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"

Prepared for
The Alliance of Automobile Manufacturers

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1.0 Executive Summary

As part of the process of periodically reviewing the scientific basis for the National Ambient Air Quality Standards (NAAQS), EPA released the Integrated Science Assessment for Carbon Monoxide – Second External Review Draft (ISA) in September, 2009 and the Risk and Exposure Assessment to Support the Review of the Carbon Monoxide Primary National Ambient Air Quality Standards: First External Review Draft (REA) in October, 2009. As requested by the Alliance of Automobile Manufacturers, AIR, Inc. performed a review of both of these EPA documents focusing on the health endpoint that EPA identified to be of most concern, cardiovascular disease (CVD). AIR, Inc. has identified a number of changes that need to be made so that these documents accurately reflect the latest scientific knowledge concerning CVD effects and carbon monoxide (CO). The documents are discussed separately.

ISA

Consistent with the first draft of the ISA, the second draft also concludes that "a causal relationship is likely to exist between relevant short-term CO exposures and cardiovascular morbidity." To enhance their case for this statement, EPA has included the results of a new, multi-city epidemiology study by Bell et al. which related ambient CO concentrations to emergency hospital admissions of patients 65 years of age or older for CVD. Because of the weight EPA gives to this new evidence, AIR, Inc. also reviewed the Bell et al. study.

The key findings pertaining to the ISA are:

- Bell et al.'s finding of a positive, statistically significant relationship only between CO and same-day CVD admissions in conjunction with a negative relationship for the next day's admissions is not plausible because of the frequent occurrence of the highest daily 1-hour maximum CO concentrations in the evenings. Because of the documented lags between the onset of high CO concentrations and the time a patient is admitted to a hospital, any relationship between CO and hospital admissions would have to include the next day's admissions for this relationship to be causal.
- The heterogeneity of Bell et al.'s individual county risk estimates, including many that are negative, and the authors' failure to report the statistical significance of the individual county estimates, raises doubts concerning the validity of a single pooled risk estimate for the entire U.S.

- Model selection is an issue that continues to be inadequately acknowledged in the ISA.
- Although publication bias is acknowledged in Chapter 1, it is ignored in the integrative synthesis.
- The pattern of acute associations for CO is remarkably similar for all the criteria pollutants raising the issue of double or triple counting of health effects.
- The overall pattern in the epidemiology literature is for multi-city studies to report a biologically implausible wide range in individual-city associations from positive to negative for each pollutant. The Bell et al. study demonstrates this pattern for CO. With 25 to 40 percent of the associations in various multi-city studies being negative, it is impossible to characterize the data as consistent.
- The ISA attempts to make the point that CO associations generally remain robust in co-pollutant models. However, the criterion for what constitutes robust in the text, that the association remains positive in co-pollutant models, is weak.
- The epidemiology studies cited in the ISA do not provide support for an independent effect of CO on cardiovascular morbidity. In contrast, the controlled human studies do show strong evidence of independent effects of CO on cardiac function above carboxyhemoglobin (COHb) levels of 2 %.
- There is now a large and growing body of literature indicating that non-toxic exposures to CO have substantial beneficial potential through non-hypoxic mechanisms. This new information is also relevant to the interpretation of the epidemiological results and should be fully discussed in the ISA.
- Although the controlled human studies do demonstrate effects on the cardiovascular system, interpreting the epidemiological 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 CO provides anti-inflammatory and cytoprotective benefits through non-hypoxic mechanisms, 3) a similar pattern of epidemiologic 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 magnitude and consistency of the epidemiological associations.

REA

The first draft 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). The distribution of CO and COHb in the target population was evaluated for two CO concentration levels. The first represented current "as is" air quality. The second represented CO air quality adjusted to simulate just meeting the current CO NAAQS.

EPA staff decided not to perform a detailed exposure analysis involving multiple monitors and multiple microenvironments, as has been done in the past. In particular, EPA chose one monitor in each area to represent the ambient concentrations throughout the area. In both areas, the monitor chosen was the monitor that has consistently reported the highest CO concentrations in the area. In addition, EPA chose to model only two

broadly-defined microenvironments, "in-vehicle" and "all others." Finally, EPA chose to evaluate two exposure scenarios for each study area -- one (Scenario A) in which all microenvironmental concentrations are set equal to the ambient concentrations measured at the single fixed-site monitor and the other (Scenario B) in which the in-vehicle microenvironment is set equal to twice the ambient monitor concentrations.

AIR, Inc. feels that this approach in assessing risk due to ambient CO exposure is inadequate and unrealistic for the following reasons:

- The assumptions regarding the use of a single monitor in both cities are entirely unrealistic and defeat the purpose of using a detailed model to account for activity and movement of the subject population. They also bias the CO and COHb levels high.
- The monitoring sites EPA chose to represent CO exposures in the two study areas are clearly worst-case situations, and, as a result, further bias the results high.
- The treatment of in-vehicle exposures is also simplistic and unrealistic and biases the results for Scenario B even higher.
- EPA acknowledges some of the biases in the REA. The final key observation in Chapter 6 is that "given the considerations described above regarding the characterization of uncertainty and the tendency of the assessment approach to overestimate exposure and dose, staff finds the utility of this assessment for the purpose of considering the adequacy of the current standards to be limited."
- Even with the biases, the REA demonstrates that the current CO standards are protective of public health.

2.0 Introduction

The U. S. Environmental Protection Agency (EPA) is in the process of reviewing the National Ambient Air Quality Standards (NAAQS) for carbon monoxide (CO). EPA issued the first external review draft of the Integrated Science Assessment for Carbon Monoxide[1] (ISA) in December 2008 and AIR, Inc. provided comments[2] on that document. EPA has now issued the second external review draft of the ISA[3] and the first external review draft of the Risk and Exposure Assessment to Support the Review of the Carbon Monoxide Primary National Ambient Air Quality Standards (REA)[4]

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[1] U. S. Environmental Protection Agency. (2009). First external review draft of the Integrated Science Assessment for Carbon Monoxide. EPA/600/R-09/019.March 2009.

