UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

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January 20, 2010

EPA-CASAC-10-005

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

Subject: Review of *Integrated Science Assessment for Carbon Monoxide (Second External Review Draft)*

Dear Administrator Jackson:

The Clean Air Scientific Advisory Committee (CASAC) Carbon Monoxide (CO) Review Panel met on November 16-17, 2009 to review EPA's *Integrated Science Assessment (ISA) for Carbon Monoxide* (Second External Review Draft, September 2009). The Panel's report was reviewed and approved by the chartered CASAC on a December 22, 2009 public teleconference. This letter begins with CASAC's overall comments and evaluation. We highlight the most important issues which need to be addressed as the ISA is finalized. The Panel and CASAC membership is listed in Enclosure A. The Panel's consensus responses to the Agency's charge questions are presented in Enclosure B. Finally, Enclosure C is a compilation of individual panel member comments.

We appreciate the responsiveness of EPA staff to our previous comments. The issues that we targeted as important in our previous review were addressed. Both the revised document, as well as statements by staff in response to our comments at the meeting, was responsive to our concerns. CASAC commends the EPA staff for the development of a comprehensive and readable second draft of the *Integrated Science Assessment for Carbon Monoxide*. The document integrates relevant evidence from the past decades while emphasizing newer evidence and a deeper understanding of mechanisms by which CO affects health. The extensive literature on CO is thoughtfully summarized and presented effectively in tables and appendices.

We are comfortable with the process used by the EPA to produce this document. The EPA has implemented a process that is consistent with current approaches to evidence review and synthesis. It has progressively refined this process in recent NAAQS reviews. The process, which is being applied across the criteria pollutants, will enhance the quality and transparency of CASAC's reviews.

Some additional major comments follow:

- CASAC previously noted that the terms "sensitive, susceptible, and vulnerable" are sometimes used interchangeably in EPA's various review documents. We reiterate the need for these terms to be used in a consistent manner. We recommend that the EPA develop a glossary of terms to be used across documents related to all criteria pollutants. Such a glossary would promote consistency in the ISAs and REAs. The definitions presented in the recently released final ISA for PM (December 2009, EPA/600/R-08/139F) may address some of CASAC's concerns.

- The Panel expresses concern about the existing CO monitoring network, both for its spatial coverage and for its utility in estimating human exposure. CO exposures may not be adequately characterized for populations that may be exposed to higher CO levels because of where they live and work. Moreover, because CO levels are often below the limit of detection of current monitors, both exposure assessment and model calculations may be limited. The Panel recommends that monitoring for CO should be improved.

- The Panel approves the broadening of the evidence base considered in the ISA. For example, the discussion of CO in relation to atmospheric chemistry and climate change is useful. Although such considerations do not drive the current standard, it is important to acknowledge climate change. While we agree that this topic merits discussion, the influence of climate change on a secondary standard is minimal because of the high level of uncertainty at present.

- Although EPA regulations for most pollutants are weighted heavily by information provided from epidemiologic studies, in the case of CO, information from well-designed clinical exposure studies has received emphasis. We agree with the weight that they are given in the current document.

- The problem of co-pollutants serving as potential confounders is particularly problematic for CO. Since exposure levels for CO are now low, consideration needs to be given to the possibility that in some situations CO may be a surrogate for exposure to a mix of pollutants generated by fossil fuel combustion. A better understanding of the possible role of co-pollutants is relevant to regulation and to the design, analysis, and interpretation of epidemiologic studies on the health effects of CO.

- Some of the challenges in interpreting and reviewing the evidence on CO in the ISA (and Risk and Exposure Assessment) reflect the great progress in reducing ambient concentrations of CO. Control measures taken over the past decades have led to greatly reduced emissions and concentrations. Notable progress has been made in reducing exposure of the public to CO. CASAC notes that the ISA documents a substantial decline in CO levels in urban areas over the past two decades, which has undoubtedly benefited public health.

CASAC agrees that the Draft CO ISA will be adequate for rulemaking with the incorporation of changes in response to the Panel's major comments and recommendations. We thank the Agency for the opportunity to provide advice on the Draft CO ISA.

Sincerely,

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

Dr. Joseph D. Brain, Chair
Clean Air Scientific Advisory Committee
Carbon Monoxide Review Panel

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

Enclosures

Enclosure A

Rosters of the CASAC CO Panel and CASAC

U.S. Environmental Protection Agency
Clean Air Scientific Advisory Committee Carbon Monoxide Review Panel

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NOTICE

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

Enclosure B

CASAC's Consensus Responses to EPA's Charge Questions

1. *Chapter 1 has been revised in response to comments from the CO Panel, as well as related comments from the CASAC PM Panel, to add information regarding criteria for study selection and evaluation, to add more CO-specific information to the framework for causal determination, and to more clearly describe the process of integrating evidence from various disciplines to classify the overall weight of evidence relating to causality. What are the views of the Panel on the extent to which this revised Chapter 1 provides necessary and sufficient background information for review of the subsequent chapters of the CO ISA?*

Chapter 1 is an important but challenging chapter. It is responsive to the comments and suggestions provided previously by CASAC. The chapter establishes a solid background to subsequent chapters of the CO ISA. The integration of Tables 1-1 and 1-2 provides a concise summary of the aspects used in epidemiology to assess causality. Section 1.6, EPA Framework for Causal Determination, now incorporates a detailed description of the criteria for causal determination. The introductory sentence to Section 1.6.3 clearly describes the process of moving from association to causation, requiring the elimination of alternative explanations for the association. In order to illustrate the criteria used to assess the quality of a study, it would be helpful to include: the definitions of confounding and effect measure modification and the criteria for determining if a factor (covariate) is a confounder; the process utilized to identify confounders and effect measure modifiers; available methods to control for confounding in the design and analysis phase of a study; and the most appropriate ways to interpret effect measure modification. In general, the ISA would greatly benefit from an improved presentation of epidemiologic concepts.

More detail on the scope of the critical review of ecological effects (in the sense of effects on the ecosystem, not ecological associations) is requested. Specifically, what literature databases were searched, using what keywords, for what time period, and for what geographic scope? Given the scant literature on the ecological effects of CO, EPA should nonetheless comment on hypotheses for ecological effects and identify key data gaps. Such information would be useful for setting a research agenda to inform the next revision of the CO NAAQS.

The terms "sensitive," "susceptible," and "vulnerable" are often used interchangeably or at least with potentially overlapping meanings. In regard to the final CO ISA, CASAC reiterates its expectation that the terminology will be consistent with the definitions in the final PM ISA and used uniformly throughout the entire document. EPA should develop a glossary of terms that are used across criteria pollutants, to ensure consistency of terminology in the ISAs and REAs for all NAAQS reviews. The term "sensitive" is in the statutory language (see footnote 1 on p. 1-3) and thus may have special regulatory significance, which should be explained. The role of identifying "susceptible" and "vulnerable" groups with respect to characterization of "sensitive" groups should be explained as well. Although a table giving definitions of these terms appears later in the document, clarification earlier would be better.

Finally, given that the epidemiologic literature on CO has grown over the past decade, the Panel recommends that EPA assess the applicability of performing quantitative meta-analyses when appropriate. Such analyses would better inform quantitative effect estimates, and allow the Agency to refine further its inferences from the scientific literature.

2. Chapter 3 has been revised and expanded in response to Panel comments regarding climate, monitoring, spatial variability, and exposure.

> *a. Evidence reviewed in Chapter 3 of the ISA indicates that the direct contribution of CO to greenhouse warming is very small, while the role of CO in atmospheric chemistry cycles involving other species makes a larger contribution to radiative forcing. This combined evidence leads to the conclusion in Chapter 2 that a causal relationship exists between current atmospheric concentrations of CO and effects on climate. What are the Panel's opinions related to this causal statement and the evidence provided to support it?*
>
> *b. Additional detail has been provided regarding the detection limits of CO monitors in the regulatory network, the number of monitors reporting at each horizontal spatial measurement scale and comparison of monitoring data at each scale, and spatial variability of CO concentrations near major sources, particularly roadways. Please comment on the usefulness of these revisions in characterizing the information provided by the CO monitoring network.*
>
> *c. The section on exposure assessment has been reorganized to provide information on exposure assessment at different spatial scales and to create a subsection containing information regarding exposure error and its implications for interpretation of epidemiologic studies. Does the Panel consider that the sources of exposure error have been appropriately characterized, and agree with the revised conclusions regarding the impact of exposure error due to spatial variability and the presence of CO as part of a combustion-related mixture on health effect estimates from time-series epidemiologic studies?*

Substantial information has been added to both Chapters 2 and 3 as well as to Annex A. The ISA has been strengthened by these additions. The review of the literature appears to be thorough, and the analysis of the scientific evidence systematic. In discussion of non-anthropogenic CO emissions (pages 3-3 to 3-5), emissions from biogenic sources, and CO generation from the oxidation of volatile organic compounds (VOCs), isoprene, and other biogenic VOCs should be added to the caption of Figure 3-1. Additionally, the discussion would benefit from the inclusion of information on the range of motor vehicle operations which favor CO emissions, such as operation under high load, emissions during cold-starts, and emissions from gross-polluting vehicles.

