10 November 2009 Preliminary Review Comments from CASAC Carbon Monoxide Review Panel on EPA's *Integrated Science Assessment for Carbon Monoxide: Second External Review Draft (September 2009)*

Comments received:

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Dr. Paul Blanc

Draft Comments on Charge Question #6

a. **Please comment on these revisions:** ***The section on policy-relevant considerations was revised to present additional detail on the concentration-response relationship observed in a multi-center controlled human exposure study, [to] present results from a new U.S. multicity epidemiologic study investigating the potential presence of a threshold and departure from linearity, and [to] summarize the evidence for susceptible populations.***

In terms of exposure response, the key Allred study appeared in 1991. It is not clear the extent to which this study informed the 1991 or the 2000 CO AQCDs . It is also not obvious why the current document refers the reader to the 1989 Allred paper given that the subsequent 1991 paper provides details of the dose response. Readers could be confused on both points; clarifying this in the text would be advisable. Leaving those issues aside, it is certainly appropriate to include the Allred concentration (exposure) response data and to point out (as in text) that this study was far larger and more powerful than any previous study. The Allred data could be presented to better effect if the point is not only linear effect but also threshold. In this regard, the Allred analysis of time until angina (Figure 12, page 112, 1991 and related text) indicates an intercept of a 1% decrease in time (± 2.1%). This is based on an analysis of room air not as zero but as the actual post-exercise room air COHb value, which did vary by site and among subjects. The ST depression intercept, of note, was significantly in the positive direction which could be argued in favor of a threshold for that endpoint.

It is a bit surprising that no attempt was made to perform a meta-analysis of the experimental data for low-level CO exposure and time until onset of angina (for example, using the data in Table 27 of Allred of multiple studies on this subject). In addition to examining exposure response across studies, because the "air" exposures varied among studies in terms of ultimate COHb, it may also be possible to test whether this low level is related to the post exposure effect, taking into account the exposure (or the exposure difference from air). The concluding statement of this section reads: *"Although the C-R relationship has not been explicitly evaluated in human clinical studies with exposures resulting in COHb concentrations < 2.0%, the findings of Allred et al. provide some evidence of a significant C-R relationship over a range of COHb concentrations relevant to the NAAQS."* This sentence is overly weak, somewhat confusing, and inexact. If human clinical studies means *controlled human exposure studies* then it is incorrect – Allred did explicitly analyze the dose response including those resulting from air (+metabolism) and these were less than 2% COHb (see above) [If it clinical studies means something else (?clinical case series) it seems out of place in context.] The wording "some evidence" operates to undermine the findings – it is evidence, which could be argued to be substantial or strong. If significant means statistically significant this should be explicit.

The analysis by Somoli in which the deviance from linearity was associated with a p value of > 0.9 should not be described as weak evidence in favor of a threshold – this would be better described as a finding that does not support the presence of a threshold. There seems to be quite an extended discussion here as to why this analysis was poorly powered to observe a threshold

and wording such as “an inability to draw conclusions” gives the appearance of bending over backwards to leave open the possibility of a threshold where, apparently, there was no threshold observed.

The inclusion and analysis of data form the multi-site epidemiological study (Bell et. al.) is commendable, given that it was only recently published. There are multiple points in which these data could have been presented in Chapter 5 beyond the limited places where the paper is cited. This same effect seems to have spilled over into the comments on the absence of a threshold effects in these data. Greater detail should be provided here because the data are so strong and so relevant. Limiting the analysis to those days with 1 PPM values or less (40% of the observed days) the point estimate for the increased hospitalization actually increased to approximately 1.75% (95% interval excludes 0). Moreover, their data reporting a re-analysis excluding any days over the 1 hour 35 ppm standard (no impact on the estimated of 0.55%) should be reported here as well.

The summary of evidence regarding “susceptible” populations (2.6.1) actually precedes the discussion of concentration response (2.6.2). This section does a fair job of summarizing lengthy text elsewhere in the document but also suffers from the organizational issues of that text. The most substantive issue here is the usage of the term “susceptible” to refer to two entirely different concepts, operationally. The first usage is consistent with the way in which susceptible is typically applied: subgroups in which an exposure identical to the general population could be expected to have a greater adverse effect. Examples of this include, and are documented: those with pre-existing cardiovascular disease, diabetics, those with pre-existing anemia, those with pre-existing hypoxemia, and the fetus. In contradistinction to this classic construct of susceptibility, the document lumps together with this individuals who are vulnerable because either they are more likely to experience higher ambient exposures (living near roads, greater commute time) or because the ambient exposure they receive will be superimposed on a higher baseline value secondary to greater than average exposure to exogenous CO or greater metabolic production of CO. Both susceptibility and vulnerability are important but the presentation would be more lucid if the distinction were spelled out explicitly.

