Compendium of Comments

CASAC Carbon Monoxide Review Panel on
CO Integrated Science Assessment (First External Review Draft, March 2009)

Dr. Milan Hazucha 2

Dr. Michael Kleinman 6

Dr. H. Christopher Frey 10

Dr. Russell R. Dickerson 19

Dr. Stephen R. Thom 24

Dr. Tom Dahms 27

Dr. Paul T. Roberts 33

Dr. Beate Ritz 40

Dr. Arthur Penn 47

Dr. Armistead (Ted) Russell 50

Dr. Laurence Fechter 55

Dr. Milan Hazucha
(May 14, 2009).

Comments on the Review of the ISA for Carbon Monoxide Chapter 4: Dosimetry and Pharmacokinetics of Carbon Monoxide.

This chapter is essentially an updated version of chapter 5 of 2000 AQCD with slightly reorganized chapter headings and subheadings. I actually like this approach since it allows easy back referencing of the material if one is interested in a more detailed presentation of the earlier studies. The essential information from the 2000 document has been incorporated in the current draft and merged well with the new findings.

Particularly section 4.3 has been expanded since cellular and molecular mechanism of CO has been studied more extensively over the last decade. These studies have raised a number of questions about potential interaction of biological effects due to these mechanisms and the effects induced by exogenous sources of CO (addition, potentiation, etc.?) that may elicit or enhance adverse health effects.

Charge Question 5: *The dosimetry and pharmacokinetics of CO are discussed in Chapter 4. Please comment on the presentation in the ISA of the current state of knowledge on the Coburn-Foster-Kane (CFK) model and model enhancements. Has the expected contribution of different exposure durations (1-24 h) to COHb levels been clearly and accurately conveyed?*

The draft presents and discusses in a sufficient detail various <u>forms of CFKE and their limitations (4.2.1).</u>

<u>The Multicompartment Model section (4.2.2)</u> covers all published models except for the most recent one by Neto et al., J Braz Soc Mech Sci Eng 30/3:253-260, 2008. The multicompartment models are more complex than CFKE but it is unclear how much more accurate they are predicting venous COHb. While most of the input physiologic parameters for CFK model can be relatively easy measured directly or estimated from a large data base, many of the parameters for the multicompartment models must be estimated from a limited data base, which may lead to wider predictive errors.
What I am missing is a brief discussion of the older mathematical models (Singh et al, 1991; Sharan et al. 1990; Selvakumar et al, 1992). How does the predictive accuracy of these models compare to CFKE and multicompartment models? Which one is the best over-all model if there is such?

Since some models under predict while others over predict venous COHb it would be very helpful as well as illustrative to develop a table/ graph comparing measured venous COHb values obtained under, e.g., several typical dynamic ambient CO concentrations profiles over 12 hour period (some older human studies provide such data) vs. predicted COHb under the same profile employing "the most accurate" mathematical, CFK, and multicompartment model (Neto et al., 2008, Smith et al, 1994, and Bruce and Bruce, 2006 as a suggestion).

Section (4.2.3) discusses CFKE application under varying CO concentration and exposure duration for a "healthy human at rest" (more detailed characterization is required). The interaction is illustrated in Figure 4-3 (note that at 24 hrs COHb will reach equilibrium at any CO concentration). Although accurately conveyed, there seem to be limits to the accuracy of this model. The cited endogenous productions of 0.39% COHb by QCP model (4.2.3) was measured under basal conditions and is an underestimate of CO production at baseline conditions at rest, the values reported in many studies. As discussed in section 4.5 endogenous CO production goes up during oxidative stress, inflammation, pregnancy, in people with metabolic syndrome and various diseases, the conditions when taken together will affect a majority of population. Under these conditions the baseline COHb value (endogenous production and possibly exogenous sources) estimates are in the 1-2% range (Piantadosi, 2002). Smaller cohort studies also report >1% COHb level in healthy individuals. Hart et al, 2006 reports baseline mean % COHb value for never smokers as 1.77 (n=547) for men and 1.53 (n=1901) for women. Thus, under increased endogenous production of CO the model will proportionally overestimate venous COHB as the time period and endogenous CO concentration increase.

The discussed models are designed to estimate venous COHb. However, the critical physiologic endpoint is arterial COHb. Several human and animals studies have shown that breathing high concentration of CO for a very short period of time will transiently increase arterial COHb to levels well above the venous COHb. Among the first organs to see higher COHb is the heart and the most active part of brain. Such, though brief exposures, may trigger pathologic response in affected organs in at-risk individuals. Therefore, it is important to explore the capability of COHb predictive models to predict accurately arterial COHb under transient exposure(s) to high CO. Underground bus stations, heavy traffic in urban street canyons, and intersections, etc., may create local environments when individuals will be transiently exposed to high CO. The issue of peak CO concentrations, resulting transiently higher arterial COHb level and arterial-venous COHb differences should be addressed in section 4.3.2.2.

Mass transfer of CO subsection (4.3.1.1) includes table 4-1a (human) and 4-1b (mice) showing CO conc. in different tissues, but for a brief sentence the relevance of these observations is not discussed. Are these differences important? Are there important differences in distribution of CO between human and mice tissues? Between tissues of other animal species? Any importance of these differences for data extrapolation, etc.? Without addressing these questions what is the point of having figure 4-1b? The same comments apply to page 4-13, lines 22-24. Moreover, the statement on line 23-24 is incorrect since according to tables 4-1a and 4-1b the distribution among organs does not quite follow the same pattern and the relative concentration of CO between tissues changes with increased ambient CO as well.

Figure 4-4: The source should be US EPA 2000 AQCD.

Subsection 4.3.1.2 Lung Diffusion of Carbon Monoxide should be expanded to include a paragraph on changes in DLCO in disease though some of it is discussed in subsection 4.4.4. At the end of paragraph the reader should be directed to the last paragraph on p.4-17 and section 4.4.4 for additional discussion on DLCO.

Subsection 4.3.2.2 Blood. Throughout this Chapter and in other chapters as well it is assumed that arterial and venous COHb are at equilibrium. However, what are the health consequences when they are not at equilibrium, particularly during a rapid CO uptake? .What are the factors affecting equilibrium? Moreover, a brief discussion of methodology of measuring COHb would be helpful (CO-oximeter, Gas chromatography and others). Subsection 4.3.2.4 Other Tissues, the statement on line 22-24 needs to be revised since the distribution between organs changes with changing COHb level. Why we have a table 4-1b? Explain.

At the end of the subsection 4.4.4 Health Status the reader should be directed to section 5.2 discussing cardiovascular effects.

The Endogenous CO production and Metabolism (4.5) has been substantially expanded as compared to previous AQCD 2000. It is a nice comprehensive review. I suggest including in the top paragraph on page 4-20 other diseases that increase endogenous production of CO like liver disease, pulmonary hypertension, metabolic syndrome, and inflammatory diseases in general. Cite the studies and provide measured endogenous CO, e.g., for asthma, allergies, drug-induced increase in CO (e.g., Zocor reduces cholesterol), and others. If these various health conditions are combined more than one half of US population will have elevated endogenous CO.

Page 4-19, line 25-26. True we do not know precisely what is the range of endogenous COHb level (important parameter in COHb modeling) in the general population. However, numerous studies suggest the baseline level range is 1-2% COHb. In disease population in can be higher.

This section should also include a discussion on differences and commonalities between the effects due to endogenous CO and exogenous CO on cell metabolism, etc. The molecule is the same but the effects may not be because there are other substances released during endogenous production that may influence metabolic pathways.
On line 32 after Manno's reference insert a reference by Bos et al, 2006. The study provides more updated findings on dihalothanes.

The Summary and Conclusions (4.6) should include a statement about which model is more accurate or suitable and under what conditions (uptake, elimination) for COHb estimation. It should also include a statement about increased production of endogenous CO in inflammatory and other diseases.

Section 5.2 Cardiovascular effects.
This section presents numerous tables of epidemiologic studies for various CV outcomes including long-term averages for CO. Most of the reported CO levels are at the range of

endogenous CO under basal conditions and almost all at the range of baseline COHb. If these CO concentrations are taken at their values it is highly unlikely that they will induce any health effects even in at-risk population. With peak CO values, which are physiologically the most important, averaged over time how is one suppose to assess clinical significance of the findings? The given mean CO values for these studies seem to be meaningless. An introductory paragraph discussing the caveats in interpretation of these epi studies would be very helpful.

Interpretation of multipollutant studies is similarly difficult without providing effect estimates for all pollutants in the mix, e.g., CO, PM_{10} and CO+PM_{10}. From my reading of CO ISA and PM ISA the same studies are interpreted differently in each document. We cannot have it both ways and the differences in interpretation need to be reconciled not only for CO and PM but for other co-pollutants and their respective ISA as well.

Dr. Michael Kleinman
Response to Charge to the CASAC CO Panel

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.

Chapter 1 clearly sets out the questions to be addressed in the NAAQS review (1-1). The literature review was extensive and covered areas of epidemiology, toxicology and clinical studies with an appropriate emphasis on elucidating the importance of exposure-response relationships and modes of action. The chapter is very general in its approach and might have been more CO-directed.

The EPA Framework for Causal Determination is clearly described in general terms (1-8) however some expansion of the discussion to include specific reference to CO would be helpful. For example the statement (p1-9, L16-17)" Data will not be available for all aspects of an assessment and those data that are available may be of questionable or unknown quality" could be amplified with which specific type of CO data might fall into this category.

The discussion of potential confounders could mention CO-specific confounders such as environmental tobacco smoke and discussions of limitations of interpreting animal study data could mention any relevant species-related differences that will be addressed in the later chapters.

2. Chapter 2 presents the integrative summary and conclusions from the health effects evidence, with the evidence characterized in detail in subsequent chapters. What are the views of the Panel on the effectiveness of the integration of atmospheric science, exposure assessment, dosimetry, pharmacokinetics, and health effects evidence in the CO ISA?

Chapter 2 summarizes the conclusions drawn from the subsequent chapters. As such it provides a roadmap of the critical junctures in the literature surveyed that influence the causal determinations and the assessment of the strength of exposure-response relationships.

With regard to exposure there is some discussion of in-vehicle to roadside comparisons. It would be helpful to mention the differences between the micro-scale (2-10m from raod) vs. more distant (>70m from road). It would also be useful to mentions what % of the population might be considered vulnerable because of near road or on-road exposures.

It might be important to mention in the discussion of compensatory mechanisms (2-4, L6) that individuals with cardiac or coronary artery disease might be unable or less able to compensate. The point is made on p2-5 that they might not be able to endure compensatory changes (which are defensive) but they also be unable to mount a defensive compensation because of medication use or tissue damage.

It might be useful to discuss the Framework structure. The framework is hierarchical. If the data are "inadequate" than one can not judge whether or not there is or is not a causal relationship. Perhaps #4 should be suggestive of NO causal relationship and #5 should be data are inadequate.

With regard to cardiac morbidity (2-7) a more explicit discussion is needed of the uncertainties that lead to a designation of "likely to be causal" rather than "causal."

3. To what extent are the atmospheric science and air quality analyses presented in Chapter 3 clearly conveyed and appropriately characterized? Is the information provided regarding CO source characteristics, CO chemistry, policy-relevant background CO, and spatial and temporal patterns of CO concentrations accurate and relevant to the review of the CO NAAQS?

The Chapter provides a comprehensive overview of the topics above. There are a few areas that need to be more completely explained. For example, Fig 3-2 identifies on-road and non-road engines as the major (~70%) of the CO emissions. However Figure 3-4 seems to suggest that Region 1 emissions are ~2x those for Region 9 which includes S. California where there are more cars than people (or so it seems).

4. How well do the choice and emphasis of exposure topics presented in Chapter 3 provide useful context for the evaluation of human health effects in the ISA? Is the discussion and evaluation of evidence regarding human exposure to ambient CO and sources of variability and error in CO exposure assessment presented clearly, succinctly, and accurately? The ISA concludes in section 3.7 that central-site monitor concentration is generally a good indicator for the ambient component of personal CO exposure. What are the views of the Panel on this conclusion and its supporting evidence?

The car/taxi data in Table 3-9 (5.7 ppm) should be contrasted with the in vehicle data Fig 3-32 which shows that the in vehicle exposure is between 18 and 40 ppm. Is that a significant consideration? The statement that measurement at a hot spot would "skew" community exposure estimates upward is true but it begs the question of what part of the community is being ignored. Perhaps it is worth discussing whether a population weighted average exposure would be a more accurate parameter for use in late exposure-response estimations.

5. The dosimetry and pharmacokinetics of CO are discussed in Chapter 4. Please comment on the presentation in the ISA of the current state of knowledge on the

The CFK model is well described however the discussion of the sensitivity of the model to uncertainties in the model parameters as a function of time (Fig 4-1) could be presented more clearly. A concrete example(s) would be very helpful. If we pick an arbitrary fractional sensitivity (i.e. FS = -0.5) and the parameter Vb, would it be correct to state that a +5% error in the value of Vb used in the computation would result in a 10% underestimate of COHb at 10 min and 2 hr after exposure and a -5% error in Vb would result in a 10% overestimate of COHb? It would also be very useful to include a table of the parameters and the range of parameter values and uncertainties that would be used for specific estimates (as a function of gender, age, body mass, etc.?)

6. The mode of action section in Chapter 5 presents information on both hypoxic and non-hypoxic mechanisms for CO health effects, with particular emphasis on recent studies evaluating the non-hypoxic effects at low to moderate CO levels. Please comment on the appropriateness of the focus, structure and level of detail in this discussion. For example, is the evidence relating to the interaction between inhaled CO and endogenous CO properly characterized?

The discussion of non-hypoxic mechanisms provides some very interesting insights but the linkage of these mechanisms to biological responses and morbidity/mortality is left as an open question. It would be appropriate to include an appraisal of what information would be needed before these non-hypoxic mechanism outcomes would be useful in setting the NAAQS. This could possibly lead to some recommendations for future research. Similarly the interaction between exogenous and endogenous CO is discussed but the way in which these interactions can be incorporated into the definition of a NAAQS is not made clear.

There might be some focus on whether these mechanisms might be a more important issue in susceptible populations. For example, do these mechanisms play a stronger role in people with anemia? Another issue that might be addressed is in the area of toxicokinetic modeling. Would the molecular kinetics be helpful in improving the ability of the CFK to predict COHb levels in exposed populations (assuming the population demographics for susceptible pops are including in the RA models).

7. 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?

