19 March 2010 Preliminary Review Comments from the CASAC CO Panel on the *Second Draft Risk and Exposure Assessment to Support the Review of the Carbon Monoxide Primary NAAQS*

Comments received:

Dr. Thomas Dahms 2
Dr. Milan Hazucha 5
Dr. Francine Laden 10
Dr. Paul T. Roberts 11
Dr. Anne Sweeney 13
Dr. Stephen Thom 14

Dr. Thomas Dahms

5. Does the Panel find the derivation and presentation of the modeling approach as a whole (Chapters 4 and 5) to be technically sound, clearly communicated, and appropriately characterized?

The detailed description of the apex model provides a helpful snapshot of the extensive nature of the model. The application of the CHAD database in modeling the physiological changes of simulated residents during their daily lives seems to be appropriately handled. This approach has been applied and vetted for other regulated air pollutants. The presentation of the material seems to be aimed at the exposure modeling community which makes it difficult to assess for someone not in the modeling community.

Appendix C contains some helpful illustrations of the variability in time spent for an individual in locations/activities during a year. It would be helpful to have a similar illustration of estimated %COHb levels of %COHb in an individual during a day with near criteria levels of atmospheric CO and also an illustration of the variability in peak levels of %COHb thoughout the year. Additions of these illustrations to the text rather than in the Appendix should be considered. It would assist the reader in understanding the variability in the modeled levels of dose of CO.

The coupling of the non-linear CFK with the CHAD in the APEX model would be more convincing if there were references to validation of this model in studies where measurements of dose were made. Without documentation of such validation, the reader is expected to accept this model based on years of improvements over other models.

Since the controlled human exposure data is a major factor in setting policy, it would be helpful to see how well the exposure model predicts the measured CO dose in these experiments. Although these exposures are for only 1 hour with subjects at rest, it would provide a means of validation of the exposure/dose modeling used for the general population. It might also provide a means of comparison of the various controlled human exposures.

6. Does the Panel find the derivation and presentation of the COHb estimates (chapters 5 and 6) to be technically sound, clearly communicated, and appropriately characterized?

The presentation of how the model arrives at estimates of %COHb in the population of Denver and Los Angeles is clear in that it follows a natural progression in this field over the past 40 years. It is clearly communicated and the improvements in the modeling over the years is clearly presented and is very rational. There are concerns with the output of the model that leads to a level of uncertainty that could be somewhat reduced as described below.

The primary goal of this section would be to determine whether or not the estimated levels of %COHb (from the model) using the current as is data are lower or higher than those estimated levels of %COHb using the current standards. It is presumed that the exposure to the current standards for CO results in a small but acceptable number of at risk persons for a given %COHb

benchmark. If the current as is data results in a smaller number of persons at that benchmark, there would be little pressure to change the standards. Therefore the issue that needs to be discussed/defined is : what is a small but acceptable number of persons who can be exposed at an acceptable benchmark. This discussion is absent.

It is not clear what background in modeling minutia the reader is expected to have to clearly understand and analyze the details of the material presented. The crux of the matter is that for carbon monoxide there is an agreed upon dose metric, %COHb, that can be used to evaluate exposure. This is not quite the case for the other regulated pollutants. There is no mention of any attempt to validate the model being used under any circumstances. No matter how sophisticated the model, without validation it is just a model with all of the attendant uncertainties.

