeed and direction for each FSM used in the REA should be evaluated to determine whether the monitor is upwind or downwind of the nearest major roadways. An assessment should be made as to whether the multiplier for in-vehicle to ambient proximity should be adjusted to take into account these meteorological conditions. This decision could be informed by sensitivity analysis with an air quality model such as CALINE4.

Charge Question 3: Does the Panel view the results of the exposure analyses to be technically sound, clearly communicated, and appropriately characterized?

Response to Charge Question 3: The exposure analysis does not appear to be technically sound. Consider that the last line in Chapter 6 is "staff finds the utility of this assessment for the purpose of considering theadequacy of the current standards to be limited." This statement implies that the REA is not useful as an input to decision making regarding whether to retain or revise the NAAQS for CO. This begs the question of what can be done to improve the quality of the REA so that it is a useful basis for informing decision making.

In Section 6.4.2, the key sources of uncertainty are identified to include:

- In-vehicle CO concentration
- Commuting
- Spatial and temporal variability of CO concentration
- Historical data used for the analysis of just meeting the standard
- Activity pattern data
- Longitudinal profile data

For some of these, such as activity pattern and longitudinal profile data, and perhaps the methodology used for estimating commuting-related exposures, there is not likely to be any improvement in the next few months.

However, there is the potential for significant improvement in the characterization of spatial and temporal variability in CO concentration. There are several possibilities for improvement:

- Rather than base the analyses on only one monitor per city, use all of the monitors in the city, and restrict the geographic domain to that associated with the nearest monitor.
- Use a spatial interpolation technique to create a concentration field based on monitoring data, to enable use of multiple monitors as input to an exposure assessment
- Use air quality model output, such as from CMAQ, to characterize spatial and temporal variability in CO concentration for each urban area, taking into account some model evaluations compared to the local monitoring data
- Use CMAQ predicted CO concentrations combined with monitoring data, such as in Bayesian framework, to create a "fused" model-monitor based estimate of spatial and temporal variability in CO concentration.

The latter would be the technically most attractive approach. This would iteratively address what EPA has identified as one of the key sources of uncertainty in the analysis.

Although there may be little prospect of obtaining more measurements of in-vehicle CO concentration relative to concentration at the vehicle exterior, the use of a better CO concentration field as an input to estimating in-vehicle concentration, still using a reasonably justifiable proximity factor such as two, would nonetheless lead to some improvement in the in-vehicle concentration estimate.

The use of land-use regression models should be considered if it could improve the prediction of concentration gradients in the proximity of roadways and thus better inform estimates of in-vehicle concentration.

Regarding the analysis of just meeting the standard, there are several fairly straightforward improvements that could be made:

- Rather than focus on one scenario, try multiple scenarios
- Rather than base the assessment on an older scenario, also consider scaling from a more recent scenario (in which case one might need to scale upward rather than downward to "just meet" the standard).

Charge Question 4: What are the views of the Panel regarding the adequacy of the assessment of uncertainty and variability? To what extent have sources of uncertainty been identified and the implications for the risk characterization been addressed? To what extent has variability adequately been taken into account? Does the Panel have any recommendations for sensitivity analyses that they feel would improve this assessment?

Response to Charge Question 4:

Variability: Table 6-24 is very useful. However, there should be more discussion that helps to identify which sources of variability lead to more variation in adverse health effects compared to others. For example, does variability in activity patterns because of temperature lead to more variability in adverse effects than the population data?

Uncertainty: The document has reasonable content regarding a qualitative assessment of uncertainty. The methodology for treatment of these topics is consistent with that in other ISAs, such as for PM.

p. 6-37, line 13. The assessment endpoint is related to exposure or effect, not air quality.
Lines 16-28. Are these categories of uncertainty based on some absolute scale or relative to each other?

Table 6-25:

- knowledge base uncertainty for adjustment of air quality to simulate just meeting the standard -- it seems not very compelling that it is "largely unknown" as to how emissions level per vehicle, etc. compare between the earlier period of time and the hypothetical condition. For example, emission factors are available for vehicle technologies typical of the time period, such as in the Mobile5b emission factor model.

- Population data base – the population data are for 2000. The air quality data are from 2006. While this is not a problem per se, a reader might misinterpret that the effects estimates are based on a 2006 population. If population has increased from 2000 to 2006, then the number of incidences would appear to be underestimate relative to a 2006 population. Thus, it is important to clearly characterize that results are based on 2000 population when reporting results in tables and figures.

- Algorithm and Input Data for All other microenvironmental CO concentrations – consideration of the lag effect associated with air exchanges might delay and lower the peak indoor concentration relative to the peak outdoor concentration, but also will increase the minimum indoor CO concentration relative to the ambient concentration.

- CHD prevalence: The Coronary Heart Disease (CHD) prevalence is estimated based on gender-specific ratios applied to all age groups. Hence, there may be some uncertainty as to the accuracy of the prevalence estimates for specific age and gender groups.

