



**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, NW
Washington, D.C. 20460

Subject: Review of the *Policy Assessment for the Review of the Carbon Monoxide National Ambient Air Quality Standards: External Review Draft*

Dear Administrator Jackson:

The Clean Air Scientific Advisory Committee (CASAC or Committee) Carbon Monoxide (CO) NAAQS Review Panel met on March 22-23, 2010 to review EPA's *Policy Assessment for the Review of the Carbon Monoxide National Ambient Air Quality Standards: External Review Draft*. This letter provides CASAC's overall comments and evaluation. We highlight the most important issues which need to be addressed as the draft Policy Assessment (PA) is revised and finalized.

The Panel expressed appreciation to EPA staff in regard to the first draft of the PA document. We recognize that limited time was available for its creation, given the court ordered deadline. We will offer the main suggestions and concerns identified by the Carbon Monoxide Panel.

The policy document needs to be clearer about how the three main sources of carbon monoxide that contribute to the carbon monoxide dose in the body combine and interact. These three primary sources are endogenous production of carbon monoxide, exposure to indoor sources, and ambient outdoor CO, and consequently, exposure to ambient CO needs to be considered in the context of these other two sources of the biologically effective dose.

The Panel found that there was too much dependence on the now classic clinical study conducted by Allred et al. and funded by the Health Effects Institute (HEI). While agreeing that this seminal study provided important evidence, its findings should not be so emphasized as to ignore more contemporary epidemiologic studies, especially those directed at coronary artery disease and at cardiovascular disease more generally. This line of evidence is important because other cardiovascular conditions affect a large number of people who are at risk from CO exposure.

We support the high level of attention to populations at risk. As for other criteria pollutants, the existence of these populations and the extent of their increased susceptibility are key to promulgating NAAQS that protect the public health. Consequently, the document should give

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1 greater emphasis to the findings of epidemiologic studies. We recommend this greater emphasis
2 across all of the CO documents, beginning with the Integrated Science Assessment and
3 extending through the PA. There needs to be greater balance in treating the various lines of
4 evidence.

5
6 The Panel was divided regarding the level of detail present in the current PA. Some thought the
7 scope of the present PA was appropriate. It may be necessary to include the considerable detail
8 which characterizes the current document. However, a substantial minority felt that an ideal PA
9 should be far shorter and more focused. Staff and the Administrator can turn to the REA and the
10 ISA for more background regarding CL as necessary. The PA could be reduced in length and be
11 a more concise summary of the evidence and how the evidence relates to alternative CO
12 standards. Also, a concise description of how the form of the standard is important would also
13 be useful.

14
15 We point with considerable pride to the decreases in CO levels. However, this success should
16 not color an objective assessment of the potential health consequences of exposures at the current
17 CO NAAQS. While measured concentrations infrequently reach the current NAAQS are
18 infrequent, evidence indicates that adverse health effects could occur at these levels. For that
19 reason, the committee expresses its preference for a lower standard.

20
21 The CASAC and Panel memberships are listed in Enclosure A. The Panel's responses to EPA's
22 charge questions are presented in Enclosure B. Finally, Enclosure C is a compilation of
23 individual panel member comments. We look forward to the Agency's response and the
24 successful completion of the CO NAAQS review.

25
26 Sincerely,

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30 Dr. Joseph D. Brain, Chair
31 CASAC CO Review Panel

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

32
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34 Enclosures

NOTICE

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

Enclosure A

Rosters of the CASAC CO Panel and CASAC

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

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Enclosure B

CASAC's Consensus Responses to EPA's Charge Questions

1. Does the Panel find the introductory and background material, including that pertaining to previous reviews of the CO standard, the current review and current air quality, to be clearly communicated and appropriately characterized?

Chapter 1 of the PA does a good job of providing background. There is a brief review of the CAA and establishment of primary and secondary NAAQS; adequate margins of safety; previous reviews; CO sources in ambient air; the monitoring network; low dose levels; new monitors/NCore network; recent ambient and steady-state decreases in ambient CO; and finally, the “staff’s evaluation of policy implications of scientific evidence in the ISA and results of quantitative analyses based on that evidence.” The PA focuses on the four basic elements of a NAAQS: indicator, averaging time, form and level. None of these elements have been clearly defined in PA. The Panel recommends including clear definitions of these four elements, consistent with previous CASAC recommendations in the review of other criteria pollutants.

2. Consistent with the revised NAAQS process which includes development of this draft Policy Assessment (PA) document, considerations with regard to the primary standard for CO have been organized around a set of policy-relevant questions for the review.

a. Does the Panel find the question posed to appropriately reflect the policy relevant questions in the review?

The questions posed raise the major issues, and the information provided in response to these questions provides the essential evidence required for making policy decisions. It is difficult to make a judgment on the adequacy of protection because there is no estimate of the total population exposed to benchmark CO concentrations. We only have numbers for two test cases, Denver and LA. Guidance needs to be given for application of the findings from these two case studies to the whole county.

The increase in scientific evidence on the effects of environmental CO since the last evaluation of CO standards, as documented in the ISA, comes primarily from epidemiology based studies. A joint consideration of the findings of epidemiological studies and controlled human exposure studies leads to the conclusion that substantial numbers of persons are significantly exposed at what are presumed to be lower concentrations (effective doses) than the doses used in the controlled human exposures. The document does not appear to give the epidemiologic studies sufficient standing (relative to the controlled human exposure data) so that a decision can be made on the adequacy of protection for these individuals. For these reasons it is sometimes difficult to judge the effectiveness of the current standards in protecting the population

One question that was not adequately posed is what are the confounding effects of non-traffic sources of CO, e.g., indoor air. Numerous studies have shown that we spend 80-90% of time indoors. For healthy elderly and people with CVD, the time they spend indoors may be even greater. The non-traffic sources of CO are at times substantial and may override the ambient CO

1 levels in contributing to dose. It is suggested that information from the 2000 criteria document on
2 indoor sources be included.

3
4 *b. Does the Panel consider the document to provide the appropriate level of detail in*
5 *addressing these policy-relevant questions?*

6
7 Yes for the controlled human studies, but not for the epidemiological studies.

8
9 *3. The discussion of the health effects evidence (e.g., section 2.2.1) draws from the most*
10 *recent information contained in the final ISA for CO and information from the previous*
11 *review described in previous Air Quality Criteria Documents.*

12 *a. Does the draft PA accurately reflect the currently available health effects evidence*
13 *for CO as characterized in the final ISA and the extent to which it differs from that*
14 *available at the time of the last review?*

15 *b. Does the Panel find the presentation to be technically sound, clearly communicated*
16 *and appropriately balanced?*

17
18 The description of the data considered by the previous EPA reviews is basically sound but too
19 focused on the Allred et al. study. There should be a way to mention key elements of other
20 controlled human studies in this document. The document continues the emphasis on the use of
21 %COHb as the optimal dose metric for assessing exposure as noted for the controlled human
22 studies. However, the discussion of the epidemiological data only casts doubt on the role of
23 COHb in the epidemiology studies which leaves the issue hanging as to mechanism. It might
24 help to show the theoretical changes in COHb that would result from an exposure of 2 or 3 ppm
25 CO. This would illustrate the issues related to using COHb as a potential mechanism in the
26 epidemiological studies.

27
28 The last review of CO was halted for several years due to the pending study and report on the
29 effects of CO at altitude and at extreme cold environments. The PA should very briefly
30 acknowledge the findings of this report. Without that information in the current document it is
31 difficult to determine to what extent this report should differ from the last review started in 1999.

32
33 In order to facilitate better understanding of the cardiovascular effects, particularly myocardial
34 ischemia, we suggest adding to the reported values of % time changes to angina on p. 2-11, top
35 paragraph, including the actual changes in seconds with the confidence intervals (CI). Moreover,
36 regarding time to angina endpoint, are there any long-term consequences on repeated exposures,
37 on the duration of angina, and frequency of occurrence without CO exposure? EPA should
38 address these questions. If data are not available, the PA should state this to be the case. This
39 information would seem to be important for the more complete understanding of the
40 uncertainties associated with using these data to support the standards

41
42 *4. The discussion of the quantitative analysis of exposure and dose (e.g., section 2.2.2) draws*
43 *from the analyses described in the second draft Risk and Exposure Assessment (REA).*

44
45 *a. Does this discussion accurately reflect the analyses contained in the draft REA?*
46

1 The Panel largely agreed that the discussion in the PA accurately reflects the analyses contained
2 in the second draft REA, although there was not a consensus as to whether the draft REA
3 analyses of exposure and dose represented the optimal approach. (Those comments are found in
4 the response to the REA charge questions). They include the discussion as to whether increased
5 emphasis could be placed on the increment that ambient CO contributes to COHb or whether the
6 emphasis should be on the final resulting %COHb concentration itself (and a related interest in
7 modeling indoor source contribution to COHb to better understand the total COHB
8 concentrations).

9
10 Panel members offered mixed opinion regarding the decision by the EPA not to pursue the 1%
11 COHb benchmark suggested by the Panel. The staff correctly pointed out that “this level
12 overlaps with the upper part of the range of endogenous levels.” One Panel member supported
13 the agency’s decision, since this complies with the EPA’s task “to establish standards that are
14 neither more nor less stringent than necessary for these purposes”, i.e., public health. However,
15 other members considered that a more advanced modeling approach could focus on the
16 increment that ambient CO contributes to %COHb, rather than the final resulting COHb
17 concentration itself. The incremental CO analysis would provide a clear context of the full range
18 of benchmarks for policy analysis. Further, if adverse effects are clearly observed in controlled
19 human exposure studies with a small sample size associated with an increase in the percent
20 COHb of 2%, then it is prudent to consider standards that would use a benchmark of ambient
21 CO-attributable COHb increases as low as 1%. This benchmark would lead to a wider range for
22 a margin of safety, given that a NOAEL for CO effects among susceptible populations has not
23 been demonstrated.

