



**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460**

**OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD**

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

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

Dear Administrator Jackson:

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

We appreciate the responsiveness of EPA staff in regard to our previous comments. The issues we targeted as important in our previous review were addressed. Both the revised document, as well as, comments at the meeting were responsive to our concerns. In general, CASAC commends the EPA staff for the development of a comprehensive and readable second draft of the *Integrated Science Assessment for Carbon Monoxide*. The document integrates relevant evidence from the past decades while emphasizing new evidence and a better understanding of mechanisms. The extensive literature is thoughtfully summarized. The document makes effective use of tables and appendices.

We are comfortable with the process used by the EPA to produce this document. The EPA has implemented a process that is consistent with current approaches to evidence review and synthesis. It has progressively refined this process in recent NAAQS reviews. We believe that uniformity will improve the quality and transparency of CASAC's reviews.

1 Some additional major comments follow:
2

- 3 • As discussed before, the terms “sensitive, susceptible, and vulnerable” are often used
4 interchangeably. We recommend that these terms be used in a consistent manner and that
5 the EPA develop a glossary of these terms to be used across all criteria pollutants. Such a
6 glossary would promote consistency in the ISAs and REAs.
7
- 8 • The panel expresses concern about the existing CO monitoring network. There are
9 concerns both about the spatial distribution of the existing network, as well as the current
10 CO detection limits. Populations who may be exposed to higher CO levels because of
11 where they live and work fail to have their CO exposures adequately characterized.
12 Moreover, the fact that CO levels are often below the detection limits hinders both
13 exposure assessment and model calculations. The panel recommends that attention and
14 investment be made in improved monitoring.
15
- 16 • The panel approves the broadening of the evidence base. For example, the discussion of
17 CO in relation to atmospheric chemistry and climate change is useful. Although such
18 considerations do not drive the current standard, it is important to recognize this topic and
19 to encourage its development. We agree that this topic should be discussed, but should
20 not be considered as affecting the secondary standard. This is because of the current high
21 level of uncertainty.
22
- 23 • Although traditionally, EPA regulations are weighted heavily to information provided
24 from epidemiologic studies. In the case of carbon monoxide, information from well
25 designed classic clinical exposures to carbon monoxide are important. We agree with the
26 weight they are given in the current document.
27
- 28 • The problem of co-pollutants serving as confounders is particularly problematic for CO.
29 Since exposure levels for CO are now low, there is an increasing likelihood that CO may
30 sometimes be serving as a surrogate for combustion of fossil fuels. A better
31 understanding of co-pollutants is important for regulation, and especially for the design
32 and analysis of carbon monoxide epidemiologic studies.
33
- 34 • Ironically, some of the challenges of the ISA (and Risk and Exposure Assessment) reflect
35 the great progress in reducing ambient concentrations of CO. Many of the strategies of
36 the past decades focusing on reduced emissions have borne fruit. This should be
37 recognized and celebrated. CASAC notes that the ISA documents a substantial decline in
38 CO levels in urban areas over the past two decades. This decline is noteworthy and
39 undoubtedly benefited public health.
40

1 CASAC reiterates its expectation that the revised ISA will be accompanied by a summary of key
2 changes. This will enhance the efficiency and targeting of subsequent reviews, and will provide
3 a transparent record of the basis for these changes.
4

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Sincerely,

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

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

14

15 Enclosures

1 Enclosure A

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3

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

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9 Environmental Health, Harvard School of Public Health, Harvard University, Boston, MA

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11

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1 Enclosure B

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

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

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

The terms “sensitive,” “susceptible,” and “vulnerable” are often used interchangeably or at least with potentially overlapping meanings. It would be helpful to define these terms in a consistent manner which would be used throughout the chapter and the entire document. EPA should develop a glossary of terms that are used across criteria pollutants, to ensure consistency of terminology in the ISAs and REAs for all NAAQS reviews. The term “sensitive” is in the statutory language (see footnote 1 on p. 1-3) and thus may have special regulatory significance, which should be explained. The role of identifying “susceptible” and “vulnerable” groups with respect to characterization of “sensitive” groups should be explained. Although a table related to these definitions appears later in the document, clarification earlier would be better.

1 Finally, given that the epidemiologic literature on criteria pollutants has multiplied greatly over
2 the past decade, it is recommended that EPA assess the applicability of performing appropriate
3 meta-analyses to better inform quantitative effect estimates, allowing it to refine further its
4 inferences from the scientific literature.

5
6 *2. Chapter 3 has been revised and expanded in response to Panel comments regarding climate,
7 monitoring, spatial variability, and exposure.*

8
9 Substantial additional information has been added to both Chapters 2 and 3 as well as in Annex A, and
10 the ISA is much stronger for it. The review of the literature appears to be thorough, and the analysis of
11 the science systematic. In discussion of non-anthropogenic CO emissions (pages 3-3 to 3-5), emissions
12 from biogenic sources, and CO generation from the oxidation of VOCs, isoprene, and other biogenic
13 VOCs should be added to the caption of Figure 3-1. Additionally, the discussion would benefit from the
14 inclusion of information on the range of motor vehicle operations which favor CO emissions, such as
15 operation under high load, emissions during cold-starts, and emissions from gross-polluting vehicles.

16
17 *a. Evidence reviewed in Chapter 3 of the ISA indicates that the direct contribution of
18 CO to greenhouse warming is very small, while the role of CO in atmospheric
19 chemistry cycles involving other species makes a larger contribution to radiative
20 forcing. This combined evidence leads to the conclusion in Chapter 2 that a causal
21 relationship exists between current atmospheric concentrations of CO and effects on
22 climate. What are the Panel's opinions related to this causal statement and the
23 evidence provided to support it?*

24
25 The addition of information on the potential impact of CO on climate is very helpful. It appears
26 that the direct impact of CO is small, but the indirect impact of CO may be substantial.
27 However, the estimates of the impacts of CO on climate are uncertain. This high level of
28 uncertainty does not favor the development of a secondary standard.

29
30 *b. Additional detail has been provided regarding the detection limits of CO monitors
31 in the regulatory network, the number of monitors reporting at each horizontal
32 spatial measurement scale and comparison of monitoring data at each scale, and
33 spatial variability of CO concentrations near major sources, particularly roadways.
34 Please comment on the usefulness of these revisions in characterizing the information
35 provided by the CO monitoring network.*

1 In general, the expanded discussions in the 2nd draft ISA Chapter 3 on CO detection limits, monitoring
2 details, and spatial CO characteristics better characterizes the information provided by the CO
3 monitoring network. The discussion helps qualify the data used in exposure estimations. Specifically,
4 the expanded discussions on monitor detection limits and monitoring locations in Chapter 3.4 (pages 3-
5 18 to 3-31 and associated Annex figures and tables) are critical to understanding CO concentrations and
6 are an important addition to the ISA. Although the limitations of insensitive existing monitors are
7 provided in the text (page 3-43, lines 13-18), these limitations need to be added at numerous other
8 locations in the text that address CO concentrations in Chapter 3.5. The relaxation of CO monitoring
9 requirements and the continued use of older, less sensitive monitors with poor levels of detection impede
10 the use of monitoring data for exposure assessments.

11
12 *c. The section on exposure assessment has been reorganized to provide information on*
13 *exposure assessment at different spatial scales and to create a subsection containing*
14 *information regarding exposure error and its implications for interpretation of*
15 *epidemiologic studies. Does the Panel consider that the sources of exposure error have*
16 *been appropriately characterized, and agree with the revised conclusions regarding the*
17 *impact of exposure error due to spatial variability and the presence of CO as part of a*
18 *combustion-related mixture on health effect estimates from time-series epidemiologic*
19 *studies?*

20
21 In general, the expanded discussions in the 2nd draft ISA Chapter 3.6 on sources of exposure and
22 resulting exposure assessment are a great improvement and are useful in characterizing the potential
23 impacts of exposure error. The section on Land Use Regression Models (Page 3-94, lines 6-23) is
24 limited in scope. It does not represent the wide range of modeling methods and of exposure results from
25 the literature. Additional discussions should help characterize the spatial concentrations of CO between
26 monitoring locations and especially near roads where concentrations are much higher than general area
27 locations. Admittedly, much of the modeling work in the literature is on pollutants other than CO, but
28 the conclusions regarding what methods work and how they relate to estimating pollutant concentrations
29 are directly applicable to CO.

30
31
32 *3. In response to comments from the CASAC CO Panel, material has been added to Chapter*
33 *4 describing comparisons among predictive COHb models, the relative influence of*
34 *differing exposure scenarios on COHb concentration, and endogenous CO production*
35 *rates in individuals with various diseases and conditions. Please comment on the*
36 *usefulness of this information in illustrating the factors influencing COHb kinetics and*
37 *potential COHb levels under various scenarios.*

38
39 Generally, we found the revised and substantially expanded Chapter 4 of the second draft
40 comprehensive and very useful in illustrating various physiologic factors and disease states that
41 influence blood levels of COHb and/or their potential adverse affects. Section 4.2 describes in
42 adequate detail various COHb predictive models. However, despite the addition of section 4.2.3
43 Model Comparison, which discusses some limitations or advantages of the respective models, it
44 is still unclear to the Panel (1) how these different models will perform under the same simulated
45 temporal exposure scenario of 30- 60 min duration with occasional peak CO concentrations and

1 (2) which one is the most accurate in predicting COHb levels. Several models, e.g., Smith et al,
2 1994, Bruce and Bruce, 2008, Gosselin et al., 2009 as well as the non-linear CFKE used by EPA
3 in the APEX model seem to be most suitable for such an inter-model comparison and evaluation.
4 This may help establish whether or not the CFKE is the best model given that activity levels are
5 evaluated on a minute-by-minute basis and ambient CO shows transient peaks. The
6 physiological parameters (V_A , DLCO, etc.) used in both Denver and LA COHb calculations also
7 should be spelled out, since DLCO and ventilation rates are different at altitude.

8
9 There are some inconsistencies among the tables, figures and text presented in the discussion of
10 the QCP model (section 4.2.4). The inconsistencies need to be reconciled, and the section
11 shortened by dropping less relevant material.

12
13 The addition of section 4.3.4 COHb Analysis Methods in this draft is very helpful in pointing to
14 limitations and inaccuracies in some of the instruments used to measure COHb. Since the
15 differences in COHb determination among methods may be substantial, we suggest indicating
16 the method/instruments used to determine COHb in tabulated studies as well as in other key
17 studies discussed in the text.

18
19 Besides cardiovascular disease there are other large population groups "potentially" at-risk from
20 CO exposure, such as patients with various forms of anemia and those with COPD. Although
21 there are no experimental studies on the effects of CO exposure on these groups at ambient
22 concentrations, these individuals may be more vulnerable to CO because their disease state
23 amplifies the action of CO. The application of COHb predictive models with the inclusion of
24 appropriate pathophysiological parameters representing such disease states, if feasible, might be
25 helpful in determining the extent of risk in such populations. Especially, if available, additional
26 details should be provided and discussed regarding the fetus as an 'at-risk' individual.

27
28 Identification of CO-specific associations with health endpoints in epidemiologic studies requires
29 complex analyses. Utilization of appropriate COHb predictive models can help in identifying
30 such associations and provide further insight into the pathophysiology of likely responses.

31
32 4. *The cardiovascular effects section has been expanded to:*

- 33 • *evaluate key uncertainties in the health evidence, particularly regarding the*
34 *biological plausibility of effects at low ambient CO concentrations and*
35 *distinguishing independent effects of CO in multipollutant ambient mixtures;*
 - 36 • *provide more detail on the design and findings of a multicenter controlled human*
37 *exposure study to clarify the levels at which effects were observed;*
 - 38 • *add description of new epidemiologic studies, including a large U.S. multicity*
39 *study and studies on associations between blood markers and ambient CO*
40 *concentrations; and*
 - 41 • *more clearly describe the integration of controlled human exposure and*
42 *epidemiologic evidence to reach a causal determination.*
- 43

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

5
6 The EPA staff should be commended for the expanded, wide-ranging and comprehensive
7 presentation in Chapter 5 of the ISA. They have added relevant material to the earlier version of
8 this chapter and included updates from articles that appeared as late as September 2009.