The presentation of the information in section 6.4 on the influence of endogenous rates of CO production on dose estimates is potentially a problem. The description of what endogenous rates were used in the model is unclear and the information on Table B-3 on page B-20 is very poorly labeled. The values used in this portion of the model need to be clearly documented and justified. This becomes and issue because this modeling data is used to justify not including 1.0 %COHb in the Policy Assessment document. The modeling of all of the parameters that impact baseline %COHb into 'endogenous rates of CO production' as the primary determinate of baseline (no CO exposure) %COHb. This comes to light in Table 6-17 on page 6-18 which shows the APEX model to result in a median value of %COHB somewhere between 0.25 and 0.50% COHb and the non-parametric distribution of values is considerable. The modelers claim that this data can not be compared to any studies in the literature because of the time frame over which the data is modeled. Unfortunately there will always be skepticism of any model that can not be validated practically with actual measurements. The study by Allred et al observed 63 subjects in 3 cities on 4 experimental days (repeated measurements on an individual occurred within 6 weeks) and all of the subjects were observed over less than a 2 year period (270 measurements of baseline levels of %COHb). The mean %COHb levels did not vary over this period of time. These values ranged between 0.62 and 0.64 %COHb with a standard deviation of 0.16% COHb. The model results does not fit these results on the population most at risk in this assessment.
The search for a alternative formats for setting standards maybe statistically enticing but would present too many problems for implementation of public health measures when the standards have been exceeded. News readers have a difficult time with the current standards provided in PPM so I can only imagine how they would attempt to explain any of the proposed alternative methods.

There is also no attempt made to employ the model in the studies dealing with controlled exposures in subjects with CAD. I know that using APEX to model a 1 hour exposure to CO is akin to killing a slug with a sledge hammer, but what other data base is as relevant to validation of the model being so widely used?

7. In the Panel's view, to what extent does the modified assessment approach employed in this second draft assessment provide results that meaningfully inform EPA's consideration of the public health implications of the current standards?

The additional information included in the current modification does not relieve the anxiety from the use of so little monitoring data to provide guidance for setting standards. Perhaps it is in the way in which the information is presented: there is no data presented or referred to that shows that including more data adds nothing to the analysis. As a result of what has currently been presented, I am still uneasy with the use of so little of the available monitoring data for this risk assessment. Does the use of data from a few monitoring cites imply that we need fewer monitors in our cities because we can accurately predict what exists in the entire metro area based upon a few monitors? How is the reader to interpret the use of data from so few sites. To state the above concern in another way, the document could be improved by showing the impact, or lack of impact, on the dose variability by including data from more monitoring sites. This could be previously published information and need not involve re-running of the models with data from these additional sites.

There is also mention of the lack of data resolution of the LA monitors vs the Denver monitors but the impact of the low resolution monitors in LA is not discussed. If it has no impact why was the issue raised?

It is my impression that the estimates of risk due to exposure to CO are to apply to entire country and not just to Denver and Los Angeles. It is clear that the detail presented for these two cities can not be also presented for all of the major metropolitan areas of the country. However it is incumbent upon the authors to address how these risk assessments for Denver and LA are to be applied to the entire population of the United States. After all the document goes to great lengths to describe how many people are in the at risk group in the country and then applies some metric to determine how many of these individuals are in Denver and in LA.

Dr. Milan Hazucha

1. Does the Panel find the summary of CO exposure and discussion of ambient CO sources, exposures, dose, health effects and risk characterization approach to be technically sound, clearly communicated, and appropriately characterized?

Qualified yes in all respects.

In addition to already mentioned endogenous CO production and exogenous sources (p. 2-6, l. 11-13), additional source is metabolic production of CO due to inhalation of, e.g., dihalomethanes, other substances and certain medication.

Do we really consider people using recreational drugs to be at-risk population and be considered in risk assessment (p. 2-8, l.19)? If so we will have to consider smokers to be at-risk population as well.

Since Allred et al. studies provide the key evidence for CO health effects assessment it would be very helpful if the document, in addition to % changes of the critical endpoint, e.g., time to angina also reported the actual mean and CI (confidence interval) values in respective endpoint units (p.2-11, l.24-27 and p.2-12, l. 10-13). How clinically significant is shorter by 22 seconds time to angina out of nearly 9 minutes? Besides reduced time to angina, was the duration and the intensity of angina affected as well? Did frequency of angina attacks increased because of CO exposure? If these endpoints were not reported by the investigators, it should be specifically stated so in REA.

