



**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 Risk and Exposure Assessment for the Review of the Carbon Monoxide Primary National Ambient Air Quality Standards: Second 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 *Risk and Exposure Assessment for the Review of the Carbon Monoxide Primary National Ambient Air Quality Standards: Second 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 Risk and Exposure (REA) is finalized.

The Panel expressed appreciation to EPA staff for the major improvements made in the second draft of the REA. The changes are responsive to the suggestions and concerns expressed by the Panel in its review of the first draft. Nonetheless, CASAC offers several suggestion and concerns to be considered as the second draft undergoes final revisions.

The Panel encourages clearer conceptual distinction between the levels set for the CO NAAQS and the concentrations at which exposures are received throughout the country. Current levels of CO are far lower than historic levels and the risk for health effects associated with these current levels may be minimal or difficult to quantify with certainty. However, the degree of protection afforded to susceptible populations by the current NAAQS needs to be considered by EPA. A greater degree of protection may be warranted.

As mentioned in its review of the first draft, the Panel felt strongly that the focus of the REA, and the associated *Policy Assessment* document, should be broader than cardiac ischemia (coronary artery disease or CAD). The Panel recognizes that the most certain evidence comes from clinical studies demonstrating a relationship between elevated levels of carboxyhemoglobin (COHb) and a reduced time to the onset of angina. These studies have been at the center of the evidence used to set the NAAQS for CO. However, there is increasing evidence that CO increases the frequency and severity of congestive heart failure and enhances susceptibility to arrhythmias. Consequently, we recommend that a broad set of health outcomes be considered,

1 beyond myocardial ischemia. The susceptible populations might also include those with
2 pulmonary disease.

3
4 In addition, the Allred et al. study should be more completely presented. While a reduction in
5 time to onset of angina is an important and easily interpretable clinical outcome. However, this
6 response is subjective. In contrast, the outcome of ST segment depression, as assessed by a
7 blinded cardiologist, is an objective measure of myocardial ischemia, which should receive
8 consideration. . Moreover, ST segment depression has been validated, both as an outcome of
9 inadequate delivery of oxygen to the myocardium and as a risk factor for more frequent
10 arrhythmias.

11
12 The Panel agreed that greater clarity was needed regarding the major contributors to COHb,
13 ambient outdoor exposures, endogenous production of CO within the body, and finally indoor
14 sources of CO from home cooking, heating, and passive smoking. The relative importance of
15 these contributors to COHb must be more clearly delineated. The REA should address how
16 these multiple sources are used in modeling and contribute to variability and uncertainty in
17 model results.

18
19 We are concerned about two aspects of the adequacy of the current CO monitoring network.
20 First, more sensitive and precise monitors need to be deployed to measure levels that are less
21 than or equal to 1 ppm. Such monitors are needed to validate CO exposure models. Second, the
22 approach for siting monitors needs greater consideration. More extensive coverage may be
23 warranted for areas where concentrations may be more elevated, such as near roadway locations.
24 The Panel found that in some instances current networks underestimated carbon monoxide levels
25 near roadways. Such underestimation is a critical issue since populations with low SES are
26 often overrepresented in those areas. People with low SES are more likely to smoke, which is a
27 substantial source of CO, and African American are subject to sickle cell disease, which affects
28 oxygen transport.

29
30 In regard to the quantitative risk assessment, the Panel recommends greater clarity in describing
31 the model that was used, along with information available about its validity. The profile of
32 COHb in time with varying CO exposures is complex since loading (increased COHb levels) is
33 much more rapid than unloading of COHb levels as ambient CO levels drop. In an analysis that
34 acknowledges multiple sources, it is essential to emphasize the increment which is attributable to
35 ambient CO.

36

4/16/2010 Working Draft Report of the CASAC CO Review Panel on the 2nd draft REA
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1 The CASAC and Panel membership are listed in Enclosure A. The Panel's responses to EPA's
2 charge questions are presented in Enclosure B. Finally, Enclosure C is a compilation of
3 individual panel member comments. We look forward to the Agency's response and the
4 successful completion of the CO NAAQS review.

5
6 Sincerely,

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10 Dr. Joseph D. Brain, Chair
11 CASAC CO Review Panel

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

12
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14 Enclosures
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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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3
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5
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7 Medicine, University of Southern California, Los Angeles, CA
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34

Enclosure B

CASAC's Consensus Responses to EPA's Charge Questions

1. Does the Panel find the summary of CO exposure and discussion of ambient CO sources, exposures, dose, health effects and risk characterization approach to be technically sound, clearly communicated, and appropriately characterized?

In general, the Panel found Chapter 2 to be well organized and technically sound. The chapter serves as a good conceptual overview of the REA, providing a sound rationale for the decision to use COHb level as the internal dose metric for assessing exposure to ambient levels of CO and characterizing associated potential for health risks in the population of persons with coronary artery disease (CAD). While some Panel members supported a cautious approach to using epidemiological data in the risk assessment, overall there were concerns that the current presentation under-emphasized the epidemiologic findings. Even if they are not used in the risk assessment, it is important to incorporate them into the discussion of risk. The epidemiological evidence provides information on non-hypoxia relevant mechanisms and on chronic outcomes that cannot be addressed by relying on COHb levels alone. Furthermore, there was continuing concerns about the selected population at risk. The choice of modeling risk for the CAD population needs to be further justified and/or expanded to include other susceptible populations. Again, the findings of epidemiological studies suggest several groups to be considered, especially the broader category of cardiovascular disease (CVD). Since this chapter serves as the introduction to the REA, it should be edited as the Panel's recommendations are incorporated into subsequent chapters.

2. Does the Panel find the considerations of current ambient carbon monoxide monitoring data, including specifically the data for the monitors included in this draft of the assessment, and the discussion of the extent to which near roadway concentrations are represented to be technically sound, clearly communicated, and appropriately characterized?

The treatment of the CO monitoring data and a description of the extent that these monitors represent near-roadway concentrations, including the data used for this version of the assessment, are improved over the first external draft REA. This discussion is technically sound, clearly communicated, and appropriately characterized. These monitors do not represent near-roadway concentrations very accurately and the REA now documents that well. The increased discussion of NCore and measurement characteristics is useful and appropriately placed.

The REA should point out that the uncertainty of the emissions estimates is too great to make a useful model prediction of CO exposure. The uncertainties in the estimates should be reduced so that chemical transport models can be useful for future exposure studies.

Should there be additional targeted monitoring for indoor and in-vehicle exposures?
Representative monitoring to evaluate emissions inventories or models may be different from monitoring to assess exposure.

1 3. *In recognition of CASAC comments of first draft REA, this draft REA is expanded from the*
2 *previous assessment in a number of ways (summarized in section 1.3 of the draft document).*
3 *The assessment study areas are in the Denver and Los Angeles study areas. We are*
4 *interested in eliciting the views of the Panel on the usefulness of this approach in informing*
5 *our review the NAAQS for CO. What are the Panel members' views on the following aspects*
6 *in which the assessment has been expanded from the previous draft?*
7

8 a. *An important change of this assessment from the first draft is the expansion of each of the*
9 *modeling domains to include a greater number of ambient monitors used as input to*
10 *APEX. Additionally, this draft assessment employs an algorithm that adjusts for temporal*
11 *and spatial heterogeneity in ambient concentrations across each study areas.*

12 An important improvement in this assessment from the first draft is the expansion of each of the
13 modeling domains to include a greater number of ambient monitors used as input to APEX.
14 Additionally, this draft assessment employs an algorithm that adjusts for temporal and spatial
15 heterogeneity in ambient concentrations across each study area.