Tables 5-4 through 5-9 would be more useful if they included a direction of change for the endpoints and a level of significance. Because the section on health effects is long and very detailed it would be useful to have a table of key endpoints and whether or not there appears to be a significant effect of CO.

a. For cardiovascular outcomes, controlled human exposure studies discussed in Chapter 5 and in previous assessments have identified cardiovascular effects in diseased individuals following exposures near the level of the current standards, while new epidemiologic studies provide evidence of cardiovascular effects at ambient concentrations. What are the opinions of the Panel on the treatment of factors influencing the interpretation of this evidence, such as the plausibility of cardiovascular effects occurring at ambient levels, the additive effect of ambient CO to baseline COHb resulting from endogenous and non-ambient CO, and the challenge of distinguishing effects of CO within a multipollutant mixture (e.g., motor vehicle emissions) in interpreting epidemiologic study results?

b. Please comment on the implementation, in Chapter 5, of the causal framework presented in Chapter 1. Does the integration of health evidence focus on the most policy-relevant studies and health findings?

It is not clear after the review of the epidemiologic, clinical and toxicological data why a causal relationship for cardiovascular morbidity is "likely" rather than definite. Some evaluation of what is still lacking to make that determination is needed. If the implication is that there is never enough certainty to state that there is a causal relationship than perhaps the framework should be restated.

Because the section on birth and developmental is long and very detailed it would be useful to have a table of key outcomes and whether or not there appears to be a significant effect of CO.

8. What are the views of the Panel on the discussion of factors affecting susceptibility and vulnerability in Section 5.7?

This section would be strengthened if some demographic statistics were added to Tables 5-18 and 5-19. These are data that will factor into the risk analysis and this would be an appropriate place to summarize them.

Post-Meeting Comments on Integrated Science Assessment for Carbon Monoxide, First External Review Draft Prepared by
Dr. H. Christopher Frey
Clean Air Scientific Advisory Committee
May 13, 2009

I have prepared responses to charge questions 1, 2, 3, 4, and 8.

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.**

Chapter 1 is generally well-written, well-organized, and useful in content.
Section 1.6, EPA Framework for Causal Determination, is appropriately very similar, or in places identical, the similar section in Section 1.6 of the Integrated Science Assessment for Particulate Matter (First External Review Draft, December 2008). As EPA receives comments on this material when reviewed by various Panels of CASAC, EPA should strive for consistency across documents. The PM Review Panel offered several comments. Appropriately, "the categorization reflects the strength of evidence and not the potential magnitude of public health benefits." This implies that there is a distinction between weight of evidence and the potential sensitivity or magnitude of the outcome . This distinction should be appropriately conveyed by discussing both weight of evidence and the magnitude or sensitivity of each health effect endpoint. A second point is that additional clarification regarding the terms "susceptible" and "vulnerable" would be useful – the PM Review Panel provided detailed comments along these lines, and for consistency these comments should be addressed across ISAs and REAs. A third point is to consider the role that publication bias might have as it relates to making weight of evidence determinations.

2. **Chapter 2 presents the integrative summary and conclusions from the health effects evidence, with the evidence characterized in detail in subsequent chapters. What are the views of the Panel on the effectiveness of the integration of atmospheric science, exposure assessment, dosimetry, pharmacokinetics, and health effects evidence in the CO ISA?**

The integrative summary and conclusions from the health effect evidence, presented in condensed form, is extremely useful to the reader. In general, Chapter 2 is very useful, and should be retained. It is very helpful to the reader to have this kind of "roadmap" as to the bottom line policy-relevant state-of-the-science.

Table 2-1 could be modified to provide additional information regarding the weight of evidence for each identified health effects endpoint, such as whether the finding is based on controlled experiments, epidemiology, toxicology, or other, and a brief justification for the finding.

On p. 2-2, line 5, it is stated that the 2002 National Emission Inventory (NEI) is the most recent data available. Perhaps that might have been true at the time that this material was drafted. However, it would be appropriate to update to the 2005 NEI (http://www.epa.gov/ttn/chief/net/2005inventory.html#inventorydata) which is now available.

Acronyms should be spelled out the first time that they are used – e.g., ETS on p. 2-3, line 10; CAD, on p 206, line 3.

Section 2.3.3, Birth Outcomes and Developmental Effects. This section is an example of the need to carefully distinguish between weight of evidence and the magnitude or sensitivity of the association. On p. 2-10, a statement is made that there is "weak evidence" of various adverse effects. Presumably, this is a statement specific to weight of evidence. But is it also the case that the magnitude of the effect is small? That is, is the intended mean that there is evidence of a weak or small decrease? Are there cases in which a weak weight of evidence is also associated with a small magnitude of effects? Section 1.6 might elucidate these kinds of situations and offer clarification on the distinction between weak weight of evidence and small magnitude of effects.

After reading Section 2.3.3 and 2.3.4, both of which have weight of evidence findings that are "suggestive of a causal relationship," one might consider whether there is consistency in these findings. Given that there are only 5 categories for weight of evidence, it is likely that there are gradations within each category. Here, it appears that there may be a stronger case for birth outcomes and developmental effects than for respiratory morbidity. Some comparative assessment of the weight of evidence findings, and the strength of the associations, could be useful.

It would help to have a "bottom line" summary of the overall assessment of the adverse effects of CO at levels comparable to current air quality and to the current standard. It seems to be the case that the document implies that the subsequent REA would focus on quantifying responses based on controlled experiments, and that the epidemiological evidence tends to be weak, associated with small effects, or confounded by co-pollutants. The chapter could offer a synthesis and summary. For example, the current Section 2.4.1 seems to focus only on clinical and epidemiological evidence with regard to the issue of concentration-response relationships. A clearer summary could be offered regarding EPA staff's view of the way forward.

The identification of vulnerable subpopulations is of significant importance because it should motivate areas of focus for exposure assessment in the REA. In particular, the relatively high exposures associated with persons who spend time in or near traffic (roadways) and those who exercise are of note.

3. **To what extent are the atmospheric science and air quality analyses presented in Chapter 3 clearly conveyed and appropriately characterized? Is the information provided regarding CO source characteristics, CO chemistry, policy-relevant background CO, and spatial and temporal patterns of CO concentrations accurate and relevant to the review of the CO NAAQS?**

The information about Sources and Emissions of CO appears to omit some key information that provides insight regarding conditions under which gasoline vehicles emit CO at high rates.

The statement that "Internal combustion engines used in mobile sources, by contrast, have widely varying operating conditions and, thus, inherently higher and varying CO formation" (p. 3-1, lines 16-17) is not accurate. Internal combustion engines, also referred to as spark-ignited (SI) engines, tend to have inherently high engine-out CO emission for reasons described below.

The reason that gasoline engines have higher uncontrolled emission rates than any other combustion based source are because they typically operate close to the stoichiometric air-to-fuel ratio, have relatively short residence times at peak combustion temperatures, and have rapid cooling of the cylinder exhaust gases. The lack of excess oxygen means and the short combustion residence time mean that carbon in the fuel is not fully oxidized to CO_2, and CO concentrations are approximately at equilibrium during the power stroke. The rapid cooling of the exhaust gas means that the concentrations of free radicals, including the hydroxyl radical, rapidly decline. As a result of this, it is not possible for CO to oxidize to CO2 fast enough during cooling of the exhaust, leading CO levels to be "frozen" well above equilibrium values at any given gas temperature in the exhaust. The very high "engine-out" CO concentrations motivate the need for post-combustion, or end-of-pipe control, using an oxidation catalyst to promote burnout of CO. A catalytic converter, or 3-way catalyst, serves this function, while also oxidizing hydrocarbons and reducing nitrogen oxides.

Diesel engines have much lower engine-out CO emissions than gasoline engines because they typically operate at very high air-to-fuel ratios. The presence of excess oxygen promotes mixing between oxygen and the fuel, leading to improved burnout of carbon during the power stroke.

Furnaces, such as those in power plants, have much slower rates of flue gas cooling compared to the rate of exhaust gas cooling in an internal combustion engine. Therefore, there is more time for most of the post-flame CO to oxidize to CO_2 by reaction with hydroxyl radicals, before the concentration of the latter drops as temperature decreases. An excellent reference that provides a scientific perspective on these issues is the textbook by Flagan and Seinfeld on *Fundamentals of Air Pollution Engineering*, Prentice Hall, 1988. Although this book is now out of print, it is far more rigorous and detailed than many more recent texts.

There are two other key factors pertaining to CO emissions from gasoline-fueled vehicles that should be mentioned: (a) cold start; and (b) fuel enrichment.

A "cold start" refers to the time period after an engine start until which the catalytic converter reaches its "light off" temperature. The latter is the temperature at which the oxidation reaction for CO becomes effective. Depending on the ambient temperature, the "soak" time (the time since the most recent engine shutdown), and the design of the engine and exhaust system, the duration of a cold start may be approximately one to three minutes. During a cold start, the tailpipe emissions are as high as the engine-out emissions for CO. Cold starts are somewhat more severe in cold weather than in warm weather, but can occur at any ambient temperature, since the light-off temperature of the catalytic converter is substantially higher than ambient temperatures.

Fuel enrichment refers to episodic situations during on-road operation in which there is high power demand from the engine. Because the oxidation of CO to CO_2 in the catalytic converter is exothermic, and because high engine power demand is usually associated with high rates of exhaust flow, the catalytic converter could overheat and become damaged. To prevent this, the fuel-to-air ratio is increased, which leads to enhanced incomplete combustion and very low levels of oxygen in the exhaust. Under these conditions, there is very little oxidation of CO to CO_2 by the catalytic converter, which prevents the catalyst from overheating, but leads to high tailpipe emissions. Fuel enrichment episodes can occur for just a few seconds associated with high accelerations, high speeds, high road grades, or combinations of these, combined with use of accessories, or other sources of load such as having many passengers or cargo in the vehicle, or towing a trailer. Although enrichment events occur on a vehicle-specific basis, it is possible to have locations on a roadway network that are conducive to producing enrichment events for many vehicles that pass through. An example would be freeway on-ramps, merges after tolls, or accelerations that take place after a red light at a signalized intersection.

Because some of the key microenvironments of concern are near-roadway or in-vehicle, the ISA should more fully and carefully explain the key factors that lead to episodes of high CO emissions, particularly from gasoline-fueled highway vehicles.

Looking ahead to new vehicle technologies, a potential concern with hybrid electric vehicles (HEVs) or Plug-in HEVs (PHEVs) is that, depending on their design, they can have many engine starts and shutdowns during onroad driving. There is the potential that engine restarts could be associated with a "cold start" effect if the soak time since the prior engine shutdown is long enough. There are not yet good data on whether this effect is significant, and generally the expectation is that HEVs and PHEVs will have lower average emission rates than comparably conventional gasoline vehicles because they typically have significantly smaller engines.

In addition to the role of the catalytic converter, the ISA should at least briefly summarize the role of oxygenated fuels as a strategy for reducing engine-out, and tail-pipe, CO emissions from vehicles. An example of an oxygenated fuel is ethanol. Although on average ethanol leads to reductions in tailpipe CO emissions, it appears to lead to increased non-methane organic gas (NMOG) emissions and slight increases in NO_x emissions. The ISA might note that, historically, here have been unintended consequences of the development and use of oxygenates for fuels; notably, MTBE. MTBE has been found to be a persistent environmental pollutant, even leading to problems associated with groundwater. Although the statutory mandate that underlies the NAAQS does not enable EPA to take these cross-media and unintended consequences into account, the lessons learned from such experiences can at least be summarized in the ISA.

The ISA should also give some attention to emerging trends, such as the potential for increased use of biofuels. It is expected that biofuels, such as ethanol or biodiesel, would lead to reduced tailpipe CO emissions since they are oxygenated. However, the reductions in total fuel life cycle emissions, including fuel production and vehicle emissions, may be less than the reductions for the tailpipe alone. Furthermore, there may be some geographic shifts in the location of CO emissions, with some increases occurring in rural areas where biofuel production activities may increase.

Regarding the discussion on the bottom of page 3-3, especially lines 15-19, the text should also mention the finding, reported in NARSTO (2005), Chapter 7, page 200, that the MOBILE6 model correctly predicts the relative change in emission rates with respect to time (see the 2nd column, top of column). Secondly, it may be too strong to infer that CO emissions are overestimated by a factor of 2. The more correct inference is that the ratio of CO to NO_x is larger for the emissions inventory than for observed ambient concentrations, which could imply that CO emissions are overestimated, NO_x emissions are underestimated, or some combination of both (See NARSTO, 2005, page 203). In particular, it is not clear that cold start emissions were appropriately accounted for in the comparisons that conclude that the CO emissions are overestimated by as much as a factor of two. For example, a tunnel study cannot provide insight on this issue, since the location of the tunnel is typically sufficiently far away from the initiation point of a trip that the vehicle would be in hot stabilized operating mode in the tunnel. NARSTO (2005) also notes that some of the findings of previous studies were contradictory, citing in particular a CRC (2004) tunnel study (this is probably the same as the Pollack et al. study cited by EPA – both are reports by ENVIRON). Hence, the information contained in this paragraph should be much more carefully interpreted. Although Parrish (2006) appears to reconcile the contradictions in the previous study, there seems to be inadequate attention to the issue of cold start, nor is there a plausible basis given as to why the CO emission inventory might be overestimated.

EPA has recently released Draft MOVES 2009 (http://www.epa.gov/otaq/models/moves/index.htm). A "final" version of MOVES is currently expected later this year, that would replace Mobile6. Draft MOVES 2009 is capable of estimating highway vehicle CO emission rates taking into account a wide

variety of driving cycles, operating conditions, vehicle characteristics, and so on. The use of MOVES as a basis for estimating CO emission rates for highway vehicles, if such rates are needed to support exposure modeling, should be considered.

p. 3-54, line 8, delete "does" and change "oxidize" to "oxidizes"

Section 3.3, chemical mechanism on top of page 3-4. This is very helpful. However, references should be cited for the information provided on this page. As a matter of notation, HCHO is perhaps a more common way to write the molecular formula for formaldehyde than CH_2O. Free radicals should have a "dot" – e.g., $HO_2\bullet$.
Page 3-9, line 7, please use "such as" rather than "like."

Page 3-21, Figure 3-11, and similar figures. The highlighted counties (especially in yellow) that are small in geographic area are very difficult to see on these maps. It may be necessary to add pointers to such counties or to include a table listing all such counties in an appendix, just to make sure that the information is conveyed completely.