The summary of uncertainty is in terms of focusing on the "direction" of uncertainty first and then considering the magnitude of uncertainty.

Page 6-41, line 12/13 (in between these) it is stated that there is "relatively less uncertainty" but intended meaning seems to be relatively 'more'

Other comments:

Where is EPA going with this? Given that the only analyses are at the level of the current standard and "as is" air quality for two cities, does this imply that EPA is merely considering to continue the current standard? What regulatory alternatives are to be considered?

To what extent can/should there be an assessment of welfare effects related to climate change?

Dr. Milan Hazucha

Updated Comments on the First External Review Draft of the REA for Carbon Monoxide

Chapter 2:

Individuals with cardiovascular disease identified as the primary target population indeed appear to be the most susceptible to CO-induced health effects. However, there are other large populations such as people with anemias that are also more susceptible to adverse effects from CO exposure. These "secondary" populations do not seem to be considered in either dose or risk metrics assessment.

Page 2-4, l. 13 and Page 5-12, l.7-8: Chapter 4 of ISA has reviewed numerous empirical, mechanistic, and mathematical COHb predictive models that are more accurate in variable ambient CO and physiologic conditions than CFKE which contains numerous assumptions with potentially inaccurate COHb values. Why not to use more accurate model?

Page 2-5, l. 13-14: Although the statement is correct I suggest clarifying it by adding that COHb levels below 2% were measured post-target (2% and 4%) exposure and at the end of exercise which further reduced COHb concentration. This will prevent quite frequent misunderstanding by even CO panel members that the "exposures" were to concentrations below 2%.

Page 2-5, l.14-16: The proposed range of benchmarks (1.5, 2.0, 2.5, and 3% COHb) is adequate for CO risk characterization. Reducing the benchmarks below 1.5 % would be problematic since, (1) recent data (Hart et al., 2006) report an average resting blood COHb level of 1.59 % in 2448 never smokers, (2) Figure 4-12 of ISA shows that the baseline COHb level is ≥ 1% for diseases/conditions listed, and (3) many diseases discussed in the ISA section 4.5, and listed in Fig.4-13 such as asthma, metabolic diseases and other inflammatory conditions result in increased blood COHb levels above 1% as well. So there is a huge population with blood COHb level ≥ 1% not due to ambient CO exposure but disease conditions. Consequently, any risk assessment below 1.5% would be highly questionable.

Chapter 4:

Page 4-2, l. 5-6: Be more specific. They are all standard protocol depending on intended test goals. Modified Naughton exercise protocol was used in the study.

Chapter 5:

The Apex model employs CFK equation for estimation of COHb (Appendix C). Though CFK is a robust model, a review of various predictive models of COHb in Chapter 4 of ISA shows that there are more sophisticated models (Smith et al, 1994; Bruce and Bruce, 2008, Gosselin et al, 2009) that do not have the limitations of CFK and are more responsive to transient changes in ambient CO concentration and thus might be better suited for APEX. The suitability of more comprehensive models in COHb module of APEX should be explored.

Another concern is the selection criteria used to characterize simulated individuals for the APEX data set. The individuals are defined by age, gender and body weight **(section 5.3.2, page 6-35 and C-7**). This info is subsequently used to develop a "personal profile" which includes physiologic variables. The derived values are then used in CFK model. However, the profile does not have build in any "health status" variable which could modify the input of physiologic variables of CFK equation. Do I understand it correctly?

It is still unclear to me how a simulated at-risk population is selected. From Section 5.3.2, table 6-24 and corresponding text it appears that the source data, i.e., for simulated individuals are derived from general population. Subsequently, based on the prevalence of specific health condition, e.g., CHD, a subset of at-risk simulated individual is created from the initial set without adjusting input variables for that (specific) health condition. Another possibility is that the generated sample includes simulated at-risk individuals at certain prevalence rate, but the physiologic variables are not adjusted accordingly either. For example, people with anemia or CAD have different Hb concentration, endogenous production of CO, etc., then healthy individuals (**ISA, 4-29 to 4-31**). Consequently, if the input variable values are not adjusted the COHb estimates will be incorrect. How is this corrected for in the APEX?

Some of the methods and formulae for parameter estimates are rather old (Allen et al, 1956; Salorinne, 1976; Galetti, 1959). Over the last 50 years the population characteristics have changed dramatically and there are more recent predictive formulae available for input parameter estimates such as blood volume, DLCO and VA. Moreover, some of the physiologic variables in CFK must be adjusted for barometric pressure. The VA is adjusted, but DLCO is not. The American Thoracic Society recommends that the value of DLCO is adjusted for altitude (ATS, 2005). This is important for Denver site exposure assessment by APEX.

Page 5-10, l.24-25: The statement is true, but only for sub-maximal exercise in healthy individuals. Need to state that. Moreover, VA/VO_2 ratio is not so constant for patients with cardiovascular disease.

