January 11, 2000

EPA-SAB-CASAC-LTR-00-002

Honorable Carol M. Browner
Administrator
U.S. Environmental Protection Agency
401 M Street SW
Washington, DC 20460

Subject: Closure by CASAC on the Document, *Air Quality Criteria for Carbon Monoxide* (EPA 600/P-99/001B)

Dear Ms. Browner:

The Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board, supplemented by expert consultants (together referred to as the "Panel"), met on November 18, 1999 to review the October 1999 draft document, *Air Quality Criteria for Carbon Monoxide* (EPA 600/P-99/001B), in a public meeting in Research Triangle Park, NC. This was the second draft of the new carbon monoxide (CO) Criteria Document, which is being prepared as part of the review of the national Ambient Air Quality Standard (NAAQS) for CO. The first draft of the document had been reviewed by the Panel on June 9, 1999.

1. CONCLUSION OF THE PANEL

The Panel reached closure on the document. At the end of the discussion, it was the unanimous view of the Panel that, after incorporation of various final changes discussed with EPA staff, the document will constitute an accurate representation of current scientific knowledge concerning the health effects of CO, and does not need to be reviewed by the Panel again. The scientific criteria contained in the final document will serve as an adequate foundation for completing the review of the appropriateness of the NAAQS for CO.

2. COMMENTS BY CHAPTER

Only the key points raised by the Panel are summarized below, to give an indication of the nature of the remaining concerns. Agreement with staff was reached during the meeting regarding the nature of the concerns and approaches to addressing them to the satisfaction of the Panel. The individual written comments of the Panel Members are attached as a part of this report (Appendix A). Staff is encouraged to take all of the attached comments into consideration and to review the transcript of the discussion at the meeting in order to fully understand the issues summarized below, and to take the complete advice of the Panel into consideration when making the final revisions to the document.

2.1 Chapter 1: Introduction

No major points were noted.

2.2 Chapter 2: Analytical Methods

The section on personal monitors needs strengthening. The distinction between personal monitors and remote monitors capable of sensing microenvironments should be clarified.

2.3 Chapter 3: Sources, Emissions, and Concentrations

The relative allocation of detail between the descriptions of indoor and outdoor sources is still questionable. It would seem appropriate to give more detail on contributions from motor vehicles and concentrations in outdoor microenvironments.

The description of the contribution of CO to production of ozone needs clarification.

Information on differences between the meteorology in different cities should be added to the sections describing results from the cities.

2.4 Chapter 4: Population Exposure

The relative importances of, and interactions between, general outdoor, outdoor microenvironmental, and indoor exposures were discussed as an evolving issue, but few specific recommendations were made. It was recommended that the discussion of the changing nature of CO exposures be strengthened if possible. This field was noted as a research need.

The potential range of compounds in addition to methylene chloride that might cause internal production of CO should be mentioned.

2.5 Chapter 5: Pharmacokinetics and Mechanisms

The lack of information on the rate of CO uptake by hemoglobin and equilibration at a given exposure level was noted. Staff is encouraged to determine if additional information exists, and if not, to note this as a research need. This information is especially important in judging the impact of exposures in microenvironments. A brief description of the current knowledge of comparative uptake rates in humans and animals should be added.

Mention of the phenomenon of compensatory vasodilation during CO exposure, and its implication in subjects with coronary artery disease, should be added to this chapter.

2.6 Chapter 6: Health Effects

A summary table of the epidemiology studies would help the reader more readily grasp the scope and nature of the current data.

Discussion of the potential contribution of the high spatial variability of CO to measurement error in the epidemiological studies should be strengthened.

The usefulness of "ED-10" (the point of 10% decrement) as a benchmark for a significant decrement in behavioral function is questionable. Decrements of less than 10% in normal subjects could have importance, and particularly for suggesting concern for subjects that are not young and well-rested. Behavioral effects could be noted as an area needing further research. The heavy horizontal line at 90% of baseline should be removed from figure 6-7. The ordinates of figures 6-6 and 6-7 are miss-labeled; the units are fractions, not percentages.

2.7 Chapter 7: Integrative Summary and Conclusions

The individual points should be removed from figure 7-1, because the lines were generated from models, not individual data points.

3. SUMMARY

When revised taking into account the issues raised above and the numerous more minor points contained in the attached individual comments, the document will provide a good foundation of scientific criteria for considering the appropriateness of the CO NAAQS.

The Panel complimented the NCEA staff for its responsiveness in addressing the issues raised by the Panel in its review of the first draft. Marked improvements were noted in all sections of the document. The Panel also complimented staff for focusing primarily on knowledge gained since the last review of the NAAQS for CO in order to develop a concise, high-quality Criteria Document. The Panel encourages staff to follow this model in the development of future Criteria Documents. We look forward to your response to the advice in this letter.

Sincerely,

Dr. Joe L. Mauderly, Chair
Clean Air Scientific Advisory Committee

U.S. Environmental Protection Agency
Science Advisory Board
Clean Air Scientific Advisory Committee (CASAC)
Carbon Monoxide Subcommittee

Chair

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APPENDIX A - Individual Panel Comments

Joe L. Mauderly

Chapter 2
2-3, 15: "Concentrations" is misspelled.

2-3, 20: "Has" should be "having".

2-20, 9: "Recent" should be inserted before "dose". Carboxyhemoglobin is only a measure of the recent dose. It is not, for example, a measure of the integrated or total dose over time, or dose received more than a few hours ago.

Chapter 3
3-23, 10: It is not clear whether this is 23% of total, or only anthropogenic emissions.

Chapter 5
5-2, 1-3: I do not agree that no reference should be given for the interspecies difference in the rate of CO uptake and COHb formation. The argument the Agency made during the oral discussion was not convincing. I have conveyed references to staff for consideration.

5-6, 4-7: It does no good to note effects at "high" concentrations without giving the concentrations. Without that information, the reader has no way to put the information in context.

5-8, 17: Define "Mb" the first time it is used. It is defined later, but do it here.

Chapter 6
6-49, Figure 6-5: Nothing in the figure legend indicates that these results are for goats and sheep. That is stated in the text, but it should also be stated in the legend.

Eva J. Pell

As per my assignment I have reviewed Chapters 1,2,3 and 7 of the Air Quality Criteria for Carbon Monoxide. I found the chapters readable and thoroughly documented. I have no additional comments regarding these chapters.

Arthur Upton

Comments on Chapter 7. Integrative Summary and Conclusions

General Comments

This chapter satisfactorily remedies the deficiencies that were noted in the previous draft and, in

my opinion, provides an adequate integration and summary of the material presented in the preceding chapters.

Although I have no substantive changes to recommend, the chapter would benefit from a number of editorial improvements, as suggested below.