The addition of information on the potential impact of CO on climate is very helpful. It appears that the direct impact of CO is small, but the indirect impact of CO may be substantial. However, the estimates of the impacts of CO on climate are uncertain. This current high level of uncertainty does not favor the development of a secondary standard.

The expanded discussions on CO detection limits, monitoring details, and spatial CO characteristics better characterizes the information provided by the CO monitoring network and helps to qualify the data used in exposure estimations. Specifically, the expanded discussions on monitor detection limits and monitoring locations in Section 3.4 and the respective Annex figures and tables are critical to understanding CO concentrations. They are an important addition to the ISA. Although the limitations of insensitive existing monitors are provided in the text (page 3-43, lines 13-18), these limitations need to be added at numerous other places in the ISA that also address CO concentrations. The relaxation of CO monitoring requirements and the continued use of older, less sensitive monitors with high detection limits the use of monitoring data for current exposure assessments.

In general, the expanded discussions of sources of exposure and resulting exposure assessment in Section 3.6 are a great improvement and are useful in characterizing the potential impacts of exposure error. The section on Land Use Regression Models (page 3-94, lines 6-23) is limited in scope. It does not represent the wide range of modeling methods nor exposure results from the literature. Additional discussions should help characterize the spatial concentrations of CO between monitoring locations and particularly near roads where concentrations are usually much higher than in general area locations. Admittedly, much of the modeling work in the literature is on pollutants other than CO, but the conclusions regarding what methods work and how they relate to estimating pollutant concentrations should be directly applicable to CO.

3. *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.*

Generally, we found the revised and substantially expanded Chapter 4 of the second draft ISA to be comprehensive and very useful in illustrating various physiologic factors and disease states that influence blood levels of COHb and/or their potential adverse affects. Section 4.2 describes in adequate detail various COHb predictive models. However, despite the addition of section 4.2.3 on Model Comparison and its discussions of the respective models' strengths and limitations, questions remain. It is unclear to the Panel: (1) how these different models will perform under the same simulated temporal exposure scenario of 30-60 minute duration with occasional peak CO concentrations, and (2) which model is the most accurate in predicting COHb levels? Several models seem to be most suitable for an inter-model comparison and evaluation, e.g., Smith et al., 1994, Bruce and Bruce, 2008, Gosselin et al., 2009, as well as the non-linear Coburn-Forster-Kane equation (CFKE) used by EPA in the Agricultural Policy EXtender (APEX) model. This comparison may help to establish whether the CFKE is the best model given that activity levels are evaluated on a minute-by-minute basis and ambient CO shows transient peaks. The physiological parameters (e.g., V_A and DL_{CO}) used in both Denver and Los Angeles COHb calculations should be spelled out, since DL_{CO} and ventilation rates vary by altitude.

There are some inconsistencies among the tables, figures and text presented in the discussion of the Quantitative Circulatory Physiology (QCP) model in section 4.2.4, which need to be reconciled. The section could be shortened by dropping less relevant material.

The addition of section 4.3.4 COHb Analysis Methods in this draft is very helpful in pointing to limitations and inaccuracies of some of the instruments used to measure COHb. Since the differences in COHb determination among methods may be substantial, we suggest indicating the method/instruments used to determine COHb in the tabulated studies as well as in other key studies discussed in the text.

In addition to people with cardiovascular disease there are other large population groups potentially at-risk from CO exposure, such as those having various forms of anemia or COPD. Although there are no experimental studies on the effects of CO exposure on these groups at ambient concentrations, these individuals may be more vulnerable to CO because their disease state amplifies the action of CO. The application of COHb predictive models with the inclusion of appropriate pathophysiological parameters representing such disease states, if feasible, might be helpful in determining the extent of risk in such populations. Especially, if available, additional details should be provided and discussed regarding the fetus as an at-risk individual.

Identification of CO-specific associations with health endpoints in epidemiologic studies often requires complex, multivariate analyses. Utilization of appropriate COHb predictive models can help in interpreting the biological plausibility of associations of CO with health endpoints and will likely provide further insight into the pathophysiological basis of responses.

4. *The cardiovascular effects section has been expanded to:*
    - *evaluate key uncertainties in the health evidence, particularly regarding the biological plausibility of effects at low ambient CO concentrations and distinguishing independent effects of CO in multipollutant ambient mixtures;*
    - *provide more detail on the design and findings of a multicenter controlled human exposure study to clarify the levels at which effects were observed;*
    - *add description of new epidemiologic studies, including a large U.S. multicity study and studies on associations between blood markers and ambient CO concentrations; and*
    - *more clearly describe the integration of controlled human exposure and epidemiologic evidence to reach a causal determination.*

Please comment on these revisions to Chapter 5 and the conclusions for each of the health outcomes evaluated in this chapter. In particular, we are requesting CASAC comment on the interpretation of the evidence and the causal determination for short-term exposure to CO and cardiovascular morbidity.

The EPA staff is to be commended for the expanded, wide-ranging and comprehensive presentation in Chapter 5 of the ISA. They have added relevant material to the earlier version of this chapter and included updates from articles that appeared as late as September, 2009. The Panel offers the following suggestions for Chapter 5 of the final ISA: additional Forest plots to

summarize CO effects on blood markers and heart rate variability, and a meta-analysis of health effects studies for selected outcomes.

Cardiovascular Morbidity. The most compelling CO-related cardiovascular results remain those from the controlled human exposure studies of Allred et al; Kleinman et al; and Sheps et al. The 1991 Allred report contains dose-response information, including responses at COHb concentrations <2%, based on the air-exposed COHb levels. More recent epidemiological studies of morbidity at ambient CO levels, including data on hospital admissions, are consistent with and reinforce the observations from the earlier controlled human studies. A large at-risk population includes people with CVD who have not yet been formally diagnosed with this condition. This undiagnosed group will likely grow in size and importance as our population ages. Many individuals that have had acute myocardial infarctions do not have already diagnosed coronary artery disease (CAD).

Although those with diagnosed CAD are the largest CVD group and may represent the most easily quantifiable highly-susceptible group for CO-related outcomes, CASAC notes that EPA's singular focus on CAD will underestimate the at-risk population. Other CVD patients, regardless of whether they carry a diagnosis of CAD or not, are at increased risk for CO-related hospital admissions. Further, limited data from people suffering myocardial infarctions (MIs), who had recently experienced high acute CO exposures, indicate that those MIs were associated with vasospasm, rather than with complications of CAD. This further indicates that CAD need not be a final common pathway to designate adverse CV outcomes. Finally, the association of stroke with small increases in ambient CO levels also supports a more broadly defined risk group going beyond those with established CAD.

In conclusion, it is CASAC's recommendation that EPA broaden the definition of the at-risk population beyond people with CAD. The Panel members concur with the ISA's conclusion that a causal relationship is likely to exist between relevant short-term CO exposure and CV morbidity. We note that data are inadequate to establish a relationship between either chronic CO exposure or transient elevations in ambient CO and morbidity.

Stroke. The Panel finds there is a strong association between elevated ambient CO levels and hospital admissions for stroke, distinct from other neurological outcomes (see above). Consideration might be given to changing the title of the neurological outcomes section to "CO and *non-stroke* CNS morbidity".

Respiratory Morbidity. Positive associations have been demonstrated between short-term exposure to CO and respiratory-related outcomes including effects on pulmonary function, respiratory symptoms, medication use, hospital admissions, and emergency department visits. However, there were no convincing data in which these relationships were consistently observed after adjusting for multiple co-pollutants, which are also risk factors for adverse respiratory outcomes. The Panel was divided, and while the majority view was in favor of "evidence suggestive of a causal relationship" others favored a designation of "inadequate to infer a causal relationship." The evidence on associations between long-term exposure to CO and respiratory-related outcomes is even more uncertain than for short-term exposures and were appropriately categorized as "inadequate." Finally, the point was made that allergy and allergic responses

should be considered separately from respiratory outcomes and that this distinction should be noted in the final ISA.

"Therapeutic" Applications of CO. There is a growing literature regarding possible therapeutic applications of CO at levels of ~250 ppm. These studies have been carried out in some animal models and in cell culture. CO is a pro-oxidant and has profound extended pro-inflammatory effects. However, in specific scenarios with distinct organ systems or specific cell types, CO may have short-term anti-inflammatory effects. Clinical trials thus far have not supported health benefits of CO administration. Further, there is no evidence that the hypothetical therapeutic results provide any insight into health effects of acute or chronic ambient exposures in the general population, and especially in subpopulations susceptible to CO effects.