Page 5-13, l. 31-32: Does this "reasonable sample" also include individuals who may be at-risk?

Page 5-20, table 5-2: The table data seem to be based on passenger cars only. Any data on pick-ups, vans, buses, trucks? Out of ~500 mil vehicles only about 250 mil are passenger cars (US Bureau of Transit Statistics). The other one half of on road vehicles is most likely polluting more than passenger cars do.

Page C-8, last paragraph: Do you run the model under instantaneous CO concentration or 1-hour averaging time? How is the averaging time selected?

Dr. Michael Kleinman

Selection and use of Health Endpoint, Target Population and Risk Metric (Chapters 2 and 4, Sections 5.3.7 and 6.2)

1. Re: The description and selection of health endpoint, target population and risk metric.
    a. The strongest evidence regarding CO health effects does relate to cardiovascular morbidity and it appears that the evidence is sufficient to indicate a causal relationship is likely to exist. The coherence of epidemiological evidence with the human controlled exposure study data supports this finding.
    b. The controlled exposure studies provide both exposure-response relationships and through use of COHb measurements as a exposure/dose biomarker there appears reasonable data to provide dose-response relationships.
    c. Having said that, Chapter 4 goes on to note the data from controlled human studies 'do not support the development of a quantitative risk assessment to characterize the dose-response relationship within the range of interest.' This conclusion is not sufficiently supported in the REA. While there are some inconsistencies in the controlled study time to angina endpoints, there seem to be sufficient data and reasonable consistency in study methods and designs that a 'meta-analysis' or comprehensive data analysis could be performed.
2. Re: Benchmark values.
    a. Extending the benchmark values below the level at which significant changes were detected in controlled exposure studies is appropriate and consistent with previous CASAC suggestions. The subjects participating in the controlled exposure studies were required to be able to perform aerobic exercise as part of the protocol, hence were not as debilitated as many individuals with CVD or IHD.
    b. The coherence of the epidemiological study results with the results of the controlled human studies also suggests that extension of consideration below 2% COHb is warranted since the epidemiology demonstrates morbidity at CO exposure levels that would produce COHb well below 2%. If the baseline level of the participants of the controlled studies is representative of the COHb of the general population of CVD and IHD patients, their average COHb is on the order of 1% or less.
3. Re: Presentation and derivation of COHb estimates.
    a. Section 5.3.7 provides a useful summary of the parameters incorporated into the CFK model. On the other hand, the ISA goes to great lengths about the problems of CFK for low levels of COHb and short-term exposures. Presumably APEX generates 8hr and 24hr CO exposure estimates. If those estimates are appropriate for the CFK, it could be explicitly stated in 5.3.7.

b. The methodology for generating the scenarios is reasonable if one accepts the premise that 1 monitoring station each in LA and Denver are sufficient to describe exposures. This seemed like a major jump, given everything previously stated in the ISA and the REA about CO being non-uniformly distributed. Given the conclusion in 6.5 'the utility of this assessment for the purpose of considering the adequacy of the current standards to be limited' suggests that the REA could be improved.
    i. Use a meta-analysis or other technique to better define the dose response curve.
    ii. Use a more comprehensive design for assessing exposures in both LA and Denver that could take into account the inhomogeneities of CO distributions.
c. The finding that the REA utility is 'limited' needs to be better qualified as to what those limitations are with respect to evaluating the current standards. At a minimum it would seem that more information on what more would be needed to consider the adequacy of the standards should be provided.

Additional REA Comments

Page	Line	Comment
4-3	22	The distinction between the quantitative risk assessment and the risk characterization should be made more clearly.
4-4	11-15	Lowering the range of consideration also may be relevant to other populations that might be at risk such as people with anemia, sickle cell disease, fetuses and perhaps severe COPD where O2 transport/delivery is impaired
5-7	16-17	The simplified approach also ignores other sources of indoor CO production such as cooking, smoking and emissions from poorly ventilated fossile-fueled appliances.
5-21	2	…the 'properly maintained automobile engine and exhaust system' does not contribute….
5-21	12	…converge to unity 'as averaging times and durations of observations increased.'
5-23	25	Were the remaining monitors placed in a way that allowed one to draw conclusions about inhomogeneity?
5-24	27	Limiting the monitoring data to a single site in Denver and a single sit in LA needs to be more strongly justified.
6-1	12	It should be mentioned in this paragraph that compa rison runs were made between the proposed simplified model and PNEM/CO that will be discussed later in Chapter 6.
6-10	22	The design value definition should be shown here rather than later in the chapter.
6-17		Use the exponential format for tables 6-8 through 6-12.
6-40		Should a row be added for the CFK algorithm which has several components that potentially contribute to biases.
6-43	15-19	The number of individuals living near roadsides is an issue that is raised at several points in the REA. Can't something be said of a more quantitative nature so that the magnitude of the problem can be assessed?