9
10 *Cardiovascular Morbidity.* The most compelling CO-related CVD results remain those from the
11 20+-year-old controlled human exposure studies of Allred et al; Kleinman et al; and Sheps et al.
12 The Allred (1991) report contains dose-response information, including responses at COHb
13 concentrations <2%, based on the air-exposed COHb levels. More recent human epidemiology
14 studies of morbidity at ambient CO levels, including data on hospital admissions, are consistent
15 with and reinforce the observations from the earlier controlled human studies. The large “at-risk”
16 population includes people with CVD who have not yet been formally diagnosed with this
17 condition. This group likely will grow in size and importance as our population ages. Many
18 individuals who have acute myocardial infarctions, including CO-related MIs, do not have prior
19 diagnosed coronary artery disease.

20
21 Although those with diagnosed coronary artery disease (CAD) are the largest CVD group and
22 may be the group that represents the most easily quantified highly susceptible group for CO-
23 related outcomes, this is an underestimate of the at-risk group. Further, other CVD patients,
24 regardless of whether they also carry a diagnosis of CAD, are at increased risk for CO-related
25 hospital admissions. Further, limited data from people suffering MIs, who had recently
26 experienced high acute CO exposures, indicate that those MIs were associated with vasospasm,
27 rather than with complications of CAD, thus indicating that CAD need not be a final common
28 pathway to adverse CV outcomes.

29
30 Finally, the association of stroke with small increases in ambient CO levels also supports a more
31 broadly defined risk group going beyond those with established CAD. Thus, beyond the
32 narrower outcome of CAD alone, the Panel members concur with the conclusion that “a causal
33 relationship is likely to exist between relevant short-term CO exposure and CV morbidity.”
34 There are “insufficient data” to establish a relationship between either chronic CO exposure or
35 transient elevations in ambient CO and mortality.

36
37 *Stroke.* The correlations between elevated ambient CO levels and hospital admissions for stroke,
38 distinct from other neurological outcomes, are strong (see above). Consideration might be given
39 to changing the title of the neurological outcomes section to “CO and *non-stroke* CNS
40 morbidity”.

41
42 *Respiratory Morbidity.* Positive associations exist between short-term exposure to CO and
43 respiratory-related outcomes including effects on pulmonary function, respiratory symptoms,
44 medication use, hospital admissions and emergency department visits. There were no convincing
45 data in which these relationships were consistently observed, however, adjusting for multiple co-

1 pollutants. Such co-pollutants are believed to be strong risk factors for adverse respiratory
2 outcomes. The Panel was divided, and while the overall view was in favor of “data suggestive of
3 a response” others held that a better designation would be “data insufficient to support a
4 response.” The associations between long-term exposure to CO and respiratory-related outcomes
5 are even less clear than those for short-term exposures and were appropriately categorized as
6 “data insufficient.” Finally, the point was made that allergy and allergic responses should be
7 considered separately from respiratory outcomes and that this distinction should be noted in a
8 revision.

9
10 *“Therapeutic” Applications of CO.* There is a growing literature regarding “therapeutic”
11 applications of CO at levels of ~250 ppm. These studies have been carried out in some animal
12 models and in cell culture. CO is a major pro-oxidant and has profound extended pro-
13 inflammatory effects. In specific scenarios however, with distinct organ systems or specific cell
14 types, CO may have short-term anti-inflammatory effects. Clinical trials have thus far not
15 supported health benefits of CO administration. Further, there is no evidence that the
16 hypothetical “therapeutic” results provide any insight into health effects of acute or chronic
17 ambient exposures in people generally, and especially in subpopulations susceptible to CO
18 effects.

19
20 *General Comments and Suggestions.* We suggest that additional Forest plots to summarize CO
21 effects on blood markers and heart rate variability be considered. We suggest that we consider
22 the feasibility of meta-analysis of health effects studies for selected outcomes.

- 23
24 5. *The section on susceptible populations has been revised substantially in response to*
25 *comments from the CASAC CO Panel and in consideration of similar comments from the*
26 *CASAC PM Panel. The definition of a susceptible population has been clarified, and*
27 *each subsection describing a susceptibility characteristic has been revised to emphasize*
28 *specific evidence from controlled human exposure studies of individuals with underlying*
29 *disease, epidemiologic studies that conducted stratified analyses to examine effect*
30 *modification, and toxicological studies using animal disease models. Does this revised*
31 *section provide appropriate characterization of populations potentially susceptible to*
32 *CO-induced health effects?*

33
34 The discussion of populations susceptible to carbon monoxide has been dramatically improved.
35 The data are now presented in a logical framework providing a clear and concise summary.
36 Section 5.7 begins with table 5-25. It produces a useful context in which to understand the
37 historical use of the terms vulnerability and susceptibility. A question was raised regarding
38 whether or not level of exposure should be considered a “vulnerability” factor. It was suggested
39 that the term “at risk” may be useful in some instances to distinguish individuals who are truly
40 more susceptible owing to some specific subject characteristic rather than to a difference in level
41 of exposure. It was also suggested that a statement concerning the meaning of “vulnerable
42 populations” common to other EPA documents be included in the first chapter of the ISA (see
43 previous comments on this topic).

1 *Cardiovascular Disease.* As indicated in the previous charge question, concern was expressed
2 that the discussion of this vulnerable subpopulation was focused too narrowly on coronary artery
3 disease. It was noted that arrhythmias and congestive heart failure should also be discussed in
4 this section. Further, coronary artery disease represents a continuous process with many more
5 individuals at risk than those carrying the diagnosis.
6

7
8 *Anemia.* One of the susceptible subpopulations included individuals with anemia from a diverse
9 range of disease states. A key mechanism by which anemia may put individuals at increased risk
10 is reduced oxygen carrying capacity. Hemoglobinopathies, including sickle cell disease, should
11 be distinguished from anemia in general, as these disorders are like to have a different
12 susceptibility relationship to carbon monoxide.
13

14 *Diabetes.* Diabetes was identified as another factor that might increase susceptibility to carbon
15 monoxide. It was noted that the current discussion does not mention the high rate of obesity and
16 metabolic syndrome as risk factors in addition to diabetes itself or the high correlation between
17 diabetes and cardiovascular disease. In particular, a recent South Korean study (not included in
18 the report) was cited by the Panel in which the effects of carbon monoxide were investigated in
19 individuals having both diabetes and cardiovascular disease (Min JY, Paek D, Cho SI, and Min
20 KB (2009). "Exposure to environmental carbon monoxide may have a greater negative effect on
21 cardiac autonomic function in people with metabolic syndrome," *Science of the Total*
22 *Environment*, 407(17), 4807-4811.).
23

24 *Gestational Development.* The focus on altered gestational development was the mother and
25 fetus. Limited data suggest the possibility of paternally mediated effects of carbon monoxide
26 owing to altered sperm production. These effects cannot be ruled out as a potential contributor to
27 the effects of carbon monoxide in gestational development, but there is currently no compelling
28 evidence.
29

30 6. *Chapter 2 has been revised and expanded to provide more information on atmospheric*
31 *science and exposure assessment, policy relevant considerations, and integration of CO*
32 *health effects.*
33

34 a. *The section on policy-relevant considerations was revised to present additional*
35 *detail on the concentration-response relationship observed in a multi-center*
36 *controlled human exposure study, present results from a new U.S. multicity*
37 *epidemiologic study investigating the potential presence of a threshold and*
38 *departure from linearity, and summarize the evidence for susceptible populations.*
39 *Please comment on these revisions.*
40

41 The inclusion and analysis of data from the multi-site epidemiological study (Bell ML, Peng RD,
42 Dominici F, Samet JM (2009). "Emergency admissions for cardiovascular disease and ambient
43 levels of carbon monoxide: Results for 126 U.S. urban counties, 1999–2005," *Circulation*, 120
44 (11), 924–927.) is commendable, given that it was published only recently. In addition, there are
45 multiple points in which these data could have been presented in Chapter 5, which is the basis of

1 the presentation in Chapter 2 (see also comments to that charge question). Greater detail should
2 be provided here in Chapter 2 because the data are particularly relevant. For example, limiting
3 the analysis to those days with 1-ppm values or less, resulted in the point estimate for the
4 increased hospitalization actually increasing to approximately 1.75%.

5
6 *b. A section and summary figure have been added to the end of Chapter 2 to*
7 *summarize the main conclusions of the ISA regarding the health effects of CO and*
8 *the range of concentrations at which effects are observed, along with*
9 *uncertainties that complicate the interpretation of the evidence. We would*
10 *appreciate CASAC comment on the material in this section and its effectiveness in*
11 *presenting the conclusions of the ISA.*
12

13 Figure 2-1 (page 2-21) is new to this revision. In principle, Figure 2-1 is appropriate and helpful,
14 but it could be improved as delineated below. The effect estimate metric as presented in the far
15 right column of Figure 2-1 should be more understandable. For example, because the lower
16 bound of the CI and the point estimate are of far more interest than the upper bound, adjusting
17 the scale is appropriate and would help the presentation visually. Also, the effects could be
18 grouped by endpoint, not by study, with total CVD top, then IHD, CHF and stroke. Finally, the
19 99th percentile of exposure may be of less interest than the 95th.

20
21 In terms of the new figure, although the CVD endpoint of Bell is included, the other specific
22 endpoint of Bell is left out. This is related to the tree plot consisting of *unadjusted* CO effects
23 only. This could be addressed with clarifying notes and with a test emphasizing that there are
24 co-pollutant adjusted values from Bell et al. These critical endpoints include ischemic heart
25 disease (IHD), congestive failure, and stroke. The data in Figure 2-1 could benefit from a formal
26 meta-analysis or, if this proves inappropriate (for example, due to heterogeneity) a comment as
27 to the rationale to forgo the presentation of such an analysis should be included. The ISA should
28 also explain why the data in Figure 2-1 are limited to findings from North America.

29
30 We also draw attention to the concluding paragraph (pages 2-24 and 2-25). Before addressing
31 uncertainties that remain, it might be more straightforward to catalogue first the uncertainties that
32 have now been substantially addressed since the 2000 CO AQCD. (In the present text this is
33 stated first in the negative: “some of these uncertainties remain.”) The lack of biological
34 plausibility argument runs counter to the rich series of recent studies that indicate the potential
35 modulatory effects of CO at low levels on a number of systems (pages 5-5 to 5-17). A separate
36 section should summarize and address this central point of improved data that has reduced much
37 of the uncertainty previously encountered. Moreover the phrase in the last sentence “biological
38 plausibility provided by CO’s role in limiting O₂ availability” seems to diminish the rich data on
39 other mechanisms and their possible mechanistic role (e.g., cell signaling independent of heme
40 moiety binding).

