Comments on the Second Draft Carbon Monoxide Risk and Exposure Assessment (REA) and the First Draft Carbon Monoxide Policy Assessment (PA)

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Executive Summary

Based on reviews of the Second External Draft of EPA's Risk and Exposure Assessment for Carbon Monoxide (REA)[1] and the First External Review Draft of the Policy Assessment for Carbon Monoxide (PA),[2] a number of changes need to be made to assure that the document accurately reflects the latest scientific knowledge concerning the exposure and 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 these assessments. The most important of these from the REA are as follows:

- The estimates of risk, for a given level of ambient carbon monoxide (CO), have not materially changed since the previous review of the CO standards. However, there needs to be a comparison of the first and second drafts to illustrate this.
- The risk (as estimated from the distribution of COHb) is overstated for the upper tail of the distribution and this needs to be acknowledged.
- There is no data indicating that the in-vehicle concentrations in the U.S. approach the upper end of the ranges used in the model. EPA needs to acknowledge this or produce data.
- Based on studies of the factors that determine in-vehicle exposures, the peak exposures assumed by EPA are biased high. EPA needs to address this.
- The cities chosen for the REA represent a "worst case" situation. EPA should choose cities and monitors that are more representative of U.S. Urban exposures.

As a result of the last four points, EPA consistently overestimates the exposure and the risks associated with current ambient air concentrations.

The most important of these from the PA are:

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[1] U. S. Environmental Protection Agency, Risk and Exposure Assessment to Support the Review of the Carbon Monoxide Primary National Ambient Air Quality Standards: Second External Review Draft, EPA-452/P-10-004, February 2010.

[2] U. S. Environmental Protection Agency Policy Assessment for the Review of the Carbon Monoxide National Ambient Air Quality Standards: External Review Draft, EPA-452/P-10-005, March 2010.

- EPA gives too much weight to the epidemiological studies of CO because:
    - EPA ignores or minimizes many of the uncertainties associated with the epidemiological studies,
    - A new study focusing on the model selection issue suggests that the epidemiological evidence relied on by EPA in the ISA is scientifically unsound and should not be used as a reason to lower the present CO NAAQS, and
    - Relying on specific single-city studies in light of the stochastic variation is unsound.
- EPA gives insufficient consideration to new information on potentially beneficial mechanisms of CO action.
- Integrating the information from the three areas of study (clinical, epidemiology and controlled human exposures) leads to the conclusion that the current standards are adequately protective of public health

Introduction

The current national ambient air quality standards for carbon monoxide (CO) are 9 parts per million (ppm), as an 8-hour average, and 35 ppm, as a 1-hour average, neither to be exceeded more than once per year. These primary standards were established to protect against the occurrence of carboxyhemoglobin (COHb) levels in human blood that were associated with health effects of concern. As part of the on-going review of the carbon monoxide air quality standards, the U.S. Environmental Protection Agency (EPA) issued the Second External Review Draft of the Risk and Exposure Assessment for Carbon Monoxide (REA)[3] and the First External Review Draft of the Policy Assessment for Carbon Monoxide (PA).[4] In November 2009, AIR provided comments[5] on the First Draft REA and on the Second Draft of the Integrated Science Assessment (ISA).

The final ISA, which was published in January 2010,[6] evaluates the scientific evidence on the health effects of CO that is relevant to the Administrator's decision whether or not to revise the standards. It includes information on exposure, the physiological mechanisms by which CO might adversely impact human health, an evaluation of the clinical evidence for CO-related effects, and an evaluation of the epidemiological evidence for CO-related effects. The REA describes a quantitative assessment conducted by the Agency to support the review of the primary CO standards, and the PA focuses the information from the ISA and REA on the judgments the EPA Administrator must make in determining whether to revise the air quality standards, and if so, how to revise the

[3] U. S. Environmental Protection Agency, supra note 1.
[4] U. S. Environmental Protection Agency, supra note 2.
[5] J. M. Heuss, D. F. Kahlbaum, and G. T. Wolff, Review and Critique of the U. S. Environmental Protection Agency's Second External Review Draft of the "Integrated Science Assessment for Carbon Monoxide" and First External Review Draft of the "Risk and Exposure Assessment to Support the Review of the Carbon Monoxide Primary National Ambient Air Quality Standards," Air Improvement Resource, Inc. Report, Prepared for The Alliance of Automobile Manufacturers, November 13, 2009.
[6] U.S. EPA, Integrated Science Assessment for Carbon Monoxide, National Center for Environmental Assessment, Research Triangle Park, NC, EPA/600/R-09/019F, January 2010.

standards.