24
25 *b. Does the Panel find the presentation to be technically sound, clearly*
26 *communicated and appropriately balanced?*
27

28 Most panel members agreed that the presentation was technically sound and appropriately
29 balanced, although most of the panel members were concerned that the presentation
30 unnecessarily diminished the value of epidemiological studies in establishing the underpinnings
31 (if not the details) of the quantitative relationship. Further, even though the policy assessment
32 may need to be based on a risk assessment drawn primarily from one particularly informative
33 controlled human exposure study (i.e., the multi-center investigation described in Allred, et al.),
34 there would be value in highlighting the supporting role of other studies, in particular the body of
35 epidemiological evidence.

36
37 The %COHb module of the APEX model, although the most important, also has weaknesses,
38 given that some physiologic data and the range of values for many variables that enter into the
39 model are not transparent. Despite these limitations, however, there seems to be sufficient
40 information for some variables that can be used to refine the estimates generated (e.g., Hb
41 concentrations stratified by race-ethnicity as should be available from NHANES or other readily
42 accessible sources).

43
44 *5. Does the document identify and appropriately characterize the important uncertainties*
45 *associated with the evidence and quantitative analysis of CO exposure and dose, particularly*

1 *those of particular significance in drawing conclusions as to the adequacy of the current CO*
2 *standards?*

3
4 Generally the uncertainties are dealt with appropriately with the exception of the item mentioned
5 below.

6
7 The current review on p. 2-32, under the guise of evaluating the uncertainty regarding ST
8 segment changes, suggests that the uncertainty is now greater than in 1991. The Allred et al.
9 study used EKG changes in the ST segment to substantiate that the subjective measure of angina
10 was indeed due to ischemia. These two indicators, one subjective and one objective, were very
11 highly correlated and not independent. Therefore, separate analyses of the two indicators should
12 be avoided.

13
14 The most thorough clinical studies remain those of Allred et al., Kleinman et al., and Sheps et al.
15 While the effects in these groups are clear, and together these subjects may be “the best
16 characterized population”, it is not clear that they represent the “most susceptible population”.
17 First, these experiments have not been repeated in the past 20 years, and second, other potential
18 susceptible groups have not been exposed to such controlled clinical conditions. Additionally,
19 the epidemiologic data on cardiovascular (heart) disease, including congestive heart failure,
20 suggesting that those groups might be at least as susceptible to CO-related stress as the coronary
21 artery disease group.

22
23 The data available in the PA and the ISA on CO and heart failure are instructive. The statements
24 in the PA, p. 2-14, lines 16-19, that there are only “...small or no associations between hospital
25 admissions” and stroke are not accurate (see next paragraph). Of the 5 studies listed in the
26 footnote at the bottom of that page, 4/5 reported increased hospital admissions for CHF.
27 A close look at Figures 5-2, 5-3 & 5-4 in the ISA supports the association of CO with CHF and
28 stroke more than for CAD. If all the studies for stroke, CHF and CAD were placed on the same
29 x-axis, uncertainty could well be heightened about CAD patients being the most susceptible to
30 CO effects.

31
32 Another possible uncertainty regards the question (PA-p. 2-34, lines 24-34) of whether CO is a
33 surrogate and whether its effects at low concentrations can be separated from those of co-
34 pollutants. There are analytical and methodological challenges in disentangling the effects of
35 CO from those of co-pollutants, although the problem does not exist in the controlled clinical
36 studies of CO alone.

37
38 *6. This document has integrated health evidence from the final ISA and risk and exposure*
39 *information from the second draft REA as it relates to reaching conclusions about the*
40 *adequacy of the current standard and potential alternative standards for consideration.*

41
42 *a. Does the Panel view this integration to be technically sound, clearly communicated,*
43 *and appropriately characterized?*
44
45

1 As discussed in several sections of this document, it may be difficult to integrate the evidence
2 from the epidemiological studies with clinical evidence (p. 2-25). Some of the conclusions are
3 not well supported. In particular, the estimation of population exposures (p. 2-5, lines 27-34, and
4 p. 2-6, lines 1-8) may underestimate exposures of those in lower socioeconomic status
5 populations because of their higher likelihood of residing in heavily trafficked areas and an
6 increased probability of exposure to secondhand tobacco smoke. Inclusion of population
7 prevalence of low income status and smoking prevalence in the simulated populations might
8 shift the distribution of estimated CO exposures towards higher levels.

9
10 The conclusion that the current evidence supports a primary focus on those with cardiovascular
11 disease is justifiably based on observations from clinical studies. However, the best characterized
12 and most extensively studied population does not necessarily coincide with the most highly
13 susceptible population. Since the last review, there are additional studies with positive findings
14 that assess effects on the fetuses. There is also strong toxicological evidence relevant to the
15 association of prenatal CO exposure with adverse pregnancy outcomes, such as premature birth
16 and low birth weight. A stronger commentary on exposure during pregnancy and reproductive
17 outcomes is needed.

18
19 *b. Does the document appropriately characterize the results of the draft REA, including*
20 *their significance from a public health perspective?*

21
22 The conclusion that the current evidence supports a primary focus on individuals with
23 cardiovascular disease is justified by current clinical research. Discussion should be added,
24 however, that the best characterized and most extensively studied population does not
25 necessarily identify the most highly susceptible population. In particular, commentary on the
26 fetus as a high at-risk group should be added because of newer data describing the effects of CO
27 on the fetus coupled with toxicological evidence for risks associated with prenatal CO exposure.

28
29 If the Policy Assessment is going to use %COHb as the dose metric, then there has to be a better
30 rationale provided for interpretation of the epidemiological data using this metric.

31
32
33 *7. What are the views of the Panel regarding the staff's discussion of considerations related*
34 *to the adequacy of the current and potential alternative standards?*

35
36 The staff has provided an extensive analysis of the adequacy of the current and potential
37 alternative primary CO standards. The current standards include a 1-hr average and an 8-hr
38 average standard of 35 ppm and 9 ppm, respectively. The form of the standard is that those
39 levels are not to be exceeded more than once per year. In reviewing the recent literature, staff
40 has documented that the "much expanded epidemiological evidence ... provides support for
41 previous conclusions regarding cardiovascular disease-related susceptibility and indications of
42 air quality conditions that may be associated with ambient CO-related risk" and concluded that a
43 causal relationship is likely to exist between relevant short term exposures to CO and
44 cardiovascular morbidity.

1 Staff also conclude that the currently available evidence provides limited but suggestive
2 epidemiologic evidence for CO-induced effects on preterm births, birth defects, and
3 developmental outcomes. Individuals with conditions limiting their ability to deliver oxygen to
4 target tissues represent groups susceptible to the adverse effects of CO, in addition to those with
5 coronary artery disease. Based on the analyses of epidemiological studies presented in the PA,
6 there is consensus in the panel that the current standards may not adequately protect public
7 health with a reasonable margin of safety, and therefore revisions that result in lowering the
8 standards should be considered.

9
10 While the epidemiologic studies provide evidence that is coherent with the controlled exposure
11 studies, the Staff determined that four of the studies cited in Table 2.1 included years in which
12 the ambient CO concentrations exceeded the 8-hr standard. However, Table 2.1 includes three
13 studies of hospitalizations for ischemic heart disease and/or congestive heart failure (CHF) from
14 Atlanta for which this was not the case (Tolbert 2007, Peel 2007, Metzger 2007), and one
15 additional study of CHF (Wellenius, 2005) which did not include data from years in which either
16 the 1-hr or the 8-hr standards were exceeded.

17
18 The PA suggests that CHF could have multiple causes, and for that reason it would be
19 problematic to use it as a health effect indicator. The three studies of ischemic heart disease
20 were consistent but only the Tolbert et al. study had clearly statistically significant results. It
21 should be recognized that new controlled exposure studies of some of the sensitive groups (e.g.,
22 infants, fetuses, individuals with CHF or MI's) would be nearly impossible to justify ethically.
23 Therefore more reliance needs to be placed on the epidemiologic studies and assessing whether
24 there are causal relationships. Pooling methods, such as quantitative meta-analyses, may also be
25 useful for developing exposure-response relationships. The available studies cover periods
26 during which the current NAAQS was exceeded as well as studies covering lower ranges. This
27 coverage of a wide range of CO concentrations makes possible a relatively robust estimation of
28 exposure-response relationships. The emphasis should be on studies that used a multipollutant
29 model approach to control for potential confounding of CO effects by those of other co-varying
30 pollutants.

31
32 While there have been no new controlled human exposures designed to examine effects of CO at
33 COHb levels below 2%, there have been numerous improvements to the exposure and COHb
34 dosimetry models employed to provide exposure and risk estimates. The Staff analysis indicates
35 that some of the uncertainties identified in previous reviews of the standard have been reduced.
36 Based on their overall analysis, they conclude that the body of evidence and the quantitative
37 exposure and dose estimates provide support for a standard at least as protective as the current
38 standards. I.e. the data provide support for retaining or revising the current 8-hr standard.

39
40 Overall the Panel agrees with this conclusion. If the epidemiological evidence is given
41 additional weight, the conclusion could be drawn that health effects are occurring at levels below
42 the current standard, which would support the tightening of the current standard. The PA should
43 include an analysis the number of exceedances that would have occurred if the standard was
44 based on the epidemiological data.