[2] Heuss J; Wolff G. (2009). Review and Critique of the U. S. Environmental Protection Agency's First External Review Draft of the Integrated Science Assessment for Carbon Monoxide. Air Improvement Resource, Inc. report prepared for The Alliance of Automobile Manufacturers. May 1, 2009.

[3] 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.

[4] U. S. Environmental Protection Agency. (2009). First external review draft of the Risk and Exposure Assessment to Support the Review of the Carbon Monoxide Primary National Ambient Air Quality Standards. EPA-452/P-09-008.October 2009.

As indicated in the second 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,[5] but did not complete the review at that time.

The second 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 combined evidence from controlled human exposure studies and epidemiologic studies indicates that a causal relationship is likely to exist between relevant short-term CO exposures and cardiovascular morbidity, particularly in individuals with coronary artery disease. The evidence for other health endpoints is described as weaker, either suggestive or inadequate to determine causality. Since the release of the first draft ISA in March, 2009, a large, multi-city epidemiological study which related ambient CO concentrations to emergency hospital admissions of patients 65 years of age and older for cardiovascular diseases (CVD) was published by Bell et al., 2009.[6] This study is the first national-scale U.S. study of CO and hospital admissions for cardiovascular disease. As a result, AIR Inc. has conducted an in-depth review of the Bell et al. study.

The first draft REA, using a similar but simplified approach to that used in prior CO NAAQS reviews, estimated CO exposures and resulting doses of COHb for the population of residents with coronary heart disease in two urban study areas (Denver and Los Angeles) associated with CO levels representing recent air quality and air quality adjusted to simulate just meeting the current CO NAAQS.

AIR Inc. reviewed the second draft ISA and the first draft REA focusing on the evidence regarding acute cardiovascular morbidity effects and the integrative synthesis of that evidence as it relates to the conclusions of the documents. In the following sections, ISA comments are provided on (1) the epidemiological evidence concerning associations of CO with emergency hospital admissions for cardiovascular disease, with emphasis on the

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[5] U. S. Environmental Protection Agency. (2000). Air Quality Criteria for Carbon Monoxide. EPA/600/R-99/001F.

[6] Bell M.L., Peng R.D., Dominici F. and Samet J.M. (2009). Emergency hospital admissions for cardiovascular disease and ambient levels of carbon monoxide: Results for 126 United States urban counties, 1999-2005. Circulation, 120: 949-955.

new Bell et al., 2009 study, (2) general issues with regard to the interpretation of epidemiological evidence in the CO ISA, and (3) the integrative synthesis of evidence regarding cardiovascular morbidity. In addition, REA comments are provided on (1) biases introduced by the simplifications EPA staff made in the REA compared to previous CO risk assessments, (2) the methodology EPA used to incorporate in-vehicle exposures in the risk assessment.

This report is organized into the following sections:

- ISA Comments
- REA Comments

3.0 ISA Comments

3.1 Review of New Bell et al. Paper

Since the release of the first draft on the CO Integrated Science Assessment in March, 2009, a large, multi-city epidemiological study which related ambient CO concentrations to emergency hospital admissions of patients 65 years of age and older for cardiovascular diseases (CVD) was published by Bell et al., 2009.[7] This study is the first national-scale U.S. study of CO and cardiovascular disease. The authors conclude: "Although much of the current research on health and traffic- related air pollution focuses on particulate matter, our study indicates that ambient CO and traffic may present a far larger health burden than suspected previously."

This conclusion is based on positive and statistically significant associations the authors found between ambient CO concentrations and same-day emergency admissions of those 65 years of age or older for total cardiovascular, ischemic heart, heart rhythm, heart failure and cerebrovascular causes for the pooled data set. Overall, they found a 1.01% increase in risk of total cardiovascular admissions with a 1 ppm increase in same-day 1-hour maximum CO concentrations. While this is a very small increase in risk it was found in a database with a median annual daily 1-hour maximum CO concentration of 1.3 ppm. This compares to the current 1-hour maximum National Ambient Air Quality Standard (NAAQS) of 35 ppm which cannot be exceeded more than once per year. Consequently, if the observed relationships are causal as the authors infer, a drastic reduction in the 1-hour NAAQS would likely be proposed.

As a result, AIR Inc. has conducted an in-depth review of the Bell et al. study and identified some issues that need to be addressed. Two of the issues, model selection and the existence of similar patterns for other pollutants for cardiovascular morbidity, will be discussed in a subsequent section that applies to epidemiological studies in general. Here the discussion will focus on two issues that are more specific, although not exclusively so, to the Bell et al. study. The first concerns the finding of a statistical association only

[7] Ibid.

at lag zero and a negative or not statistically significant relationship at lag one, and the second is the spatial heterogeneity of the results.

The Lag Zero Issue

For 126 urban U.S. counties, Bell et al. examined the statistical relationship between daily maximum 1-hour CO concentrations and CVD emergency admissions for patients 65 years of age and older for lag zero (admission on the same day as the exposure) and at lags of one and two days. This range of lags encompasses the lags reported in previous studies cited in the ISA.[8] As shown in Figure 2 in Bell et al., positive and statistically significant relationships were found at lag zero for total CVD, ischemic heart, heart rhythm, heart failure and cerebrovascular admissions. With a lag of one day, the relationship became negative for total CVD, ischemic heart and cerebrovascular admissions while the other two, heart rhythm and heart failure, remained positive but no longer statistically significant. This means that the effects are seen on the same day as the exposure. Since the measure used by Bell et al. is the daily 1-hour maximum concentration, the observed relationship could only be causal if the exposure preceded the hospital admission.

