UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

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May 19, 2010

EPA-CASAC-10-012

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

Subject: Review of the *Risk and Exposure Assessment for the Review of the Carbon Monoxide Primary National Ambient Air Quality Standards (NAAQS): Second External Review Draft*

Dear Administrator Jackson:

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

The Panel expressed appreciation to EPA staff for the major improvements made in the second draft of the REA. The changes are responsive to the suggestions and concerns expressed by the Panel in its review of the first draft. Nonetheless, CASAC offers several suggestions and concerns to be considered as the second draft undergoes final revisions.

The Panel encourages a clearer distinction between the levels set for the CO NAAQS and the concentrations at which exposures are currently experienced throughout the country. Current levels of CO are far lower than historic levels and the risk for health effects associated with these current levels may be minimal or difficult to quantify with certainty. However, the degree of protection afforded to susceptible populations by the current NAAQS still needs to be considered by EPA. A greater degree of protection may be warranted.

As mentioned in its review of the first draft, the Panel felt strongly that the focus of the REA, and the associated *Policy Assessment* document, should be broader than cardiac ischemia (coronary artery disease or CAD). The Panel recognizes that compelling evidence comes from clinical studies demonstrating a relationship between elevated levels of carboxyhemoglobin

(COHb) and a reduced time to the onset of angina. These studies have been at the center of the evidence used to set the NAAQS for CO. However, there is increasing evidence that CO increases the frequency and severity of congestive heart failure and enhances susceptibility to arrhythmias. Consequently, we recommend that a broad set of health outcomes be considered, beyond cardiac ischemia. The susceptible populations might also include those with pulmonary disease and the fetus. The Allred et al. (1989) study should be more completely presented. While a reduction in time to onset of angina is an important and easily interpretable clinical outcome, this response is subjective. In contrast, the outcome of ST segment depression, as assessed by a blinded cardiologist, is an objective measure of myocardial ischemia and should receive greater consideration. Moreover, ST segment depression has been validated, both as an outcome of inadequate delivery of oxygen to the myocardium and as a risk factor for more frequent arrhythmias.

The Panel recommends greater clarity regarding the major contributors to COHb: ambient outdoor exposures, endogenous production of CO within the body, and finally indoor sources of CO from home cooking, heating, and passive smoking. The relative importance of these contributors to COHb must be more clearly delineated. The REA should address how these multiple sources are used in modeling and contribute to variability and uncertainty in model results.

We are concerned about two aspects of the adequacy of the current CO monitoring network. First, more sensitive and precise monitors need to be deployed to measure levels that are less than or equal to 1 ppm. Such monitors are needed to validate CO exposure models. Second, the approach for siting monitors needs greater consideration. More extensive coverage may be warranted for areas where concentrations may be more elevated, such as near roadway locations. The Panel found that in some instances current networks underestimated carbon monoxide levels near roadways. Such underestimation is a critical issue since populations with low social economic status (SES) are often overrepresented in those areas. People with SES are more likely to smoke, a substantial source of CO. In addition, African Americans have a higher incidence of sickle cell disease, which affects oxygen transport.

In regard to the quantitative risk assessment, the Panel recommends greater clarity in describing the model that was used, along with information available about its validity. The profile of COHb in time with varying CO exposures is complex since loading (increased COHb levels) is much more rapid than unloading of COHb levels as ambient CO levels drop. In an analysis that acknowledges multiple sources, it is essential to emphasize the increment which is attributable to ambient CO.

The CASAC and Panel membership are listed in Enclosure A. The Panel's responses to EPA's charge questions are presented in Enclosure B. Finally, Enclosure C is a compilation of individual panel member comments. We look forward to the Agency's response and the successful completion of the CO NAAQS review.

Sincerely,

/Signed/ ***/Signed/***

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

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

Enclosures

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 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. Paul Roberts, Executive Vice President, Sonoma Technology, Inc., Petaluma, CA

Dr. Armistead (Ted) Russell, Professor, Department of Civil and Environmental Engineering, Georgia Institute of Technology, Atlanta, GA

Dr. Anne Sweeney, Professor of Epidemiology, Department of Epidemiology and Biostatistics, School of Rural Public Health, Texas A&M Health Science Center, College Station, TX

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Enclosure B

CASAC's Consensus Responses to EPA's Charge Questions

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?