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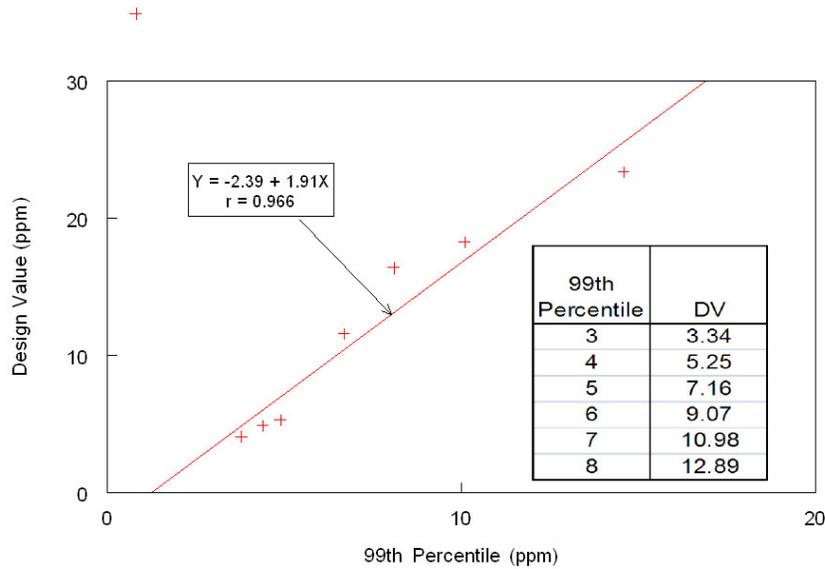
8. Staff believes that the evidence presented in the final ISA and the exposure and risk information presented in the second draft REA supports a range of policy options for the CO standards.

The Staff have proposed a range of policy options based on the quantitative risk analyses performed. As a starting point, the Staff indicates that the evidence is consistent with maintaining standards that are at least as protective as the current levels. However, given new evidence, primarily epidemiological, that there are many individuals potentially at risk in addition to those with coronary artery disease (e.g., fetuses, pregnant women, people with congestive heart disease, and people with anemia of various types), there is reason to consider reducing the standard below the current level(s).

The Panel suggests describing example policy options such as:

- 8 hr – retain the 8-hr averaging time with consideration given to levels within the range of 3 to 6 ppm, with no more than a single exceedance or revise the form of the standard to 99th percentile with a concentration range of 3-5 ppm. See also Figure 1 which shows the linear relationship between the 99th percentile and the design value measured for epidemiologic studies summarized in PA Table 2-1 that showed significant IHD hospitalizations.
- 1 hr – retain the current standard to provide protection against infrequent acute exposures. Consider a range of concentrations from 5 ppm to 15 ppm, combined with a 99th percentile or fourth-highest daily maximum. The panel does not concur with revoking the 1 hr standard.

Relating 99th Percentile to Design Values
Using Data from Epidemiology Studies (PA Table 2-3)



26
27

Figure 1

1 a. *To what extent does the document provide sufficient rationale to justify this range*
2 *of options?*

3
4 The risk models were based on effects in people with coronary artery disease. They were used to
5 estimate the percentages of individuals in LA and Denver that would reach benchmark levels of
6 COHb ranging from <1.5% COHb to <2% COHb. These were summarized in Tables 2-6 and 2-
7 7 in the PA document. The overall guidance for the policy was not clearly described and the
8 wide range of options needs better definition. It might be useful to present the options in a table
9 with the pros and cons of each laid out. The information is embedded in the RA and PA
10 documents, but the options and their respective advantages or disadvantages need to be more
11 clearly summarized.

12
13 The panel concurs with the staff that the 1 hr standard might provide protection independent of
14 the type of protection provided by the 8 hr standard (2-54; L 14); however, the discussion
15 supporting this statement should be more clearly documented.

16
17 b. *Does the Panel have any recommendations regarding additional considerations*
18 *which should inform characterization of these options for both the 8-hour and 1-*
19 *hour standards?*

20
21 In choosing a more stable form of the standard, such as the 99th percentile, which would allow
22 more days on which the standard can be exceeded in a given year, the level of the standard must
23 be reduced to insure that the degree of health protection is sufficient. EPA should consider
24 conducting an evaluation of the representativeness of the risk analysis to the entire US.
25 Currently, the PA is based on two very different cities. Spatial heterogeneity of CO exposures
26 that increase exposures near major sources, i.e. near and on roadways, should be given more
27 weight since these might drive some of the adverse health effects.

28
29 9. *What are the Panel's views regarding the level of detail presented in this chapter?*

30
31 The PA concludes that there is insufficient information at this time to support the consideration of a
32 secondary standard for CO. In general, the level of discussion detail is appropriate; however, some
33 additional detail could be added at the end of chapter 3 on what information is missing in order to make
34 a determination regarding a secondary standard.

35
36
37 10. *The discussion of the CO-related welfare effects draws from the most recent information*
38 *contained in the final ISA for CO.*

39 a. *Does the draft PA accurately reflect the currently available evidence as characterized*
40 *in the final ISA?*

41
42 The Panel agrees that the Policy Assessment appropriately characterizes the evidence as presented in the
43 ISA.

44 b. *Does this discussion effectively summarize the information on climate-related effects of*
45 *CO?*

1 Yes, but there should be a clear statement, to match a similar assertion in the ISA, that there is some
2 evidence that CO has effects on climate. In addition, it would be appropriate in the last paragraph of this
3 chapter to summarize what information is missing and thus needed, such as more accurate U.S. and
4 global emissions inventory, monitoring specifically for climate rather than just for standards and
5 exposure, and improvements in localized chemical reactions between CO, CH₄, and O₃ within global
6 models.

7
8 *11. What are the Panel's views regarding the appropriateness of staff's initial conclusions*
9 *related to considering a secondary standard for CO?*

10
11 The PA concludes that there is insufficient information at this time to support consideration of a
12 secondary NAAQS. Nonetheless, there is substantial evidence that CO has adverse effects on
13 climate. It would be appropriate in the last paragraph of this chapter to summarize what
14 information is missing. For example, U.S. and global emissions inventories must achieve a
15 certain level of accuracy before a secondary standard could be established. Is the level of
16 uncertainty sufficient and if not how can it be reduced?

17
18 The basic question of what form is needed for regulations or standards should be addressed. A
19 concentration-based standard would probably be inappropriate. Emissions standards such as are
20 being considered for CO₂ would be more applicable to the issue of how to control CO emissions.
21 The ISA (Figure 3.8) shows nicely how CO is "low hanging fruit" with respect to short term (20-
22 year) climate forcing. The PA may be an appropriate forum to provide guidance to how these
23 environmental benefits may be realized.
24

Enclosure C

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Review Comments from the CASAC CO Panel on the *Policy Assessment for the Review of the Carbon Monoxide National Ambient Air Quality Standards: First External Review Draft*

Comments received:

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Dr. Paul Blanc

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*4. The discussion of the quantitative analysis of exposure and dose (e.g., section 2.2.2) draws from the analyses described in the second draft Risk and Exposure Assessment (REA).
a. Does this discussion accurately reflect the analyses contained in the draft REA?
b. Does the Panel find the presentation to be technically sound, clearly communicated and appropriately balanced?*

The Policy Assessment perpetuates and to a degree magnifies the fundamental misunderstanding of the REA in relation to susceptibility based to narrowly on CAD alone (i.e., past MI or angina) rather than on cardiovascular disease as a group. In both cases this is a misread of the ISA and marks a failure to grasp what the accumulated epidemiological evidence shows. Thus this presentation is unbalanced, in interpreting the ISA through the flawed “lens” of the REA.

*6. This document has integrated health evidence from the final ISA and risk and exposure information from the second draft REA as it relates to reaching conclusions about the adequacy of the current standard and potential alternative standards for consideration.
a. Does the Panel view this integration to be technically sound, clearly communicated, and appropriately characterized?
b. Does the document appropriately characterize the results of the draft REA, including their significance from a public health perspective*

It is very difficult to decipher the conclusions of Policy Assessment beyond an unequivocal position that what ever is done the current standards should not be *weakened*. I would characterize the conclusion as clearly communicating a sense of not wishing to communicate something definitive, at this point at least. The rationale for not considering how many at risk persons are pushed over a threshold of body burden of COHb because they have baseline exposures form non-ambient sources seems ill-judged and counter-intuitive in terms of public health protection. Perhaps there are parallels in considerations of ambient lead exposure limits?

Dr. Thomas Dahms

Charge Question 2. Consistent with the revised NAAQS process which includes development of this draft Policy Assessment (PA) document, considerations with regard to the primary standard for CO have been organized around a set of policy-relevant questions for the review.

a. Does the Panel find the question posed to appropriately reflect the policy relevant questions in the review?

I believe that the questions posed raise the major issues and the information provided in response to these questions provides the essential data required for making policy decisions. These questions regarding 1. the adequacy of protection by the current standards; 2. does new information alter previous conclusions regarding health effects; 3. should COHb continue to be the dose indicator for CO exposure; 4. the health effects of ambient CO levels; and 5. any reduction in the uncertainties regarding CO.

Regarding the adequacy of protection: it is difficult to make a judgement in this area for two reasons.