5. *The section on susceptible populations has been revised substantially in response to comments from the CASAC CO Panel and in consideration of similar comments from the CASAC PM Panel. The definition of a susceptible population has been clarified, and each subsection describing a susceptibility characteristic has been revised to emphasize specific evidence from controlled human exposure studies of individuals with underlying disease, epidemiologic studies that conducted stratified analyses to examine effect modification, and toxicological studies using animal disease models. Does this revised section provide appropriate characterization of populations potentially susceptible to CO-induced health effects?*

The discussion of populations susceptible to carbon monoxide has been greatly improved. The data are now presented in a logical framework providing a clear and concise summary. Section 5.7 begins with Table 5-25, which provides a useful context for understanding the historical use of the terms vulnerability and susceptibility. A question was raised during the Panel's deliberations regarding whether level of exposure should be considered a "vulnerability" factor. It was suggested that the term "at risk" may be useful in some instances to distinguish individuals who are truly more susceptible owing to some specific subject characteristic rather than to a difference in level of exposure.

Cardiovascular Disease. As indicated in the previous charge question, the Panel finds that the discussion of vulnerable subpopulation is focused too narrowly on coronary artery disease (CAD). It has been noted that arrhythmias and congestive heart failure should also be discussed in this section. Further, CAD represents a continuous progression with many more individuals at risk than those carrying a doctor diagnosis.

Anemia. A susceptible subpopulation is individuals with anemia from a diverse range of disease states. A key mechanism by which anemia may put individuals at increased risk is the reduction in the capacity to carry oxygen. Hemoglobinopathies, including sickle cell disease, should be distinguished from anemia in general, as these disorders are likely to have a different susceptibility relationship with carbon monoxide.

Diabetes. Diabetes was identified as another factor condition might increase susceptibility to carbon monoxide. During the Panel's deliberations, it was noted that the ISA does not mention the high rate of obesity and metabolic syndrome as risk factors in addition to diabetes itself or

the high correlation between diabetes and cardiovascular disease. In particular, the Panel cited the results of a recent South Korean study (not included in the report) in which the effects of carbon monoxide were investigated in individuals having both diabetes and cardiovascular disease[1].

Gestational Development. The focus on altered gestational development included both the mother and fetus. Limited data suggest the possibility of paternally mediated effects of carbon monoxide owing to altered sperm production[2]. These effects cannot be ruled out as a potential contributor to the effects of carbon monoxide in gestational development, but there is currently no compelling evidence for this concern.

6. *Chapter 2 has been revised and expanded to provide more information on atmospheric science and exposure assessment, policy relevant considerations, and integration of CO health effects.*

    a. *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, present results from a new U.S. multicity epidemiologic study investigating the potential presence of a threshold and departure from linearity, and summarize the evidence for susceptible populations. Please comment on these revisions.*

    b. *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. We would appreciate CASAC comment on the material in this section and its effectiveness in presenting the conclusions of the ISA.*

The inclusion and analysis of data from a multi-site epidemiological study [3] is commendable, given that it was published only recently. In addition, there are multiple points in which these data could have been presented in Chapter 5, which is the basis of the presentation in Chapter 2 (see also comments to that charge question). Greater detail should be provided here in Chapter 2 because the data are particularly relevant. For example, limiting the analysis to those days with 1 ppm values or less resulted in the point estimate for the increased hospitalization actually increasing to approximately 1.75%.

Figure 2-1 is new to this revision, and is appropriate and helpful. The Panel offers the following suggestions for improving Figure 2-1. The effect estimate metric as presented in the far right

[1] Min JY, Paek D, Cho SI, and Min KB (2009). "Exposure to environmental carbon monoxide may have a greater negative effect on cardiac autonomic function in people with metabolic syndrome," Science of the Total Environment, 407(17), 4807-4811.

[2] Rubes J, Rybar R, Prinosilova P, Vesnick Z, Chvatalova I, Solansky I, and Sram RJ. 2009. Genetic polymorphisms influence the susceptibility of men to sperm DNA damage associated with exposure to air pollution. *Mutat. Res*. Oct. 2.

[3] Bell ML, Peng RD,Dominici F, Samet JM (2009). "Emergency admissions for cardiovascular disease and ambient levels of carbon monoxide: Results for 126 U.S. urban counties, 1999–2005," Circulation, 120 (11), 924–927.

column of Figure 2-1 should be more understandable. For example, because the lower bound of the CI and the point estimate are of far more interest than the upper bound, adjusting the scale is appropriate and would help the presentation visually. Also, the effects could be grouped by endpoint, not by study, with total CVD top, then IHD, CHF, and stroke. Finally, the 99th percentile of exposure may be of less interest than the 95th.

Although the CVD endpoint of Bell is included in Figure 2-1, the other specific endpoint of Bell is left out. This is related to the tree plot consisting of *unadjusted* CO effects only. A clarifying note with text emphasizing that there are co-pollutant adjusted values from Bell et al. should be added. These critical endpoints include ischemic heart disease (IHD), congestive failure, and stroke. The data in Figure 2-1 could be summarized with a formal meta-analysis or, if this proves inappropriate due to heterogeneity, a comment as to the rationale for not having such an analysis should be included. The ISA should also explain why the data in Figure 2-1 are limited to findings from North America.

We draw attention to the concluding paragraph in Chapter 2. Before addressing uncertainties that remain, it might be more straightforward to first catalogue the uncertainties that have been substantially addressed since the 2000 CO AQCD. (In the present text this is stated first in the negative: "some of these uncertainties remain.") The argument with regard to the lack of biological plausibility runs counter to the rich series of recent studies that indicate the potential modulatory effects of CO at low levels on a number of systems (pages 5-5 to 5-17). A separate section should summarize this central point of improved data that has reduced much of the uncertainty previously encountered. Moreover, the phrase in the last sentence "biological plausibility provided by CO's role in limiting O_2 availability" seems to diminish the rich data on other mechanisms and their possible role (e.g., cell signaling independent of heme moiety binding).

The concluding paragraph refers to the "many new epidemiological studies adding to the body of evidence showing associations." The EPA could modify this statement to include the adjective *convincingly*, to be consistent with the next sentence regarding definitive cardiovascular effects in controlled exposures. At various points, but most importantly in the very last sentence, the phrase "relevant… exposures" is used. If this means exposure at or below the current EPA CO NAAQS, this should be explicitly stated. Relevant could imply that other exposure levels are *irrelevant* to the assessment of health effects, which of course is not intended as they may be relevant through the mechanistic insights they provide. The Panel found the focus on cardiovascular endpoints in the concluding paragraph appropriate. Nonetheless, an additional sentence acknowledging that there is at least a suggestive relationship with several other endpoints is warranted. Also, a restatement of the association with global warming would be appropriate in this concluding paragraph.

There is agreement among the Panel with the ISA's conclusion that there is a likely causal association between acute ambient CO exposures in the range of the current air quality standard and adverse cardiovascular endpoints. In contrast, there is scant evidence in the health effects section related to chronic CO exposure effects on cardiovascular morbidity. Even though these data may be categorized as "inadequate," this category appears to have been omitted from Table

2-1 and should be added. Also, the 2006 publication by Hedblad et al. [4] seems to be missing from the discussion. It is relevant to Chapter 5.

There is heterogeneity of views among the Panel regarding the summary statement that acute CO exposure has a suspected association with adverse respiratory outcomes. The Panel recommends tempering the narrative by explicitly indicating that for this association the evidence borders between suggestive and inadequate. In particular, the epidemiological evidence was limited by an absence of co-pollutant data. We lack studies showing substantive attenuation of CO risk estimates when co-pollutant modeling is performed.

There is a consensus of the Panel that the evidence on the relationship between chronic CO exposure and mortality should be categorized as inadequate. This view is based in large part on the difficulty in epidemiologically differentiating between mortality due to multiple acute effects compared to prolonged lower level effects without peaks. Also, we believe that chronic outcomes in myocardial infarction and stroke can be presumed to include excess mortality.