AIR, Inc. reviewed the two documents focusing on the scientific basis for the judgments that the Administrator will make.

Comments on Second Draft Risk and Exposure Assessment

The ISA and REA note that the best-characterized health effect associated with CO is hypoxia (reduced oxygen availability) induced by increased COHb levels in blood. The formation of COHb reduces the oxygen carrying capacity of the blood and impairs the release of oxygen from oxy-hemoglobin complexes to the tissues. The REA includes estimated CO exposures and resulting doses of COHb for the population of adult residents with coronary heart disease in two urban study areas (Denver and Los Angeles). Prior reviews of the CO air quality standards in 1985, 1994, and 2000 included similar analyses of exposure to ambient CO and associated internal dose of COHb to characterize population risk.

EPA needs to acknowledge that the estimates of risk, for a given level of ambient CO, have not materially changed since the previous review of the CO standards

The second draft REA is a distinct improvement over the first draft. AIR had criticized the first draft since it had used CO measurements at only one site in each city to represent the exposure of the entire population. By taking the spatial variation in CO concentrations and several micro-environments into account, the distribution of COHb exposures reported in the REA is now much more realistic. However, there is no comparison provided to show the substantial reduction in estimated risk that occurred from the first draft to the second draft. At a minimum, EPA should include a direct comparison for CASAC and the public. For example, comparing Tables 6-11 and 6-12 in the second draft with Tables 6-22 and 6-23 in the first draft, one can see that, for CO levels that just meet the current standard, the percentage of persons with maximum COHb levels at or above 2% was reduced by over a factor of ten, from 6.6 % to 0.5 % in Los Angeles, and from 56.5% to 3.4% in Denver. We commend EPA for using more realistic assumptions.

In addition to the distribution of maximum COHb levels, we commend the inclusion of the data on person-days and person-days per person in various tables. These data are extremely important in evaluating the risk and putting it into a public health perspective. For example, in Los Angeles as shown in Table 6-12, just meeting the current standard results in only 0.002% of the person-days in the population of adults with coronary heart disease with COHb levels at or above 2%. In fact less that 0.1% of the person-days are above 1.5%. This demonstrates that the current standard is highly protective. Since "as-is" CO concentrations are now below the standard, as documented in Tables 6-9 and 6-10, the risk from current ambient CO is even lower. In addition, the REA documents that the second draft REA risk estimates are quite similar to the risks estimated in the previous review (carried out in the year 2000 using the pNEM model) for Los Angeles,

but somewhat higher for Denver. Thus, the estimates of risk, for a given level of ambient CO, have not materially changed since the previous review of the CO standards.

The risk (as estimated from the distribution of COHb) is overstated for the upper tail of the distribution

There are two important reasons why the analysis is biased to overstate the upper tail of the COHb distribution. One applies primarily to the Denver analysis and the other applies to both cities.

First, as noted above, the risk in Denver in the current analysis is somewhat higher than was estimated in the 2000 pNEM analysis. We believe that the upper tail of the COHb distribution estimated for Denver in the second draft is too high because one of the four sites is a micro-scale site located on a triangular-shaped traffic island at the intersection of major arterial roads. In the previous analysis, six monitoring sites were used to characterize the exposures. By reducing the number of sites, the importance of each remaining site is magnified. Since one of the remaining sites is a micro-scale site within a few meters of heavy traffic, the concentrations measured at that site will dominate the upper tail of the distribution of CO (and hence COHb) exposures. Although the analysis simulates CO in a number of microenvironments, the base exposures, from which the micro-environmental exposures are calculated (or adjusted up or down from), are developed from the monitoring data. Thus, the analysis uses CO exposures for a substantial portion of the population of interest that are determined from measurements at a site that is not representative of where anybody lives or works or spends very much time. This biases the distribution upward by overstating the number of people exposed to high CO concentrations and the fraction of time they are exposed to high concentrations.

Second, there is a key assumption that causes the Agency to over-estimate the upper tail of the COHb distribution. Although it is well established that the in-vehicle or on-road exposures on busy highways can be higher relative to up-wind monitors, we have concerns that the procedure EPA used in the REA to estimate the incremental increase due to in-vehicle exposures overestimates in-vehicle concentrations in heavy traffic and/or under adverse meteorology. In the first draft the Agency used a multiplicative factor of two to model the in-vehicle micro-environment. That factor was based primarily on the Shikiya et al. 1989 study in Los Angeles. CASAC was concerned that EPA was not taking the variability in the ratio of in-vehicle to monitor measurements into account. In the second draft, a methodology similar to that used in the 2000 was used, with a multiplicative factor with a geometric mean of 3.2 and 5^{th} and 95^{th} percentiles of 1.5 and 6. The ISA documents that the ratio between in-vehicle measurements and ambient monitors is highly variable. The change resulted in an increase in the maximum in-vehicle CO concentrations in the analysis. As indicated in Figure 16 of the staff presentation on the draft REA at the March 22-23, 2010 CASAC meeting, in-vehicle 1-hour CO concentrations that are greater than 60 ppm are included in the analysis, and the elevated in-vehicle exposures are responsible for the upper tail of the CO and COHb distribution.