Page 3-35 and related material. The analysis of the location and data for monitors in Pittsburgh is interesting. Having lived in Pittsburgh for a number of years, I notice that monitor "A" is located very close to the Ohio River, Monitor "B" seems to be in an urban canyon setting within Pittsburgh's "Golden Triangle," and Monitor "C" seems to be close to roads and ramps that represent major points of egress or ingress for the downtown area. Depending on wind direction and time of day, Monitor "A" could be influenced by heavy traffic on the Fort Pitt bridge, and perhaps by emissions exiting the bore of the Fort Pitt tunnel. However, the text attributes variability among these three monitors to "mountainous" terrain. While there are hills on the Northside (northern bank of the Allegheny River) and the Southside (southern bank of the Monongehela River), the terrain in the immediate vicinity of the three monitors is not significantly hilly. Not surprisingly, Monitor "A" is weakly correlated with Monitors "B" and "C" (correlations of 0.43 to 0.52) probably because Monitor "A" is not in the downtown core and the local wind conditions are likely to be highly influenced by the close proximity to the Ohio River. Monitors "B" and "C have a correlation of 0.73, which is moderate, and is likely because both are in the downtown core, for which there is likely to be very high correlation in traffic conditions within the surrounding area that influences each of these two monitors. However, given that these monitors are only 0.7 km apart, the correlation of 0.73 seems to indicate that there local factors. One might hypothesize an urban canyon effect for Monitor "B" and perhaps also some kind of near-roadway geometry effect for Monitor "C." Some discussion of the site-specific nature of each monitor and the relative importance of various factors would provide more insight into the variability between them, rather than the very brief discussion that ends with a laundry list of factors on page 3.35 and lines 23-24.

Section 3.5.1.3 – page 3-39. This material is very important, especially given that near-roadway and in-vehicle exposures are among the most important of the exposure microenvironments. It would be useful to include some example graphs here to illustrate the concentration gradient as one moves away from a roadway center or edge, with and

without either a sound barrier or vegetation, to support the material given on p 3-40, lines 5-18.

Figure 3-22. This figure takes a lot of time to figure out. It would help if the figure panels were labeled. The reader has to go back and forth between the legend and the caption to figure out what each curve is.

Page 3-43, lines 1-3. The "laundry list" given here could be interpreted more specifically with regard to the site being discussed. Rather than list many factors, which implies that they are all equally important, is it possible to offer judgments as to which factors may be more important than others?

Pages 3-48, 3-49. Please label the x-axes in each group or at least for the bottom most graphs.

General comment: while "diel" is a correct word to use, why not use "daily" instead?
Section 3.5.3 Associations with Co-Pollutants

Figure 3-28. Somewhat like Figure 3-22, these figures are not reader friendly. To avoid confusion, these figures could be split into two separate groups of figures. The first group would focus on correlations with other co-pollutants. The second group would focus on correlations with different averaging times and forms of CO concentrations. Also, clarity is needed regarding how correlations were calculated for data that seem to be of different averaging times – for example, how does one get hourly PM_{10} or $PM_{2.5}$ concentrations if these are typically measured using filter-based methods? Or are the comparisons to TEOM data? What are the sample sizes associated with these comparisons?

The interpretation of Figure 3-28 given on Page 3-51 may not be correct. Figure 3-28 appears to describe the inter-monitor variability in correlation coefficients (for what time period?). Not sure what the figure caption means by "nationwide correlations" – shouldn't this be "variability in correlations among national monitoring sites"? If the figure depicts variability in correlation, then it is not correct to interpret the results as if they represent uncertainty. Variability refers to real differences in values among members of a population; whereas uncertainty refers to lack of knowledge regarding the true value of a quantity or distribution. One cannot infer whether correlations are significantly different from zero by looking at a distribution of variability among individual sites. The determination of the statistical significance of a correlation coefficient depends on the magnitude of the correlation coefficient, the sample size of data upon which the correlation coefficient was calculated, and the sampling distribution for random statistical error in the estimate of the correlation for the individual site. Thus, while it might be true that a few of the sites have correlations that are not significantly different from zero, the correlations of some if not many of the sites were significantly different from zero for each and every season considered. Hence, this entire paragraph needs to be carefully rewritten.

The ranges shown in Figure 3-28 are not confidence intervals. A confidence interval is inferred from a sampling distribution. A sampling distribution is a frequency distribution for a statistic based on random sampling error. The distributions shown here appear to represent variability between monitoring sites. Hence, they represent frequency ranges.

The paragraph of page 3-51, lines 1-21 should be divided into multiple paragraphs for clarity – one paragraph should focus on the results and findings for CO and SO_2, and then results and findings for NO_x, O_3, PM_{10}, and $PM_{2.5}$ can be given in one or more additional paragraphs.

Page 3-51, line 24 – does this refer to daily CO concentrations and daily NO_2 concentration?

Page 3-55, line 5: does this refer to area-wide or near-roadway CO concentrations?

Page 3-56, lines 20-29. The text here is a bit confusing because it is written as if the quantity alpha (□) is defined in Equation (3-4). This quantity should be defined in a new equation for clarity, and then discussed.

Page 3-63, lines 8-19. The text here appears to inaccurately describe the data reported by Abi Esber and El-Fadel (2008). In their study, the did not measure "engine CO concentrations." They measured the CO concentrations outside the vehicle – see Figure 1 of their paper which provides a photograph of the "Out-vehicle air intake location." This needs to be corrected in the text and in the caption for Figure 3-32.

Page 3-67. Lines 21-22, Regarding the statement about the possibility of community-to-community differences in measurement errors, can a specific example be provided to support this? i.e. is this of real concern or is there a specific reason to believe this is the case?

Page 3-67, line 32. Hydrocarbons are another co-pollutant, sometimes characterized as volitale organic compounds, reactive organic gases, non-methane organic gases, and so on. These include many species of compounds, including compounds identified as hazardous air pollutants (HAPs) under the NESHAPs and as Urban Air Toxics. There are some compounds, such as benzene, formaldehyde, 1,3-butadiene, and some others that are referred to a Mobile Source Air Toxics (MSATs). These points should be introduced here. The co-emission of CO and HCs is quite common, along with NOx and PM, from mobile sources. This section briefly mentioned benzene and toluene on p. 3-68, line 28, but the co-varation in emissions and various classes and species of HCs merits at least its own paragraph, if not a few paragraphs.

p. 3-74, line 13, there are repeated references to errors of the "Berkson type" - the first time this is mentioned (earlier in the chapter) it should be defined and there should be citation to reference(s).

p. 3-74, lines 6-7 versus lines 10-11 . It seems contradictory to state that there are significant local factors leading to variability in exposures associated with proximity to roadways and then to conclude that fixed site measurements are a good indicator of CO exposure. This apparent contradiction should be resolved. Fixed site measurements are a poor indicator of exposure in-vehicles or near roadways.

4. **How well do the choice and emphasis of exposure topics presented in Chapter 3 provide useful context for the evaluation of human health effects in the ISA? Is the discussion and evaluation of evidence regarding human exposure to ambient CO and sources of variability and error in CO exposure assessment presented clearly, succinctly, and accurately? The ISA concludes in section 3.7 that central-site monitor concentration is generally a good indicator for the ambient component of personal CO exposure. What are the views of the Panel on this conclusion and its supporting evidence?**

In general, the exposure assessment material is well organized and appropriate. However, central-site monitors are not a good indicator of CO exposure in microenviroments that are influenced by local factors, such as in-vehicle and high proximity to roadways. Although this point is acknowledged in various places, it does not seem to be consistently conveyed throughout the document.

8. **What are the views of the Panel on the discussion of factors affecting susceptibility and vulnerability in Section 5.7?**

Please see also the comments by CASAC and the PM Panel members on a similar section in the 1st draft of the PM ISA. Sometimes it is difficult to completely separate a susceptibility factor from a vulnerability factor, and these situations should be acknowledged. For example, ability to exercise, which is related to vulnerability, can be associated with nutritional status and other factors related to susceptibility. This is not to say that the categories provided are incorrect; merely to point out that it would be appropriate to acknowledge and characterize areas of overlap. Another example is medication use, which is related to pre-existing disease. The tables 5-18 and 5-19 could more clearly indicate what are the key factors and what are surrogate indicators of the factors. For example, is air conditioning really a surrogate for SES? Is proximity to roadways a subset of geographic location?

Review of

"Integrated Science Assessment for Carbon Monoxide" and the "CO NAAQS: Scope and Methods Plan for Health Risk and Exposure Assessment"

Dr. Russell R. Dickerson
Professor, Department of Atmospheric and Oceanic Science
CSS Bldg, Stadium Dr.
The University of Maryland, College Park, MD 20742

The documents seem in general to be well researched and thorough. The Executive Summary lacks punch, and the ISA would benefit from a list of top findings and recommendations. The plan determining exposure of individuals for epidemiological studies looks sound, given available observations. Most of the fundamental concepts concerning local air quality and global atmospheric chemistry are at least covered. There are areas in which the ISA, and by inference the Health Risk Plan, needs to evolve with the state of science. Comments on those follow.

Comments on the ISA.

As emissions from the American vehicle fleet decrease and the number of violations of the NAAQS approach zero, it is time to both congratulate EPA and the State agencies for their success and to reassess our approach to monitoring emissions and ambient concentrations of CO as well as personal exposure. The existing network of CO monitors, designed to demonstrate compliance with the current NAAQS, measure reliably, but with coarse resolution and inadequate sensitivity most of the time. The ambient concentrations are more often than not below the detection limit of the monitors. Section 3 of the ISA shows that there are insufficient monitors for epidemiological studies. For example, at most sites the median concentration is near the detection limit of the monitors used. This is recognized on page 3-25, but there is no discussion of how to correct this problem.

CO is an important precursor to pollutant ozone and is useful tracer of vehicular emissions as well as transport and mixing processes in the atmosphere. On the local scale, numerical simulation of photochemical smog with models such as CMAQ can be effectively evaluated with CO measurements. Because of the moderate lifetime (~ 1 month) and relatively simple chemistry (loss by OH attack) CO offers a good tracer for evaluation of emissions and meteorology in models. Boundary layer depth, for example impacts profoundly concentrations of most pollutants, and if the models can capture the CO vertical profile then there can be more confidence in their ability to capture mixed layer dynamics. Such studies require measurements with greater sensitivity and resolution.

On page 3-11 the ISA states "The most sensitive trace-level versions of these instruments can detect minimum CO concentrations of ~0.04 ppm; the required lower detection limit for FRMs in the EPA network is 1.0 ppm (40 CFR 53.20 Table B-1)." The issue of sensitivity of the current and next generation of monitors deserves more attention in the ISA. There is mention of NCORE, (not in the acronym list) but no details on the plans for superior monitors. Some information is available on the EPA website:
http://www.epa.gov/ttn/amtic/files/ambient/monitorstrat/AAMS%20for%20SLTs%20%20-%20FINAL%20Dec%202008.pdf
This is a little thin, but may still provide some guidance for planning. My understanding is that this network will go into effect in 2011, and the ISA should discuss these plans and how they relate to the environmental and health effects of CO.

With increasing attention being paid to local and global climate change, a better understanding of the global atmospheric chemistry of CO has become increasing important. This relates to the need for a secondary standard for CO. The role of CO as an important local and global sink for OH is mentioned in Section 3.3; the ISA should call for monitoring with sufficient sensitivity, in other words new or modified instruments. This is no great technological challenge.

The mean global concentration of CO decreased through the 1990's but appears to have leveled off [*Duncan and Logan*, 2008; *Duncan et al.*, 2007]; see also Novelli, 2008.
http://www.esrl.noaa.gov/gmd/publications/annmeet2008/Poster_Final.pdf
Because emissions from sources in the US have decreased does this imply that emissions from the rest of the world have increased? Is that an environmental hazard for the US? The ISA should have a section on consideration of a secondary standard for CO as promised on page 1 of the "Plan for Health Risks", but I cannot find one.

The literature since the 2000 CD has been reviewed reasonably well, but there have been a series of studies that support the contention that vehicular emissions have decreased considreably and that MOBILE 5 and 6 overestimate emissions substantially. For example [*Pokharel et al.*, 2002; *Pokharel et al.*, 2003] demonstrate improvements in tailpipe exhaust of CO for several American cities. There is also evidence of improvements in the Diesel truck fleet emissions [*Burgard et al.*, 2006]. The observations of *Parrish* (2006) have been verified [*Bishop and Stedman*, 2008]. See also *Stedman et al.* (2009). These results have implications for Inspection and Maintenance Programs as well as for numerical modeling of emissions.

On page 5-126 is stated "Because CO measurements tend to reflect more local impacts, due to the location of monitors, than NO_2 (which is a secondary pollutant and therefore more spatially uniform) it is also possible that CO, the less precisely measured pollutant in terms of spatial distribution, may "lose" in the multipollutant model. Thus, it may not be accurate to interpret these results as evidence of 'confounding by NO_2.'" Of these two pollutants CO is more spatially uniform. NO_2 is secondary only in the sense of it being formed from NO within the first minutes of emission. The lifetime of NO_2 is less than a day while that of CO is more than a month.

Section 3.2 states that less CO is produced at higher burn temperatures, but thermodynamics dictate that a fair amount of CO is formed from CO_2 decomposition and that the equilibrium favors CO and $\frac{1}{2}O_2$ at higher temperatures, especially in internal combustion. The remainder of the para is good.

The color scale of Figures 3-11 and 3-12 is inappropriate – there are only two of the five colors visible. Correlations of CO and ozone can be misleading – CO is a precursor for ozone but some ozone is titrated out by NO that is co-emitted with CO. Both O_3 and SO_2 tend to peak in the middle of the day so 24-hr means of trace gas concentrations might reveal more wrt atmospheric chemistry.

References

Stedman et al., On-Road Motor Vehicle Emissions including Ammonia, Sulfur Dioxide and Nitrogen Dioxide 19th Coordinating Research Council, On-Road Vehicle Emissions Workshop, San Diego, CA. March 23-25, 2009**.**

Dalton, T.R., D.H. Stedman and J.D. Ray, Winter Motor-Vehicle Emissions in Yellowstone National Park, G.A. Bishop, D.A. Burgard, *Environ. Sci. Technol*., 40:2505-2510, 2006.

Bishop, G. A. and D. H. Stedman (2008), A decade of on-road emissions measurements, *Environmental Science & Technology*, *42*, 1651-1656.

Burgard, D. A., G. A. Bishop, D. H. Stedman, V. H. Gessner, and C. Daeschlein (2006), Remote sensing of in-use heavy-duty diesel trucks, *Environmental Science & Technology*, *40*, 6938-6942.

Duncan, B. N. and J. A. Logan (2008), Model analysis of the factors regulating the trends and variability of carbon monoxide between 1988 and 1997, *Atmospheric Chemistry and Physics*, *8*, 7389-7403.

Duncan, B. N., J. A. Logan, I. Bey, I. A. Megretskaia, R. M. Yantosca, P. C. Novelli, N. B. Jones, and C. P. Rinsland (2007), Global budget of CO, 1988-1997: Source estimates and validation with a global model, *Journal of Geophysical Research-Atmospheres*, *112*.

Pokharel, S. S., G. A. Bishop, and D. H. Stedman (2002), An on-road motor vehicle emissions inventory for Denver: an efficient alternative to modeling, *Atmospheric Environment*, *36*, 5177-5184.

