Alliance OF AUTOMOBILE MANUFACTURERS

May 8, 2009

U.S. Environmental Protection Agency
Office of Environmental Information (OEI) Docket
Mail Code: 2822T
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: First External Review Draft Integrated Science Assessment for Carbon Monoxide
Docket ID number EPA-HQ-ORD-2007-0925

Submitted electronically

The Alliance of Automobile Manufacturers appreciate the opportunity to provide comments on the First External Review Draft Integrated Science Assessment for Carbon Monoxide. Attached please find our comments prepared by Jon Heuss and George Wolff of AIR Improvement Resource, Inc.

If you should have any questions, please contact Giedrius at (248) 357-4796.

Sincerely,

Giedrius Ambrozaitis
Director, Environmental Affairs

Attachment

Review and Critique of the U. S. Environmental Protection Agency's First External Review Draft of the "Integrated Science Assessment for Carbon Monoxide"

By
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Prepared for
The Alliance of Automobile Manufacturers

May 7, 2009

Executive Summary

Based on a review of the First External Draft of EPA's Integrated Science Assessment for Carbon Monoxide (CO), a number of changes need to be made to assure that the document accurately reflects the latest scientific knowledge concerning the health effects of carbon monoxide. In these general and specific comments, a number of key findings in the literature have been identified that are especially relevant to the integrative synthesis. The most important of these are as follows:

- The most compelling evidence of a CO-induced effect on the cardiovascular system at carboxyhemoglobin levels relevant to the current NAAQS comes from a series of controlled human exposure studies among individuals with coronary artery disease. These studies were used to establish the current CO air quality standards and remain the best available information on CO cardiovascular effects. (pages 13-15)
- The conclusions from the 2000 CO Criteria Document concerning CO and cardiovascular morbidity are miss-represented by ignoring caveats contained in the 2000 CD. Also, the strength and consistency of the new epidemiological associations concerning cardiac effects are overstated. (pages 13-18)
- The evidence for a causal CO- mortality relationship is very weak and inconsistent as the associations display unexplained city-to-city and geographic variability. (pages 22-23)
- The epidemiological studies that explore relationships between CO and short-term respiratory effects do not demonstrate convincing relationships between CO and symptoms, hospital admissions or emergency room visits, and the animal toxicology studies do not provide support for respiratory effects at concentrations anywhere near ambient levels. (pages 20-22)
- Claims made that the evidence is suggestive of a causal relationship between CO exposure and cardiac birth defects are not supported by the studies that are cited in the actual discussions in the body of the document. (pages 18-20)

- Epidemiology studies which EPA claims are suggestive of a causal relationship between CO and fetal developmental effects are not compelling or consistent. (pages 18-19)
- EPA dismisses a growing body of evidence that low levels of CO can have beneficial anti-inflammatory, anti-proliferative, and cytoprotective effects (pages 11-13)
- The spatial heterogeneity of ambient CO in urban areas and the existence of non-ambient sources of CO cast doubts on the credibility of epidemiological studies that rely on ambient data from a centrally-located monitoring site. (pages 9-10)
- Model selection issues, publication bias, and stochastic variation in the epidemiologic studies have not been adequately addressed by EPA. (pages 3-7)

Introduction

The U. S Environmental Protection Agency (EPA) initiated the next review of the National Ambient Air Quality Standards (NAAQS) for carbon monoxide (CO) with the issuance of the first external review draft of the Integrated Science Assessment for Carbon Monoxide[1] (ISA) in December 2008. As indicated in the draft ISA, CO elicits various health effects by binding with and altering the function of a number of heme-containing molecules, mainly hemoglobin (Hb). The formation of carboxyhemoglobin (COHb) reduces the O_2-carrying capacity of blood and impairs the release of O_2 from O_2Hb to the tissues. Clinical studies of the impact of CO on angina patients along with an understanding of the well-established mechanism of tissue hypoxia were used to establish the current CO air quality standards of 35 ppm for 1-hour and 9 ppm for 8-hours. Both standards are concentrations not to be exceeded more than once per year. The current CO standards were re-affirmed in 1994. EPA completed a revised Criteria Document in 2000,[2] but did not complete the review at that time.

The draft ISA also discusses new information concerning potential non-hypoxic mechanisms of CO action. These include free radical production and initiation of cell signaling. With regard to health effects of CO, the draft ISA presents and discusses the results from epidemiology, toxicology, and human clinical studies in Chapter 5 organizing the material by health endpoint. The draft ISA uses the same framework for causal determinations that EPA has developed for use in recent ISAs for other criteria pollutants. Within this framework, the draft concludes that the evidence for effects of CO on acute cardiovascular morbidity is likely causal while the evidence for other endpoints is weaker.

AIR, Inc. reviewed the draft ISA and provides both general and specific comments on the document. The review focused on the evidence regarding acute cardiovascular effects, the endpoints of greatest public health concern, such as mortality and hospital admissions, and on new information since the last CO Criteria Document.

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[1] U. S. Environmental Protection Agency, First external review draft of the Integrated Science Assessment for Carbon Monoxide, EPA/600/R-09/019, March 2009.
[2] U. S. Environmental Protection Agency, Air Quality Criteria for Carbon Monoxide, EPA/600/R-99/001F, June 2000.

General Comments

Much of the new information discussed in the draft ISA since the publication of the 2000 CD comes from epidemiology. There are important issues in interpreting environmental epidemiology that apply throughout the ISA. Therefore, we raise these issues in general comments. First, it should be remembered that epidemiologic studies can only demonstrate a statistical relationship and cannot demonstrate causality. Without supporting clinical and toxicological studies, causality is a judgment call. Second, the draft mischaracterizes the consistency and coherence of the acute health effects from epidemiology. There is a wide range of associations reported for acute mortality and morbidity with ambient CO. However, publication bias, model selection uncertainty, stochastic variation, and potential confounding cloud the interpretation of the data.

Concerns with model selection in Epidemiological Studies

In interpreting the epidemiological evidence, the draft downplays major new findings concerning uncertainty due to model selection issues. Model selection uncertainty relates to confounding of air pollutant associations by temporal trends, weather and co-pollutants. During the last ozone review, EPA acknowledged that the uncertainties in the estimates of pollutant effects are understated by consideration of the statistical uncertainty of the fitted model alone. Much more uncertainty arises from the lack of information regarding the choice of appropriate models for adjusting confounding by other covariates, and the choice of appropriate lag structures. As Lumley and Sheppard (2003) point out:

> Estimation of very weak associations in the presence of measurement error and strong confounding is inherently challenging. In this situation, prudent epidemiologists should recognize that residual bias can dominate their results. Because the possible mechanisms of action and their latencies are uncertain, the biologically correct models are unknown. This model selection problem is exacerbated by the common practice of screening multiple analyses and then selectively reporting only a few important results.[3]

Others have also pointed out the critical importance of model choice, particularly when effect estimates are small. For example, Smith et al. caution:

> From a statistical point of view, the common epidemiological practice of choosing variables (including lagged variables, co-pollutants, etc.) that maximize the

[3] T. Lumley and L. Sheppard, "Time series analyses of air pollution and health: straining at gnats and swallowing camels?" Epidemiology, 14, 13-14, 2003.

> resulting effect estimates is a dangerous approach to model selection, particularly when the effect estimates are close to 0 (i.e., RR close to 1).[4]

Smith et al. note that Lumley and Sheppard (2000)[5] showed that the effect of choosing lags in this fashion has a bias which is of the same order of magnitude as the relative risk being estimated. Morris has also shown a similar result. [6] He showed using the theory of extreme value distributions that evaluating multiple lags and reporting the maximum effect, even when there is no underlying effect, can yield estimates of effect size with a magnitude similar to those routinely reported for air pollutants.