16 While use of a larger number of ambient air monitors may have improved exposure assessment,
17 we are not convinced that spatial heterogeneity driven by proximity to sources can be adequately
18 captured by the current ambient monitoring network. In fact, exposures in homes and in
19 workplaces closer to roadways might be underestimated.
20

21 It would be helpful to describe with greater clarity how data from overlapping districts, zones
22 and areas were treated for input into the APEX model. What approach was used to avoid
23 duplication of input data from overlapping zones? For Los Angeles, was one of the areas
24 designated as a dominant source or was each area considered separately in the assessment?
25

26 In generating simulated individuals, demographic variables should include socioeconomic status
27 (SES) and race. These variables will impact other APEX modules, particularly COHb.
28

29 We find the tables of exposure values vs. estimated number and percentage of CHD persons
30 affected at specific CO concentrations to be very instructive. Tables showing estimated COHb
31 levels vs. number of people with CHD and persons/days are similarly instructive. Additional
32 calculations and tabulation of endogenous COHb level using APEX and additional plots
33 reflecting contribution of endogenous COHb to total COHb are illustrative.
34

35 b. *The current draft assessment also include an increase in the number of*
36 *microenvironments modeled over that in the first draft (from two to eight) and improved*
37 *the representation of variability in estimated microenvironmental concentrations,*
38 *including in-vehicles.*

39 The Panel has no major issues with this approach.
40

41 c. *This draft assessment has implemented the mass-balance model for estimating*
42 *concentrations in indoor microenvironments.*
43

44 We consider the selection of the mass-balance model for indoor air appropriate.

1
2 *4. Does the Panel view the results of the draft exposure analyses to be technically*
3 *sound, clearly communicated, and appropriately characterized?*
4

5 The Panel questions EPA's assumption that it has captured spatial heterogeneity in homes and
6 workplaces near busy roadways. We agree with the summary of findings (p. A-5) that the
7 current physiology file data is obsolete and may even be incorrect for some variables. While
8 some variables were already updated, others such as race, SES, THb and DLco should be either
9 added to or replace the old data in the input module. With these qualifications, the Panel
10 answers affirmatively to question #4.

11
12 *5. Does the Panel find the derivation and presentation of the modeling approach as a whole*
13 *(chapters 4 and 5) to be technically sound, clearly communicated, and appropriately*
14 *characterized?*

15 The data added to the ambient source inputs for the exposure modeling reflect commendable
16 responsiveness to the feedback we provided in the previous review of the initial REA draft. The
17 modeling appears to be technically sound.
18

19 The subject matter is complex and highly challenging to communicate clearly, in particular the
20 material in Chapter 4. The presentation of this material seems to be aimed at the exposure
21 modeling community, which makes it difficult for others. Nonetheless, the detailed description
22 of the APEX model provides a helpful snapshot of the extensive nature of the model. In sum, the
23 derivation and presentation of the modeling approach as a whole, are well presented. Moreover,
24 the application of the "CHAD" database in modeling the physiological changes of simulated
25 residents during their daily lives appears to be appropriately handled. This approach has been
26 applied and vetted for other regulated air pollutants. Nonetheless, the coupling of the non-linear
27 CFK with the CHAD in the APEX model would be more convincing if there was validation of
28 this approach in field studies where measurements of delivered dose were available. We
29 understand, however, that such validation is not possible on practical grounds. Moreover,
30 previous approaches are less sophisticated from a modeling point of view and also lack field
31 validation for the same reasons of feasibility.
32

33 Appendix C contains some helpful illustrations of the variability in time spent for a given
34 individual in locations/activities throughout the year. It might be helpful, additionally, to have
35 similar illustrations of:

- 36 1. Estimated %COHb levels for an individual during a day with exposures that were near
37 current criteria (maximum allowable) levels of atmospheric CO
38 2. An illustration of the potential variability in peak levels of %COHb throughout the year.

39 Indeed, inclusion of such illustrative scenarios in the text, rather than in the Appendix, should be
40 considered. This material could assist the reader in understanding the variability in the modeled
41 levels of CO exposure.
42

43 *6. Does the Panel find the derivation and presentation of the COHb estimates (Chapters 5*
44 *and 6) to be technically sound, clearly communicated, and appropriately characterized?*
45

1 The derivation and presentation of the %COHb estimates are clearly communicated and
2 characterized, but nonetheless, the final %COHb estimates, as presented in the REA, are
3 potentially problematic. This is related, in part, to their derivation (the basic assumptions made in
4 arriving at these values, not the computational operations of the APEX system). Modeling
5 %COHb, as a biological marker of ambient CO exposure, presents particular challenges arising
6 out of varying sources of exposure, each which can potentially contribute to the final %COHb
7 estimate. These sources include: endogenous production; ambient air pollution; and indoor air
8 sources not accounted for by ambient pollution tracking indoors (e.g., combustion byproducts
9 from home heating or cooking and secondhand smoking-associated CO). Extensive modeling in
10 the REA appropriately deals with scenarios of ambient CO contributions to the indoor exposure
11 environments. It was only well into Chapter 6 that modeling including “Internal Sources” of
12 COHb was introduced [a confusing word choice since this does not mean *internal* in the sense of
13 *endogenous metabolism*]. As shown in Tables 6-15 and 6-16, excluding these indoor sources,
14 modeled %COHb values (i.e., from ambient exposures levels) are similar between the 2000
15 model that also provides the indoor (“internal”) estimates and the current APEX model. Key is
16 that *inclusion* of the indoor sources of exposure drives up exposure such that 5 percent of the
17 population hits a 3% COHb level and roughly 2 percent of the population reaches a 4.0% COHb
18 level.

19
20 The Panel appreciated the additional attention given to endogenous CO production (again, not
21 the “Internal” metric above). There was concern that this discussion could lead to confusion,
22 because the modeled levels of endogenous %COHb are quite a bit lower than population means
23 for non-smokers. This is because non-smoking population data reflect the sum of ambient
24 exposure, indoor exposure, and endogenous CO production. Clarifying these distinctions,
25 explicitly, might be useful. Beyond issues of presentation, the modeled distribution of
26 endogenous %COHb values appears to be too narrow. It appears to be based on “normal” healthy
27 population estimates of endogenous production (albeit with a variety of activity levels).
28 Literature demonstrating elevated endogenous %COHb values in certain subpopulations (for
29 example, in persons with sickle cell disease) may be difficult to take into account in these
30 models, but attempting to address this is warranted (or at least the document should directly
31 acknowledge this limitation).

32
33 Further confusion may be introduced through the random subset estimations, given that the
34 central tendency (mean) of this random sub-sample seems to differ from the larger modeling
35 estimate (apparently a chance observation). The narrower distribution is produced by the limited
36 intra-person variation since most of the data points are derived from multiple runs on a relatively
37 small subset – (this should not explain the shift in the mean). It may even be relevant to
38 acknowledge that certain groups at risk for higher endogenous production *systematically* may be
39 more likely to have higher ambient scenarios (e.g., a low-income, sickle cell disease resident
40 dwelling near a major roadway). Further confusion may arise from a lack of transparency in the
41 endogenous production model even as applied. The description of what endogenous rates were
42 used in the model is unclear and the information in Table B-3 on page B-20 is poorly labeled.
43 Despite these limitations, the material on endogenous production of CO and its contribution to
44 the overall %COHb in combination with ambient levels of CO is very informative and indeed
45 necessary.

46

1 In summary, the Panel is concerned that there is no modeling of %COHb that covers indoor non-
2 ambient sources *and* endogenous CO production *and* ambient exposure.

3
4 In an improvement over the REA draft itself, the staff presentation at the meeting included
5 additional analyses of the contribution of ambient CO to the COHb% levels. While the data
6 were apparently computationally intensive to develop, some panel members felt that this could
7 be an extremely useful avenue to further develop as an underpinning of the standard. Indeed,
8 since the *a priori* focus of the influential Allred et al. papers was on a specified increase in
9 %COHb over the subjects' pre-exposure or filtered air exposure and not on the magnitude of the
10 final %COHb, it may well be that the ambient-attributable *increment* in %COHb is the most
11 directly analogous dose for consideration in assessment of risk.