1. There is no definition presented of what is considered to be an acceptable risk and 2. The number of persons in the at risk groups exposed to criteria levels of CO is not defined for the country. The only description of numbers exposed is for two cities: Los Angeles and Denver with no guidance provided for extrapolation to the whole country. For example, if the document is to discuss the numbers of persons in the U.S. with CAD, then the reader needs to have some estimate of how many of these persons would reach criteria levels of COHb on an annual basis given the current standards. Therefore it is difficult to judge the effectiveness of the current standards in protecting the population

2. The new information in this area all comes from epidemiological studies that are crucial to the interpretation of the meaning of the controlled human exposures. The adverse health effect of limiting the amount of work a person with CAD can perform with doses of CO near the current standard has been clearly established. However it is not clear that the extent of limitation has any further impact on the health of this at risk group. This concern is implied in the discussion regarding the uncertainty about the significance of ST segment changes on page 2-32. The epidemiological studies are designed to provide one means of determine if low CO doses have measureable impacts on health by correlating CO exposure with hospital based treatment for CV related events. This link between the two types of studies is clear in my mind but I'm not sure that the connection is clearly stated in this document.

3. Carbon monoxide is unique among the regulated air pollutants because it has a clear marker of dose, %COHb. The document indicates that the well established effects of COHb are related to the reduction in oxygen delivery to the tissues. This is in the face of the immerging evidence of effects of the partial pressure of CO, P_{CO} , as a messenger molecule, which could result in various patho-physiological conditions in combination with CO exposure. What is missing from the REA and carried through to the PA is a brief description of the relationship between P_{CO} and %COHb. This could possibly provide some prospective for the reader as to the importance of the physiological tensions of carbon monoxide in

1 tissues of interest. This would not distract from the current understanding that the dose
2 indicator of %COHb is currently the primary focus for policy assessment.
3

4 4. The decreasing ambient levels of CO in the United States makes it ever more difficult to
5 demonstrate health effects of CO based on the concept of sufficient exogenous dose to result
6 in %COHb levels that have been shown to have pathophysiological effects. It would appear
7 that the epidemiological effects of CO occur at such low levels of exposure as to result in
8 very little increases in %COHb. Accepting the premise that the epidemiological results
9 attributed primarily to CO exposure implies that adverse health effects occur at levels of
10 %COHb considerably below those shown to have statistically significant effects in controlled
11 human exposures. For these effects to be consistent with the controlled human exposure
12 data, one would have to accept the statement that the effects of CO are without threshold
13 (page 2-11, Line 9; 2-12, L4; 2-15, L24; 2-16, L26; 2-40, L2). Are we to assume that the
14 reason that the epidemiological studies can show significant effects of very low levels of
15 exposure (very small increases in %COHb) is due to the large number of subjects being
16 studied. Or is there another hypothesis regarding how these effects are mediated?
17

18 5. The uncertainties related to CO exposure have not been lessened.
19
20

21 *b. Does the Panel consider the document to provide the appropriate level of detail in*
22 *addressing these policy-relevant questions?*
23

24 Yes but brief verbiage linking concepts as noted above would be helpful in creating
25 transitions between the types of information.
26

27 *Charge question 3. The discussion of the health effects evidence (e.g., section 2.2.1) draws from*
28 *the most recent information contained in the final ISA for CO and information from the previous*
29 *review described in previous Air Quality Criteria Documents.*

30 *a. Does the draft PA accurately reflect the currently available health effects evidence*
31 *for CO as characterized in the final ISA and the extent to which it differs from that*
32 *available at the time of the last review?*

33 *b. Does the Panel find the presentation to be technically sound, clearly communicated*
34 *and appropriately balanced?*
35

36 The description of the current state of knowledge includes suggestive information regarding
37 cellular processes that can result in regional increases in endogenous levels of CO that could be
38 altered by exogenous exposure. Given the considerable amount of current research in this area,
39 mention of this data should exist in this document. The last review of CO was halted for several
40 years due to the pending study and report on the effects of CO at altitude and at extreme cold
41 environments. The document should very briefly acknowledge the findings of this report.
42 Without that information in the current document it is difficult to determine how this report
43 should differ from the last review started in 1999.
44

1 *Charge Question 4. The discussion of the quantitative analysis of exposure and dose (e.g., section*
2 *2.2.2) draws from the analyses described in the second draft Risk and Exposure Assessment*
3 *(REA).*

4 a. *Does this discussion accurately reflect the analyses contained in the draft REA?*

5
6 The discussion focuses on the detail of one multicenter study following brief mention of the
7 supporting studies. I believe that this information could be strengthened by working in the
8 information that the CO exposures in the other studies was very similar with confirming
9 evidence regarding time to angina. This would address the current concern of imbalance in the
10 discussion of the studies in this area.

11
12 b. *Does the panel find the presentation to be technically sound, clearly communicated*
13 *and appropriately balanced?*

14 There are some concerns regarding the technical soundness of the descriptions given which do
15 make physiological sense.

16
17 i. Inaccuracy: page 2-8, line 26. The statement “This binding to reduced iron...” is
18 very misleading. It has been transferred from the REA description of CO binding
19 to hemoglobin. In particular it comes from the mathematical fiddle noted in
20 Appendix B of the REA on page B-5 which states: “In working with the CFK
21 model it is convenient to express COHb as a percent of [RHb]₀.” This false
22 concept should not be repeated in the text of the document. The fundamental
23 relationship as described by Haldane clearly indicates that the much higher
24 affinity of hemoglobin for CO vs Oxygen results in CO displacing O₂ from
25 oxygenated hemoglobin. The implication that CO binds preferentially to only
26 reduced Hb is incorrect and needs to be corrected.

27 ii. Page 2-9, line 1. The statement “...or increased cardiac output) is not clear. The
28 preceding sentence is discussing cardiovascular disease in the context of CAD.
29 Therefore the normal compensatory mechanism that exist in healthy individuals is
30 increased myocardial blood flow through vasodilatation, not vasodilatation and
31 increased cardiac output. The current verbiage does not make sense and needs to
32 be changed.

33
34 *Charge Question 5. Does the document identify and appropriately characterize the important*
35 *uncertainties associated with the evidence and quantitative analysis of CO exposure and dose,*
36 *particularly those of particular significance in drawing conclusions as to the adequacy of the*
37 *current CO standards?*

38
39 Generally the uncertainties are dealt with appropriately with the exception of the item mentioned
40 below.

41
42 The current review on page 2-32 under the guise of evaluating the uncertainty regarding ST
43 segment changes suggests that the uncertainty is now greater than it was in 1991. The policy
44 assessment is based on the adverse health effects of 2% COHb resulting in reducing the amount
45 of work a person with CAD can perform before chest pain develops with is due to myocardial
46 ischemia. The Allred et al study used EKG changes in the ST segment to substantiate that the

1 subject measure of angina was indeed due to ischemia. These two indicators, one subjective and
2 one objective, were very highly correlated and not independent. Therefore the separation of the
3 two indicators (page 2-32, line 25-28) is a reflection of the reviewers not understanding the study
4 design. (This should have been corrected throughout the ISA, REA and the PA. The statement
5 attributed to the ISA, p.48 –assumed to be 5-48—on page 2-32 needs to have a line reference
6 otherwise it is difficult to locate this conclusion in the ISA.) In fact the ever increasing amount of
7 epidemiological data on the effects of CO probably reduces the uncertainty of the effects of CO
8 exposure in individuals with cardiovascular disease.

9

10 Exposure/Risk-based Considerations

11 Page 2-40 lines 3-10. The rationale for not using the benchmark of 1% COHb is flawed. In the
12 version of the ISA dated January 2010, I cannot find a reference to the range of endogenous
13 levels of %COHb: the source needs to be better documented. There is a list of rates of
14 endogenous product provided in the Appendix but there are multiple studies listed. If one of
15 these studies is the source it should be identified. The rationale for requesting the inclusion of
16 this benchmark was the sense that ‘the effects of CO are without threshold (page 2-11, Line 9; 2-
17 12, L4; 2-15, L24; 2-16, L26; 2-40, L2).’ The %COHb data that is being used is that of Allred et
18 al cited on page 2-11, line 1 as showing %COHb levels for exposure to 0-2 ppm CO as being
19 0.6%. The benchmark of 1% does not appreciably overlap 0.6% any more than one would expect
20 there to be overlap between 1.5% and 2.0%. What is not stated is that the Apex model may
21 overestimate the range of values resulting from no exposure to exogenous CO.

22 Without the 1% COHb benchmark how are the epidemiologic studies to be interpreted? Are
23 these effects due to the effects of a pollutant that is not measured but very highly correlated to
24 atmospheric CO? If the Policy Assessment is going to use %COHb as the dose metric, then
25 there has to be a rationale provided for interpretation of the epidemiological data using this
26 metric. If the result is a very high number of individuals with CAD having doses of 1%COHb
27 and very few appearing in the ER or being admitted, this point should be discussed.

Dr. Russell Dickerson

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The Policy Assessment in Chapter 3 addresses the issue of a secondary standard.

9. What are the Panel's views regarding the level of detail?

The detail is a little light as indicated below.

10. a. Does the draft PA accurately reflect the currently available evidence?

Within the limits of what is written yes.

b. Does this discussion effectively summarize the information on climate related effects of CO?

See below.

11. What are the Panel's views regarding the appropriateness of the initial conclusions?

The PA concludes that there is insufficient information at this time to support the consideration of a secondary NAAQS. None-the-less, there is evidence that CO has adverse effects on climate.

It would be appropriate in the last paragraph of this chapter to summarize what information is missing. For example, U.S. and global emissions inventories must achieve a certain level of accuracy before a secondary standard is established. Is the level of uncertainty sufficient and if not what would it take? Monitoring was being phased out – should this policy be reconsidered? Representative monitoring to evaluate emissions inventories or models may look different from monitoring to assess exposure. The basic question of what form is needed for regulations or standards should be addressed. A concentration-based standard would probably be inappropriate. Emissions standards such as are being considered for CO₂ would be more applicable to the issue of how to control CO emissions. The ISA (Figure 3.8) shows nicely how CO is low hanging fruit with respect to short term (20-year) climate forcing. The PA may be an appropriate forum to provide guidance to how these environmental benefits may be realized.