The "revised analyses"[7] necessitated by the problems with the commonly used software for time-series analyses clearly show that methods used for controlling temporal trends and weather can profoundly affect the results. To make matters worse, there appears to be no objective statistical test to determine whether these factors have been adequately controlled. The HEI Expert Panel for the re-analysis states, "Ritov and Bickel (1990)[8] have shown, however, that for any continuous variable, no strictly data-based (i.e., statistical) method can exist by which to choose a sufficient number of degrees of freedom to insure that the amount of residual confounding due to that variable is small. This means that no matter what statistical method one uses to select the degrees of freedom, it is always logically possible that even if the true effect of pollution is null, the estimated effect is far from null due to confounding bias." The HEI Expert Panel concluded further, "Neither the appropriate degree of control for time, nor the appropriate specification of the effects of weather, has been determined for time-series analyses". In other words, it is impossible to adjust temporal trends without accurate information from external sources regarding the appropriate degrees of freedom to use. Such information, however, simply does not exist.

With regard to uncertainty due to model selection, the Koop and Tole 2004[9] Bayesian model averaging study, which thoroughly evaluated model selection in one city for many air pollution and meteorological variables, concludes:

> Point estimates of the effect of numerous air pollutants all tend to be positive, albeit small. However, when model uncertainty is accounted for in the analysis, measures of uncertainty associated with these point estimates became very large.

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[4] R. Smith, P. Guttorp, L. Sheppard, T. Lumley, and N. Ishikawa, "Comments on the Criteria Document for Particulate Matter Air Pollution," Northwest Research Center for Statistics and the Environment Technical Report Series No. 66, July 2001.

[5] T. Lumley and L. Sheppard, "Assessing seasonal confounding and model selection bias in air pollution epidemiology using positive and negative control analyses," Environmetrics, 11, 705-717 (2000).

[6] R. Morris, "Airborne Particulates and Hospital Admissions for Cardiovascular Disease: A Quantitative Review of the Evidence," Environ. Health Perspect.., **109**, Supplement 4, 495-500 (2001).

[7] Health Effects Institute, Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health, Health Effects Institute, Cambridge, Massachusetts, at 267, 269 (2003).

[8] Y. Ritov and P. Bickel, "Achieving information bounds in non- and semi-parametric models," Ann. Stat., 18, 925-938 (1990).

[9] G. Koop and L. Tole, Measuring the Health Effects of Air Pollution: to What Extent Can We Really Say that People are Dying from Bad Air, J. of Environmental Economics and Management, 47, 30-54. (2004).

> Indeed they became so large that the hypothesis that air pollution has no effect on mortality is not implausible. On the basis of these results, we recommend against the use of point estimates from time-series data to set regulatory standards for air pollution exposure.

Koop and Tole showed that a single model based on a sequence of hypothesis tests will overestimate the certainty of the results. This is not a new finding in the statistical literature. The 2004 PM CD notes that "testing many models to identify the model with the best fit can lead to an underestimation of uncertainty" and "if the observed confidence intervals were arrived at by a number of prior model specification searches, eliminating some worse fitting models, the true interval may well be wider."[10]

Despite the issues concerning uncertainty due to model selection that were acknowledged in the 2000 CO CD, in the 2004 PM CD, in the HEI Special Panel report, and in the publications referenced above, the draft CO ISA is essentially silent on this issue (and any changes in the relevant science). The final ISA must acknowledge and address the uncertainty due to model selection as it affects the interpretation of epidemiological results.

Concerns with Publication Bias in Reported Epidemiology Studies

Publication bias is another major issue in interpreting the epidemiology. The commentary by Goodman concerning meta-analyses is particularly insightful.[11] He noted a factor of at least three difference between the results of ozone meta-analyses and the NMMAPS data which are not affected by publication bias. Goodman concludes that the implications of an EPA-sponsored exercise of funding three separate meta-analyses "go far beyond the question of the ozone mortality effect." He cautions that "depending on published single-estimate, single-site analyses are an invitation to bias." He notes that "the most plausible explanation is the one suggested by the authors, that investigators tend to report, if not believe, the analysis that produces the strongest signal; and in each single-site analysis, there are innumerable model choices that affect the estimated strength of that signal." A separate review by a panel of ten knowledgeable scientists[12] concluded that "taken together, the meta-analyses provide evidence of a disturbingly large publication bias and model selection bias."

Similarly, Anderson et al. 2005[13] concluded that publication bias is present in single-city time series studies of ambient particles. After correcting for publication bias, they still report a positive association. However, they also note that the regression estimates from the multi-city studies (which are not prone to publication bias) and the corrected single-

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[10] U. S. Environmental Protection Agency, Air Quality Criteria for Particulate Matter, Volume I, EPA/600/P-99/002aF, October 2004; Volume II, EPA/600/P-99/002bF, October 2004, at page 8-226.
[11] S. Goodman, "The Methodologic Ozone Effect," Epidemiology, 16, 430-435 (2005).
[12] Report of a Working Conference, Critical Considerations in Evaluating Scientific Evidence of Health Effects of Ambient Ozone, held in Rochester, New York, June 2007.
[13] H. Anderson, R. Atkinson, J. Peacock, M. Sweeting, and L. Marston, "Ambient Particulate Matter and Health Effects: Publication Bias in Studies of Short-Term Associations," Epidemiology, **16**, 155-163 (2005).

city studies are approximately half of the mortality estimates of the mid-1990's, that the correction for publication bias may not be complete, and that differential selection of positive lags may also inflate estimates.

Thus, publication bias is a major concern inflating the size of any potential effect. As EPA has reviewed other criteria pollutants, the Agency has acknowledged[14] that the summary of health effects evidence is vulnerable to the errors of publication bias and multiple testing. The only reference in the draft CO ISA to publication bias is found on page 5-120 in a discussion of the multi-city studies. Since there is now substantial evidence that publication bias inflates the apparent magnitude and consistency of air pollution health effects in single-city studies, the final CO ISA must address and discuss the important impact of publication bias in the integrative sections.

Concerns with Similar Patterns of Acute Associations with All Criteria Pollutants

Another issue that needs to be recognized is that the pattern of acute associations is remarkably similar for all the criteria pollutants in single-pollutant models, raising the issue of double or triple counting of health effects. A similar pattern of associations was observed for all the major pollutants in single pollutant models in NMMAPS. For each pollutant, at each of the three lags evaluated, an implausibly wide range in individual-city associations from negative to positive was observed.[15] An implausibly wide range, from strongly positive to strongly negative, is present in all multi-city studies that report the individual-city associations. The presence of such a wide range indicates that there are a substantial number of false positives and false negatives in the data. With a few exceptions, the false negatives do not get into the literature, since no-one expects pollutants to have beneficial effects. However, the false positive associations do tend to get into the literature along with any "true" effects. This inflates the apparent strength and consistency of the epidemiological evidence. The final ISA must acknowledge that there is more stochastic variation in the data than heretofore thought.

Steib et al.[16] evaluated 109 acute mortality studies and reported that there are positive associations with mortality for all the major pollutants in single pollutant models, and that

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[14] U. S. EPA, Second External Review Draft of Integrated Science Assessment for Oxides of Nitrogen-Health Criteria, EPA 600/R-07/093aB, March 2008 at page 3-2; U. S. EPA, Integrated Science Assessment for Oxides of Sulfur-Health Criteria, EPA/600/R-07/047F, September 2008 at pages 3-1 and 3-48.