Information on the time of day of the hospital admissions is not available, but information on the diurnal profiles of the CO concentrations exists in the EPA air quality database. In Figure 3-33 of the ISA,[9] EPA presents mean diurnal patterns for 11 U.S. cities for the period 2005-2007. As shown in this figure, most areas experience two peaks in the hourly CO concentrations. A sharp peak corresponds to the morning rush hour and a broader peak occurs in the evening which starts at the onset of the evening rush hour but extends into the later evening hours. The morning peak dissipates quickly due to the enhanced atmospheric mixing associated with the breakup of the morning inversion and increasing daytime wind speeds. In the evening, the opposite occurs. The evening rush hour typically starts when the atmospheric ventilation rate is diminishing as the nocturnal inversion begins to form and the wind speed begins to decrease. Consequently, the CO concentrations stay elevated even as fresh emissions from rush hour decrease. Since nine of these diurnal plots of CO in Figure 3-33 contain the averages from multiple monitoring sites, the resulting diurnal patterns may not reflect the structure of individual monitoring sites. As a result one site from each of the cities (except Anchorage which was not used in the Bell et al. study) was identified that had data from the same time period (1999-2005) that was used by Bell and the diurnal patterns and the distribution of 1-hour daily maximum concentrations were examined.

The diurnal patterns for 1999-2005 are plotted in Figures 1A-J (each letter is for a different city). All sites except Seattle more or less exhibit the dual-peak diurnal pattern described above. Seattle has a broad daytime peak that starts increasing with the morning rush hour and stays high all day before it begins to decrease at 10 p.m. In addition it has a secondary peak that results in the maximum concentration at 5 p.m. It should be noted

[8] ISA, *supra* note 3, at pages 5-52 to 5-55.
[9] ISA, *supra* note 3, at page 3-74.

that Boston does not collect data during the 10 p.m. hour and Los Angeles does not collect data during the 4 a.m. hour.

In Figures 2A-J, the frequency distributions of the daily 1-hour CO concentrations as a function of the hour of the day are plotted. In general most of the sites have the highest frequency of occurrence of the daily 1-hour maximum CO concentrations in the morning during the 6 a.m. to 8 a.m. hour time frame with hour 6 a.m. or 7 a.m. being the single hour with the greatest frequency. Boston and Seattle are exceptions with both of these cities experiencing their most frequent 1-hour maximums during the evening rush hours. However, it is clear from these plots that all the cities have a high frequency of occurrence of a maximum 1-hour CO concentration some time during the evening. This is further demonstrated in Table 1, which shows the percentage of time the daily 1-hour maximum concentration occurs during different time intervals throughout the day in the cities. For all the cities, between 7.5% and 26.1% of the daily 1-hour CO maxima occur in the last 3 hours of the day, 25.6 to 42.7% occur in the last 6 hours of the day, and 34.7 to 50.8% occur in the last 9 hours of the day. It is not plausible to expect that all the individuals who are exposed during these periods and experience a CVD incident would make it into the emergency room before midnight of the same day. Consequently there should be some carryover into the next day.