The concluding sentence “Overall the controlled human exposure, epidemiologic, and toxicological studies evaluated in this assessment provide evidence for increased susceptibility among various populations” is overly weak. By saying that the evidence for those with CAD is “strongest” in the next sentence, the implication could be drawn that the other “evidence” is somehow weak. It could be argued that the strongest evidence of susceptibility to CO, per se, is for fetal exposure [The comment page 2-16 that kinetics differ “in part” because of fetal HB affinity was a bit surprising – this would better be described as the dominant mechanism]. The evidence is certainly strong to convincing in a number of other scenarios. Also in the sentence in question, if toxicological means animal toxicology this should be stated and a fourth category of human clinical toxicology cases added. Overall in the document there seems to have been little use made of human case reports insofar as the implications that might be drawn. This may reflect EPA policy in some way. One specific example: human case reports clearly have shown that coronary artery spasm appears to mediate CO-induced MI in some individuals (post CO-cause MI coronary vessels without underlying CAD consistent with MI)

The various scenarios of vulnerability (susceptibility) seem to ignore indoor air sources of supplemental CO exposure. Most glaringly, secondhand smoke exposure is missing [it can also be argued that this can be an outdoor ambient issue in areas with heavy concentrations of smokers at the threshold of edifices; also why it the term ETS used rather than secondhand smoke?] . So too, deficient home heating which may also be a risk and is likely to run with lower socioeconomic status. Or living in colder parts of the US in the winter months. In the same vein, occupational exposures superimposed with ambient exposure should be taken into account. The degradation of "dihalomethanes" is mentioned but this would be better stated a predominantly methylene chloride (which has also been in some consumer products).

Diabetics are mentioned but I did not see referenced here or in the health effects section recent relatively large study (n=986) from Korea (Min PY et al, Sci Total Environ Aug 2009) with effect modification for autonomic dysfunction [decreased heart rate variability] from CO by fasting blood glucose.

b. **We would appreciate CASAC comment on the material in this section and its effectiveness in presenting the conclusions of the ISA:** ***"A section and summary figure have been added to the end of Chapter 2 to summarize the main conclusions of the ISA regarding the health effects of CO and the range of concentrations at which effects are observed, along with uncertainties that complicate the interpretation of the evidence."***

Figure 2-1 (page 2-21) is apparently new to this revision. The Figure, in principal is appropriate and helpful, but it could be improved upon in ways delineated in the points below. The effect estimate (far right of Figure 2-1) should have the metric at the top not the bottom. Also because the lower bound of the CI and the point estimate are far more of interest than the upper bound – scaling so that the span is up to 1.2 only and the scale is bigger would help. The effects should be grouped by endpoint not by study with total CVD top, then IHD, CHF and stroke. (This will also help layout) The 99th percentile of exposure may be of less interest than the 95th.

Although the CVD endpoint of Bell is included the other specific endpoint of Bell are left out, inexplicably. This includes IHD, Failure, and stroke (cerebra-vascular events). For some reason the health effects chapter (carried over here) differentiates between a single study of "MI" and all other studies of IHD – this separation is confusing and counterproductive.

There is another problem in the health effects chapter that impacts this one – the treatment of stroke as if there were not also a neurological endpoint. Reading the text it is apparent how this came about – perhaps referring to neurological outcomes other than CVA elsewhere would make it clear that this obvious fact is taken into account. Is there a compelling reason why the Figure 2-1 is limited to findings form North America? These data really call out for a formal meta-analysis. Table 2-2 is almost misleading in this regard.

The concluding paragraph (pages 2-24 and 2-25). Before addressing some uncertainties that remain it is important to catalogue the uncertainties (listed in detail in terms of the 2000 CO AQCD) that have now been substantially addressed. It should not be stated first in the negative as "some of these uncertainties remain." The argument re: lack of biological plausibility runs

counter to the rich series of recent studies indicating the potential modulatory effects of CO at low levels on a number of systems (see pages 5-5 to 5-17). If fact as separate section to the policy section should summarize and address this central point. Moreover the phrase "biological plausibility provided by CO's role in limiting O2 availability" [last sentence] basically cuts out the rich data on other mechanisms form any plausible role.

Earlier in the text this same paragraph refers to the "many new epidemiological studies adding to the body of evidence showing associations.." This should be modified this to include the adjective *convincingly*, consistent with the next sentence re: definitive cardiovascular effects in controlled exposures. Taking these together with the *major* uncertainties previously noted that have largely been addressed, the determination could move up from likely causal to causal. The concluding paragraph reads as if it is arguing for a downgrade to suggestive.

At various points but most importantly in the very last sentence, the phraseology "relevant….exposures" is used. Where this means exposure at or below the current EPA CO NAAQS this should be so stated. By saying relevant it could imply that other exposure levels are irrelevant to the assessment of health effects (through understanding mechanisms etc), which of course is not intended. There is evidence in the health effects section re: chronic CO exposure effects on cardiovascular morbidity. These may be categorized as inadequate but should nonetheless be included in Table 2-1 [note: Hedblad B. et al, *Scand J Public health*, 2006 seems to be missing from that discussion and seems on topic].

It is appropriate to focus on cardiovascular endpoints in the concluding paragraph, but a sentence acknowledging that there is at least a suggestive relationship with several other endpoints.

Dr. Thomas Dahms

Statement: In response to comments from the CASAC CO Panel, material has been added to Chapter 4 describing comparisons among predictive COHb models, the relative influence of differing exposure scenarios on COHb concentration, and endogenous CO production rates in individuals with various diseases and conditions.