41
42 The concluding paragraph refers to the “many new epidemiological studies adding to the body of
43 evidence showing associations.” The EPA could modify this statement to include the adjective
44 *convincingly*, to be consistent with the next sentence re: definitive cardiovascular effects in
45 controlled exposures. At various points, but most importantly in the very last sentence, the

1 phrase “relevant... exposures” is used. If this means exposure at or below the current EPA CO
2 NAAQS, this should be explicitly stated. “Relevant” could imply that other exposure levels are
3 *irrelevant* to the assessment of health effects, which of course is not intended (they are relevant
4 through mechanistic insights they provide, for example). The Panel found the focus on
5 cardiovascular endpoints in the concluding paragraph appropriate. Nonetheless, an additional
6 sentence acknowledging that there is at least a suggestive relationship with several other
7 endpoints is warranted. Also, a restatement of the association with global warming would be
8 appropriate in this concluding paragraph.
9

10 There is agreement among the Panel with the ISA’s conclusion that there is a likely causal
11 association between acute ambient CO exposures in the range of the current air quality standard
12 and adverse cardiovascular endpoints. In contrast, there is scant evidence in the health effects
13 section related to the chronic CO exposure effects on cardiovascular morbidity. Even though
14 these data may be categorized as “inadequate,” this category appears to have been omitted from
15 Table 2-1 and should be added. Also, the publication by Hedblad et al. (*Scand J Public Health*,
16 2006) seems to be missing from the discussion. It is relevant to Chapter 5.
17

18 There is heterogeneity of views among the Panel regarding the summary statement that acute CO
19 exposure has a suspected association with adverse respiratory outcomes. The Panel recommends
20 tempering the narrative by explicitly indicating that this association is on the borderline between
21 suggestive and “insufficient data.” In particular, the epidemiological evidence was limited by an
22 absence of co-pollutant data. We lack studies showing substantive attenuation of CO risk
23 estimates when co-pollutant modeling is performed.
24

25 There is a consensus by the Panel that the relationship between chronic CO exposure and
26 mortality would be better categorized as “insufficient data” rather than “unrelated.” This view is
27 based in large part on the difficulty in epidemiologically differentiating between mortality due to
28 multiple acute effects compared to prolonged lower level effects without peaks and the fact that,
29 logically, chronic outcomes in myocardial infarction and stroke can be presumed to include
30 excess mortality.
31
32

1 Enclosure C

2

3 Compendium of Review Comments from CASAC Carbon Monoxide Review Panel on EPA's
4 *Integrated Science Assessment for Carbon Monoxide: Second External Review Draft (September*
5 *2009)*

6

7 **Comments received:**

8

9	Dr. Paul Blanc	16
10	Dr. Thomas Dahms	21
11	Dr. Russell Dickerson	25
12	Dr. Laurence Fechter.....	29
13	Dr. H. Christopher Frey	30
14	Dr. Milan Hazucha.....	35
15	Dr. Michael Kleinman	39
16	Dr. Francine Laden.....	40
17	Dr. Arthur Penn	41
18	Dr. Beate Ritz	44
19	Dr. Paul T. Roberts.....	47
20	Dr. Armistead Russell.....	52
21	Dr. Anne Sweeney	53
22	Dr. Stephen Thom.....	56

1 **Dr. Paul Blanc**

2
3 Comments on Charge Question #6

4
5 a. **Please comment on these revisions:** *The section on policy-relevant considerations was revised to present additional detail on the concentration-response relationship observed in a multi-center controlled human exposure study, [to] present results from a new U.S. multicity epidemiologic study investigating the potential presence of a threshold and departure from linearity, and [to] summarize the evidence for susceptible populations.*

6
7
8
9
10
11 It is appropriate to include the Allred concentration (exposure) response data and to point out
12 (as is done in the text) that this study was far larger and more powerful than any previous
13 controlled exposure study. In terms of exposure (concentration) response, the key Allred study
14 appeared in 1991 (the current document refers the reader to the 1989 Allred paper, although the
15 subsequent 1991 paper provides details of the exposure [concentration]; clarifying this point in
16 the text would be advisable). The Allred data could be presented to better effect if the point is not
17 only the linear relationship, but also the presence of a threshold. In this regard, the Allred
18 analysis of time until angina (from the actual paper, Figure 12, page 112, 1991 and related text)
19 indicates that there was an intercept value (at 0% carboxyHb) of a 1% decrease ($\pm 2.1\%$; not
20 different from zero) in time until angina onset. This is based on an analysis of room air not as
21 “zero,” but as the actual post-exercise room air COHb value (which varied by site and among
22 subjects). The ST depression intercept, of note, was significantly in the positive direction, which
23 could be argued in favor of a threshold for that endpoint. This can be discussed more explicitly
24 than as it appears in the current draft. Also in regard to threshold, the analysis by Somoli, in
25 which the deviance from linearity was associated with a p value of > 0.9 , should not be described
26 as “weak evidence in favor of a threshold” – this would be better described as a finding that does
27 not support the presence of a threshold. Moreover, there is an overextended discussion here as to
28 why this analysis was poorly powered to observe a threshold, including wording such as “an
29 inability to draw conclusions.” This could give the appearance of trying too hard to leave open
30 the possibility of a threshold effect where none was no threshold observed.

31
32 No attempt was made to perform an integrated analysis of the experimental data for low-level
33 CO exposure and time until onset of angina from multiple studies (for example, using the data in
34 Table 27 of Allred of multiple studies on this subject, taking into account baseline room air
35 carboxyhemoglobin and post exposure levels). It may be that the data, ultimately, so not permit
36 this. If so, a brief statement in this regard in the text would nonetheless be useful.

37
38 The concluding statement of this section reads: “*Although the C-R relationship has not been*
39 *explicitly evaluated in human clinical studies with exposures resulting in COHb concentrations*
40 *< 2.0%, the findings of Allred et al. provide some evidence of a significant C-R relationship over*
41 *a range of COHb concentrations relevant to the NAAQS.*” This sentence is overly weak,
42 somewhat confusing, and inexact. Allred, in fact, did explicitly analyze the concentration
43 response including those resulting from air (ambient CO +metabolism). Many of these
44 observations included in that regression were less than 2% COHb (see above, re: threshold). The
45 wording “some evidence” operates to undermine the findings – it is “evidence,” which could be

1 argued to be substantial or strong (as opposed to the indeterminant “some”). If “significant” as
2 used in this text means statistically significant, then this should be explicit as well. Also on this
3 topic of concentration response, a comment voiced in the meeting was that, in addition the
4 potential differences between concentration response and delivered dose response based on
5 biological monitoring should be acknowledged, either here or elsewhere in the document.
6

7 The summary of evidence regarding “susceptible” populations (2.6.1) actually precedes the
8 discussion of concentration response (2.6.2). This section does a fair job of summarizing lengthy
9 text elsewhere in the document, but also suffers from the organizational issues of that text. The
10 most substantive issue here is the usage of the term “susceptible” to refer to two entirely different
11 concepts, operationally. The first usage is consistent with the way in which susceptible is
12 typically applied: subgroups in which an exposure identical to the general population could be
13 expected to have a greater adverse effect. Examples of this include, and are documented: those
14 with pre-existing cardiovascular disease, diabetics, those with pre-existing anemia, those with
15 pre-existing hypoxemia, and the fetus. In contradistinction to this classic construct of
16 susceptibility, the document lumps together with this individuals who are susceptible because
17 either they are more likely to experience higher ambient exposures (living near roads, greater
18 commute times) or because the ambient exposure they receive will be superimposed on a higher
19 baseline value secondary to greater than average exposure to exogenous CO or due to greater
20 metabolic production of CO. Susceptibility by both routes are important, but the presentation
21 would be more lucid if the distinction were spelled out explicitly.
22

23 The concluding sentence “Overall the controlled human exposure, epidemiologic, and
24 toxicological studies evaluated in this assessment provide evidence for increased susceptibility
25 among various populations” is overly weak. By saying that the evidence for those with CAD is
26 “strongest” in the next sentence, the implication could be drawn that the other “evidence” is
27 somehow weak. It could be argued that the strongest evidence of susceptibility to CO, per se, is
28 for fetal exposure, on kinetic grounds of a longer half-life. The evidence of susceptibility is
29 certainly strong to convincing in a number of other scenarios. Also in the sentence in question, if
30 toxicological means animal toxicology this should be stated and a fourth category of human
31 clinical toxicology cases added, or toxicology be clarified to mean both..
32

33 Overall in the document there seems to have been little use made of human toxicology case
34 reports insofar as the implications that might be drawn from such data. One specific example:
35 human case reports clearly have shown that coronary artery spasm appears to mediate CO-
36 induced MI in some individuals (post CO-caused MI coronary vessels without underlying CAD
37 consistent with MI). [See for example: Marius Nunez AL, Myocardial infraction with normal
38 coronary arteries after acute exposure to carbon monoxide. Chest 1990; 97:491-4 and related
39 case reports]. There was, however, another minority view presented by a panel member that
40 argued against consideration of any data in which high levels of exposure had occurred as being
41 irrelevant to lower level scenarios.
42

43 The various scenarios of susceptibility seem to ignore indoor air sources of supplemental CO
44 exposure. Most glaringly, secondhand smoke exposure is missing [it can also be argued that this
45 can be an outdoor ambient issue in areas with heavy concentrations of smokers at the threshold

1 of edifices. This is also relevant to secondhand smoke exposure to vehicular passengers in
2 automobiles, already exposure to higher roadway levels of CO. Related to this issue, term
3 secondhand smoke (SHS) should be substituted for “ETS” where currently used in the document.
4 Paralleling the SHS issue, deficient home heating which may also be a risk and is likely to run
5 with lower socioeconomic status and or living in colder parts of the US in the winter months,
6 also relevant to susceptibility. In the same vein, occupational exposures superimposed on
7 ambient exposure should be taken into account as a potential susceptibility factor. Further, the
8 metabolism of “dihalomethanes” is mentioned as an enteric source of CO, but this would be
9 better stated a predominantly methylene chloride (which has also been in some consumer
10 products). In regard to metabolism, there could be further clarification of data gaps in the overlap
11 or non-overlap of similar systemic levels of carboxyhemoglobin from internal metabolism
12 compared to extrinsic exposure. Finally, diabetics are mentioned, but a recent relatively large
13 study (n=986) from Korea (Min PY et al, Sci Total Environ Aug 2009) with effect modification
14 for autonomic dysfunction [decreased heart rate variability] from CO by fasting blood glucose
15 was not cited or discussed. Many of these points are also relevant to the more detailed
16 presentation of susceptibility in Chapter 5.

17
18

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

24

25 Figure 2-1 (page 2-21) is new to this revision. The Figure, in principal, is appropriate and
26 helpful, but it could be improved upon in ways delineated in the points below. The effect
27 estimate (far right of Figure 2-1) should have the metric presented more clearly graphically. For
28 example, because the lower bound of the CI and the point estimate are far more of interest than
29 the upper bound – scaling so that the scale is bigger would help the presentation visually. Also,
30 the effects could be grouped by endpoint, not by study, with total CVD top, then IHD, CHF and
31 stroke. Finally, the 99th percentile of exposure may be of less interest than the 95th.

32

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

42

43 In terms of the new Figure, although the CVD endpoint of Bell is included the other specific
44 endpoint of Bell are left out. This is related to the tree plot being of unadjusted CO effects only,
45 but this could be addressed with clarifying notes and with test emphasizing that there are co-

1 pollutant adjusted values from Bell et al. These critical endpoints include IHD, congestive
2 failure, and stroke.
3

4 The data in Figure 2-1 could benefit from a formal meta-analysis or, if this proves
5 inappropriate (for example, due to heterogeneity) a comment as to the rationale to forgo the
6 presentation of such an analysis should be included. (Also in regard to Figure 2-1, a compelling
7 rationale as to why the data are limited to findings from North America is not provided and
8 should be inserted).
9

10 The concluding paragraph (pages 2-24 and 2-25) is hampered by the logic of its presentation.
11 Before addressing uncertainties that remain, it might be more straightforward to first catalogue
12 the uncertainties that have now been substantially addressed since the 2000 CO AQCD. (In the
13 present text this is stated first in the negative: “some of these uncertainties remain.”) The
14 argument re: lack of biological plausibility runs counter to the rich series of recent studies
15 indicating the potential modulatory effects of CO at low levels on a number of systems (see
16 pages 5-5 to 5-17). Indeed, a separate section as part of the policy section should summarize and
17 address this central point of an improved data that has reduced much of the uncertainty
18 previously encountered. Moreover the phrase “biological plausibility provided by CO’s role in
19 limiting O2 availability” [last sentence] basically cuts out the rich data on other mechanisms
20 from any plausible mechanistic role [e.g., cell signaling independent of heme moiety binding].
21

22 Earlier in the text, this same paragraph refers to the “many new epidemiological studies
23 adding to the body of evidence showing associations..” This could be modified to include the
24 adjective *convincingly*, consistent with the next sentence re: definitive cardiovascular effects in
25 controlled exposures.
26