I support very cautious approach to some epidemiology studies reports of the effects of CO on respiratory system (p.2-10, 2-13, 2-18). I fully agree with EPA assessment that the interpretation of CO-induced lung-related outcomes "is affected by uncertainties including with regard to the biological mechanism that could explain CO-induced outcomes" (p. 2-13, l. 8-11).

As far 1% COHb benchmark suggested by the Panel, the staff correctly pointed out that "this level overlaps with the upper part of the range of endogenous levels" and decided not to focus on dose estimates (p.2-16, l. 26-34). I support this approach since this complies with the EPA's task "to establish standards that are neither more nor less stringent than necessary for these purposes", .i.e. public health.

2. Does the Panel find the considerations of current ambient carbon monoxide monitoring data, including specifically the data for the monitors included in this draft of the assessment, and the discussion of the extent to which near roadway concentrations are represented to be technically sound, clearly communicated, and appropriately characterized?

Yes in all respects.

3. In recognition of CASAC comments of first draft REA, this draft REA is expanded from the previous assessment in a number of ways (summarized in section 1.3 of the draft document). The assessment study areas are 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. What are the Panel members' views on the following aspects in which the assessment has been expanded from the previous draft?

A. *An important change of this assessment from the first draft is the expansion of each of the modeling domains to include a greater number of ambient monitors used as input to APEX. Additionally, this draft assessment employs an algorithm that adjusts for temporal and spatial heterogeneity in ambient concentrations across each study areas.*

The bulleted list of modified/expanded sections is very helpful. Similarly, the flow chart showing input points and flow of data has been very helpful as well.

Generally, larger number of monitors should improve exposure assessment. Figure 5.1 shows a considerable overlay of air districts, meteorological zones and for Los Angeles study areas as well. Although the overlapping districts, zones and areas were adjusted for as far as exposure goes, how were they treated in terms of input data into other modules of APEX? What approach was used to avoid duplication of input data? For L. A., was one of the areas designated as a dominant source or each area was considered separately in the assessment?

How does the expansion of modeling domains in this REA compare to REA1? Were the estimates about the same or different and how they were different?

In generation of simulated individuals, demographic variables should include socio-economic status and race. These variables will impact other APEX modules, particularly the COHb one.

B. *The current draft assessment also include an increase in the number of microenvironments modeled over that in the first draft (from two to eight) and improved the representation of variability in estimated microenvironmental concentrations, including in-vehicles.*

In the current draft the number of microenvironments was increased to 4 indoor, 3 outdoor and 1 in-vehicle. Such expansion may improve strategies and enhance the validity as well as credibility of the assessment. More realistic scenarios provide stronger and more representative base for decision making.

C. *This draft assessment has implemented the mass-balance model for estimating concentrations in indoor microenvironments.*

I consider the selection of mass-balance model for indoor air appropriate.

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

Qualified yes to all respects.

The various modules of APEX model are regularly upgraded to improve the simulation process making it as realistic as possible. Yet the COHb module to estimate venous blood COHb level, the ultimate endpoint remains the same, i.e. based on CFKE (p.4-34, l.20-31). As already commented on this matter by several panel members including myself in the past why is EPA so adamant exploring more recent and more sophisticated CFK equations? Replacing original CFK with an enhanced, e.g. Bruce and Bruce module should be simple enough. If there are no substantial differences, then no change is necessary. However, if there are differences in COHb estimates, then we may search and evaluate the factors that may have affected the change. Such information may potentially useful in standard setting.

Moreover, regardless of a mathematical model employed in COHb module, the COHb estimates can be improved by tuning some of the explicit input variables such as THb and DLco.

Appendix A: I absolutely agree with the summary of findings (p. A-5) that the current physiology file data is obsolete and may even be incorrect for some variables. The overall approach to replacing obsolete physiologic variables with more representative values is highly desirable.