Q: Please comment on the usefulness of this information in illustrating the factors influencing COHb kinetics and potential COHb levels under various scenarios.

General comments: This section provides an excellent review of the modeling of CO uptake and release. It provides the essential information needed to understand most of the variables involved in relating CO exposure and CO dose. What follows are suggestions/questions that may lead to further improvement and clarification of the material presented.

I. With the increasing amount of epidemiology data being considered in this database changes in atmospheric CO levels with various adverse health effects, the exposure models need to provide guidance to the reader regarding likely levels of exposure in some of these studies. The evidence from the atmospheric data demonstrates a steady fall in monitored levels of atmospheric levels of CO yet significant relationships with seemingly small changes in environmental CO continue to be identified. How can the exposure models provide insight into what might be occurring? I presume that this would include a discussion of the limitations of the use of the current atmospheric monitoring data to estimate exposure? I realize that there is data in the RFA and in the 2000 CO ACQD pertaining to this situation but it is scattered and it would help the reader if the salient issues were summarized as they pertain to the epidemiologic studies.

II. The modeling discussion in most of chapter 4 is based on factors influencing equilibrium values for COHb given different exposure conditions. In Section 4.2.3 (Model Comparison), the brief mention of the Bruce and Bruce model for predicting COHb levels with transient CO uptake conditions , page 4.9 lines14-20 or the QCP model deserves much greater consideration based upon what we know from real life exposure scenarios. If the primary exposures to CO occur during periods of commuting, which model more accurately predicts the CO uptake during the 30 to 60 minutes of exposure? Section 4.2.3 mentions the value of the Bruce and Bruce model but then proceeds to use the QCP model in the following section 4.2.4.without discussion or examples as to how the QCP compares to the other models. If the models in section 4.2.3 were all compared to observed data, this distinction needs to be made. Otherwise the use of untested mathematical modeling in section 4.2.4 does not make sense.

III. Given that adverse health effects have been demonstrated at 2% COHb, the discussion on page 4-5 lines 23-26 report that application of unspecified scenarios in some form of the CFK model yield ranges of exposure levels required to reach 2% COHb. For the 1 hour (transient) exposure, these atmospheric levels of CO are 24-48 ppm which encompasses the 35 ppm hourly criteria. However for the 8 hour exposure (equilibrium) the required exposure values are 11 to 13 ppm which is above the 9 ppm standard. This data needs to be better referenced since it applies so directly to the standards.

IV. Use of modeling information:

1. With the paucity of actual measurements of COHb distributions in the population (nothing since NHANES II), modeling is proposed to provide data relevant exposure data.
2. Since there are other pieces of missing data from the ideal data base from which to make assumptions regarding risks from CO exposure, I would propose that modeling be used to provide guidance for identified at risk groups for which there is little or no data. These groups would include those frequently mentioned:

a. anemia.

For the past 30 years patients with anemia has been identified as being an at risk group for adverse health effects due to CO exposure. It is discussed again in this document in Section 5.7.1.3. This would be a particularly sensitive subset of patients with CAD since both elevated COHb and reduced hemoglobin concentrations reduce oxygen delivery to the myocardium. It should be noted that anemia is a significant risk factor for development of angina. Yet there appear to be no studies available addressing this issue. The extent of exposure risk for this sizable group of people (approximately 4 million over 65 with anemia) needs to be addressed.

The treatment of anemia in this document focuses on the increased risk due to elevated endogenous production of CO. It is unclear what influence the elevated endogenous rates have on adverse health effects. One would suppose that in the four-element (Section 4.2. page 4-2 lines 28-29) CFK model that when the largest element changed would be the storage compartment (total body hemoglobin) that exposure conditions would be reduced in order to result in the same measures of effective dose (%COHb). One would expect an increase in the transfer interface with the hyperdynamic state due to the anemia, but the impact of this component would be less clear. It is likely that the lack of a sizeable storage compartment in anemic individuals would result in reaching levels of COHb of concern at lower atmospheric levels during 1 hour or 8 hour exposures. The relative importance of endogenous production, reduced storage capacity and increased transfer rates could be determined through the use of modeling.

(The number of individuals in the USA with anemia is significant. According to NHANES III, 10-12% of the population over 65 yrs of age (40 million) has anemia.
The number of individuals with CAD and anemia is more difficult to estimate but the numbers range from 8-15% of those patients with CAD also have anemia.)

b. COPD and Emphysema

According to NHANESIII there are 24 million individuals in the US with some amount of COPD. This is such a sizable at risk group that application of various models of CO exposure using the impaired pulmonary function parameters would be helpful in determining the extent of risk in this population.

V. Section 4.5.

Whenever COHb is mentioned the method of analysis should also be indicated otherwise the reader would be misled assuming that all of the values were equivalent when they are not. This is

particularly relevant when discussion the impact of endogenous CO production because the resultant COHb levels are very low.