There is no data indicating that the in-vehicle concentrations in the U. S. approach the upper end of the ranges used in the model

There is no data cited in the ISA or REA that demonstrates that in-vehicle 1-hour concentrations of anywhere near 60 ppm CO have been measured in the U. S. in locations that just attain the current CO air quality standards. In fact, there are numerous studies that report significantly lower concentrations. For example, the Rodes et al., 1998 study of in-vehicle exposures to CO and other pollutants reported in-vehicle CO concentrations between 3 and 5.4 ppm for two-hour measurements during "simulated commutes" on heavily-traveled freeways and major arterial roads in the Los Angeles Basin. The measurements were made in the fall of 1997, a year when the ambient CO design value was 15 ppm as compared to the 9 ppm standard. Importantly, the CO concentrations on major arterial routes were similar to those on more-heavily travelled freeways.

The Shikiya et al., 1989 study of Los Angeles similarly reported in-vehicle commuting exposures in Los Angeles from data gathered in 1987. Both the Shikiya et al. and Rodes et al. studies were carried out for California air pollution control agencies. A comparison of the two studies, conducted in 1987 and 1997 respectively, shows that the in-vehicle CO concentrations were reduced by over a factor of two in the intervening decade. The reduction in both ambient and in-vehicle CO concentrations has continued due to the nation's motor vehicle control program. In addition, although both the Shikiya et al. and Rodes et al. studies report peak CO concentrations of the order of 50 ppm, those measurements are peak 1-minute concentrations not peak 1-hour concentrations.

The CO measurements (made in the year 2003) from the Westerdahl et al., 2005 study in the Los Angeles Basin are particularly informative. The authors measured CO and other pollutants in an instrumented electric vehicle driving on freeways in Los Angeles with a traffic density greater than 200,000 vehicles per day. The vehicle was driven on a freeway- dominated loop that took approximately two hours. Westerdahl et al. specifically report that roadway CO averaged from 2 to 4 ppm and was usually no more than twice the ambient concentration. This study, conducted on major freeways in the Los Angeles Basin, an area with historic high CO concentrations, high traffic density, and adverse meteorology demonstrates the magnitude of on-roadway exposures in worst-case driving situations. When the three Los Angeles studies are compared, it is evident that in-vehicle CO concentrations have been dramatically reduced from 1987 to 2003. Importantly, even the peak 1-minute CO concentrations have been reduced substantially, with the peak 1-minute concentration measured during the Westerdahl et al. study being 14 ppm. Since the California and federal motor vehicle control programs are continuing to reduce vehicle CO emissions, current and future on-road exposures will be even lower.

The in-vehicle CO measurements reported in other studies referenced in the ISA and REA also provide no evidence of 1-hour CO exposures approaching the peak levels in the REA modeling analysis.

Based on studies of the factors that determine in-vehicle exposures, the peak exposures assumed by EPA are biased high

Since day-to-day emissions are relatively constant, the wide distribution in ambient CO concentrations arises due to differences in dispersion that are driven by variations in meteorology. Dispersion around a roadway is a function of wind speed, wind direction, and atmospheric stability. High ground-level concentrations result from low wind speeds and limited vertical dispersion due to the presence of inversions. However, as Chock and others have shown, the concentration fields around roadways are also influenced by the mechanical turbulence generated by the traffic that effectively limits the build-up of CO and other pollutants under adverse meteorological conditions.

Since a high ratio of on-road increment to background can occur in a situation where the actual on-road increment (in concentration units) is low and the background is very low, applying that high ratio to an urban situation with a high background can substantially over-estimate the on-road increment. Rather than use the ratio method, EPA should analyze the data in terms of the increment in concentration units and the traffic counts, since the magnitude of the on-road CO source is the major determinant of the on-road increment. Under conditions of adverse meteorology that lead to the highest ambient concentrations, low wind speeds and limited vertical dispersion, a high ratio is not likely. This is because the traffic that generates the CO also generates a great deal of mechanical mixing that acts to dilute the emissions.