In general, the Panel found Chapter 2 to be well organized, technically sound and a good conceptual overview of the REA. The chapter provides a sound rationale for the decision to use COHb level as the internal dose metric for assessing exposure to ambient levels of CO and for characterizing the potential for health risks in the population of persons with coronary artery disease (CAD). While some Panel members supported a cautious approach to using epidemiological data in the risk assessment, overall there were concerns that the current presentation under-emphasized the epidemiologic findings. Even if the epidemiological data are not used in the risk assessment, it is important to incorporate them into the discussion of risk. The epidemiological evidence provides information on non-hypoxia relevant mechanisms and chronic outcomes that cannot be addressed by relying on COHb levels alone.

The Panel continued to be concerned with EPA's designation of the at-risk population. The choice of modeling risk for the CAD population needs to be further justified and/or expanded to include other susceptible populations. Again, the findings of epidemiological studies suggest several groups to be considered, especially the broader category of cardiovascular disease (CVD). Since this chapter serves as the introduction to the REA, it should be edited as the Panel's recommendations are incorporated into subsequent chapters.

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 is technically sound, clearly communicated, and appropriately characterized. The treatment of the CO monitoring data, the description of the extent that these monitors represent near-roadway concentrations, and the data used in this iteration of the assessment are improved over the first external draft REA. The current monitoring network does not represent near-roadway concentrations very accurately, which is now well-documented in the REA. The increased discussion of NCore and measurement characteristics is useful and appropriately placed.

Should there be additional monitoring for indoor and in-vehicle exposures? Representative monitoring to evaluate emissions inventories or models may be different from monitoring to assess exposure.

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.

An important improvement in this assessment from the first draft is the expansion of each modeling domain to include a greater number of ambient monitors for input to APEX. Additionally, this draft assessment employs an algorithm that adjusts for temporal and spatial heterogeneity in ambient concentrations across each study area. While use of a larger number of ambient air monitors may have improved exposure assessment, we are not convinced that spatial heterogeneity driven by proximity to sources can be adequately captured by the current ambient monitoring network. In fact, exposures outdoor, in homes and in workplaces near roadways might be underestimated.

It would be helpful to describe with greater clarity how data from overlapping districts, zones and areas were treated for input into the APEX model. What approach was used to avoid duplication of input data from overlapping zones? For Los Angeles, was one of the areas designated as a dominant source or was each area considered separately in the assessment? These are all questions that should be addressed in future analyses.

In generating simulated individuals, demographic variables should include socioeconomic status (SES) and race if possible. These variables will impact other APEX modules, particularly COHb. If not, future data collection efforts should provide sufficient coverage.

We find the tables of exposure values vs. estimated number and percentage of CHD persons affected at specific CO concentrations to be very instructive. Tables showing estimated COHb levels vs. number of people with CHD and persons/days are similarly instructive. Additional calculations and tabulation of endogenous COHb level using APEX and additional plots reflecting contribution of endogenous COHb to total COHb are illustrative.

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.

The Panel has no major issues with this approach.

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

We consider the selection of the mass-balance model for indoor air to be appropriate.

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

The Panel questions EPA's assumption that it has captured spatial heterogeneity in homes and workplaces near busy roadways. We 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. While some variables were already updated, others such as race, SES, total hemoglobin (THb) and DLco should be either added or replaced in the input module. With these qualifications, the Panel answers affirmatively to question 4.

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 data added to the ambient source inputs for the exposure modeling reflect commendable responsiveness to the feedback we provided in the previous review of the initial REA draft. The modeling appears to be technically sound.

The subject matter is complex and highly challenging to communicate clearly, particularly the material in Chapter 4. The presentation of this material seems to be aimed at the exposure modeling community, which makes it difficult for others to readily grasp. Nonetheless, the detailed description of the APEX model provides a helpful snapshot of the extensive nature of the model. The derivation and presentation of the modeling approach as a whole are well presented. Moreover, the application of the "CHAD" database in modeling the physiological changes of simulated residents during their daily lives appears to be appropriately handled. This approach has been applied and vetted for other regulated air pollutants. Nonetheless, the coupling of the non-linear CFK with the CHAD in the APEX model would be more convincing if this approach had been validated with actual field study measurements of delivered dose. We understand, however, that such validation is not possible on practical grounds. Moreover, previous approaches are less sophisticated from a modeling point of view and also lack field validation for the same reasons of feasibility.