The limitations of the easy-to-use and reproducible CO-oximeter data was outlined in section 2.6.1 of the 2000 CO AQC D. There are many assays with sufficient sensitivity available for use as used by Coburn et al. to produce the data shown in Figure 4-12. However much of the other data in this Figure was collected with instruments not designed for accurate measurements of low levels of COHb (De las Heras et al used a CO-Oximeter).

Editorial and minor comments:

1. Section 4.1. page 4-1, line 3. deoxyhemoglobin should read hemoglobin. CO will competitively compete with oxygen for hemoglobin. The use of deoxyhemoglobin is probably a carry over from the assumptions used in the CFK modeling of McCartney (013162).
2. Section 4.2.1. page 4-2, line 17. altitude should read exposure time and altitude.
3. Section 4.2.1. page 4-3, line 29. Vco is not shown in Figure 4-1.
4. Section 4.2.1 page 4-4, lines 11-14. The discrepancy between arterial and venous blood CO levels is mentioned without any interpretation as to why this is important. Also in this section the absolute errors in COHb are mentioned without providing any sense of what the mean increase in COHb was under these conditions.
5. Section 4.2.1. page 4-5, lines 23-26. A reference is needed.
6. Section 4.2.4, page 4-5.,lines 27-28. No explanation is given for reduced uptake by babies which appears to contradict information given in section 4.1. lines 20-22.
7. Section 4.2.3. page 4-9, line7. ‘differ ±0.5%’ needs clarification. 0.5% COHb or of the value obtained?
8. Section 4.2.4, page 4-9, line 21. Population data for COHb are available in (Radford and Drizd, 1982) so this statement needs to be clarified.

Dr. Russell Dickerson

Comments on ISA Charge Question 2a

In reference to ISA Chapters 2&3 that discuss a causal relationship between current atmospheric concentrations of CO and effects on Climate. "What are the Panel's opinions related to this causal statement and the evidence to support it?"

Substantial additional information has been added to both Chapters 2 and 3 as well as in Annex A, and the ISA is much stronger for it. The review of the literature appears to be thorough, and the analysis of the science systematic. One substantive comment I would make is that the evidence all points to the need for new regulations for the climate effects of CO. The current ambient concentration-based standards are not appropriate for large-scale global atmospheric concentration concerns aimed at protecting welfare. This will have to be emissions-based regulations similar to those being planned for CO_2. I suspect that the state of the science not yet adequate to establish a specific CO emissions cap, and if that is the judgment of the EPA authors then the Integrated Science Assessment should clearly state that further research is needed to establish a numerical value for American CO emissions. Do we know what the safe level of CO in the atmosphere is? If not then the ISA should so state.

The review of satellite measurements for establishing PRB concentrations is fair –existing instruments lack sensitivity in the PBL. Remote sensing is already useful for model evaluation and may some day be helpful for low-altitude measurements, and is

There is one more relevant paper that came out in *Science* after the draft was finished; it shows gas/aerosol interactions can amplify the effects of non-CO_2 trace gases on radiative forcing [*Shindell et al.*, 2009].

Comments on ISA Charge Question 2b

In reference to Chapters 2&3 that additional detail has been added on detection limits, number and spatial variability of CO monitors etc. "Please comment on the usefulness of theses revisions…."

Table A-1 is a great addition. This shows that highly sensitive instruments are commercially available. Page 3-20. The LOD is given as 0.04 ppm, but Table A-1 shows 0.02 ppm. The ISA should say the replacement monitors should have the lower LOD's.

Page 3-12 Figure 3-8 is hard to read, perhaps a scatter plot.

Page 3-22 The ISA should state the revoking the CO monitoring requirements impedes our scientific understanding of air quality and climate. The paragraph on NCORE is a great addition.

Page 3-33. The bar has a black stripe on top that looks like it should be a red stripe.

The additional detail in 3.5.1.2 is great. Page 3-45. The tale on top with E C A B D does not seem to correspond to the columns below.

Comments on ISA Charge Question 6b

A section and summary figure have been added to the end of Chapter 2. "We would appreciate CASAC comments…."

Figure 2.1 gives a good demonstration of the morbidity risks associated with CO, and is understandable by non-specialists in epidemiology.

General Comments on ISA Chapters 2 & 3.

There is some redundancy between Chapters 2 & 3 as well as within the chapters that could be eliminated without loss of coherence.

Section 3.2 There is a need for a bottom line here: substantial uncertainties in emissions continue to exist. On page 3-4 is states that the reviewed literature is consistent in determining a decrease of 5% per year in on-road CO emissions. Does that agree with Figure 3.2? It might be but it would be nice to see it explicitly compared.

Page 3-10. CH_3OOH is not really soluble; the Henry's Law coefficient is about 300 M/atm, much less that H_2O_2.

Page 3-13. OH does not react with the major CFC's that are fully halogenated (such as CFC-11 and 12). There needs to be a hydrogen atom bound to the carbon somewhere.

The Summary and Conclusions should state that:

1. There are substantial uncertainties in the emissions inventories.

2. The current state of the science is insufficient to determine what level of CO emissions is adequate to protect welfare from adverse changes in global or local climate and in the oxidizing capacity of the atmosphere.