Pokharel, S. S., G. A. Bishop, D. H. Stedman, and R. Slott (2003), Emissions reductions as a result of automobile improvement, *Environmental Science & Technology*, *37*, 5097-5101.

Further Comments on the Carbon Monoxide ISA and the Health Effects Plan
21 May 2009

Carbon monoxide is more than a primary pollutant. It is a major precursor to ozone and alters the oxidizing capacity of the atmosphere. Because the atmospheric chemistry of

CO is relatively simple and well known, CO makes an excellent tracer for polluted air masses and is useful for evaluating air quality models such as CMAQ. Some examples are given in the references at the end. The lifetime is long relative to synoptic events, and the concentration of CO over the US is driven primarily by boundary conditions, emissions (and *in situ* formation), and transport. Agreement of observed and modeled temporal trends in surface CO concentrations indicates that advection and mixing are appropriately simulated. Altitude profiles of CO can be a powerful tool for determining how well vertical mixing is represented in a model, and vertical mixing is critical to understanding the spatial and temporal variability of ozone and PM. In order to evaluate modeled vertical profiles, modeled emissions must be correct, thus both high-resolution measurements and reliable emissions estimates are necessary for evaluating chemical transport models used for air quality planning.

To make a quantitative recommendation, with typical concentrations of about 200 ppb CO, precision in the observations of 10 % or about 20 ppb is desirable for evaluation of numerical simulations. Uncertainty on the order of 20 ppb is achievable with modified commercial instruments, and may be possible with careful operation of newer detectors as delivered, but this remains to be demonstrated.

Concerning recent measurements of CO there is room for improvement, but also substantial confusion on the accuracy and precision of the monitors in use. Newer instruments may have superior sensitivity, but the detectors vary in age. For example, the State of Maryland operates two instruments with a detection limit around 20 ppb, and Georgia apparently operates several similar instruments, but such high sensitivity is not an EPA requirement. High resolution monitoring is a State initiative and therefore subject to substantial variability across the US.

The ISA should make an attempt to compile information on precision, accuracy and uncertainty of the measurements, especially where long term averages are driven by high values. Some new instruments are improved substantially. (For the record the gas-filter correlation detectors of which I am aware are NDIR). High sensitivity NDIR analyzers are available from Thermo Scientific (Model 48CHL), Teledyne Instruments (Model 300E), and Environment S.A (Model CO12M), and all report a lower detectable limit of about 0.040 ppm. All manufacturers also reported precision or zero drift of about 0.10 ppm. It may be worth while for EPA to evaluate these instruments, but given the reported specifications, these instruments off the shelf (as purchased) will not provide adequate sensitivity when the typical concentration is 200 ppb (0.2 ppm). It has been possible in the past to use frequent checks of the zero point to improve the accuracy of commercial CO detectors. New instruments may be amenable to this procedure.

How can the actual <u>dose</u> of CO be determined? As reviewed in the ISA, street canyon level models exist. They must however be evaluated with high precision observations. This will require multiple measurement points for the course of a few days because the diurnal (diel) patterns are important.

As reported in the ISA, MOBILE6 appears to overestimate CO emissions. NOx emissions are probably overestimated too, although by not as much. How will MOVES improve upon this? There is at lease one report that MOVES calculates lower VOC's (and presumably CO), but higher NOx emissions than MOBILE 6. http://www.marama.org/calendar/events/2009_02Annual.html

For the abatement of the global-scale adverse effect of excess CO on atmospheric composition and climate, an emissions limit rather than an ambient concentration standard is appropriate. The ISA should consider a discussion of such a limit; what for example would be the total American CO emissions if all on-road vehicles meet the current emissions standards? How would this change if all the non-road vehicles and stationary internal combustion engines were regulated to the same level? The IPCC reports estimates the radiative forcing (on the decadal time scale) due to CO from which one can estimate the CO_2-equivalent impact on climate, The ISA could/should discuss the science behind pursuing such a goal and the appropriate credit the US should get for greenhouse forcing avoided.

References

A global simulation of tropospheric ozone and related tracers: Description and evaluation of MOZART, version 2 Author(s): Horowitz LW, Walters S, Mauzerall DL, et al. Source: JOURNAL OF GEOPHYSICAL RESEARCH-ATMOSPHERES Volume: 108 Issue: D24 Article Number: 4784 Published: DEC 24 2003

Convective transport of biomass burning emissions over Brazil during TRACE A Author(s): Pickering KE, Thompson AM, Wang YS, et al.
Source: JOURNAL OF GEOPHYSICAL RESEARCH-ATMOSPHERES Volume: 101 Issue: D19 Pages: 23993-24012 Published: OCT 30 1996

Nighttime chemistry in the Houston urban plume, Luria M, Valente RJ, Bairai S, et al. Source: ATMOSPHERIC ENVIRONMENT Volume: 42 Issue: 32 Pages: 7544-7552 Published: OCT 2008

Dr. Stephen R. Thom
Professor of Emergency Medicine, M.D., Ph.D.
Chief, Hyperbaric Medicine
Medical Director, PennStar Flight
University of Pennsylvania
3620 Hamilton Walk
Philadelphia PA 19104-6068

Ch 1: 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.

The approach and background are well done. Introduction of the problem with absence of alternate dose indicators (vs COHb) is important.

Ch 2: What are the views of the Panel on the effectiveness of the integration of atmospheric science, exposure assessment, dosimetry, pharmacokinetics, and health effects evidence in the CO ISA?

Again, well done.

Ch 3: To what extent are the atmospheric science and air quality analyses presented in Chapter 3 clearly conveyed and appropriately characterized? Is the information provided regarding CO source characteristics, CO chemistry, policy-relevant background CO, and spatial and temporal patterns of CO concentrations accurate and relevant to the review of the CO NAAQS?

They are standard facts – well done.

How well do the choice and emphasis of exposure topics presented in Chapter 3 provide useful context for the evaluation of human health effects in the ISA? Is the discussion and evaluation of evidence regarding human exposure to ambient CO and sources of variability and error in CO exposure assessment presented clearly, succinctly, and accurately? The ISA concludes in section 3.7 that central-site monitor concentration is generally a good indicator for the ambient component of personal CO exposure. What are the views of the Panel on this conclusion and its supporting evidence?

Issues are well presented and conclusion is valid.

Ch 4: Please comment on the presentation in the ISA of the current state of knowledge on the Coburn-Foster-Kane (CFK) model and model enhancements. Has the expected contribution of different exposure durations (1-24 h) to COHb levels been clearly and accurately conveyed?

The discussion is well developed. I have only a small issue. I believe there is an error in Table 4-1a. Even in the original publication ther was confusion as to the units on the table, but I believe the CO concentration should be in pmol/mg (NOT 100 g ww tissue).

Ch 5: Please comment on the appropriateness of the focus, structure and level of detail in discussion on hypoxic and non-hypoxic mechanisms of CO health effects. For example, is the evidence relating to the interaction between inhaled CO and endogenous CO properly characterized?

Once again, the authors did a very good job. There is an obvious concern pertaining to compounding the effect of endogenous CO with an exogenous (inhaled) source. It might make some sense to introduce the concept that we really still have a poor understanding of the local, intracellular CO concentration in close vicinity to heme oxygenase activity. Therefore, the proportionate effect of exogenous CO and how much this will alter intracellular CO concentrations requires more study.

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?

I believe they are – well done.

For cardiovascular outcomes, controlled human exposure studies discussed in Chapter 5 and in previous assessments have identified cardiovascular effects in diseased individuals following exposures near the level of the current standards, while new epidemiologic studies provide evidence of cardiovascular effects at ambient concentrations. What are the opinions of the Panel on the treatment of factors influencing the interpretation of this evidence, such as the plausibility of cardiovascular effects occurring at ambient levels, the additive effect of ambient CO to baseline COHb resulting from endogenous and non-ambient CO, and the challenge of distinguishing effects of CO within a multipollutant mixture (e.g., motor vehicle emissions) in interpreting epidemiologic study results?

The document authors have handled discussion on factors influencing the interpretation of cardiovascular risk in a fair and balanced manner. I think the data support caution and concern that there is indeed a cardiovascular risk at near-ambient CO concentrations for individuals with coronary vascular disease.

Please comment on the implementation, in Chapter 5, of the causal framework presented in Chapter 1. Does the integration of health evidence focus on the most policy-relevant studies and health findings?

The framework is logical and coherent.

What are the views of the Panel on the discussion of factors affecting susceptibility and vulnerability in Section 5.7?

The authors have done an extremely good job.

Dr. Tom Dahms
ISA CO comments

Chapter 3: Source to Exposure
General Comments
This chapter is very important to the ISA in that it provides the basis for the understanding of CO sources, trends in CO levels from sources and exposures of both populations and individuals. Sections 3.1 through section 3.4.1 are well constructed and provide an overview of sources and trends in atmospheric CO over the past 2 decades. This material contains detailed information along with sufficient interpretive information to provide the reader with consensus findings.

Given that much of the recent literature that pertains to health effects of CO is based on epidemiological data, this chapter emphasizes the value of atmospheric monitoring data as the best estimate of exposure to CO for the epidemiologist. . If one scans the Figures and Tables in Chapter 5. Integrated Health Effects, data has been compiled from major cites around the world. Health effect end-points are being assessed relative to atmospheric changes in CO collected from urban networks of monitors. No insight is provided (in Chapter 3 or in Annex A) to help the reader understand the validity of these international atmospheric monitoring systems. Given the significant reduction in atmospheric levels of CO since 1980, these international studies are important to the understanding of potential effects of CO. Therefore some means of altering the material in this Chapter should be undertaken to aid with the improved understanding of these international studies.

Charge question 4.

A. **How well do the choice and emphasis of exposure topics presented in Chapter 3 provide useful context for the evaluation of human health effects in the ISA**?

Given that much of the recent literature that pertains to health effects of CO is based on epidemiological data, this chapter presents the case for atmospheric CO from fixed site monitors as the best estimate of exposure to CO. If one scans the Figures and Tables in Chapter 5. Integrated Health Effects, data presented in this ISA has been compiled from major cites around the world. Health effect end-points have been assessed relative to atmospheric changes in CO in those international locations. Unfortunately no insight is provided (in Chapter 3 or in Annex A) to help the reader understand the validity of these international atmospheric monitoring systems. Some background information on these international sites would be of value.

The emphasis of this chapter discussion is placed on establishing the validity of the use of ambient monitoring information as the best available means for estimating exposure to CO.

Although the information is presented in some detail regarding the variability of exposure due to individuals moving through different microenvironments, the variability due to these personal exposures is discounted in its importance. This is a considerable deviation from the consideration of these issues in previous AQCD for CO where considerable concern was placed on the use of exposure models like pNEM/CO (APEX) that placed emphasis on personal exposure. Given the information reviewed in this Chapter for the potential for individual variability in exposure to CO due to activity patterns, geographic or spatial locations (e.g. in transit, proximity to roadways), it is very difficult to accept the premise that atmospheric monitoring data provides the best means of assessing exposure. Data from fixed site monitors is probably the best approximation of assessing exposure for epidemiological studies, however the limitations clearly need to be clearly stated.

B. Is the discussion and evaluation of evidence regarding human exposure to ambient CO and sources of variability and error in CO exposure assessment presented clearly, succinctly and accurately?

Beginning with section 3.4.2 the presentation of the information changes to what often reads as a long string of facts. This appears to be due to the attempt to mention so many of the recent studies in this area without any concluding sentence that would justify the inclusion of the listed material. The result is confusion regarding the intended focus of the information being presented. For example on page 3-13 lines 4-6 indicates that data will be presented to determine if ambient monitors adequately characterize population exposure. Information is presented but no conclusion is drawn from the information in this paragraph. However in the remainder of the Chapter, material is presented that suggests that fixed site monitors are good for estimating exposure to ambient CO. It would be logical to make this statement early and then proceed to defend the statement.

The Chapter would be much more readable if it had been more focused and carefully edited with the intended reader in mind. For example many paragraphs do not have a topical sentence that indicates to the reader what is to follow. The Chapter contains excessive jargon that makes it difficult to follow for example: *"In the context of determining the effects of ambient pollutants on human health, the association between the ambient component of personal exposures and ambient concentrations is more relevant than the association between total personal exposures (ambient component + non-ambient component) and ambient concentrations."* The meaning of ambient seems to be clear to the author but not always to the reader so there needs to be a brief definition of terms----what is a non-ambient component that is presumably inhaled? I had to assume that ambient in this context is taken to mean atmospheric levels of CO found in the outdoor air at distances from the surface available for humans to inhale. Yet, the potential exposures shown in Figure 3-31 on page 3-58 show that there are a wide variety of ambient conditions that are all mixtures that are composed of some percentage of atmospheric levels of CO. This material could benefit from editing with an eye toward making the material clear to readers from a diverse scientific background.

Chapter 3 contains a significant amount of atmospheric monitoring data that appears to be focused on justifying the use of atmospheric measurements of CO for purposes of assessing exposure to CO. This reviewer is not an expert in modeling of atmospheric CO but the information with which I am familiar seems to have been accurately described. It appears that the author(s), in the attempt to be comprehensive, developed very little in depth information directly focusing on health effect exposures to CO. This assessment has not been clearly nor succinctly presented. For example the material found in pages 3-10 to 3-54 concerns the intricacies of atmospheric monitoring and modeling. The application of the specific points of atmospheric monitoring need to be related to CO exposure assessment as a focus of the presentation of this material.

Not being an expert in the area of atmospheric monitoring, I have checked some of the references and the assertions in the text agree with the author's conclusions. Therefore I assume that the material presented is accurate.

C..The ISA concludes in section 3.7 that central-site monitor concentration is generally a good indicator for the ambient component of personal CO exposure. What are the views of the Panel on this conclusion and its supporting evidence?

In the 1991 AQCD for CO on page 8-79 the following statement was made: *"The authors concluded that fixed outdoor CO monitors alone are, in general, not providing useful estimates of CO exposure of urban residents*." This statement was made on the basis of COHb measurements from the NHANES II study where only 0.03% of the variance in COHb was due to ambient CO data.

In the 2000 AQCD for CO the following summary statement was made: *"Fixed-site monitors often are used in urban areas to estimate the ambient concentrations to which individuals in the surrounding areas may be exposed. These measurements tend to overestimate 8-h exposure values for people living in areas of lower traffic and underestimate the exposure of people living in areas of higher traffic."* This conclusion was reached based on the evidence from personal exposure monitors and from the analysis of various micro-environments that showed levels of CO not detected by atmospheric monitors. The evidence for this statement was not based on any analysis of dose of CO (COHb) as was the 1991 statement.