[4] Hedblad B, Engstrom G, Janzon E, et al. COHb% as a marker of cardiovascular risk in never smokers: results from a population-based cohort study. *Scand J Public Health* 2006; 34:609–615

Enclosure C

Compendium of 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:

Dr. Paul Blanc

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.***

It is appropriate to include the Allred concentration (exposure) response data and to point out (as is done in the text) that this study was far larger and more powerful than any previous controlled exposure study. In terms of exposure (concentration) response, the key Allred study appeared in 1991 (the current document refers the reader to the 1989 Allred paper, although the subsequent 1991 paper provides details of the exposure [concentration]; clarifying this point in the text would be advisable). The Allred data could be presented to better effect if the point is not only the linear relationship, but also the presence of a threshold. In this regard, the Allred analysis of time until angina (from the actual paper, Figure 12, page 112, 1991 and related text) indicates that there was an intercept value (at 0% carboxyHb) of a 1% decrease (± 2.1%; not different from zero) in time until angina onset. This is based on an analysis of room air not as "zero," but as the actual post-exercise room air COHb value (which varied 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. This can be discussed more explicitly than as it appears in the current draft. Also in regard to threshold, 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. Moreover, there is an overextended discussion here as to why this analysis was poorly powered to observe a threshold, including wording such as "an inability to draw conclusions." This could give the appearance of trying too hard to leave open the possibility of a threshold effect where none was no threshold observed.

No attempt was made to perform an integrated analysis of the experimental data for low-level CO exposure and time until onset of angina from multiple studies (for example, using the data in Table 27 of Allred of multiple studies on this subject, taking into account baseline room air carboxyhemoglobin and post exposure levels). It may be that the data, ultimately, so not permit this. If so, a brief statement in this regard in the text would nonetheless be useful.

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. Allred, in fact, did explicitly analyze the concentration response including those resulting from air (ambient CO +metabolism). Many of these observations included in that regression were less than 2% COHb (see above, re: threshold). The wording "some evidence" operates to undermine the findings – it is "evidence," which could be argued to be substantial or strong (as opposed to the indeterminant "some"). If "significant" as

used in this text means statistically significant, then this should be explicit as well. Also on this topic of concentration response, a comment voiced in the meeting was that, in addition the potential differences between concentration response and delivered dose response based on biological monitoring should be acknowledged, either here or elsewhere in the document.

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 susceptible because either they are more likely to experience higher ambient exposures (living near roads, greater commute times) 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 due to greater metabolic production of CO. Susceptibility by both routes 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, on kinetic grounds of a longer half-life. The evidence of susceptibility 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, or toxicology be clarified to mean both..

Overall in the document there seems to have been little use made of human toxicology case reports insofar as the implications that might be drawn from such data. One specific example: human case reports clearly have shown that coronary artery spasm appears to mediate CO-induced MI in some individuals (post CO-caused MI coronary vessels without underlying CAD consistent with MI). [See for example: Marius Nunez AL, Myocardial infraction with normal coronary arteries after acute exposure to carbon monoxide. Chest 1990; 97:491-4 and related case reports]. There was, however, another minority view presented by a panel member that argued against consideration of any data in which high levels of exposure had occurred as being irrelevant to lower level scenarios.

The various scenarios of 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. This is also relevant to secondhand smoke exposure to vehicular passengers in automobiles, already exposure to higher roadway levels of CO. Related to this issue, term

secondhand smoke (SHS) should be substituted for "ETS" where currently used in the document. Paralleling the SHS issue, deficient home heating which may also be a risk and is likely to run with lower socioeconomic status and or living in colder parts of the US in the winter months, also relevant to susceptibility. In the same vein, occupational exposures superimposed on ambient exposure should be taken into account as a potential susceptibility factor. Further, the metabolism of "dihalomethanes" is mentioned as an enteric source of CO, but this would be better stated a predominantly methylene chloride (which has also been in some consumer products). In regard to metabolism, there could be further clarification of data gaps in the overlap or non-overlap of similar systemic levels of carboxyhemoglobin from internal metabolism compared to extrinsic exposure. Finally, diabetics are mentioned, but a 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 was not cited or discussed. Many of these points are also relevant to the more detailed presentation of susceptibility in Chapter 5.

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 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 presented more clearly graphically. For example, because the lower bound of the CI and the point estimate are far more of interest than the upper bound – scaling so that the scale is bigger would help the presentation visually. Also, the effects could be grouped by endpoint, not by study, with total CVD top, then IHD, CHF and stroke. Finally, the 99^{th} percentile of exposure may be of less interest than the 95^{th}.

The inclusion and analysis of data from the multi-site epidemiological study (Bell et. al.) is commendable in the text and to a limited extent in the Figure, given that it was published only recently. There are multiple points in which these data could have been presented in Chapter 5 (which is the basis of the presentation in Chapter 2 – see also comments to that charge question) beyond the limited places where the paper is cited). Greater detail should be provided here in Chapter 2 because the data are so relevant (for example: that limiting the analysis to those days with 1 PPM values or less, the point estimate for the increased hospitalization actually increased to approximately 1.75% [95% interval excludes 0)] or that a re-analysis excluding any days over the 1 hour 35 ppm standard had no impact on the estimated of 0.55%).

In terms of the new Figure, although the CVD endpoint of Bell is included the other specific endpoint of Bell are left out. This is related to the tree plot being of unadjusted CO effects only, but this could be addressed with clarifying notes and with test emphasizing that there are co-pollutant adjusted values from Bell et al. These critical endpoints include IHD, congestive failure, and stroke.

The data in Figure 2-1 could benefit from a formal meta-analysis or, if this proves inappropriate (for example, due to heterogeneity) a comment as to the rationale to forgo the presentation of such an analysis should be included. (Also in regard to Figure 2-1, a compelling rationale as to why the data are limited to findings from North America is not provided and should be inserted).

The concluding paragraph (pages 2-24 and 2-25) is hampered by the logic of its presentation. Before addressing uncertainties that remain, it might be more straightforward to first catalogue the uncertainties that have now been substantially addressed since the 2000 CO AQCD. (In the present text this is stated first in the negative: "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). Indeed, a separate section as part of the policy section should summarize and address this central point of an improved data that has reduced much of the uncertainty previously encountered. 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 from any plausible mechanistic role [e.g., cell signaling independent of heme moiety binding).

Earlier in the text, this same paragraph refers to the "many new epidemiological studies adding to the body of evidence showing associations.." This could be modified to include the adjective *convincingly*, consistent with the next sentence re: definitive cardiovascular effects in controlled exposures.

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. "Relevant" could imply that other exposure levels are *irrelevant* to the assessment of health effects, which of course is not intended (they are relevant through mechanistic insights they provide, etc).

In summary, there was a consensus of the Panel agreeing with the conclusion that there was a likely causal association between acute ambient CO exposures in the range of the current air quality standard and adverse cardiovascular endpoints. In contrast to this, there is only scant evidence in the health effects section re: chronic CO exposure effects on cardiovascular morbidity. Even though these data may be categorized as "inadequate," this category appears to have been dropped from Table 2-1 and this row should be added [note: Hedblad B. et al, *Scand J Public health*, 2006 seems to be missing from that discussion and seems on topic; this would be relevant to Chapter 5].

In terms of the summary that acute CO exposure has a suspected association with adverse respiratory outcomes, there was a heterogeneity of views on the Panel, with a suggestion that this might be tempered in the narrative with explication indicating that this association was borderline between suggestive and "insufficient data." In particular, the epidemiological evidence was limited by an absence of co-pollutant data or was marked by CO risk estimates were substantively attenuated when co-pollutant modeling was performed.

In terms of chronic CO exposure and mortality, there was a consensus view that this would be better categorized as “Insufficient data” rather than “unrelated.” This view is based in large part on the difficulty in epidemiologically differentiating between mortality due to multiple acute effects compared to prolonged lower level effects without peaks and the fact that, logically, chronic outcomes in myocardial infarction and stroke can be presumed to include excess mortality.

In summary, it is appropriate to focus on cardiovascular endpoints in the concluding paragraph as written. Nonetheless, an additional sentence acknowledging that there is at least a suggestive relationship with several other endpoints is warranted and also a restatement of the association with global warming would be appropriate in this concluding paragraph.

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 ithe 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 encompases 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).

Additional major concern:

Section 5.7.1.3. The primary concern for individuals with anemia when exposed to CO is that the tissue hypoxia due to the anemia will be exacerbated by the additional reduction in oxygen delivered to the tissues due to COHb. This should be the common theme for many of the pre-existing diseases. Insufficient oxygen delivery making the heart tissue more susceptible to any increase in oxygen demand as occurs during exercise from the underlying disease should be the primary reason for concern. This is the case for the current state of our knowledge in the area of tissue effects of CO as stated multiple times in this document. The only reference to the pathophysiology of anemia is in line 31 on page 5-170 and the information is not correct. By convention hypoxia implies a reduced oxygen supply. The blood does not have the reduced oxygen supply in the lungs in anemia, only the tissues have a reduced supply of oxygen. The information provided could be: ….and result in a reduced arterial oxygen content due… The focus of this section should not be on the etiology of anemias but on the combined effects of two different causes of tissue hypoxia.