[15] While the full range of individual city results is presented in some multi-city studies, there has been a tendency to omit the individual city results in some recent publications. However, when the HEI sponsors requested that the individual city results from the re-analysis of NMMAPS be made available, the individual city results for PM_{10} and the various gases were posted on the Johns Hopkins website. The data show a remarkable similarity in that there was a biologically impossible wide range of associations from positive to negative for each pollutant on each lag that was evaluated. This data was also provided to EPA and CASAC during the PM review process; J. Heuss, Comments on the 4th Draft Criteria Document for Particulate Matter, AIR, Inc. comments prepared for the Alliance of Automobile Manufacturers, August 20, 2003.

[16] D. Steib, S. Judek, and R. Burnett, "Meta-analysis of time series studies of air pollution and mortality: Effects of gases and particles and the influence of cause of death, age, and season," *J. Air & Waste Manage. Assoc*., **52**, 470-484 (2002) and Stieb et al., *J. Air & Waste Management Association*, **53**, 258-261, 2003.

for each, when other pollutants are included, the association with the first pollutant, on average, is decreased. In addition, the Steib et al. analysis shows that the distribution of results published for each pollutant is remarkably similar, ranging from a few negative associations, to many small positive but non-significant associations, to some larger and significant associations. Thus, based on a comprehensive survey of the acute mortality epidemiology, no one pollutant is implicated over the others in single pollutant models. Although effect sizes were generally reduced in multi-pollutant models, the effects for PM_{10} and SO_2 remained statistically different from zero. The results for multi-pollutant models cannot be considered definitive because the underlying data base differs for each pollutant, there being wide differences from study to study for how many and which pollutants were included.

As EPA has considered each criteria pollutant in turn, single-pollutant model results have been used to estimate the strength and consistency of association. Single-pollutant associations were used in the draft PM ISA to implicate PM as causing cardiovascular hospital admissions and now in the draft CO ISA to implicate CO as causing cardiovascular hospital admissions. In a similar manner, single-pollutant associations with PM,[17] ozone, [18] NO_2, and SO_2[19] have been used recently as evidence of respiratory health effects from these pollutants.

In each case, the Agency has plotted selected individual city associations from the literature in the same manner and used the resulting figures to make the argument for respiratory or cardiovascular health effects caused by the pollutant under consideration. Visual inspection of the figures referenced above reveals a remarkably similar pattern. This raises three issues. First, as the air quality standard for each pollutant is reviewed in turn, the current practice of selecting specific studies and selecting specific single-pollutant associations for that pollutant results in a false appearance of consistency. If the various ISA documents for different pollutants are to be a scientifically sound basis for policy, more thorough analyses considering the full suite of pollutants is mandatory. Second, claiming health effects for each pollutant based on single-pollutant models raises the issue of double-, triple-, or even quadruple-counting of health effects.

Third, the remarkably similar pattern for each pollutant, together with the evidence of stochastic variability, model selection uncertainty, and publication bias, raise the concern that it is beyond the capability of current methods to identify which positive associations may be real health effects and which are not. Time-series epidemiology of air pollution associations is only capable of very blunt analysis. CASAC raised this issue in a June 2006 letter to the Administrator, noting that "because results of time-series studies implicate all of the criteria pollutants, findings of mortality time-series studies do not seem to allow us to confidently attribute observed effects specifically to individual pollutants."[20] The ISA needs to acknowledge the stochastic variability in time series

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[17] Figure 1 in proposed PM rule, 71 Federal Register 2620, January 17, 2006.
[18] Figure 1 in proposed ozone rule, 72 Federal Register 37818, July 11, 2007.
[19] July 2008 NOx ISA, EPA/600/R-08/071, at page 5-9, Figure 5.3-1; September 2008 SOx ISA, Figures 5-1 and 5-2 at pages 5-6 and 5-7.
[20] R. Henderson, CASAC letter, EPA-CASAC-06-07, June 5, 2006 at page 3.

associations (both positive and negative) and consider the implications of that variability in both the interpretation of the epidemiology and its integration with results from controlled studies.

Specific Comments

Comments on Chapter 2, Integrated Health Effects Overview

Chapter 2 provides a summary of the material in the other chapters and does not contain any new analysis. As such, it will need to be revised substantially as the main chapters are revised in response to public and CASAC comments. The main changes in the draft ISA that are recommended in response to AIR comments are:

- The implications of the growing body of controlled studies demonstrating beneficial anti-inflammatory, anti-proliferative, and cytoprotective effects of CO needs to be discussed and weighed more heavily in the integrative synthesis.

- The limitations of the epidemiologic studies cited in the draft ISA due to model selection issues, publication bias, stochastic variation, and potential confounding need to be fully acknowledged and discussed in the ISA in relation to all the health endpoints. For example, the cautions "it is unclear if CO is acting alone or as a surrogate for other combustion-related pollutants" and "the results also underscore the limitation of current analytical methods to disentangle the health effects associated with one pollutant in the complex air pollution mixture" that are included in the discussion of mortality associations apply equally to all the health endpoints that are evaluated in the ISA. In addition, the reliance on single pollutant model results in the draft ISA when combined with model selection and publication biases results in the document overstating the strength and consistency of the epidemiologic associations.

- The integrative synthesis needs to discuss and weigh the evidence regarding the interpretation of the epidemiological results not just present arguments in favor of causality. Since there are now numerous examples of a similar pattern of statistical associations with relevant health endpoints for all the criteria pollutants in systematic analyses, the integrative synthesis needs to be broadened to consider the plausibility, in terms of kinds of effects and doses that can cause such effects, for all the pollutant and weather factors that are included in the statistical analyses.

As a result of these changes, the final ISA will need to acknowledge that the epidemiological evidence regarding CO health effects is weaker than expressed in the draft ISA. For example:

> The evidence for a causal CO-mortality relationship is very weak and inconsistent as the associations display unexplained city-to city and geographic variability.

The epidemiological studies that explore relationships between CO and short-term respiratory effects do not demonstrate convincing relationships between CO and symptoms, hospital admissions or emergency room visits, and the animal toxicology studies do not provide support for respiratory effects at concentrations anywhere near ambient levels.

Claims made in the draft ISA that the evidence is suggestive of a causal relationship between CO exposure and cardiac birth defects are not supported by the studies that are cited in the actual discussions in the body of the document.

Epidemiology studies which EPA claims are suggestive of a causal relationship between CO and fetal developmental effects are not compelling or consistent.

While the evidence for cardiovascular morbidity below the level of the current NAAQS appears to be stronger than for other health endpoints, interpreting this evidence as causal is even more difficult than it was in 2000 because 1) ambient levels of CO are now extremely low compared to levels that cause effects in controlled animal or human studies, 2) there is now evidence that low levels of CO provide anti-inflammatory and cytoprotective benefits, 3) a similar pattern of associations is apparent with fine particles and other pollutants, and 4) there is now greater appreciation that model selection issues and publication bias overstate the certainty of the results.

Comments on Chapter 3, Sources to Exposure

Chapter 3 contains much useful information, but four issues warrant comments. The issues are: historical emissions and air quality data, the heterogeneity of the spatial concentration data, the policy relevant background, and the personal versus ambient exposures issue. Recent emissions trends from 1990 to 2002 are displayed in Figure 3-2. By starting the trend data only from 1990, the magnitude of the progress made in reducing CO emissions from all sources and, in particular, from on-road vehicles is not fully appreciated. Previous EPA trend reports showed that US CO emissions peaked around 1972 and have been declining since. We suggest that EPA begin this plot with the peak year so the ISA shows the full progress that has been made by their air quality management strategy. In addition, the air quality trends provided from 1980 to 2006 in Figure 3-24 should be augmented by information on CO trends from earlier EPA trends documents that cover the 1970s.