Specific Comments

Page 7-1, line 29: limit should be changed to limits.
Page 7-2, line 20: CO should be inserted before combined.
Page 7-2, line 22: their should be changed to its.
Page 7-8, line 29: large should be changed to much; have should be inserted before tested; and work should be changed to research.
Page 7-9, line 9: higher than should be changed to above the; and the levels resulting from should be inserted after people.
Page 7-9, line 26: A smaller sensitive group should be deleted.
Page 7-9, line 27: also should be inserted before experience.
Page 7-10, line 31: the data should be inserted after but.
Page 7-11, line 18: smaller and more specific should be deleted.
Page 7-11, line 22: heart disease exacerbation should be changed to exacerbation of heart disease; and with should be inserted after than.
Page 7-11, line 27: more should be deleted.
Page 7-12, line 2: much greater should be changed to increased.
Page 7-12, line 3: at increasing ages should be changed to with increasing age.
Page 7-13, line 29: better should be deleted; and more precisely should be inserted after determine.
Page 7-15, lines 15-16: already may have should be changed to may have baseline.
Page 7-15, lines 16-17: have a progression should be changed to have CO cause a progression.
Page 7-15, lines 23-24: this sentence should be reworded, as follows: Epidemiological observations on the relation between short-term ambient CO levels and the frequency of respiratory disease cannot yet be interpreted with confidence.
Page 7-16, line 20: of should be changed to at.
Page 7-17, line 24: have should be inserted before raised.
Page 7-17, line 25: heart disease exacerbation should be changed to exacerbation of heart disease.
Page 7-17, line 27: CO should be inserted after and.
Page 7-17, line 28: mix should be changed to mixture.

Sverre Vedal

Cardiovascular
Epidemiological studies

This chapter is markedly improved, takes a more balanced approach to presenting and reviewing studies, and reflects an appropriate level of responsiveness to reviewer comments on the part of the authors. Note should be made that this section addresses outcomes other than just cardiovascular outcomes. The title may therefore need revision. The following comments are of a relatively minor nature.

Introduction

6-4 -why use statistical significance?

6-5 -"limited weight"? the issue here is likelihood of confounding, not qualitative difference in studies.

6-6 -do the chronic studies really provide a context for the acute studies?
-how about using the term "sensitivity" rather than "proportional differences"?
-I would emphasize effects of smoothing rather than autocorrelation and overdispersion. The latter two are relatively minor issues that affect the size of the standard errors and are almost non-issues anyway when appropriate smoothing and other adjustments are performed. The choice of smoothing "span" however can have substantial impacts on the estimated effects.
-Encouraging multipollutant analyses ignores collinearity as a big problem in interpreting the effect estimates. Some middle ground is appropriate, one that acknowledges resultant instability of estimates and the need to control for confounding.

6-7 -again, use of "proportional differences".
-item (3)-this is sensitivity issue again.
-item (4)-prompted by NMMAPS harvesting work. A longer time scale is problematic in interpretation and raises issue of longer time trend confounding. Also, this is not really a statistical issue and I would ignore it in this context.
-another unresolved statistical issue, of more acute import for CO than for other pollutants, is measurement error. Spatial variability is more significant for CO, although CO outdoors is essentially the same as CO indoors. What is needed is information on the correlation of CO measured at a fixed ambient site and personal CO over time, information that we now have for PM. Perhaps these data for CO are available. If so, they would be critical for the interpretation of the epidemiological findings.

6-9 -2nd para repetitious of p 6-8.

Heart disease exacerbation

General: Improved and more complete and better balanced presentation. Good use of tables. An overall summary table would still be useful.

6-10 -Does average lag last day of lag 0 mean essentially no averaging?

6-13 -I would use the full scale for y-axis fig. 6-1.
-There is too much detail presented on Schwartz and Morris relative to other studies.

6-17 -I would drop the "PIA" abbreviation here.

6-18 -Were no confidence intervals included for fig. 6-2?

6-19 -Add "effect".
-Note that the Poloniecki study had low CO concentrations.

6-20 -I would not speculate in the Poloniecki study about the effect of using 1-day lag, instead noting that it may not be comparable to other studies.

6-21 -Devoting a large and complex table such as this for Poloniecki study (which arguably is a "negative" study and with low CO levels) does not seen warranted.

6-25 -Poloniecki is also a "negative" study (confounded by SO2 and BS), not just Burnett, and in winter. Pantaz. study did not assess 2-pollutant models. Why is this para (the 1st) here, as it seems to be discussion?
-re: Yang et al. - how does ARIMA handle 2 time series?
S no independent effects of CO were tested.

6-26 -No seasonal season stratification was done in Schwartz 1999.

6-27 -Better expressed as no CO effect in St. Paul, yet large effect in Minneapolis.

6-30 -In Burnett 1999, what does "not measured directly" mean?

Daily mortality

General: Improved and more complete

6-33 -Note CO concentrations in Athens study were very high - is this the reason this is a positive study?

6-35 -Note Burnett mortality CO shows effects on all types of mortality.
-Saldiva study should also be included under general mortality given assessment in elderly.

Low birth weight

Note these are not time series studies, so that spatial confounding is an issue (see p.38).

Respiratory illness

General: this is a good addition, even though plausibility is questionable. The findings should give us pause.

Warren H. White

Chapter 3

I appreciate the authors' generous efforts to address my comments on the first draft.

Overall balance

The section on indoor sources of CO has been significantly shortened, but still dwarfs the cursory discussion of motor vehicles. As the summary notes (page 3-75/line 18), "Emissions from transportation dominate other sources of CO within the United States." And yet this is the only thing the summary deems worth noting about motor vehicle emissions. Meanwhile it goes on for two pages on indoor appliances, differentiating between gas and kerosene, blue-flame and yellow-tipping, convective and radiant, ranges and ovens, and so on and so on. I suggest adding two figures from

Lawson (1993) to convey some of the same sort of detail for motor vehicles.

My comments below on pages 3-21,22 identify a number of 1990's findings that illuminate the distribution of CO emissions among the motor vehicle population. These obviously bear on implementation strategies, which I recognize are outside the scope of the CD. But they also bear on concerns relevant to risk assessment: How reliable are our emissions inventories? How have actual emissions (as opposed to inventories) changed in recent years, and how much improvement is likely from additional measures such as reformulated gas and I/M?

The indoor sources section is an undigested mass of unrelated results, many of them predating 1991 and presumably carried over from the previous CD. What are the key points that OAR/OAQPS should take away from their reading? Is it just that CO concentrations vary greatly from microenvironment to microenvironment? If so, then why does it take so much longer to say this for stoves than for cars? Is it some general ranking, like (page 3-59/lines 18-19) "Peak CO concentrations from the use of unvented gas heaters were also generally higher than unvented kerosene heaters and gas cooking stoves"? That's a tune I can hum, but it doesn't seem supported by the subsequent Figures 3-31 and 3-32. If you must give us a basket of numbers in a variety of units, then please don't leave before giving us clues on how to arrange them so as to make sense.