6-43	25-26	The statement that the utility of this assessment is limited needs to be followed up with a suggestion of what will be done next to consider the adequacy of the current standards.

Dr. Beate Ritz

CO: EPA Review Risk and Exposure Assessment, Draft Comments Characterization of Exposure (Chapters 5 and 6)

Question 5. To what extent does the simplified approach taken in the document help to characterize the public health implications of the current standard.

A simplified approach is certainly justified when the data needed for a complex model is unavailable (such as a lack of enough spatially well defined CO monitoring data – note however that I do not understand why there is a 'lack of temporal variability in available ambient monitoring data as stated on page 5-24 line 24), or when modeling one of the seven steps in the conventional APEX models is not likely to impact the estimation overall; for example, since the reported ratio for indoor/outdoor CO levels is close to 1 without additional indoor sources, distinguishing between in-and outdoor activities in the population does not seem necessary. These model simplifications then are necessary and not just convenient. It would be helpful for the reader of the REA to see a table (similar to table 6-24) that lists all capacities of the APEX model for all 7 steps in one column and in a second column lists which steps were employed and what the assumptions were when doing so or why certain steps were omitted due to lack of detailed input data or because modeling was not necessary (such as when a microenvironment does not contribute to exposure differences).

Similarly, it seems that a more complex approach of estimating spatial distributions of exposure across cities might not have been possible since the density of the monitoring network and the sensitivity of instruments (with relatively high detection limits around 0.5 ppm) is not adequate to produce reliable small scale exposure surfaces for CO even in the cities with larger numbers of monitors such as LA. Moreover most monitors – even those at micro-scale levels, would not be likely to pick up the true levels for the micro-environment of greatest concern, i.e. the roadway. Thus, using one monitor that might represent proximity to roadway exposure best in both LA and Denver seems justified.

Yet, for the in-road micro-environment, it has to be recognized that these monitors are still removed from roadways and do not represent exposures in roadways and it might be questionable whether a factor of 2 to estimate in-roadway or closest proximity to roadways exposures is correct. Also exposures for residents very close to roadways maybe higher in winter during stagnant air conditions and it is not clear whether and how this type of meteorology has been taken into account. In fact, I did not understand how the weather data was being used in the APEX model. This should be clarified.

Thus overall, the simplified approach that does not model micro-environments and uses a larger radius and the monitor most reflective of roadway exposures seems justified. What seems less well justified, given the new wealth of epidemiologic data, is using only adult CVD as one of the simulated outcomes. This limits what can be taken seen as possible health effects from even low levels of CO exposure in large populations to mostly elderly individuals, when it is likely that

fetal development is affect and more than 4 million children born in the US might be a sensitive subpopulation for CO effects as well.
It is not easily understandable how the large differences in end-of-hour COHb levels for individuals above 2% for both exposure scenarios are obtained in Denver and not LA, i.e. the 26% and 56% versus 2 and 7% in Denver and 3 and 8% in LA (page 6-26); it seems that these differences depend solely on the upper percentiles of the exposure distributions that are higher in Denver than LA. How well these upper percentiles are reflecting the exposure distributions in each city ofr those in the most highly exposed micro-environments when using an ambient monitoring station to estimate personal exposures is then a question, i.e. I would like to understand better how these large differences are generated since they seem to point towards a major uncertainty in these models.

Question 6. Does the Panel have any recommendations regarding how the approach might be modified to better characterize the public health implications of the current standards, in light of the uncertainty associated with the simplified approach, the current data and time constraints on this review?

It would have been helpful if the evaluation of uncertainties had not just been done qualitatively but been accompanied by some data on how modeling specifications would change be changing the estimates. Having at least some quantitative data for one or two of the strongest and weakest factors to calibrate our judgments against would have helped understand the magnitude of their impacts and consolidated the qualitative judgments presented.

Dr. Paul T. Roberts

Revised Comments on 1st draft REA

Air Quality Considerations (Chapter 3), REA Charge Question 1: Does the Panel find the considerations of current ambient CO monitoring data and the discussion of the extent to which near roadway concentrations are represented to be technically sound, clearly communicated, and appropriately characterized?

I think EPA did a very good job on the summary and presentation of the ambient CO data and the near-roadway data; however, I have some concerns about the classification of the ambient data from the sites in Denver and LA, and thus the use of that data as 'near-road' in the model in Chapters 5 and 6. My comments on this follow. In addition, I have a few minor comments and some suggested minor edit; these are included at the end.