Appendix C contains some helpful illustrations of the variability in time spent for a given individual in locations/activities throughout the year. It might be helpful, additionally, to have similar illustrations of:

1. Estimated %COHb levels for an individual during a day with exposures that were near current criteria (maximum allowable) levels of atmospheric CO, and
2. An illustration of the potential variability in peak levels of %COHb throughout the year.

Indeed, inclusion of such illustrative scenarios in the text, rather than in the Appendix, should be considered. This material could assist the reader in understanding the variability in the modeled levels of CO exposure.

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 clearly communicated and characterized. However, the final %COHb estimates, as presented in the REA, are potentially problematic. This is related, in part, to their derivation and the basic assumptions made in arriving at these values, not the computational operations of the APEX system. Modeling %COHb, as a biological marker of ambient CO exposure, presents particular challenges stemming from the various sources of exposure, each of which can potentially contribute to the final %COHb estimate. These sources include: endogenous production; ambient air pollution; and indoor air sources not accounted for by ambient pollution tracking indoors (e.g., combustion byproducts from home heating or cooking and secondhand smoking-associated CO). Extensive modeling in the REA appropriately deals with scenarios of ambient CO contributions to the indoor exposure environments. It was only well into Chapter 6 that modeling including "Internal Sources" of COHb was introduced. The Panel further takes issue with the confusing word choice since this does not mean *internal* in the sense of *endogenous metabolism*. As shown in Tables 6-15 and 6-16, excluding these indoor sources, modeled %COHb values (i.e., from ambient exposures levels) are similar between the 2000 model that also provides the indoor ("internal") estimates and the current APEX model. Key is that *inclusion* of the indoor sources of exposure drives up exposure such that five percent of the population hits a 3% COHb level and roughly two percent of the population reaches a 4.0% COHb level.

The Panel appreciated the additional attention given to endogenous CO production (again, not the "Internal" metric above). There was concern that this discussion could lead to confusion, because the modeled levels of endogenous %COHb are quite a bit lower than population means for non-smokers. This is because the actual data for the non-smoking population reflect the sum of ambient exposure, indoor exposure, and endogenous CO production. It might be useful to clarify these distinctions explicitly. Beyond issues of presentation, the modeled distribution of endogenous %COHb values seems too narrow. It appears to be based on "normal" healthy population estimates of endogenous production (albeit with a variety of activity levels). Literature demonstrating elevated endogenous %COHb values in certain subpopulations (for example, in persons with sickle cell disease) may be difficult to account for in these models, but an attempt to address them is warranted. At a minimum, the REA should directly acknowledge this limitation of the model estimates.

Further confusion may be introduced through the random subset estimations, given that the central tendency (mean) of this random sub-sample seems to differ from the larger modeling estimate (apparently a chance observation). The narrower distribution is produced by the limited intra-person variation since most of the data points are derived from multiple runs on a relatively small subset – (this should not explain the shift in the mean). It may even be relevant to acknowledge that certain groups at risk for higher endogenous production *systematically* may be more likely to have higher ambient scenarios (e.g., persons with sickle cell disease, low SES, and those living/working near a major roadway). The lack of transparency in the endogenous production model as applied may also contribute to confusion. The description of what endogenous rates were used in the model is unclear and the information in Table B-3 on page B-20 is poorly labeled. Despite these limitations, the material on endogenous production of CO and its contribution to the overall %COHb in combination with ambient levels of CO is very informative and indeed necessary. In summary, the Panel is concerned that there is no modeling

of %COHb that covers indoor non- ambient sources and endogenous CO production, as well as ambient exposure.