Line by line

(page/line)

3-5/1-4	This is a run-on sentence. Drop the run-on, "this increase presumably resulted from...", as lines 9-14 give a more substantive discussion of the same point.
3-5/23-26	Move the citation "Mahieu et al., 1997" from line 26 to sentence break on line 25, to clarify where "measurements obtained with a similar technique over the Alps" came from.
3-9/7-8	It may be true that most wildfires today arise from human activities, but the reader needs to be cautioned against naively inferring that they are thereby unnatural. The article by Fox et al. in the current (November 1999) EM discusses this point, and probably should be cited here. The issue of attributing fire also bears on statements at 3-10/9-12 and 3-74/25.
3-13/23-25	The meaning of "the lifetime of CO is much longer than typical residence times of CO in urban areas (assuming a diurnally averaged CO level of $3x10^6$ in urban areas)..." is unclear. Do you mean to assume the level of OH rather than CO? If CO, then what are the units of $3x10^6$?
3-16/28-29	The terms IM240 and FTP need introduction.
3-16/29-30	The intended sense of "increase" in this sentence is unclear. I think you mean "This change yielded significantly higher exhaust emission rates, ..."
3-21/13	I suggest "sampling in tunnels" as a plain-language substitute for "roadside tunnel sampling."
3-21/21-22	OVER 50% of CO emissions are LESS THAN 10% of the vehicles, according to Bishop and Stedman (1990) and Lawson (1993).

3-21/23-29	[suggested text] These “high emitters” are typically older, poorly maintained vehicles [insert Figure 3 from Lawson (1993), Quintile plot for CO emissions]. High emitters appear among all model years, however, and the more numerous representatives from recent model years contribute much of the fleet total [insert Figure 5 from Lawson (1993), Quintile plot for percent of fleet total]. Observed causes of high emissions include tampering with emissions control systems to improve milage or performance, defects in untampered closed-loop emissions control systems, the use of contaminated fuels that interfere with the proper operation of emissions control systems, and the removal or lack of maintenance of emissions control equipment (Lawson, 1993; Bishop et al., 1996). In addition to the above activities, so-called off-cycle ...
3-22/1-3	[start new paragraph] Roadside remote sensing data have been used to evaluate the effectiveness of inspection and maintenance programs in a number of locations (Zhang et al., 1996; Stedman et al., 1997; Stedman et al., 1998; Lawson, 1993; Bishop et al., 1996). These studies have generally yielded disappointing results, indicating undetectable or smaller than expected effects of inspection on vehicle emissions. Detailed analyses implicate behavioral responses, such as shopping for a passing test (Bishop et al., 1996) and re-registrating non-conforming vehicles in neighboring counties (Stedman et al., 1997; Stedman et al., 1998). Roadside emissions data have also been used to evaluate the effects of reformulated fuels on emissions. Remote sensing (Bishop and Stedman, 1990) and tunnel measurements (Gertler et al., 1999) both indicate fleet CO reductions in the 15-20% range.
3-24/22-24	Move “In 1996" from the end to the beginning of this sentence to help readers recognize the distinction being drawn with the preceding sentence.
3-29/Fig.5	This figure covers “all sites in the United States REPORTING AT LEAST 8 YEARS OF DATA, 1988 to 1997.”
3-32/16	Delete either “Only” or “however”.
3-34/12	“the four cities ... HAVE been”.
3-51/3	This is a bogus statistic, as noted at the CASAC meeting. Moreover, it is unnecessary – all you really need to motivate section 3.5 is the observation that “The general United States population spends the majority of its time indoors.”
3-52/25-26	I am skeptical that “Emissions of CO from gas top ranges will depend on ... air infiltration into the microenvironment.” I think you have concentrations in mind.
3-56/1-10	BTU should be converted to kJ (or vice versa).
3-56/24-25	This sentence on prototypes should start the next paragraph.
3-68/Table	Change “FOR ALL HOMES” to “FOR CALIFORNIA HOMES” in title.
3-75/13	CO can participate in the formation of 20 to 40% of background ozone without being “responsible” for it.
3-75/15	The earlier text mentions only 6 June 1988 in Atlanta, not “the few urban areas that have been examined” claimed here, or the “several urban air sheds” cited on page E-3.
3-75/19-21	Delete the unsupported claim that “a sizable fraction of the CO observed in rural air may be produced by the photochemical oxidation of isoprene ...”

3-75/25+ This paragraph is a good model for the summary section, digesting the facts given earlier in the chapter and laying out their implications for air quality management. I.e., good job!

3-76/24-31 This list of numbers, most of them pre-1991, some of them with no source in the previous text (e.g. 54 to 344 ug/kJ), and given in a variety of units, should be deleted. The real point of this paragraph is the qualitative rationale for the forecast of a continued decline in emissions.

3-77/26-30 Delete "The CO concentration from the use of a radiant-tile unit was 13.4 ppm, ... used to supplement another heat source (<9.0 ppm)." This is more number junk that just obscures the qualitative message: "Catalytic gas and convective kerosene space heaters emit the smallest amount of CO. Radiant and infrared unvented space heaters emit higher amounts of CO. The decreasing usage of unvented space heaters is likely to result in decreased CO emissions from this source."

3-78/3-6 "The average CO source strength for airtight stoves ranged from 0.08 to 0.27 g/h (10 to 140 cm^3/h) versus 0.32 to 2.18 g/h (220 to 1,800 cm^3/h) for nonairtight stoves. ..." I can't discern any relationship here between g/h and cm^3/h: if 0.08 g/h = 10 cm^3/h, for example, then how is 0.32 g/h = 220 cm^3/h? And what are "wood heaters", as distinct from wood stoves and fireplaces? And why no mention of the fireplace emission rates as high as 70 g/h mentioned on page 3-57? More number junk, this time lacking even a qualitative message.

3-78/9-10 It's hard to see the value of knowing that "An estimated 487 billion cigarettes were sold during that year."