In the mid-1970s when the catalytic convertor was introduced to reduce emissions, because of concerns that the sulfur in gasoline would be oxidized over the catalyst and cause excessive near roadway exposures to sulfate, General Motors and EPA carried out an experiment on a test track at the General Motors Proving Ground that simulated an expressway with a traffic density of 5462 cars per hour.[7] Experiments were conducted on the early morning of 17 days in October 1975, in order to collect data under the most adverse meteorological conditions available. Using the results from an array of chemical and meteorological measurements around the roadway, Chock demonstrated that the turbulence and heat generated by the traffic had a significant effect on the on-road and near-road wind and concentration fields.[8] For example, in the first 50 meters downwind of the road, mechanical mixing dominates the mixing due to stability considerations so that the vertical dispersion parameters in the first 50 meters approach neutral stability, regardless of the ambient stability. In addition, at very low wind speeds, the heat from the traffic lifts the exhaust above the Gaussian plume axis. These effects limit the concentrations that can build up on and near roadways under adverse ambient meteorology.

A review paper by EPA authors, Baldauf, et al. 2009, makes the same point, noting:[9]

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[7] S. Cadle, D. Chock, P. Monson, and J. Heuss, "General Motors Sulfate Dispersion Experiment: Experimental Procedures and Results," J. Air Pollut. Control Assoc., **27**, 33-38 (1977).
[8] D. Chock, "General Motors Sulfate Dispersion Experiment: Assessment of the EPA HIWAY Model," J. Air Pollut. Control Assoc., 27, 39-45 (1977).
[9] R. Baldauf, N. Watkins, D. Heist, C. Bailey, P. Rowley, and R. Shores, Near-road air quality monitoring: Factors affecting network design and interpretation of data, Air Qual. Atmos. Health, **2,** 1–9 (2009).

> Regardless of roadway design, the activity of vehicles on the road induces turbulence at the point of pollutant emission, leading to enhanced pollutant mixing. In addition, the elevated temperature of exhaust emissions enhance thermal buoyancy in the plume, providing an initial mixing zone for vehicle-emitted pollutants that depends on the number, type, and speed of vehicles on the road. The more turbulence present, the more initial dilution of pollutants will occur.

Thus, the mechanical mixing and turbulence generated by vehicles acts to limit the build-up of CO and other pollutants emitted on roadways under adverse ambient meteorology.

The three Los Angeles Basin studies noted above all concluded that the in-vehicle CO levels on major arterial roads are similar to that on major expressways. This arises because there is greater mechanical mixing and turbulence on expressways than on arterial roads due to the higher speeds on expressways, offsetting the difference in traffic count.

The cities chosen for the REA represent a "worst case" situation

During the March 22-23 CASAC meeting the panel discussed a need to put the results of REA into a national perspective. The upper extremes of the COHb distributions in the Denver and Los Angeles analyses are determined by the ambient measurements at the CAMP site in Denver and the Lynwood site in Los Angeles. It has been long recognized that these two monitors are particularly problematic due to unique meteorological and topographical conditions. The CO situations in Denver, in general, and at the CAMP and Lynwood sites, in particular, were intensively evaluated in a National Research Council (NRC) study a few years ago.[10] The unique meteorological and topographical factors that lead to higher CO concentrations at these sites are discussed in the NRC study in a section that includes references to earlier studies of the cause of higher CO at these sites. Thus, the upper extremes of the COHb distributions in the REA represent a national "worst case" situation.

Any attempt to extrapolate the results to a national analysis of CO and COHb exposure needs to acknowledge that the cities chosen for the analysis are not average or typical, but represent more of a "worst case." In addition, any attempt to derive a national risk estimate must also acknowledge that the nation's CO monitoring program has historically focused on sites that are expected to have maximum exposures at each of several monitoring scales, with the sites at each monitoring scale skewed to identify maximum exposures, not average exposures, at that monitoring scale. For example, in recent years there have been 57 microscale sites that are typically 2 to 10 meters from a roadway and sited to identify maximum exposures in the near-road or street canyon environment. There are another 71 monitors for which no scale is defined. Even in the case of neighborhood scale monitoring, the guidelines stress the need to put monitors in neighborhoods with the highest population density. Thus, the monitoring network is not designed to determine a national average CO exposure, but is skewed to measure higher

[10] National Research Council. (2003). Managing Carbon Monoxide Pollution in Meteorological and Topographical Problem Areas. The National Academies Press. Washington DC. pages 96 to 99.

than average exposures at each monitoring scale.