27 At various points, but most importantly in the very last sentence, the phraseology
28 “relevant....exposures” is used. Where this means exposure at or below the current EPA CO
29 NAAQS, this should be so stated. “Relevant” could imply that other exposure levels are
30 *irrelevant* to the assessment of health effects, which of course is not intended (they are relevant
31 through mechanistic insights they provide, etc).
32

33 In summary, there was a consensus of the Panel agreeing with the conclusion that there was a
34 likely causal association between acute ambient CO exposures in the range of the current air
35 quality standard and adverse cardiovascular endpoints. In contrast to this, there is only scant
36 evidence in the health effects section re: chronic CO exposure effects on cardiovascular
37 morbidity. Even though these data may be categorized as “inadequate,” this category appears to
38 have been dropped from Table 2-1 and this row should be added [note: Hedblad B. et al, *Scand J*
39 *Public health*, 2006 seems to be missing from that discussion and seems on topic; this would be
40 relevant to Chapter 5].
41

42 In terms of the summary that acute CO exposure has a suspected association with adverse
43 respiratory outcomes, there was a heterogeneity of views on the Panel, with a suggestion that this
44 might be tempered in the narrative with explication indicating that this association was
45 borderline between suggestive and “insufficient data.” In particular, the epidemiological

1 evidence was limited by an absence of co-pollutant data or was marked by CO risk estimates
2 were substantively attenuated when co-pollutant modeling was performed.
3

4 In terms of chronic CO exposure and mortality, there was a consensus view that this would
5 be better categorized as “Insufficient data” rather than “unrelated.” This view is based in large
6 part on the difficulty in epidemiologically differentiating between mortality due to multiple acute
7 effects compared to prolonged lower level effects without peaks and the fact that, logically,
8 chronic outcomes in myocardial infarction and stroke can be presumed to include excess
9 mortality.
10

11 In summary, it is appropriate to focus on cardiovascular endpoints in the concluding
12 paragraph as written. Nonetheless, an additional sentence acknowledging that there is at least a
13 suggestive relationship with several other endpoints is warranted and also a restatement of the
14 association with global warming would be appropriate in this concluding paragraph.
15

1 **Dr. Thomas Dahms**

2
3 **Statement: In response to comments from the CASAC CO Panel, material has been added**
4 **to Chapter 4 describing comparisons among predictive COHb models, the relative**
5 **influence of differing exposure scenarios on COHb concentration, and endogenous CO**
6 **production rates in individuals with various diseases and conditions.**

7
8 *Q: Please comment on the usefulness of this information in illustrating the factors influencing*
9 *COHb kinetics and potential COHb levels under various scenarios.*

10
11 General comments: This section provides an excellent review of the modeling of CO uptake and
12 release. It provides the essential information needed to understand most of the variables involved
13 in relating CO exposure and CO dose. What follows are suggestions/questions that may lead to
14 further improvement and clarification of the material presented.

15
16 I. With the increasing amount of epidemiology data being considered in this database changes in
17 atmospheric CO levels with various adverse health effects, the exposure models need to provide
18 guidance to the reader regarding likely levels of exposure in some of these studies. The evidence
19 from the atmospheric data demonstrates a steady fall in monitored levels of atmospheric levels of
20 CO yet significant relationships with seemingly small changes in environmental CO continue to
21 be identified. How can the exposure models provide insight into what might be occurring? I
22 presume that this would include a discussion of the limitations of the use of the current
23 atmospheric monitoring data to estimate exposure? I realize that there is data in the RFA and in
24 the 2000 CO ACQD pertaining to this situation but it is scattered and it would help the reader if
25 the salient issues were summarized as they pertain to the epidemiologic studies.

26
27 II.. The modeling discussion in most of chapter 4 is based on factors influencing equilibrium
28 values for COHb given different exposure conditions. In Section 4.2.3 (Model Comparison), the
29 brief mention of the Bruce and Bruce model for predicting COHb levels with transient CO
30 uptake conditions , page 4.9 lines14-20 or the QCP model deserves much greater consideration
31 based upon what we know from real life exposure scenarios. If the primary exposures to CO
32 occur during periods of commuting, which model more accurately predicts the CO uptake during
33 the 30 to 60 minutes of exposure? Section 4.2.3. mentions the value of the Bruce and Bruce
34 model but then proceeds to use the QCP model in the following section 4.2.4.without discussion
35 or examples as to how ithe QCP compares to the other models. If the models in section 4.2.3
36 were all compared to observed data, this distinction needs to be made. Otherwise the use of
37 untested mathematical modeling in section 4.2.4. does not make sense.

38
39 III.. Given that adverse health effects have been demonstrated at 2% COHb, the discussion on
40 page 4-5 lines 23-26 report that application of unspecified scenarios in some form of the CFK
41 model yield ranges of exposure levels required to reach 2% COHb. For the 1 hour (transient)
42 exposure, these atmospheric levels of CO are 24-48 ppm which encompasses the 35 ppm hourly
43 criteria. However for the 8 hour exposure (equilibrium) the required exposure values are 11 to 13

1 ppm which is above the 9 ppm standard. This data needs to be better referenced since it applies
2 so directly to the standards.

3 IV. Use of modeling information:

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

11 a. anemia.

12 For the past 30 years patients with anemia has been identified as being an at risk group for
13 adverse health effects due to CO exposure. It is discussed again in this document in Section
14 5.7.1.3. This would be a particularly sensitive subset of patients with CAD since both
15 elevated COHb and reduced hemoglobin concentrations reduce oxygen delivery to the
16 myocardium. It should be noted that anemia is a significant risk factor for development of
17 angina. Yet there appear to be no studies available addressing this issue. The extent of
18 exposure risk for this sizable group of people (approximately 4 million over 65 with anemia)
19 needs to be addressed.

20
21 The treatment of anemia in this document focuses on the increased risk due to elevated
22 endogenous production of CO. It is unclear what influence the elevated endogenous rates
23 have on adverse health effects. One would suppose that in the four-element (Section 4.2.
24 page 4-2 lines 28-29) CFK model that when the largest element changed would be the
25 storage compartment (total body hemoglobin) that exposure conditions would be reduced in
26 order to result in the same measures of effective dose (%COHb). One would expect an
27 increase in the transfer interface with the hyperdynamic state due to the anemia, but the
28 impact of this component would be less clear. It is likely that the lack of a sizeable storage
29 compartment in anemic individuals would result in reaching levels of COHb of concern at
30 lower atmospheric levels during 1 hour or 8 hour exposures. The relative importance of
31 endogenous production, reduced storage capacity and increased transfer rates could be
32 determined through the use of modeling.

33
34 (The number of individuals in the USA with anemia is significant. According to NHANES
35 III, 10-12% of the population over 65 yrs of age (40 million) has anemia.

36 The number of individuals with CAD and anemia is more difficult to estimate but the
37 numbers range from 8-15% of those patients with CAD also have anemia.)

38
39 b. COPD and Emphysema

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

1 V. Section 4.5.

2 Whenever COHb is mentioned the method of analysis should also be indicated otherwise the
3 reader would be misled assuming that all of the values were equivalent when they are not. This is
4 particularly relevant when discussion the impact of endogenous CO production because the
5 resultant COHb levels are very low.

6
7 The limitations of the easy to use and reproducible CO-oximeter data was outlined in section
8 2.6.1 of the 2000 CO AQC D. There are many assays with sufficient sensitivity available for use
9 as used by Coburn et al to produce the data shown in Figure 4-12. However much of the other
10 data in this Figure was collected with instruments not designed for accurate measurements of low
11 levels of COHb (De las Heras et al used a CO-Oximeter).

12

13 **Additional major concern:**

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

27

1 Editorial and minor comments:

- 2 1. The use of deoxyhemoglobin is probably a carry over from the assumptions used in the
- 3 CFK modeling of McCartney (013162) which should be ignored because it is not correct. .
- 4 2. Section 4.2. page 4-2, line 17. altitude should read exposure time and altitude.
- 5 3. Section 4.2.1. page 4-3, line 29. Vco is not shown in Figure 4-1.
- 6 4. Section 4.2.1 page 4-4, lines 11-14. The discrepancy between arterial and venous blood
- 7 CO levels is mentioned without any interpretation as to why this is important. Also in this
- 8 section the absolute errors in COHb are mentioned without providing any sense of what the
- 9 mean increase in COHb was under these conditions.
- 10 5. Section 4.2.1. page 4-5, lines 23-26. A reference is needed.
- 11 6. Section 4.2.4, page 4-5.,lines 27-28. No explanation is given for reduced uptake by
- 12 babies which appears to contradict information given in section 4.1. lines 20-22.
- 13 7. Section 4.2.3. page 4-9, line7. 'differ $\pm 0.5\%$ ' needs clarification. 0.5% COHb or of the
- 14 value obtained?
- 15 8. Section 4.2.4, page 4-9, line 21. Population data for COHb are available in (Radford and
- 16 Drizd, 1982) so this statement needs to be clarified.
- 17 9. Section 5.7.1.1. In this section the distinction between the terms CAD and IHD needs to
- 18 be spelled out probably according to ICD-9 codes since these disease codes are the basis for
- 19 most of the epidemiology studies. The term CHD should be dropped or noted as being of
- 20 historic value only.

1 **Dr. Russell Dickerson**

2
3
4 Carbon monoxide, as the major sink for OH in the global troposphere has a substantial role in the
5 oxidizing capacity of the atmosphere. For example Shindell et al. (2006) and [Isaksen et al.,
6 2009] show that the lifetime of methane can change by a factor of two depending on the range of
7 tropospheric CO mixing ratios. Uncertainties in the budget of OH are such that the current state
8 of the science is insufficient to establish the safe level of CO based for example on a 1°C
9 temperature rise. The ISA should reflect this uncertainty and point out the need for further
10 experiments and theory to inform the EPA. Because CO (like SO₂ and NO_x) is both a local
11 pollutant and contributor to global climate change, a standard based only on the local maximum
12 concentration is inappropriate for protecting welfare. Reduction of total emissions is appropriate
13 for pollutants such as CH₄ and CO₂ with adverse effects on a global scale. The ISA should
14 discuss the scientific basis for emissions-based standards or guidelines for CO.
15

16
17 **Comments on ISA Charge Question 2a**

18
19 In reference to ISA Chapters 2&3 that discuss a causal relationship between current atmospheric
20 concentrations of CO and effects on Climate. “What are the Panel’s opinions related to this
21 causal statement and the evidence to support it?”
22

23 Substantial additional information has been added to both Chapters 2 and 3 as well as in Annex
24 A, and the ISA is much stronger for it. The review of the literature appears to be thorough, and
25 the analysis of the science systematic. One substantive comment I would make is that the
26 evidence all points to the need for new regulations for the climate effects of CO. The current
27 ambient concentration-based standards are not appropriate for large-scale global atmospheric
28 concentration concerns aimed at protecting welfare. This will have to be emissions-based
29 regulations similar to those being planned for CO₂. I suspect that the state of the science not yet
30 adequate to establish a specific CO emissions cap, and if that is the judgment of the EPA authors
31 then the Integrated Science Assessment should clearly state that further research is needed to
32 establish a numerical value for American CO emissions. Do we know what the safe level of CO
33 in the atmosphere is? If not then the ISA should so state.
34

35 The review of satellite measurements for establishing PRB concentrations is fair –existing
36 instruments lack sensitivity in the PBL. Remote sensing is already useful for model evaluation
37 and may some day be helpful for low-altitude measurements, and is
38

39 There is one more relevant paper that came out in *Science* after the draft was finished; it shows
40 gas/aerosol interactions can amplify the effects of non-CO₂ trace gases on radiative forcing
41 [Shindell et al., 2009].
42

43 **Comments on ISA Charge Question 2b**

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

4
5
6 Table A-1 is a great addition. This shows that highly sensitive instruments are commercially
7 available. Page 3-20. The LOD is given as 0.04 ppm, but Table A-1 shows 0.02 ppm. The ISA
8 should say the replacement monitors should have the lower LOD’s.