While listing the quantitative factoids noted above, the indoor summary simultaneously disavows them by emphasizing the dependence of emissions and concentrations on particular circumstances. This latter point is in fact beaten to death, in repetitious laundry lists of self-evident and redundant factors:
"Carbon monoxide concentrations in the indoor compartment is influenced by the CO emission rate of the unvented combustion source, the ambient CO concentration, infiltration through the building envelope, building volume, AER, and air mixing within the indoor compartments." [3-76/15-18]
"Carbon monoxide emissions from gas ranges vary from range to range for both the top burners and the oven burners and are dependent on the type of pilot light, the fuel consumption rate, the frequency of use, and the operating condition." [3-76/20-23]
"Emissions from unvented space heaters are a function of the appliance design, combustion efficiency, length and frequency of use, and the fuel type and consumption rate." [3-77/16-17]
"Emissions will vary based on the type and brand of tobacco product. Concentrations ... will be dependent on the CO emission rate of the tobacco product, number of cigarettes smoked, smoking rate, size of the indoor compartment, ventilation rate, and ambient CO concentrations." [3-78/11-15]

References

G.A. Bishop and D.H. Stedman (1990) On-road carbon monoxide emission measurement comparisons for the 1988-1989 Colorado oxy-fuels program. ES&T 24, 843-847.

G.A. Bishop, D.H. Stedman, and L. Ashbaugh (1996) Motor vehicle emissions variability. JAWMA 46, 667-675.

D.G. Fox, W.C. Malm, B. Mitchell, and R.W. Fisher (1999) Where There's Fire, There's Smoke: Fine Particulate and Regional Haze. EM, November 1999.

A.W. Gertler, J.C. Sagebiel, W.A. Dippel, and C.M. O'Connor (1999) The impact of California phase 2 reformulated gasoline on real-world vehicle emissions. JAWMA 49, 1339-1346.

D.R. Lawson (1993) "Passing the test" – human behavior and California's smog check program. Air & Waste 43, 1567-1575.

Philip Hopke

1) Page 2-18, line 19 refers to a section 2.2.4 which does not exist in this version. There needs to be some rewriting in this subsection to reflect changes between versions.

2) Although others suggested the need for more detail on electrochemical methods on page 2-19, I believe the references to the technique given are adequate and further description is not really needed. I also do not think that remote sensing is personal monitoring so it may be useful to change the title of this subsection.

3) Page 3-3, line 14 The definition should be the "concentration resulting from anthropogenic and natural emissions outside North America, and natural sources within North America." The second definition is the concentration that results from only natural sources within and outside of North America. The term "levels" is used and should be replaced by "concentrations." On line 28, "mixing ratio" is used and again on line 30 and again on page 3-4, line 3. On page 3-5, line 5 "levels" is used. Again on line 18, etc so a good global search is needed to at least replace level with concentration. I am less concerned with the use of "mixing ratio" since that really is the appropriate term. "Level" should not be used at all.

4) Page 4-8, lines 3-4, Why is there specifics of "after corrections were made for instrumental measurement drift"? Was there a second analysis before drift was discovered? Should there be a reference to these multiple analyses? Generally one expects data to be correted for any known systematic biases so why is this called out explicitly?

5) Although most of the data available is for methylene chloride as an *in vitro* producer of CO, it seems likely that other compounds could also produce the same results. There should be some indication of the possibility that other compounds could behave in an analogous manner.

6) Please take the points out of figure 7.1 and just use 4 distinct lines. The points give the impression that these are measurements and not model results.

Thomas E. Dahms

The document in general contains the information necessary to bring the user up to date in the field as well as providing a review of the relevant information that forms the background data base for regulating CO in the environment. The following comments are offered in an attempt to make the document clearer to the eventual reader. I my mind there are two major problems that run throughout the document that need to be remedied because when these issues are presented they are not stated fully in the correct sequence so that the document is understandable from front to back. Without the inclusion of these concepts (especially concern #1) in the correct sequence the document is potentially misleading to the reader.

Major Concerns:

1. The first item deals with the underlying assumptions regarding how CO exerts its physiological effects.

The current underlying physiologic principle that forms the conceptual basis for health effects studies to date is that exposure to CO results in a reduction in the oxygen carried by each milliliter of blood supplied to the tissues in the body. Since the oxygen delivered to a tissue (oxygen content X the blood flow) is regulated at a constant value relative to the oxygen demand of the tissue, the body compensates for this reduced oxygen content by increasing the blood flow. It is only when this increased blood flow cannot compensate for the reduced oxygen content, that decrements in performance have been observed. Reductions in performance have been reported in normal subjects at maximal exercise (when blood flow to the muscle reaches its limit and therefore no compensation is possible) and in individuals with coronary artery disease (where increases in blood flow are not possible) at what would be expected submaximal levels of effort because the underlying diseased vessels can not dilate to increase blood flow to compensate. When compensatory changes can occur as following CO exposure with submaximal exercise in healthy subjects, there is no decrement in performance. The physiologic effects of CO can be observed only when a sufficient decrease in blood oxygen content occurs and the compensatory increase in blood flow is inadequate to meet the tissue need for oxygen.

If the effects of CO were only brought about be a reduction in oxygen transported in the blood as currently described in the text, then effects of CO would be observable at low levels of exercise stress in healthy subjects. This may be the case if the findings of Thom et al can be demonstrated at low levels of COHb. At this point we don't know what pathophysiologic endpoints to measure pending further data from this area of research. At this point in time there is insufficient information regarding specific effects of CO (unrelated to oxygen delivery problems caused by the formation of carboxyhemoglobin) to provide substance for regulatory decisions.

2. The second concern relates to the descriptions in the document regarding relative rates of uptake and elimination of CO. The description again is not precise enough to make it clear in the reader's mind at to why the uptake of a given mass of CO is much faster than the elimination of the same mass of CO.

In fact the physical and physiological mechanisms governing CO uptake and elimination are the same. To explain the concept of changing effective doses the discussion is best put in terms of mass transfer of CO under the two conditions. When a subject enters an environment containing elevated CO, an initial gradient exists between the CO tension in the air in the lung and CO tension in the blood in the lung. This gradient remains relatively high during any exposure to CO because as the CO enters the blood it is tightly, but reversibly, bound to the hemoglobin resulting in very little back pressure. Under conditions of elimination which occurs when a person with elevated CO tension in the blood enters an environment with lower CO tension in the inhaled air. This results in a gradient from higher CO in the blood into the alveolar air and a loss of CO from the body store of CO. However due to the avidity of the hemoglobin for the CO, this gradient is much less than the gradient for the uptake. Given

the same physiological status of the exposed person, this blood-alveolar air gradient for CO will be the rate determining step in the mass transfer of CO under both conditions. The rate of uptake vs the rate of elimination for exchanging the same body burden of CO can be described by the ratio of the gradients under these conditions. The uptake of CO can be shown to be several fold faster than the elimination in the regulated range and much higher with higher levels of exposure. The faster relative mass transfer during uptake with higher exposures is intuitive because the alveolar air to blood CO gradient will be greater. Since the time required to eliminate a given body burden of CO is constant, the uptake to elimination transfer ratios will increase with higher exposures (of shorter duration) that result in the same body burden of CO. It is the alveolar air to blood gradient thatis the primary determinate of CO transfer.