The staff's presentation at the meeting included additional analyses of the contribution of ambient CO to the COHb% levels. The Panel found the analyses presented during the meeting represented an improvement of the discussions in the REA itself. Although the data were apparently computationally intensive to develop, some Panel members believe that the additional analyses could be an extremely useful avenue for further development of the standard. The specific increase in %COHb over the subjects' pre-exposure or filtered air exposure was the focus of the influential Allred et al. papers and not on the magnitude of the final %COHb. It may well be that the ambient-attributable *increment* in %COHb is the most directly analogous dose for consideration in a risk assessment. Using incremental %COHb as the metric for ambient-attributable dose could simplify the risk assessment because the issue of "overlap" with the endogenous range of final COHb% (let alone indoor non ambient contributions) would be parsed-out. This treatment could still delineate the other sources of exposure as above-noted and would address the Panel's concerns with regard to the continuity of the CO exposure-response in experimental studies. The presentation of *incremental* exposure data and estimated %COHb combined and separately would allow policy makers to consider ambient exposure alone, as well as in the context of other sources of exposure.

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 the EPA's consideration of the public health implications of the current standards.

The modified assessment approach has two key components: estimated exposure and estimated at-risk (susceptible) population. In terms of exposure, it should also be noted that the additional information included in the current modification does not relieve uncertainties from the use of a relatively limited data set (i.e., two case studies in Denver and Los Angeles), even with the additional monitoring data. The REA could be improved by showing the impact, or lack of impact, on dose variability that resulted from the inclusion of data from more monitoring sites. Data resolution from the two case studies and inclusion of data from more monitoring sites will be particularly relevant for national extrapolations. The Panel has provided additional suggestions to strengthen the exposure component in response to other charge questions. Such improvements could serve to better inform the EPA's consideration of the public health implications of the current CO standard.

There are serious potential data uncertainties in the estimates of the "at risk" population, many of which might lead to a systematic *underestimation* of the public health impact of CO exposure. The REA continues to rely singularly on the National Health Interview Survey (NHIS) data to provide a population estimate of persons at risk. The "at risk" population has been narrowly defined as self-reported coronary artery disease, which was the Panel's primary point of contention and critique of the first draft REA. The revision now includes an estimate of "undiagnosed" disease that represents approximately 40% in addition to the base population. This is an important acknowledgment of one aspect of systematic underestimation, although the American Heart Association source of the mathematical value used is far from convincing. It is

recommended that EPA incorporate a female>male differential to address the probable sex-based gap in CAD diagnosis.

Data from NHANES and the Behavioral Risk Survey are easily accessible and will generally support the NHIS-based, restricted subset of susceptible persons based on a CAD definition. However, the narrowly-defined CAD prevalence estimate, to the exclusion of all others with cardiac disease, misinterprets the ISA (particularly Tables 4-9, 5-10, 5-11 and Figures 5-5 though 5-7). Revisiting the NHIS, the prevalence rates for "all heart disease" are considerably greater than those of narrowly defined CAD. It is very likely that most, if not all, of these persons are at increased risk for adverse cardiovascular effects from ambient CO in ways that cannot be distinguished epidemiologically from the CAD subset. It is certainly appropriate for the REA to present estimates, as indeed it did, using a narrow CAD definition of "at risk" to inform an EPA public health assessment. However, this approach alone is not sufficient. Much effort is spent on multiple scenarios of exposure, while falling short in the critical area of defining alternate measures of the vulnerable population. As a consequence of the approach suggested above, a population more broadly defined with cardiovascular disease is likely to overlap to a meaningful extent with adults with chronic obstructive lung disease (through shared risk factors), which may be another at risk group for adverse CO exposure effects. This is not a determining factor, however, in the rationale for applying a more broadly-defined cardiac disease definition in modeling the at-risk population.

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 better addresses variability and thus general uncertainty in exposure and dose. However, the use of the power 0.621 in equations 4-11 and 4-22, reduces the CO concentration at an outdoor location, relative to the nearest central monitor, and thus possibly reduces the number of occurrences of the highest CO concentrations.

In addition, all three contributors to COHb (ambient, endogenous production, and indoor sources, excluding smoking) should be considered in modeling and as contributing to variability and uncertainty in model results.

Enclosure C

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. Paul Blanc 15
Dr. Thomas Dahms 18
Dr. Russell Dickerson 21
Dr. Milan Hazucha 23
Dr. Francine Laden 29
Dr. Arthur Penn 30
Dr. Beate Ritz 31
Dr. Paul T. Roberts 32
Dr. Anne Sweeney 34
Dr. Stephen Thom 35

Dr. Paul Blanc

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?