9
10 Page 3-12 Figure 3-8 is hard to read, perhaps a scatter plot.

11
12 Page 3-22 The ISA should state the revoking the CO monitoring requirements impedes our
13 scientific understanding of air quality and climate. The paragraph on NCORE is a great addition.

14
15 Page 3-33. The bar has a black stripe on top that looks like it should be a red stripe.

16
17 The additional detail in 3.5.1.2 is great. Page 3-45. The tale on top with E C A B D does not
18 seem to correspond to the columns below.

19
20 **Comments on ISA Charge Question 6b**

21 A section and summary figure have been added to the end of Chapter 2. “We would appreciate
22 CASAC comments....”

23
24 Figure 2.1 gives a good demonstration of the morbidity risks associated with CO, and is
25 understandable by non-specialists in epidemiology.

26
27 **General Comments on ISA Chapters 2 & 3.**

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

30
31 Section 3.2 There is a need for a bottom line here: substantial uncertainties in emissions
32 continue to exist. On page 3-4 is states that the reviewed literature is consistent in determining a
33 decrease of 5% per year in on-road CO emissions. Does that agree with Figure 3.2? It might be
34 but it would be nice to see it explicitly compared.

35
36 Page 3-10. CH₃OOH is not really soluble; the Henry’s Law coefficient is about 300 M/atm,
37 much less that H₂O₂.

38
39 Page 3-13. OH does not react with the major CFC’s that are fully halogenated (such as CFC-11
40 and 12). There needs to be a hydrogen atom bound to the carbon somewhere.

41
42 The Summary and Conclusions should state that:

43
44 1. There are substantial uncertainties in the emissions inventories.
45

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

4
5 **Minor points on ISA**

6 1. Page 2-20 line 14 space.

7
8 2. Page 3-14 line 22 semicolon where a comma should be.

9
10 3. The caption to Figure 3-10 and other similar figures should say that the circles indicate
11 the position of the monitors.

12
13 4. AADT is not in the table of acronyms.

14
15 5. The word 'fraught' on page 3-85 seems odd to my ear.

1
2 **Reference and some additional papers that may be of value to EPA.**
3
4

5 [Clements *et al.*, 2009; El-Fadel and Abi-Esber, 2009; Saide *et al.*, 2009; Tomlin *et al.*, 2009;
6 Wang and Zhang, 2009; Zhu *et al.*, 2009]
7

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

12 El-Fadel, M. and L. Abi-Esber (2009), In-vehicle Exposure to Carbon Monoxide Emissions from
13 Vehicular Exhaust: A Critical Review, *Critical Reviews in Environmental Science and
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Dr. Laurence Fechter

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Comments on ISA question 5

The discussion of susceptible populations to carbon monoxide has been dramatically improved. The data are now presented in a logical framework providing a clear and concise summary. The only minor change I would propose on page 5-167 2nd complete sentence is to revise as follows:
"These analyses require the proper identification of confounders and their subsequent adjustment in statistical models, which helps eliminate spurious associations."

1 **Dr. H. Christopher Frey**

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4 **Review of Carbon Monoxide Second Draft of Integrated Science Assessment**

5
6 **Charge Question 1:** Chapter 1 has been revised in response to comments from the CO Panel, as
7 well as related comments from the CASAC PM Panel, to add information regarding criteria for
8 study selection and evaluation, to add more CO-specific information to the framework for causal
9 determination, and to more clearly describe the process of integrating evidence from various
10 disciplines to classify the overall weight of evidence relating to causality. What are the views of
11 the Panel on the extent to which this revised Chapter 1 provides necessary and sufficient
12 background information for review of the subsequent chapters of the CO ISA?

13
14 **Response to Charge Question 1:**

15
16 Chapter 1 is generally very good.

17
18 The chapter should define the terms “sensitive,” “susceptible,” and “vulnerable” when they are
19 first introduced. The term “sensitive” seems to be in the statutory language (see footnote 1 on p.
20 1-3) and thus may have special regulatory significance. This should be explained. The role of
21 identifying “susceptible” and “vulnerable” groups with respect to characterization of “sensitive”
22 groups should be explained. Furthermore, these terms should be used consistently throughout
23 the chapter. Moreover, EPA should develop a glossary of terms that are used across criteria
24 pollutants, just to ensure consistency of terminology for ISAs and REAs for each criteria
25 pollutant.

26
27 Figure 1-1 should be revised. The current figure is unclear with respect to what it is depicting. It
28 would be helpful if this figure follows the flow of an individual study or paper that is identified
29 in the literature review. (will provide an alternative diagram).

30
31 EPA has explained the criteria for study selection and evaluation. However, some additional
32 explanation as to why the focus of the literature review is on studies conducted in the U.S. and
33 Canada is needed. In particular, given the scarcity of literature on welfare effects, have studies
34 from other countries been considered?

35
36 In Section 1.4, the topic of welfare effects should be discussed more fully. EPA should
37 explicitly comment on welfare effects or lack of information about welfare effect, so that the
38 reader can understand the decision process that leads to lack of treatment of this topic in the ISA,
39 and that the omission is intentional and well-reasoned.

40
41 In Section 1.5, the text on page 1-10, line 22 refers to “the extensive body of literature” but only
42 four references are cited. The text could be more clear as to the scope of the literature review
43 and how it was narrowed to the four references cited.

1 The scope of the critical review of ecological effects needs more detail. Specifically, what
 2 literature databases were searched, using what keywords, for what time period, geographic
 3 scope, and so on. Given the scarcity of literature on ecological effects of CO, can EPA
 4 nonetheless comment on hypotheses for ecological effects and identify what are the key data
 5 gaps. Such information would be useful for setting a research agenda to inform the next revision
 6 of the CO NAAQS.

7
 8 Page 1-11, line 4, the term “necessarily” seems out of place.

9
 10 The discussion of the framework for causality determination is much improved from the first
 11 draft, and nicely addresses CO-specific examples.

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

14
 15 Page 1-13, line 3, the term “susceptible” is used. Here is unclear as to whether this is meant to
 16 inform a determination of “sensitive” groups.

17
 18 Section 1.6.3. The term “measure” is unclear. Does this refer to an empirical quantity that is
 19 measured, estimated, or predicted? Or does it refer to a metric for a quantity? Suggest that the
 20 term “measure” should be replaced with more specific or descriptive terms.

21
 22 Should avoid use of “etc.” (e.g., p. 1-13, line 16) and attempt to enumerate all items in a list.

23
 24 P. 1-13, line 22. An “assumption” is essentially an untested hypothesis. For example, an
 25 assumption that an interior indoor space is well-mixed is a hypothesis. More critical discussion
 26 of assumptions would be helpful.

27
 28 p. 1-13, line 25. Earlier, the term uncertainty “characterization” is defined as qualitative, but
 29 here it is implied to be quantitative. Use terminology consistently.

30
 31 p. 1-13, line 27. “assessing the evidence from across studies” – does “evidence” here refer to
 32 evidence for causality, or does it refer to empirical information from which scenarios, models,
 33 and model inputs are inferred?

34
 35 p. 1-16, line 5, please define “transfer of effects”

36
 37 Table 1-2 on p. 1-20 is very useful. Another table would also be useful. Recommend that a table
 38 be added that relates “aspects” to the “Weight of Evidence” categories. Example:

39

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

Biological Gradient					
Strength of observed association					
Experimental Evidence					
Temporal Resolution					
Specificity					
Analogy					

- 1
2 The entries in each row could either be text descriptions specific to each case, or some
3 combination of graphics and text. A table such of this could be used in ISAs for all criteria
4 pollutants.
5
6 Page 1-21, line 9-10. Missing here is “exposure-response.” Dose and exposure are not the same
7 thing, nor are exposure and concentration. Some discussion on these points would be helpful.
8
9 Page 1-21, line 13-14. Here again, terms “susceptible” and “vulnerable” are used but not
10 defined. How do these relate to “sensitive”?
11
12 Page 1-21, line 29-31. Should also mention the role of exposure misclassification if ambient
13 concentration is used instead of exposure.
14
15 Page 1-22, line 5: it is not entirely self-evident that averaging will “linearize” a signal, and
16 assumption such as this might introduce error. If the goal of a model is to predict individual
17 incidences of adverse health effects (e.g., number of individuals affected), then averaging as
18 discussed here might be problematic.
19
20 **Charge Question 6:** Chapter 2 has been revised and expanded to provide more information on
21 atmospheric science and exposure assessment, policy relevant considerations, and integration of
22 CO health effects.
23 a. The section on policy-relevant considerations was revised to present additional detail on the
24 concentration-response relationship observed in a multi-center controlled human exposure
25 study, present results from a new U.S. multicity epidemiologic study investigating the potential
26 presence of a threshold and departure from linearity, and summarize the evidence for
27 susceptible populations. Please comment on these revisions.
28
29 b. A section and summary figure have been added to the end of Chapter 2 to summarize the main
30 conclusions of the ISA regarding the health effects of CO and the range of concentrations at
31 which effects are observed, along with uncertainties that complicate the interpretation of the
32 evidence. We would appreciate CASAC comment on the material in this section and its
33 effectiveness in presenting the conclusions of the ISA.

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Response to Charge Question 6:

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

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

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

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

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

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

Page 2-5, line 31, define “pCO”

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

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

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

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

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

Section 2.6, policy-relevant considerations.

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

- 1 Section 2.6.2 concentration-response
2 The chapter would benefit from a discussion somewhere of the difference between
3 concentration, exposure, and dose. Terms should be used consistently. For example, p. 2-18, line
4 32 refers to “dose-response” but might actually be based on potential dose or exposure.
5 Similarly, top of page 2-19, isn’t it the case that clinical studies deal with potential dose and not
6 merely concentration?
7
8 Table 2-1, label the number scale at the bottom of the last column – i.e. define “effect estimate.”
9
10 Page 2-22 seems repetitive of Section 2.5
11
12 Page 2-22 and 2-23. There seems to be contradictory text to the effect that exposure
13 misclassification leads to bias (see p 3-113, lines 2-4) and then later that it would only widen
14 confidence intervals (p-23, lines 17-18).
15
16 Page 2-25, line 14 – seems to presume a linear dose-response relationship. This should be stated
17 and discussed.
18
19 What about ecological effects? Health effects associated with climate change?
20
21
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1 **Dr. Milan Hazucha**

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

5
6 Charge: *“In response to comments from the CASAC CO Panel, material has been added to*
7 *Chapter 4 describing comparisons among predictive COHb models, the relative influence of*
8 *differing exposure scenarios on COHb concentration, and endogenous CO production rates in*
9 *individuals with various diseases and conditions. Please comment on the usefulness of this*
10 *information in illustrating the factors influencing COHb kinetics and potential COHb levels*
11 *under various scenarios”.*

12
13 This chapter of the Second Draft is much more comprehensive in discussing the respective
14 material. The Chapter has been expanded by more than one third. New subsections were added
15 (4.2.3, 4.3.4, 4.4.3.1) and most of the old subsections were expanded, some substantially (4.2.4,
16 4.5). This is mostly to the benefit by facilitating better understanding of the section topics.
17 In general, the authors adequately addressed CASAC’s CO panel comments by appropriate
18 revisions and addition of relevant material discussed in sufficient detail. One question, however,
19 which in my view was not satisfactorily answered, is “Which COHb model is the best in
20 estimating venous COHb”?
21

22 **Section 4.2.1 The Coburn-Forster-Kane and Other Models**

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

28 **Section 4.2.3 Model Comparison”**

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

34 **Section 4.2.4 Mathematical Model Usage**

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

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

3 **Section 4.3.2.4 Other Tissues**

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

9 **Section 4.3.4 COHb Analysis Methods**

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

13 **Section 4.4.3.1 Fetal Pharmacokinetics**

14 Short and concise new subsection with a figure, pointing out to maternal-fetal differences in
15 COHb buildup and elimination. However, there are more recent studies published on
16 maternal/fetal COHb correlation that should be briefly discussed as well (Hayde et al., Early
17 Human Development 58:205-212, 2000 and other articles from this group., Ziaei et al, Paediat
18 Perinat Epidemiol 19:27-30, 2005). Although these studies are concerned with specific diseases
19 they have used healthy controls.