Specific comments:

Chapter 1.
Section 1.3.1
Page 1-6. Lines 7-9. I can not find a basis for this statement in the text of the document. What does this mean?
Lines 27-29. Is this supposed to be confusing?
Page 1-7. Lines 2-4. This sounds like a stab in the dark with poor underpinnings. Is this what is meant to be communicated ?

Section 1.4.8.
Page 1-11. Lines 26-27. There is no documentation for this statement in the literature. In fact low levels were studied by Wittenberg and Wittenberg and could not find any supportive evidence for this speculation. It would make sense but it apparently does not happen see section 5.6.2. I would suggest including some form of the above major concern #1 at this point in the document.

Section 1.4.9.
Developmental Toxicity P.1-13, line 7. These exposures were probably chronic and need to be stated as such.
Line 20. Define high altitude as being greater than x ft.

Section 1.5
P.1-15 lines 2-3. I believe that the epidemiology data has far more implications at this time relative to regulation of ambient levels of CO than do the cellular mechanism studies. This distinction is not clear to the reader.

Chapter 5
Section 5.2.1.2.
Lines 28-29 ...contribute little to Va/Q inequality. This confusing given the information preceding it. Does it mean that shunts are low or that VA/Q is anything other than shunt or dead space ?

Section 5.2.1.3.
Page 5-4, lines 7-8. The word pass should be replaced by diffuse and enter should be diffuse into.

Page 5-5, line 1. ..by immediate and tight binding of CO to Hb. May not contribute anything to the rest of this sentence.
Lines 5-6. The air-blood pressure gradient for CO is usually much higher than the blood-air gradient; this is too cryptic. Blood pressure has a confusing implication in this usage. See the general statement #2 above.
Lines 7-8. The rate of CO release also will be affected by metabolic and endogenous production of CO. This is not clear to the reader that there is a distinction between metabolic and endogenous sources of CO. I believe that the author is referring to back pressure from this source of CO.
Lines 13 and 18. Diffusion should be replaced with diffusion capacity.

Section 5.2.2.1
Page 5-5. Lines 29-30. This sentence seems to be confusing mass transfer into a tissue with diffusion across the tissue.
Page 5-6. Lines 4-8. The issues are relative surface area and diffusion distance limiting uptake of CO in the areas discussed. Stating this concept would make this section more understandable.
Section 5.2.2.2
Page 5-8. Lines 14-20. This material has been inserted into the text but not integrated into the document.
Line 16. The 77% figure does not agree with the statement on page 7-5, line 3.

Section 5.2.2.3.
Page 5-9. Lines 1-18. If CO affects myoglobin oxygen transfer, either skeletal or heart muscle function should show some evidence at moderate if not low levels. Since this is not evident what is the basis for the statement on lines 15-16: consequent reduction in .... ?

Section 5.2.2.4.
Page 5-9. Lines 21-22. I don't understand the term concentration as used in this context. Is the difference due to the amount of blood present per volume of neural tissue?

Section 5.2.3
Page 5-10. Lines 4-7. This sentence needs to be retranslated.
Lines 19-31. It is difficult to understand this material in light of the CFK when it has yet to be presented. Consider using the above concern #2 which does not invoke CFK.

Section 5.3.
Page 5-12. Lines 19-23. Consider starting this section with this paragraph.
Page 5-12. Lines 30-31. How does increasing enzyme concentration without increasing substrate concentration increase CO production? What evidence is there that excess substrate is present for HO ?

Page 5-13. Lines 29-31. This material needs to be referenced.
Page 5-14. Lines 1-8. This material also needs to be appropriately referenced.

Section 5.4.1. The concepts provided in concern #2 above should be included in a rewrite of this section.

Section 5.4.4.
Page 5-19, Lines 17-22. This material encompasses my above concern #1 but it is buried in this section. It should appear in section 1.4.8. The material in section 1.4.8 is too speculative regarding the effects on myoglobin which have never been shown to exist at less than 40% COHb (see Section 5.6.2). Inserting the failure of vasodilation to compensate under mechanism of action would be much more appropriate. This would also spur future research into looking into the mechanism of CO induced vasodilatation at more reasonable levels of COHb.

Section 5.5.1.1.
Page 5-20. Lines 18-21. The back tension of dissolved CO that must occur at these high levels of exposure, makes this material not relevant to the discussion of exposure to expected/allowed ambient levels. Eliminate this material.

Section 5.5.1.3.
Page 5-24.Lines 25-31. This material needs to be demonstrated to be relevant to ambient exposures or eliminated.
Page 5-25. Lines 19-27. Provide references or eliminate this speculative discussion.

Section 5.6.
The previous sections of this Chapter contain information regarding the dose of CO or concentration of CO that produces an effect, but this section does not do this rigorously.

Section 5.6.1.
Page 5-27. Lines 20-21. This statement is not correct please see concern #1 above.
Page 5-28. Lines 2-3. The study by Kimmell does not agree with many animal experiments in a wide variety of species too numerous to identify. So it seems hard to swallow that one investigator's findings are presented as fact while ignoring all of the previous animal exposure data.

Section 5.7.1
Page 5-33. Lines 1-14. This material does not seem to be relevant to understanding health effects of CO at more reasonable exposures.

Section 5.7.3.
Page 5-34. Lines 16-18. I don't know what this is trying to say. Lines 29-30. I don't think that this material has been substantiated, in fact I believe that it was refuted in material cited in the previous criteria document.

Page 5-35. Lines 10-13. Did the indicator actually 'leak' or was it mere bound at a greater extent to the tissue ? The indicator left the system but where did it go?

Section 5.9
Page 5-37. Lines 2-4. Please see major concern #1 above. What is written is misleading.

Chapter 6.
Table 6-7. I did not comment on this publicly because the issue involves a paper that I authored. However any review of this material regarding arrhythmogenic properties of CO would not reach the conclusion implied by the material in this table. The data presented shows positive findings only when less than straight forward statistical analyses were employed. In addition there is evidence in the literature refuting these findings. At best this is not a balanced representation of the field.

Chapter 7.
This chapter needs some editing by a cardiovascular physiologist to make sense of some the statements scattered throughout the chapter. For example in Section 7.1 line 17-18 the formation of COHb during exercise is dependent upon the alveolar ventilation but what is stated is the "increases both the amount of air inhaled and exhaled..." Another example is Section 7.5 lines 2-10. This mechanism does not include the concepts included in the above concern #1 and is therefore misleading. In section 7.7.1 page 7-11 lines11-14 . Where is this information supposed to lead the reader?

Section 7.7.4.
This section is disproportionately represented in the summary relative to the data presented in the various chapters. It should be reduced by 2/3.

