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Laurence Fechter 04/30/09
Critique of Draft CO ISO

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.

Stephen R. Thom Comments 05/04/09

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. Milan Hazucha 05/04/09

(May 12-13, 2009).<u>Comments on the Review of the ISA for Carbon Monoxide (Chapter 4) and Carbon Monoxide NAAQS: Scope and Methods Plan for Health Risk and Exposure Assessment (Chapter 2).</u>

Chapter 2: Health Effects and Approach to Risk Characterization

This chapter outlines carefully prepared and reasoned approach to Health Effects and Risk Characterization. The supporting evidence will be based on controlled human exposure studies (unfortunately almost all of them decades old), epidemiologic, and toxicologic (??) studies. What toxicologic studies are to be integrated? Should they be even considered?

The outlined plan for "integrative synthesis" seems to depend heavily on 1991 and 2000 ACQD evidence and conclusions (p. 8). As for the integration of new epidemiologic studies published since 2000 the Staff paper acknowledges that "it is difficult to determine from this groups of studies the extent to which CO is independently associated with cardiovascular disease outcomes or if CO is a marker for the effects of another traffic-related pollutant or mix of pollutants" and that "this complicates the effort to disentangle specific CO-related health effects". Indeed, these concerns raise the key questions that have to be specifically answered before any recommendations and conclusions can be made (see Fig. 5-5, page 5-43 ISA 2009). The Staff nevertheless concludes that a robust CO association in co-pollutant models and the endpoint coherency with evidence from human studies *"support a direct effect of short-term CO exposure on cardiovascular morbidity at ambient concentrations below the current NAAQS level."* However, the robust association with co-pollutants and the coherence with experimental evidence do not necessarily provide supporting evidence for the above statement particularly when the target physiologic and clinical endpoints for CO and co-pollutant are the same. Therefore, it is important that both the old and the new studies are critically re-evaluated before any conclusions are reached.

The Risk Characterization section (2.2) appropriately suggests more cautious approach in studies interpretation and notes that currently we do not have enough data to "conduct a quantitative risk assessment for this health endpoint", i.e., the quantitative dose-response relationship. Therefore, the risk characterization will be based solely on the controlled human exposure literature with the proposed benchmark COHb levels at 2.0, 2.5 and 3.0%. However, the conditions under which these levels will be reached are not given (at rest, exercise, static CO levels, etc. ?). As subsequently stated the calculation of dose will be based on the "well-established" CFK equation from 1965. A consideration should be given to the enhanced CFK models, like the one published by Smith et al., 1994 which takes into account additional physiologic factors and estimates more accurately venous COHb. Some multicompartment models that claim to be even more precise particularly under dynamic conditions of exposure should be considered as well.

The Staff has appropriately expressed a number of concerns regarding Risk Characterization for cardiovascular effects in epidemiologic studies. As suggested the issues of concern need to be discussed a depth at this or subsequent meetings.

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 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 vs. predicted COHb under the same profile employing "the most accurate" CFK, mathematical, and multicompartment model. <u>Section (4.2.3) discusses CFKE</u> application under varying CO concentration and exposure duration for a "healthy human at rest" (more detailed definition is required). The interaction is illustrated in Figure 4-3 (note that at 24 hrs COHb equilibrium will be reached at any CO concentration). Although accurately conveyed, the question that still remains to be answered is:" Is the selected CFK model the best all-around model for dose estimation?" The comparative evaluation of various models under a dynamic CO exposure conditions as suggested earlier will answer the question.

The cited endogenous productions of 0.39% COHb by QCP model (4.2.3) was measured under baseline conditions and is an underestimate of production at rest. The production goes up during oxidative stress, inflammation, pregnancy, in people with metabolic syndrome and various diseases, conditions that apply to a majority of population. The baseline COHb values (endogenous production and 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.

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 most active part of the brain and the heart. 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 situations when individuals will be transiently exposed to high CO. The issue of peak CO concentrations and resulting arterial COHb levels s should be addressed in the 4.2.3 section as well.