Insofar as the increase inputs to the ambient source inputs to the models, this revision was quite responsive to the input that it received in review of its initial draft and is to be commended. This aspect of the approach appears to be technically sounds. This subject matter is complex and highly challenging to communicate clearly, in particular the material in Chapter 4. .

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 final COHb estimates in 6 are problem-ridden. This is related in part to the derivation (including under this the basic assumptions made, not simply the mathematical operations of the APEX system). The presentation magnifies certain issues by potentially obscuring points presumed to be manifest but that may be to be more explicit.

Modeling COHb, as a biological marker of ambient air pollution exposure, presents a particular challenge because there are 4 principal domains of exposure, each which can potentially contribute to the end concentration measured. These 4 domains are: endogenous production; ambient air pollution; active cigarette smoking; and supplemental sources of carbon monoxide beyond these three. This fourth domain, for most persons, is drive by indoor air exposure to CO from combustion byproducts from home heating or cooking and secondhand smoking-associated CO [although other sources of exposure within this domain may be important for population subsets, e.g., occupationally-related CO exposure].

Chapter 5, in relation to CO exposure modeling leading to COHb is focused entirely on the domain of ambient CO, although extensive modeling deals with scenarios of contributions of ambient CO to indoor exposure environments. This can be a bit confusing because internal combustion engine contributions to exposure in certain indoor scenarios are essentially point sources (service station and auto repair GM 2.97 [PPMs although not labeled]). Of note, another indoor facility group includes (Manufacturing facility) and is rather low – GM 0.089. One assumes fork lifts or truck deliveries not considered. The salient point however is: these scenarios exclude other likely concomitant sources of exposure.

It is not until well into Chapter 6 that modeling that includes the domain of "Internal Sources" of COHb is introduced. The term Internal as used here is unfortunate, since it actually is intended to mean "indoor – not from ambient sources" i.e., what I refer to as the 4th domain above. ***If*** this also includes endogenous production it is by no means clear. As shown in Tables 6-15 and 6-16, excluding these indoor sources these estimated exposures levels are similar between a 2000 model and the current APEX model – but ***inclusion*** of this critical source of exposure drives up exposure such that 5% of the population hits a 3% COHb level and roughly 2% a 4.0% COHb

level. Remarkably there is no simulation or other estimation combining current indoor sources with the ambient estimates.

Despite the short-shrift give the indoor exposure issue, a great deal of attention is then given to endogenous CO production. This, of course, is not "Internal" as used above, but rather refers to "normal" metabolic production of CO. This section is likely to lead to some confusion because, quite appropriately, the modeled levels of COHb% (population mean 0.255%) are quite a bit lower than population means for non-smokers. The reason of course if that observed non-smoking population data reflect the sum of domains 1,2,and 4, no simply endogenous production (thus the baseline samples in the Allred study, etc). This is a point of blurred presentation, not modeling. The modeling itself, however, could benefit from more transparency. The reader is told that a certain number of studies informed the metabolic parameters as detailed in B but in fact it is hard to tease-out which references there are the ones in question. These seem to be fairly dated (Coburn's work from the 1960s) and this may be the best there is. Nonetheless, more recent literature exploring moderately elevated COHb in certain conditions (for example, sickle cell disease) suggests that the model specifications and simulations yielding a maximum endogenous value of 1.54 is not likely to be reflective of population variability. This may be driven by simulating 59 individuals only, albeit with 8,760 hours of modeled observation. To capture endogenous variability, within person hour to hour activity inputs is not nearly as important as between person variability. Moreover, it is likely that certain at risk groups may be more likely to have ambient scenarios (and indoor scenarios) of higher exposure: eg. a low income resident of south-central LA dwelling near a freeway with sickle cell disease (and heating the home with a gas stove in the winter).

Integrating the comments above, there is no apparent modeling of COHb that includes variable indoor not ambient sources (exclusive of direct cigarette smoking) + endogenous CO production (anticipation a possible bimodal distribution, with certain disease states contributing a sub-group of outliers) and ambient exposure.

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 the EPA's consideration of the public health implications of the current standards.