Editorial and minor comments:

1. The use of deoxyhemoglobin is probably a carry over from the assumptions used in the CFK modeling of McCartney (013162) which should be ignored because it is not correct. .
2. Section 4.2. 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.
9. Section 5.7.1.1. In this section the distinction between the terms CAD and IHD needs to be spelled out probably according to ICD-9 codes since these disease codes are the basis for most of the epidemiology studies. The term CHD should be dropped or noted as being of historic value only.

Dr. Russell Dickerson

Carbon monoxide, as the major sink for OH in the global troposphere has a substantial role in the oxidizing capacity of the atmosphere. For example Shindell et al. (2006) and [*Isaksen et al.*, 2009] show that the lifetime of methane can change by a factor of two depending on the range of tropospheric CO mixing ratios. Uncertainties in the budget of OH are such that the current state of the science is insufficient to establish the safe level of CO based for example on a $1^{o}C$ temperature rise. The ISA should reflect this uncertainty and point out the need for further experiments and theory to inform the EPA. Because CO (like SO_2 and NOx) is both a local pollutant and contributor to global climate change, a standard based only on the local maximum concentration is inappropriate for protecting welfare. Reduction of total emissions is appropriate for pollutants such as CH_4 and CO_2 with adverse effects on a global scale. The ISA should discuss the scientific basis for emissions-based standards or guidelines for CO.

Comments on ISA Charge Question 2a

<u>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?"</u>

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.

Isaksen, I. S. A., C. Granier, G. Myhre, T. K. Berntsen, S. B. Dalsoren, M. Gauss, Z. Klimont, R. Benestad, P. Bousquet, W. Collins, T. Cox, V. Eyring, D. Fowler, S. Fuzzi, P. Jockel, P. Laj, U. Lohmann, M. Maione, P. Monks, A. S. H. Prevot, F. Raes, A. Richter, B. Rognerud, M. Schulz, D. Shindell, D. S. Stevenson, T. Storelvmo, W. C. Wang, M. van Weele, M. Wild, and D. Wuebbles (2009), Atmospheric composition change: Climate-Chemistry interactions, *Atmospheric Environment*, *43*, 5138-5192.

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.

Shindell, D.T., et al. *J. Geophys., Res*., (2006) 111 D19306. doi :10.1029/2006JD007100.

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. H. Christopher Frey

Review of Carbon Monoxide Second Draft of Integrated Science Assessment

Charge Question 1: Chapter 1 has been revised in response to comments from the CO Panel, as well as related comments from the CASAC PM Panel, to add information regarding criteria for study selection and evaluation, to add more CO-specific information to the framework for causal determination, and to more clearly describe the process of integrating evidence from various disciplines to classify the overall weight of evidence relating to causality. What are the views of the Panel on the extent to which this revised Chapter 1 provides necessary and sufficient background information for review of the subsequent chapters of the CO ISA?

Response to Charge Question 1:

Chapter 1 is generally very good.

The chapter should define the terms "sensitive," "susceptible," and "vulnerable" when they are first introduced. The term "sensitive" seems to be in the statutory language (see footnote 1 on p. 1-3) and thus may have special regulatory significance. This should be explained. The role of identifying "susceptible" and "vulnerable" groups with respect to characterization of "sensitive" groups should be explained. Furthermore, these terms should be used consistently throughout the chapter. Moreover, EPA should develop a glossary of terms that are used across criteria pollutants, just to ensure consistency of terminology for ISAs and REAs for each criteria pollutant.

Figure 1-1 should be revised. The current figure is unclear with respect to what it is depicting. It would be helpful if this figure follows the flow of an individual study or paper that is identified in the literature review. (will provide an alternative diagram).

EPA has explained the criteria for study selection and evaluation. However, some additional explanation as to why the focus of the literature review is on studies conducted in the U.S. and Canada is needed. In particular, given the scarcity of literature on welfare effects, have studies from other countries been considered?

In Section 1.4, the topic of welfare effects should be discussed more fully. EPA should explicitly comment on welfare effects or lack of information about welfare effect, so that the reader can understand the decision process that leads to lack of treatment of this topic in the ISA, and that the omission is intentional and well-reasoned.

In Section 1.5, the text on page 1-10, line 22 refers to "the extensive body of literature" but only four references are cited. The text could be more clear as to the scope of the literature review and how it was narrowed to the four references cited.

The scope of the critical review of ecological effects needs more detail. Specifically, what literature databases were searched, using what keywords, for what time period, geographic

scope, and so on. Given the scarcity of literature on ecological effects of CO, can EPA nonetheless comment on hypotheses for ecological effects and identify what are the key data gaps. Such information would be useful for setting a research agenda to inform the next revision of the CO NAAQS.

Page 1-11, line 4, the term "necessarily" seems out of place.

The discussion of the framework for causality determination is much improved from the first draft, and nicely addresses CO-specific examples.

Page 1-12, line 7, what is meant by "assessment?" Does this refer to "endpoint"?

Page 1-13, line 3, the term "susceptible" is used. Here is unclear as to whether this is meant to inform a determination of "sensitive" groups.

Section 1.6.3. The term "measure" is unclear. Does this refer to an empirical quantity that is measured, estimated, or predicted? Or does it refer to a metric for a quantity? Suggest that the term "measure" should be replaced with more specific or descriptive terms.

Should avoid use of "etc." (e.g., p. 1-13, line 16) and attempt to enumerate all items in a list.

P. 1-13, line 22. An "assumption" is essentially an untested hypothesis. For example, an assumption that an interior indoor space is well-mixed is a hypothesis. More critical discussion of assumptions would be helpful.

p. 1-13, line 25. Earlier, the term uncertainty "characterization" is defined as qualitative, but here it is implied to be quantitative. Use terminology consistently.

p. 1-13, line 27. "assessing the evidence from across studies" – does "evidence" here refer to evidence for causality, or does it refer to empirical information from which scenarios, models, and model inputs are inferred?

p. 1-16, line 5, please define "transfer of effects"

Table 1-2 on p. 1-20 is very useful. Another table would also be useful. Recommend that a table be added that relates "aspects" to the "Weight of Evidence" categories. Example:

Aspect	Causal	Likely to be Causal	Suggestive of Causal	Inadequate to Infer	Not Likely to be Causal
Consistency					
Coherence					
Biological Plausibility					
Biological Gradient					

Strength of observed association					
Experimental Evidence					
Temporal Resolution					
Specificity					
Analogy					

The entries in each row could either be text descriptions specific to each case, or some combination of graphics and text. A table such of this could be used in ISAs for all criteria pollutants.

Page 1-21, line 9-10. Missing here is "exposure-response." Dose and exposure are not the same thing, nor are exposure and concentration. Some discussion on these points would be helpful.

Page 1-21, line 13-14. Here again, terms "susceptible" and "vulnerable" are used but not defined. How do these relate to "sensitive"?

Page 1-21, line 29-31. Should also mention the role of exposure misclassification if ambient concentration is used instead of exposure.

Page 1-22, line 5: it is not entirely self-evident that averaging will "linearize" a signal, and assumption such as this might introduce error. If the goal of a model is to predict individual incidences of adverse health effects (e.g., number of individuals affected), then averaging as discussed here might be problematic.

Charge Question 6: Chapter 2 has been revised and expanded to provide more information on atmospheric science and exposure assessment, policy relevant considerations, and integration of CO health effects.

a. 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, present results from a new U.S. multicity epidemiologic study investigating the potential presence of a threshold and departure from linearity, and summarize the evidence for susceptible populations. Please comment on these revisions.

b. 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. We would appreciate CASAC comment on the material in this section and its effectiveness in presenting the conclusions of the ISA.

Response to Charge Question 6:

There should be more clear discussion and justification of the absence of treatment of ecological effects.

Page 2-2, line 11-12; it may not be entirely correct to state that CO is formed by photochemical reactions. While there is a role of photochemistry in secondary CO formation, CO can also be formed from chemistry involving radical attack on various hydrocarbon species. Hence, suggest splitting this sentence into one for primary emissions of CO, and one for secondary formation of CO.

Page 2-3, line 7, please state what is the inferred PRB for CO for CONUS.

Page 2-5, it should be stated that correlation in ambient CO concentration between monitors may not imply the same spatial correlation in CO exposure.

Page 2-5, line 15. Exposure assessment is not complicated by multipollutant mixtures that include CO. The epidemiological inferences may be.

Page 2-5, line 18, does "spatial and temporal variability" refer to exposure here?

Page 2-5, line 31, define "pCO"

Page 2.6, line 4, lack of definition of "susceptibility" in Chapter 1 leads to lack of clarity as to what are the various categories of susceptibility that are not listed here.

Page 2-8, line 21-23. A policy question is whether NAAQS should be protective of incremental health effects to smokers from exposure to ambient pollution, and whether the concentration-response, exposure-response, or dose-response relationship for effects associated with ambient CO are linear or not. These points should be clarified.

Page 2-9, line 1: do the increases refer to smokers, or nonsmokers?