I am still concerned about the characterization of the selected LA and Denver sites as 'near road', which then sets-up the base for the 2-mircroenvironmental model used in Chapters 5 and 6. The text on page 3-16 (correctly) states that current CO monitors are located near roads of moderate traffic (<100,000 AADT), but, in fact, the sites with the highest CO concentrations are really at the very low end of the moderate traffic range, at best; 10,000-17,200 AADT for Denver and 35,000 AADT for LA (see text at page 5-25, lines 11-20). In addition, the LA site is 350 m from the 35,000 AADT freeway, well outside the recommended range for micro-scale CO monitors of 2-10 meters (EPA monitoring guidance, 40 CRF Part s 53 and 58; ref below) or for the proposed NO2 near-roadway monitors of 50 meters (Proposed NO2 NAAQS Factsheet, ref below).

In addition, there are a couple more references to illustrate characteristics of 'near-road' monitoring locations, including:

- http://www.fhwa.dot.gov/environment/airtoxicmsat/protocol.htm Detailed Monitoring protocol for the U.S. 95 Settlement Agreement, June 12, 2006 by Battelle for FHWA....should only consider locations with freeway traffic of at least 150,000 AADT
- http://www.epa.gov/air/nitrogenoxides/pdfs/20090722fs.pdf Proposed NO2 near-roadway monitoring locations "...A second monitor would be required near a major road in areas with either: (1) population greater than or equal to 2.5 million people, or (2) one or more road segment with an annual average daily traffic (AADT) count greater than or equal to 250,000 vehicles. .....EPA also is proposing specific criteria for siting new NO_2 air quality monitors near major roads. These include identifying road segments ranked with the highest traffic levels by AADT and identifying locations where the highest peak concentrations of NO_2 are expected to occur, and placing monitors no more than 50 meters (about 164 feet) away from the edge of the nearest traffic lane."
- EPA monitoring site guidance suggests that microscale (street canyon or traffic corridor) sites be located 2-10 meters from the edge of the nearest traffic lane (40 CFR Parts 53 and 58, October 17, 2006, page 504,

http://www.epa.gov/ttn/amtic/files/ambient/pm25/092706sign.pdf Note that this is a link to the final, but not the published version; I can't seem to find that version on the EPA/AMTIC web site)

Page 5-25, lines 20-23: This statement attributed to Rodes et al. (1998) is not supported by the text or tables in that report, especially due to the poor detection limit of the CO monitors used both in the vehicles and for roadside and ambient CO measurements. See, for example the comments on page 146 of Rodes et al., 1998 regarding in-vehicle CO ("The relatively low levels of CO currently found in commuting California vehicles posed a significant measurement problem for portable monitors with a MQL of 2 ppm") and on page 140 for ambient and roadside monitors (" The very low concentrations measured at both ambient and roadside sites were consistently below the MDL of the study monitors. This makes it impossible to draw conclusions about the predictive relationships for CO."). By the way, based on data for other pollutants for which they had better detection, they make the statement that "Roadside pollutant measurement provided significantly better indications of in-vehicle pollutant concentrations than did ambient sites, but were still low by factors of 2 or more [for] many commuting scenarios." Rodes, et al., 1998, bottom of page 150. Given these qualifications in the published report, I am not sure that these data should be relied on strongly for the conclusions using Table 5-2, for example.

Characterization of Exposure (Chapters 5 and 6): The following comments are in regard to the usefulness of the simplified approach to exposure assessment...and on the relative merits of alternatives or modifications to this approach, in light of uncertainties and limitations of timefor this review.

Overall, I am concerned about the decision to take the CASAC Panel comments regarding the inadequacy of the monitoring data to represent the spatial extent of human exposure (REA, page 1-5, lines 15-19, Brain and Samat, 2009) so seriously that EPA staff did only a draft, screening-level analysis around one site in each of two cities. I thought that those comments would influence EPA to develop an adaptive approach using monitoring data and GIS, traffic count data, etc., or some other method, such as land-use regression, to estimate the spatial variability of exposures, similar to what is mentioned on page 3-11, lines 15-17. Note that this more-detailed analysis is what is often done for the exposure analysis for many health studies (see, for example, publications from the Children's Health Study such as Gauderman, Avol, Lurmann, Kuenzli, Filliland, Peters, and McConnell "Childhood Asthma and Exposure to Traffic and Nitrogen Dioxide, Epidemiology 2005; 16, 737-743). I did not expect EPA to perform only a simple, two-microenvironment model for exposure with just one environment represented by monitoring data and one in-transit microenvironment. It seems like this approach places all of the variability in exposure on the various parameters associated with individuals and none of the variability on the actual ambient concentrations to which those individuals might be exposed (as summarized in Table 6-24, plus the uncertainties summarized in Table 6-25). So my question becomes: does the range of CO concentration represented by the ambient and in-transit microenvironments and the assumed time of exposure in those microenvironments properly represent the true exposures? I am not sure that this is the case. It seems to me that this draft, screening-level assessment is a good first step, but I would prefer to see a follow-on, more-detailed analysis to be confident in the results, or a convincing discussion that these properly represent the variabilities and uncertainties of the actual exposure.