The issue of spatial concentration heterogeneity has important ramifications in the interpretation of epidemiology studies which EPA relies heavily on in their attempt to demonstrate health impacts at low ambient concentrations. The CO ISA, like the recent PM ISA and the most recent ozone CD, rely heavily on epidemiologic studies to establish relationships between some health outcome and pollution measured at some central monitoring site. However, Chapter 3 demonstrates that there are some significant differences in the observed spatial patterns of CO compared to O_3 and $PM_{2.5}$. The spatial pattern for CO is very heterogeneous compared to more homogeneous patterns displayed

for O_3 and $PM_{2.5}$ in urban areas. This is expected because CO concentrations are dominated by local sources while regional sources dominate the spatial distribution of O_3 and $PM_{2.5}$.

The heterogeneous patterns are demonstrated in the intersite correlation matrices shown in Tables 3-7 and 3-8 and in Appendix A. Intersite correlation coefficients within an urban area are generally low ($r \leq 0.4$) unless the sites are less than 10 km apart. However, in areas with hilly terrain, like Pittsburgh (table 3-8), sites as close as 1.8 km have an r of only 0.43.

This means that the practice of estimating population-wide exposure over a county or large metropolitan area by using a centrally located monitor or by averaging all the monitors in an area will not generate a realistic measure of exposure for CO. As a result, exposure misclassification is an issue that warrants the attention of EPA.

Unlike the recent O_3 and PM NAAQS reviews, the CO ISA derives policy relevant background concentrations from remote CO monitoring site rather than from global atmospheric chemistry-transport models. We commend the Agency for using actual data and hope that future reviews of the other Criteria Pollutants do the same.

The last issue in this chapter focuses on a statement made on page 3-57 of the ISA, "Wilson and Brauer (2006) showed significantly stronger associations between health effects and ambient exposure than between health effects and total personal exposure." Wilson and Brauer (2006)[21] came to this conclusion for $PM_{2.5}$, not for CO. Implicit in their analysis was the assumption that the chemical composition (and toxicity) of non-ambient particles was different from that of ambient particles and that the ambient particles were more toxic. For CO, it is impossible for this to be the case because CO from all sources is the same. Consequently EPA rationalization that central monitoring data is a better measure of CO exposure and predicting health outcomes is wrong. This and the issue discussed above on spatial heterogeneity needs to be address more fully in the next ISA because they cast doubts on the credibility of the epidemiology studies that rely on central monitoring data.

Comments on Chapter 4, Dosimetry and Pharmacokinetics

While both the draft ISA and the 2000 CD cover the same body of scientific information, the material is organized somewhat differently in the two documents. The 2000 CD has a chapter entitled Pharmacokinetics and Mechanisms of Action that covers these topics as well as dosimetry. Chapter 4 in the draft ISA covers dosimetry and pharmacokinetics but mechanisms of action are covered in the first section of Chapter 5. While either organization can work, we recommend that the mechanisms of action discussion be kept with the dosimetry and pharmacokinetics material in Chapter 5 since it provides a framework and basis for the integrative discussion of CO effects.

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[21] Wilson WE; Brauer M. (2006). Estimation of ambient and non-ambient components of particulate matter exposure from a personal monitoring panel study. Journal of Exposure Science and Environmental Epidemiology 16:264-274.

Comments on Chapter 5, Integrated Health Effects

Section 5.1 Mechanisms of Action

As the ISA notes, the basic understanding of the hypoxic mechanism of CO action, formation of COHb and reduction of oxygen-carrying capacity of the blood, has not changed substantially since the 2000 CD. For example, the ISA notes that research on the basics of CO pharmacokinetics dates back to the 1890s, but since the late 1970s has become limited. The draft notes that current literature primarily focuses on endogenous CO produced by the metabolic degradation of heme by heme oxygenase (HO) and its role as a gaseous messenger. While the endogenous production of CO has been known for a long time, the role of the CO produced as an active participant in cellular processes rather than as a waste product is of more recent vintage. The 2000 CD discussed this new information as a growing recognition that CO may play a role in normal neurotransmission and vasomotor control and an increased interest in the ability of CO to cause free-radical-mediated changes in tissues. However, the 2000 CD concluded that the impact of ambient CO on these processes and the roles they may have in pathophysiology was not yet well understood.

Section 5.1.3.1 of the draft ISA summarizes the information on non-hypoxic mechanisms from the 2000 CD, Section 5.1.3.2 discusses new information on non-hypoxic mechanisms, and Section 5.1.3.3 discusses the implications of this material. Ultimately, the draft concludes "whether or not environmentally relevant exposures to CO can affect endogenous CO signaling pathways and lead to adverse health effects is an open question for which there are no definitive answers at this time."

The presentation of results and discussion in Section 5.1.3 focuses on the potential for non-hypoxic mechanisms to cause or contribute to health effects at low ambient concentrations and downplays important new findings that exposure to low concentrations may have beneficial or protective effects. For example the draft notes:

> This assessment evaluates these non-hypoxic mechanisms in terms of their potential to contribute to health effects associated with environmentally-relevant CO exposures. As discussed above, CO at high concentrations may promote oxidative stress, cell injury and death, inflammation and endothelial dysfunction. Whether lower CO concentrations trigger these same processes is of key interest since these can potentially contribute to adverse health effects."

The draft goes on to acknowledge that "in addition, a large number of studies published since the 2000 CO AQCD has focused on the role of CO as an endogenous signaling molecule and the potential therapeutic effects of exogenous CO administered at high concentrations." However, the draft notes "the assessment addresses these topics only briefly, as they pertain to the evaluation of health effects associated with environmentally-relevant CO exposures."

There is now a large and growing body of literature indicating that non-toxic exposures to CO have substantial beneficial potential. This new information is also relevant to the interpretation of the epidemiological results and should be fully discussed in the ISA. The new information suggests that rather than triggering oxidative stress, cell injury and death, inflammation and endothelial dysfunction, low concentrations of CO actually protect against such effects through CO's role in cell signaling.

The draft ISA acknowledges that "recent studies suggest that exogenous CO at low concentrations may have beneficial anti-inflammatory, anti-proliferative and cytoprotective effects under certain circumstances" referencing Ryter et al. 2006. Ryter et al. in their extensive review note that inhalation CO has been effective in animal models of inflammation, hypertension, organ transplantation, vascular injury, and ventilation-induced lung injury. They also review the development of carbon monoxide releasing compounds that may be effective means to deliver therapeutic levels of CO to relevant tissues.

A number of studies referenced in the draft ISA have provided new insight into the potential beneficial effects and the mechanisms underlying such effects. The draft notes these studies in various ways but does not fully consider the results of the studies. For example, the draft ISA references the Chin et al. 2007 study with regard to altitude effects. Chin et al. elucidated the impacts CO induced in macrophages. Chin et al. concluded that CO did not reduce the influx of macrophages to the site of injury, but rather reprogrammed their state of activation toward one of protection versus aggression. They point out that harnessing the immune system is in part how CO and HO-1 act to maintain homeostasis. The draft ISA questions whether exogenous CO and endogenous CO have different impacts. However, Chin et al. note:

> The potential relevance of the effects of CO as studied here to that generated endogenously by heme oxygenase (HO)-1 was recently supported by D'Amico et al. [22] where comparisons were made between exogenous CO at concentrations similar to ones used here with those generated endogenously by HO. They found remarkable similarities in the effects on cellular respiration.