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 findings 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. Particularly the statement on line 23-24 is incorrect since according to tables 4-1a and 4-1b the distribution 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 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.

True we do not know precisely what is the range of endogenous COHb level (important in

COHB modeling) in the general population (page 4-19, line 25-26). However, numerous studies suggest the baseline level range is 1-2% COHb. In disease population in can be higher.

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 for COHb estimation is more accurate. It should also include a statement about increased production of endogenous CO in inflammatory and other diseases.

Dr. Arthur Penn 05/04/09

Initial response to CASAC CO ISA scope/methods

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 chapter seven 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 CO result in exacerbation of a variety of health outcomes. This is true for cardiovascular 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 higher than 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 relevance to 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) The focus 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 that nationwide 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 TIAs might 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. change of <10 gm (up or down) for increases of 0.5 ppm in 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".

Russell R. Dickerson 05/05/09

Review of

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

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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.

Comments on the "Plan for Health Risk"

The section on microenvironments in could be more specific on how the modeled concentrations of CO compare to observations. The uncertainty/sensitivity measures (Appendix A) look good, but how accurate are personal monitors and what are their detection limits; are they adequate? At least refer to section 3.6.3.2 of the ISA. Do wood burning stoves of fireplaces (popular around Denver) contribute to personal exposure?

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Beate Ritz 05/06/09
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.

Armistead Russell 05/06/08 - Review of CO ISA

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:

9. 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.

10. 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.

11. 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.

12. 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.

13. 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?

14. 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?

15. 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?

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

Armistead Russell 05/06/08 - Review of EPA CO Scope and Methods

Given that the Scope and Methods (SM) document describes the approach to be taken mainly in general terms, it succeeds in laying out a reasonable plan to achieve the objective of providing a quantitative assessment of exposure to CO using various target levels. The use of Los Angeles and Denver make sense, though Fairbanks or Anchorage would be of interest as well given the extreme conditions found there. The use of APEX makes sense, though this again argues for a more robust evaluation of APEX across pollutants.

A second concern I have is that it is not apparent how the results from LA and Denver will be generalized to a national scale. In the end, I suspect the panel will want to know what the resulting exposures will be at a national level to various level/forms of the standard.

In replying to the given questions:

1. As discussed in the Plan, at this time there does not appear to be sufficient controlled human exposure data to support development of quantitative dose-response relationships for the health effects reported in subjects with angina. Following the same overall approach used in prior CO NAAQS reviews, the planned approach is to characterize risks associated with these effects by estimating exposures and resulting dose (i.e., COHb levels) and estimating the number and frequency of occurrences over several potential health effect benchmark levels for the cardiovascular disease population. The potential health effect benchmark levels are expressed in terms of COHb levels and are based on the evaluation of the controlled human exposure studies in the draft ISA. With regard to this planned approach for risk characterization for cardiovascular related health effects reported in controlled human exposure studies reporting decreased time to onset of angina, what are the Panel members' views on:
    a. The overall planned approach, which is to estimate the number and percent of the population with cardiovascular disease that would exceed potential health effect benchmark levels upon just meeting various CO air quality scenarios;

Answer: This is appropriate if done at the national scale, or a strong linkage can be made to what is found for Denver and LA with the rest of the country.

    b. The range of potential health effect benchmark COHb levels (i.e., 2.0, 2.5, and 3.0 percent COHb) that staff plans to use to characterize these health risks.

2. While the first draft ISA reaches the conclusion that the overall health effects evidence supports the judgment that ambient CO concentrations are likely causal for cardiovascular morbidity as a category, the document recognizes the uncertainties that exist with respect to evaluating studies of the association between emergency room visit and hospital admissions, respectively, for cardiovascular effects and ambient CO concentrations. In particular, the ISA raises the question of whether ambient CO levels are serving as a surrogate for one or more elements of the traffic-related air pollution mix. With regard to the approach for risk characterization, the Plan raises several study-related

issues affecting judgments about whether the evidence is supportive of developing quantitative risk estimates for emergency department visits and hospital admissions for cardiovascular effects related to ambient CO concentrations.

a. What are the Panel members' views on whether the concerns raised about ambient CO levels potentially serving as a surrogate for one or more components of the overall traffic-related air pollutant mixture limit the utility of a quantitative risk assessment for these health endpoints?