Dr. Milan Hazucha

The first external draft of the document provides a comprehensive overview of the legislative requirements and approaches to policy decision making process. The draft presents in a succinct way all aspects of the scientific evidence required for a successful policy assessment. The staff has reviewed and discusses key scientific and technical knowledge with clear understanding of health effects associated with CO presence in the ambient air. Various related issues are presented in sufficient detail and clearly communicated.

Asking specific questions throughout the document and answering them in a succinct manner has been very helpful in focusing on the critical aspect of the policy setting.

Answers to charge questions and specific comments:

Introduction and Background for the Policy Assessment (Chapter 1)

1. Does the Panel find the introductory and background material, including that pertaining to previous reviews of the CO standard, the current review and current air quality, to be clearly communicated and appropriately characterized?

I find the introductory and background material pertaining to the previous and current reviews to be clearly communicated and appropriately characterized. All the important factors needed to make an informed judgment are adequately presented and briefly discussed.

Review of the Primary Standard (Chapter 2)

2. Consistent with the revised NAAQS process which includes development of this draft Policy Assessment (PA) document, considerations with regard to the primary standard for CO have been organized around a set of policy-relevant questions for the review.

a. Does the Panel find the questions posed to appropriately reflect the policy-relevant questions in this review?

Qualified yes in all respects. One question that was not posed is about the confounding effects of no-traffic sources of CO, e.g., indoor air. Numerous studies have shown that we spend ~80% of time indoors. For healthy elderly and people with CVD the time spend indoors may be even longer. The non-traffic sources of CO are at times substantial and will override the ambient CO levels.

b. Does the Panel consider the document to provide the appropriate level of detail in addressing these policy-relevant questions?

Yes, in all respects. The PA is well written, providing sufficient details, and highlighting important factors/concerns so that the policy relevant questions can be addressed both quantitatively and qualitatively.

1 3. The discussion of the health effects evidence (e.g., section 2.2.1) draws from the most recent
2 information contained in the final ISA for CO and information from the previous review
3 described in previous Air Quality Criteria Documents.

4
5 a. Does the draft PA accurately reflect the currently available health effects evidence for
6 CO as characterized in the final ISA and the extent to which it differs from that available at the
7 time of the last review?

8
9 Yes, in all respects. The currently available scientific evidence is evaluated, characterized
10 and presented in a sufficient detail supporting the adequacy of the protection afforded by the
11 current CO standard. The differences with the last review are clearly presented. There are no
12 new human laboratory studies or exposure/risk-based evidence that would alter the
13 conclusions. The evidence from new epidemiologic studies has been presented in a balanced
14 way. The PA correctly points out to limitations in integrating the evidence from laboratory
15 and epidemiologic studies.

16
17 Based on the current scientific evidence and practical considerations (e.g. arterial blood
18 draw) venous blood COHb level is the optimal indicator of "CO health."

19
20 b. Does the Panel find the presentation to be technically sound, clearly communicated, and
21 appropriately balanced?

22
23 Qualified yes. In order to facilitate better understanding of the cardiovascular effects,
24 particularly myocardial ischemia, I suggest to add to the reported values of % time changes
25 to angina on p.2-11, top paragraph, the actual changes in seconds with the confidence
26 intervals (CI) included as well. For example, the reported 4.2% shorter time to angina from a
27 control ~ 9 min interval amounts to 22 sec, with the CI=8.7%. Since Allred et al. studies are
28 considered the key studies, it would be very helpful to comment briefly on the clinical
29 significance of the shortened time. Moreover, regarding time to angina endpoint, are there
30 any long-term consequences on repeated exposures, on the duration of angina, and frequency
31 of occurrence without CO exposure? EPA should address these questions and if we do not
32 have respective data the PA should state so.

33 Moreover, the first part of the statement in footnote #12 (p. 2-12) commenting on the
34 difficulty determining association of CO with CVD and as a marker for traffic-related
35 pollutants should, because of its importance, be moved from the footnote to the body of
36 respective paragraph. Recently published HEI Special Report #17 (Jan. 2010)
37 entitled: "Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions,
38 Exposure, and Health Effects" discusses CO as a marker for another traffic-related pollutants
39 such as PM and NO₂ and not as a major health hazard.

40 The review of the epidemiologic evidence (p.2-14) accurately reflects the difficulties to
41 establish causal relationship between CO and reported effects. Similarly, well reasoned
42 section (p. 2-25) points to difficulties integrating laboratory/clinical findings and
43 epidemiologic observations.

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45 4. The discussion of the quantitative analysis of exposure and dose (e.g., section 2.2.2) draws
46 from the analyses described in the second draft Risk and Exposure Assessment (REA).

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a. Does this discussion accurately reflect the analyses contained in the draft REA?

Qualified yes. The COHb module of the APEX model though the most important is also the weakest, since we do not have sufficient physiologic data or the range of values for many variables that enter into the model. However, despite this limitation there seems to be sufficient information for some variables that can be used to tune the estimates, e.g. Hb concentration for whites and blacks.

As far 1% COHb benchmark suggested by the Panel, the staff correctly pointed out that “this level overlaps with the upper part of the range of endogenous levels” and decided not to focus on dose estimates (p.2-40). I support this approach since this complies with the EPA’s task “to establish standards that are neither more nor less stringent than necessary for these purposes”, .i.e. public health.

b. Does the Panel find the presentation to be technically sound, clearly communicated and appropriately balanced?

Yes, in all respects. Again, because of the importance of the statement, the first sentence of the footnote #25 on the difficulty to determine association between CO and CVD in interpreting epidemiological evidence should be moved to the body of a respective paragraph.

5. Does the document identify and appropriately characterize the important uncertainties associated with the evidence and quantitative analysis of CO exposure and dose, particularly those of particular significance in drawing conclusions as to the adequacy of the current CO standards?

Yes, in all respects; The key uncertainties associated with exposure and dose estimates should, besides traffic, list other sources of CO, such as indoor air, smoking, occupational exposures, to name the main ones (p.2-42, 1.31). A succinct discussion of how these sources can override the protection afforded by the current CO standard would be helpful.

6. This document has integrated health evidence from the final ISA and risk and exposure information from the second draft REA as it relates to reaching conclusions about the adequacy of the current standard and potential alternative standards for consideration.

a. Does the Panel view this integration to be technically sound, clearly communicated, and appropriately characterized?

Yes, in all respects

b. Does the document appropriately characterize the results of the draft REA, including their significance from a public health perspective?

Yes, in all respects

1
2 7. What are the views of the Panel regarding the staff's discussion of considerations related to
3 the adequacy of the current and potential alternative standards?
4

5 I find the initial staff conclusion "for either retaining or revising the current 8-hour standard"
6 (p. 2-46) based on the available estimates of exposure ambivalent. Does this mean that EPA
7 is undecided or that the evidence is split 50/50? It is true, as subsequently stated, that a
8 variety of factors will be considered in judging the adequacy of the current standard. But
9 such adequacy should be based primarily on the evidence from laboratory/clinical studies and
10 not on policy and other considerations. The evidence from the epidemiology studies, as
11 commented on in several previous sections of this document, is difficult to evaluate and
12 integrate with clinical evidence (p. 2-25).

13 The CO concentrations reported in epidemiology studies will produce COHb levels within a
14 normal range. From reading interpretation of these studies in the latest EPA PM ISA the
15 dominant effects in these studies are due to PM. Since we do not have any measurements of
16 COHb level or other adverse effects that can be specifically associated with CO the studies
17 provide no proof beyond statistics that there is a causal relationship. CO is primarily known
18 for its anti-inflammatory effects. However, CO is highly correlated with PM and other
19 pollutants, therefore, it is very likely that CO acts as a surrogate for PM and other pollutants.
20 Thus based strictly on scientific evidence, I agree with the staff interpretation of
21 epidemiology studies and their leaning towards retaining the current 8-hour standard.
22 The section 2.3 of the discussion of the averaging time, the form and level of alternative
23 standard and potential alternative levels is succinct and well reasoned. What is not clear what
24 form might the alternative standard have?
25

26 8. Staff believes that the evidence presented in the final ISA and the exposure and risk
27 information presented in the second draft REA supports a range of policy options for the CO
28 standards.
29

30 a. To what extent does the document provide sufficient rationale to justify this range of
31 options?
32

33 Yes, the staff provides sufficient rationale for discussion of the range of options, particularly
34 the policy options.
35

36 b. Does the Panel have any recommendations regarding additional considerations which
37 should inform characterization of these options for both the 8-hour and 1-hour standards?
38

39 There should be a greater emphasis on the evidence based on laboratory/clinical studies.
40

41 Consideration of a Secondary Standard (Chapter 3) 42

43 9. What are the Panel's views regarding the level of detail presented in this chapter?
44

45 The level of detail presented in this chapter is sufficient.
46

1 10. The discussion of the CO-related welfare effects draws from the most recent information
2 contained in the final ISA for CO.

3
4 a. Does the draft PA accurately reflect the currently available evidence as characterized in
5 the final ISA?

6
7 Yes, in all respects

8
9 b. Does this discussion effectively summarize the information on climate-related effects of
10 CO?

11
12 Yes, in all respects

13
14 11. What are the Panel's views regarding the appropriateness of staff's initial conclusions related
15 to considering a secondary standard for CO?

16
17 Fully agree with staff conclusions.