Figures 1A to 1J: Average hourly CO concentrations

Figure 1A

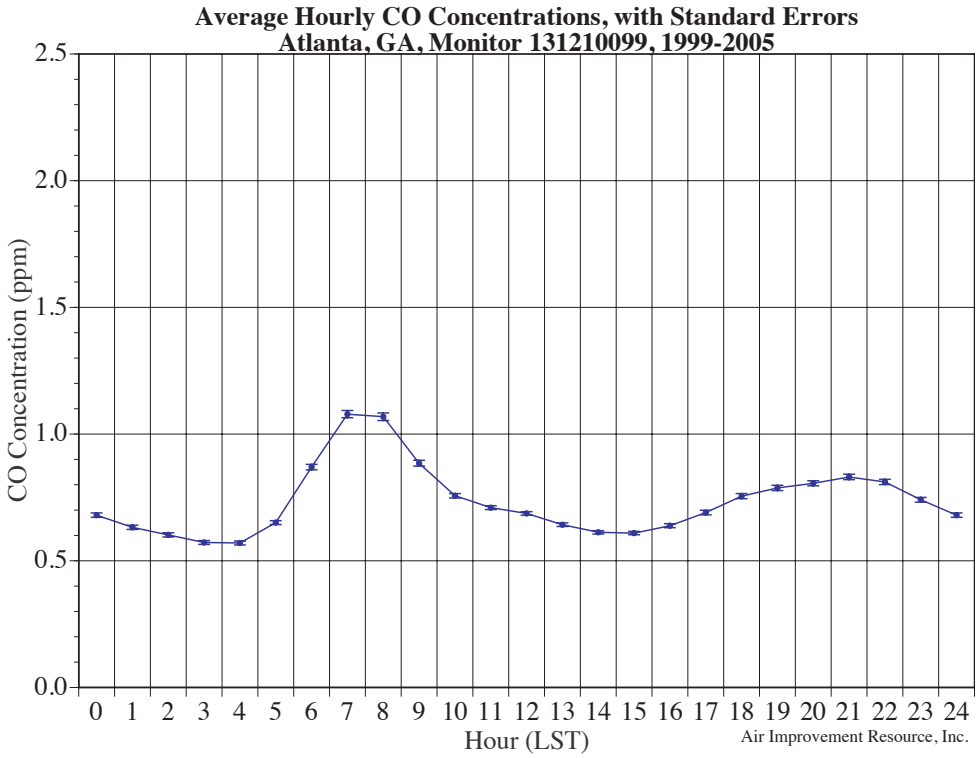


Figure 1B

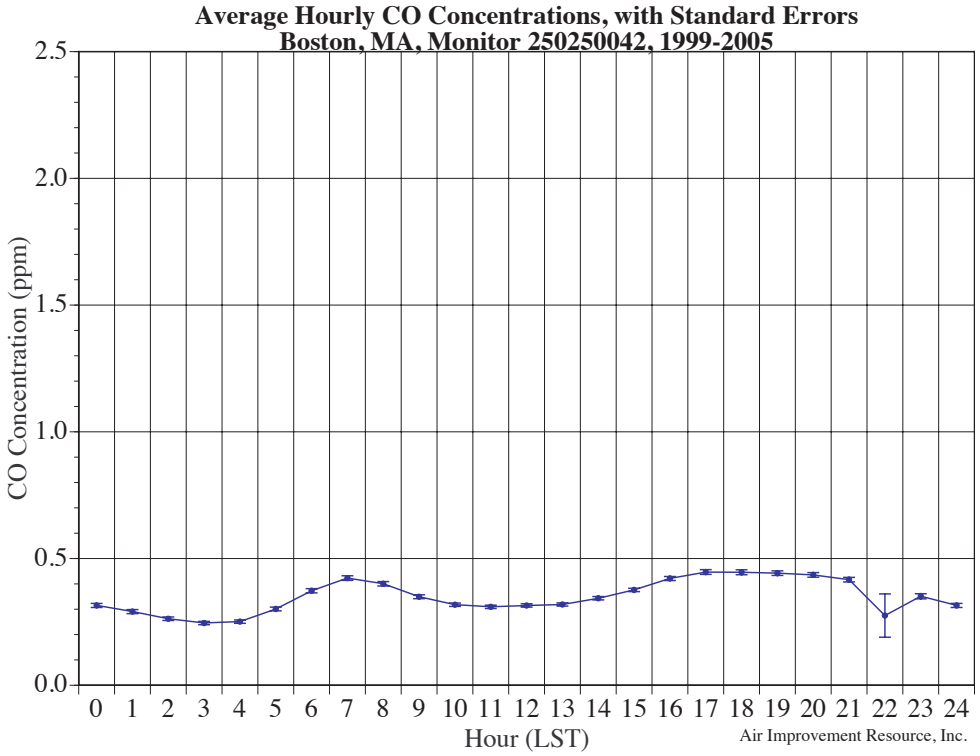