5. Does the Panel find the derivation and presentation of the modeling approach as a whole (chapters 4 and 5) to be technically sound, clearly communicated, and appropriately characterized?

Yes in all respects. The staff did an excellent job of presenting and discussing APEX model. I agree with well reasoned arguments and the conclusions.

Any concerns about the effect of missing concentration values on their distribution were cleared by addition of descriptive statistics tables (5-7 through 5-10). The tables demonstrate that the missing values whether estimated and corrected for or not do not influence the distribution of hourly values either in Denver or Los Angeles. Similar approach to estimation of missing temperature values required by APEX likely resulted, as stated in the document, in negligible differences.

6. Does the Panel find the derivation and presentation of the COHb estimates (chapters 5 and 6) to be technically sound, clearly communicated, and appropriately characterized?

Qualified YES in all respects.

The estimates of respective endpoints tabulated in section 6.1 “Estimated Exposures” are based on different years of ambient CO concentrations in. Why some estimates are based on ambient data from 1995 and 1997, while others on 2006 data? The ambient CO levels are more than 50% lower in 2006 than 1995 and 1997. Moreover, it would be helpful to be consistent in organization of the tables, e.g. some tables list COHb levels in ascending order while others in descending order.

Section 6.3.1 referenced in the document is likely section 6.4.1.

The section 6.4 on endogenous production of CO and its contribution to overall COHb in combination with ambient levels of CO is very informative. Table 6-17 clearly shows that even at 0 ppm CO in ambient air several hundred individuals will reach COHb level as high as 1.8%. It would be instructive to identify groups of individuals (e.g. with anemia) who exceeded 1% COHb level due to endogenous production.

Figure 6-2 shows, as expected, that endogenous CO will not influence COHB level if the ambient CO concentration exceed the one produced endogenously (this needs to be stated more clearly on p. 6-21, l. 6-8). Figure 6-4 indeed confirms the above statement.

Appendix B. COHB module:
p. B-3: The P_{Ico} , should be defined as a partial pressure.
p. B-5 In eq. B-11 and B-14 P_{co2} subscript should be correct to read not as CO_2 (carbon dioxide) but as c_{O2} (capillary O_2).

Suggest to move the second paragraph on page B-8 as the first paragraph of the section, otherwise without the explanation, the statement is misleading.

p. B-9- B-14. Section C4: The COHb module seems to be the weakest of the APEX modules. Primarily, it is because we do not have sufficient data over the physiologic range for many variables. However, though still limited some physiologic data are available for healthy and at-risk groups and they should be integrated into data base for COHb module. From the tables nor the text it does not look like that many critical variables such as Hb, DLco, endogenous CO and others were, besides age and gender, adjusted for other physical characteristics or disease conditions. For example, the amount of Hb will determine the rate of COHb formation and is a critical variable. There are substantial differences between blood concentration of Hb in whites and blacks.

> *7. In the Panel's view, to what extent does the modified assessment approach employed in this second draft assessment provide results that meaningfully inform EPA's consideration of the public health implications of the current standards?*

I agree with the expanded approach and I believe that it will allow for more accurate assessment and risk-characterization.

8. 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 characterized? To what extent has variability adequately described and represented?

The staff adequately described uncertainty and variability. However, from table 7-1 it appears that CHD has been considered to be the only sources of variability and no other disease conditions were considered in the model. Why no other relevant diseases were considered? Was socio-economic status in any way considered in estimating uncertainty?

Does APEX model has build in any internal consistency check between factors used in the calculations (p. 7-2)? For example, randomly selected oxygen uptake which may be high maybe assigned to an individual with CHD who is unable to achieve such uptake level.

Activity patterns of persons 30 years ago used as APEX input are very much different for current activity patterns (p. 7-8). Can CHAD data be limited only to more recent activity patterns?

Dr. Francine Laden

1. Does the Panel find the summary of CO exposure and discussion of ambient CO sources, exposures, dose, health effects and risk characterization approach to be technically sound, clearly communicated, and appropriately characterized?