Chin et al. also note that there is increasing awareness of the salutary effects of CO at low concentrations (15–250 ppm) in preclinical animal models of disease. They point out that CO, initially thought of as a highly toxic molecule, is presently considered a novel therapeutic.

The draft ISA also references the Zhang et al. 2005 study of signaling pathways impacted by CO. Zhang et al. note that CO is emerging as a gaseous molecule with profound and potentially therapeutic biologic effects. They note that exposing mice to exogenous CO in sublethal ranges up to 500 ppm dramatically attenuates inflammation, apoptosis, and lethality in a variety of injury and transplantation models. They also note that elucidating the signaling mechanisms of CO-mediated effects will be important if we are to precisely

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[22] D'Amico G, Lam F, Hagen T, Moncada S (2006) J Cell Sci 119:2291–2298.

delineate the biology and potential applications of this often misunderstood gas.

The draft ISA discusses the Ghio et al. 2006 study in a subsection titled Disruption of Iron Homeostasis but is mischaracterized. The Ghio et al. paper reported that CO altered iron homeostasis and had a number of cell functional effects that were consistent with anti-inflammatory and anti-proliferative effects of the gas.

In contrast to the new view that CO plays a beneficial role through these non-hypoxic mechanisms, and has potential therapeutic impacts, the summary of Section 5.1.3 raises the concern that:

> The endogenous generation and release of CO from HO-1 and HO-2 is tightly controlled, as is any homeostatic process. Thus, exogenously-applied CO has the capacity to disrupt myriad heme-based signaling pathways due to its nonspecific nature.

This view is speculation that is not supported by the literature cited in the ISA and should be removed. It should be replaced by a statement acknowledging the growing body of information that non-hypoxic levels of CO can have beneficial effects.

Table 5-1 of the draft summarizes the responses to low and moderate CO exposures. It is difficult to interpret these changes since some are potentially adverse, some are beneficial, and many are of uncertain clinical significance. If such a table is to be included in the ISA, some discussion of the relevance of the biological responses should be included in the table and in the text for the non-expert reader.

The draft ISA acknowledges that CO is a ubiquitous cell signaling molecule and the physiological functions of HO-derived CO are numerous. The final statement in the section -- whether or not environmentally relevant exposures to CO can affect endogenous CO signaling pathways and lead to adverse health effects is an open question for which there are no definitive answers at this time – should be modified to add the thought that environmentally relevant exposures may also have beneficial effects.

Section 5.2 Cardiovascular Effects

The draft ISA correctly concludes that the most compelling evidence of a CO-induced effect on the cardiovascular system at COHb levels relevant to the current NAAQS comes from a series of controlled human exposure studies among individuals with coronary artery disease. These studies, which were described in the 1991 and 2000 CO Criteria Documents, demonstrated decreases in the time to onset of exercise-induced angina and ST-segment changes following CO exposures resulting in COHb levels of 3-6%, with one multicenter study reporting similar effects at COHb levels as low as 2.4%. These studies were used to establish the current CO air quality standards and remain the best available information on CO cardiovascular effects.

The draft also claims that the controlled human exposure studies are coherent with

findings of recent epidemiologic studies conducted since the 2000 CO CD which observed associations between ambient CO concentration and emergency department (ED) visits and hospital admissions for ischemic heart disease (IHD), congestive heart failure (CHF) and all-cause cardiovascular disease (CVD). The Integrative Overview in Chapter 2 refers to Figure 5-1, which with one exception shows associations of CO with increases in hospital admissions and ED visits for ischemic heart disease between 0.2% and 19.8% per standardized increase in CO concentration. The draft ISA claims that the recent studies build upon the conclusions of the 2000 CO AQCD that short-term variations in ambient CO concentrations are associated with daily hospital admissions for heart disease. The draft also claims that these health outcomes are consistent with a role for CO in limiting O_2 availability (i.e., hypoxic mechanisms) in individuals with coronary heart disease. Finally, the Integrative Overview refers to recent toxicological studies suggesting that CO may also act through non-hypoxic mechanisms by disrupting cellular signaling.

There are three major problems with a claim that the epidemiology demonstrates effects of CO below the current air quality standards. First, the draft ISA miss-represents the strength of the evidence based on the state of science and the conclusions drawn in the 2000 CD. Second, by focusing on single pollutant model results from primarily single-city studies, the draft overstates the strength of association and consistency of CO cardiovascular associations. As a result, the draft overstates the likelihood of CO, per se, causing cardiovascular morbidity at concentrations below the current air quality standards. Third, the draft overstates the likelihood of low levels of exogenous CO causing adverse effects by disrupting cellular signaling. Each of these problems will be discussed in turn.

Miss-representation of the 2000 CD's conclusions

While the 2000 CD does present and discuss a substantial body of studies that report CO associations with cardiovascular hospital admissions in single pollutant models, the Executive Summary summarizes the state of science as follows:

> Some recent epidemiology studies are suggestive of community average ambient CO variations being positively associated with fluctuations of indicators (e.g., cardiac-related hospital admissions) of heart disease exacerbation. However, these findings are not considered conclusive because of questions regarding (a) internal inconsistencies and coherence of the reported results within and across studies, (b) the representativeness of the average ambient CO levels of spatially heterogeneous ambient CO values derived from fixed monitoring sites or of personal exposures that often include nonambient CO, and (c) the biologic implausibility of any harmful effects occurring with the very small changes in COHb levels (from near 0 up to about 1.0%) over typical baseline levels (about 0.5%) that would be expected with the low average ambient CO levels (< 5.0 ppm, 1-h daily max) evaluated in the epidemiology studies.[23]

[23] 2000 CD at page E-6.

The 2000 CD includes a balanced discussion of the issues involved in air pollution epidemiology raising issues such as the sensitivity of effect estimates to model selection and specification, potential confounding of air pollutant and weather effects, and insufficient reporting of statistical uncertainty due to model tuning.[24] The observed associations of ambient CO with heart disease exacerbation are described as having some biological plausibility and being of potential public health concern.[25] However, the 2000 CD indicates that these associations should be interpreted cautiously. The point is made that ambient CO could be a surrogate for general combustion-related or mobile-source air pollution.[26] A point is also made that modeled effects estimates for single pollutants are likely to be inaccurate.[27] Finally, the 2000 CD notes[28] that pathophysiologically, it remains difficult to reconcile the small expected ambient CO-induced changes in COHb saturation with the reported increased overt exacerbation of heart disease in the community setting.

While the 2000 CD includes a balanced discussion of all these issues, the draft ISA downplays or ignores all the reasons to interpret the epidemiological associations cautiously. In order to be a proper integrated synthesis, all the issues acknowledged in the 2000 CD must be addressed in the ISA. In particular, any new information which would lead one to change the interpretation in the 2000 CD should be highlighted and discussed.

<u>Overstatement of the strength and consistency of epidemiological associations and likelihood of causality</u>

While there is now a large database of studies for almost all of the cardiovascular health endpoints compared to the situation in 2000, there are many issues with and inconsistencies in the data that render its use in drawing positive conclusions regarding CO causality problematic. In addition, the way the draft ISA presents and discusses the results of many studies can be misleading. Due to publication bias, almost all studies report some positive finding. However, the ability to measure many possible biomarkers or other endpoints in a given study means that there can be many positive outcomes in the literature when the overall impact is that of no effect. In addition, most of the studies cited in the draft ISA evaluated a suite of pollutants that included CO. By focusing primarily on the CO associations, the draft ignores the fact that the recent draft ISA for Particulate Matter (PM) used single-pollutant PM associations with cardiovascular hospital admissions for ischemic heart disease and congestive heart failure to claim a causal relation with that pollutant.[29] By not considering the pattern of pollutant associations in the literature for all the pollutants evaluated, the draft ISA does not provide an integrative synthesis that allows one to properly weigh the strength of evidence.