The specific statement regarding the above question is found in the 2009 draft ISA_CO is found in Section 3.6.5.3.page 3-65 lines 7-10 which is repeated in section 3.7.5 page 3-74lines 10,11. *"For the general U.S.population, exposure error analysis for epidemiologic studies indicates that fixed-site measured ambient CO concentration is generally a good indicator of ambient exposure to CO, as discussed in more detail below*." The evidence that seems to have influenced these statements can be found in Section 3.6.2, page 3-57 lines 15-31 where the study of Wilson and Brauer (2006) is used as evidence. As noted this study was on 16 subjects who were studied for exposure

to PM. It is not clear what assumptions are involved in accepting the transference of PM exposure to CO exposure.

Wallace and Ziegenfus (1985 in the 1991 AQCD for CO) actually tested the hypothesis that the fixed outdoor CO monitors provide useful estimates of CO exposure. As noted above the data of Wallace and Ziegenfus does not support this hypothesis. The current ISA Chapter 3 reviews data that reaches the opposite conclusion but without data from persons exposed to CO to support the hypothesis. If this assertion of the value of fixed-site monitors is to be convincing, the study of Wallace and Ziegenfus needs to be carefully analyzed to show why it should be discarded.

Charge Question 6.

The mode of action section in Chapter 5 presents information on both hypoxic and non-hypoxic mechanisms for CO health effects, with particular emphasis on recent studies evaluating the non-hypoxic effects at low to moderate CO levels. Please comment on the appropriateness of the focus, structure and level of detail in this discussion. For example, is the evidence relating to the interaction between inhaled CO and endogenous CO properly characterized?

Although the roles for CO in signaling are increasing at a rapid pace, the application of this information to understanding the adverse health effects of CO is limited. The information presented in Chapter 5 reflects this situation and I believe is very appropriate in scope and focus. There are many obstacles to applying the non-hypoxic effects of CO to the health effects data base. The biggest hurdle to date is that the adverse health effects of CO observed in patients with coronary artery disease occurred with partial pressures of CO of 0.012-0.015 torr or 15-20 ppm. There are very few non-hypoxic effects observed with exposures in this range. One reason is that most of the animal models or tissues studied are healthy i.e., not from animals that in any way mimic the cells from ischemic heart tissue or other disease models. Another aspect of these studies lie in the difficulties of attempting to reproduce endogenous release of CO from focal distribution of heme-oxygenase with global exposures to CO. It is hoped that eventually this field will develop approaches and methods that will lend themselves directly to addressing health effects.

The limited similarity to endogenous production of CO and exogenous CO are well described in section 5.1.3.3.

The impact of endogenous CO production on COHb levels (hypoxic effect) is incorporated in the CFK equation 4.1. Perhaps some statement could be made regarding the factors, other than hemolytic states, that might lead to significant levels of endogenous CO production.

If non-hypoxic effects of CO were observed that pertained to myocardial ischemia and the resultant disturbances in both membrane potentials and membrane permeability, the

effects observed in patients with CAD might be less skeptically received by the medical community.

There are some encouraging studies along these lines: Thom and Ischiropoulos showed that 10 ppm CO resulted in increased free NO along with other studies indicating that exposure to CO results in increased concentrations of ROS.

Concern over study quality.

One of the outcomes of the discussion of the epidemiology data in the ISA regarding effects of CO on cardiovascular end points, was a request that was made by Dr. Ritz for the authors of the ISA to provide information that pertained to study quality. In Chapter 1 lines 1 and 2 state that the ISA is meant to be "a concise evaluation and synthesis of the most policy relevant science for reviewing the NAAQS." In my view this document falls short on the evaluation aspect of the studies reviewed. This document seems to be more of a compendium of current publications without critical analysis of the information presented. Inclusion of this analysis would enable the reader to determine which studies should take precedence or have the most influence in supporting the conclusions drawn from the review of the literature. In fact this approach should be utilized throughout the document. Without such evaluation of the material presented, the reader can only drawn conclusions from the number of studies (presumed to be equal in quality) showing effects vs those that do not show health effects. For example how many of the studies have insufficient power to avoid a Type II error?

The consensus of the review panel based on the information in the ISA, the data that provides the strongest evidence for support of the health effects of CO are the controlled human exposure studies and the epidemiology studies. These two groups of studies clearly warrant the closest evaluation in the ISA.

During the recent CASAC_CO Panel meeting, EPA staff raised the issue in several ways that suggest a reluctance to base decisions on study quality. This point was emphasized by Dr. Ritz's comments that she found it difficult to evaluate the epidemiological data because of the lack of presentation of quality indicators for each study in the ISA document. The interpretation of the exchange between Dr. Ritz and staff is that greater consideration of the data from studies of higher quality should go into the evaluation of effects. There seems to be a tendency in the document to look for multiple studies confirming the same effect and to use the median or range of effects observed from those studies. The ideal situation is to look for multiple high quality studies showing the same effects at the same level of exposure. Without belaboring the point, a series of studies designed with inadequate power to show intended effects and therefore showing no effect are just as dangerous. There needs to be more of an attempt to identify studies in all areas of the CO database where quality indicators are identified and reliable data published. In short there needs to be more critical evaluation of studies presented in stead of what currently exists as a serial presentation of information with little insight into relative importance of the studies presented.

Having been part of the multicenter Allred et. al. study using controlled exposure of high risk subjects, it has become clear to me that such analysis is lacking not in just the epidemiological data base but in other areas as well. I will review what went into the Allred study as an example of what I think is important for producing a defensible scientific basis to support a standard. This does not detract from other studies that have confirmed these findings but there is a clear difference in the studies.

It was determined in the mid 1980s that the data produced by Aranow could not be relied upon for reasons of scientific misconduct and that this data was a key piece of the basis for the 1979 NAAQS for CO. The proponents of loosening the NAAQS for CO had legal grounds for a challenge. Therefore a study had to be designed and carried out to test the Aranow hypothesis in such detail and with unquestionable quality assurance standards that the findings would clearly test the hypothesis to everyone's satisfaction. To accomplish this task required considerable resources not normally made available to a group of investigators. However the NAAQS for CO seemed to hinge on this study. (In fact after the release of these findings congressional staff made the point of acknowledging that legislation in support of all NAAQS was altered because of the findings of this study.) What set this study apart were the following key elements: its multicenter nature, sound a priori statistical design, multiple dose design to provide potential dose-response effects, well characterized subjects, tight exposure and dose controls, and audited quality assurance. These features provided all parties with the assurance that the findings would be defensible in any legal proceedings. There are other studies that confirm these findings but without the Allred et al study, they would be subject to criticism because one or more of the elements listed above were missing.

In away this study has been acknowledged by the intended levels of COHb that will be used in the Risk Assessment.

Without going into great detail the authors of the ISA should provide the guidance requested by Dr. Ritz and others as to standards that set studies apart from others in their findings.

Dr. Paul T. Roberts
Revised Comments on 1st draft ISA by Paul T. Roberts for CASAC CO Panel, May 21, 2009

ISA Charge Question 3. To what extent are the atmospheric science and air quality analyses presented in Chapter 3 clearly conveyed and appropriately characterized? Is the information provided regarding CO source characteristics, CO chemistry, policy-relevant background CO, and spatial and temporal patterns of CO concentrations accurate and relevant to the review of the CO NAAQS?

In general, the discussions in ISA Chapter 3 on CO source characteristics, CO chemistry, and policy-relevant background CO are accurate and relevant to the CO NAAQS review. Most of my comments are on limitations/qualifications of the measurement data and the use of that data; see comments below.

Regarding Figure 3-2 (and Figure 3-4) and associated text: I realize that inventories older than 1990 are not comparable to more-recent inventories, but it is hard to properly compare emissions trends from 1990-2002 with air quality trends from 1980-2006 as is done in Chapter 3.5.2.1. I think that the 2005 NEI inventory is now available and should be used to at least partly update this comparison.

On line 13, page 3-5: it would be good to convert the 30 Tg to MT for the reader to also see the comparison with other emissions data in this part of the ISA.

Regarding Chapter 3.4.1 Ambient Measurements: I am concerned that lower detection limits, zero drift in monitors, and precision of the reported CO data are not being treated sufficiently to understand the uncertainty of the data and thus properly use and qualify the data in exposure estimates and models.

1. Lower detection limits (line 6-7 of page 3-11): The 1.0 ppm listed here as required is sufficient for determining compliance with the current NAAQS, but is no longer sufficient for typical urban concentrations, since concentrations have decreased significantly. Even the 2000 CO AQCD acknowledged that "At many existing *(urban)* monitoring sites, the mixing ratio is frequently below the lower detectable limit specified in Table 2-1." (page 2-2). The DL in Table 2-1 of the 2000 AQCD was the same as in the current ISA (1.0 ppm). Again, from the same page: "A CO monitor with precision of 500 ppb would be adequate to prove compliance with the CO standard, but would not provide adequate input data for CTMs." Many of the manufacturers quote a lower detection limit of 0.04 or 0.05 ppm, which would be sufficient in most cases if the monitors met that spec. However, in practice this can only be met with a frequent (every hour or so) automatic zero drift correction, since the zero drift can be 0.1 ppm per day, but only the newer models have an auto zero-drift option. And some agencies don't select the auto-zero option, at least they didn't in the past. Also note that agencies have a wide range of monitors in service, including many older models with worse DL and zero-drift specs, and without auto zero-drift correction. Due to these points, I do not agree with the statement regarding zero drift on lines 11-12 on page 3-11. If all US monitors had the zero-drift option, I agree, but this is not the case; many states or agencies have only

recently bought their first CO monitor with an auto zero drift option (and Georga, for example, has only recently finished testing their first monitor with the auto-zero option)..

2. I suggest that the ISA should provide the results of calculations on in-use detection limits and precision to demonstrate that the monitors being used for the reported data are sufficient for use in exposure models. Otherwise, what does the data mean for exposure? In fact, the text at lines 32-36 on page 3-35, referring to Table 3-8, recognizes the DL issue and says that these results should be used with some caution. An example of how to provide the precision information is the following excerpt from the 2000 CO AQCD, page 2-8, although the reported statistics were already old at that time. Similar statistics for detection limit and precision should be calculated on the recent ambient data that is being used in the ISA, based on the information reported to AQS for each reporting site, and such statistics should be reported in the revised ISA. "The error analysis is a statistical evaluation of the accuracy and precision of air quality data. Guidelines have been published by EPA (Smith and Nelson, 1973) for calculating an overall bias and standard deviation of errors associated with data processing, measurement of control samples, and water vapor interference, from which the accuracy and precision of CO measurements can be determined. Since January 1, 1983, all state and local agencies submitting data to EPA must provide estimates of accuracy and precision of the CO measurements based on primary and secondary calibration records (Federal Register, 1978). The precision and accuracy audit results through 1985 indicate that the 95% national probability limits for precision are ±9%, and the 95% national probability limits for accuracy are within ±1.5% for all audit levels up to 85 ppm. The results (accuracy) for CO exceed comparable results for other criteria pollutants with national ambient air quality standards (Rhodes and Evans, 1987)." If appropriate data is not easily available in AQS for the sites being used in the ISA, then EPA staff should calculate detection limit and precision statistics for at least a few example sites and report those results in the revised ISA.

3. In addition, it is especially important that data below detection limit is reported properly, since 8-hr CO concentration averages, for example, might include several hours of low CO concentrations. If the measured value is at or below the detection limit, or the EPA specified detection limit, that data value is often just reported as that value, say 0.5 ppm, for example, or even as 0.0; but using this data in averages can lead to biased averages (see the discussion of this issue in the EPA Toxics Workbook, McCarthy et al., 2008). Using a value of DL/2 or a distribution of values below the DL may be more appropriate in this application.

Chapter 3.4.2.1 Monitor Siting Requirements (page 3-12): Discussion on lines 6-9 covers microscale sites. It seems like knowing the number of these sites being used for all of the following tables and graphs would be important, since concentrations at a microscale or near-roadway site could be 2-10 times higher than nearby concentrations (see, for example, later near-roadway discussions, page 3-39 to 3-42). I suggest the number of microscale, middle scale, and neighborhood scale sites being used in these analyses be mentioned here. However, I think it is also important to mention especially the number of microscale sites when discussing the population representativeness (Figures 3-7 to 3-10 and figures in Annex A), distributions of CO data (Tables 3-3 to 3-6), the seasonal distribution plots (Figures 3-14 ff), the inter-site statistics

(Tables 3-7 ff), and the diel plots where data from multiple sites are averaged together (Figures 3-26 and 3-27). In each of these cases, the number and location of a microscale site could significantly bias the data in the table or figure (and thus bias the result of using the data in exposure analyses). In fact, I suggest that a second set of many of these table and figures be added for just the 70 microscale sites (or for those sites among these 70 which are judged to best represent microscale sites).

Tables 3-3, to 3-6 distribution of CO data: As mentioned earlier, I think the data in these tables need some qualifications, either in the table/footnotes to the table or in the associated text. What is the reported detection limit for the reported data, since so much of the data distribution are low? How many microscale sites have their data averaged in with data from middle or neighborhood scale sites? And most importantly, how do these issues influence the interpretation of the results? Maybe separate lines or table should be developed for the microscale sites?

Population coverage, page 3-13 and Figure 3-7: I don't agree that the current Phoenix CO monitors properly cover the total population; there are areas of significant population and population density to the southeast and the northeast of the central area that are not covered. I suggest changing the words to better reflect the representativeness of these sites.

Location of monitors, relative to roadways, lines 23-27 page 3-13 and Figures 3-13 and 3-15 (plus figures in Annex A): I see the usefulness of these figures in general (central city versus boundary), but I can not determine from them how close sites are to major roadways (and I think this is their major purpose). To be useful, it seems like the figures need something about traffic density and something about how close (in meters) the sites actually are to a major road. In addition, the text needs a conclusion about this (something like "many sites are very near major roads" or "only a few sites are near major roads" and "thus the results shown in Table 3-3ff and Figures 3-16ff are biased (or not) for Phoenix, but not for Pittsburgh, etc. due to x and y".

Lines 4-5 page 3-24 Highest CO in Ogden: Since this concentration is so much higher than others, please explain what caused it. Was this an 'exceptional event'?

Lines 32-36 page 3-35, lines 1-4 page 3-36 and Table 3-8: As mentioned earlier, the caution due to a high monitoring detection limit is a significant limitation of this and other data displays. The words here are good and name some specific sites where these limitations may be problems. I suggested that statistics be added on detection limits and precision of the actual monitors used where ever data is reported.

Chapter 3.5.1.3 Near-roadway discussion: This discussion on page 3-39 and 3-40 is good and mentions the importance of this issue for exposure. However, comments could be added on the potential influence of lower wind speeds on concentrations (to the discussion on lines 5-18 page 3-40) and on the influence of varying wind directions on the CO distributions within urban canyons (lines 19-36 page 3-40). Both conditions will reduce the gradients discussed and thus distribute the roadway CO more spatially within the urban canyon.

