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

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Dr. Paul Blanc

CO: EPA Review Risk and Exposure Assessment, Draft Comments

Characterization of Exposure (Chapters 5 and 6)

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

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

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

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

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

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

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

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

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

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

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

Dr. Thomas Dahms

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Dr. Russell Dickerson

Air Quality Considerations (Chapter 3)

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

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

Dr. Laurence Fechter

Comments on Risk and Exposure Assessment document for CO

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

Dr. Milan Hazucha

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

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

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

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

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

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

Page 5-10, l.24-25: The statement is true, but only for sub-maximal exercise in healthy individuals. Need to state that. Moreover, VA/VO2 ratio is not so constant for patients with cardiovascular disease.

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

Page 5-20, table 5-2: The table data seem to be based on passenger cars only. Any data on pick-ups, vans, buses, trucks? Out of ~500 mil vehicles only about 250 mil are passenger cars (US Bureau of Transit Statistics).

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

Dr. Michael Kleinman

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

1. Re: The description and selection of health endpoint, target population and risk metric.
    a. The strongest evidence regarding CO health effects does relate to cardiovascular morbidity and it appears that the evidence is sufficient to indicate a causal relationship is likely to exist. The coherence of epidemiological evidence with the human controlled exposure study data supports this finding.
    b. The controlled exposure studies provide both exposure-response relationships and through use of COHb measurements as a exposure/dose biomarker there appears reasonable data to provide dose-response relationships.
    c. Having said that, Chapter 4 goes on to note the data from controlled human studies 'do not support the development of a quantitative risk assessment to characterize the dose-response relationship within the range of interest.' This conclusion is not sufficiently supported in the REA. While there are some inconsistencies in the controlled study time to angina endpoints, there seem to be sufficient data and reasonable consistency in study methods and designs that a 'meta-analysis' or comprehensive data analysis could be performed.
2. Re: Benchmark values.
    a. Extending the benchmark values below the level at which significant changes were detected in controlled exposure studies is appropriate and consistent with previous CASAC suggestions. The subjects participating in the controlled exposure studies were required to be able to perform aerobic exercise as part of the protocol, hence were not as debilitated as many individuals with CVD or IHD.
    b. The coherence of the epidemiological study results with the results of the controlled human studies also suggests that extension of consideration below 2% COHb is warranted since the epidemiology demonstrates morbidity at CO exposure levels that would produce COHb well below 2%. If the baseline level of the participants of the controlled studies is representative of the COHb of the general population of CVD and IHD patients, their average COHb is on the order of 1% or less.
3. Re: Presentation and derivation of COHb estimates.
    a. Section 5.3.7 provides a useful summary of the parameters incorporated into the CFK model. On the other hand, the ISA goes to great lengths about the problems of CFK for low levels of COHb and short-term exposures. Presumably APEX generates 8hr and 24hr CO exposure estimates. If those estimates are appropriate for the CFK, it could be explicitly stated in 5.3.7.
    b. The methodology for generating the scenarios is reasonable if one accepts the premise that 1 monitoring station each in LA and Denver are sufficient to describe exposures. This seemed like a major jump, given everything previously stated in the ISA and the REA about CO being non-uniformly distributed. Given the conclusion in 6.5 'the utility of this assessment for the purpose of considering the adequacy of the current standards to be limited' suggests that the REA could be improved.

    i. Use a meta-analysis or other technique to better define the dose response curve.
    ii. Use a more comprehensive design for assessing exposures in both LA and Denver that could take into account the inhomogeneities of CO distributions.

c. The finding that the REA utility is 'limited' needs to be better qualified as to what those limitations are with respect to evaluating the current standards. At a minimum it would seem that more information on what more would be needed to consider the adequacy of the standards should be provided.

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 focus here 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 a 3.8% increase in visits for CHF;

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.

Blood Markers of CO Exposure-Coagulation (but not inflammation)

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. Paul T. Roberts

Preliminary Comments on 1st draft REA by for CASAC CO Panel

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

I think EPA did a very good job on the summary and presentation of the ambient CO data and the near-roadway data; see my minor comments below.

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

Detailed comments:

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

Page 1-5, lines 25-30: Typically, "a draft, screening-level assessment" implies that there will be further, more-detailed, steps in the assessment, based on the result of the screening-level assessment. What are the EPA staff's ideas about these next steps? I realize that this is a question being asked of the CASAC CO Panel too.

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

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

Page 3-10, line 26: Modify to read "…great than measurement taken at…" since they used on set of monitors to take the measurements at all distances, not separate monitors.

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

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

Minor edits and typos in the 1st draft REA:

- Page iii: The title for Figures 5-1, 5-2, and 5-3 are duplicated in the List of figures.
- Page 2-1, lines 4-6: this part of the introductory sentence is quite awkward.
- Page 2-2, line 14: use "are also important"
- Page 2-2, line 19: delete "on".
- Page 2-5, lines 9-10: "using GC" is confusing. How about "using GC analysis of blood"? As opposed to "measured by CO-oximeter <u>on exhaled breath</u>" on page 4-3, line 11. Please expand both phrases to help the reader understand the methods and substrate are different.
- Page 3-2, line 3: the details for footnote 2 are missing.
- Page 3-10, line 31: insert a comma after estimates.
- Page 3-11, line 12: Make end of line read "(draft ISA, Figure 3-17)". Similar comment for page
- Page 4-2, line 3: add the dates for the reference (1989a, 1989b).
- Page 4-2, line 29: it would read better if the word "decrease" were inserted after "and".

Dr. Stephen Thom

RISK AND EXPOSURE ASSESSMENT – FIRST DRAFT:

Charge questions:

Air quality considerations (Chapter 3)

I found the discussion clear and appropriate.

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

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

Characterization of Exposures (Chapters 5 and 6)

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