20 **Section 4.5 Endogenous CO Production and Metabolism**

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

25

26 **More specific comments:**

27 Reference list needs to be updated.

28 Page 4-3, lines 1-9: It would be easier to follow parameter and variable description if they were
29 listed in two columns.

30 Page 4-3, line 17 and p.4-9, line 7: Clarify. Do you mean $\pm 0.5\%$ of the nominal value?

31 Page 4-5, l. 9: Which two parameters? Be more specific.

32 Page 4-9, l.13 Clarify. Is it Gosselin's model?

33 Page 4-9, l.14: Clarify. Is it linear or non-linear CFK model?

34 Page 4-10, l. 6: There is no 4 ppm value in table 4-1.

35 Page 4-10, table: increase font size for V_A

36 Page 4-10, l. 16: This study was done in police cars which are regularly maintained and tuned.
37 So the real CO value is somewhere between 5 and 50 ppm.

38 Page 4-14, l.14: insert after "interface" the words "into plasma and subsequently into RBC"

39 Page 4-15, fig. 4-7. Unusual referencing of the source. Why not simply say that the source is
40 U.S.EPA 2000.

- 1 Page 4-16, l. 22: The value for Haldane constant M is reported to be 218. However, some
2 sections report the use of other values, like 230. The M value should be used uniformly,
3 whenever possible.
- 4 Page 4-17, l. 17: Suggest replacing “quickly” with “2-10 min”.
- 5 Page 4-20, table 4-3; I am not sure that we need this table. For most of exposure conditions listed
6 in the table COHb levels are well beyond the scope of this document. Suggest deleting.
7 The three sentences in the text (line 11-14) are sufficient.
- 8 Page 4-21, l. 2-15: Similarly, the discussion of rodent’s data does not seem to be too relevant. In
9 some referenced studies, though not on the list, %COHb levels were as high as 80%.
- 10 Page 4-23, l.17: “distribution” might be a better word than “uptake”.
- 11 Page 4-28, l. 27-29: Delete, not relevant.
- 12 Page 4-31, l 6: Suggest replacing “processes” with “function”
- 13 Page 4-31, l.8: Suggest replacing “combat” with “compensate for”

14
15 **Chapter 5: Integrated Health Effects of the Second External Review Draft of the ISA for**
16 **Carbon Monoxide (sections 5.1 and 5.5).**
17

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

26
27 In contrast, the summary statement on **p. 5-31, 1.25-26**, over interprets the reviewed studies in
28 this subsection (**5.2.1.8**). Considering all the caveats these studies report, there is a lack of
29 coherence between the endpoints and the evidence of the effects is of uncertain significance.

30
31 **Section 5.5 Respiratory Effects.** The author(s) of this section should have been more critical
32 evaluating the studies discussed in this section, particularly when summarizing the findings. For
33 example, on **p.5-118, 1.13-17** how can the Asthma study findings, to quote “suggest a potential
34 effects of CO on lung function at relatively low CO concentration..” when CO is 3.8 ppm? This
35 is a concentration which will result in <1% COHb. Moreover, in asthmatics the endogenous
36 production is higher than 3.8 ppm (section **4.5**)! At this level CO has no effects on lung function!

37
38 Similarly, contrary what is stated on **p.5-120, 1.7-9** European studies do not provide stronger
39 evidence than the US studies. Their findings are also full of caveats which make the conclusions
40 uncertain.

41
42 **Page 5-143, 1.13-14** state that “epidemiologic studies provide evidence of positive
43 association.....” However, statements on **1.18-23** which is a correct summary of available
44 evidence contradict this assertion.

45

1 **Page 5-143, 1.29-30** statement should be reconciled with subsequent statement on **1.31-32** which
2 correctly summarizes the available evidence.

3

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Dr. Michael Kleinman

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

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

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

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

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

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

1 **Dr. Francine Laden**

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3
4 Section 5.1.3.2. Recent Studies of Non-Hypoxic Mechanisms, is an excellent summary and I
5 agree with its conclusions. The multicenter controlled human exposure study is well described
6 and the levels at which effects were observed are now clear.

7
8 One editorial comment, the definitions of Hb and Mb should be repeated at the beginning of each
9 chapter

10
11 The descriptions of the epidemiologic studies and the studies of the associations between blood
12 markers and ambient CO concentrations are good. The following reference should be added to
13 5.2.1.8:

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

18
19 A table or figure summarizing the results from the blood markers studies (much like the ones
20 included later in the chapter) would be very helpful.

21
22 A similar table or figure summarizing the results of the HRV, ECG abnormalities, arrhythmias,
23 blood pressure (Sections 5.2.1.1. through 5.2.1.7. would be helpful as well.

24
25 In Figure 5.6. it should be made clearer that the other pollutants, used as separators, are included
26 as co-pollutants in the models of CO with the different cardiovascular outcomes.

27
28 I agree with the conclusions of each of the other health outcomes: CNS, birth outcomes,
29 respiratory effects, mortality , and of susceptible populations.

1 **Dr. Arthur Penn**

2
3 Initial response to CO ISA, 2nd external review draft

4
5 Many of the conclusions presented in the 2nd external review of the ISA, are retained
6 (understandably) from the 1st ISA, My focus here is on areas of CVD-related outcomes on which
7 less emphasis has so far been placed and which I believe deserve additional attention since they
8 deal with biological plausibility of CVD outcomes in response to elevations in low daily ambient
9 CO levels. These outcomes also are consistent with the statement at the top of p. 5-67 “It is
10 conceivable that the most sensitive individuals respond to levels of COHb lower than 2%” as
11 well as with the “causal relationship” statement at the bottom of that page.

12
13 Ambient CO Effects on CVD

14
15 The most impressive CO-related CVD results remain the 20+-year-old controlled human
16 exposure studies of Allred et al; Kleinman et al; Sheps et al; however, a direct
17 connection between these results and the predictions for CO effects on CVD morbidity/mortality
18 at CO levels close to ambient has yet to be made. The effective CO exposure levels in those 3
19 studies were > 2 orders of magnitude above ambient levels and resulted in COHb levels of 2-
20 4%. With ambient CO levels at 0.5-0.6 ppm and associated COHb levels well below 2%, the gap
21 between a) the controlled studies with small numbers of high-risk volunteers exposed
22 to ≥100ppm CO and b) real-life, large population exposures to small increases (≤1 ppm) in daily
23 max [CO] is too large to discount at present. Further, other studies (Adir et al, 1999; Kizakevich
24 et al, 2000) with healthy volunteers suggest little or no major responses to elevated (as high as
25 3000 ppm) CO exposure levels. In those studies there were no reported arrhythmias, no changes
26 in lactate/pyruvate, no effects on ST-segment changes or on cardiac rhythm.
27 The focus on possible CO effects in patients with major artery occlusion and MI history is
28 understandable from the perspective of a potentially highly susceptible population, but moves
29 attention away from other populations that may be more likely at risk to elevations in ambient
30 CO.

31
32 Alternative populations meriting attention are the groups suffering from CHF (pp. 5-43 to 5-45)
33 and arrhythmias (pp. 5-24 to 5-26). While most of the evidence here is carried over from the 1st
34 ISA Draft, some of the reports summarized in this section + others noted in other sections of
35 Chapter 5 are worthy of further consideration. In addition I have added some studies from the
36 past 12 years that were not mentioned in the 2nd ISA Draft.

37
38 Results reported by Yang (JTEH, 2008) on Taipei data for the years 1996-2004--while CHF
39 hospital admissions (HAs) were associated with all 5 major air pollutant groups for warm days,
40 the only association on cold days was with increases in ambient CO.

41
42 Mann et al (EHP, 2002) reported that a 1ppm increase in 8-hr average CO in So. California was
43 associated with a 3.6% increase in same-day IHD HAs for patients with a 2^o diagnosis of CHF
44 and 2.99% increase for those with a 2^o diagnosis of arrhythmias.

1 Peel et al, (Am J Epidemiol, 2007) reported an association between a 1 ppm elevation in 1 hr
2 max CO and HAs for patients with dysrhythmias and CHF who had hypertension as a co-morbid
3 condition. This was an 8-year study with > 4.4 million patient visits to 31 Atlanta area hospitals.
4

5 Other relevant CO/CHF studies include:
6

7 a) Morris et al (AJPH, 1995)--elevated ambient CO levels in 7 US cities were associated with
8 increased HAs for CHF in elderly patients;
9

10 b) Burnett et al (Epidemiology, 1997)--daily high hour ambient CO levels on day of HA had the
11 strongest association of any of the 5 major air pollutants with HAs for CHF;
12

13 c) Morris and Naumova (EHP, 1998)--HAs in Chicago for CHF were most strongly associated
14 with increases in ambient CO--effect was strongest at lowest temperature (see Yang, above);
15

16 d) Stieb et al (Environ Hlth, 2004)--in a multicity study in Canada (1980s & early 1990s), for
17 every 0.7 ppm increase in 24-hr mean [CO], there was a 2.6% increase in ED visits for
18 MI/angina, but a 3.8% increase in visits for CHF;
19

20 e) most recently, Bell et al (EHP, 2009- in ISA reference list, but not discussed??) in a study of
21 emergency HAs for CVD and their association with 1 hr max. CO levels in 126 US urban
22 counties (av. max CO level=1.6 ppm) found the highest % increase in CO-related risk for HAs
23 (~1%) was for heart failure in patients > 65 yrs of age. HAs for 9.3 million patients over 7 years
24 were examined.
25

26 The downside of these studies--that they are association/correlation studies--is countered by the
27 large #s of patient records screened in each of these independent studies and the similarity of the
28 findings for urban CHF/arrhythmia patients in the US, Canada & Taiwan.
29

30
31 Blood Markers of CO Exposure-Coagulation (but not inflammation)

32 A few recent studies (Baccarelli et al, 2007; Delfino et al, 2008; Rudez et al, 2009) point to
33 increased platelet activation and pro-coagulation effects associated with elevations in ambient
34 CO. In these and other studies (Ruckerl et al, 2006, 2007; Steinvil et al, 2008) elevations in
35 fibrinogen in response to elevated CO are largely absent. Many of these studies note that
36 elevations in ambient CO were not associated with any inflammatory responses (see question to
37 Panel members below). One exception was the recent report of Ljungman et al, (EHP, 2009).
38 Among 955 MI survivors, the 16% with specific polymorphisms in both IL-6 & fibrinogen genes
39 showed larger IL-6 responses to elevated CO than did MI survivors without these
40 polymorphisms.
41

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

- 1 models of injury/disease (sickle cell disease, I/R injury, lung injury associated with
- 2 cardiopulmonary bypass) have reported on the therapeutic value of treatment with “low”, i.e.,
- 3 250 ppm, doses of CO.