Comments on First Draft Policy Assessment

There are three major sources of information on CO health effects. The first is controlled studies of CO effects. The second is observational or epidemiological studies of the association of CO with various health endpoints. The third is studies of the mechanism of CO's action in the body. Each of these is discussed in turn followed by a summary section that integrates the information and leads to conclusions regarding the adequacy of the current standards.

Great weight should be placed on the controlled studies for which the interpretation of risk is unchanged from previous reviews

The staff indicates that great weight should be placed on the controlled studies. AIR agrees. The first effects of CO involve exercise-induced aggravation of angina in controlled exposures of patients with diagnosed ischemic heart disease (IHD) to elevated CO concentrations. These effects have been documented in a series of clinical studies carried out by various investigators between 1973 and 1991.

The current CO standards were established in 1971 and have been retained in several reviews. Although EPA initiated a review in 1997 and completed both a new Criteria Document and exposure analysis in 2000, a rulemaking was not initiated at that time. Thus, the last full review was completed in 1994. As discussed above, the estimated COHb exposures due to ambient CO, for a given ambient CO level, have not changed substantially from that estimated in prior reviews. In addition, due to the issues raised concerning a bias to overestimate in-vehicle exposures, the draft REA analysis overestimates the upper percentiles of the COHb exposures and hence overestimates the risk.

In order to properly portray the risk in the PA, we urge the staff to add information from the REA on the percent of person-days of COHb above the various benchmarks to Tables 2-5, 2-6, and 2-7. The overall distribution of person-days of COHb is a more appropriate metric to evaluate the public health risk than just the maximum COHb in a year. This metric was used by the Administrator in past reviews to judge the public health risk and should be a major consideration in the current review.

Little weight should be given to the epidemiological studies of CO

In the draft policy assessment document,[11] EPA concludes that the body of evidence supports a CO NAAQS at least as protective as the current suite of standards to avoid unacceptable public health risks. In coming to this conclusion, they reason that "recognition of limitations in the epidemiological evidence for CO with regard to its use

[11] U. S. Environmental Protection Agency. (2010). Policy Assessment for the Review of the Carbon Monoxide National Ambient Air Quality Standards. EPA-452/P-10-005. March 2010. P. 2-56.

in drawing quantitative conclusions"[12] would provide a basis for retaining the present standards. One the other hand, if they place weight on three epidemiology studies conducted in Atlanta (which meets the present 8-hour standard), they would have to consider a lower standard. Thus, if EPA chooses to promulgate standards more stringent than present, it will be based on their interpretation of the epidemiological data. As pointed out in our November 13, 2009 comments,[13] however, their interpretation is problematic as they ignore or minimize many of the uncertainties associated with such studies. EPA gives credence to the epidemiology studies that is unwarranted. Even as they gloss over the uncertainties, the ISA[14] can conclude only that "a causal relationship is *likely* between *relevant* short-term CO exposures and cardiovascular morbidity (emphasis added)."

The November 2009 AIR comments provided detailed reasons why the epidemiology summarized in the ISA should be given little weight. First, the pattern of acute associations reported for CO is remarkably similar to that of all the criteria pollutants. Second, multi-city studies report a wide range in individual-city associations from positive to negative for each pollutant. This range of associations from harmful to protective is not biologically plausible. With 25 to 40 percent of the associations in various multi-city studies being negative, it is impossible to characterize the data as consistent. Third, with such stochastic variation, relying on any one individual study or a small cluster of studies is unreliable. Fourth, there is now greater appreciation that model selection uncertainty, publication bias, and issues of surrogacy or confounding limit the interpretation of the published associations as true effects.

A new study focusing on the model selection issue suggests that the epidemiological evidence relied on by EPA in the ISA is scientifically unsound and should not be used as a reason to lower the present CO NAAQS

A new study by Koop et al. (2010)[15] underscores many of the issues raised in the preceding paragraph and adds additional insights as to the reasons why the real relationships between morbidity and air pollution at relevant exposures are small and insignificant. In this study, the authors conduct a comprehensive analysis on air pollution morbidity relationships for eleven Canadian cities over a long record from 1974 to 1994. As a result, they have a unique data set that allowed the examination of both spatial and temporal variations. In addition to including the five criteria pollutants, CO, PM, SO_2, NO_2, and O_3, they also controlled for socioeconomic factors, smoking and meteorology.