Minor points on ISA

1. Page 2-20 line 14 space.

2. Page 3-14 line 22 semicolon where a comma should be.

3. The caption to Figure 3-10 and other similar figures should say that the circles indicate the position of the monitors.

4. AADT is not in the table of acronyms.

5. The word 'fraught' on page 3-85 seems odd to my ear.

Reference and some additional papers that may be of value to EPA.

[*Clements et al.*, 2009; *El-Fadel and Abi-Esber*, 2009; *Saide et al.*, 2009; *Tomlin et al.*, 2009; *Wang and Zhang*, 2009; *Zhu et al.*, 2009]

Clements, A. L., Y. L. Jia, A. Denbleyker, E. McDonald-Buller, M. P. Fraser, D. T. Allen, D. R. Collins, E. Michel, J. Pudota, D. Sullivan, and Y. F. Zhu (2009), Air pollutant concentrations near three Texas roadways, part II: Chemical characterization and transformation of pollutants, *Atmospheric Environment*, *43*, 4523-4534.

El-Fadel, M. and L. Abi-Esber (2009), In-vehicle Exposure to Carbon Monoxide Emissions from Vehicular Exhaust: A Critical Review, *Critical Reviews in Environmental Science and Technology*, *39*, 585-621.

Saide, P., R. Zah, M. Osses, and M. O. de Eicker (2009), Spatial disaggregation of traffic emission inventories in large cities using simplified top-down methods, *Atmospheric Environment*, *43*, 4914-4923.

Shindell, D. T., G. Faluvegi, D. M. Koch, G. A. Schmidt, N. Unger, and S. E. Bauer (2009), Improved Attribution of Climate Forcing to Emissions, *Science*, *326*, 716-718.

Tomlin, A. S., R. J. Smalley, J. E. Tate, J. F. Barlow, S. E. Belcher, S. J. Arnold, A. Dobre, and A. Robins (2009), A field study of factors influencing the concentrations of a traffic-related pollutant in the vicinity of a complex urban junction, *Atmospheric Environment*, *43*, 5027-5037.

Wang, Y. J. and K. M. Zhang (2009), Modeling Near-Road Air Quality Using a Computational Fluid Dynamics Model, CFD-VIT-RIT, *Environmental Science & Technology*, *43*, 7778-7783.

Zhu, Y. F., J. Pudota, D. Collins, D. Allen, A. Clements, A. DenBleyker, M. Fraser, Y. L. Jia, E. McDonald-Buller, and E. Michel (2009), Air pollutant concentrations near three Texas roadways, Part I: Ultrafine particles, *Atmospheric Environment*, *43*, 4513-4522.

Dr. Laurence Fechter

Comments on ISA question 5

The discussion of susceptible populations to carbon monoxide has been dramatically improved. The data are now presented in a logical framework providing a clear and concise summary. The only minor change I would propose on page 5-167 2nd complete sentence is to revise as follows:

> "These analyses require the proper identification of confounders and their subsequent adjustment in statistical models, which helps eliminate spurious associations."

Dr. Milan Hazucha

Comments on Chapter 4: Dosimetry and Pharmacokinetics of Carbon Monoxide of the Second External Review Draft of the ISA for Carbon Monoxide

Charge: *"In response to comments from the CASAC CO Panel, material has been added to Chapter 4 describing comparisons among predictive COHb models, the relative influence of differing exposure scenarios on COHb concentration, and endogenous CO production rates in individuals with various diseases and conditions. Please comment on the usefulness of this information in illustrating the factors influencing COHb kinetics and potential COHb levels under various scenarios".*

This chapter of the Second Draft is much more comprehensive in discussing the respective material. The Chapter has been expanded by more than one third. New subsections were added (4.2.3, 4.3.4, 4.4.3.1) and most of the old subsections were expanded, some substantially (4.2.4, 4.5). This is mostly to the benefit by facilitating better understanding of the section topics.

In general, the authors adequately addressed CASAC's CO panel comments by appropriate revisions and addition of relevant material discussed in sufficient detail. One question, however, which in my view was not satisfactorily answered, is "Which COHb model is the best in estimating venous COHb"?

Section 4.2.1 The Coburn-Forster-Kane and Other Models

The discussion of various models has been slightly expanded and a most recent model by Gosselin et al, 2009 is discussed as well. This model has been developed for and commissioned by Health Canada, Air Health Effects Division. It is a comprehensive model based on CFKE and it seems to estimate experimental data very well under a variety of environmental and occupational conditions.

Section 4.2.3 Model Comparison"

This is a new very helpful section. It discusses strengths and weaknesses of various models reviewed in previous sections. However, at the end, there is no conclusion, no recommendation as to which model is the best in estimating venous COHb. With so many different COHb prediction models it will be difficult for most of the readers to select the best model. If not here, maybe section **4.6 Summary and Conclusions** could be more specific.