1 **Dr. Beate Ritz**

- 2
- 3 1. *The framework for causal determination presented in Chapter 1 was developed and*
- 4 *refined in other ISAs (e.g., the PM ISA). During previous reviews, CASAC generally*
- 5 *endorsed this framework in judging the overall weight of the evidence for health effects.*
- 6 *Please comment on the extent to which Chapter 1 provides necessary and sufficient*
- 7 *background information for review of the subsequent chapters of the CO ISA.*
- 8

9 This chapter has improved but still does not adequately address and present methodologic

10 concepts in epidemiology and, thus, lacks clarity in how epidemiologic studies are evaluated and

11 determined to be “high or low quality studies” as necessary for applying the criteria listed in

12 Table 1.2 (i.e. for assessing the weight of evidence for causal determination).

13

14 A minor point: I previously recommended using the more appropriate term ‘*effect measure*

15 *modification*’ instead of ‘effect modification’ but the wording in this chapter has not been

16 corrected. More importantly, however, while there is some improvement, the authors of this

17 chapter still seem to not be fully understanding nor formulating adequately some of the issues

18 involved in confounding and confounder control. They claim on page 1-15 that “deciding which

19 variables to control for in a statistical analysis of the association between exposure and disease or

20 health outcome depends on knowledge about possible *mechanisms* and the distribution of these

21 factors in the population under study. Identifying these *mechanisms* ...”. Knowledge of

22 ‘mechanisms’ may help, but such knowledge is not needed to decide whether a covariate is a

23 potential confounder neither is it necessary to know mechanisms to assess confounding. It is

24 furthermore completely obscure what the authors mean by the following sentence on page 1-15

25 “adjustment for potential confounders can be influenced by differential exposure measurement

26 error”; here they seem to confuse error in measuring confounding variables with error in

27 exposure assessment? Finally on page 1-13 the second sentence under 1.6.3. “Uncertainty can be

28 defined...” seems to confuse precision and validity or at least does not acknowledge that these

29 are two different concepts that have a different place in judging study results. These confusions

30 of concepts does not instill much confidence in the ability of staff who wrote this chapter to

31 judge epidemiologic studies adequately according to established criteria for study validity and

32 precision (both contributing to accuracy); this is further confirmed by the chapter 5 qualitative

33 reviews that are still grossly lacking in consistency and interpretation of epidemiologic results.

34

35 The criteria for causal determination detailed in table 1-2 are similar to those used by the

36 IOM and the International Agencies for Research on Cancer. Yet, they leave open what the

37 criteria are for deciding that a study is high quality (for example, confounding is a bias, so why

38 list bias and confounding apart from chance?) and it is also unclear what is meant by “replicated”

39 results and why this would be a criterion. Again, without a standardized approach to the review

40 of epidemiologic studies or a quantitative meta-analysis based review, these criteria remain

41 ambiguous. Since the epidemiologic literature on criteria air pollution health effects has

42 multiplied greatly in the past decade, it would be appropriate if EPA staff abandoned qualitative

43 reviews in favor of quantitative effect estimates based on meta-analytic procedures to draw

44 inferences about the scientific literature and used standardized and transparent rules for data

1 abstraction. Such a systematic and quantitative procedure requires making the authors'
2 assumptions explicit rather than allowing authors to emphasize studies they agree or disagree
3 with and to pick the results they like to emphasize over others. Such quantitative reviews could
4 be contracted out to entities that are able to conduct meta- or pooled analyses.
5
6

7 5. *Chapter 5 presents information on cardiovascular, central nervous system,*
8 *developmental, respiratory, and mortality outcomes following exposure to CO. To what*
9 *extent are the discussion and integration of toxicological, clinical, and epidemiologic*
10 *evidence for these health effects scientifically sound, appropriately balanced, and clearly*
11 *communicated? Are the tables and figures presented in Chapter 5 appropriate,*
12 *adequate, and effective in advancing the interpretation of these health studies?*
13

14 In Chapter 5, the qualitative description of epidemiologic studies improved somewhat but is
15 still inadequate; the level of detail devoted to each study in the text seems still arbitrary and the
16 information provided in tables and figures selective without being systematic; for example why
17 did the authors decide to present in Figure 5-8 the citywide and negative associations for the
18 Australian CO study of PTB (Jalaludin) and not the positive associations for births within a 5km
19 radius of a monitor. The review of birth weight and air pollution is lacking a discussion of the
20 difference between LBW and term LBW sorely needed since LBW includes preterm birth
21 outcomes that are then discussed separately and studies examining LBW are possibly more
22 comparable in their results to those examining PTB; only term LBW is a mutually exclusive
23 outcome. Also the measure of birthweight as a continuous outcome compared to the
24 dichotomous variables LBW and PTB deserve some more general introduction about their
25 general value (similar to the discussion of SGA versus IUGR), i.e. do we really expect the whole
26 birthweight distribution to shift according to ambient air pollution exposures or only the most
27 susceptible infants to be affected.
28

29 Surprisingly, there is still a lot of information I requested in my first review missing from this
30 new draft. This includes the following: no information is provided in the tables concerning the
31 type of study design employed (e.g. Table 5-12). I also already mentioned previously that many
32 of tables report mean CO levels and mention 24 hrs or 8 hrs in brackets; this is misleading for
33 pregnancy outcome studies in which the averages are for trimesters, weeks, or months (e.g. the
34 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-
35 9 am period – however this mean represents a mean over the whole *first month* of pregnancy and
36 the Wilhelm and Ritz (2005) study mentions a 1.4 ppm mean for 24 hrs but this is in fact a *first*
37 *trimester* mean of 24 daily measurements; the way this data is shown now the bracketed 24 hour
38 mention seems to imply similar averaging period and comparability in effect estimates. I also
39 mentioned already previously that while the Ritz et al 2007 study is listed in table 5-12 no results
40 for this study are presented in figure 5-6. I had also recommended to rescale quartiles to a
41 continuous estimates rather than leaving results from important papers out of a figure that gives
42 an overview over all study results.
43

44 Also I mentioned previously that according to the text accompanying the figures, the
45 estimated increase in CO presented have been ‘standardized’, however, how this might have

1 been done across so many different study types and averages for differing exposure periods
2 (rather than 24 hour averages as the authors of these chapters seem to imply) has not been
3 explained. Also, in figure 5.1 the title says that the effect estimates have been standardized to a
4 1ppm increase in ambient CO for 1-hr max CO concentrations, 0.75 ppm for 8-h max CO
5 concentrations and 0.5 ppm for 24 hrs avg CO concentrations, but the figure does not tell us
6 which scale has originally been used in which study and it might be questionable whether effect
7 estimate sizes based on these different scales and based on different length lag periods are
8 comparable to each other (indicating which study used which scale would be informative.
9

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

1 **Dr. Paul T. Roberts**

2
3 **Revised Comments on 2nd draft ISA**

4
5 **ISA Charge Question 2. Chapter 3 has been revised and expanded in response to Panel comments**
6 **regarding climate, monitoring, spatial variability, and exposure.**

7
8 **2b. Additional detail has been provided regarding Please comment on the usefulness of these**
9 **revisions in characterizing the information provided by the CO monitoring network.**

10
11 In general, the expanded discussions in the 2nd draft ISA Chapter 3 on CO detection limits, monitoring
12 details, and spatial CO characteristics are very useful in characterizing the information provided by the
13 CO monitoring network and in qualifying the data for use in exposure estimations. My detailed
14 comments are provided below.

15
16 **In discussion of non-anthropogenic CO emissions on page 3-5:** it is confusing in the first paragraph
17 (starting on line 3) to have fire emissions of about 13% (14.5 MT) shown in Figure 3-1, but biogenic
18 emissions of about 5% not shown in Figure 3-1, and the text implies that the geogenic emissions are
19 included (in the miscellaneous category?). This is confusing to the reader and makes it difficult to
20 compare these smaller, but still important sources. Please add biogenics to Figure 3-1 and make it clear
21 what is included.

22
23 **Comments on discussion of Hudman et al and Figures 3-3 and 3-4, starting on page 3-5 at line 21:**
24 First, I suggest that this be a new paragraph; it is a different topic from the non-anthropogenic emissions.
25 In addition, the CO from oxidation of VOCs, of isoprene, and of other biogenic VOCs (see lines 27-29),
26 which are apparently huge in this simulation, relative to the anthropogenic CO emissions, have not been
27 discussed before. These secondary emissions sources needed to be discussed in the overall context of
28 CO emissions first (or put the general discussion in with the Climate text, Chapter 3.3.1). In addition,
29 the potential influence of this huge source of CO on the results of the simulation and the conclusion
30 needs to be discussed. I also suggest that Figure 3-3 be dropped, since I find it hard to compare these
31 colored spatial plots. In contrast, Figure 3-4, as an example of the results, gets the point across that
32 reducing the anthropogenic emissions by 60 % made significantly better comparisons with
33 measurements. Maybe also add a statement saying that other results in the paper support this general
34 conclusion.

35
36 **Additional comment on the paragraph on page 3-5, lines 21-29:** I suggest that a sentence be added
37 translating the Tg amounts to MT, so that these emissions can be placed in context with the rest of the
38 emissions discussion.

39
40 **Comments on page 3-7, lines 13-15:** I suggest that a comment be added (either in the text or the figure
41 caption) about general transport winds being from west to east at this latitude, thus carrying the
42 emissions from the Alaska fires across Canada and the northern US and into the north Atlantic, as shown
43 in Figure 3-5 (assuming the data support this).

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

5
6 **Page 3-12, lines 8-9:** The comments on limited mixing between the hemispheres would benefit from an
7 additional comment that northern hemisphere CO emissions are significantly larger than the emissions
8 in the southern hemisphere, plus a representative reference.

9
10 **In general, the expanded discussions on monitor detection limits and monitoring locations in**
11 **Chapter 3.4 (pages 3-18 to 3-31 and associated Annex figures and tables) are critical to**
12 **understanding CO concentrations and are an important addition to the ISA. However, these**
13 **limitations are still often left out of the discussions on CO concentrations in Chapter 3.5. In**
14 **general, the relaxation of CO monitoring requirements and the continued use of older, less**
15 **sensitive, monitors with poor levels of detection impedes the use of monitoring data for exposure**
16 **assessments and climate, especially in the future as CO concentrations decrease. See my detailed**
17 **comments below.**

18
19 **Page 3-19, lines 20-23:** This discussion on the needs for trace-level CO measurements should include
20 the use of low-level CO data for improved exposure estimates at current ambient concentrations in many
21 locations in the US.

22
23 **Table 3-2:** Please fix the first row of the table. I think there should be a header row labeling the
24 columns as “Parameter” and “Specification”, for example, plus the current first row should be part of the
25 body of the table and left justified in each column.

26
27 **Page 3-20 lines 3, 12, and 18:** The LODs listed on these lines are not the same as listed in the
28 referenced Table A-1 in the Annex, which lists the LOD of the trace-level monitor as 0.02, not 0.04.
29 Thus, the value listed as 50% of the LOD on line 6 should be 0.01. Note also that several of the LOD
30 levels listed in slide 10 of the presentation should be 0.02, not 0.04.

31
32 **Page 3-20, line 5:** I suggest that this line start with “When the monitored value is below the LOD, some
33 states...”

34
35 **Page 3-20, line 14, page 3-21 and Figure 3-8:** This discussion on a comparison of older and newer
36 monitors with specific quantifications is a good one, and important to include here. However, the last
37 sentence of the paragraph (lines 6-8) does not make sense to me. Also, the CO axis of the figure needs
38 to be labeled and the units of the time axis needs to be added (hours since some start time, or?). The
39 similar figure in slide 10 of the presentation is much better at showing the data, plus the axis are labeled;
40 these are good modifications and address my comments on the figure.

1 The limitation of the LOD issues discussed in Chapter 3.4 need to be added in several places in Chapter
2 3.5, including at the beginning of the sentence that starts on line 11 of page 3-36, in Figures 3-7, 3-8,
3 and 3-9. In particular, statements similar to the paragraph at lines 13-18 on page 3-43 (good job there!)
4 could be added to address this issue at these locations in the text and in the conclusions (3.7.3) and the
5 summary of conclusions (2.1).

6
7 **Page 3-41, lines 1-3:** What was the cause of the 10.9 ppm CO measured at the Newkirk, OK site? This
8 seems like an unusual concentration.

9
10 **Page 3-43, lines 13-18:** This is a good qualifying paragraph which is needed here and other places. On
11 line 15, I suggest the following wording: "...in large part very near or below the detection ..."

12
13 **Figure 3-18 on page 3-45 (and Figure 3-20):** How is the data below LOD treated for this and similar
14 figures? Might this influence the lower ends of the box-whisker plots? I suggest that a comment on this
15 be added.

16
17 **Chapter 3.5.1.2:** Add a note that all of these monitors in LA and Denver are older, higher LOD,
18 monitors, and add some comments similar to the comments at lines 13-18 on page 3-43.

19
20 **Page 3-60, lines 14-15:** I don't see how the data shown in Figure 3-24 can lead to a statement that
21 includes the following words "...near-road CO concentrations..".