Page 2-14, line 6-7. Could clarify that the interaction is for CO as part of a mixture.

Page 2-14, should bring up exposure misclassification issues here and how they affect the weight of evidence discussion and inferences regarding possibility of health effects.

Section 2.6, policy-relevant considerations.

Please add a table that defines and lists attributes of "susceptible," "vulnerable," and "sensitive"
Page 2-16, line 21, is the 10-15% increase on a relative basis or in terms of COHb percentage points? Reader infers the former, but this could be more clear.

Section 2.6.2 concentration-response
The chapter would benefit from a discussion somewhere of the difference between concentration, exposure, and dose. Terms should be used consistently. For example, p. 2-18, line 32 refers to "dose-response" but might actually be based on potential dose or exposure. Similarly, top of page 2-19, isn't it the case that clinical studies deal with potential dose and not merely concentration?

Table 2-1, label the number scale at the bottom of the last column – i.e. define “effect estimate.”

Page 2-22 seems repetitive of Section 2.5

Page 2-22 and 2-23. There seems to be contradictory text to the effect that exposure misclassification leads to bias (see p 3-113, lines 2-4) and then later that it would only widen confidence intervals (p-23, lines 17-18).

Page 2-25, line 14 – seems to presume a linear dose-response relationship. This should be stated and discussed.

What about ecological effects? Health effects associated with climate change?

Dr. Milan Hazucha

Revised 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. However, there are more recent studies published on maternal/fetal COHb correlation that should be briefly discussed as well (Hayde et al., Early Human Development 58:205-212, 2000 and other articles from this group., Ziaei et al, Paediat Perinat Epidemiol 19:27-30, 2005). Although these studies are concerned with specific diseases they have used healthy controls.

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"

Chapter 5: Integrated Health Effects of the Second External Review Draft of the ISA for Carbon Monoxide (sections 5.1 and 5.5).

Section 5.1 Mode of Action of CO toxicity. This revised section covers in adequate depth various mechanisms of CO effects at a cellular level, including NO and CO signaling, redox status and modulation of kinase activity. I would highlight very important but easily overlooked determination stated on **p.5-16, line 7-8** which says that "...**the situation of increased endogenous CO production and of exogenous CO exposure are not equivalent."** This distinction is critical to understanding the cellular mechanisms of action of CO from different sources. Thus, exogenous CO tissue effects at low concentration are more general and the pathways of action are not necessarily the same as that of endogenous CO.

In contrast, the summary statement on **p. 5-31, l.25-26**, over interprets the reviewed studies in this subsection **(5.2.1.8).** Considering all the caveats these studies report, there is a lack of coherence between the endpoints and the evidence of the effects is of uncertain significance.

Section 5.5 Respiratory Effects. The author(s) of this section should have been more critical evaluating the studies discussed in this section, particularly when summarizing the findings. For example, on **p.5-118, l.13-17** how can the Asthma study findings, to quote "suggest a potential effects of CO on lung function at relatively low CO concentration.." when CO is 3.8 ppm? This is a concentration which will result in <1% COHb. Moreover, in asthmatics the endogenous production is higher than 3.8 ppm (section **4.5**)! At this level CO has no effects on lung function!

Similarly, contrary what is stated on **p.5-120, l.7-9** European studies do not provide stronger evidence than the US studies. Their findings are also full of caveats which make the conclusions uncertain.

Page 5-143, l.13-14 state that "epidemiologic studies provide evidence of positive association....." However, statements on **l.18-23** which is a correct summary of available evidence contradict this assertion.

Page 5-143, l.29-30 statement should be reconciled with subsequent statement on **l.31-32** which correctly summarizes the available evidence.

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 2odiagnosis of CHF and 2.99% increase for those with a 2o 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. Beate Ritz

1. *The framework for causal determination presented in Chapter 1 was developed and refined in other ISAs (e.g., the PM ISA). During previous reviews, CASAC generally endorsed this framework in judging the overall weight of the evidence for health effects. Please comment on the extent to which Chapter 1 provides necessary and sufficient background information for review of the subsequent chapters of the CO ISA.*

This chapter has improved but still does not adequately address and present methodologic concepts in epidemiology and, thus, lacks clarity in how epidemiologic studies are evaluated and determined to be "high or low quality studies" as necessary for applying the criteria listed in Table 1.2 (i.e. for assessing the weight of evidence for causal determination).

A minor point: I previously recommended using the more appropriate term '***effect measure modification'*** instead of 'effect modification' but the wording in this chapter has not been corrected. More importantly, however, while there is some improvement, the authors of this chapter still seem to not be fully understanding nor formulating adequately some of the issues involved in confounding and confounder control. They claim on page 1-15 that "deciding which variables to control for in a statistical analysis of the association between exposure and disease or health outcome depends on knowledge about possible ***mechanisms*** and the distribution of these factors in the population under study. Identifying these ***mechanisms …***". Knowledge of 'mechanisms' may help, but such knowledge is not needed to decide whether a covariate is a potential confounder neither is it necessary to know mechanisms to assess confounding. It is furthermore completely obscure what the authors mean by the following sentence on page 1-15 "adjustment for potential confounders can be influenced by differential exposure measurement error"; here they seem to confuse error in measuring confounding variables with error in exposure assessment? Finally on page 1-13 the second sentence under 1.6.3. "Uncertainty can be defined…." seems to confuse precision and validity or at least does not acknowledge that these are two different concepts that have a different place in judging study results. These confusions of concepts does not instill much confidence in the ability of staff who wrote this chapter to judge epidemiologic studies adequately according to established criteria for study validity and precision (both contributing to accuracy); this is further confirmed by the chapter 5 qualitative reviews that are still grossly lacking in consistency and interpretation of epidemiologic results.

The criteria for causal determination detailed in table 1-2 are similar to those used by the IOM and the International Agencies for Research on Cancer. Yet, they leave open what the criteria are for deciding that a study is high quality (for example, confounding is a bias, so why list bias and confounding apart from chance?) and it is also unclear what is meant by "replicated" results and why this would be a criterion. Again, without a standardized approach to the review of epidemiologic studies or a quantitative meta-analysis based review, these criteria remain ambiguous. Since the epidemiologic literature on criteria air pollution health effects has multiplied greatly in the past decade, it would be appropriate if EPA staff abandoned qualitative reviews in favor of quantitative effect estimates based on meta-analytic procedures to draw inferences about the scientific literature and used standardized and transparent rules for data abstraction. Such a systematic and quantitative procedure requires making the authors'

assumptions explicit rather than allowing authors to emphasize studies they agree or disagree with and to pick the results they like to emphasize over others. Such quantitative reviews could be contracted out to entities that are able to conduct meta- or pooled analyses.

5. *Chapter 5 presents information on cardiovascular, central nervous system, developmental, respiratory, and mortality outcomes following exposure to CO. To what extent are the discussion and integration of toxicological, clinical, and epidemiologic evidence for these health effects scientifically sound, appropriately balanced, and clearly communicated? Are the tables and figures presented in Chapter 5 appropriate, adequate, and effective in advancing the interpretation of these health studies?*

In Chapter 5, the qualitative description of epidemiologic studies improved somewhat but is still inadequate; the level of detail devoted to each study in the text seems still arbitrary and the information provided in tables and figures selective without being systematic; for example why did the authors decide to present in Figure 5-8 the citywide and negative associations for the Australian CO study of PTB (Jalaludin) and not the positive associations for births within a 5km radius of a monitor. The review of birth weight and air pollution is lacking a discussion of the difference between LBW and term LBW sorely needed since LBW includes preterm birth outcomes that are then discussed separately and studies examining LBW are possibly more comparable in their results to those examining PTB; only term LBW is a mutually exclusive outcome. Also the measure of birthweight as a continuous outcome compared to the dichotomous variables LBW and PTB deserve some more general introduction about their general value (similar to the discussion of SGA versus IUGR), i.e. do we really expect the whole birthweight distribution to shift according to ambient air pollution exposures or only the most susceptibly infants to be affected.

Surprisingly, there is still a lot of information I requested in my first review missing from this new draft. This includes the following: no information is provided in the tables concerning the type of study design employed (e.g. Table 5-12). I also already mentioned previously that many of tables report mean CO levels and mention 24 hrs or 8 hrs in brackets; this is misleading for pregnancy outcome studies in which the averages are for trimesters, weeks, or months (e.g. the Ritz et al. (2000) study of PTB is listed in table 5-12 as having a Mean CO of 2.7 ppm for the 6-9 am period – however this mean represents a mean over the whole *first month* of pregnancy and the Wilhelm and Ritz (2005) study mentions a 1.4 ppm mean for 24 hrs but this is in fact a *first trimester* mean of 24 daily measurements; the way this data is shown now the bracketed 24 hour mention seems to imply similar averaging period and comparability in effect estimates. I also mentioned already previously that while the Ritz et al 2007 study is listed in table 5-12 no results for this study are presented in figure 5-6. I had also recommended to rescale quartiles to a continuous estimates rather than leaving results from important papers out of a figure that gives an overview over all study results.