Pages 3-42 and 3-43, Figure 3-23 using monitor comparisons for understanding neighborhood variability: The statement on line 1 of page 3-42 is very important and thus information on CO concentrations on this scale (microscale) need to be used in the subsequent CO exposure modeling, in order to properly represent this issue. In addition, the results of Figure 3-23 could be significantly different if some of the sites were microscale sites, so please state if they are or not and discuss the implications of the result.

Figures 3-26 and 3-27 and associated text on pages 3-46 to 3-47 hourly variation in CO: I think that averaging data from multiple sites together to get average diurnal profiles is fraught with problems, and I think the results in these figures illustrate those problems.

1. For example, averaging data from different sites with potentially different (or even slightly different) diurnal profiles will distribute that profile over multiple hours and make it look like a flat diurnal profile. On the other hand, if the sites have the same diurnal profile, it will reinforce the peaks and valleys. Or if there is only one site (Seattle, for example), then the profile will keep its shape and not be diluted by data from another site. At a minimum, these qualifications should be discussed in the text with the conclusions (and I think they are significant limitations); however, I suggest that it is more appropriate to re-do the text and figures (or show only diurnal curves for only one representative site for each area).
2. In addition, I do not understand how the number of monitor days (N) is correct. For example, for Seattle (only one site), 3 years of weekday only data (Figure 3-26) would be about 780 monitor days; how can it be 1577? See also Figure 3-27, where weekend only data at 1 Seattle site would be about 312 monitor days, so what does the 639 mean? On the other side, for Phoenix there are 5 sites, thus 3 years of weekday only data would be about 3900 monitor days. The value of 1021 implies only about 25% data recovery; this does not make sense. The text tells us that Anchorage is included, but does not operate year-round; this statement implies that all the other sites do operate year round. In addition, the text talks about using only data from site with 75% data completeness (page 3-12 line 17). Maybe I am doing something wrong here, but please explain.

Lines 18-21 page 3-51 Comment on non-collocated monitors: I agree with comment regarding influence if CO monitor is not collocated with monitors for other pollutants, but the text at line 5 page 3-50 says only collocated data was used for Figure 3-28 and similar figures in Annex A. What is the actual case here? If only a few pairs include a non-collocated CO monitor, then why not just drop those few cases and then the results don't have to be qualified?

There should be a conclusion or "so what" statement added at the end of Chapter 3.6.3.2, Measurement Error in Personal Exposure Modeling.

In the Summary and Conclusions, Chapter 3.7.3 Ambient CO Measurements: Please add information here on detection limits and precision, plus a discussion of the implications of DL and precision on the descriptions of CO concentrations and thus exposure estimates. In addition, note that the sentence on microscale monitors (lines 11-13) is new information not mentioned previously in the details of Chapter 3; as mentioned earlier, the number and influence of microscale monitors should be discussed earlier and then summarized here.

In the Summary and Conclusions, Chapter 3.7.4 Environmental CO Concentrations: For the sentence on lines 7-10 which discusses the diel profiles, please add significant qualifications for averaging data from multiple sites together, etc., as discussed earlier. In addition, it may be necessary to change these conclusions if the plots are redone, based on my earlier comments.
ISA Charge Question 4. How well do the choice and emphasis of exposure topics presented in Chapter 3 provide useful context for the evaluation of human health effects in the ISA? Is the discussion and evaluation of evidence regarding human exposure to ambient CO and sources of variability and error in CO exposure assessment presented clearly, succinctly, and accurately? The ISA concludes in Chapter 3.7 that central-site monitor concentration is generally a good indicator for the ambient component of personal CO exposure. What are the views of the Panel on this conclusion and its supporting evidence?

The exposure topics presented in Chapter 3 are appropriate and useful for the evaluation of human health effects in the ISA. However, there are no significant discussions of CO measurement errors in either this section of Chapter 3.4. **Chapter 3.6.3.1 line 1 page 3-58:** The "associated monitoring errors" are NOT discussed in Chapter 3.4; see my earlier comments that this should be added to Chapter 3.4.1. In the rest of the paragraph, I am most concerned about differences in errors in CO concentration, since some sites may have very old monitors with larger precision and larger zero drift while other sites may have new monitors with auto zero drift corrections, etc. Please discuss the influence of this type of error on health outcomes. The last sentence of the paragraph kind of leaves the reader hanging; what is the implication of this issue for exposure estimates? And again in the last sentence at line 23 of page 3-59, what is the influence of the potentially large personal measurement error on exposure estimates and how should this be treated?

Chapter 3.6.5.3 CO Exposure Assessment Variability and Error (page 3-65): How does the statement on lines 7-10 follow from the previous text, given the specific text on lines 3-7 page 3-63 for an example of high in-vehicle exposures (or Figure 3-34 or other text earlier) or lines 12-13 on page 3-61 for an example of near-roadway exposures? It seems like the comments/qualifications on lines 17-21 may apply to the first 8 locations in Figure 3-34, but do not apply to the in-vehicle location in Figure 3-34. Thus, not including in-vehicle and near-road CO exposures could lead to significant errors in exposure estimation and thus in health outcomes.

Chapter 3.6.7: In light of the currently-planned method for preparing the CO concentration fields for the exposure model (as discussed at May 13 panel meeting and in slide 13 of the presentation), the discussion and references cited on pages 3-70 and 3-71 (in Chapter 3.6.7) are not sufficient to support the methods plan and should be significantly expanded. There is only one reference cited for concentration surfaces, which will be a major tool in the analysis; many more are needed. A few additional references that I can easily find are listed at the bottom of my comments. Note that many of these references are for pollutants other than CO, since few studies are currently being done on CO; however, the methods can be reviewed and used as guidance for similar applications for CO. In addition, I think that the exposure modeling Chapter (3.6.7) should include much more specifically about the methods that will be used to address in-vehicle and near-road exposures. A recent HEI report is now available on the web at:

http://pubs.healtheffects.org/view.php?id=306; this report has an excellent summary of the current literature and thinking on near-roadway exposures and a good reference list.

Regarding the Chapter 3.7 conclusion that central-site monitor concentrations is generally a good indicator for the ambient component of personal CO exposure: Total personal exposure to CO is the time weighted sum of exposure to all microenvironments including multiple outdoor environments (not just multiple indoor environments). Therefore the central-site monitor concentration is not viewed as 'a good general indicator for the ambient component of personal CO exposure'. Equation 3.4 should be reformulated to include multiple outdoor microenvironments, including at least near roadway exposures (ref section 3.5.1.3 and Figure 3-34). Equation 3.4 should also distribute the concentration term to both outdoor and indoor microenvironments as a concentration within both the sum of the indoor components and the sum of the outdoor components (into a new summation term) specifically as the concentration in each microenvironment, Ci for both indoor and outdoor. This will also require that the following sections (and any others) be modified to reflect that more-complex exposure: Lines 30-31, page 3-57; lines 7-10, page 3-65 and page 3-74 lines 10-11.

In the Summary and Conclusions, Chapter 3.7.5 Exposure Assessment...: Same comment as above for lines 10-11 on page 3-74 of the Summary. i.e not including in-vehicle and near-road CO exposures could lead to significant errors in exposure estimation and thus in health outcomes.

In the Summary and Conclusions, Chapter 3.7.5 Exposure Assessment...: On page 3-74, lines 2-5 there is a conclusion regarding the importance of commute time on CO exposure – I do think this is important, but I did not see it discussed in the earlier part of the Chapter. Please include a discussion of this topic in the main Chapter (put in Chapter 3.3.5?). In general, this section and the exposure modeling information in general, should be re-evaluated in light of the OAQPS presentation on May 13 and the approach they now propose to use for the REA; there may be portions of Chapter 3 that need strengthening besides just Chapter 3.6.7 as discussed above.

Comments on the COHb versus CO concentration space: Both the discussion of COHb and its response to CO concentrations (Chapter 4.2.3) and the discussions on CO uptake and elimination (e.g. Chapter 4.4.1) could include additional information and data from open-air exposures at higher CO concentrations. For example, there is published data on COHb levels in people exposed to high concentrations of CO (up to maximum 8-hour averages of 20-40 ppm) in an open-air setting at Lake Havasu, AZ; see the CDC MMWR: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5315a3.htm and the Journal of the American Medical Association: http://jama.ama-assn.org/cgi/reprint/291/22/2692.pdf This data could be used to expand to higher CO concentrations the discussion on the relationship of COHb levels to CO concentrations.

Minor edits and typos in the ISA:

- US EPA 2000 references (2) in second paragraph of Chapter 1.2 should be US EPA 1991
- The bullet on line 9-10 of page 1-6 does not really properly describe Annex A. Annex A only contains maps, tables, and charts of CO data
- The yellow colored areas, especially when small, are very hard to see on Figures 3-11, 3-12 and similar figures here and in Annex A.
- Shouldn't the word maximum be added to line3 page 3-44, so that it would read "...an outdoor worker's maximum exposure over the course of the day..."?
- Change more to the most on line 4 page 3-46 (or add what it is more than).
- I suggest the word "only" be added in front of the 12% on line 11 of page 3-61.
- Shouldn't the date in line 32 of page 3-68 be 1997, and the following review start with what has been published since 1997, since the 2000 AQCD did not have literature on exposure modeling past 1997?
- Add the complete reference for Flachsbart, line 35 of page 3-69.
- The sentence that starts "Given reductions...." on line 11 of page 3-70 does not make sense to me.
- I suggest the word compared instead of "judged" in line 1 of page 3-73.
- The text on line 15 of page 3-73 should read "...Figures 3-14 and 3-16)".
- Add " ...Policy-relevant Background (PRB)." to line 25 of page 3-73.

Selected, easy for me to find, references for spatial mapping (see above discussion for Chapter 3.6.7):

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. Beate Ritz
May 2009
Charge to the CASAC CO Panel

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.

The wording in this chapter could be improved and is not always consistent with the latest definitions and uses of terminology in epidemiology; for example instead of 'effect modification' it should read 'effect measure modification', also instead of 'health effects' one might consider using 'adverse health outcomes' or 'changes in (lung) function' etc.; 'effect' seems to imply an etiologic factor that is not mentioned but has an effect on health. Also, the authors of this chapter move back and forth between the concepts of confounding and effect measure modification as if both are of concern for study validity. Yet effect measure modification is not a concern when assessing bias and these concepts should not be mixed. The way these concepts are referred to now in the text suggests a lack of appreciation for the differences in these two concepts; this might be due to the fact that similar statistical methods (stratification) are used to assess these two different concepts in data. In short, effect measure modification should not be subsumed under or confused with bias assessment in observational studies.

The criteria for causal determination detailed in table 1-2 are very similar to those used by the IOM and the International Agencies for Research on Cancer, however one important difference is that these agencies convene expert committees to review the literature in depth and to apply these criteria in order to arrive at conclusions about causality; they do NOT ask staff to perform this task for the agencies with external reviewers simply commenting. Thus, these qualitative criteria are applied to the scientific literature in face-to face meetings that include different groups of experts, all of whom have reviewed the literature in their fields in great detail and thus are fully aware of the strengths and weaknesses of the studies included and weighted in the qualitative review. Under these circumstances, these qualitative criteria suffice to guide an expert based judgment including lengthy discussions of the strengths and weaknesses of the evidence at hand. But without a standardized or quantitative review of the literature at hand, these criteria are ambiguous if not outright subjective. When applied in a qualitative literature review all judgment concerning the strengths and weaknesses of studies is left to the author and thus subjective unless quantified or made very explicitly. The overall judgment whether an observational study suffers from any substantial bias or to what degree they suffer from bias remains qualitative and subject to the author's judgment and should be made open for challenge by other experts who reviewed the literature according to the same criteria. While qualitative reviews have been widely used in the past and may be appropriate when there are less than 5 studies published in a subject area they leave much room for a subjective and biased reading, reporting, and interpretation of the literature. Since the epidemiologic literature on criteria air pollution health effects has multiplied greatly in the past decade –as can be seen in Chapter 5 - and in many areas there are now more than 5 studies available, it would be much more appropriate to apply standardized and transparent rules for data abstraction and to derive quantitative effect estimates based on meta-analytic procedures before drawing inferences about the scientific literature. More important than even deriving a singular effect estimate is that a systematic and quantitative procedure requires making the authors' assumptions explicit rather than allowing authors to emphasize studies they agree or disagree with.

Page 1-8 " The most compelling evidence of a causal relationship between pollutant and exposure and human health effect comes from human clinical studies" – meaning experimental chambers studies – this statement needs to be qualified since chamber or other experimental studies in humans are impossible to conduct for the assessment of long-term exposures and chronic health outcomes of interest since these types of experiments per se can only be applied in a context of short term changes in air pollution and physiologic biomarkers that do not results in continued harm to a subject, i.e. such experiments can only be set up for certain outcomes or exposures. Hence, observational studies are imperative and likely present the only data available for a number of health outcomes and exposure scenarios. This should be acknowledged and seems to be neglected in this description. These clinical and chamber studies do not provide the type of evidence that is 'most important' for human health risk assessment but rather the type of evidence that can be obtain within the ethical constraints of human experimentation. Also on page 1-10, not only do epidemiologic studies provide exposures in 'natural settings' but rather they are often the only form of data available for certain outcomes and exposures, i.e. in instances for which chambers studies are impossible to conduct (such as predicting mortality and adverse birth outcomes). This general attitude of overvaluing short-term experimental human studies seems to be carried through in this report and for the health risk assessment proposal that proposes to only consider modeling based on short term changes in cardiac outcomes from chamber studies extrapolated to cardiovascular morbidity (on page 11 of the Scope and Method Plan for Health Risk and Exposure Assessment "Potential health benchmark values to be used in the planned risk characterization linked to the exposure/dose analyses will be derived solely based on the controlled human exposures literature"). At this point I am wondering why the epidemiologic literature is reviewed at all if it has no bearing on these estimates.

2. Chapter 2 presents the integrative summary and conclusions from the health effects evidence, with the evidence characterized in detail in subsequent chapters. What are the views of the Panel on the effectiveness of the integration of atmospheric science, exposure assessment, dosimetry, pharmacokinetics, and health effects evidence in the CO ISA?

The same critique mentioned above applies to these summaries that ignore the epidemiologic evidence in favor of human controlled exposure studies for cardiovascular morbidity. The summaries by outcome category should be more explicit in stating what type of data the causality determinations are based on, such as 'one chamber study plus x number of epidemiologic study in which the following biases were or were not present etc etc…"

3. To what extent are the atmospheric science and air quality analyses presented in Chapter 3 clearly conveyed and appropriately characterized? Is the information provided regarding CO source characteristics, CO chemistry, policy-relevant background CO, and spatial and temporal patterns of CO concentrations accurate and relevant to the review of the CO NAAQS?