Figure 1C

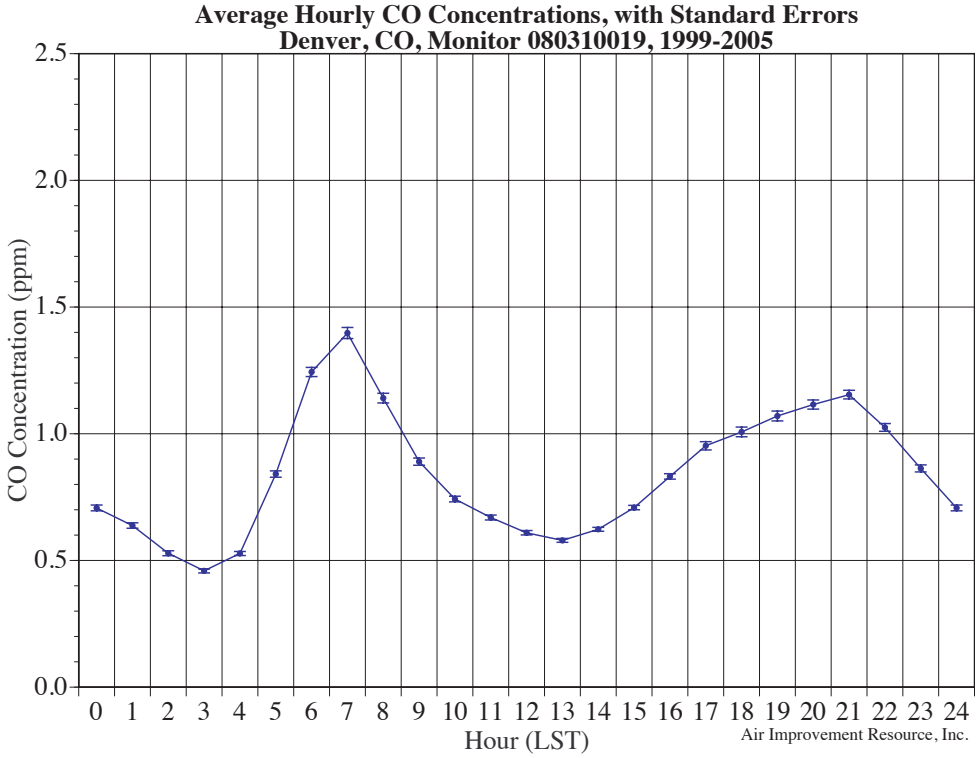


Figure 1D

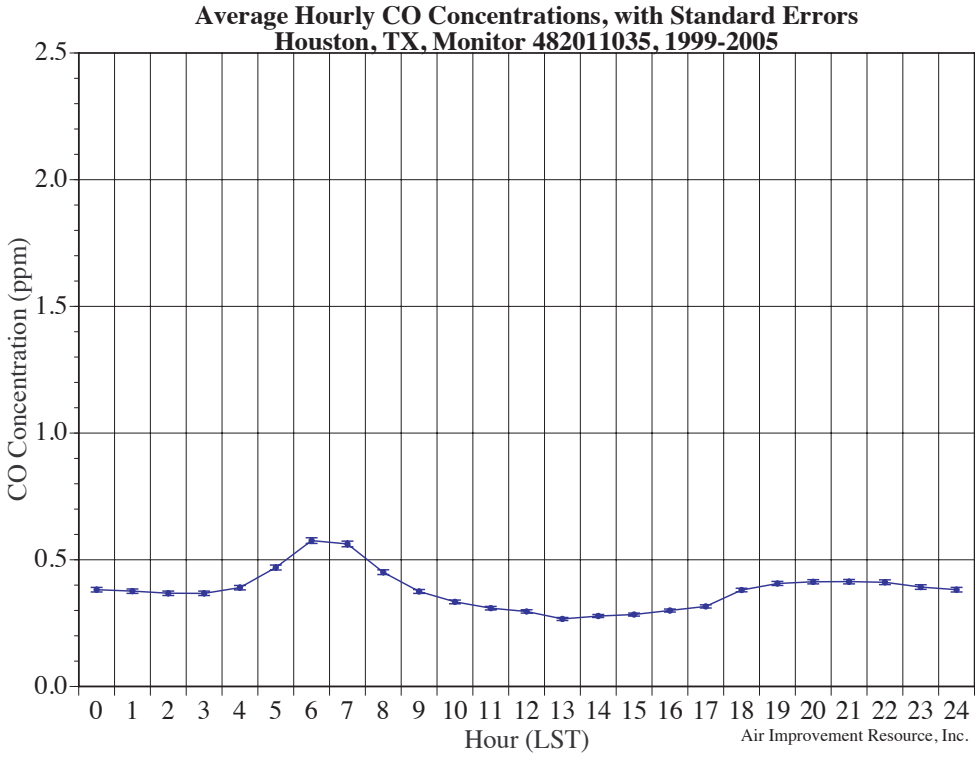


Figure 1E