Also I mentioned previously that according to the text accompanying the figures, the estimated increase in CO presented have been 'standardized', however, how this might have been done across so many different study types and averages for differing exposure periods (rather than 24 hour averages as the authors of these chapters seem to imply) has not been

explained. Also, in figure 5.1 the title says that the effect estimates have been standardized to a 1ppm increase in ambient CO for 1-hr max CO concentrations, 0.75 ppm for 8-h max CO concentrations and 0.5 ppm for 24 hrs avg CO concentrations, but the figure does not tell us which scale has originally been used in which study and it might be questionable whether effect estimate sizes based on these different scales and based on different length lag periods are comparable to each other (indicating which study used which scale would be informative.

There are also sentences in this review chapter that are plainly wrong, e.g. on page 5-71 and OR of 1 (95% CI 0.96-1.04) is called a positive association.

Dr. Paul T. Roberts

Revised Comments on 2nd draft ISA

ISA Charge Question 2. Chapter 3 has been revised and expanded in response to Panel comments regarding climate, monitoring, spatial variability, and exposure.

2b. Additional detail has been provided regarding ..... Please comment on the usefulness of these revisions in characterizing the information provided by the CO monitoring network.

In general, the expanded discussions in the 2nd draft ISA Chapter 3 on CO detection limits, monitoring details, and spatial CO characteristics are very useful in characterizing the information provided by the CO monitoring network and in qualifying the data for use in exposure estimations. My detailed comments are provided below.

In discussion of non-anthropogenic CO emissions on page 3-5: it is confusing in the first paragraph (starting on line 3) to have fire emissions of about 13% (14.5 MT) shown in Figure 3-1, but biogenic emissions of about 5% not shown in Figure 3-1, and the text implies that the geogenic emissions are included (in the miscellaneous category?). This is confusing to the reader and makes it difficult to compare these smaller, but still important sources. Please add biogenics to Figure 3-1 and make it clear what is included.

Comments on discussion of Hudman et al and Figures 3-3 and 3-4, starting on page 3-5 at line 21: First, I suggest that this be a new paragraph; it is a different topic from the non-anthropogenic emissions. In addition, the CO from oxidation of VOCs, of isoprene, and of other biogenic VOCs (see lines 27-29), which are apparently huge in this simulation, relative to the anthropogenic CO emissions, have not been discussed before. These secondary emissions sources needed to be discussed in the overall context of CO emissions first (or put the general discussion in with the Climate text, Chapter 3.3.1). In addition, the potential influence of this huge source of CO on the results of the simulation and the conclusion needs to be discussed. I also suggest that Figure 3-3 be dropped, since I find it hard to compare these colored spatial plots. In contrast, Figure 3-4, as an example of the results, gets the point across that reducing the anthropogenic emissions by 60 % made significantly better comparisons with measurements. Maybe also add a statement saying that other results in the paper support this general conclusion.

Additional comment on the paragraph on page 3-5, lines 21-29: I suggest that a sentence be added translating the Tg amounts to MT, so that these emissions can be placed in context with the rest of the emissions discussion.

Comments on page 3-7, lines 13-15: I suggest that a comment be added (either in the text or the figure caption) about general transport winds being from west to east at this latitude, thus carrying the emissions from the Alaska fires across Canada and the northern US and into the north Atlantic, as shown in Figure 3-5 (assuming the data support this).

Page 3-11, lines 9-10: The comment on the significant quantities of aromatics in gasoline is likely no longer true, since regulations have significantly reduced aromatics in gasoline (and these references are old). I suggest that these comments be modified to say that this used to be the case, but less so with current fuel content.

Page 3-12, lines 8-9: The comments on limited mixing between the hemispheres would benefit from an additional comment that northern hemisphere CO emissions are significantly larger than the emissions in the southern hemisphere, plus a representative reference.

In general, the expanded discussions on monitor detection limits and monitoring locations in Chapter 3.4 (pages 3-18 to 3-31 and associated Annex figures and tables) are critical to understanding CO concentrations and are an important addition to the ISA. However, these limitations are still often left out of the discussions on CO concentrations in Chapter 3.5. In general, the relaxation of CO monitoring requirements and the continued use of older, less sensitive, monitors with poor levels of detection impedes the use of monitoring data for exposure assessments and climate, especially in the future as CO concentrations decrease. See my detailed comments below.

Page 3-19, lines 20-23: This discussion on the needs for trace-level CO measurements should include the use of low-level CO data for improved exposure estimates at current ambient concentrations in many locations in the US.

Table 3-2: Please fix the first row of the table. I think there should be a header row labeling the columns as "Parameter" and "Specification", for example, plus the current first row should be part of the body of the table and left justified in each column.

Page 3-20 lines 3, 12, and 18: The LODs listed on these lines are not the same as listed in the referenced Table A-1 in the Annex, which lists the LOD of the trace-level monitor as 0.02, not 0.04. Thus, the value listed as 50% of the LOD on line 6 should be 0.01. Note also that several of the LOD levels listed in slide 10 of the presentation should be 0.02, not 0.04.

Page 3-20, line 5: I suggest that this line start with "When the monitored value is below the LOD, some states...

Page 3-20, line 14, page 3-21 and Figure 3-8: This discussion on a comparison of older and newer monitors with specific quantifications is a good one, and important to include here. However, the last sentence of the paragraph (lines 6-8) does not make sense to me. Also, the CO axis of the figure needs to be labeled and the units of the time axis needs to be added (hours since some start time, or?). The similar figure in slide 10 of the presentation is much better at showing the data, plus the axis are labeled; these are good modifications and address my comments on the figure.

The limitation of the LOD issues discussed in Chapter 3.4 need to be added in several places in Chapter 3.5, including at the beginning of the sentence that starts on line 11 of page 3-36, in Figures 3-7, 3-8, and 3-9. In particular, statements similar to the paragraph at lines 13-18 on page 3-43 (good job there!) could be added to address this issue at these locations in the text and in the conclusions (3.7.3) and the summary of conclusions (2.1).

Page 3-41, lines 1-3: What was the cause of the 10.9 ppm CO measured at the Newkirk, OK site? This seems like an unusual concentration.

Page 3-43, lines 13-18: This is a good qualifying paragraph which is needed here and other places. On line 15, I suggest the following wording: "...in large part very near or below the detection ..."

Figure 3-18 on page 3-45 (and Figure 3-20): How is the data below LOD treated for this and similar figures? Might this influence the lower ends of the box-whisker plots? I suggest that a comment on this be added.

Chapter 3.5.1.2: Add a note that all of these monitors in LA and Denver are older, higher LOD, monitors, and add some comments similar to the comments at lines 13-18 on page 3-43.

Page 3-60, lines 14-15: I don't see how the data shown in Figure 3-24 can lead to a statement that includes the following words "...near-road CO concentrations.." .

Page 3-76, lines 5-6: I suggest this sentence be moved to the end of the paragraph at lines 12-21 on page 3-77. In addition, the sentence should read "....analogous to Figures 3-36 and 3-37 for ....in Annex A, Figures A.44 to A.48."

Page 3-77, line 11: I suggest these are meteorological, not micrometeorological factors.

2c. The section on exposure assessment has been reorganized to provide information on ..... Does the Panel consider that the sources of exposure error have been appropriately characterized, and agree with the revised conclusions regarding the impact of exposure error due to spatial variability and the presence of CO as part of a combustion-related mixture on health effect estimates from time-series epidemiological studies?

In general, the expanded discussions in the 2nd draft ISA Chapter 3.6 on sources of exposure and exposure assessment are a great improvement and are very useful in characterizing the potential impacts of exposure error. My detailed (minor) comments are provided below.

Page 3-93, lines 18 and 29: Please explain or modify the terms "driven cavity" and "posterior probability distribution function".

Page 3-94, lines 6-23, section on Land Use Regression Models: This section is still very limited in scope and does not represent the wide range of results from the literature. Admittedly, much of the LUR work in the literature is on pollutants other than CO, but the types of conclusions regarding what methods work and how they relate to estimating pollutant concentrations are directly applicable to CO. See the list of references I suggested last time (re-listed at the end of my comments), plus there must be many more than I could easily find.

Page 3-98, line 11: How can a regression coefficient be 1.99 (greater than 1.0)? Also, the results in lines 9-11 and in lines 13-14, although from the same reference, seem inconsistent; please explain how they are consistent or different.

Page 3-114, line 26: Table A-1 says the LOD for trace-level FRMs is 0.02, not 0.04 as stated here.