12
13 Through such an approach, more attention to the ambient-attributable increment metric in
14 consideration of dose could simplify the assessment of risk, as the issue of "overlap" with the
15 endogenous range of final COHb% (let alone indoor non ambient contributions) would be
16 parsed-out. This presentation could still delineate the other sources of exposure noted above.
17 This would address differing, but not necessarily opposing, concerns voiced in the Panel in
18 regard to the continuity of the CO exposure-response in experimental studies, rather than purely
19 the metric of an incremental added exposure and the response to that. Thus, providing exposure
20 data and estimated %COHb combined and separately would allow policy makers to consider
21 ambient exposure alone (the *increment* emphasized above) as well as in the context of other
22 sources of exposure.

23
24 *7. In the Panel's view, to what extent does the modified assessment approach employed in*
25 *this second draft assessment provide results that meaningfully inform the EPA's*
26 *consideration of the public health implications of the current standards.*

27
28 The modified assessment approach has two key components: estimated exposure and the
29 estimated at-risk (susceptible) population. In terms of exposure, it should also be noted that the
30 additional information included in the current modification does not relieve uncertainties from
31 the use of a relatively limited data set (case studies in two cities only) to provide guidance for
32 setting standards, even with the additional monitoring data. The document could be improved by
33 showing the impact, or lack of impact, on the dose variability that resulted including data from
34 more monitoring sites as was done in on this revision (including data resolution across the two
35 sites). This is particularly relevant to any national extrapolations. The exposure component can
36 also be improved, as other comments to the previous charge questions indicate. Such
37 improvements could serve to better inform the EPA's consideration of the public health
38 implications of the current CO standard.

39
40 Insofar as the "at risk" population estimates are concerned, there are serious potential data
41 uncertainties, many of which might lead to a systematic *underestimation* of the public health
42 impact of CO exposure. The REA continues to rely on National Health Interview Survey (NHIS)
43 data alone to provide a population estimate of persons at risk, narrowly defined as self-reported
44 coronary artery disease. This was a matter of focused critique of the first draft document. The
45 revision now includes an estimate of "undiagnosed" disease (approximately 40% in addition to
46 the base population). Conceptually, this is an important acknowledgment of one aspect of

1 systematic underestimation, although the American Heart Association source of the
2 mathematical value used is far from convincing. Whatever value is used should incorporate a
3 female>male differential given a probable sex-based gap in diagnosis. In addition, in terms of the
4 restricted subset of susceptible persons based on a CAD definition, supportive prevalence data
5 based on NHANES and the Behavioral Risk Survey are easily accessible and will generally
6 support the NHIS-based values.
7

8 More fundamentally, the narrowly-defined CAD prevalence estimate, to the exclusion of all
9 others with cardiac disease, misreads and misinterprets the ISA, particularly Tables 4-9, 5-10, 5-
10 11 and Figures 5-5 through 5-7. Revisiting the NHIS, the prevalence rates for “all heart disease”
11 are considerably more than for narrowly defined CAD. It is very likely that most, if not all, of
12 these persons are at increased risk for adverse cardiovascular effects from ambient CO in ways
13 that cannot be distinguished epidemiologically from the CAD subset. It is certainly appropriate
14 for the REA to present estimates, as indeed it did, using a narrow CAD definition of “at risk” to
15 inform an EPA public health assessment, but this approach alone is not sufficient. Much effort is
16 spent on multiple scenarios of exposure, while falling short in the critical area of the defining
17 alternate measures of the vulnerable population. As a consequence of the approach suggested
18 above, a population more broadly defined with cardiovascular disease is likely to overlap to a
19 meaningful extent with adults with chronic obstructive lung disease (through shared risk factors),
20 which may be another at risk group for adverse CO exposure effects. This is not a determining
21 factor, however, in the rationale for applying a more broadly-defined cardiac disease definition
22 in modeling the at-risk population.
23

24 *8. What are the views of the Panel regarding the adequacy of the assessment of uncertainty*
25 *and variability? To what extent have sources of uncertainty been identified and the*
26 *implications for the risk characterization been characterized? To what extent has*
27 *variability adequately described and represented?*
28

29 In general, the incorporation of more monitors in each area, more microenvironments, and
30 variability in various variables within APEX better addresses variability and thus general
31 uncertainty in exposure and dose. However, the use of the power 0.621 in equations 4-11 and 4-
32 22, reduces the CO concentration at an outdoor location, relative to the nearest central monitor,
33 and thus possibly reduces the number of occurrences of the highest CO concentrations.
34

35 In addition, all three contributors to COHb (ambient, endogenous production, and indoor
36 sources, excluding smoking) should be considered in modeling and as contributing to variability
37 and uncertainty in model results.

Enclosure C

Review Comments from the CASAC CO Panel on the *Second Draft Risk and Exposure Assessment to Support the Review of the Carbon Monoxide Primary NAAQS*

Comments received:

9	Dr. Paul Blanc	15
10	Dr. Thomas Dahms	18
11	Dr. Russell Dickerson	21
12	Dr. Milan Hazucha	23
13	Dr. Francine Laden	29
14	Dr. Arthur Penn	30
15	Dr. Beate Ritz	31
16	Dr. Paul T. Roberts	32
17	Dr. Anne Sweeney	34
18	Dr. Stephen Thom	35

Dr. Paul Blanc

1
2
3 *5. Does the Panel find the derivation and presentation of the modeling approach as a whole*
4 *(Chapters 4 and 5) to be technically sound, clearly communicated, and appropriately*
5 *characterized?*
6

7 Insofar as the increase inputs to the ambient source inputs to the models, this revision was quite
8 responsive to the input that it received in review of its initial draft and is to be commended. This
9 aspect of the approach appears to be technically sounds. This subject matter is complex and
10 highly challenging to communicate clearly, in particular the material in Chapter 4. .
11

12 *6. Does the Panel find the derivation and presentation of the COHb estimates (Chapters 5*
13 *and 6) to be technically sound, clearly communicated, and appropriately characterized?*
14

15 The final COHb estimates in 6 are problem-ridden. This is related in part to the derivation
16 (including under this the basic assumptions made, not simply the mathematical operations of the
17 APEX system). The presentation magnifies certain issues by potentially obscuring points
18 presumed to be manifest but that may be to be more explicit.
19

20 Modeling COHb, as a biological marker of ambient air pollution exposure, presents a particular
21 challenge because there are 4 principal domains of exposure, each which can potentially
22 contribute to the end concentration measured. These 4 domains are: endogenous production;
23 ambient air pollution; active cigarette smoking; and supplemental sources of carbon monoxide
24 beyond these three. This fourth domain, for most persons, is drive by indoor air exposure to CO
25 from combustion byproducts from home heating or cooking and secondhand smoking-associated
26 CO [although other sources of exposure within this domain may be important for population
27 subsets, e.g., occupationally-related CO exposure].
28

29 Chapter 5, in relation to CO exposure modeling leading to COHb is focused entirely on the
30 domain of ambient CO, although extensive modeling deals with scenarios of contributions of
31 ambient CO to indoor exposure environments. This can be a bit confusing because internal
32 combustion engine contributions to exposure in certain indoor scenarios are essentially point
33 sources (service station and auto repair GM 2.97 [PPMs although not labeled]). Of note, another
34 indoor facility group includes (Manufacturing facility) and is rather low – GM 0.089. One
35 assumes fork lifts or truck deliveries not considered. The salient point however is: these
36 scenarios exclude other likely concomitant sources of exposure.
37

38 It is not until well into Chapter 6 that modeling that includes the domain of “Internal Sources” of
39 COHb is introduced. The term Internal as used here is unfortunate, since it actually is intended to
40 mean “indoor – not from ambient sources” i.e., what I refer to as the 4th domain above. *If* this
41 also includes endogenous production it is by no means clear. As shown in Tables 6-15 and 6-16,
42 excluding these indoor sources these estimated exposures levels are similar between a 2000
43 model and the current APEX model – but *inclusion* of this critical source of exposure drives up
44 exposure such that 5% of the population hits a 3% COHb level and roughly 2% a 4.0% COHb

1 level. Remarkably there is no simulation or other estimation combining current indoor sources
2 with the ambient estimates.