Victor G. Laties

General comments: This revised document is much improved. Here are some further comments. The main points concern (1) the sharp contrast between how the cardiovascular and behavioral studies are treated; and(2) the ambiguous conclusions concerning the COHb levels associated with reliable behavioral changes.

6.2.2 Controlled Laboratory Studies Page 6-46, Table 6-6.
* This table deals primarily with the cardiovascular effects of CO and the data supplied are discussed in lines 3 to 13 on this page, immediately above the table. But why does the table also present data on schedule-controlled behavior, developmental effects, and lung morphology and function, all topics taken up later in the chapter? Besides, the results for these three endpoints appear to be largely redundant, already being given in Figure 6-6 on page 6-52 (for the behavioral data), in text at lines4 to 6 on page 6-56 (developmental data), and at lines 25ff. on page 6-57 (lung pathology data).

* If this table is not modified because summarizing data on the LOEL for four CO endpoints in one

place is thought to be important, shouldn't it be expanded to include data from the studies now named in the text but otherwise ignored. For example, only one of the three developmental studies cited on page 6-56 is included in the table? Only one of the three lung studies cited on page 6-57 included in the table.

* Finally, if such an inclusive table is presented, shouldn't it be placed nearer the end of the chapter so that it would serve as a summary?

6.3.1 Brain Oxygen Metabolism Page 6-49, Figure 6-5.
* Do you really trust the curve-fitting program that you have used to deal with those very few---and highly variable!---data points below 20% COHb? Shouldn't the fit be made to reflect your belief that the experimental evidence indicates that there are different physiological phenomena at work on two sections of the curve?

6.3.2 Behavioral Effects of Carbon Monoxide Page 6-50, line 28.
* Putz et al., 1976 is an unpublished NIOSH report. Why not cite instead the 1979 Human Factors paper by Putz alone, which contains only the dual task performance results but has the virtue of having appeared in a peer-reviewed journal? (In it, Putz refers on p. 18 to the NIOSH report.) Its Fig. 2 contains the tracking error data used in the Benignus (1994) analysis and in the current report.

Page 6-51, lines 11-12.
* I suggest cutting out the dependent clause("Because single-blind...significant),"), simply stating that the meta-analysis was confined to double-blind studies. Isn't a Type I error a chance error, not one due to the biases that may influence a result when the experimenter or subject is not blind as to the conditions in force?

Page 6-51, lines 22ff.
* Choosing a 10% decrement as the criterion of change does not match what is done with every other variable presented in this document. Why should such a figure be used solely for the behavioral experiments? The statement that "...human behavioral impairments of 10% (ED-10)should not be expected until COHb exceeds 20%."is an hypothesis, not a conclusion based upon empirical behavioral data. (See below for more on this point.)

Pages 6-51, 6-53, 6-54, 6-55 and Figure 6-7. The description of this figure and the conclusions drawn therefrom start on page 6-51, line 28 and runs to the end of the section on page 6-55. I disagree with much of it:

1) If the low-level CO exposures were completely ineffective, would not one expect the points to cluster nearer to the baseline level, which is at 1.0 on this graph? In fact, almost all the curves turn down as COHb levels increase. Only one data point reaches as much as 4% above the baseline whereas about ten are more than 4% below.

2) I don't believe that this summary reflects the totality of the evidence in the figure regarding CO and behavior. For example, consider just the "good"compensatory tracking studies presented in Figure 6-7, which are the two by Putz ($ and *), plus the two by Benignus (X and +). Both Putz studies and one Benignus study showed statistically significant decrements at between 5 and 8% COHb. The other Benignus study showed changes in the same direction. A meta-analysis of these four experiments taken together could only lead to a conclusion that the effect is believable. The same argument applies to all the studies taken together, the dominant direction of the points being down, with much scatter (See #13below). I have doubts about the propriety of throwing so many different types of behavior together but won't go down that road now.

3) On Page 6-54, line 6: "...only a few levels of COHb...."But the four dashed curves on this figure now each show only a single CO level. However, Putz et al (1976)actually used two exposure levels, 35 and 70 ppm.

4) The next sentence, on Page 6-54, lines 6-8, says "Studies in which more and higher COHb levels..." didn't find significant effects. However, if the first sentence covers up to and including two levels, there remains only a single study that used three levels: Benignus (1987) (I don't believe that Stewart et al., 1973, which studied subjects in a group setting, should be here in the first place.) The sentence should be recast or omitted. Actually, a single multi dose instance (or even two) is not sufficient to support the conclusion, although there is merit to the prejudice in favor of multiple levels; e.g., having many exposure levels helps keep both experimenter and subjects truly blind.

5) The horizontal line on Figure 6-7. The decision made on page 6-51, lines 22ff., to report behavioral measures always in comparison to an arbitrary decrease in performance, rather than with reference to rejection of a null hypothesis, makes comparison with other endpoints difficult and confusing. With regard to Figure 6-7, adding a horizontal line at 0.9,which serves to discount the importance of any behavioral response decrement less than 10%, strikes me as unwarranted. It depends upon the reader accepting the authors' decision to demand behavioral impairments of 10%, which stems from conclusions reached in the Benignus (1994) article regarding the lessened possibility of any changes occurring if compensatory mechanisms play a role.(Cf., page 6-54, lines 16-18.)

Why not report the observed behavioral changes first be without comment about these interesting physiological results, then introduce them as a possible path to a deeper understanding of what seems to be happening? The validity of any theories concerning cerebral oxygen supply and metabolism can be only be tested through comparisons with behavioral results. The behavior itself is the primary variable; no amount of argument concerning the underlying mechanisms can overturn trustworthy behavioral findings. Questions can be raised about how good the studies are but ultimate physiological and biochemical explanations must themselves be verified with solid behavioral data. Theory-derived argument must yield to empirically-derived data, not the reverse.

Let me make the argument against use of an ED10in another way by using the data on the

cardiovascular effects of CO, summarized a few pages earlier in Figure 6-4.On Page 6-45, the discussion mentions "a wide distribution of professional judgments on the clinical significance of small performance decrements," as well as the fact that the time-to-angina changes are"within the range of reproducibility of the test."Suppose that the authors had decided, on the basis of that discussion, to require a decrease of at least10% in time-to-angina before shouting an alarm. Adding a horizontal line at 10%, with a statement about how an increase of less than that wouldn't matter in real life situations, would affect our interpretation of all but the Anderson et al. articles, and thereby thus would force us to base the current standard on Instead, all the relevant studies have been presented before their importance is interpreted in subsequent paragraphs. Why not follow the same procedure with the behavioral data?

If you remove the horizontal line on the figure, I suggest that you also remove the discussion of the merits of various EDs on page 6-54, lines 18 through 24.