Chapter 2, background on assessing ambient CO exposure and risk, is well organized and technically sound. EPA appropriately characterized what they did do, as well as what they did not do. The discussion explaining the uncertainties associated with directly using studies of the association of cardiovascular morbidity with measurements of ambient CO is important for motivating the focus on COHb levels. It may not be immediately obvious to all readers why ambient CO exposures are not the exposure of interest. One concern is that most of the monitoring data and the laboratory data crucial to the assessment is quite old and could thus effect the determination of risk. Is EPA confident that current situations can be extrapolated appropriately from what was observed in the past? Perhaps some statement to this uncertainty would be valuable, as well as acknowledgement that there are not any appropriate-more recent studies available. For the most part the chapter is clearly communicated. However, the chapter overall would benefit from some careful editing.

5. Does the Panel find the derivation and presentation of the modeling approach as a whole (chapters 4 and 5) to be technically sound, clearly communicated, and appropriately characterized?

The derivation and presentation of the modeling approach as a whole is very well presented. I had one trivial question: Could the prevalence of undiagnosed CHD be greater for women than for men? The model assumes that the ratios of undiagnosed cases to diagnosed cases are identical for each gender and also that this ratio has not changed since 1990. The text should at least acknowledge that this might not be so.

6. Does the Panel find the derivation and presentation of the COHb estimates (chapters 5 and 6) to be technically sound, clearly communicated, and appropriately characterized?

The derivation and presentation of the COHb estimates are technically sound, clearly communicated and appropriately characterized.

7. In the Panel's view, to what extent does the modified assessment approach employed in this second draft assessment provide results that meaningfully inform EPA's consideration of the public health implications of the current standards?

The draft assessment provides results that meaningfully inform EPA's consideration of the public health implications of the current standards. Given that CO levels have decreased significantly over the years, that levels rarely approach the standards, and that elevated levels of COHb estimated by the risk assessment are quite low, the usefulness of the current standards may need to be reassessed.

Dr. Paul T. Roberts

2. Does the Panel find the considerations of current ambient carbon monoxide monitoring data, including specifically the data for the monitors included in this draft of the assessment, and the discussion of the extent to which near roadway concentrations are represented to be technically sound, clearly communicated, and appropriately characterized?

In general, the treatment of the CO monitoring data and the (admittedly poor) extent that these monitors represent near-roadway concentrations, including the data used for this version of the assessment, are improved over the 1st external draft REA, technically sound, clearly communicated, and appropriately characterized. In addition, the use of data from more monitors as input to the exposure modeling is a significant improvement.

Characterization of Exposure (Chapters 4 and 5)

The following changes from the 1st external draft REA are significant improvements and help the results from this REA do a much better job of informing our review of the CO NAAQS.

- Expansion of the modeling domain to include more monitors in both Denver and LA.
- Adjusting for both spatial and temporal heterogeneity in ambient CO concentrations in each study area.
- A significant increase in the modeled microenvironments.
- The use of a mass-balance model for estimating CO concentrations in indoor environments (factors are reasonable estimates for the other microenvironments).

However, I am concerned about the use of the power of .621 in equations 4-11 and 4-22, which reduces the CO concentration at an outdoor location, relative to the nearest central monitor. The main justification for this is given on lines 33 to 35 of page 4-27 as a way to get the pNEM/CO and APEX models to agree, but I do not understand the physical rationale for this. On page 5-23, lines 8-10, it is suggested that the resulting "compression effect" is consistent with Wilson et al (1995). However, even if we agree that this might be occurring near most residences, as in the Wilson study, it does not occur at near-roadway or in-vehicle locations. In fact, the net result of using this as part of the factor calculation for estimated CO concentrations is that near-roadway and in-vehicle concentrations are a fair amount lower than was documented in the 1st REA, section 5.4.2 (in-vehicle concentrations) and in the ISA for near-roadway. Since these two microenvironments might be contributing a fair amount to total exposure, I think this is an important issue to resolve. In addition, the use of this factor for near-road and in-vehicle microenvironments has probably decreased the percent of people who experience the highest concentration exposures, for example in Chapter 6.