18

Dr. Michael Kleinman

7. *What are the views of the Panel regarding the staff's discussion of considerations related to the adequacy of the current and potential alternative standards?*

The staff has provided an extensive analysis of the adequacy of the current and potential alternative primary CO standards. The current standards include a 1-hr average and an 8-hr average standard of 35 ppm and 9 ppm, respectively. The form of the standard is that those levels are not to be exceeded more than once per year. In reviewing the recent literature staff has documented that the “much expanded epidemiological evidence ... provides support for previous conclusions regarding cardiovascular disease –related susceptibility and indications of air quality conditions that may be associated with ambient CO-related risk” and concluded that a causal relationship is likely to exist between relevant short term exposures to CO and cardiovascular morbidity. Staff also conclude that the currently available evidence provides limited but suggestive epidemiologic evidence for CO-induced effects on pre-term births, birth defects, developmental outcomes and that individuals with conditions limiting their ability to deliver oxygen to target tissues represent groups susceptible to the adverse effects of CO, in addition to those with coronary artery disease. Based on the analyses of epidemiological studies presented in the PA there is a consensus in the panel that the current standards may not adequately protect public health with a reasonable margin of safety and therefore revisions that result in reducing the standards should be considered.

While the epidemiologic studies provide evidence of coherence with the controlled exposure studies, the Staff determined that four of the studies cited in Table 2.1 included years in which the ambient CO concentrations exceeded the 8 hr standard. However Table 2.1 includes 3 studies of hospitalizations for ischemic heart disease and/or congestive heart failure (CGF) from Atlanta for which this was not the case (Tolbert 2007, Peel 2007, Metzger 2007) and one additional study of CGF (Wellenius, 2005) which did not include data from years in which the either the 1 hr or the 8 hr standards were exceeded. The PA suggests that CHF could have multiple causes and for that reason it would be problematic to use as a health effect indicator. The 3 IHD studies were consistent but only the Tolbert study had clearly statistically significant results. It should be recognized new controlled exposure studies of some of the sensitive groups (e.g. infants, fetuses, individuals with CHF or MI's) would be nearly impossible to justify ethically. Therefore more reliance needs to be placed on the epidemiologic studies and uncovering causal relationships may require methods such as meta-analyses to develop exposure-response curves. For this purpose the fact that some studies included periods in which the current standard was exceeded becomes less important because there are also studies at lower levels so that CR relationships can be interpolated (as opposed to extrapolated). The emphasis should be on studies that used a multipollutant model approach to control for potential confounding of CO effects by other co-varying pollutants.

While there have been no new controlled human exposures that were designed to examine effects of CO at COHb levels below 2%, there have been numerous improvements to the exposure and COHb dosimetry models employed to provide exposure and risk estimates. The Staff analysis

1 indicates that some of the uncertainties identified in previous reviews of the standard have been
2 reduced and that based on their overall analysis conclude that the body of evidence and the
3 quantitative exposure and dose estimates provide support for a standard at least as protective as
4 the current standards, i.e. the data provide support for retaining or revising the current 8-hr
5 standard. Overall the panel agrees with this conclusion, at the bare minimum. If the
6 epidemiological evidence is given additional weight, than one might conclude that health effects
7 are accruing at levels below the current standard and therefore the evidence might be leaning in
8 the direction of revising the current standard. An issue is that some of the epidemiological
9 studies were under conditions in which the current standard was exceeded at least in some part.
10 More complete details of the degree to which the standard was exceeded should be summarized
11 in the PA document, i.e. some studies covered as many as 7 years; would it have been excluded
12 for as little as 1 exceedence in 7 years?

13
14 *8. Staff believes that the evidence presented in the final ISA and the exposure and risk*
15 *information presented in the second draft REA supports a range of policy options for the CO*
16 *standards.*

17
18 The Staff have proposed a range of policy options based on the quantitative risk analysis
19 performed. As a starting point the Staff indicates that the evidence is consistent with maintaining
20 standards that are at least as protective as the current levels. However, given the new evidence,
21 primarily epidemiologic, that there are many individuals potentially at risk in addition to those
22 with coronary artery disease (e.g. fetuses, pregnant women, people with congestive heart disease,
23 people with anemia of various types) there is reason to consider reducing the standard below the
24 current level(s).

25
26 The panel suggests example policy options such as:

27 8 hr – retain the 8h r averaging time with consideration given to levels within the range of
28 3 to 6 ppm, with no more than 1 exceedance or revise the form of the standard to 99th percentile
29 with a concentration range of 3-5. Note see Figure 1 which shows the linear relationship
30 between the 99th percentile and the design value measured for epidemiologic studies summarized
31 in PA Table 2-1 that showed significant IHD hospitalizations.

32 1 hr – retain the current standard to provide protection against infrequent acute exposures.
33 Consider a range of concentrations from 5 ppm to 15 ppm, combined with a 99th percentile or
34 fourth-highest daily maximum. The panel does not concur with revoking the 1 hr standard..

35
36 *a. To what extent does the document provide sufficient rationale to justify this range*
37 *of options?*

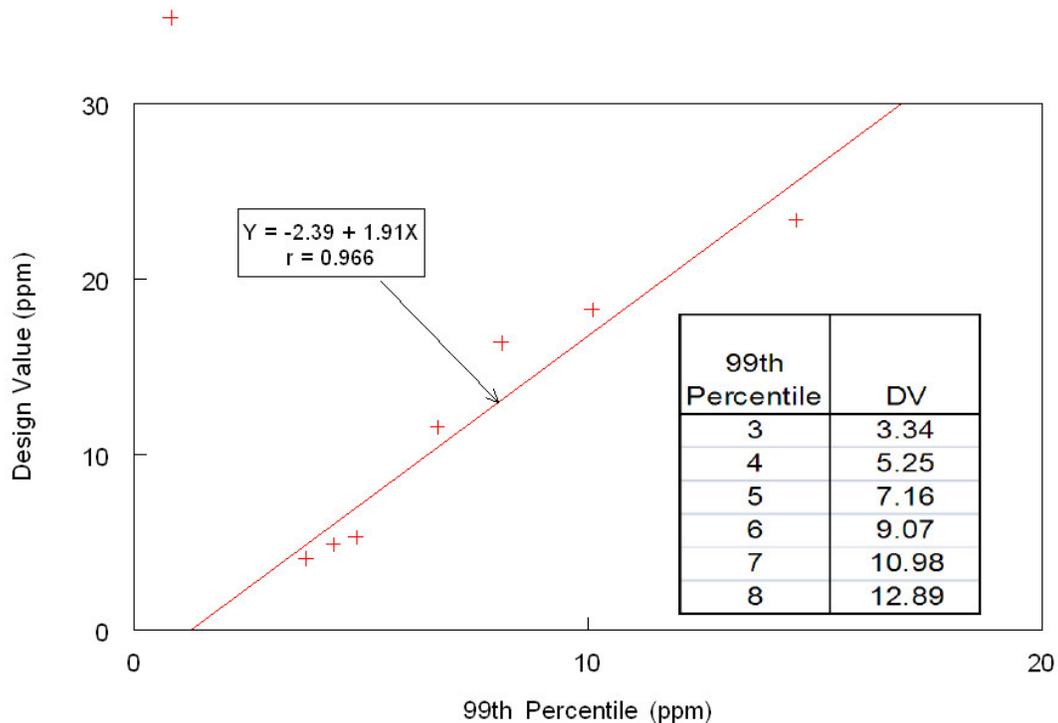
38
39 The risk models were based on coronary artery disease effects and were used to
40 estimate the percents of individuals in LA and Denver that would reach benchmark
41 levels of COHb ranging from <1.5% COHb to <2% COHb. These were summarized
42 in Tables 2-6 and 2-7 in the PA document. The overall guidance for the policy was
43 not very clearly described and the wide range of options needs better definition. It
44 might be useful to present the options in a table with the pros and cons laid out. The
45 information is embedded in the RA and PA documents but the options and their
46 respective advantages or disadvantages need to be more clearly summarized.

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2 The panel concurs with the staff that the 1 hr standard might provide protection
3 independent of the type of protection provided by the 8 hr standard (2-54; L 14),
4 however the discussion supporting this statement should be more clearly documented.
5

6 *b. Does the Panel have any recommendations regarding additional considerations*
7 *which should inform characterization of these options for both the 8-hour and 1-*
8 *hour standards?*

- 9 i. In choosing a more stable form of the standard, such as the 99th percentile,
10 which would allow more days on which the standard can be exceeded in a
11 given year, the level of the standard must be reduced to insure that the
12 degree of health protection is sufficient.
- 13 ii. A summary of the options and their pros or cons would be more helpful.
- 14 iii. An evaluation of how representative the risk analysis which is based on 2
15 very different cities is with regard to the entire US.
- 16 i. Spatial heterogeneity of CO exposures that increase exposures near major
17 sources i.e. near and on roadways should be given some weight since these
18 might drive a lot of the adverse health effects.

Relating 99th Percentile to Design Values Using Data from Epidemiology Studies (PA Table 2-3)



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Figure 1

Dr. Francine Laden

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2. Consistent with the revised NAAQS process which includes development of this draft Policy Assessment (PA) document, considerations with regard to the primary standard for CO have been organized around a set of policy-relevant questions for the review.

a. Does the Panel find the questions posed to appropriately reflect the policy relevant questions in this review?

Yes – the questions appropriately reflect the policy relevant questions.

b. Does the Panel consider the document to provide the appropriate level of detail in addressing these policy-relevant questions?

Yes – the level of detail is appropriate.

3. The discussion of the health effects evidence (e.g., section 2.2.1) draws from the most recent information contained in the final ISA for CO and information from the previous review described in previous Air Quality Criteria Documents.

a. Does the draft PA accurately reflect the currently available health effects evidence for CO as characterized in the final ISA and the extent to which it differs from that available at the time of the last review?