3
4 Despite the short-shrift given the indoor exposure issue, a great deal of attention is then given to
5 endogenous CO production. This, of course, is not “Internal” as used above, but rather refers to
6 “normal” metabolic production of CO. This section is likely to lead to some confusion because,
7 quite appropriately, the modeled levels of COHb% (population mean 0.255%) are quite a bit
8 lower than population means for non-smokers. The reason of course if that observed non-
9 smoking population data reflect the sum of domains 1,2,and 4, not simply endogenous production
10 (thus the baseline samples in the Allred study, etc). This is a point of blurred presentation, not
11 modeling. The modeling itself, however, could benefit from more transparency. The reader is
12 told that a certain number of studies informed the metabolic parameters as detailed in B but in
13 fact it is hard to tease-out which references there are the ones in question. These seem to be fairly
14 dated (Coburn’s work from the 1960s) and this may be the best there is. Nonetheless, more
15 recent literature exploring moderately elevated COHb in certain conditions (for example, sickle
16 cell disease) suggests that the model specifications and simulations yielding a maximum
17 endogenous value of 1.54 is not likely to be reflective of population variability. This may be
18 driven by simulating 59 individuals only, albeit with 8,760 hours of modeled observation. To
19 capture endogenous variability, within person hour to hour activity inputs is not nearly as
20 important as between person variability. Moreover, it is likely that certain at risk groups may be
21 more likely to have ambient scenarios (and indoor scenarios) of higher exposure: eg. a low
22 income resident of south-central LA dwelling near a freeway with sickle cell disease (and
23 heating the home with a gas stove in the winter).

24
25 Integrating the comments above, there is no apparent modeling of COHb that includes variable
26 indoor not ambient sources (exclusive of direct cigarette smoking) + endogenous CO production
27 (anticipation a possible bimodal distribution, with certain disease states contributing a sub-group
28 of outliers) and ambient exposure.

29
30 *7. In the Panel’s view, to what extent does the modified assessment approach employed in*
31 *this second draft assessment provide results that meaningfully inform the EPA’s*
32 *consideration of the public health implications of the current standards.*

33
34 The modified assessment approach has two key components: estimated exposure and the
35 estimated at risk (susceptible) population. All of the comments above (charge questions 5 and 6)
36 relate to the exposure assessment. To the extent that the exposure issues raised above can be
37 addressed, this would serve to better inform the EPA’s consideration of the public health
38 implications of the current CO standard. Even as is, this portion of the Risk and Exposure
39 Assessment is not fundamentally flawed.

40
41 Insofar as the at risk population estimates are concerned, the document as currently constituted is
42 prone to several sources of data uncertainties, all of which would tend to systematically
43 underestimate the public health impact of exposure. The document continues to rely on National
44 Health Interview Survey (NHIS) to provide a population estimate of persons at risk, narrowly
45 defined as self reported coronary artery disease. This was a matter of focused critique of the first
46 draft document. The revision now includes an estimate of “undiagnosed” disease (approximately

1 40% in addition to the base population). Conceptually this is an important acknowledgment of
2 the one aspect of systematic underestimation, although the American Heart Association source of
3 the mathematical value used is far from convincing (and whatever value is used should
4 incorporate a female>male differential given the clear sex-based gap in diagnosis. In addition, in
5 terms of the restricted subset of susceptible persons based on CAD, supportive prevalence data
6 based on NHANES and the Behavioral Risk Survey are easily accessible and will generally
7 support the NHIS-based values. More fundamentally, the narrowly defined CAD prevalence
8 estimate, to the exclusion of all others with cardiac disease misreads and misinterprets the ISA
9 particularly Tables 4-9, 5-10, 5-11 and Figures 5-5 though 5-7. Revisiting the NHIS, the
10 prevalence rates for “all heart disease” are considerably more than for narrowly defined CAD. It
11 is very likely that most if not all of these are at risk as from adverse cardiac effects from ambient
12 CO in ways that cannot be distinguished epidemiologically from the CAD subset (this includes
13 in term of RR). It is certainly appropriate for the REA to present estimates, as it did, using a
14 narrow definition of “at risk”; to inform an EPA public health assessment, this approach alone is
15 unacceptable. It is ironic that so much effort is spent on multiple scenarios of exposure, while
16 falling short in the critical area of the key vulnerable population.

Dr. Thomas Dahms

1
2
3 *5. Does the Panel find the derivation and presentation of the modeling approach as a whole*
4 *(Chapters 4 and 5) to be technically sound, clearly communicated, and appropriately*
5 *characterized?*
6

7 The detailed description of the apex model provides a helpful snapshot of the extensive nature of
8 the model. The application of the CHAD database in modeling the physiological changes of
9 simulated residents during their daily lives seems to be appropriately handled. This approach has
10 been applied and vetted for other regulated air pollutants. The presentation of the material seems
11 to be aimed at the exposure modeling community which makes it difficult to assess for someone
12 not in the modeling community.
13

14 Appendix C contains some helpful illustrations of the variability in time spent for an individual
15 in locations/activities during a year. It would be helpful to have a similar illustration of
16 estimated %COHb levels of %COHb in an individual during a day with near criteria levels of
17 atmospheric CO and also an illustration of the variability in peak levels of %COHb throughout
18 the year. Additions of these illustrations to the text rather than in the Appendix should be
19 considered. It would assist the reader in understanding the variability in the modeled levels of
20 dose of CO.
21

22 The coupling of the non-linear CFK with the CHAD in the APEX model would be more
23 convincing if there were references to validation of this model in studies where measurements of
24 dose were made. Without documentation of such validation, the reader is expected to accept this
25 model based on years of improvements over other models.
26

27 Since the controlled human exposure data is a major factor in setting policy, it would be helpful
28 to see how well the exposure model predicts the measured CO dose in these experiments.
29 Although these exposures are for only 1 hour with subjects at rest, it would provide a means of
30 validation of the exposure/dose modeling used for the general population. It might also provide a
31 means of comparison of the various controlled human exposures.
32

33 *6. Does the Panel find the derivation and presentation of the COHb estimates (chapters 5*
34 *and 6) to be technically sound, clearly communicated, and appropriately characterized?*
35

36 The presentation of how the model arrives at estimates of %COHb in the population of Denver
37 and Los Angeles is clear in that it follows a natural progression in this field over the past 40
38 years. It is clearly communicated and the improvements in the modeling over the years is clearly
39 presented and is very rational. There are concerns with the output of the model that leads to a
40 level of uncertainty that could be somewhat reduced as described below.
41

42 The primary goal of this section would be to determine whether or not the estimated levels of
43 %COHb (from the model) using the current as is data are lower or higher than those estimated
44 levels of %COHb using the current standards. It is presumed that the exposure to the current
45 standards for CO results in a small but acceptable number of at risk persons for a given %COHb

1 benchmark. If the current as is data results in a smaller number of persons at that benchmark,
2 there would be little pressure to change the standards. Therefore the issue that needs to be
3 discussed/defined is : what is a small but acceptable number of persons who can be exposed at
4 an acceptable benchmark. This discussion is absent.