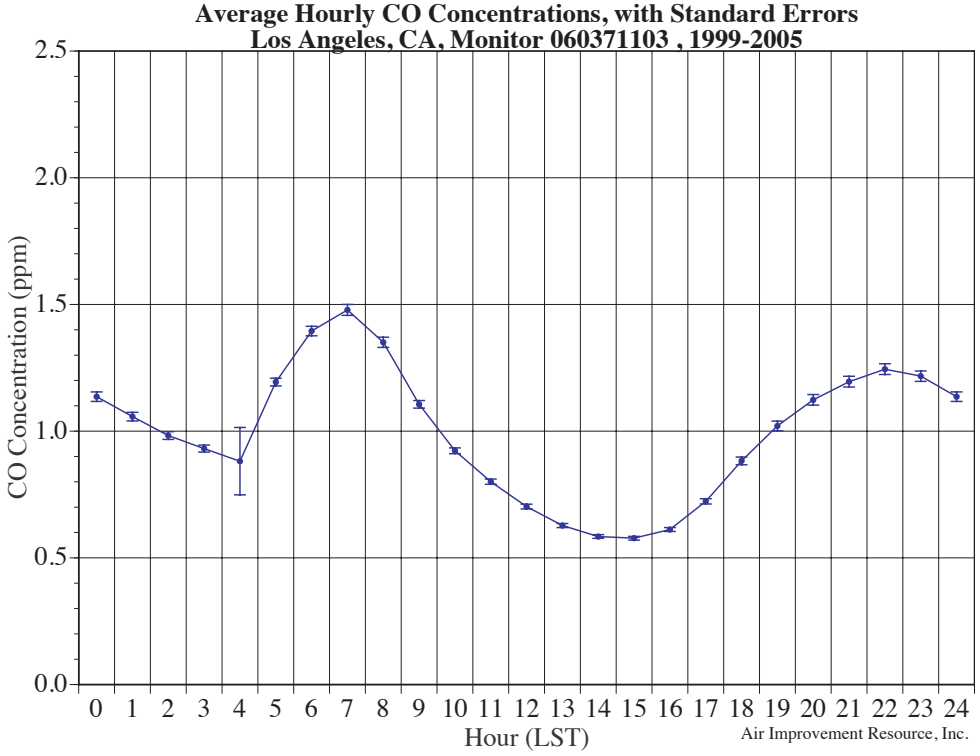


Figure 1F

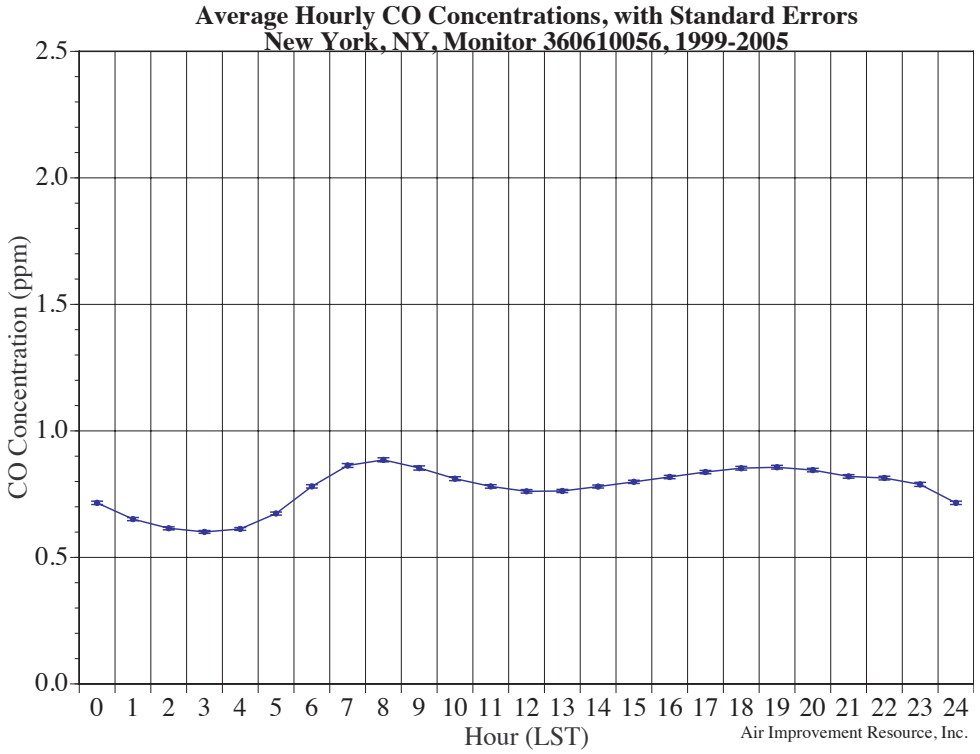


Figure 1G

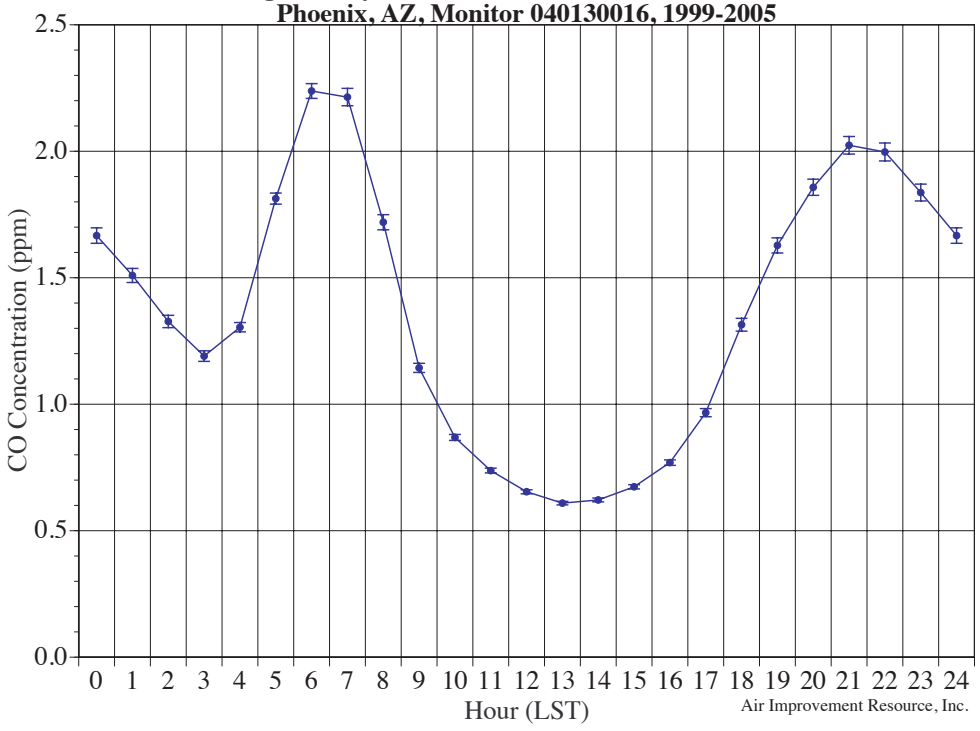