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[24] 2000 CD at pages 6-4 and 6-5.
[25] 2000 CD at pages 6-7.
[26] 2000 CD at pages 6-4 and 6-10.
[27] 2000 CD at page 6-21.
[28] 2000 CD at page 6-8.
[29] U. S. Environmental Protection Agency, First external review draft of the Integrated Science Assessment for Particulate Matter, EPA/600/R-08/139, December 2008, at pages 2-15 and 2-16.

Figures 5-1 to 5-5 are used to evaluate consistency. However, as noted in our general comments, the range in individual-city results in multi-city time series studies of hospital admissions and mortality is extremely wide, with individual-city associations ranging from strongly negative to strongly positive. This wide range is obscured by the practice of plotting only selected combined results from the multi-city studies along with selected results from individual-city publications in these figures. If the full range of individual-city results were shown in Figures 5-1 to 5-5, it would be apparent that the draft ISA could not appropriately claim consistency in these data.

In addition, each of the studies evaluated multiple pollutants. By not reporting the full results of the studies and not mentioning the author's conclusions concerning the implications of their results, the draft ISA omits pertinent information that should be considered in the integrative synthesis.

For example, Mann et al. 2002 reported associations with CO and other pollutants and indicated that they may be surrogates for the air pollution mix. Peel et al. 2007 reported positive associations with CO and three other pollutants. They also attribute their results to effects of the air pollution mix. Peel et al. also point out that their results did not corroborate the results from Mann et al., who reported an increased risk of hospital admissions for ischemic heart disease in relation to carbon monoxide among persons with a secondary diagnosis of congestive heart failure. They note that they observed the opposite trend in their results; patients with comorbid congestive heart failure had a decreased risk of emergency department visits for ischemic heart disease compared with patients without comorbid congestive heart failure.

The multi-city study by von Klot et al. 2005 evaluated five pollutants including CO in five European cities. All five pollutants had small positive combined associations, but the pattern in the individual cities was wide, with some cities showing no association and some cities showing strong associations for each pollutant as shown in their Figure 2. Von Klot et al. do not single out CO but attribute their results to effects of both primary and secondary air pollutants.

The Barnett et al. 2006 multi-city study of 7 cities in either Australia or New Zealand reported positive associations for four of the five pollutants tested. As with other multi-city studies, there was a wide range in individual city associations for each pollutant as shown in their Figure 1. They point out that it is difficult to separate the associations for different pollutants because there are common emission sources.

The individual-city studies by Koken et al. 2003 and Wellenius et al. 2005b evaluating congestive heart failure admissions also reported positive associations with several pollutants in addition to CO. Interestingly, the Wellenius et al. 2006b reference[30] in the draft ISA is for a multi-city study of congestive heart failure admissions and PM that did

[30] The Wellenius et al. 2006b reference in the list of references is there by mistake. The text refers to a Wellenius et al. 2006 toxicological study of CO, but the Wellenius et al. 2006 epidemiological study is listed in the references.

not evaluate other pollutants and reports a combined positive association with PM but a wide range in individual-city associations ranging from negative to strongly positive.

As noted in the general comments, the overall pattern in this literature is for multi-city studies to report a biologically implausible wide range in individual-city associations from positive to negative for each pollutant. Even though there are only a limited number of multi-city studies evaluating CO associations with hospital and ED admissions, and these studies evaluated only a limited number of cities, the same pattern has emerged. In addition, there is evidence potentially implicating all of the criteria pollutants, not just CO. Therefore, as CASAC noted several years ago, the results from epidemiological time-series studies "do not seem to allow us to confidently attribute observed effects specifically to individual pollutants."[31]

Indeed the draft CO ISA acknowledges that "it is difficult to determine from this group of studies the extent to which CO is independently associated with CVD outcomes or if CO is a marker for the effects of another traffic-related pollutant or mix of pollutants."[32]

Given this difficulty, along with the understanding that model selection bias and publication bias exaggerate the strength and consistency of association, the statement in the draft ISA that "the evidence indicates that CO associations generally remain robust in copollutant models, are coherent with the effects demonstrated by controlled human exposure and animal toxicological studies, and supports a direct effect of short-term CO exposure on CVD morbidity at ambient concentrations below the current NAAQS level"[33] cannot be supported.

Even though there is the appearance of consistent associations of CO with congestive heart failure and ischemic heart disease admissions in single-pollutant models, it is not clear that this is a causal relation. There are a large number of studies reporting positive associations of congestive heart failure admissions and other cardiovascular admissions with other pollutants. One of the weaknesses of the draft ISA is the reliance on single-pollutant models and the limited discussion of the extent of evidence for similar findings with other pollutants and/or weather parameters.

For example, Ebi et al. 2004[34] evaluated associations between weather parameters and cardiovascular hospital admissions in three California regions. They document a strong seasonality in heart failure admissions and report that temperature changes increased hospitalizations by 6%–11% for acute myocardial infarction and congestive heart failure. In discussing the pathophysiological changes underlying such associations they note that seasonal and temperature variations have been described for blood pressure, blood viscosity, vasoconstriction, serum lipids, fibrinogen levels, and other blood components.

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[31] R. Henderson, CASAC letter, EPA-CASAC-06-07, June 5, 2006 at page 3.
[32] Draft ISA at page 5-45.
[33] Ibid.
[34] K. Ebi, K. Exuzides, E. Lau, M. Kelsh, and A. Barnston, "Weather changes associated with hospitalizations for cardiovascular diseases and stroke in California, 1983–1998," Int. J. Biometeor., **49**, 48-58 (2004).

Since changes in some of these biomarkers and physiological parameters are associated with morbidity and mortality from cardiovascular disease, the ISA should evaluate the bio-meteorology literature to determine the magnitude of physiological changes associated with weather and weather changes to compare with those associated with PM and other pollutants. A thorough search of the biometeorology literature may reveal alternative weather variables and factors to implement in air pollution regression models. For example, Kolb et al. 2007[35] report that a number of changes in weather are associated with changes in daily mortality in an elderly population diagnosed with congestive heart failure in Montreal.

In order to properly evaluate the likelihood of CO causing cardiovascular effects at concentrations below the current NAAQS, the ISA should carry out a more comprehensive integrated synthesis and evaluation as discussed above. In particular, the ISA should discuss what new information is available that might change the interpretation of epidemiological data in the 2000 CD. For example, the ambient concentrations of CO have been reduced substantially since 2000 with mean concentrations of the order of 0.5 ppm in recent years as shown in Tables 3-3 and 3-4 of the draft ISA. It should also be borne in mind that at least 70 monitors across the U.S. have been positioned at microscale within 10 m of a road to capture near-road concentrations. Thus, in the more recent studies, it is even more biologically implausible than thought in 2000 that there are any harmful effects occurring with the very small changes in COHb levels over typical baseline endogenous levels. In addition, evidence is accumulating that low and moderate levels of CO have protective effects.