6) The behavioral studies were of "healthy young adult humans" who also were usually well rested and likely to be highly motivated to perform well. Generalizations to other populations must done with care. Note that the cardiovascular data used in this chapter were collected from individuals who were both old and afflicted with coronary artery disease. For instance, the mean age of the Allredet al. subjects was 62, with a SD of 8. Too bad some behavioral data couldn't have been collected from them.

7) Has there been any work on cerebral oxygen consumption in aged humans? Would the argument about compensatory mechanisms hold for them as well?

8) Discounting the validity of statistically significant decrements because other studies didn't report significant changes is a dicey business, especially if technical flaws can't be cited while rejecting the positive studies. Negative studies offer little when not accompanied by internal evidence that the measurements would have detected a true change if it had been present. No study in this collection yielded a dose-effect curve encompassing exposure levels high enough to produce both a significant effect plus sufficient intermediate levels to reliably determine the entire functional relationship. Almost all studies that provide negative data at the lower COHb levels do not also provide positive data at higher levels or, failing that, positive data on some other treatment that would assure us that the measures used were adequately sensitive. Since human subjects committees would probably frown on collecting data on COHb levels much above 20%, other substances or procedures should be included as positive controls.

9) Note that this report contain no modern, double-blind behavioral work that demonstrates significant changes at 20 to 30% COHb levels! One consequence is that we can't afford to limit our assessment of the evidence to studies done during the past few decades. Even Haldane, sniffing CO a hundred years ago, can tell us something.

10) Incidentally, I know of no evidence that investigators are publishing selectively in this area, failing to publish their negative studies. (Are there any such in EPA files? What about OSHA?) Perhaps this is because almost all work on CO and behavior is done within governmental agencies that are highly likely to mandate publication. In fact, the only unpublished studies whose data are used in this section report positive results: e.g., Weir et al.,1973; Putz, 1976.

11) Page 6-54, lines 25 to 30. I suggest recasting this argument slightly, moving the thought in the first sentence to later in the paragraph so that it reads as follows(I am starting at line 28, rewriting slightly):

"Behavioral work should be encouraged, in an effort to determine whether reliable decrements in behavior are truly associated with low levels of COHb. However, any new experiments should involve several CO exposure levels, including one high enough to produce changes. In addition, inclusion of some other procedure or a reference dose of some other active substance would serve to verify the sensitivity of the behavior under study, thereby facilitating interpretation of any negative data collected at the chosen COHb levels. Studies that do not satisfy these specifications would most likely be unfruitful and only further confuse the literature. In addition, other experiments should be designed to contribute to our understanding of how CMRO2 relates to COHb elevation and behavioral changes."

12) Other comments on Figure 6-7. There are several errors in the legend and on the figure itself:

* There are typos in the vertical labels on both this figure and on Figure 6-6: They should read "Behavioral"rather than "Behavoral."
* There is only one curve labeled "P" in the figure whereas both Roche and Weir articles are labeled "P"in the legend; is one of these "&" ? The ampersand appears on the figure but not in the legend.
* The words "and=Ramsey (1973)" should be removed from the last line of the legend. Ramseyis already listed earlier.
* Also, is Groll-Knapp et al. supposed to be "KC"as in the legend or "K" as in the Figure? This study (which I have not seen) is of word recall, according to Benignus (1994). Should it be included on this graph? A meta-analysis should encompass results from a homogeneous group of experiments.
* Putz (1979) included data on exposure to methylene chloride, which produced a COHb level and a behavioral effect similar to produced by CO exposure. I am unaware of an attempt to replicate this finding; has there been one? On the other hand, does the finding increase confidence in Putz's CO data?

13) The first complete paragraph on page 6-55is confusing, initially talking of behaviors that have been"implicated by research findings [as adversely affected by CO] and then questioning whether "these behaviors should be cited as effects" because of their "unreliability." However, we are left with the task of interpreting what we have. This always includes a certain amount of speculation about how the experiments were actually carried out and the believability of the results. Shouldn't the final sentence read: "Until better evidence of reliable behavioral effects are published, preferably in studies that demonstrate dose-related changes, we are left with the current record and must form conclusions that emerge from that set of experimental data."

The 1991 CO criteria document concluded:"Effects on behavior of COHb elevation above 20% have been unambiguously demonstrated in both human and animal studies. Below this level, results are less consistent. It seems unwise, however, to ignore frequent evidence in favor of effects on human performance at COHb levels as low as 5%. " [p. 10-143, CO Criteria Document final report, 1991]

Because Figure 6-7 presents data from studies that considered to have been done with some care(at least, they were double-blind), the conclusion for the current document must reflect what is shown there. Placing the data points from all these studies effectively weights them equally and permits only a simple fitting by eye to the points. I can't see how the current re-examination of the same database---no new studies at all!---can lead to a change in the 1991conclusions. Compensatory mechanisms were thoroughly considered in that document and even the physiological database has been enriched only slightly by new experimental work since then. Now argumentation is being made to carry the burden that rightly belongs to empirical studies; interpretation can't substitute for data. However, interpretation can suggest that a linear relationship may not be most likely, given the probable presence of compensatory mechanisms.

14) The final paragraph in the section, which concern show COHb-induced elevated brain blood flow could affect brain toxicants, stresses the importance of "physiological simulation using whole-body physiological models that are currently under development." Again, I would stress the equal need for hard data, without putting down the importance of theory and modeling.

6.4 Developmental Toxicity Page 6-56, line 6.
The reference to "Table 6-6"adds nothing because no further information is added in the table.

6.7 Physiological Responses to Carbon Monoxide Exposure
The view of compensatory mechanisms expressed in this section appears to be quite different from that in Section 6.3.1 (page 6-47, line 24), where at least some aspects of the organism show effects that are"...documented amply in the literature...."

7.6 Health Effects of Carbon Monoxide Page 7-8, lines 29 though line 1 on the following page. This conclusion concerning "work conducted since the last criteria document review" should be revised to reflect any changes made to Chapter 6. Regardless of any modeling and interpretation of possibly important physiological mechanisms, the governing principle remains that no change should be made in the 1991 CO criteria document conclusions, given the absence of new experimental work---and, to our shame, none has appeared since 1990.

Lawrence Longo

Strengths. In general, this document represents a well organized, coherent, understandable synthesis of the literature and thinking in this field since the last such review. James A. Raub and his fellow contributors are to be congratulated for producing such a fine piece of work.

Possible Weaknesses

Chapter 5, Pharmacokinetics …

p 5-27ff I appreciate the work that has gone into this section, particularly in regard to cellular/molecular mechanisms. The past three years have seen a great increase in the literature in this area. Although this can not contain an exhaustive analysis, the authors might consider a few new references in regard to the effects of CO relating to free radicals, cell cycle regulation, enzyme function and hypoxia-inducible genes: HIF, heme oxygenase, vascular endothelial growth factor (VEGF), glucose transport and so forth. This is a hot area! As I mentioned at the meeting, a recent PubMed search on "CO Hypoxia and Molecular Mechanisms" came up with about 90 citations.