Based on the discussions during the meeting, and the available time to complete this review, my comments and recommendations are as follows:

- I do not agree with the comments on page 6-13, lines 30-35 and continuing on page 6-14, lines 1-2. As stated above, although these monitoring sites are the best available ones, they do not properly represent the exposure near busy roadways in LA or probably in Denver (I don't have the data on traffic on other roadways in Denver, so can't make as specific comments as I can about LA). See my comments above on the level of traffic on the roadways near these sites, which are way below busy roadways in LA (less than 10,000-35,000 versus the 150,000 plus on many other roadways in the LA area. Also, as mentioned above, these sites are actually not very close to the roadways; they should be 2-10 or maybe up to 50 meters from the edge of the roadway to properly represent near-roadway concentrations. Even given that the suspected zone of influence may be much larger during nighttime or low-wind conditions, monitoring sites need to be close to represent the daytime period.

- The simplest approach, given this late data and the time still available to finish this review, would be to run some cases as sensitivity runs of the model with an additional microenvironment to better represent near-roadway exposures. For example, maybe use the measured ambient data to represent data beyond 300 meters, use the ambient data increased by a multiplier from the literature, and then use the in-vehicle multiplier, such as 2 used in the current draft REA, to increase the near-road value to represent the in-vehicle concentration. However, given that the selected LA and Denver sites probably represent something closer than the 300 meter 'urban background' from papers such as Zhu et al., 2002, maybe the factor should not be as large as the factor of 10 from the Zhu et al., 2002 paper (see discussion on page 3-10, lines 19-29). Staff could review the various LA papers (Zhu et al, 2002; Zhu et al., 2006; papers by the Sioutas group at USC, plus others) and select a ratio less than 10. I recognize that some of these papers do not have CO data, but they have data for other primary vehicle pollutants which can support the selection of a ratio. Also, there is not similar literature data for Denver, but I think the general drop-off in concentrations for LA can be used for Denver. Maybe this approach could be implemented as scenario C, in order to compare with the A and B scenarios. Using this approach would result in higher numbers of person-days at specific CO concentrations levels, compared with numbers for scenarios A and B in the "As Is" columns of Tables 6-8 to 6-14, and thus illustrate the results for a full range of exposures with more-realistic near-road exposure conditions.

The in-vehicle to near-road ratios suggested (2, for the model) are reasonable. However, there is additional literature which could be added to Table 5-2, Page 5-20. For example, I am not sure why recent California ARB papers are not included here? Papers such as those by Westerdahl (2005) and Fruin (2008) could be included.

My comments regarding the characterizations of uncertainty, as represented in Table 6-25 and surrounding text, for example, are as follows:

- Although I do agree that the CO exposures are over-estimated for MOST individuals, I believe that CO exposures are actually underestimated for the large fraction of individuals who live or work or go to school near roadways and spend significant time commuting. See my earlier comments on my reasons and potential ways to address this.
- I think that the most significant uncertainties from this table could be better quantified by using sensitivity runs of the model. Sensitivity runs might include variations in the fractions of individuals living, etc. close enough to a major roadway to receive the higher, near-road concentration in scenario C, for example, and variations in transit time that would represent longer periods of exposure to the in-vehicle microenvironment.

Additional detailed comments:

Page 1-2, lines 3-6: Several places in the REA, a previous report is mentioned, such as this NRC report. It was really help the reader if a one or two sentence summary were also provided. Other places include page 1-4, lines 25-27, page 5-2, lines 18-19,

Page 3-3, lines 7-16: In this discussion, it is implied that the trace-level monitors are needed for exposure analysis at current CO concentration levels, but it would be better to state it directly, possibly at the beginning of the list of reasons on lines 12-16.

Page 3-3, lines 19-29: The ISA text (page 3-20, for example) used the term LOD while the REA uses MDL; please be consistent or explain the difference. Also, Table A-1 in the ISA listed MDL for the trace-level monitors as 0.02 (there are no 0.04 MDLs listed), so delete the reference to 0.04 MDLs in lines 25 and 29. Also provide the reference in the ISA for all this.

Page 3-10, line 26: Modify to read "…greater than *measurements taken* at…" since they used one set of monitors and moved them around to represent concentrations at all distances, not separate monitors at each distance from the roadway. Note that this means the measurements at different distances are not at the same time.

Page 3-11, lines 13-17: Note that this more-detailed analysis is what is often done for the exposure analysis for many health studies; see, for example, publications from the Children's Health Study such as Gauderman, Avol, Lurmann, Kuenzli, Filliland, Peters, and McConnell "Childhood Asthma and Exposure to Traffic and Nitrogen Dioxide, Epidemiology 2005; 16, 737-743.

Page 4-3, lines 22-23 and 31-32: It seems like these two statements are contrary to each other; please explain. How can the data be insufficient for a dose-response relationship but one could confidently attribute a COHb dose level to a CO exposure?