Yes – the draft PA accurately reflects the currently available health effects evidence for CO. One minor point: On page 2-9, it is stated that “it was concluded that there is not likely to be a causal relationship between relevant long-term CO exposures and mortality.” Is EPA confident of this conclusion, or is there not sufficient data to address this relationship?

b. Does the Panel find the presentation to be technically sound, clearly communicated, and appropriately balanced?

Yes – the presentation is technically sound, clearly communicated and appropriately balanced.

Dr. Arthur Penn

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2
3 *1. Does the Panel find the introductory and background material, including that pertaining*
4 *to previous reviews of the CO standard, the current review and current air quality, to be*
5 *clearly communicated and appropriately characterized?*
6

7 Chapter 1 of the PA does a good job, in a limited # of pages, of providing intro/background for
8 the PA. There is a brief review of the CAA and establishment of NAAQS (1^o, 2^o); adequate
9 margins of safety; previous reviews; CO sources in ambient air; the monitoring network; low
10 dose levels; new monitors/NCore network; recent ambient and steady-state decreases in ambient
11 CO; and finally, the “staff’s evaluation of policy implications of scientific evidence in the ISA
12 and results of quantitative analyses based on that evidence”.

13
14 There is one item on p. 1-1 that could benefit from some clarification and possible change of
15 location. Lines 22-25 on that page emphasize that the focus of the PA is on the 4 basic elements
16 of NAAQS: indicator, averaging time, form and level. None of these items is explicitly defined
17 in the first 46 pages of the PA. “Indicator” & “averaging time” both on p. 2-47 are clearly
18 defined. “Level” is not defined explicitly, but its meaning is implicit in Tables 2-6 & 2-7.
19 “Form” (pp. 2-48 & 2-49) is never defined clearly. “Concentration-based form”, apparently an
20 area of focus, also is not defined. Lines 15-23 on p. 2-49 suggest that “form” = percentile. Is that
21 correct? Is it ever anything else? If it = percentile, why not say so?
22

23 If everything in the PA is based on these 4 elements, perhaps they should be defined on p.1.
24
25

26 *5. Does the document identify and appropriately characterize the important uncertainties*
27 *associated with the evidence and quantitative analysis of CO exposure and dose,*
28 *particularly those of particular significance in drawing conclusions as to the adequacy of*
29 *the current CO standards?*
30
31

32 2 major uncertainties are listed on pp. 2-26 & 2-27. 3 others are listed on pp. 2-4 & 2-5; + 5 on p.
33 2-53.
34

35 There are a couple of other conclusions of the PA that have raised questions for me. Whether
36 they rise to the level of uncertainty depends on how other CASAC CO panelists respond.
37 p.2-18: The most thorough clinical studies remain those of Allred-Kleinman-Sheps. While the
38 effects in these similar subject groups are clear, and together these subjects may be “the best
39 characterized population” it is not clear that they represent the “most susceptible population”.
40 Since a) these experiments have not been repeated in the past 20 years and b) no other groups
41 have been exposed to such controlled clinical conditions, it’s difficult to conclude that this is the
42 “most susceptible population”. Additionally, the epidemiologic data on congestive heart failure
43 and stroke patients, while minimized in the PA write-up, suggest that those groups might be at
44 least as susceptible to CO-related stress as the coronary heart disease group.
45

1 The data available in the PA and the ISA on CO/heart failure are instructive. The statements in
2 the PA, p 2-14, lines 16-19, that there are only "...small or no associations between hospital
3 admissions" and stroke are not accurate (see next paragraph). This tone continues on p. 2-27,
4 lines 8-10, where the document states that "...we did not include studies of associations with
5 CHF... for which the evidence is less clear". Unless I've misread the data, of the 5 studies listed
6 in the footnote at the bottom of that page, 4/5 reported increased hospital admissions for CHF.
7 A close look at Figures 5-2, 5-3 & 5-4 in the ISA supports the CO association with CHF and
8 stroke more than for CHD. In those 3 figures the range of relative risk (RR) values on the x-axis
9 varies widely. In Figure 5-2 the range is from 1.0-1.4, so small changes in RR appear to be larger
10 than they are. On the other hand, the wider ranges of RR values for CHF (1.0-2.20) and for
11 stroke (1.0-4.5) make larger RR values in those figures appear smaller than they really are. In
12 Figure 5-2 (CHD) 27/31 values have a $RR < 1.05$ and only 4/31 with values between 1.10 & 1.18.
13 In Figure 5-3 (stroke) at least 6 studies reported a RR of at least 1.25 and one was as high as 2.8.
14 In Figure 5-4 (CHF), 4/10 studies had RR between 1.2-1.75. If all the studies for stroke, CHF
15 and CHD were placed on the same x-axis, uncertainty could well be heightened about CHD
16 patients being the most susceptible to CO effects. In addition, the mean ambient CO levels (24
17 hr) reported in 2 of the studies with large increases in RR were ~0.8 ppm, i.e., even lower than
18 the 1 ppm value recommended by the CASAC CO panel at its Nov. 2009 meeting as worthy of
19 attention.

20

21 Another possible uncertainty regards the question (PA-p. 2-34, lines 24-34) of whether CO is a
22 surrogate and whether its effects at low concentrations can be untangled from those of co-
23 pollutants. While there may be administrative reasons for focusing on these distinctions, the
24 science justification is not clear. Both CO and organic particles in ambient air are largely
25 products of incomplete combustion (PICs). In real-world (and in most laboratory) situations it is
26 essentially impossible to generate, and therefore to breathe, organic particle PICs without
27 volatiles, including CO. So, disentangling CO effects from those of co-pollutants (not a problem
28 in the Allred-Kleinman-Sheps controlled clinical studies) is not only difficult, but likely also
29 artificial.

Dr. Beate Ritz

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4 7. *What are the views of the Panel regarding the staff's discussion of considerations related to*
5 *the adequacy of the current and potential alternative standards?*

6
7 In reviewing the recent literature EPA staff has concluded that a causal relationship is likely to
8 exist between relevant short term exposures to CO and cardiovascular morbidity based mainly on
9 the coherence between the results from controlled human chamber studies and the more recent
10 epidemiologic literature. However, the PA makes an argument that epidemiologic studies of
11 IHD and CVD are including some areas with CO concentrations that exceeded the 8-hour
12 standards but also cited and commented on 3 studies from Atlanta for which this was not the case
13 (Tolbert 2007, Peel 2007, Metzger 2007) and stated that 2 of the three studies reported non-
14 statistically significant results.

15
16 For the Atlanta studies, first this statement is incorrect, i.e. all 3 studies from Atlanta reported
17 significant results for CVDs (I checked the original papers and this is also not correct according
18 to the ISA table on page C-25), and second the effect estimate sizes are all very comparable (in
19 all three studies) and this is more important than statistically significance testing. Nevertheless,
20 since the 3 Atlanta studies do not use mutually exclusive data and the Tolbert study is the most
21 comprehensive one with regard to the time frame and # of hospitals covered, this largest study
22 can be considered the most informative of the three. Concerning the studies covering areas that
23 exceeded the current standards during the study period, it seems not completely justified to
24 disregard them because of this fact when assessing whether or not to use alternate standards,
25 unless these studies can be shown to be less valid in principle or show some kind of threshold
26 effect rather than a dose response and are very different in the estimated effect sizes reported.
27 Thus, altogether Page 2- 27-28 provide an example of a general tendency of the PA to mis-
28 interpretate and mis-represent epidemiologic study results that is even more evident when it
29 comes to interpreting results for other types of health outcomes.

30
31 This is very obvious on page 2-33 in the text addressing the available evidence for CO-induced
32 effects on pre-term births, birth defects, developmental outcomes; the PA states that “the
33 epidemiologic evidence ...has somewhat expanded, although the available evidence is still
34 considered limited with regard to effects ..” This, is a misrepresentation of the large expansion of
35 data on these outcomes in the epidemiologic literature in past decade. The category of limited
36 evidence is not attributable to little or conflicting epidemiologic evidence but rather to the lack or
37 impossibility of human chamber studies and valid animal models for many of these outcomes
38 and a general tendency of the EPA staff to not attribute causality solely on the basis of
39 epidemiologic evidence alone.

40
41 The EPA staff indicates that some of the uncertainties identified in previous reviews of the
42 standard have been reduced and they provide support for a standard at least as protective as the
43 current standards, i.e. the data provide support for retaining or revising the current 8-hr standard.
44 In fact if the epidemiological evidence was not down-weighted or outright ignored as much as it

1 currently is in this PA, enough evidence has accrued at levels below the current standard to
2 revise them downwards in the interest of public health in general (not just for CVD outcomes).

3
4 8. *Staff believes that the evidence presented in the final ISA and the exposure and risk*
5 *information presented in the second draft REA supports a range of policy options for the CO*
6 *standards.*

7
8 a. *To what extent does the document provide sufficient rationale to justify this range of*
9 *options?*

10
11 Yes, the sufficient rationale for discussion of the range of options is provided

12
13 b. *Does the Panel have any recommendations regarding additional considerations which*
14 *should inform characterization of these options for both the 8-hour and 1-hour standards?*

15
16 Spatial heterogeneity of CO exposures that increase exposures near major sources i.e. near
17 and on roadways should be given some weight since these might drive a lot of the adverse health
18 effects.