Section 4.2.4 Mathematical Model Usage

This is a substantially expanded section by discussing comprehensively The Quantitative Circulatory Physiology (QCP) model supported by several plots. Extensive discussion of this model seems to suggest that this is another "preferred" model for COHb estimation. So it appears that we now have two "preferred" models, Gosselin et al, 2009 and QCP. Again, which one gives the best estimation of venous COHb? Since these models have been described in a considerable detail, why not to compare COHb estimates utilizing one of exposure profiles, e.g., like in fig. 4-2. Moreover, all of the discussed models are predicting venous COHb. Is it possible to use these two or any other models to estimate transient arterial COHb level? It would be

helpful to have a one paragraph discussion of utility of these models, if any, in estimating transient arterial COHb level if such data exist.

Section 4.3.2.4 Other Tissues

Although this is only a page long section with two tables, I was (in the first draft) and am still struggling with presented material. There is a substantial discussion of animal studies. However, the data were based on CO exposures with COHb levels as high as 80%. I do not think that these data are relevant. Maybe, table 4-2 showing human data, though some at very high COHb would be sufficient, and drop table 4-3.

Section 4.3.4 COHb Analysis Methods

This new section gives a very good discussion of current methods used for COHb analyses. It discusses advantages and limitations of various methods which is helpful in interpretation of data.

Section 4.4.3.1 Fetal Pharmacokinetics

Short and concise new subsection with a figure, pointing out to maternal-fetal differences in COHb buildup and elimination.

Section 4.5 Endogenous CO Production and Metabolism

Substantially expanded and quite comprehensive. The authors went beyond CASAC's CO panel suggestions for revisions and discuss in detail, including very helpful tables, various health conditions and diseases that can increase endogenous CO production and subsequently elevated COHb. This is all supported with abundance of references. It is an excellent review.

More specific comments:

Reference list needs to be updated.

Page 4-3, lines 1-9: It would be easier to follow parameter and variable description if they were listed in two columns.
Page 4-3, line 17 and p.4-9, line 7: Clarify. Do you mean ±0.5% of the nominal value?
Page 4-5, l. 9: Which two parameters? Be more specific.
Page 4-9, l.13 Clarify. Is it Gosselin's model?
Page 4-9, l.14: Clarify. Is it linear or non-linear CFK model?
Page 4-10, l. 6: There is no 4 ppm value in table 4-1.
Page 4-10, table: increase font size for V_A
Page 4-10, l. 16: This study was done in police cars which are regularly maintained and tuned. So the real CO value is somewhere between 5 and 50 ppm.
Page 4-14, l.14: insert after "interface" the words "into plasma and subsequently into RBC"
Page 4-15, fig. 4-7. Unusual referencing of the source. Why not simply say that the source is U.S.EPA 2000.
Page 4-16, l. 22: The value for Haldane constant M is reported to be 218. However, some sections report the use of other values, like 230. The M value should be used uniformly, whenever possible.
Page 4-17, l. 17: Suggest replacing "quickly" with "2-10 min".

Page 4-20, table 4-3; I am not sure that we need this table. For most of exposure conditions listed in the table COHb levels are well beyond the scope of this document. Suggest deleting. The three sentences in the text (line11-14) are sufficient.

Page 4-21, l. 2-15: Similarly, the discussion of rodent's data does not seem to be too relevant. In some referenced studies, though not on the list, %COHb levels were as high as 80%.

Page 4-23, l.17: "distribution" might be a better word than "uptake".

Page 4-28, l. 27-29: Delete, not relevant.

Page 4-31, l 6: Suggest replacing "processes" with "function"

Page 4-31, l.8: Suggest replacing "combat" with "compensate for"

Dr. Michael Kleinman

Charge question 3: Material has been added to Chapter 4 describing differences among models that predict COHb concentrations as a function exposure and physiological parameters. This is useful however the summary and conclusions do not make it apparent which model will be preferred for health risk assessments and why.

Specific Comments: The new illustrative material could be better coordinated. Table 4-1 for example demonstrates that COHb concentrations increase with increasing ventilation rates after 1- and 8-hr of exposure but begin to decrease at 24 hr. The explanation may come later in the chapter but it would be useful to mention the rationale in the description of the Table.

Figure 4-4 does not seem to agree numerically with Table 4-1 for the higher exposure concentrations. Also COHb levels for exposures at 20 ppm seem to be increasing during the first 8 hours and those at 50 ppm are decreasing. The curves appear to be show them approaching the same concentration if the subject continued to sleep. It would be helpful to add a graph of Va used for the model keyed to the right Y axis.

Figure 4-5 data for endogenous production 0.007 does not appear to be consistent with Table 4-1.

Figure 4-6 seems unnecessary since the scenario it presents is not related to any real-world case and its importance is not explained in the text.

The Bruce and Bruce model is claimed to better predict COHb levels when inspired CO levels change rapidly, as might occur during start-up conditions in some combustion emission scenario and is said to better predict CO washout than does the CFK. However the previous examples seem to have been calculated using the CFK. Some reason for why the Bruce and Bruce model is not selected would be useful.

Dr. Francine Laden

Section 5.1.3.2. Recent Studies of Non-Hypoxic Mechanisms, is an excellent summary and I agree with its conclusions. The multicenter controlled human exposure study is well described and the levels at which effects were observed are now clear.