4. How well do the choice and emphasis of exposure topics presented in Chapter 3 provide useful context for the evaluation of human health effects in the ISA? Is the discussion and evaluation of evidence regarding human exposure to ambient CO and sources of variability and error in CO exposure assessment presented clearly, succinctly, and accurately? The ISA concludes in section 3.7 that central-site monitor concentration is generally a good indicator for the ambient component of personal CO exposure. What are the views of the Panel on this conclusion and its supporting evidence?

5. The dosimetry and pharmacokinetics of CO are discussed in Chapter 4. Please comment on the presentation in the ISA of the current state of knowledge on the Coburn-Foster-Kane (CFK) model and model enhancements. Has the expected contribution of different exposure durations (1-24 h) to COHb levels been clearly and accurately conveyed?

6. The mode of action section in Chapter 5 presents information on both hypoxic and non-hypoxic mechanisms for CO health effects, with particular emphasis on recent studies evaluating the non-hypoxic effects at low to moderate CO levels. Please comment on the appropriateness of the focus, structure and level of detail in this discussion. For example, is the evidence relating to the interaction between inhaled CO and endogenous CO properly characterized?

While this is an important discussion it seems irrelevant as long as the health risk assessment does not take any of the non-hypoxic mechanisms for CO health outcomes into consideration.

7. 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?

Throughout Chapter 5, epidemiologic studies receive very different levels of attention and review; the level of detail in the text seems to be depending on how many studies were published for each outcome category, e.g. if there were 20 studies addressing a health outcome each studies is described in a cursory manner with a sentence or two, while for a health outcome for which only 2 studies have been published, these few studies are described and evaluated in much more detail. The brief mention of studies leaves a lot of questions open concerning the validity and methods used in the 20 studies i.e. for the reader it is impossible to assess from the qualitative review text presented whether or not or to what degree these studies may be biased or the study design may have been adequate in addressing the question at hand; i.e. the brief and almost cursory mention of each study in the text does not allow the reader to inspect the actual data and evaluate the results in the same manner as possible for the much better described fewer studies. Also, since it is much more likely that 20 studies are heterogeneous with respect to their results as well as method than the two studies, having more data available may end up being worse then having less since there in this report there is also an emphasis on mentioning inconsistencies such that data richer areas are receiving more scrutiny that data poorer areas when in fact the opposite would make more sense, i.e. homogeneity of results for only 2 studies might be much less meaningful and informative than heterogeneity across 20 reports. While I find the tables and figures helpful and they should provide the necessary detail on all studies reviewed, they lack some key information in each chapter, e.g. there is no mention of the type of study design employed for studies of heart rate variability and study results are neither presented in tabulated format or in a figure (why the only figure presented is for IHD hospitalizations is not clear). Also it seems strange that a study with a total subject N of 6 in table 5.4 is given as much attention as one with an N of 6784 without further qualifications, e.g. in table 5.4 studies that employed ambient exposure assessment and those using personal exposure assessment could have been grouped together to emphasize these important differences in exposure assessment. Furthermore, many of the tables report mean CO levels and mention 24 hrs or 8 hrs in brackets, however this misleading at least in those studies I know well i.e. pregnancy outcome studies in which the averages are trimester, weekly, or monthly averages of 24 hour measurement rather than 24 hour averages in lagged time series models (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. Also it is surprising to see the Ritz et al 2007 study listed in table 5-12 but no results for this study presented in figure 5-6 - possibly because this paper only presented estimates per quartile of CO increase rather than per 1ppm increases in CO; however, rescaling quartiles to a continuous estimates is a possibility that should be considered rather than leaving results from important papers out of a figure that gives an overview over all study results). According to the text, the estimated increase in CO presented in the figures 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, thus at least indicating which study used which scale might be informative. Also, since many of the cardiovascular studies investigated more than one outcome, it seems like the studies themselves could be tabulated first in much more detail that includes information about exposure assessment and biases; then in outcome specific sections it would suffice to only mention the specific results; as done now the studies are being mentioned in each subchapter by outcome as if these were stand alone documents and nowhere is this kind of information presented.

a. For cardiovascular outcomes, controlled human exposure studies discussed in Chapter 5 and in previous assessments have identified cardiovascular effects in diseased individuals following exposures near the level of the current standards, while new epidemiologic studies provide evidence of cardiovascular effects at ambient concentrations. What are the opinions of the Panel on the treatment of factors influencing the interpretation of this evidence, such as the plausibility of cardiovascular effects occurring at ambient levels, the additive effect of ambient CO to baseline COHb resulting from endogenous and non-ambient CO, and the challenge of distinguishing effects of CO within a multipollutant mixture (e.g., motor vehicle emissions) in interpreting epidemiologic study results?

All of these issues could be nicely addressed in a quantitative framework of a meta-analysis that follows a standardized protocol, why this has not been done is unclear. Also, the plausibility of cardiovascular effects occurring at ambient levels cannot be assessed without doing an in-depth review and assessment of all epidemiologic studies based on a thorough reading of this literature by experts in the field in lieu of a formal meta-analysis. Again from the present text, assessing and judging this is not possible since information on study design, exposure assessment and possible biases is not always presented in a enough detail and a standardized manner to allow a reader of these summaries alone to come to any conclusion, I and others on this panel would need to go back to all of the original literature to form an informed opinion.

b. Please comment on the implementation, in Chapter 5, of the causal framework presented in Chapter 1. Does the integration of health evidence focus on the most policy-relevant studies and health findings?

See my comments above

8. What are the views of the Panel on the discussion of factors affecting susceptibility and vulnerability in Section 5.7?

The factors mentioned are adequately and discussed well; however, it is unclear how they will be playing any role in the health risk assessment since epidemiologic results overall do not seem to be informing much if any of the planned calculations.

Dr. Arthur Penn
Initial response to CASAC CO ISA scope/methods 5-4-09

General Comments
Chapter 1 of the ISA provides a worthwhile Introduction, especially regarding the distinctions between causation and association. The conclusions summarized in Chapter 2 ("Sufficient to conclude…Suggestive… Inadequate…") based on studies especially those related to cardiovascular diseases (CVD) described in Chapter 5, may need to be re-evaluated. Chapters 3 & 4 appear to be the strongest chapterseven though they each raise some questions.

Surprisingly, the data summarized in Chapter 5 of the ISA '09 CO draft do not provide strong support for the contention that spikes in levels of ambient COresult in exacerbation of a variety of health outcomes. This is true forcardiovascular diseases (CVD) despite the "sufficient to conclude" label in Chapter 2, and for respiratory diseases and pre- &peri-natal outcomes, despite the "suggestive of a causal relationship" labels in Chapter 2. Issues include statistical significance vs. "real-life" health concerns (alluded to in Chapter 1); very limited changes in outcome for large population groups in response to spikes in ambient CO levels; no apparent correlation between responses to very high levels of CO in controlled studies with volunteers vs. responses to transient changes in ambient CO levels (i.e., the assumption that we can extrapolate from responses to very high levels of CO back to responses at ambient levels needs to be supported);difficulties in distinguishing between CO and co-pollutant effects; insufficient justification for proposed studies on risk characterization and population exposure/dose analysis; and finally—an issue barely noted in the ISA—the growing evidence that CO at levels that are orders of magnitude higherthan ambient levels may have important therapeutic value for certain serious medical conditions.

Specific Comments (regarding Chapters 2 & 5)

1) There is an unstated (and unsupported)assumption in the ISA that every reported statistically significant change represents a major change in (clinical, health-related) outcome. Summary data are often presented in the ISA as percentage change or as increases in relative risk (RR) or in odds ratio (OR), without any consideration of the actual magnitude of change in the units being measured. When the actual numbers are calculated from the original sources, the results are often underwhelming; e.g., is there any clinical relevanceto a (statistically significant) increase of 1heart beat/min in response to an increase in ambient [CO]??

NB: see additional comments on PTB, LBW &IUGR below.

2)For CVD, the largest data sets available for analysis are from studies of outcomes (e.g., CHD, MI, angina, CHF) "associated" with ambient CO levels that exceed the 1-hr or 8-hr limits by 0.5-1.0ppm. In most cases the relationship between spikes in ambient CO and CVD outcomes can be generously described as very weak associations. It is insufficient to conclude that a "relationship is likely to exist". In the section on increased admissions

for IHD (pp. 5-24 &-25), data from ~ 55,000 patients collected over 7 years from multiple hospitals in So. Calif. reveal that for a 0.75 ppm increase in 8-hr max CO levels, there are a total of 4 extra admissions/wk (!) across the entire So. Calif. region for people with IHD,but only if theyalso had a diagnosis of CHF.For IHD patients without CHF, there were only 2 extra admissions/wk. In Montreal, a 14% increase in daily ED visits for IHD works out to only 3 extra visits/wk. In the Atlanta study of >4.4 million people over 7 years, the effect of a 1ppm increase in 1-hr max [CO] was a 1.6% increase in RR over baseline #of CVD-related visits/day. This works out to 4 extra CVD-related visits/wk in the greater Atlanta area, above the baseline of 260 CVD visits/wk. The ISA reports that this is of "borderline significance" (statistical). It's likely to be of even less clinical significance. (If the data on CVD-related visits/wk were reassessed, would those weeks corresponding to spikes in ambient CO always have higher #s of visits than weeks where there were no spikes in ambient CO?)

For MIs, the effect of elevated ambient CO was minimal or non-existent in the 3 studies summarized.

3 & 4) Thefocus of the Health Assessment Plan on investigating decreased time to onset of angina is not justified clearly. The only large population study reported to date, from Tehran for a 0.5 ppm [CO] increase over 24 hr., resulted in an increased OR for admission of 1.005 (i.e., ½ of 1% increased OR).

On the other hand, controlled studies on human volunteers reveal clear effects on specific health outcomes; however, these require volunteers to be exposed to CO levels orders of magnitude higher than ambient CO levels.The results of Allred et al, (NEJM, 321: 1426-32,1989) on the effects of CO exposure on men with angina who are exercising are instructive. Allred et al demonstrated a dose-response for increasing doses of CO and a) time to onset of angina and b) ST wave depression, The time to angina onset dropped 19 sec. from 8 min. 21 sec. (room air, 0.6% COHb) to 8 min. 2 sec. (117 ppm CO for 1 hr, 2% COHb),and then another 17 sec. to 7 min. 45 sec.,as the [CO] doubled (253 ppm CO for 1 hr, 4% COHb). The results from these exposures to high levels of CO, relative to ambient CO levels are clear. No reasonable prediction can be made regarding how male angina sufferers who are exercising would respond to spikes in ambient CO levels.

Further, the ISA (p. 2-22) notes thatnationwide between 2005-07 there were <10 days on which the max. 8-hr CO level was exceeded and only one day when the 1-hr max level was exceeded..Even at these rare high CO levels, COHb levels will likely be << 1%. Q. What vital new information can we expect to gain by repeating this study at 2% COHb and then adding tests at 2.5% and 3% COHb?It is not clear how either the Allred study or the proposed study relates to expected responses arising from spikes in ambient CO.

The Kiazevich results (2000) summarized on p. 5-47, yielded CO-related results in healthy exercising adults, but to get these results, volunteers were exposed to 1000 or 3000 ppm (!!)CO for 4-6 min. and then to maintenance levels of 27-100 ppm CO→COHb levels of 5-20%. Again, it is not apparent that there is any predictive value that these results might have for exposures to spikes of CO above ambient levels.

The summary of CO effects on all CVD outcomes (pp. 5-37 thru 5-44) is not compelling. The most pronounced effects in the graph on p. 43 are all from 1 study in Seoul, Korea. All the other studies report < 10% effect, regardless of outcome. When combined with co-pollutants, CO effects often disappear.

NB: The correlations between elevated ambient CO levels and hospital admissions for stroke (pp. 5-30 to 5-32) are stronger than for any CVD outcome group. Controlled elevated CO studies of animal models for stroke or TIAsmight be more informative regarding a possible outcome than the proposed human volunteer angina studies.

The data on PTB, LBW and IUGR (pp. 5-57 to 5-70) also emphasize statistical significance rather than actual magnitude of change. The Australia data (p. 5-65) report a 21.7 gm drop in body wt. for a 0.75 ppm increase in ambient CO levels for 8-hr exposures. This drop =3/4 oz. of total birth wt. vs. that for control neonates. In Fig. 5-7, 16/19 studies showed a neonatal wt. changeof <10 gm (up or down) for increases of 0.5 ppmin ambient CO. This is<1/3 oz./neonate.Are these decreases associated with a corresponding poor prognosis for neonatal birth outcomes? for long-term health effects?

The effects of ambient CO elevations on respiratory responses(asthma, COPD, rhinitis) in M & F, children/adults, US & abroad (pp. 5-95→ 5-114) are slight, when they are found, and often cannot be distinguished from co-pollutant responses.

The suitability of CO as a surrogate for other classes of airborne pollutants is questionable. The association of NOx, SO_2, O_3 and PM with various health effects seems to be stronger than for CO. The studies in Chapter 5 indicate that marginal CO effects are often lost when CO is present with other pollutants. The likelihood of a quantitative risk assessment for CO at ambient levels seems low.

The points raised in section 5.7 regarding vulnerability and susceptibility are important and informative. It is however, not clear how controlled studies at very high CO levels with human volunteers relate to susceptibility/vulnerability issues.

There is an apparent ambivalence in the ISA regarding how different levels of CO are classified. For much of the document, especially relating to human studies, the focus is on ambient CO levels, These levels are low, often <1ppm. On the other hand, for toxicology studies, CO levels of up to 750 ppm (!!) are described in the ISA as being low (p. 5-55),Because animals can withstand these levels, just as human volunteers can tolerate 3000 ppm, doesn't mean those levels are "low".

Review of CO ISA

Dr. Armistead (Ted) Russell

In general, this first draft of the ISA suggests that the final ISA will provide the scientific foundation for EPA staff and CASAC to make recommendations on possible changes to the CO NAAQS. However, there are areas that need to be strengthened. In particular, I do not believe that the issue of confounding has been adequately dealt with in regards to interpreting the epidemiologic results, and I am not sure it can be at this time. Given the source of CO, it will be found concurrently with other automotive pollutants, and the ISA needs to spend much more effort identifying what species are in the mix of automotive pollutants, the suspected health effects of these other compounds, and what that means in terms of identifying the impact of CO on health. There really is little way around the presence of all of these other compounds (both measured and unmeasured), and the typical epi study has not controlled for the mix of other automobile-generated pollutants. Thus, strong clinical results are needed, and as pointed out in the ISA, such studies have been lacking in recent years.