<u>Overstatement of potential adverse effects due to non-hypoxic mechanisms</u>

As discussed above, there is ample evidence that low and moderate levels of CO have potential benefits from non-hypoxic mechanisms. These anti-inflammatory, anti-proliferative and cytoprotective effects need to be considered in detail in the ISA and weighed against the evidence that low levels of CO may cause potential adverse effects. The discussion of toxicology in section 5.2.3 treats any change whether protective or adverse as potentially dangerous. In addition, the discussion does not discriminate between changes that occur at very high concentrations and changes at exposures more relevant to ambient CO exposures. The question of coherence and biological plausibility is both a question of the kinds of effects that are observed as well as the concentrations at which they are observed. Since it ignores the issue of dose plausibility, the statement in the toxicology summary that "these studies provide a strong basis for the development of adverse health effects resulting from exposures to CO at environmentally-relevant concentrations" cannot be supported.

Section 5.4 Birth Outcomes and Developmental Effects

In their summary (section 5.4.3) of this section, EPA concludes that based on the "epidemiologic studies and the resulting coherence for these associations in animal and

[35] S. Kolb, K. Radon, M-F Valois, L. Hugey, and M. Goldberg, "The short-term influence of weather on daily mortality in congestive heart failure," Arch. Environ. Occup. Health, **62**, 169-176 (2007).

toxicological studies, **the evidence is suggestive of a causal relationship between long-term exposures to relevant CO concentrations and developmental effects and birth outcomes.**" They say the most "compelling evidence for a CO-induced effect on birth and developmental outcomes is for PTB (preterm birth) and cardiac birth defects." Although they discuss a number of possible other effects, these comments focus on what EPA considers their most "compelling evidence."

Developmental Studies not Compelling or Consistent

Figure 5-6 in the ISA contains a summary of effect estimates for PTB associated with maternal exposure to ambient CO. It contains 12 estimates from 5 studies. Of the 12 estimates, 4 are negative (2 are statistically significant), one is zero, and 7 are positive but only one positive estimate is statistically significant. Given the limited availability of detailed information on maternal lifestyle factors and time-activity patterns during pregnancy, these results are not compelling or consistent.

Similarly, Figure 5-8 in the ISA summarizes the effect estimates for low birth weight studies associated with maternal exposure to ambient CO. Of the 17 estimates given, 6 are negative (2 are statistically significant), one is zero, and 9 are positive but only 4 are statistically significant. Again, these results are neither compelling nor consistent.

Cardiac Birth Defect Studies Do Not Support EPA's Claims

For the cardiac birth defects, EPA cites two studies – one from Southern California[36] and one from Texas.[37] EPA summarizes the results of the two studies: "The main results from the southern California study showed that CO was associated with an increased risk of ventricular septal defects and this was exhibited by an exposure-response pattern across the quartiles of exposure, yet there was no indication that ambient CO concentration in Texas was associated with ventricular septal defects. Conversely, ambient CO concentration in Texas was associated with an increased risk of conotruncal defects, yet there was no indication that CO in southern California was associated with conotruncal defects, and on the contrary, reported results of a protective effect." After some further discussion, EPA concludes on the bottom of page 5-72: "Overall, there is little evidence that maternal exposure to CO is associated with an increased risk of congenital anomalies, namely heart defects and cleft lip and palate." This not only lacks compelling evidence for cardiac birth defects, it contradicts EPA's conclusion in the section summary.

EPA also cites the coherence between the epidemiologic and toxicological studies to support their conclusions. In the 5 PTB studies cited by EPA, the mean CO

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[36] Ritz B; Yu F; Chapa G; Fruin S. (2000). Effect of air pollution on preterm birth among children born in Southern
California between 1989 and 1993. Epidemiology 11: 502-511.

[37] Gilboa SM; Mendola P; Olshan AF; Langlois PH; Savitz DA; Loomis D; Herring AH; Fixler DE. (2005). Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997-2000. American
Journal of Epidemiology 162: 238-252.

concentrations ranged from 0.8 ppm to 2.7 ppm while the Southern California and Texas cardiac studies, the mean CO concentrations were 1.57 ppm and 0.5 ppm, respectively. In the toxicology studies, the animals were exposed to CO concentrations ranging from 65 to 500 ppm. Comparing observed effects in animals exposed to CO concentrations 24 to 1000 times higher than the concentrations experienced in the epidemiology studies, which reported mixed and inconsistent results, does not demonstrate coherence of results.

Section 5.5 Respiratory Effects

The ISA concludes that the evidence is suggestive of a causal relationship between short-term exposure to CO and respiratory morbidity but that the evidence is inadequate to conclude that a causal relationship exists between long-term exposure and respiratory morbidity. They claim that epidemiologic studies that examined the effects of short-term exposure to CO and lung related outcomes show positive outcomes and that animal toxicological studies demonstrate "the potential for an underlying biological mechanism." Consequently, we will focus on these short-term epidemiological studies and the animal toxicological studies. The epidemiological studies that EPA relies on examined the following outcomes: changes in pulmonary functions, respiratory symptoms, hospital admissions and emergency department visits.

Pulmonary Function Studies Do Not Provide Evidence for Causal Relationship – EPA examines 8 studies that looked at changes in pulmonary function. The mean CO concentration in these studies ranged from 0.35 to 6.4 ppm. All of these studies suffer from the inability to say definitively the changes in the tests are due to CO because they do not control for other pollutants which are correlated with CO. In addition, the results are mixed with one of the two US studies showing no effect, and the other showing no effect for one year but a slight effect the second year which experienced higher PM and NO_2 concentrations. No attempt was made in this study to distinguish between the effects of the different pollutants.

In summary, without adequate consideration of the confounding effects of copollutants, these studies do not provide evidence for a causal relationship for CO exposure and changes in pulmonary function.

Respiratory Symptoms Studies Do Not Provide Evidence for Causal Relationship – EPA cites 7 studies that show a positive relationship between asthma symptoms or medication use by asthmatics and CO. However, only one study measured anything other than CO.[38] In the studies that only measured CO, it is impossible to implicate CO as a causal agent because it is correlated with other pollutant species. In the one study that considered other pollutants, they did find a positive relationship with CO, but the authors concluded that $PM_{2.5}$ "may" be the causal agent.
In their summary for this section, EPA states: "A lack of copollutant analyses among this group of studies complicates the efforts to disentangle the health effects attributed to CO

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[38] Schildcrout JS; Sheppard L; Lumley T; Slaughter JC; Koenig JQ; Shapiro GG. (2006). Ambient air pollution and
asthma exacerbations in children: an eight-city analysis. American Journal of Epidemiology 164: 505-517.

from the larger traffic-related pollutant mix. Additional uncertainty exists as to a biologically plausible mechanism which could explain the effect of CO on respiratory health." Such evidence hardly supports a causal relationship.

Hospital Admissions Studies Do Not Provide Evidence for Causal Relationship – For hospital admissions, EPA cites 5 studies. The first is Cakmak et al. (2006)[39] and EPA reports that they reported a positive statistically significant relationship. What they failed to report is that when other pollutants were added in a multiple pollutant model, the association vanished and was not statistically significant.

The second study they cite is Linn et al. (2000)[40] which EPA says they reported a weak association. What EPA does not say is that it was only statistically significant in the autumn and it was not significant in the winter, spring, and summer or on an annual basis.

For the third study, Slaughter et al. (2005),[41] EPA admits they reported a null association.

The fourth study, Burnett et al. (2001)[42] should not be included in the discussion because it used the Generalized Additive Model (GAM) before the discovery of the flawed default value which resulted in premature convergence and erroneous results.

EPA states that the fifth study, Yang et al. (2003)[43] report significant associations between CO and hospital admissions for both pediatric and elderly patients. What they fail to mention is that both associations disappeared and became insignificant in multiple pollutant models.