[12] Ibid at p. 2-54.
[13] Heuss, J., Kahlbaum, D. and Wolff, G. T. (2009). Review and Critique of the U. S. Environmental Protection Agency's Second External Review Draft of the "Integrated Science Assessment for Carbon Monoxide" and First External Review Draft of the "Risk and Exposure Assessment to Support the Review of the Carbon Monoxide Primary National Ambient Air Quality Standards."Air Improvement Resource, Inc. report prepared for the Alliance of Automobile Manufacturers. November 13, 2009.
[14] U. S. Environmental Protection Agency. (2009). Second external review draft of the Integrated Science Assessment for Carbon Monoxide. EPA/600/R-09/019B. September 2009. P. 5-67.
[15] Koop, G., McKitrick, R. and Tole, L. (2010). Air pollution, economic activity and respiratory illness: Evidence from Canadian cities, 1974-1994. Environ. Model. Softw. Doi.10.1016/j.envsoft.2010.01.010 (in press).

Much shorter subsets of this data set have been studied without the socioeconomic and smoking variables by a number of research groups to demonstrate significant relationships with a number of health outcomes and individual pollutants. The long data set enables the present investigators to explore the impact of significantly improved air quality at the end of the data set compared to the beginning. Koop et al. also employed the two major methods used to formulate statistical models in time-series studies: model selection by the use of some statistical criteria and Bayesian Model Averaging (BMA) to address the all important issue of model selection uncertainty.

As Koop et al. noted and we noted in our November, 2009 comments, the results in the general body of the air pollution epidemiology literature are conflicted. In other words, the results range from positive to negative and from significant to insignificant for all pollutants and for all health endpoints. Koop et al. state:

> One of the reasons for this profusion of apparently contradictory results is model uncertainty. With very few exceptions (e.g. Clyde, 2000;[16] Clyde and DeSimone-Sasinowska, 1997[17] and Koop and Tole, 2004,[18] 2006[19]), previous studies on air pollution-health effects have used model selection methods, i.e. choosing one or a few regression specifications and reporting point estimates and their associated variances conditional on that being the true model. However, the estimation exercise is inherently opportunistic. Many plausible covariates could be included, but the choice is not dictated by theory so much as by data availability. Hence there is not only uncertainty about regression slope coefficients conditional on the model selection, but about the model specification itself.[20]

Compounding the issue of selecting the true model is the large number of potential explanatory variables and possible forms that will influence the model results. As Koop et al. articulate it:

> However, the number of potential confounding variables implies that a huge number of models could be used to explain health effects. The number of potential models is on the order of 2^k where k is the number of potential explanatory variables, including lags. Since results can be sensitive to the particular regression specification, and since the number of potential models is so large, model uncertainty has been shown to be an important issue in this literature (Clyde, 2000; Koop and Tole, 2004).[21]

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[16] Clyde, M., 2000. Model uncertainty and health effect studies for particulate matter. Environmetrics 11, 745–764.
[17] Clyde, M., DeSimone-Sasinowska, H., 1997. Accounting for Model Uncertainty in Poisson Regression Models: Particulate Matter and Mortality in Birmingham, Alabama. Institute of Statistics and Decisions Sciences, Duke University Discussion Paper 97-06.
[18] Koop, Gary, Tole, Lise, 2004. Measuring the health effects of air pollution: to what extent can we really say that people are dying from bad air? J. Environ. Econ. Manage. 47, 30–54.
[19] Koop, Gary, Tole, Lise, 2006. An Investigation of thresholds in air pollution mortality effects. Environmental Modelling & Software. 21 (12), 1662–1673.
[20] Koop et. al., supra note 5 at 3.
[21] Ibid at 2.

To address the model biases and uncertainties, the authors use BMA, which weights information from every potential model. The BMA results are weighted averages of the estimates from each model. The weights are proportional to the support the data give each model.

The results of the BMA analyses show that the health outcomes are explained by the smoking and the socioeconomic variables and that none of the air pollutants showed a statistically positive relationship with health. In fact, most pollutant relationships were slightly negative, albeit not robust, so with this particular data set, the BMA results were largely similar (except NO_2 showed an effect in a single model) to the results obtained by selecting a single model. This is in contrast to their earlier results (Koop and Tole, 2004[22]) for Toronto which found many relationships when a single model was used. In the earlier paper, a shorter data record was used and the smoking and socioeconomic variables were not included. This may explain the differences and underscores the importance of including these variables in a longer time-series in these types of studies.

In summary, this study demonstrates the importance of: 1) incorporating smoking and socioeconomic variable into the models, 2) using a longer time series that has significantly different pollutant concentrations at the beginning and end of the study, 3) using the BMA approach which minimizes model selection uncertainties and finds insignificant health impacts. This suggests that the epidemiological evidence relied on and summarized by EPA in the ISA is scientifically unsound and should not be used as a reason to lower the present CO NAAQS.