5
6 It is not clear what background in modeling minutia the reader is expected to have to clearly
7 understand and analyze the details of the material presented. The crux of the matter is that for
8 carbon monoxide there is an agreed upon dose metric, %COHb, that can be used to evaluate
9 exposure. This is not quite the case for the other regulated pollutants. There is no mention of any
10 attempt to validate the model being used under any circumstances. No matter how sophisticated
11 the model, without validation it is just a model with all of the attendant uncertainties.

12
13 The presentation of the information in section 6.4 on the influence of endogenous rates of CO
14 production on dose estimates is potentially a problem. The description of what endogenous rates
15 were used in the model is unclear and the information on Table B-3 on page B-20 is very poorly
16 labeled. The values used in this portion of the model need to be clearly documented and justified.
17 This becomes an issue because this modeling data is used to justify not including 1.0 %COHb
18 in the Policy Assessment document. The modeling of all of the parameters that impact baseline
19 %COHb into 'endogenous rates of CO production' as the primary determinate of baseline (no
20 CO exposure) %COHb. This comes to light in Table 6-17 on page 6-18 which shows the APEX
21 model to result in a median value of %COHB somewhere between 0.25 and 0.50% COHb and
22 the non-parametric distribution of values is considerable. The modelers claim that this data can
23 not be compared to any studies in the literature because of the time frame over which the data is
24 modeled. Unfortunately there will always be skepticism of any model that can not be validated
25 practically with actual measurements. The study by Allred et al observed 63 subjects in 3 cities
26 on 4 experimental days (repeated measurements on an individual occurred within 6 weeks) and
27 all of the subjects were observed over less than a 2 year period (270 measurements of baseline
28 levels of %COHb). The mean %COHb levels did not vary over this period of time. These values
29 ranged between 0.62 and 0.64 %COHb with a standard deviation of 0.16% COHb. The model
30 results does not fit these results on the population most at risk in this assessment.
31 The search for an alternative format for setting standards maybe statistically enticing but would
32 present too many problems for implementation of public health measures when the standards
33 have been exceeded. News readers have a difficult time with the current standards provided in
34 PPM so I can only imagine how they would attempt to explain any of the proposed alternative
35 methods.

36
37 There is also no attempt made to employ the model in the studies dealing with controlled
38 exposures in subjects with CAD. I know that using APEX to model a 1 hour exposure to CO is
39 akin to killing a slug with a sledge hammer, but what other data base is as relevant to validation
40 of the model being so widely used?

41
42 *7. In the Panel's view, to what extent does the modified assessment approach employed in*
43 *this second draft assessment provide results that meaningfully inform EPA's consideration of*
44 *the public health implications of the current standards?*
45

1 The additional information included in the current modification does not relieve the anxiety from
2 the use of so little monitoring data to provide guidance for setting standards. Perhaps it is in the
3 way in which the information is presented: there is no data presented or referred to that shows
4 that including more data adds nothing to the analysis. As a result of what has currently been
5 presented, I am still uneasy with the use of so little of the available monitoring data for this risk
6 assessment. Does the use of data from a few monitoring sites imply that we need fewer monitors
7 in our cities because we can accurately predict what exists in the entire metro area based upon a
8 few monitors? How is the reader to interpret the use of data from so few sites. To state the above
9 concern in another way, the document could be improved by showing the impact, or lack of
10 impact, on the dose variability by including data from more monitoring sites. This could be
11 previously published information and need not involve re-running of the models with data from
12 these additional sites.

13
14 There is also mention of the lack of data resolution of the LA monitors vs the Denver monitors
15 but the impact of the low resolution monitors in LA is not discussed. If it has no impact why was
16 the issue raised?

17
18 It is my impression that the estimates of risk due to exposure to CO are to apply to entire country
19 and not just to Denver and Los Angeles. It is clear that the detail presented for these two cities
20 can not be also presented for all of the major metropolitan areas of the country. However it is
21 incumbent upon the authors to address how these risk assessments for Denver and LA are to be
22 applied to the entire population of the United States. After all the document goes to great lengths
23 to describe how many people are in the at risk group in the country and then applies some metric
24 to determine how many of these individuals are in Denver and in LA.

Dr. Russell Dickerson

2.
2.
3.
4. *Does the Panel find the considerations of current ambient carbon monoxide monitoring data, including specifically the data for the monitors included in this draft of the assessment, and the discussion of the extent to which near roadway concentrations are represented to be technically sound, clearly communicated, and appropriately characterized?*

8
9 The revised draft is much improved, and generally meets expectations. EPA is faced with the
10 situation that ambient measurements are more accurate than emissions. This makes
11 measurement/model comparisons difficult. Although Chemical Transport Models (CTM's) are
12 not used in Chapter 3 or the REA, that chapter should point out that such tools *should* be used
13 and continued evaluations and improvements (if necessary) in emissions are needed.

14
15 The increased discussion of NCore and Analytical Sensitivity are useful and appropriately placed
16 near the front.

17
18 Key Observations (page 3-18 and 3-19) are appropriate, except I could not find much on the
19 uncertainties in emissions (see also comments on ISA) and their impact on model output.

20
21 Chapter 5 appears to reflect the state of knowledge.

22
23 Preliminary Comments on the ISA (relevant to REA)

24
25 In one last reading of the ISA, Chapter 2 does a thorough job of providing an overview of our
26 technical understanding of CO.

27
28 A few comments:

- 29 1. Page 2-3 might mention HCHF's are removed by OH
- 30 2. The caption to Figure 3-1 might include the word DIRECT so people don't go looking for
31 isoprene.
- 32 3. Section 3.2.2 looks really good, as does Figure 3-8. This makes an important point that should
33 appear in the PA.
- 34 4. The sections on ambient measurements, detection limits and NCore are all much improved.
- 35 5. Based on a quick read, Section 3.5 looks solid now.

36
37
38 In poking around the literature I have found a few more papers that evaluate the emissions
39 inventories of CO. Kuhns et al. (2004) and Yu et al. (2007; 2009) also found evidence of
40 overestimates of CO emissions in Mobile6 or CMAQ. Marmur et al. (2009) in contrast seem to
41 find that the CO emissions are underestimated. Zhang and Batterman (2010) find that Mobile 6
42 matches plume dispersion models and a roadside monitor reasonably well. We are just about to
43 submit a paper that evaluates Mobile6 CO emissions using about 100 altitude profiles and find
44 that modeled emissions are high but not in gross error. If the paper is accepted soon enough I
45 will send a preprint.

- 1
2 Kuhns, H. D., et al. (2004), Remote sensing of PM, NO, CO and HC emission factors for on-
3 road gasoline and diesel engine vehicles in Las Vegas, NV *Science of the Total Environment*,
4 322, 123-137.
- 5 Marmur, A., et al. (2009), Evaluation of model simulated atmospheric constituents with
6 observations in the factor projected space: CMAQ simulations of SEARCH measurements,
7 *Atmospheric Environment*, 43, 1839-1849.
- 8 Yu, S.C., et al. (2007), A detailed evaluation of the Eta-CMAQ forecast model performance for
9 O₃, its related precursors, and meteorological parameters during the 2004 ICARTT study,
10 *Journal of Geophysical Research*, 112, D12S14.
- 11 Yu, S.C., et al. (2009), Eta-CMAQ air quality forecasts for O₃ and related species using three
12 different photochemical mechanisms (CB4, CB05, SAPRC-99): comparisons with
13 measurements during the 2004 ICARTT study, *Atmospheric Chemistry and Physics*
14 *Discussions*, 9, 22955-22992.
- 15 Zhang, K., and S. Batterman, Near-road air pollutant concentrations of CO and PM_{2.5}: A
16 comparison of MOBILE6.2/CALINE4 and generalized additive models, *Atmospheric*
17 *Environment*, doi:10.1016/j.atmosenv.2010.02.008, in press 2010.