Page 3-115, lines 13-17: Please add the limitation statement on LOD to this section regarding characteristic concentrations.

Page 3-117, line 15: I suggest that the word "nearby" be added, so that the sentence would read "...at a location with few nearby CO sources could...".

In summary, Chapter 3 of this 2nd External Review Draft of the ISA clearly conveys and appropriately characterizes the atmospheric science and air quality analyses. The information provided regarding CO source characteristics, CO chemistry, policy-relevant background CO, and spatial and temporal patterns of CO concentrations accurate are relevant to the review of the CO NAAQS.

Minor edits and typos in the 2nd draft ISA:

- page 3-2, line 22: word near end of the line should be "inherent"
- Page 3-41, line 16: suggest that "medians" be replaced with "median correlation coefficients (r)"
- Figures 3-17 and 3-19: I can barely make out the lines for the highways (whereas the ones in the Annex are fine); lease make darker.
- Make bolder the lines separating the scales in Tables 3-10 and 3-11; it is currently difficult to read.
- Page 3-72, line 2 should read: "...as shown in Figure 3-6." not in Figure 3-32.
- It is very hard to see the 95th and 5th percentile lines in Figures 3-33 and 3-34; please make darker or bolder.
- Page 3-85, lines 17 and 24-25: I suggest that you use words other than "fidelity" in line 17 (and line 4 of page 3-86) and "fraught" in line 25; maybe "accurately" and "are difficult". Also, add a comma after troposphere in line 24.

Selected, easy for me to find, references for Land Use Regression and spatial mapping (see above discussion on Chapter 3.6.3):

Gauderman, Avol, Lurmann, Kuenzli, Filliland, Peters, and McConnell "Childhood Asthma and Exposure to Traffic and Nitrogen Dioxide, Epidemiology 2005; 16, 737-743.

Ross, Jerrett, Ito, Tempalski, and Thurston "A land use Regression for predicting fine particulate matter concentrations in the New York City region", Atmospheric Environment 41 (2007) 2255-2269.

Hoek, Beelen, Hoogh, Vienneau, Gulliver, Fischer, and Briggs "A review of land-use regression models to assess spatial variation of outdoor air pollution" Atmospheric Environment 42 (2008) 7561-7578.

Henderson, Beckerman, Jerrett, and Brauer “Application of Land Use Regression to Estimate Long-Term Concentrations of Traffic-Related Nitrogen Oxides and Fine Particulate Matter ES&T 2007, 41, 2422-2428.

Molitor, Jerrett, Chang, Molitor, Gauderman, Berhane, McConnel, Lurmann, Wu, Winer, and Thomas “Assessing Uncertainty in Spatial Exposure Models for Air Pollution Health Effects Assessment EHP vol 115,no 8, August 2007.

Popawski, Gould, Setton, Allen, Su, Larson, Henderson, Brauer, Hystad, Lightowlers, Keller, Cohen, Silva, and Buzzelli “Intercity transferability of land use regression models for estimating ambient concentrations of nitrogen dioxide” J Exposure Science & Environmental Epidemiology (2008), 1-11.

Dr. Armistead Russell

Review of CO ISA 2nd Draft

In general, I am pleased with the modifications to the ISA, and believe that the 2nd draft is stronger in general. It provides the level of information needed to support the REA and policy analyses.

In response to specific Charge Questions:

2. Chapter 3 has been revised and expanded in response to Panel comments regarding climate, monitoring, spatial variability, and exposure.

I appreciate the substantial information added in regards to the potential impact of CO on climate. As noted, the impact is likely small, and highly uncertain, though the physics are such that it almost has to have an impact, even if unknown or not soon knowable. While this lack of certainty may inhibit developing a related secondary standard, it should motivate the appropriate research to assess the likely magnitude of the impact. The section on monitoring and instrumental capabilities is likewise strengthened. This section should continue to stress the utility of CO as an indicator for gasoline-powered automobile emissions, and the CO monitoring network has tremendous value beyond just demonstrating attainment.

> *a. Evidence reviewed in Chapter 3 of the ISA indicates that the direct contribution of CO to greenhouse warming is very small, while the role of CO in atmospheric chemistry cycles involving other species makes a larger contribution to radiative forcing. This combined evidence leads to the conclusion in Chapter 2 that a causal relationship exists between current atmospheric concentrations of CO and effects on climate. What are the Panel's opinions related to this causal statement and the evidence provided to support it?*
>
> A causal statement is appropriate, though it should also note that the extent of the impact is highly uncertain which inhibits using a causal determination to develop a secondary standard at this time.
>
> *b. Additional detail has been provided regarding the detection limits of CO monitors in the regulatory network, the number of monitors reporting at each horizontal spatial measurement scale and comparison of monitoring data at each scale, and spatial variability of CO concentrations near major sources, particularly roadways. Please comment on the usefulness of these revisions in characterizing the information provided by the CO monitoring network.*
>
> This addition strengthens the document. Further discussion of the adequacy of the current monitoring network and the potential implementation of a near-road network should be considered.

Dr. Anne Sweeney

Legislative Requirements: Page 1-3. Lines 25-28 (selecting a margin of safety): include a reference to the EPA's Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens (2005)

Identification of studies for inclusion in the ISA: Page 1-7, line 4: "included approaches to evaluate issues related to confounding and effect modification *by other pollutants*"---add "and/or host characteristics"; i.e., the level of control for all potential confounding/effect measure modification.
Page 1-7, line 5: "Addressed health points and populations not previously extensively researched": a word of caution in that new evidence can alter previously accepted results.

Scientific Evidence Used in Establishing Causality (1.6.1) Page 1-12, lines 10-13: Add case control design to types of observational studies

Page 1-7, lines 7-10 (and elsewhere): need to discuss volunteer bias in human clinical studies

Application of framework for causal determination: (1.6.4) Page 1-17: Add to line 21: Strength of the association"

Effects on Human Populations: (1.6.5.1) Page 1-22, lines 26-32: Include references to articles published regarding critical windows of susceptibility (from the 2000 EPA workshop on same) I strongly agree with Dr. Ritz's suggestion to conduct meta-analyses on the growing number of studies assessing air pollution and adverse human health effects.

Additional references on Gestational Development

Jensen TK, Bonde JP, and Joffee M. 2006. The influence of occupational exposure on male reproductive function. *Occup. Med. (Lond.)* 56(8):544-553.
Hauser R, Meeker JD, Duty S, Silva MJ, and Calafat AM. 2006. Altered semen quality in relation to urinary concentrations of phthalate monoester and oxidative metabolites. *Epidemiol*. 17(6):682-691.
Hauser R. 2006. The environment and male fertility: recent research on emerging chemicals and semen quality. *Semin. Reprod. Med.* 24(3):156-167.

Hauser R. 2008. Urinary phthalate metabolites and semen quality: a review of a potential marker of susceptibility. *Int. J. Androl.* 31:112-117.

De Rosa M, Zarrilli S, Paesano L, Carbone U, Boggia B, Petretta M, Maisto A, Cimmino F, Puca G, Colao A, and Lombardi G. 2003. Traffic pollutants affect fertility in men. *Hum. Reprod.* 18(5):1055-1061.

Guven A, Kayikci A, Cam K, Arbak P, Balbay O, and Cam M. 2008. Alterations in semen

parameters in toll collectors working at motorways: does diesel exposure induce detrimental effects on semen? *Andrologia* 40:346-351.

Hammoud A, Carrell DT, Gibson M, Sanderson M, Parker-Jones K, and Peterson CM. 2009. Decreased sperm motility is associated with air pollution in Salt Lake City. *Fertil. Steril.* [Epub ahead of print]:19217100.

Hsu PC, Chen I-Y, Pan CH, Wu KY, Pan MH, Chen JR, Chen CJ, Chien G-C, Hsu CH, Liu CS, and Wu MT. 2006. Sperm DNA damage correlates with polycyclic aromatic hydrocarbons biomarker in coke-oven workers. *Int. Arch. Occup. Environ. Health* 79(5):349-356.

Rubes J, Rybar R, Prinosilova P, Vesnick Z, Chvatalova I, Solansky I, and Sram RJ. 2009. Genetic polymorphisms influence the susceptibility of men to sperm DNA damage associated with exposure to air pollution. *Mutat. Res*. Oct. 2.

Sokol RZ, Kraft P, Fowler IM, Mamet R, Kim E, and Berhane KT. 2006. Exposure to environmental ozone alters semen quality. *Environ. Health Perspect* 114(3):360-365.

Xia Y, Han Y, Zhu P, Gu A, Wang L, Lu C, Fu G, Song L, and Wang X. 2009. Relation between urinary metabolites of polycyclic aromatic hydrocarbons and human semen quality. *Environ. Sci. Technol.* 43(12):4567-4573.

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.