Also, I trust that a summary chapter is coming, and that each chapter will have a brief section highlighting the most important conclusions that are relevant to assessing whether we need to change the NAAQS, and if so, what the level, form, etc. of the new standard should be.

Chapter 2:

As noted above, Chapter 2 should deal more directly with confounding by other automobile-generated pollutants and how that impacts the identification of CO-specific health effects at atmospherically-relevant (i.e., US current) concentrations. Also, should smokers be identified as a potentially susceptible/vulnerable population?

Chapter 3: Source-to-Exposure

Again, I like this framework for such a chapter. It tends to reduce the amount of unneeded information (though I am not sure why we need to know that the C atom is covalently bonded to the O atom and that it has a mass of 28.0101: remember the intended use of this document).

I like the CO emissions section showing the current emission sources and trends. I think that it would also be useful to include a forecast of 2020 emissions given the current regulations. The section on physics and chemistry is reasonable, though a bit bleak. By that I mean that we may not know the detailed gas phase kinetics of many compounds, but we also know a good deal about most of the more important species, and even without the details, we have a reasonable understanding vis-à-vis how much CO is produced. I would provide increased focus on CO production from biogenics and compare that to anthropogenic emissions. At the bottom of page 3-9, the ISA correctly identifies CO as a compound that reacts with OH. However, the reaction produces HO2,

so it is not a loss of odd hydrogen/odd oxygen/radicals, so the role in this case is mixed. It can add to ozone formation, and thus increase OH.

The section on instrumentation should provide a better idea of what instrument capabilities are out there, not just what is required. Is the typical network monitor really only good to 1.0 ppm?

The section on associations with co-pollutants really, really needs to deal with associations with other automobile-derived pollutants, including EC, OC, benzene, 1,3 butadiene, formaldehyde, Cu, and other both exhaust and non-exhaust emissions. It is true such information is not as abundant as for the traditional pollutants, but it is of much more relevance. You have results for Atlanta, but you should search for more.

The section on PRB is in need of some rethinking. The statement is made that "PRB concentrations can best be determined from the extensive and long-running network of …" This statement needs to be supported by some stronger reasoning. In particular, why would one use monitored values to find the PRB for CO, but use modeling for find the PRB for ozone? I could readily see using CMAQ to find the PRB for CO, and this would capture the CO formation from biogenic emissions. Given the other ways one can calculate PRB concentrations, this section needs to be very careful about what is said and to support the statements made.

Something missing from this chapter is a thorough description of APEX and results from prior applications, particularly to CO. While there is a brief section on exposure modeling, it is not up to fully supporting the future use of APEX in the REA. The consistent reliance on APEX for conducting NAAQS-related exposure analysis should lead EPA to doing a more thorough assessment of APEX across pollutants.

Minor:

3-13 l 14: Sentence beginning "As concerns…" is awkward.
Figs. 3-7,8,9: The way monitors are shown is sub-optimal.
Tables 3-3-6: Can you add Ogden?
Page 3-24: Explain why Ogden had such an incredibly high 1-hr CO.
Table 3-7,8: Please explain further.
Figure 3-16: Why is the third quarter of monitor A so high, first quarter so low? Mointor A appears to behave very differently than the others.
Figure 3-24: "… highest DAILY 8-hour…"
Page 3-52: "1 part per billion" (no s)
Page 3-63. To me, Figure 3-32 does not look logarithmic, and physically, that is not the functional form expected.
Page 3-64, line 18… Isn't this getting in to dose?
3-64: Last paragraph. This paragraph is unclear.

At the end of the day, you are going to need to re-assure the various parties that there is a reasonable chance that the health effects being seen are due to CO, not the other associated pollutants. This requires a good deal more attention being paid to how well you deal with the co-pollutant issues, including source characterization, atmospheric dynamics and concentrations (particularly spatial and temporal associations), and epidemiologic study results where they have adequately considered automobile-derived pollutants. Controlling for PM2.5/10, and SO2 is almost meaningless in this context. My read of the health chapters suggests that when considering automobile derived pollutants (e.g., NO2 and BS/EC), the effects typically were significantly reduced and became insignificantly different from zero in many cases. These studies did not control for other automobile-derived pollutants that are of increasing concern (e.g., metals, resuspended road dust). I think it would be good to have a very extensive assessment of the issues associated with the concurrent exposure to the variety of automobile-derived pollutants, and how such should be considered in the context of interpreting the epidemiologic analyses.

Responses to Charge Questions:

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.

2. Chapter 2 presents the integrative summary and conclusions from the health effects evidence, with the evidence characterized in detail in subsequent chapters. What are the views of the Panel on the effectiveness of the integration of atmospheric science, exposure assessment, dosimetry, pharmacokinetics, and health effects evidence in the CO ISA?

As noted above, I do not believe that Chapter 2 (or any of the chapters) delves as deeply in to the issue of co-pollutants as is necessary for the issue at hand. This issue needs its own section in Chapter 2 with the take-home message very clearly spelled out and supported.

3. To what extent are the atmospheric science and air quality analyses presented in Chapter 3 clearly conveyed and appropriately characterized? Is the information provided regarding CO source characteristics, CO chemistry, policy-relevant background CO, and spatial and temporal patterns of CO concentrations accurate and relevant to the review of the CO NAAQS?

As discussed above, Chapter 3 does a reasonable job, with a few shortcomings. CO formation from isoprene could be brought out a bit more, and the PRB discussion needs to be better supported, particularly since other ISA's come to an opposite conclusion regarding the use of models versus observations.

4. How well do the choice and emphasis of exposure topics presented in Chapter 3 provide useful context for the evaluation of human health effects in the ISA? Is the discussion and evaluation of evidence regarding human exposure to ambient CO and sources of variability and error in CO exposure assessment presented clearly, succinctly, and accurately? The ISA concludes in section 3.7 that central-site monitor concentration is generally a good indicator for the ambient component of personal CO exposure. What are the views of the Panel on this conclusion and its supporting evidence?

A shortcoming here is the rather short discussion about exposure modeling. Exposure modeling will be a main focus of the REA, and as such, this section needs to be made to fully support that future effort, with particular emphasis on model evaluation. Also, as mentioned above, the discussion of co-exposure to other automobile-derived pollutants, including non-exhaust components, needs to be fortified.

5. The dosimetry and pharmacokinetics of CO are discussed in Chapter 4. Please comment on the presentation in the ISA of the current state of knowledge on the Coburn-Foster-Kane (CFK) model and model enhancements. Has the expected contribution of different exposure durations (1-24 h) to COHb levels been clearly and accurately conveyed?

6. The mode of action section in Chapter 5 presents information on both hypoxic and non-hypoxic mechanisms for CO health effects, with particular emphasis on recent studies evaluating the non-hypoxic effects at low to moderate CO levels. Please comment on the appropriateness of the focus, structure and level of detail in this discussion. For example, is the evidence relating to the interaction between inhaled CO and endogenous CO properly characterized?

7. 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?

    a. For cardiovascular outcomes, controlled human exposure studies discussed in Chapter 5 and in previous assessments have identified cardiovascular effects in diseased individuals following exposures near the level of the current standards, while new epidemiologic studies provide evidence of cardiovascular effects at ambient concentrations. What are the

opinions of the Panel on the treatment of factors influencing the interpretation of this evidence, such as the plausibility of cardiovascular effects occurring at ambient levels, the additive effect of ambient CO to baseline COHb resulting from endogenous and non-ambient CO, and the challenge of distinguishing effects of CO within a multipollutant mixture (e.g., motor vehicle emissions) in interpreting epidemiologic study results?

b. Please comment on the implementation, in Chapter 5, of the causal framework presented in Chapter 1. Does the integration of health evidence focus on the most policy-relevant studies and health findings?

8. What are the views of the Panel on the discussion of factors affecting susceptibility and vulnerability in Section 5.7?

Critique of Draft CO ISO
Dr. Laurence Fechter

Charge question 7: Is the discussion in chapter 5 scientifically sound?

I have focused on the issues of CO's effects on the CNS and on the developing subject as these are my primary areas of expertise.

Section 5.3 CNS effects
A general comment on this section is that the use of topic sentences to provide some orientation to the reader would be welcome. Many subsections consist of descriptions of multiple studies of CO exposures at various levels and various durations. Having a topic sentence suggesting a range of values that yield consistent outcomes would call attention to the most relevant studies. For example, section 5.4.2.1 would benefit from a topic sentence indicating a range of CO values associated with decreased birth weight.

The epidemiological study results present data on relative risk and confidence intervals. Many of the relative risk values, are quite modest. How much faith can we put in a RR of 1.02? Some guidance is important for interpreting the data. Moreover, there seems to be some inconsistency between the size of the OR for CO exposure's effects on birth weight vs. congenital anomalies and the interpretation (i.e. larger OR for congenital anomalies yet a statement that there is little evidence for increased risk).

Section 5.4.1.2. Birth weight, etc.

The data presented in this section are not especially consistent. It might be appropriate to add a sentence or 2 identifying the far clearer effects of maternal tobacco smoking on birth weight (even though MTS is a very complex exposure) as a relatively clear outcome and a possible rationale for *looking for* a relationship between CO exposure per se and reduced birth weight, prematurity etc.

Section 5.4.2.1

See comment above about use of topic sentence

Line 22 Fechter and Annau found a 5 % decrease in birth weight in rats. As written it suggests that either CO levels or HbCO levels were 5%.

P 5-76 line 16-17 mistakenly states that Fechter and Annau (1977) did NOT find a significant birth weight effect after prenatal CO. This statement is also inconsistent with statement on previous page.

p 5-77 line 26 correct to read " given various protein diets…."
P 5-78 spelling of toxicity line 15

5-80 Placenta section….define high altitude; should this not state "chronic *potential* hypoxia exposure"?

P 16 that same section. How relevant is the dose used to inhalation exposure studies?

Section 5.4.2.2 it appears that 75 ppm is commonly a NOAEL whereas 150ppm is a LOAEL. Could this be stated directly or else suggested in an effort to facilitate the reader's task of assessing this section?

page 5.860- line 14 guinea pigs are suggested as a good model for human CNS development. This may require some added qualification as the newborn guinea pig is in many respects far more mature than the human at birth.

p. 5-87 I'm not certain that the term "demasculination" is the most useful in understanding a shift in DA release after amphetamine.(Is demasculination a word?)

P 5-88 a comment on the permanence v. transient effects observed under neonatal hyperthermia effects on neurotransmitters would be helpful

p 5-88-5-91

An important sub-section entitled "The Developing Auditory System" delineates the results of a series of reports published by researchers at UCLA in which the effects of *postnatal* CO exposure are assessed in rats maintained in an artificial rearing system. These studies are important to describe accurately because the CO levels selected for use include the lowest levels employed in studies designed to evaluate nervous system development (12, 25, 50 and 100 ppm). Moreover, the exposure levels selected do have some relevance to ambient CO concentrations. Also presented in this sub-section is the result of a human study in which auditory function was assessed in neonates who were offspring of non-smokers, and heavy, medium, and light smokers. The conclusion of this section, in my judgment over-interprets the data as supportive of an adverse effect of CO exposure at very low exposure levels on the developing auditory system. Moreover, one must be somewhat circumspect about the laboratory animal data presented because the nature of the artificial rearing system a rather invasive procedure. It is possible that the developing auditory system is especially vulnerable to CO exposure. However, there is clear evidence from adult rats showing that CO by itself can produce transient functional impairment of the peripheral auditory system only when near life-threatening CO concentrations are employed.

The laboratory studies described (Webber et al., 2003 ….date missing from ref on p 5-88 line 26….. Webber et al., 2005….date missing from ref on p. 5-90 line 26….Lopez et al., 2003, and Stockard-Sullivan et al., 2003) consist of a set of studies in which neonatal rats are exposed to low levels of CO while maintained in an artificial rearing system in which rat pups are fed through a gastronomy tube and maintained effectively in floating cups placed in a water bath. Notably, brain weight is reduced for both the artificially reared and artificially-reared carbon monoxide exposed neonates compared to the maternally

reared non-CO exposed control subject (Stockard-Sullivan et al., 2003). Most of the studies describe immunohistological changes or qualitative histological observations in either the cochlea or the inferior colliculus of artificially reared CO exposed rats. Whether the changes noted have functional consequences is uncertain. In only one manuscript by this group (Stockard-Sullivan et al., 2003) were functional measures taken from the auditory system and these studies are quite limited (e.g. measurement of DPOAE generation as a measure of cochlear function performed over a very narrow range of frequencies that is rather low compared to the normal rat audiogram).

The second full paragraph on p 5-89 describes the outcome of the Korres et al (2007) paper and briefly describes two non-invasive measures of auditory function. Notably, the otoacoustic emission (OAE) is described as an "echo" recorded by a microphone placed in the external ear canal. Actually, what is measured is an active tone that is produced by the cochlea and *not* a passive echo. Indeed, the distortion product otoacoustic emission is remarkable because it occurs with totally different frequency characteristics than do the two primary tones that are delivered to the ear. The description of the Korres paper, however, requires a bit more explanation. Specifically, it needs to be pointed out that neonates were grouped by mother's smoking history (none, low level, moderate, and high level). The transient ototacoustic emission was indeed significantly lower among the offspring of smokers than non-smoking mothers only at the highest test frequency used (4 kHz). This might be meaningful because high frequency hearing might be predicted to be more vulnerable to hypoxia. However, there was no evidence of a relationship between level of maternal smoking and the reduction in the otoacoustic emission recorded. Thus, this study cannot be considered to be definitive for a link between tobacco smoke exposure and impaired auditory system development.

Charge question 8. factors affecting susceptibility and vulnerability in section 5.7

While relevant *potential* susceptible populations are identified, clear conclusions (even those stating that the current literature does not fully inform on the question of susceptibility) are not always present. While susceptibility factors are identified, there is no overt attempt made to address the likelihood that these factors would most likely be of differing seriousness. For example, males and females may well differ in terms of intrinsic production of COHb, but there might be other factors such as occupation that predispose one sex to higher CO exposure. Moreover, there may well be other factors that predispose males to cardiovascular disease rendering them more sensitive to CO. My point is that the gender issue is multifactorial and the discussion presented does little to inform on the risk that being male per se plays in vulnerability.

- The discussion of cardiovascular disease as a risk factor is generally appropriate.
- Under obstructive lung disease, I am a bit troubled by the comment that smokers who already have a high COHb level may have little reserve for further increases in COHb resulting from ambient sources. It may be more accurate to focus on the potential for ambient CO exposure to reduce the rate of elimination of CO resulting from smoking. Finally, the issue of establishing permissible exposure

levels for ambient CO in a subpopulation that self-exposes to far higher CO levels needs to be recognized.