Figure 1H

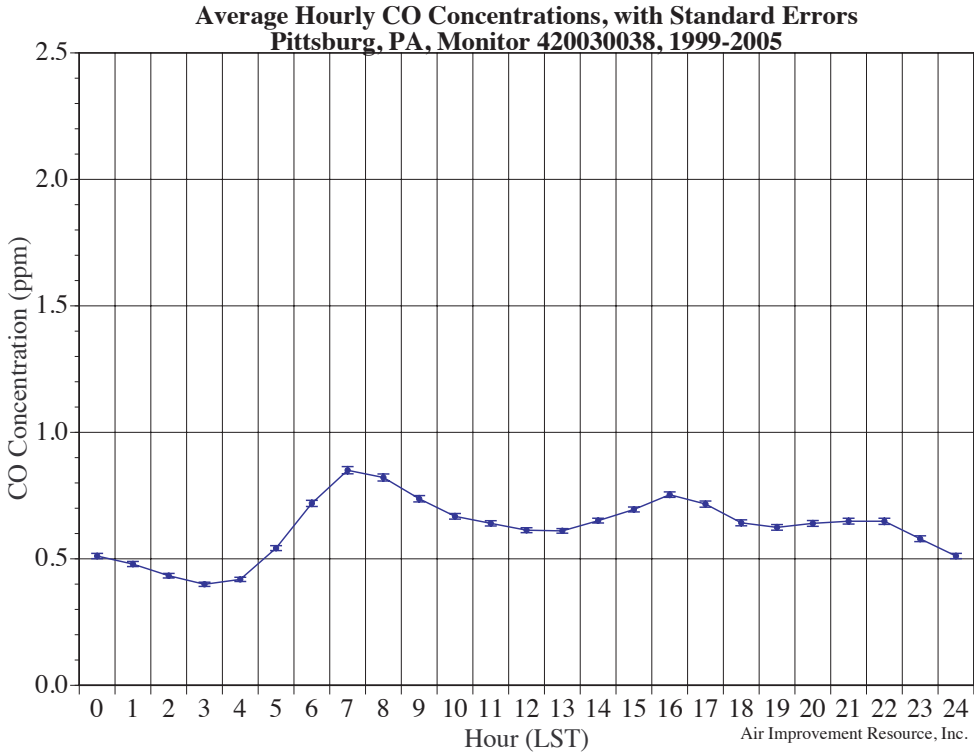


Figure 1I

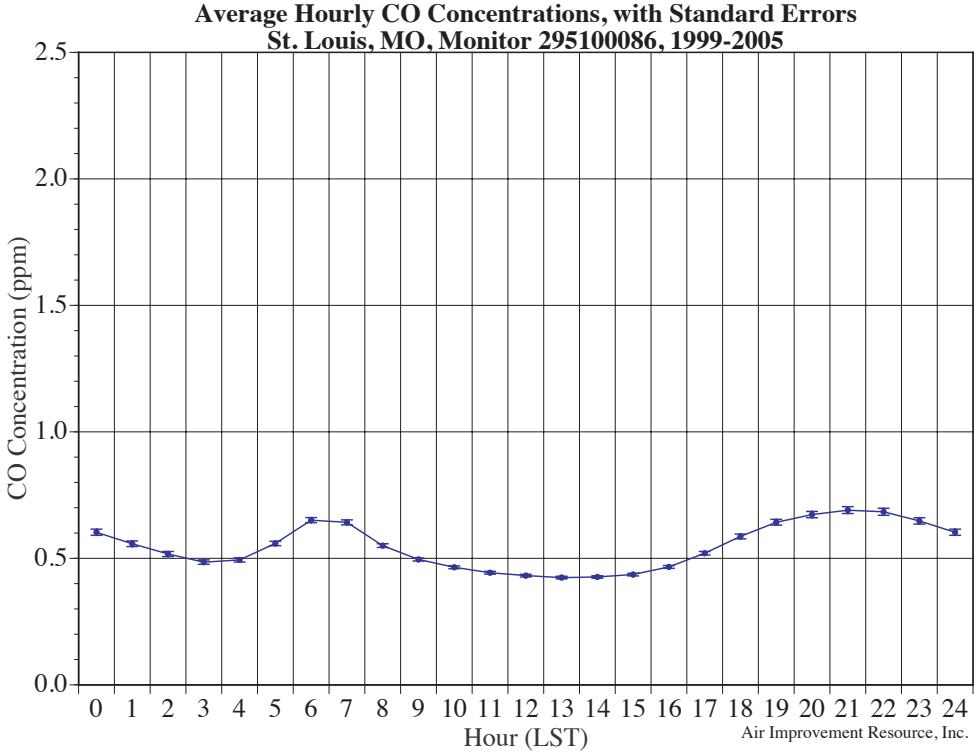
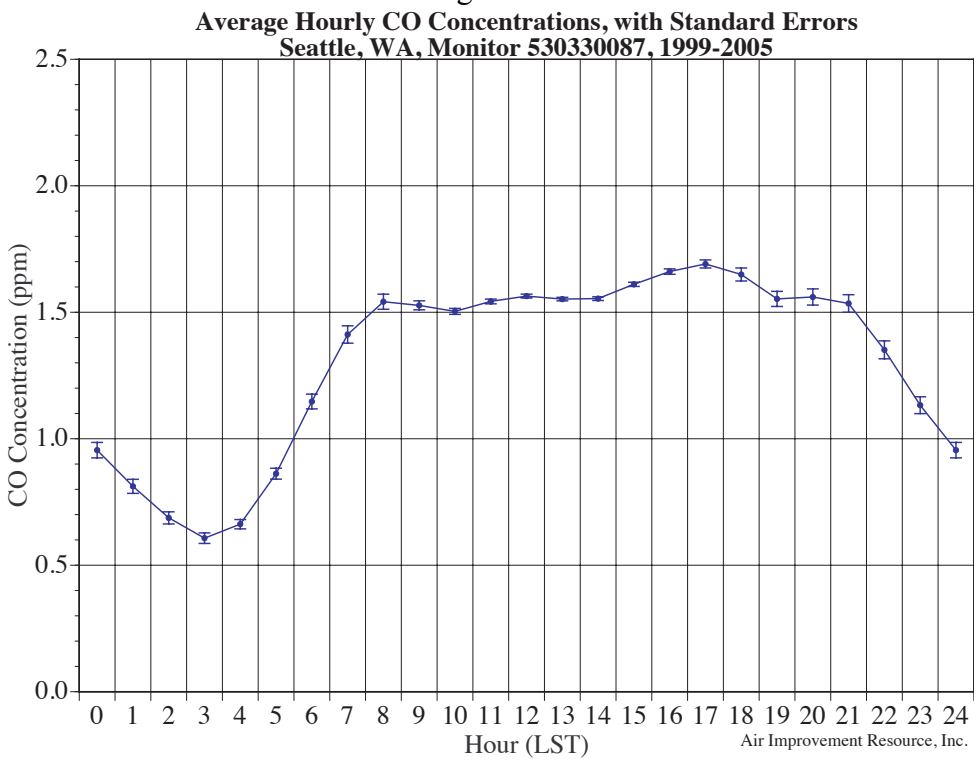