Chapter 5, sections 5.1-5.3 on the APEX model: This is a great discussion of the model's capabilities; however, I would like to see an emphasis on those capabilities that are actually used in this analysis; maybe a short section with a list of what is used here would help. [I see in a few places where the text says that this current aspect is not used, but a summary at the end would be much better and help the reader recognize what is used in one place].

Minor edits and typos in the 1st draft REA:

- Page iii: The title for Figures 5-1, 5-2, and 5-3 are duplicated in the List of figures.
- Page 2-1, lines 4-6: this part of the introductory sentence is quite awkward.
- Page 2-2, line 14: use "are also important"
- Page 2-2, line 19: delete "on".
- Page 3-2, line 3: the details for footnote 2 are missing.
- Page 3-10, line 31: insert a comma after estimates.
- Page 3-11, line 12: Make end of line read "(draft ISA, Figure 3-17)".
- Page 4-2, line 3: add the dates for the reference (1989a, 1989b).

- Page 4-2, line 29: it would read better if the word “decrease” were inserted after “and”.
- Page 5-16, line 11: I think this reference should be draft ISA, page 3-98, Figure 3-43.
- Page 5-21, line 24 and 5-22, line 1: this should be Table 5-3.
- Table 6-25, page 6-38: please include the footnote regarding INF and KB on all 3 pages of the table.

Additional references:

Zhu Y, Kuhn T, Mayo P, Hinds WC. Comparison of daytime and nighttime concentration profiles and size distributions of ultrafine particles near a major highway. *Environmental Science & Technology* 2006;40(8):2531-2536.

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Westerdahl, et al (2005). Mobile platform measurements of ultrafine particles and associated pollutant concentrations on freeways and residential streets in Los Angeles, Atmospheric Environment ISSN 1352-2310, 2005, vol. 39, n°20, pp. 3597-3610

Fruin, S.A., Westerdahl, D., Sax, T., Fine, P.M., Sioutas, C. Measurements and predictors of in-vehicle ultrafine particle concentrations and associated pollutants on freeways and arterial roads in Los Angeles. Atmospheric Environment, 42(2):207-219, 2008.

Dr. Armistead (Ted) Russell

In general, the CO Risk and Exposure Characterization was clear and informative, and is a good start on a more comprehensive REA. I think it begins to provide a foundation for the coming policy assessment to link potential primary standards to potential health effects. On the other hand, it was a bit disappointing.

The major disappointment had to do with how the exposure modeling was done in that it appears to be a step backwards from what was done in the last CO review, and the current analysis is biased. I would prefer taking an approach that is unbiased (or at least less needlessly biased), and individuals can interpret the results and add their individual amount of conservatism later in the process. Specifically I refer to using the highest monitor in the region, with a 20 mile impact radius, rather than a number of monitors each with a smaller area-of-influence. Using the highest monitor leads to the greatest modeled exposures, one that is likely biased high. Using multiple monitors reduces this bias. I was also disappointed by not using indoor sources in the modeling. Thus, the prior modeling was more comprehensive and informative. It would be better to provide less biased estimates and an assessment of the uncertainties. I was glad to see both the prior and current results provided. A question that came to mind is whether APEX has changed in such a way as to significantly impact the model results. If not the prior results may be more informative. If so, the degree to which model changes have impacted results should be discussed.

One problem with presenting the results as COHb levels is that it was not easy to assess the severity of the exposures with likely health outcomes, and the document was weak on this issue as well. What are the likely health ramifications of COHb levels of 1.5, 2, 3 or possibly higher? How does this interplay with COHb levels at those levels to a given fraction of the population? The discussion on pages 6-42/43 need to be more informative on this issue. This is both a risk and exposure document, and there should be more on what are the likely risks. It would be valuable to have a succinct discussion of the likely current risks from CO exposure nationally. That brings up an additional need is how the analyses for LA and Denver relate to risks and exposures nationally. The analysis done as part of the PM Risk Assessment was effective in this direction (Chapters 4 and 5 of the RA for PM… though that document would benefit from a Chapter 6 integrating them.)

I would also have appreciated examining other potential standards if changes are to be made. The current analysis suggests that there are potential exposures of concern (using COHb cutoffs of 2.0% or so), but there is no information as to how the fraction of potential exposures will respond to lower ambient CO levels reflecting tighter standards.

I also note that, like NO_2, the highest exposures to CO will likely happen in-vehicle or near to the road. If a near-road network monitoring network is to be developed, the maximum ambient levels observed will likely increase, and the in-vehicle-ambient monitoring relationships will likely change, possibly dramatically. This should be explored here. The information available in making the policy assessment should provide the needed risk and exposure characterization to

adequately inform the determination of a standard if a new network design were to be put in place.

In summary, this is a solid start. I am glad to see the exposure modeling, though it should have been more realistic (use more monitors, larger area, similar to, or preferably beyond that done in 2000). Next, if a change in standards is envisioned, this document should evaluate how a such a change might impact exposures. Without such, an important part of the foundation for future action is missing. Third, if there is going to be a change in the monitoring network,, the REA should assess the implications of such a change.