Dr. Milan Hazucha

Background on assessing ambient CO exposure and risk (Chapter 2).

Charge Question 1: Does the Panel find the summary of CO exposure and discussion of ambient CO sources, exposures, dose, health effects and risk characterization approach to be technically sound, clearly communicated, and appropriately characterized?

Qualified yes in all respects.

In addition to already mentioned endogenous CO production and exogenous sources (p. 2-6, l. 11-13), additional source is metabolic production of CO due to inhalation of, e.g., dihalomethanes, other substances and certain medication.

Do we really consider people using recreational drugs to be at-risk population and be considered in risk assessment (p. 2-8, l.19)? If so we will have to consider smokers to be at-risk population as well.

Since Allred et al. studies provide the key evidence for CO health effects assessment it would be very helpful if the document, in addition to % changes of the critical endpoint, e.g., time to angina also reported the actual mean and CI (confidence interval) values in respective endpoint units (p.2-11, l.24-27 and p.2-12, l. 10-13). How clinically significant is shorter by 22 seconds time to angina out of nearly 9 minutes? Besides reduced time to angina, was the duration and the intensity of angina affected as well? Did frequency of angina attacks increased because of CO exposure? If these endpoints were not reported by the investigators, it should be specifically stated so in REA.

I support very cautious approach to some epidemiology studies reports of the effects of CO on respiratory system (p.2-10, 2-13, 2-18). I fully agree with EPA assessment that the interpretation of CO-induced lung-related outcomes “is affected by uncertainties including with regard to the biological mechanism that could explain CO-induced outcomes” (p. 2-13, l. 8-11).

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.2-16, l. 26-34). 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.

1 Air Quality Considerations (Chapter 3 and 5)

2 **Charge Question 2:** Does the panel find the considerations of current ambient carbon
3 monoxide monitoring data, including specifically the data for the monitors included in this draft
4 of the assessment, and the discussion of the extent to which near roadway concentrations are
5 represented to be technically sound, clearly communicated, and appropriately characterized?
6

7 Yes in all respects.
8

9 Characterization of Exposure, Dose and Potential Risk (Chapter 4-6)

10 **Charge Question 3:** In recognition of CASAC comments of first draft REA, this draft REA is
11 expanded from the previous assessment in a number of ways (summarized in section 1.3 of the
12 draft document). The assessment study areas are in the Denver and Los Angeles study areas. We
13 are interested in eliciting the views of the Panel on the usefulness of this approach in informing
14 our review the NAAQS for CO. What are the Panel members' views on the following aspects in
15 which the assessment has been expanded from the previous draft?
16

17 The charge questions span across 3 chapters: Ch. 4 Overview of APEX modeling, Ch. 5
18 Application of APEX, and Ch. 6 Simulated exposure and COHb dose results.
19

20 However, it is difficult to comment on the chapters in general since the sub-questions are
21 rather specific.
22

23 **A.** An important change of this assessment from the first draft is the expansion of each of the
24 modeling domains to include a greater number of ambient monitors used as input to
25 APEX. Additionally, this draft assessment employs an algorithm that adjusts for temporal
26 and spatial heterogeneity in ambient concentrations across each study areas.

27 The bulleted list of modified/expanded sections is very helpful. Similarly, the flow
28 chart showing input points and flow of data has been very helpful as well.
29

30 How does the expansion of modeling domains in this REA compare to REA1? Were
31 the estimates about the same or different and how they were different?
32

33 Generally, larger number of monitors may improve exposure assessment. Figure 5.1
34 (p.5-5) shows a considerable overlay of air districts, meteorological zones and for Los
35 Angeles study areas as well. Although the overlapping districts, zones and areas were
36 adjusted for as far as exposure goes, how were they treated in terms of input data into
37 other modules of APEX? What approach was used to avoid duplication of input
38 data? For L. A., was one of the areas designated as a dominant source or each area
39 was considered separately in the assessment?
40

41 In generation of simulated individuals, demographic variables should include socio-
42 economic status and race. These variables will impact other APEX modules,
43 particularly the COHb one.
44

45 Chapter 6: The tables tabulating exposure values vs estimated number and percentage
46 of CHD persons affected at specific CO concentrations are very instructive and

1 revelatory. Tables showing estimated COHb levels vs number of CHD persons and
2 persons/days are similarly instructive. Generally, these table show that the current
3 level of both standards is protective as required by the legislation, i.e., “standards that
4 are neither more nor less stringent than necessary.”
5

6 Additional calculations and tabulation of endogenous COHb level using APEX has
7 been also very helpful. Table 6-18 (p.6-19) shows that the endogenous contribution to
8 a total COHb is “less than 0.5%, though for a limited number of hours, the
9 endogenous contribution could be over 1.0% COHb.” The additional plots reflect
10 contribution of endogenous COHb to a total COHb level essentially following
11 physiologic laws of Haldane.
12

13 Section 6.5 Key Observations (p.6-24) summarizes the main observations presented
14 in this chapter. One of the important conclusions is that more than 95% of simulated
15 at-risk population of L.A. study areas will experience an annual daily maximum end-
16 of-hours COHb level below 1.5%. Moreover, when considering alternative standards
17 “only 0.1% of the CHD population was estimated to experience a maximum end-of
18 hour COHb at or above 2%. Similar values are provided for Denver.
19

- 20 **B.** The current draft assessment also include an increase in the number of
21 microenvironments modeled over that in the first draft (from two to eight) and improved
22 the representation of variability in estimated microenvironmental concentrations,
23 including in-vehicles.

24 Chapter 4: Table 4-4 (p. 5-21) and 4-5 (p. 4-29) lists 15 microenvironments used in
25 estimates in pNEM/CO model in 2000, and the same number and type in APEX4.3.
26 However, the number for this draft is reduced to 8. Did this change in any way
27 affected the estimates?
28

29 It would have been helpful instead of making a general statement on how better
30 APEX is, to actually list in 4.5 Key Observations section(p. 4-35) specific
31 enhancements of APEX over pNEM/CO.
32

33 The two important conclusions were that (1) the policy relevant background was
34 negligible, and (2) the fixed site monitoring data could be adjusted. The tables
35 provide sufficiently detailed data to evaluate all 5 scenarios.

36 In the current draft the number of microenvironments was increased to 4 indoor, 3
37 outdoor and 1 in-vehicle. Such expansion may improve strategies and enhance the
38 validity as well as credibility of the assessment. More realistic scenarios provide
39 stronger and more representative base for decision making.
40

- 41 **C.** This draft assessment has implemented the mass-balance model for estimating
42 concentrations in indoor microenvironments.