One editorial comment, the definitions of Hb and Mb should be repeated at the beginning of each chapter

The descriptions of the epidemiologic studies and the studies of the associations between blood markers and ambient CO concentrations are good. The following reference should be added to 5.2.1.8:

> Delfino RJ, Staimer N, Tjoa T, Gillen DL, Polidori A, Arhami M, Kleinman MT, Vaziri ND, Longhurst J, Sioutas C. Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms. Environ Health Perspect. 2009 Aug;117(8):1232-8.

A table or figure summarizing the results from the blood markers studies (much like the ones included later in the chapter) would be very helpful.

A similar table or figure summarizing the results of the HRV, ECG abnormalities, arrhythmias, blood pressure (Sections 5.2.1.1. through 5.2.1.7. would be helpful as well.

In Figure 5.6. it should be made clearer that the other pollutants, used as separators, are included as co-pollutants in the models of CO with the different cardiovascular outcomes.

> I agree with the conclusions of each of the other health outcomes: CNS, birth outcomes, respiratory effects, mortality , and of susceptible populations.

Dr. Arthur Penn

Initial response to CO ISA, 2nd external review draft

Many of the conclusions presented in the 2nd external review of the ISA, are retained (understandably) from the 1st ISA, My focushere is on areas of CVD-related outcomes on which less emphasis has so far been placed and which I believe deserve additional attention since they deal with biological plausibility of CVD outcomes in response to elevations in low daily ambient CO levels. These outcomes also are consistent with the statement at the top of p. 5-67 "It is conceivable that the most sensitive individuals respond to levels of COHb lower than 2%" as well as with the "causal relationship" statement at the bottom of that page.

Ambient CO Effects on CVD

The most impressive CO-related CVD results remain the 20+-year-old controlled human exposure studies of Allred et al; Kleinman et al; Sheps et al; however, a direct connectionbetween these results and the predictions for CO effects on CVD morbidity/mortality at CO levels close to ambient has yet to be made. The effective CO exposure levels in those 3 studies were > 2 orders of magnitude above ambient levels and resulted in COHb levels of 2-4%.With ambient CO levels at 0.5-0.6 ppm and associated COHb levels well below 2%, the gap between a) the controlled studies with small numbers of high-risk volunteers exposed to≥100ppm CO and b) real-life,large population exposures to small increases (≤1 ppm) in daily max [CO] is too large to discount at present. Further, other studies (Adir et al, 1999; Kizakevich et al, 2000) with healthy volunteers suggest little or no major responses to elevated (as high as 3000 ppm) CO exposure levels. In those studies there were no reported arrhythmias, no changes in lactate/pyruvate, no effects on ST-segment changes or on cardiac rhythm.
The focus on possible CO effects in patients with major artery occlusion and MI history is understandable from the perspective of a potentially highly susceptible population, but moves attention away from other populations that may be more likely at risk to elevations in ambient CO.

Alternative populations meriting attention are the groups suffering from CHF (pp. 5-43 to 5-45) and arrhythmias (pp. 5-24 to 5-26). While most of the evidence here is carried over from the 1st ISA Draft, some of the reports summarized in this section + others noted in other sections of Chapter5 are worthy of further consideration. In addition I have added some studies from the past 12 years that were not mentioned in the 2nd ISA Draft.

Results reported by Yang(JTEH, 2008) on Taipei data for the years 1996-2004--while CHF hospital admissions (**HA**s) were associated with all 5 major air pollutant groups for warm days, the only association on cold days was withincreases in ambient CO.

Mann et al (EHP, 2002) reported that a 1ppm increase in 8-hr average CO in So. California was associated with a 3.6% increase in same-day IHD HAs for patients with a 2°diagnosis of CHF and 2.99% increase for those with a 2° diagnosis of arrhythmias.

Peel et al, (Am J Epidemiol, 2007) reported an association between a 1 ppm elevation in 1 hr max CO and HAs for patients with dysrhythmias and CHF who had hypertension as a co-morbid condition. This was an 8-year study with > 4.4 million patient visits to 31 Atlanta area hospitals.

Other relevant CO/CHF studies include:

a) Morris et al (AJPH, 1995)--elevated ambient CO levels in 7 US cities were associated with increased HAs for CHF in elderly patients;

b) Burnett et al (Epidemiology, 1997)--daily high hour ambient CO levels on day of HA had the strongest association of any of the 5 major air pollutants with HAs for CHF;

c) Morris and Naumova (EHP, 1998)--HAs in Chicago for CHF were most strongly associated with increases in ambient CO-effect was strongest at lowest temperature (see Yang, above);

d) Stieb et al (Environ Hlth, 2004)--in a multicity study in Canada (1980s & early 1990s), for every 0.7 ppm increase in 24-hr mean [CO], there was a 2.6% increase in ED visits for MI/angina, but <u>a 3.8% increase in visits for CHF</u>;

e) most recently, Bell et al (EHP, 2009- in ISA reference list, but not discussed??) in a study of emergency HAs for CVD and their association with 1 hr max. CO levels in 126 US urban counties (av. max CO level=1.6 ppm) found the highest % increase in CO-related risk for HAs (~1%) was for heart failure in patients > 65 yrs of age. HAs for 9.3 million patients over 7 years were examined.