Relying on specific single-city studies in light of the stochastic variation is unsound

The arguments in the PA for more stringent CO standards rely on cardiovascular hospital admissions associations reported in three Atlanta studies. In the one study that reports a statistically significant positive association with CO, the authors do not ascribe the positive association to an effect of CO, per se, but rather raise the same issues of CO acting as an indicator that are acknowledged in the draft PA.

Relying on one or a small cluster of CO studies from the literature, when there is so much stochastic variation, is akin to choosing one point from a scatter plot of all results. The wide variation in individual-community results in single-pollutant models and the highly variable changes in multi-pollutant models (with some CO associations increasing, some decreasing, and others relatively unchanged) are demonstrated in the following figure, taken from the supplemental material for the Bell et al., 2009 study of emergency hospital admissions for cardiovascular disease.

As documented in detail in the AIR November 13, 2009 comments, the pattern of associations reported by Bell et al. is not consistent with a causal relationship. In addition to the stochastic variation shown below and in other figures in the Bell et al. supplementary material for the lag 0 individual-community associations, the combined association on lag1 was negative, even though one would expect a positive association

[22] Koop and Tole supra note 8.

from the evening peak in the CO on day 0 if CO were actually causing cardiovascular hospital admissions.

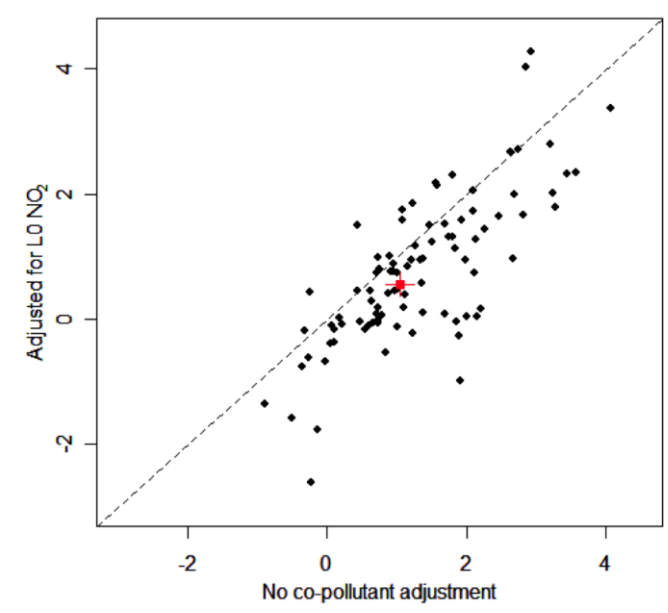

Fig. IIa. With and without adjustment by same day NO_2

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New information on potentially beneficial mechanisms of CO action needs to be considered

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. The ISA notes, however, 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.

There is now a large and growing body of literature indicating that non-toxic exposures to CO may have substantial beneficial potential. This new information is also relevant to the interpretation of the epidemiological results and should be fully discussed in the PA.

The ISA acknowledges that work from numerous laboratories has demonstrated the potential for CO to be used as a therapeutic gas with numerous possible clinical applications, since it can produce anti-inflammatory, anti-apoptotic, and anti-proliferative effects, referencing Ryter et al., 2006 and Durante 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. The implications of the growing body of controlled studies demonstrating beneficial anti-inflammatory, anti-proliferative, and cytoprotective effects of CO under certain circumstances needs to be weighed more heavily in the PA.

Integrating the information from the three areas of study leads to the conclusion that the current standards are adequately protective of public health

Clinical Studies: In judging the public health implications of attaining the current CO standards, it is useful to consider the judgments that were made by CASAC and the Administrator in the 1994 review concerning the clinical studies. As summarized in section 2.2.1 of the PA, EPA and CASAC recognized the existence of a range of views among health professionals on the clinical significance of the responses observed in the clinical studies, but the dominant view was that they should be considered "adverse or harbinger of adverse effect." Despite the uncertainty associated with the clinical importance of the cardiovascular effects that resulted from COHb levels of 2 to 3 percent, EPA and CASAC agreed that exposures to such levels should be minimized. Although EPA and CASAC recognized the possibility that there is no threshold for these effects even at lower COHb levels, the health significance of the small changes in ST-segment depression observed was considered somewhat minor. Furthermore, the first effects identified in healthy adults, findings of short-term reduction in maximal work capacity measured in trained athletes exposed to CO, occurred only at higher levels of COHb of 3 to 7 percent. The ISA notes that the decreases in exercise duration were relatively small and only likely to be noticed by competing athletes. Studies with healthy adults also found no cardiovascular effects on ST-segment depression or cardiac rhythm with exercising adults who had COHb levels up to 20 percent.