43 I consider the selection of mass-balance model for indoor air appropriate.
44

1 **Charge Question 4.** Does the Panel view the results of the draft exposure analyses to be
2 technically sound, clearly communicated, and appropriately characterized?
3

4 Qualified yes to all respects.
5

6 The various modules of APEX model are regularly upgraded to improve the simulation
7 process making it as realistic as possible. Yet the COHb module to estimate venous blood
8 COHb level, the ultimate endpoint remains the same, i.e. based on CFKE (p.4-34, 1.20-31).
9 As already commented on this matter by several panel members including myself in the past
10 why is EPA so adamant exploring more recent and more sophisticated CFK equations?
11 Replacing original CFK with an enhanced, e.g. Bruce and Bruce module should be simple
12 enough. If there are no substantial differences, then no change is necessary. However, if
13 there are differences in COHb estimates, then we may search and evaluate the factors that
14 may have affected the change. Such information may potentially useful in standard setting.
15

16 Moreover, regardless of a mathematical model employed in COHb module, the COHb
17 estimates can be improved by tuning some of the explicit input variables such as THb and
18 DLco.
19

20 Appendix A: I agree with the summary of findings (p. A-5) that the current physiology file
21 data is obsolete and may even be incorrect for some variables. While some variables were
22 already updated, others such as race, SES, THb and DLco should be either added to or
23 replace the old data in the input module.
24

25 **Charge Question 5:** Does the Panel find the derivation and presentation of the modeling
26 approach as a whole (chapters 4 and 5) to be technically sound, clearly communicated, and
27 appropriately characterized?
28

29 Yes in all respects. The staff did an excellent job of presenting and discussing APEX model.
30 I agree with well reasoned arguments and the conclusions.
31

32 Any concerns about the effect of missing concentration values on their distribution were
33 cleared by addition of descriptive statistics tables (5-7 through 5-10). The tables demonstrate
34 that the missing values whether estimated and corrected for or not do not influence the
35 distribution of hourly values either in Denver or Los Angeles. Similar approach to estimation
36 of missing temperature values required by APEX likely resulted, as stated in the document,
37 in negligible differences.
38

39 **Charge Question 6:** Does the Panel find the derivation and presentation of the COHb estimates
40 (chapters 5 and 6) to be technically sound, clearly communicated, and appropriately
41 characterized?
42

43 Qualified YES in all respects.
44

45 Section 6.3.1 referenced in the document is likely section 6.4.1.

1 The section 6.4 on endogenous production of CO and its contribution to overall COHb in
2 combination with ambient levels of CO is very informative. Table 6-17 clearly shows that
3 even at 0 ppm CO in ambient air several hundred individuals will reach COHb level as high
4 as 1.8%. It would be instructive to identify groups of individuals (e.g. with anemia) who
5 exceeded 1% COHb level due to endogenous production.
6

7 Figure 6-2 shows, as expected, that endogenous CO will not influence COHB level if the
8 ambient CO concentration exceed the one produced endogenously (this needs to be stated
9 more clearly on p. 6-21, l. 6-8). Figure 6-4 indeed confirms the above statement.
10

11 *Appendix B. COHB module:*
12

13 p. B-3: The $P_{I_{CO}}$, should be defined as a partial pressure.
14

15 p. B-5 In eq. B-11 and B-14 P_{CO_2} subscript should be correct to read not as CO₂ (carbon
16 dioxide) but as c_{O_2} (capillary O₂).
17

18 Suggest to move the second paragraph on page B-8 as the first paragraph of the section,
19 otherwise without the explanation, the statement is misleading.
20

21 p. B-9- B-14. Section C4: The COHb module seems to be the weakest of the APEX modules.
22 Primarily, it is because we do not have sufficient data over the physiologic range for many
23 variables. However, though still limited some physiologic data are available for healthy and
24 at-risk groups and they should be integrated into data base for COHb module. From the
25 tables nor the text it does not look like that many critical variables such as Hb, DLco,
26 endogenous CO and others were, besides age and gender, adjusted for other physical
27 characteristics or disease conditions. For example, the amount of Hb will determine the rate
28 of COHb formation and is a critical variable. There are substantial differences between blood
29 concentration of Hb in whites and blacks.
30

31 **Charge Question 7:** In the Panel's view, to what extent does the modified assessment approach
32 employed in this second draft assessment provide results that meaningfully inform EPA's
33 consideration of the public health implications of the current standard?
34

35 I agree with the expanded approach and I believe that it will allow for more accurate
36 assessment and risk-characterization.
37

38 Characterization of Variability and Uncertainty (Chapter 7)

39 **Charge Question 8:** What are the views of the Panel regarding the adequacy of the assessment
40 of uncertainty and variability? To what extent have sources of uncertainty been identified and the
41 implications for risk characterization been characterized? To what extent has variability
42 adequately described and represented?
43

44 The staff adequately described uncertainty and variability. However, from table 7-1 it appears
45 that CHD has been considered to be the only sources of variability and no other disease

1 conditions were considered in the model. Why no other relevant diseases were considered? Was
2 socio-economic status in any way considered in estimating uncertainty?

3
4 Does APEX model has build in any internal consistency check between factors used in the
5 calculations (p. 7-2)? For example, randomly selected oxygen uptake which may be high maybe
6 assigned to an individual with CHD who is unable to achieve such uptake level.

7
8 Activity patterns of persons 30 years ago used as APEX input are very much different for current
9 activity patterns (p. 7-8). Can CHAD data be limited only to more recent activity patterns??

Dr. Francine Laden

1
2
3 *1. Does the Panel find the summary of CO exposure and discussion of ambient CO sources,*
4 *exposures, dose, health effects and risk characterization approach to be technically sound,*
5 *clearly communicated, and appropriately characterized?*
6

7 Chapter 2, background on assessing ambient CO exposure and risk, is well organized and
8 technically sound. EPA appropriately characterized what they did do, as well as what they did
9 not do. The discussion explaining the uncertainties associated with directly using studies of the
10 association of cardiovascular morbidity with measurements of ambient CO is important for
11 motivating the focus on COHb levels. It may not be immediately obvious to all readers why
12 ambient CO exposures are not the exposure of interest. One concern is that most of the
13 monitoring data and the laboratory data crucial to the assessment is quite old and could thus
14 effect the determination of risk. Is EPA confident that current situations can be extrapolated
15 appropriately from what was observed in the past? Perhaps some statement to this uncertainty
16 would be valuable, as well as acknowledgement that there are not any appropriate-more recent
17 studies available. For the most part the chapter is clearly communicated. However, the chapter
18 overall would benefit from some careful editing.
19

20 *5. Does the Panel find the derivation and presentation of the modeling approach as a whole*
21 *(chapters 4 and 5) to be technically sound, clearly communicated, and appropriately*
22 *characterized?*
23

24 The derivation and presentation of the modeling approach as a whole is very well presented. I
25 had one trivial question: Could the prevalence of undiagnosed CHD be greater for women than
26 for men? The model assumes that the ratios of undiagnosed cases to diagnosed cases are
27 identical for each gender and also that this ratio has not changed since 1990. The text should at
28 least acknowledge that this might not be so.
29

30 *6. Does the Panel find the derivation and presentation of the COHb estimates (chapters 5*
31 *and 6) to be technically sound, clearly communicated, and appropriately characterized?*
32

33 The derivation and presentation of the COHb estimates are technically sound, clearly
34 communicated and appropriately characterized.
35

36 *7. In the Panel's view, to what extent does the modified assessment approach employed in*
37 *this second draft assessment provide results that meaningfully inform EPA's consideration of*
38 *the public health implications of the current standards?*
39

40 The draft assessment provides results that meaningfully inform EPA's consideration of the
41 public health implications of the current standards. Given that CO levels have decreased
42 significantly over the years, that levels rarely approach the standards, and that elevated levels of
43 COHb estimated by the risk assessment are quite low, the usefulness of the current standards
44 may need to be reassessed.

Dr. Arthur Penn

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9

1. Does the Panel find the summary of CO exposure and discussion of ambient CO sources, exposures, dose, health effects and risk characterization approach to be technically sound, clearly communicated, and appropriately characterized?

No major issues with this chapter. The summaries are well-done and the health effects and risk characterization approach are presented clearly and seem technically sound.

Dr. Beate Ritz

3. *What are the Panel members' views on the following aspects in which the assessment has been expanded from the previous draft?*

A. *An important change of this assessment from the first draft is the expansion of each of the modeling domains to include a greater number of ambient monitors used as input to APEX. Additionally, this draft assessment employs an algorithm that adjusts for temporal and spatial heterogeneity in ambient concentrations across each study area.*

While the larger number of ambient air monitors may have improved exposure assessment, I am not convinced that this in fact gives more correct estimates of exposure near roadways - mainly in homes since only one singular distribution was used for all homes and this distribution may not adequately reflect near roadways exposures in homes i.e. I am not convinced that spatial heterogeneity driven by proximity to sources can be adequately captured by the ambient monitoring network. In fact, the exposure both in homes and in work places closer to roadways might be underestimated.