The modified assessment approach has two key components: estimated exposure and the estimated at risk (susceptible) population. All of the comments above (charge questions 5 and 6) relate to the exposure assessment. To the extent that the exposure issues raised above can be addressed, this would serve to better inform the EPA's consideration of the public health implications of the current CO standard. Even as is, this portion of the Risk and Exposure Assessment is not fundamentally flawed.

Insofar as the at risk population estimates are concerned, the document as currently constituted is prone to several sources of data uncertainties, all of which would tend to systematically underestimate the public health impact of exposure. The document continues to rely on National Health Interview Survey (NHIS) to provide a population estimate of persons at risk, narrowly defined as self reported coronary artery disease. This was a matter of focused critique of the first draft document. The revision now includes an estimate of "undiagnosed" disease (approximately

40% in addition to the base population). Conceptually this is an important acknowledgment of the one aspect of systematic underestimation, although the American Heart Association source of the mathematical value used is far from convincing (and whatever value is used should incorporate a female>male differential given the clear sex-based gap in diagnosis. In addition, in terms of the restricted subset of susceptible persons based on CAD, supportive prevalence data based on NHANES and the Behavioral Risk Survey are easily accessible and will generally support the NHIS-based values. More fundamentally, the narrowly defined CAD prevalence estimate, to the exclusion of all others with cardiac disease misreads and misinterprets the ISA particularly Tables 4-9, 5-10, 5-11 and Figures 5-5 though 5-7. Revisiting the NHIS, the prevalence rates for "all heart disease" are considerably more than for narrowly defined CAD. It is very likely that most if not all of these are at risk as from adverse cardiac effects from ambient CO in ways that cannot be distinguished epidemiologically from the CAD subset (this includes in term of RR). It is certainly appropriate for the REA to present estimates, as it did, using a narrow definition of "at risk"; to inform an EPA public health assessment, this approach alone is unacceptable. It is ironic that so much effort is spent on multiple scenarios of exposure, while falling short in the critical area of the key vulnerable population.

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. Russell Dickerson

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 revised draft is much improved, and generally meets expectations. EPA is faced with the situation that ambient measurements are more accurate than emissions. This makes measurement/model comparisons difficult. Although Chemical Transport Models (CTM's) are not used in Chapter 3 or the REA, that chapter should point out that such tools *should* be used and continued evaluations and improvements (if necessary) in emissions are needed.

The increased discussion of NCore and Analytical Sensitivity are useful and appropriately placed near the front.

Key Observations (page 3-18 and 3-19) are appropriate, except I could not find much on the uncertainties in emissions (see also comments on ISA) and their impact on model output.

Chapter 5 appears to reflect the state of knowledge.

<u>Preliminary Comments on the ISA (relevant to REA)</u>

In one last reading of the ISA, Chapter 2 does a thorough job of providing an overview of our technical understanding of CO.

A few comments:
1. Page 2-3 might mention HCHF's are removed by OH
2. The caption to Figure 3-1 might include the word DIRECT so people don't go looking for isoprene.
3. Section 3.2.2 looks really good, as does Figure 3-8. This makes an important point that should appear in the PA.
4. The sections on ambient measurements, detection limits and NCore are all much improved.
5. Based on a quick read, Section 3.5 looks solid now.

In poking around the literature I have found a few more papers that evaluate the emissions inventories of CO. Kuhns et al. (2004) and Yu et al. (2007; 2009) also found evidence of overestimates of CO emissions in Mobile6 or CMAQ. Marmur et al. (2009) in contrast seem to find that the CO emissions are underestimated. Zhang and Batterman (2010) find that Mobile 6 matches plume dispersion models and a roadside monitor reasonably well. We are just about to submit a paper that evaluates Mobile6 CO emissions using about 100 altitude profiles and find that modeled emissions are high but not in gross error. If the paper is accepted soon enough I will send a preprint.

Kuhns, H. D., et al. (2004), Remote sensing of PM, NO, CO and HC emission factors for on-road gasoline and diesel engine vehicles in Las Vegas, NV *Science of the Total Environment, 322,* 123-137.

Marmur, A., et al. (2009), Evaluation of model simulated atmospheric constituents with observations in the factor projected space: CMAQ simulations of SEARCH measurements, *Atmospheric Environment, 43,* 1839-1849.