The information on health effects related to various COHb levels from the clinical studies has not changed from the 1994 review or the 2000 CD. As noted above, the information on the COHb exposures expected from a given CO exposure has not changed. Therefore, there is no reason from the clinical studies to change the conclusion that the current CO standards are adequately protective of public health.

Epidemiology: Although there is a substantial increase in the number of studies that report weak associations of CO with various health endpoints since the 2000 CD, the issues with interpreting that data for CO that were voiced in the 2000 CD have not changed. Although the controlled human studies do demonstrate effects on the cardiovascular system at 2% COHb and above, interpreting the epidemiological evidence as causal below the level of the current standards is even more difficult than it was in 2000 because 1) ambient levels of CO are now much lower than the levels that cause effects in controlled animal or human studies, 2) there is now evidence that both

endogenous and exogenous CO have anti-inflammatory and cytoprotective properties through non-hypoxic mechanisms.

As EPA has reviewed the air quality standards for each of the criteria pollutants, the pattern of epidemiological evidence and the discussion of that evidence are remarkably similar. Each CD or ISA focuses on the single-pollutant associations for the pollutant under consideration. The primary display of the evidence is in figures where only the combined association for multi-city studies is plotted, thereby obscuring the full range of associations from positive to negative. The text discusses the data without regard to whether the authors of the study implicated the pollutant under consideration or air pollution in general or another pollutant. The ISA considers multi-pollutant models to some degree and concludes that at least for some endpoints, the results are generally robust to other pollutants. The summary discussion refers to the data in terms that range from mixed and inconsistent to generally consistent. In no place is the wide range of associations in systematic analyses or multi-city studies addressed. Although publication bias and model selection uncertainty may be mentioned somewhere in the document, their implications for the final conclusions are not fully considered. Based on the qualitative discussion in the text, the document applies the causality framework EPA has developed from other, similar framework. For the most part, the evidence for effects in various health endpoint categories is categorized as likely causal or suggestive of causality. There is also discussion with respect to how the observational studies compare to the controlled studies of the pollutant under consideration. If there are known respiratory or cardiovascular effects from the pollutant, the epidemiology in that category is bumped up one causality category because of coherence with the clinical studies. There is also the obligatory discussion that the pollutant may have an independent effect or be considered an indicator of some other pollutant.

An examination of the epidemiological evidence shows that, whether in systematic analyses or in the figures in EPA's recent ISAs and CDs, the pattern looks remarkably similar. The remarkably similar pattern for each pollutant, together with the evidence of stochastic variability, model selection uncertainty, and publication bias, raises 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."[23]

Despite this concern, as the Administrator and the various CASAC panels consider the epidemiological information, the conclusion is drawn that the pollutant under consideration has an independent effect and that is used as a reason to tighten the existing air quality standard. This has occurred recently in the NO_2, SO_2, and ozone proposals to revise those standards and is also included in the first draft PA for particulate matter that is undergoing CASAC and public review. This leads to double, triple, or quadruple

[23] Henderson R. (2006). CASAC letter. EPA-CASAC-06-07. June 5, 2006. at page 3.

counting of health effects.

The comprehensive new study of 20 years of Canadian data in 11major cities by Koop, McKitrick and Tole discussed above confirms the prior AIR concerns with air pollution epidemiology. The authors conclude:

> We also illustrated the danger that incomplete modeling efforts could yield apparent pollution-health correlations that are not robust to reasonable variations in estimation methods. Model selection methods applied to a subset of the data, or without use of the appropriate socioeconomic controls, can (for example) yield an apparently significant health effect from increased carbon monoxide levels, but such effects change sign and/or become insignificant upon application of more complete empirical methods.

In discussing the example of a limited data set in which there is a positive CO association with respiratory hospital admissions, they note:

> Consequently, this finding mainly serves as an example of how a positive and significant relationship between pollution and illness can be found in a data set with some digging, but may not be robust to a change in modeling technique nor an extension of the data back in time.

Given the limitations on the use of time series and other epidemiological studies to set ambient standards that we and others have identified, EPA should not rely on one or a few studies that report positive CO associations in single pollutant models to determine the appropriate range for the level of the CO standards.

Mechanisms of action: The hypoxic mechanism for CO action is well established. The clinical significance of the first known changes, which occur at or above 2% COHb in exercising adults with coronary heart disease, is not entirely clear. The previous judgment was that the effects should be considered as adverse or a harbinger of adverse effects. There is no reason to change that conclusion.

While there is now a great deal of interest in non-hypoxic mechanisms, there is now growing evidence that both endogenous and exogenous CO have anti-inflammatory and cytoprotective properties through non-hypoxic mechanisms.