Some selected references are as follows:

Acevedo, CH and A Ahmed. Hemeoxygenase-1 inhibits human myometrial contractility via carbon monoxide and is upregulated by progesterone during pregnancy. *J Clin Invest* 101:949-955, 1998.

Bunn HF and RO Poyton. Oxygen sensing and molecular adaptation to hypoxia. *Physiol. Rev.* 76:839-885, 1996.

Glabe, A, Y Chung, D Xu, and T Jue. Carbon monoxide inhibition of regulatory pathways in myocardium. *Am. J. Physiol.* 274:H2143-H2151, 1998.

Haddad, GG and C Jiang. O_2 sensing mechanisms in excitable cells: role of plasma membrane K^+ channels. *Annu. Rev. Physiol.* 59:23-43, 1997.

Kourembanas S, T Morita, Y Liu and H Christou. Mechanisms by which oxygen regulates gene expression and cell-cell interaction in the vasculature. *Kidney Int.* 51:438-443, 1997.

Ostadal B, I Ostadalova, and NS Dhalla. Development of cardiac sensitivity to oxgyen deficinecy: comparative and ontogenetic aspects. *Physiol. Rev.* 79:635-659, 1999.

Wenger RH and M Gassmann. Oxygen(es) and the hypoxia-inducible factor-1. *Biol. Chem.* 378:609-616, 1997.

Wenger RH, I Kvietikova, A Rolfs, M Gassmann, and HH Marti. Hypoxia-inducible factor-1" is regulated at the post-mRNA level. *Kidney Int.* 51:560-563. 1997.

Yan SF, S Ogawa, DM Stern, and DJ Pinsky. Hypoxia-induced modulation of endothelial cell properties: regulation of barrier function and expression of interleukin-6. *Kidney Int.* 51:419-425, 1997.

Chapter 6, Health Effects …

p 6-36 As I mentioned at our recent meeting, an important new idea is the so-called "Barker Hypothesis", e.g. that adult hypertension, coronary artery disease, type II diabetes, and so forth may be a consequence of prenatal programming as a result of intrauterine hypoxia or other stress. The epidemiologic evidence amassed by Barker and his team at the Medical Research Council Unit in the United Kingdom is compelling, and includes results from studies, not only in the U.K., but in Chile, China, India, Scandinavia, *et cetera*. Several references are as follows.

Barker, DJP. *Mothers, Babies and Health in Later Life.* 2nd Ed., London, Churchill Livingston, 1998. (First edition, 1994)

Barker, DJP. *Fetal and Infant Origins of Adult Disease*. London, BMJ Publishing, 1992.

Barker, DJP. Fetal origins of coronary heart disease. *Brit. Med. J.* 311:171-174, 1995.

Campbell, DM, MH Hall, DJP Barker, J Cross, AW Shiell, and KM Godfrey. Diet in pregnancy and the offspring's blood pressure 40 years later. *Br. J. Obstet. Gynaecol.* 103:273-280, 1996.

Seckl, JR. Physiologic programming of the fetus. *Clin. Perinatol.* 25:939-962, 1998.

p 6-55 In regards to developmental toxicity, the authors might also include references to CO interactions with drugs and "alternative medicines".

Chapter 7, Integrative Summary …

As I read this section, I was struck that some facts were presented which I did not recall from the main text. Several examples follow.

p 7-1, ¶1 First sentence "CO is a colorless …"

p 7-2, ¶4 First few sentences, "About half … "

p 7-3, ¶2 Some of the specific concentrations in this paragraph.

p 7-4, ¶2 The sentence "For example, commute exposure … fell from a high of 37 ppm in Los Angeles … to a low of 3 ppm for New Jersey" doesn't make sense. Shouldn't you compare the fall

from a high value to a low one in both Los Angeles and New Jersey?

p 7-5, ¶3 The COHb data on chain smokers did not appear earlier.

p 7-12, ¶1 "Almost 14 million Americans …" should be given in Chapter 6 on Health Effects.

p 7-13, 14 It would seem to me that Figures 7-2 and 7-3 should be given in Chapter 6 on Health Effects. Then the data could be referred to here.

p 7-15 Again, Figure 7-3 and the details on COHb in sickle cell disease and in subjects with Hb Zurich should be given earlier.

p 7-16, ¶5 Same as above regarding smokers at high altitude.

Appendix A

p A-1 Include BS for black smoke (p 6-19).

For each chapter I would conclude with a short section on gaps in the data base, research needs, and areas to be explored.

Other Specific Comments

p E-8 Subpopulations at risk - Pregnant women, children.

p 4-34 "Methyl chloride" or "methylene" chloride

p 5-13 Evidence of HO induction

p 5-14 Exercise CO uptake vs elimination (Kimker, 1992)

p 5-18 Physiology hemodilution in pregnancy - anemia - 9 [Hb]

p 5-27 Intracellular

p 5-29 List of key equations for free radicals

p 6-19 BS = Black Smoke

p 6-52, Fig. 6-6 "Behavioral" misspelled

p 6-53, Fig. 6-7 "Behavioral" misspelled

Conclusion

Again, I wish to compliment you and your staff for producing an excellent synthesis on which EPA can base its recommendations to the Secretary and to Congress.

Steven Ayres

I was very pleased with the content and format of the Air Quality Criteria for Carbon Monoxide document we recently reviewed. There are two additions I would like to suggest be added to the document. The first deals with the unique ability of carbon monoxide to produce ischemia in states where vasodilation is limited because of vascular disease.

Add 6.2 Cardiovascular Effects

Carbon monoxide is unique among air pollutants, since it is harmful in small quantities only in individuals with impaired vascular systems. Persons with a normal cardiovascular system can tolerate substantially concentrations of carbon monoxide they vasodilate in response to hypoxemia produced by carbon monoxide. In contrast, individuals unable to vasodilate in response to carbon monoxide exposure may show evidence of ischemia at low concentrations of carboxyhemoglobin. For this reason, experiments on health animals are unlikely to show effects at low concentrations of exposure.

Add Action of Carbon Monoxide 5.7

Add immediately after Haldan equation 5-1

Haldane and Lorrain-Smith in 1895 showed that "partial saturation of a hemoglobin solution with CO causes oxygen to bind to the remaining hemes with a higher affinity and results in a less sigmoid curve." (HaldaneJ, and Lorrain Smith,J J Physiol) 20,497-520). The velocity of the association reaction is greater than that of the dissociation reaction.