In response to the Charge Questions:

1. Air Quality Considerations

This discussion is fine.

2. Selection of Health Endpoints, etc.

2.1. Health endpoint… sound, clear and appropriate?

2.2. Does the range of benchmark reflect the ISA

2.3. Is the derivation of COHb levels sound, clean, appropriate.

3. Characterization of exposure

3.1. Relationship between in-vehicle and ambient … sound, clear and appropriate?

While the approach taken is clearly communicated and well characterized, it is somewhat over simplified. The in-vehicle and ambient concentration data relationship is variable, and it a more comprehensive treatment of this variability would be appropriate. Given the isse of using just the highest monitor for CO concentrations, there is a potential for hidden bias in that the studies upon which the factor is based typically relate in-vehicle data to a central site monitor, not the highest central site monitor. As noted in the REA, there is also the issue of vehicles having much higher CO emissions at the time of the studies mentioned than are typically present today. The potential for being near a high emitting vehicle was greater, leading to an excessively, and unrepresentatively for present conditions, high CO level in the vehicle. The biggest concern, here, however, is that the ratio of two is taken using three locations that do not represent the highest CO levels in the area.

3.2. Approach taken

As might be evident from the above, there is likely unexplored bias in the approach taken. I would prefer using methods without such bias built in.

3.3. Exposure analysis … sound, clear and appropriate?

The exposure modeling is well laid out, clear, and given the assumptions made, using an appropriate approach. However, it is disappointing to see that the prior REA was done in a way I think is better, with less built in bias, and able to better catch the distribution of exposures.

3.4. Adequacy of the assessment of uncertainty and variability? Sensitivity analysis?

The first sensitivity analysis I would conduct is to use a variety of CO monitors in the analysis, e.g., similar to what was done in 2000 as part of the prior REA. Second, I would, if possible, do a head-to-head comparison of the models used in 2000 and this time. A third sensitivity

analysis should assess how concentrations that would be measured near the road would be reflected in a simulated in-vehicle concentration.

3.5. How does the simplified approach help?

3.6. Recommendations regarding how the approach might be modified?

Additional Comments:

2-2/23 Make sure we use susceptibility and vulnerability consistently between documents. (I personally like the distinction, but recognize some do not because of the ambiguities.)
3-3: Define GFC (I did not immediately see it defined, above)
3-3/29 Replace below with "better than"
3-4/21: The number of stations belongs further up, e.g., Page 2-1 or 2-2, as part of the network description.
3-12: How much does the PRB contribute to COHb? If it is straight forward to calculate, that might be of interest.

Dr. Anne Sweeney

REA Charge Questions 5-6, Chapters 5 and 6

1. Page 5-14, lines 33-34. This may present a problem, as many people commute long distances from their homes, and may experience a change in air quality over the route.

   E.g., in a ranking of large cities (with populations of 250,000 or more), New York (38.3 minutes); Chicago (33.2 minutes); Newark, N.J. (31.5 minutes); Riverside, Calif. (31.2 minutes); Philadelphia (29.4 minutes); and Los Angeles (29.0 minutes) had among the nation's highest average commute times. The average two-way commute distance in Los Angeles is 29.8 miles
   http://www.census.gov/Press-Release/www/releases/archives/american_community_survey_acs/004489.html
   (http://www.zevnet.org/car_summit/01%20Summit_Recker.pdfay)

2. The simulated population was assigned age and gender distributions to be representative of the target population. However, there is no mention of active or second hand smoking status, which would greatly influence the study results. Consideration of at minimum second hand smoke exposure is recommended.

Dr. Stephen Thom

RISK AND EXPOSURE ASSESSMENT – FIRST DRAFT:

Charge questions:

Air quality considerations (Chapter 3)

I found the discussion clear and appropriate.

Selection of health endpoints, etc (Chapters 2 and 4, Sections 5.3.7 and 6.2)

Rationale for selecting health effects benchmark values of 1.5, 2.0, 2.5 and 3.0 %: Research supports - and the ISA states - that there is no threshold for CO mediated health effects. I recognize that benchmark values had to be chosen to satisfy pragmatic needs. The choices were arbitrary but logical given the range of exposures in controlled health effects studies. Moreover, use of these levels in the modeling charts (e.g. Tables 6-12 and 6-13) was useful for demonstrating the small portion of the population at risk.

Characterization of Exposures (Chapters 5 and 6)

The history of the EPA's human exposure and dose model (APEX) is clear. The additional discussion on microenvironments and especially the importance of indoor and in-vehicle exposure assessments was also logical but leads to a rather fundamental question. Does the emphasis/concern pertaining to microenvironments render APEX unusable or are there data for CO uptake and elimination patterns relevant to indoor and in-vehicle environments (*e.g.* activity estimates which influence uptake, etc.)?