The downside of these studies-that they are association/correlation studies—is countered by the large #s of patient records screened in each of these independent studies and the similarity of the findings for urban CHF/arrhythmia patients in the US, Canada & Taiwan.

<u>Blood Markers of CO Exposure-Coagulation (but not inflammation)</u>
A few recent studies (Baccarelli et al, 2007; Delfino et al, 2008; Rudez et al, 2009) point to increased platelet activation and pro-coagulation effects associated with elevations in ambient CO. In these and other studies (Ruckerl et al, 2006, 2007; Steinvil et al, 2008) elevations in fibrinogen in response to elevated CO are largely absent. Many of these studies note that elevations in ambient CO were not associated with any inflammatory responses (see question to Panel members below). One exception was the recent report of Ljungman et al, (EHP, 2009). Among 955 MI survivors, the 16% with specific polymorphisms in both IL-6 & fibrinogen genes showed larger IL-6 responses to elevated CO than did MI survivors without these polymorphisms.

Q. for Panel members: In light of the EPA's interest both in controlled human studies with responses to exposures to≥ 100 ppm CO and responses of large populations to 1 ppm increases in peak ambient CO, are there any Panel members concerned (intrigued?) by the growing interest in therapeutic uses of CO as an anti-inflammatory agent? A number of recent studies on animal models of injury/disease (sickle cell disease, I/R injury, lung injury associated with

cardiopulmonary bypass) have reported on the therapeutic value of treatment with “low”, i.e., 250 ppm, doses of CO.

Dr. Stephen Thom

Modifications in the second draft are well done and improve the Integrated Science Assessment (ISA) for carbon monoxide. It was a good idea to include sections that integrate health effects risks, but there seem to be some internal contradictions in reviews of pulmonary injury outlined in chapters 2 (starting on page 2-12) and 5 (starting on page 5-144). The ISA may be open to criticism because conclusions pertinent to short term and long-term CO exposures differ, but the discussions outline similar limitations in the data. The statements below are mostly excerpts taken directly from the ISA, but they were put in a different order than in the actual document.

Morbidity assessments for short and long term CO exposure:

Animal toxicological studies provide evidence that short-term exposure to CO (50-100 ppm) can cause oxidative injury and inflammation and alter pulmonary vascular remodeling. Controlled human exposure studies have not extensively examined the effect of short-term exposure to CO on respiratory morbidity. Positive associations between short-term exposure to CO and respiratory-related outcomes include effects on pulmonary function, respiratory symptoms, medication use, hospital admissions, and ED visits. The problem is that the majority of this literature does not report results of extended analyses to examine the potential influence of model selection, effect modifiers, or confounders on the association between CO and respiratory morbidity. In particular, the lack of co-pollutant models prevents assessment of which effects are due to CO versus other combustion-related pollutants. Yet, the ISA conclusion is that evidence is *suggestive of a causal relationship* between short-term exposure to relevant CO concentrations and respiratory morbidity.

The ISA outlines limitations in studies that have examined the association between long-term exposure to CO and respiratory morbidity including the lack of replication and absence of validation studies to evaluate some of the epidemiological statistical methodologies, whether health effects observed can be explained by the known biological mechanisms and an absence of co-pollutant analyses to disentangle the respiratory effects from CO versus other combustion-related pollutants. The conclusion was that the evidence is *inadequate to conclude that a causal relationship* exists between long-term exposure to relevant CO concentrations and respiratory morbidity.

Mortality assessments for short and long term CO exposure:

Epidemiological evidence was reviewed from multi- and single-city studies which suggest that there is an association between short-term exposure to CO and mortality. The limitations in the data were highlighted along with the observation that CO risk estimates were attenuated in co-pollutant models. Despite the uncertainty as to whether CO was acting alone or as an indicator of effects related to other combustion-related pollutants the ISA concluded that *evidence suggests there is a causal relationship* between short-term exposure to relevant CO concentrations and mortality from respiratory disorders (page 5-158).

With regard to pulmonary-related mortality from long-term CO exposure, the ISA outlines the consistent null and negative associations observed across epidemiologic studies which included cohort populations encompassing potentially susceptible subpopulations. The discussion includes an assessment that there is a lack of evidence for respiratory and cardiovascular morbidity outcomes following long-term exposure to CO (Note that page 5-56 discusses long-term cardiovascular effects observed in epidemiological studies. A conclusion is offered that there is a direct effect of short term exposure and cardiovascular disease morbidity – see page 5-67, but no summary statements are made regarding long term exposures). These assessments, along with an absence of specific mechanisms to explain the progression from morbidity to mortality, are used to conclude that it is *unlikely that there is a causal relationship* between long-term exposure to CO and mortality (page 5-166).

To conclude, my impression is that similar limitations exist in the data for pulmonary effects from short term and long term CO exposure. Despite this similarity, short term effects on morbidity and mortality are given a stronger summary assessment of risk (evidence suggests there is a causal relationship) whereas long-term CO exposure is said to be unlikely to be causally linked to respiratory morbidity and mortality.