19

Dr. Anne Sweeney

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2
3 CQ. 7. The discussion of considerations related to the adequacy of the current and potential
4 alternative standards was comprehensive and clearly established the context for the ensuing
5 discussions. However, some of the conclusions reached were not well-supported, including:

6 a. The Estimation of Population Exposures (Page 2-5, lines 27-34, and page 2-6, lines 1-8).
7 The contribution of ambient air CO levels to indoor CO levels would be especially relevant
8 among lower socioeconomic status populations. Given environmental justice concerns
9 rendering lower income individuals more likely to reside in heavily trafficked areas, as well
10 as lower income resulting in lack of air conditioning and extended periods of time with
11 windows opened allowing influx of ambient air, and an increased probability of exposure to
12 tobacco smoke, it seems critical to examine the contribution of indoor CO exposures in the
13 modeling. Inclusion of population prevalence of low income status and smoking prevalence
14 (based on income status) in the simulated populations would greatly enhance the ability to
15 estimate CO exposures.

16
17 b. Regarding Evidence-based Considerations (2.2.1): The conclusion that the current
18 evidence supports a primary focus on cardiovascular disease (CVD) is justifiably based on
19 the research examining formation of COHb and related CVDs as the most extensively
20 studied adverse health effect supporting an association with CO. It is stated on Page 2-18,
21 lines 15-18 that “.. *the population with pre-existing cardiovascular disease associated with*
22 *limitation in oxygen availability continues to be the est characterized population at risk of*
23 *adverse CO-induced effects..*”. However, the best characterized and most extensively studied
24 population does not necessarily identify the most highly susceptible population. The
25 expansion of studies with positive findings evaluating effects on fetuses since the previous
26 review, supported by strong toxicological evidence for the finding of prenatal CO exposure
27 and adverse pregnancy outcomes, warrants more attention to this subpopulation. As stated
28 on Page 2-16, lines 12-18: “*With regard to potential effects of CO on birth outcomes and*
29 *developmental effects, the currently available evidence includes limited but suggestive*
30 *epidemiologic evidence for a CO-induced effect on preterm birth, birth defects, decrease in*
31 *birth weight, other measures of fetal growth, and infant mortality (ISA, section 5.4.3). The*
32 *available animal toxicological studies provide some support and coherence for these birth*
33 *and developmental outcomes, although a clear understanding of the mechanisms underlying*
34 *potential reproductive and developmental effects is still lacking (ISA, section 2.5.3).*” This
35 reviewer agrees that the number of human studies in these areas is limited, however, the
36 strength of the evidence to date supports an association of greater concern than the current
37 evaluation bestows.
38

1 CQ. 8.

2 a. Overall, the range of options recommended by the staff support at minimum the
3 continuation of the current CO standards and possibly a lowering of those standards to
4 provide increased public health protection (Page 2-56, lines 23-27). This position is well-
5 supported chiefly by the review of the effects of ambient CO exposure at levels at or below
6 the current standards and the effects on CVD endpoints.
7

8 b. Again, the additive or multiplicative effects of ambient and indoor CO exposures need to
9 be given more consideration. In assessing averaging time (section 2.3.2). the 8-hour
10 averaging time was selected in part because “.. *this time-frame represented a good basis for*
11 *tracking continuous exposures during any 24-hour period, recognizing that most people may*
12 *be exposed in approximately 8-hour blocks of time (e.g., working or sleeping).*” The
13 comments regarding indoor CO exposures especially among lower income populations are
14 relevant here as well.

Dr. Stephen Thom

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2
3 1. Background/introduction is clear and appropriate.
4

5 2. Chapter 2.1 - the approach taken to review primary standards for CO is well organized.
6

7 Section 2.2 discusses the adequacy of the current standard by listing key questions. The format
8 involves reiterating much of the rationale listed in the REA, sometimes stating the same evidence
9 used in conclusions multiple times (*e.g.* the Allred, *et al.* findings – page 2-10 lines 4 – 26; page
10 2-22, lines 17 – 31; page 2-23, lines 7 – 13; page 2-32, line 36 – 37; page 2-33, line 1 – 5). This
11 seems quite redundant.
12

13 Of greater concern, there are instances where questions are posed but not answered. Therefore,
14 this reviewer feels that some sections are poorly communicated. For example, section 2-2 poses
15 the question: “Does the currently available scientific evidence and exposure/risk-based
16 information, as reflected in the ISA and draft REA, support or call into question the adequacy of
17 the protection afforded by the current CO standards?” I cannot find any place in the document
18 where the question is answered. Instead section 2-2 is broken down into other questions in
19 sections 2.2.1 and 2.2.2, some of which are answered and some are not.
20

21 3. In section 2.2.1 on page 2-8, line 9 the question “Does the current evidence alter our
22 conclusions from the previous review regarding the health effects associated with exposure to
23 CO” is answered (page 2-16, line 23-27). On page 2-16 the question, “Does the current evidence
24 continue to support a focus on COHb ... or does the current evidence provide support for ...
25 alternate dose indicators ...” is answered (page 2-17, line 29-31). On page 2-18, line 1 the
26 question “Does the current evidence alter our understanding of populations that are particularly
27 susceptible to CO exposures?” is answered (page 2-21, line 17 – 20). Of note, there is also a
28 second question posed on line 2-19 that is redundant with that posed on 2-18. The question on
29 page 2-22, line 1, “Does the current evidence alter our conclusions from the previous review
30 regarding the levels of CO in ambient air associated with health effects?” is not answered. The
31 staff reiterates much of the uncertainty with the current state of CO pathophysiology but never
32 offers a conclusion. Moreover, there are parts of this section that are unnecessarily convoluted
33 (*e.g.* the paragraph on page 2-27, lines 14 – 22). The question posed on page 2-31, line 29, “To
34 what extent have important uncertainties identified in the last review been reduced and/or have
35 new uncertainties emerged?” is answered (page 2-35, line 12-19).
36

37 4. In section 2.2.2 the end of the first paragraph has the sentence: “These questions are intended
38 to inform consideration of the following overarching question.”, but no question stated. On page
39 2-40 two questions read, “What is the magnitude of ... COHb levels estimated to occur in areas
40 [that] just meet the current CO standards” and “What proportion of the population experience
41 maximum COHb levels above levels of potential health concern?” The answers to these
42 questions are, for the most part, outlined in table 2-5 but there is no written summary. The
43 question on page 2-42, “What are the key uncertainties associated with our exposure and dose
44 estimates ... ?” This question is clearly answered in the ensuing paragraph. The question on page
45 2-43, “To what extent are the estimates of at-risk population COHb levelsimportant from a

1 public health perspective?” is not answered. Instead, the staff state that the answer depends on
2 public health policy (page 2-44, line 26). This is common sense and does not draw upon the
3 scientific data outlined in the ISA.

4
5 To conclude, the section 2.2 starts with a question: “Does the currently available scientific
6 evidence and exposure/risk-based information, as reflected in the ISA and draft REA, support or
7 call into question the adequacy of the protection afforded by the current CO standards?”. This is
8 clearly important but it remains unanswered in the current policy assessment.

9
10 5. Section 2.2.3 is said to offer conclusions on the adequacy of the current standard. The first two
11 paragraphs clearly outline the rationale taken by the staff and why they give weight to the 8-hour
12 standard (versus the 1-hour standard). The first three sentences of the third paragraph state what
13 appear to be truisms and in the fourth sentence the “conclusion” is that the eight hour standard
14 should be either retained or revised. Hence, there is no conclusion.

15
16 6. Section 2.3, considerations of alternative standards, is organized by posing a series of
17 questions. The first question (page 2-46) is, “To what extent does ... information ... support
18 consideration of alternatives to the current CO standards ... ?” is broken down into sub-headings
19 and more questions. Section 2.3.1 states the indicator for carbon monoxide is carbon monoxide
20 (not sure this is really necessary). Alternatively, you fail to mention the issues outlined in ISA
21 chapter 3. Might it be appropriate to mention that CO is an O₃ precursor and there is a localized
22 chemical interdependency of the CO-CH₄-NO_x system, although these alternative products are
23 not used in estimating local CO production? Section 2.3.2 is said to consider alternatives to the
24 current averaging times of 1- and 8-hour exposures. A question (page 2-47) is then posed, “Do
25 health effects ... assessments provide support for considering different exposure ... times?”. It
26 seems to me the answer is stated on page 2-24, line 4 (... retain the 1- and 8- hour averaging
27 times) but then the staff back away from this in later sections. A new question is posed on page
28 2-48, “What is the range of alternative levels and forms for the standard ... ?” The ensuing
29 paragraphs and sections discuss use of a 99th percentile concentration-based form and the
30 ‘exceeded only once per year’ form. Much of the discussion in the REA is recapitulated in the
31 following pages and the ‘conclusions’, summarized in section 2.3.4, are that the standards could
32 be either revised or retained. Hence, the document offers no conclusion. A minor comment on
33 the tables 2-6 and 2-7 is uncertainty over the term ‘level’ in the second columns. I assume, but
34 am unsure that ‘level’ refers to ppm of CO.

35
36 7. I think discussion of current and potential alternative standards is adequate. I have one last
37 comment pertaining to the uncertainties sections of the staff analysis. This relates to the APEX
38 modeling. The discussion in the REA document includes information that most fixed monitors
39 have a 1 ppm CO lower detectable limit so the modelers added 0.5 ppm CO to all measured
40 values to remove zeros and negative numbers thought to be related to monitor drift. It seems to
41 me that this severely weakens estimates of the at-risk population and threshold COHb levels and
42 thus contradicts consideration of changes from the current standards. However, I defer to other
43 Review Panel members with modeling expertise on whether my concerns are valid.

1 8. I do not think the options listed by the staff are helpful. They merely state what was obvious
2 before starting the entire review process – that is, the guidelines can be left as they are or they
3 could be changed.

4
5 9. Section 3 pertaining to consideration of a secondary standard for CO concludes, I think
6 justifiably, that the science does not support establishing a secondary standard. I think the level
7 of detail presented is adequate.

8
9