22
23 **Page 3-76, lines 5-6:** I suggest this sentence be moved to the end of the paragraph at lines 12-21 on
24 page 3-77. In addition, the sentence should read "...analogous to Figures 3-36 and 3-37 forin Annex
25 A, Figures A.44 to A.48."

26
27 **Page 3-77, line 11:** I suggest these are meteorological, not micrometeorological factors.

28
29
30 **2c. The section on exposure assessment has been reorganized to provide information on Does
31 the Panel consider that the sources of exposure error have been appropriately characterized, and
32 agree with the revised conclusions regarding the impact of exposure error due to spatial
33 variability and the presence of CO as part of a combustion-related mixture on health effect
34 estimates from time-series epidemiological studies?**

35
36 In general, the expanded discussions in the 2nd draft ISA Chapter 3.6 on sources of exposure and
37 exposure assessment are a great improvement and are very useful in characterizing the potential impacts
38 of exposure error. My detailed (minor) comments are provided below.

39
40 **Page 3-93, lines 18 and 29:** Please explain or modify the terms "driven cavity" and "posterior
41 probability distribution function".
42

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

7
8 **Page 3-98, line 11:** How can a regression coefficient be 1.99 (greater than 1.0)? Also, the results in
9 lines 9-11 and in lines 13-14, although from the same reference, seem inconsistent; please explain how
10 they are consistent or different.

11
12 **Page 3-114, line 26:** Table A-1 says the LOD for trace-level FRMs is 0.02, not 0.04 as stated here.

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

16
17 **Page 3-117, line 15:** I suggest that the word “nearby” be added, so that the sentence would read “...at a
18 location with few nearby CO sources could...”.

19
20
21 **In summary, Chapter 3 of this 2nd External Review Draft of the ISA clearly conveys and**
22 **appropriately characterizes the atmospheric science and air quality analyses. The information**
23 **provided regarding CO source characteristics, CO chemistry, policy-relevant background CO,**
24 **and spatial and temporal patterns of CO concentrations accurate are relevant to the review of the**
25 **CO NAAQS.**

26
27
28 **Minor edits and typos in the 2nd draft ISA:**

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

41
42 Selected, easy for me to find, references for Land Use Regression and spatial mapping (see above
43 discussion on Chapter 3.6.3):
44

- 1 Gauderman, Avol, Lurmann, Kuenzli, Filliland, Peters, and McConnell “Childhood Asthma and
2 Exposure to Traffic and Nitrogen Dioxide, *Epidemiology* 2005; 16, 737-743.
3
- 4 Ross, Jerrett, Ito, Tempalski, and Thurston “A land use Regression for predicting fine particulate matter
5 concentrations in the New York City region”, *Atmospheric Environment* 41 (2007) 2255-2269.
6
- 7 Hoek, Beelen, Hoogh, Vienneau, Gulliver, Fischer, and Briggs “A review of land-use regression models
8 to assess spatial variation of outdoor air pollution” *Atmospheric Environment* 42 (2008) 7561-7578.
9
- 10 Henderson, Beckerman, Jerrett, and Brauer “Application of Land Use Regression to Estimate Long-
11 Term Concentrations of Traffic-Related Nitrogen Oxides and Fine Particulate Matter *ES&T* 2007, 41,
12 2422-2428.
13
- 14 Molitor, Jerrett, Chang, Molitor, Gauderman, Berhane, McConnel, Lurmann, Wu, Winer, and Thomas
15 “Assessing Uncertainty in Spatial Exposure Models for Air Pollution Health Effects Assessment *EHP*
16 vol 115,no 8, August 2007.
17
- 18 Popawski, Gould, Setton, Allen, Su, Larson, Henderson, Brauer, Hystad, Lightowlers, Keller, Cohen,
19 Silva, and Buzzelli “Intercity transferability of land use regression models for estimating ambient
20 concentrations of nitrogen dioxide” *J Exposure Science & Environmental Epidemiology* (2008), 1-11.

1 **Dr. Armistead Russell**

2
3 **Review of CO ISA 2nd Draft**

4
5 In general, I am pleased with the modifications to the ISA, and believe that the 2nd draft is
6 stronger in general. It provides the level of information needed to support the REA and policy
7 analyses.

8
9 In response to specific Charge Questions:

10
11 *2. Chapter 3 has been revised and expanded in response to Panel comments regarding*
12 *climate, monitoring, spatial variability, and exposure.*

13
14 I appreciate the substantial information added in regards to the potential impact of CO on
15 climate. As noted, the impact is likely small, and highly uncertain, though the physics are such
16 that it almost has to have an impact, even if unknown or not soon knowable. While this lack of
17 certainty may inhibit developing a related secondary standard, it should motivate the appropriate
18 research to assess the likely magnitude of the impact. The section on monitoring and
19 instrumental capabilities is likewise strengthened. This section should continue to stress the
20 utility of CO as an indicator for gasoline-powered automobile emissions, and the CO monitoring
21 network has tremendous value beyond just demonstrating attainment.

22
23 *a. Evidence reviewed in Chapter 3 of the ISA indicates that the direct contribution of CO*
24 *to greenhouse warming is very small, while the role of CO in atmospheric chemistry*
25 *cycles involving other species makes a larger contribution to radiative forcing. This*
26 *combined evidence leads to the conclusion in Chapter 2 that a causal relationship exists*
27 *between current atmospheric concentrations of CO and effects on climate. What are the*
28 *Panel's opinions related to this causal statement and the evidence provided to support it?*

29
30 A causal statement is appropriate, though it should also note that the extent of the impact
31 is highly uncertain which inhibits using a causal determination to develop a secondary
32 standard at this time.

33
34 *b. Additional detail has been provided regarding the detection limits of CO monitors in*
35 *the regulatory network, the number of monitors reporting at each horizontal spatial*
36 *measurement scale and comparison of monitoring data at each scale, and spatial*
37 *variability of CO concentrations near major sources, particularly roadways. Please*
38 *comment on the usefulness of these revisions in characterizing the information provided*
39 *by the CO monitoring network.*

40
41 This addition strengthens the document. Further discussion of the adequacy of the
42 current monitoring network and the potential implementation of a near-road network
43 should be considered.

1 **Dr. Anne Sweeney**

2
3 **Individual Comments**

4 Figure 1-1 should be revised. The current figure is unclear with respect to what it is depicting. It
5 would be helpful if this figure follows the flow of an individual study or paper that is identified
6 in the literature review. (will provide an alternative diagram).
7

8 EPA has explained the criteria for study selection and evaluation. However, some additional
9 explanation as to why the focus of the literature review is on studies conducted in the U.S. and
10 Canada is needed. In particular, given the scarcity of literature on welfare effects, have studies
11 from other countries been considered?
12

13 In Section 1.5, the text on page 1-10, line 22 refers to “the extensive body of literature” but only
14 **four** references are cited. The text could be more clear as to the scope of the literature review
15 and how it was narrowed to the four references cited.
16

17 Page 1-11, line 4, the term “necessarily” seems out of place.
18

19 Page 1-12, line 7, what is meant by “assessment?” Does this refer to “endpoint”?
20

21 Section 1.6.3. The term “measure” is unclear. Does this refer to an empirical quantity that is
22 measured, estimated, or predicted? Or does it refer to a metric for a quantity? Suggest that the
23 term “measure” should be replaced with more specific or descriptive terms.
24

25 Should avoid use of “etc.” (e.g., p. 1-13, line 16) and attempt to enumerate all items in a list.
26

27 P. 1-13, line 22. An “assumption” is essentially an untested hypothesis. For example, an
28 assumption that an interior indoor space is well-mixed is a hypothesis. More critical discussion
29 of assumptions would be helpful.
30

31 p. 1-13, line 27. “assessing the evidence from across studies” – does “evidence” here refer to
32 evidence for causality, or does it refer to empirical information from which scenarios, models,
33 and model inputs are inferred?
34

35 p. 1-16, line 5, please define “transfer of effects”
36

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

1
2

Aspect	Causal	Likely to be Causal	Suggestive of Causal	Inadequate to Infer	Not Likely to be Causal
Consistency					
Coherence					
Biological Plausibility					
Biological Gradient					
Strength of observed association					
Experimental Evidence					
Temporal Resolution					
Specificity					
Analogy					

3

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

7

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

10

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

13

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

16

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

21

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

25

26 **Identification of studies for inclusion in the ISA:** Page 1-7, line 4: “included approaches to
27 evaluate issues related to confounding and effect modification by *other pollutants*”---add “and/or

1 host characteristics”; i.e., the level of control for all potential confounding/effect measure
2 modification.

3 Page 1-7, line 5: “Addressed health points and populations not previously extensively
4 researched”: a word of caution in that new evidence can alter previously accepted results.

5
6 **Scientific Evidence Used in Establishing Causality** (1.6.1) Page 1-12, lines 10-13: Add case
7 control design to types of observational studies

8
9 Page 1-7, lines 7-10 (and elsewhere): need to discuss volunteer bias in human clinical studies

10
11 **Application of framework for causal determination:** (1.6.4) Page 1-17: Add to line 21:
12 Strength of the association”

13
14 **Effects on Human Populations:** (1.6.5.1) Page 1-22, lines 26-32: Include references to articles
15 published regarding critical windows of susceptibility (from the 2000 EPA workshop on same)
16 I strongly agree with Dr. Ritz’s suggestion to conduct meta-analyses on the growing number of
17 studies assessing air pollution and adverse human health effects.

1 **Dr. Stephen Thom**

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

10
11 Morbidity assessments for short and long term CO exposure:

12
13 Animal toxicological studies provide evidence that short-term exposure to CO (50-100 ppm) can
14 cause oxidative injury and inflammation and alter pulmonary vascular remodeling. Controlled
15 human exposure studies have not extensively examined the effect of short-term exposure to CO
16 on respiratory morbidity. Positive associations between short-term exposure to CO and
17 respiratory-related outcomes include effects on pulmonary function, respiratory symptoms,
18 medication use, hospital admissions, and ED visits. The problem is that the majority of this
19 literature does not report results of extended analyses to examine the potential influence of model
20 selection, effect modifiers, or confounders on the association between CO and respiratory
21 morbidity. In particular, the lack of co-pollutant models prevents assessment of which effects are
22 due to CO versus other combustion-related pollutants. Yet, the ISA conclusion is that evidence is
23 *suggestive of a causal relationship* between short-term exposure to relevant CO concentrations
24 and respiratory morbidity.

25
26 The ISA outlines limitations in studies that have examined the association between long-term
27 exposure to CO and respiratory morbidity including the lack of replication and absence of
28 validation studies to evaluate some of the epidemiological statistical methodologies, whether
29 health effects observed can be explained by the known biological mechanisms and an absence of
30 co-pollutant analyses to disentangle the respiratory effects from CO versus other combustion-
31 related pollutants. The conclusion was that the evidence is *inadequate to conclude that a causal*
32 *relationship* exists between long-term exposure to relevant CO concentrations and respiratory
33 morbidity.

34
35 Mortality assessments for short and long term CO exposure:

36
37 Epidemiological evidence was reviewed from multi- and single-city studies which suggest that
38 there is an association between short-term exposure to CO and mortality. The limitations in the
39 data were highlighted along with the observation that CO risk estimates were attenuated in co-
40 pollutant models. Despite the uncertainty as to whether CO was acting alone or as an indicator of
41 effects related to other combustion-related pollutants the ISA concluded that *evidence suggests*
42 *there is a causal relationship* between short-term exposure to relevant CO concentrations and
43 mortality from respiratory disorders (page 5-158).

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

12
13 To conclude, my impression is that similar limitations exist in the data for pulmonary effects
14 from short term and long term CO exposure. Despite this similarity, short term effects on
15 morbidity and mortality are given a stronger summary assessment of risk (evidence suggests
16 there is a causal relationship) whereas long-term CO exposure is said to be unlikely to be
17 causally linked to respiratory morbidity and mortality.

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