Yu, S.C., et al. (2007), A detailed evaluation of the Eta-CMAQ forecast model performance for O_3, its related precursors, and meteorological parameters during the 2004 ICARTT study, *Journal of Geophysical Research, 112*, D12S14.

Yu, S.C., et al. (2009), Eta-CMAQ air quality forecasts for O_3 and related species using three different photochemical mechanisms (CB4, CB05, SAPRC-99): comparisons with measurements during the 2004 ICARTT study, *Atmospheric Chemistry and Physics Discussions, 9,* 22955-22992.

Zhang, K., and S. Batterman, Near-road air pollutant concentrations of CO and PM2.5: A comparison of MOBILE6.2/CALINE4 and generalized additive models, *Atmospheric Environment,* doi:10.1016/j.atmosenv.2010.02.008, in press 2010.

Dr. Milan Hazucha

Background on assessing ambient CO exposure and risk (Chapter 2).
Charge Question 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.

Air Quality Considerations (Chapter 3 and 5)

Charge Question 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.

Characterization of Exposure, Dose and Potential Risk (Chapter 4-6)

Charge Question 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?

The charge questions span across 3 chapters: Ch. 4 Overview of APEX modeling, Ch. 5 Application of APEX, and Ch. 6 Simulated exposure and COHb dose results.

However, it is difficult to comment on the chapters in general since the sub-questions are rather specific.

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.

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?

Generally, larger number of monitors may improve exposure assessment. Figure 5.1 (p.5-5) 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?

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.

Chapter 6: The tables tabulating exposure values vs estimated number and percentage of CHD persons affected at specific CO concentrations are very instructive and

revelatory. Tables showing estimated COHb levels vs number of CHD persons and persons/days are similarly instructive. Generally, these table show that the current level of both standards is protective as required by the legislation, i.e., "standards that are neither more nor less stringent than necessary."

Additional calculations and tabulation of endogenous COHb level using APEX has been also very helpful. Table 6-18 (p.6-19) shows that the endogenous contribution to a total COHb is "less than 0.5%, though for a limited number of hours, the endogenous contribution could be over 1.0% COHb." The additional plots reflect contribution of endogenous COHb to a total COHb level essentially following physiologic laws of Haldane.

Section 6.5 Key Observations (p.6-24) summarizes the main observations presented in this chapter. One of the important conclusions is that more than 95% of simulated at-risk population of L.A. study areas will experience an annual daily maximum end-of-hours COHb level below 1.5%. Moreover, when considering alternative standards "only 0.1% of the CHD population was estimated to experience a maximum end-of hour COHb at or above 2%. Similar values are provided for Denver.

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.

Chapter 4: Table 4-4 (p. 5-21) and 4-5 (p. 4-29) lists 15 microenvironments used in estimates in pNEM/CO model in 2000, and the same number and type in APEX4.3. However, the number for this draft is reduced to 8. Did this change in any way affected the estimates?

It would have been helpful instead of making a general statement on how better APEX is, to actually list in 4.5 Key Observations section(p. 4-35) specific enhancements of APEX over pNEM/CO.

The two important conclusions were that (1) the policy relevant background was negligible, and (2) the fixed site monitoring data could be adjusted. The tables provide sufficiently detailed data to evaluate all 5 scenarios.
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.

Charge Question 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 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. While some variables were already updated, others such as race, SES, THb and DLco should be either added to or replace the old data in the input module.

Charge Question 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.

Charge Question 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.

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.

Charge Question 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 standard?

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

Characterization of Variability and Uncertainty (Chapter 7)

Charge Question 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 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. Arthur Penn

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?

No major issues with this chapter. The summaries are well-done and the health effects and risk characterization approach are presented clearly and seem technically sound.

Dr. Beate Ritz

3. 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.

While the larger number of ambient air monitors may have improved exposure assessment, I am not convinced that this in fact gives more correct estimates of exposure near roadways - mainly in homes since only one singular distribution was used for all homes and this distribution may not adequately reflect near roadways exposures in homes i.e. I am not convinced that spatial heterogeneity driven by proximity to sources can be adequately captured by the ambient monitoring network. In fact, the exposure both in homes and in work places closer to roadways might be underestimated.

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.

yes

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

yes

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

Yes, except for the assumption about having captured spatial heterogeneity in homes and work places near busy roadways.

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).