Table 5-16 is a good summary of the various conditions in the 8 microenvironments, especially with the distributions. I did noticed, however, in Appendix that a couple of locations codes are probably mis-assigned, although these are probably small contributions: bicycle should be 5, as shown in Table 5-16, and all the boat categories should be 8, since boats are uncontrolled for CO

and produce significantly high CO concentrations (they should probably be much higher than 8, but again this is probably a small contributor).

> *8. 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 characterized? To what extent has variability adequately described and represented?*

In general, the incorporation of more monitors in each area, more microenvironments, and variability in various variables within APEX is an important method for addressing variability and thus general uncertainty in exposure and dose.

Although I still think that the most significant uncertainties from this table could be better quantified by using sensitivity runs of the model, I understand the time constraints on the current NAAQS process. I believe that the significant improvements in representing near-roadway and in-vehicle exposures has reduced the uncertainties associated with that end of the exposued population, as represented in Table 7-2.

Dr. Anne Sweeney

1. Does the Panel find the summary of CO exposure and discussion of ambient CO sources, exposures, dose, health effects and risk characterization approach to be technically sound, clearly communicated, and appropriately characterized?

Overall, Chapter 2 is a very well-written comprehensive background that describes the issues and considerations that were confronted in the effort to assess ambient air CO exposure and human health risks. The contributions of the various sources of both ambient and indoor CO levels were clearly described and supported by numerous published studies. Exposure pathways and the importance of the microenvironment were also well-documented.

The justification for the utilization of persons with CHD as the unit of analysis in the quantitative assessment is appropriate, given the lack of data on COHb levels in other potentially high risk groups. However, characteristics of this simulated population that should be included in the modeling include the population prevalence of income level (a surrogate for several important covariates, e.g., residence near congested traffic areas) and smoking (also related to income level).

Dr. Stephen Thom

1. Does the Panel find the summary of CO exposure and discussion of ambient CO sources, exposures, dose, health effects and risk characterization approach to be technically sound, clearly communicated, and appropriately characterized?

The summary is accurate and appropriate.

2. Does the Panel find the considerations of current ambient carbon monoxide monitoring data, including specifically the data for the monitors included in this draft of the assessment, and the discussion of the extent to which near roadway concentrations are represented to be technically sound, clearly communicated, and appropriately characterized?

The discussion on current air quality monitoring is accurate and appropriate.

3. In recognition of CASAC comments on first draft REA, this draft REA is expanded from the previous assessment in a number of ways (summarized in section 1.3 of the draft document). The assessment study areas are 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. What are the Panel members' views on the following aspects in which the assessment has been expanded from the previous draft?

A. An important change of this assessment from the first draft is the expansion of each of the modeling domains to include a greater number of ambient monitors used as input to APEX. Additionally, this draft assessment employs an algorithm that adjusts for temporal and spatial heterogeneity in ambient concentrations across each study area.

B. The current draft assessment also includes an increase in the number of microenvironments modeled over that in the first draft (from two to eight) and improved the representation of variability in estimated microenvironmental concentrations, including in-vehicles.

C. This draft assessment has implemented the mass-balance model for estimating concentrations in indoor microenvironments.

I found the document to be generally well written. My one question pertains to the APEX modeling, as raised in my review of the Policy Assessment document. The discussion in the REA document includes information that most fixed monitors have a 1 ppm CO lower detectable limit so the modelers added 0.5 ppm CO to all measured values to remove zeros and negative numbers thought to be related to monitor drift. It seems to me that this makes it exceedingly difficult to accept estimates of the at-risk population and threshold COHb levels.

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

I am unsure if the draft exposure analysis is technically sound (see comment #3).