Answer: I do view this as a serious limitation, and while the ISA does bring up the co-exposures to other pollutants, I do not view that the ISA has gone as deeply as it should. I think this uncertainty does make a quantitative risk assessment of less value.

b. Given the potential for CO at ambient levels to act as a marker for the effects of another traffic-related pollutant or mix of pollutants, what are the Panel members' views on whether or not the results of co-pollutant models provide sufficient evidence to support a quantitative risk assessment for CO effects at ambient levels?

Answer: I do not see that there are sufficient studies that have investigated the range of co-pollutants to adequately model the impacts of these co-pollutants, and thus, I would be hesitant to conduct a quantitative risk assessment.

<u>Chapter 3 – Scope and Approach for Population Exposure/Dose Analysis</u>

1. We plan to build upon the basic structure and design of the exposure assessment conducted in the previous review. Since that time there have been major improvements in the exposure model and in the data for input to the model. Are the Panel members aware of information sources that would help inform further improvements that would be worth considering in the current review?

Answer: No.

2. One of the main issues in this analysis is how to estimate ambient CO concentrations on and near roadways, which can be significant contributors to ambient CO exposures. The relationship between CO levels measured at ambient fixed site monitors is highly variable due to the spatial and temporal variability of on- and near-roadway CO concentrations. In the previous review, proximity factors were used to adjust the concentrations measured at monitors to estimate roadway-related concentrations of CO. We plan to conduct a review of the literature and draw upon the results of near-road studies to update the proximity factor distributions. Do the Panel members have recommendations for improvements or alternatives to this approach?

Answer: It would appear that, if you have the time and resources, using a more detailed Gaussian model would be good, or possibly a land use based model. In the end, resource constraints will dominate, and while I think a proximity-based modeling approach is not scientifically the best, it likely produces results that will get over the bar. Such a proximity

model should take in to account traffic intensity and fleet mix, not just distance to road.

3. The planned approach for addressing uncertainty is primarily qualitative with a focus on sensitivity analysis and a limited quantitative analysis for those variables determined to be most influential with respect to exposure and/or dose estimation and where supporting data are available.
    a. What are the Panel members' views concerning this general approach?

Answer: I think that staff should be as quantitative as possible right up front, and provide best estimates of the uncertainties. These estimates can be caveated and discussed, but without going through this exercise, it is possible to mis-label an uncertainty as to be low, medium or high.

    b. Spatial and temporal gradients in ambient CO relative to CO concentrations measured at fixed-site monitors are potentially a major source of uncertainty in the exposure and dose estimates. Do the Panel members have suggestions for how best to characterize the uncertainties in this relationship?

I would use the results of the Gaussian modeling and the various detailed monitoring experiments that have been conducted. Some sort of synthesis of the two would be of interest.

Paul T. Roberts 05/06/09

Preliminary Comments by Paul T. Roberts for CASAC CO Panel, May 6, 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 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, and that inventories newer than 2002 may not be finished, 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.

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. 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 ISA (1.0 ppm). Again "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." (same page). 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 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 no 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; yes, if all US monitors have 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.

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. 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 this information is the following excerpt from the 2000 CO AQCD, page 2-8, although the reported statistics were already old at that time. These statistics should be calculated on the data being used in the ISA, based on the information reported to AQS for each reporting site. "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)."

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 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).

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.

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"
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?

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.

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 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. These qualifications should be discussed in the text with the conclusions (and I think they are significant limitations).
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?

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 need to be 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?

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. What is 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. Maybe the exposure modeling Chapter (3.6.7) should include more specifically about how to address in-vehicle and near-road exposures? Thus, I do not think that Chapter 3.7 supports the conclusion that central-site monitor concentration is generally a good indicator for the ambient component of personal CO exposure. In fact, I suggest below that Chapter 3 suggests otherwise.

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 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?).

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.