Emergency Department Visits Studies Do Not Provide Evidence for Causal Relationship – For ED visits, EPA cites 3 studies. The first two studies, Peel et al. (2005)[44] and

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[39] Cakmak S; Dales RE; Judek S. (2006). Do gender, education, and income modify the effect of air pollution gases
on cardiac disease? J Occup Environ Med 48: 89-94.

[40] Linn WS; Szlachcic Y; Gong H, Jr.; Kinney PL; Berhane KT. (2000). Air pollution and daily hospital admissions in metropolitan Los Angeles. Envir on Health Perspect 108: 427-434

[41] Slaughter JC; Kim E; Sheppard L; Sullivan JH; Larson TV; Claiborn C. (2005). Association between particulate
matter and emergency room visits, hospital admissions and mortality in Spokane, Washington. J Expo Anal Environ Epidemiol 15: 153-159.

[42] Burnett RT; Smith-Doiron M; Stieb D; Raizenne ME; Brook JR; Dales RE; Leech JA; Cakmak S; Krewski D.
(2001). Association between ozone and hospitalization for acute respiratory diseases in children less than 2 years of age. American Journal of Epidemiology 153: 444-452.

[43] Yang Q; Chen Y; Shi Y; Burnett RT; McGrail KM; Krewski D. (2003). Association between ozone and respiratory admissions among children and the elderly in Vancouver, Canada. Inhalation Toxicology 15: 1297-1308.

[44] Peel JL; Tolbert PE; Klein M; Metzger KB; Flanders WD; Todd K; Mulholland JA; Ryan PB; Frumkin H. (2005).
Ambient air pollution and respiratory emergency department visits. Epidemiology 16: 164-174.

Tolbert et al. (2007),[45] were both conducted in Atlanta and use similar data set and overlapping time periods. As EPA states, both find a positive and statistically significant associations between CO and respiratory ED visits. However, what EPA fails to emphasize is that the association with CO becomes insignificant in any two or more pollutant models. For the third study, Slaughter et al. (2005)[46] examined only single pollutant models and their results were not statistically significant for CO and respiratory ED visits.

Toxicological Studies Not Conducted at "Environmentally-Relevant CO Concentrations – EPA states the animal toxicological studies demonstrate the potential for an underlying biological mechanism. While it is true that there are a few studies that indicated biochemical changes in the lung at concentrations EPA describes as "environmentally-relevant," we do not think 50 ppm is relevant in the US. In the US and Canadian epidemiology studies that examined for respiratory health outcomes, the mean CO concentrations ranged from 0.78 ppm to 1.82 ppm. The lowest "environmentally relevant" concentrations are 27 to 64 times higher than observed ambient concentrations.

Section 5.6 Mortality

The ISA concludes that the evidence is "suggestive of no causal relationship between long-term exposure to CO and mortality," but is "suggestive of a causal relationship between short-term exposure to relevant CO concentrations and mortality." While we agree with the first part of this conclusion, we believe the evidence for the second part is overstated. Consequently, we will focus our discussion on the evidence for a short-term causal relationship.

Evidence for Causal CO-Mortality Relationship Is Weak and Inconsistent

The evidence presented for this relationship consists of 5 single-city and 3 multi-city epidemiological studies. EPA weighs the multi-city studies more because of their higher statistical power and the attenuation of most, but not all, of the associations between CO and mortality when other copollutants were included in the regression models in the single-city studies. In addition, collectively, single-city studies suffer from publication bias. Consequently, we will focus on the multi-city studies.

The first is the NMMAPS study.[47] This study found a 0.23% increase in mortality per 0.5 ppm increase in 24-hr average CO for the 80 largest US cities with CO monitors.

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[45] Tolbert PE; Klein M; Peel JL; Sarnat SE; Sarnat JA. (2007). Multipollutant modeling issues in a study of ambient air quality and emergency department visits in Atlanta. Journal of Exposure Science and Environmental
Epidemiology 17 Suppl 2: S29-35.

[46] Slaughter JC; Kim E; Sheppard L; Sullivan JH; Larson TV; Claiborn C. (2005). Association between particulate
matter and emergency room visits, hospital admissions and mortality in Spokane, Washington. J Expo Anal Environ Epidemiol 15: 153-159

[47] Dominici F; McDermott A; Daniels M; Zeger S.L; Samet J.M. (2003b). Mortality among residents of 90 cities.

However, these results are nearly identical for all the other pollutants examined (PM_{10}, O_3, SO_2 and NO_2). In addition, when the values for the individual cities are examined, the data show wide unexplained variability which is not biologically plausible. Individual city data were not presented in their report, but were available at their web site.[48]

The range for the individual cities is from -6.5% to +4.1%. Of the 80 cities included, only 5 are statistically significant and positive while 1 is statistically significant and negative. Of the remaining, 27 are negative, 3 are zero, and 44 are positive but not statistically significant. The results also demonstrate a geographical variation with the strongest effect in the Midwest and Northeast and little or no association in the Northwest, the Southwest and Southeast.

Similar geographic patterns and city to city variability have been reported for PM_{10} by the NMMAPS investigators. They speculated that the PM response variability was due to geographically varying PM_{10} composition which is plausible. However, all CO emissions are equally toxic so a similar explanation for CO is not possible. Thus, the NMMAPS results for CO are not credible.

The second study cited by EPA is Burnett et al., 2004 who examined the mortality relationships with NO_2, CO, SO_2, $PM_{2.5}$, and the coefficient of haze (CoH – a measure of elemental carbon). In a single pollutant model, mortality increased 0.33% per 0.5 ppm increase in the 24-hr CO concentration. When NO_2 was included in a two pollutant model, the increased risk from CO decreased to 0.04%. CO was never included in a model with $PM_{2.5}$ or CoH. Since CO, NO2, $PM_{2.5}$, and CoH were highly correlated confounding is surely occurring, so we do not believe anything can be concluded concerning CO playing a causal role.

The last study cited by EPA was the European APHEA study[49] which reported on the CO-mortality associations in 19 European cities. This study suffers from some of the concerns we had with NMMAPS. First, the range of effects in the individual cities is implausibly large ranging from about -3% to +9%. Second, they report geographic variability. The greatest effect is reported for western cities, followed by southern cities

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Revised Analyses of Time-Series Studies of Air Pollution and Health Special Report Boston, MA: Health Effects Institute: 9–24.

[48] While the full range of individual city results is presented in some multi-city studies, there has been a tendency to omit the individual city results in some recent publications. However, when the HEI sponsors requested that the individual city results from the re-analysis of NMMAPS be made available, the individual city results for PM_{10} and the various gases were posted on the Johns Hopkins website. The data show a remarkable similarity in that there was a biologically impossible wide range of associations from positive to negative for each pollutant on each lag that was evaluated. This data was also provided to EPA and CASAC during the PM review process; J. Heuss, Comments on the 4th Draft Criteria Document for Particulate Matter, AIR, Inc. comments prepared for the Alliance of Automobile Manufacturers, August 20, 2003.

[49] Samoli E; Touloumi G; Schwartz J; Anderson HR; Schindler C; Forsberg B; Vigotti MA; Vonk J; Kosnik M;
Skorkovsky J; Katsouyanni K. (2007). Short-term effects of carbon monoxide on mortality: an analysis within the APHEA project. Environ Health Perspect 115: 1578-1583.

and no effect for eastern cities. Consequently, we question the credibility of these results for the same reasons we question NMMAPS results.

In summary, the evidence for a causal CO-mortality relationship is very weak as the associations display unexplained city-to city and geographic variability. The reported associations are also inconsistent.