B. *The current draft assessment also includes an increase in the number of microenvironments modeled over that in the first draft (from two to eight) and improved the representation of variability in estimated microenvironmental concentrations, including in-vehicles.*

yes

C. *This draft assessment has implemented the mass-balance model for estimating concentrations in indoor microenvironments.*

yes

4. *Does the Panel view the results of the draft exposure analyses to be technically sound, clearly communicated, and appropriately characterized?*

Yes, except for the assumption about having captured spatial heterogeneity in homes and work places near busy roadways.

Dr. Paul T. Roberts

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4 *2. Does the Panel find the considerations of current ambient carbon monoxide monitoring*
5 *data, including specifically the data for the monitors included in this draft of the*
6 *assessment, and the discussion of the extent to which near roadway concentrations are*
7 *represented to be technically sound, clearly communicated, and appropriately*
8 *characterized?*
9

10 In general, the treatment of the CO monitoring data and the (admittedly poor) extent that these monitors
11 represent near-roadway concentrations, including the data used for this version of the assessment, are
12 improved over the 1st external draft REA, technically sound, clearly communicated, and appropriately
13 characterized. In addition, the use of data from more monitors as input to the exposure modeling is a
14 significant improvement.

15
16 Characterization of Exposure (Chapters 4 and 5)
17

18 The following changes from the 1st external draft REA are significant improvements and help the results
19 from this REA do a much better job of informing our review of the CO NAAQS.

- 20 • Expansion of the modeling domain to include more monitors in both Denver and LA.
21 • Adjusting for both spatial and temporal heterogeneity in ambient CO concentrations in each
22 study area.
23 • A significant increase in the modeled microenvironments.
24 • The use of a mass-balance model for estimating CO concentrations in indoor environments
25 (factors are reasonable estimates for the other microenvironments).
26

27 However, I am concerned about the use of the power of .621 in equations 4-11 and 4-22, which
28 reduces the CO concentration at an outdoor location, relative to the nearest central monitor. The
29 main justification for this is given on lines 33 to 35 of page 4-27 as a way to get the pNEM/CO
30 and APEX models to agree, but I do not understand the physical rationale for this. On page 5-
31 23, lines 8-10, it is suggested that the resulting “compression effect” is consistent with Wilson et
32 al (1995). However, even if we agree that this might be occurring near most residences, as in the
33 Wilson study, it does not occur at near-roadway or in-vehicle locations. In fact, the net result of
34 using this as part of the factor calculation for estimated CO concentrations is that near-roadway
35 and in-vehicle concentrations are a fair amount lower than was documented in the 1st REA,
36 section 5.4.2 (in-vehicle concentrations) and in the ISA for near-roadway. Since these two
37 microenvironments might be contributing a fair amount to total exposure, I think this is an
38 important issue to resolve. In addition, the use of this factor for near-road and in-vehicle
39 microenvironments has probably decreased the percent of people who experience the highest
40 concentration exposures, for example in Chapter 6.
41

42 Table 5-16 is a good summary of the various conditions in the 8 microenvironments, especially
43 with the distributions. I did noticed, however, in Appendix that a couple of locations codes are
44 probably mis-assigned, although these are probably small contributions: bicycle should be 5, as
45 shown in Table 5-16, and all the boat categories should be 8, since boats are uncontrolled for CO

1 and produce significantly high CO concentrations (they should probably be much higher than 8,
2 but again this is probably a small contributor).

3

4 *8. What are the views of the Panel regarding the adequacy of the assessment of uncertainty*
5 *and variability? To what extent have sources of uncertainty been identified and the*
6 *implications for the risk characterization been characterized? To what extent has*
7 *variability adequately described and represented?*

8

9 In general, the incorporation of more monitors in each area, more microenvironments, and
10 variability in various variables within APEX is an important method for addressing variability
11 and thus general uncertainty in exposure and dose.

12

13 Although I still think that the most significant uncertainties from this table could be better
14 quantified by using sensitivity runs of the model, I understand the time constraints on the current
15 NAAQS process. I believe that the significant improvements in representing near-roadway and
16 in-vehicle exposures has reduced the uncertainties associated with that end of the exposed
17 population, as represented in Table 7-2.

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Dr. Anne Sweeney

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1. Does the Panel find the summary of CO exposure and discussion of ambient CO sources, exposures, dose, health effects and risk characterization approach to be technically sound, clearly communicated, and appropriately characterized?

Overall, Chapter 2 is a very well-written comprehensive background that describes the issues and considerations that were confronted in the effort to assess ambient air CO exposure and human health risks. The contributions of the various sources of both ambient and indoor CO levels were clearly described and supported by numerous published studies. Exposure pathways and the importance of the microenvironment were also well-documented.

The justification for the utilization of persons with CHD as the unit of analysis in the quantitative assessment is appropriate, given the lack of data on COHb levels in other potentially high risk groups. However, characteristics of this simulated population that should be included in the modeling include the population prevalence of income level (a surrogate for several important covariates, e.g., residence near congested traffic areas) and smoking (also related to income level).

Dr. Stephen Thom

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4 *1. Does the Panel find the summary of CO exposure and discussion of ambient CO sources,*
5 *exposures, dose, health effects and risk characterization approach to be technically sound,*
6 *clearly communicated, and appropriately characterized?*
7

8 The summary is accurate and appropriate.
9

10 *2. Does the Panel find the considerations of current ambient carbon monoxide monitoring*
11 *data, including specifically the data for the monitors included in this draft of the assessment,*
12 *and the discussion of the extent to which near roadway concentrations are represented to be*
13 *technically sound, clearly communicated, and appropriately characterized?*
14

15 The discussion on current air quality monitoring is accurate and appropriate.
16

17 *3. In recognition of CASAC comments on first draft REA, this draft REA is expanded from*
18 *the previous assessment in a number of ways (summarized in section 1.3 of the draft*
19 *document). The assessment study areas are in the Denver and Los Angeles study areas.*
20 *We are interested in eliciting the views of the Panel on the usefulness of this approach in*
21 *informing our review the NAAQS for CO. What are the Panel members' views on the*
22 *following aspects in which the assessment has been expanded from the previous draft?*
23

24 *A. An important change of this assessment from the first draft is the expansion of each*
25 *of the modeling domains to include a greater number of ambient monitors used as*
26 *input to APEX. Additionally, this draft assessment employs an algorithm that adjusts*
27 *for temporal and spatial heterogeneity in ambient concentrations across each study*
28 *area.*
29

30 *B. The current draft assessment also includes an increase in the number of*
31 *microenvironments modeled over that in the first draft (from two to eight) and*
32 *improved the representation of variability in estimated microenvironmental*
33 *concentrations, including in-vehicles.*
34

35 *C. This draft assessment has implemented the mass-balance model for estimating*
36 *concentrations in indoor microenvironments.*
37

38 I found the document to be generally well written. My one question pertains to the APEX
39 modeling, as raised in my review of the Policy Assessment document. The discussion in the
40 REA document includes information that most fixed monitors have a 1 ppm CO lower detectable
41 limit so the modelers added 0.5 ppm CO to all measured values to remove zeros and negative
42 numbers thought to be related to monitor drift. It seems to me that this makes it exceedingly
43 difficult to accept estimates of the at-risk population and threshold COHb levels.
44

1 4. *Does the Panel view the results of the draft exposure analyses to be technically sound,*
2 *clearly communicated, and appropriately characterized?*

3

4 I am unsure if the draft exposure analysis is technically sound (see comment #3).

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