Figure 1J



Figures 2A to 2J: Frequency of occurrence of the Daily Maximum 1-hour CO

Figure 2A

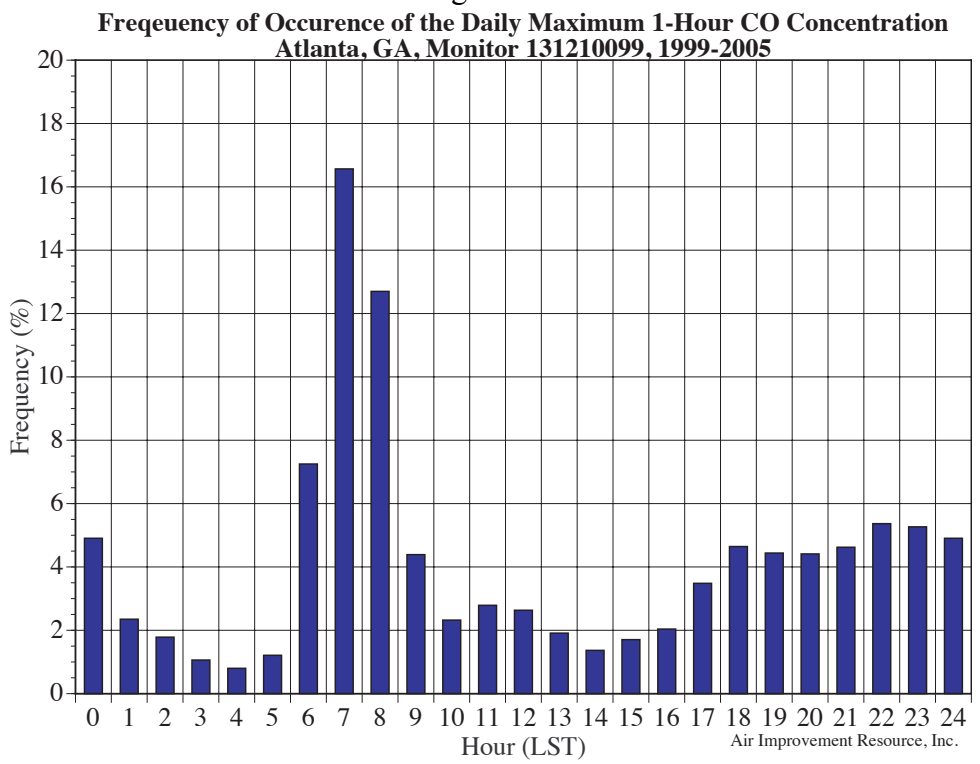


Figure 2B

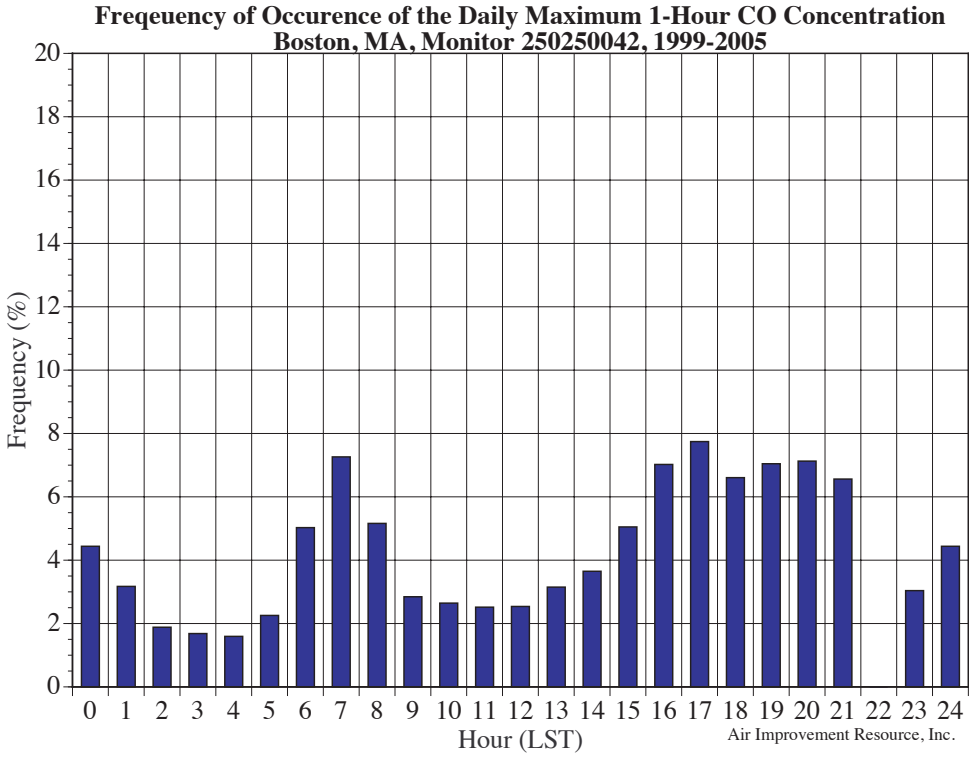


Figure 2C

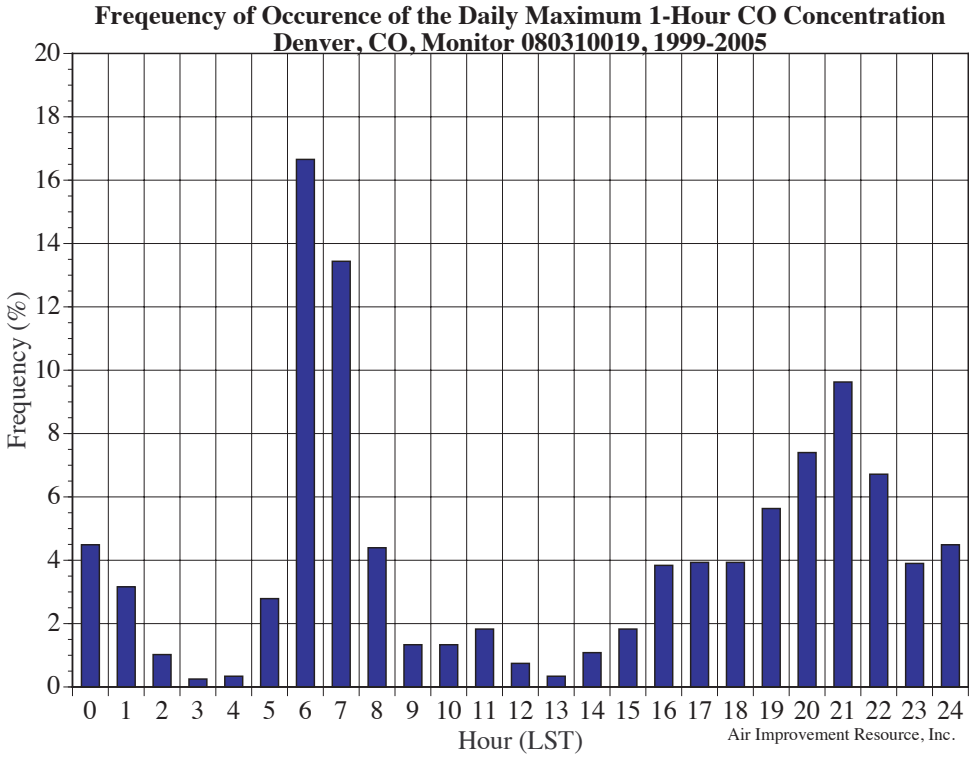


Figure 2D

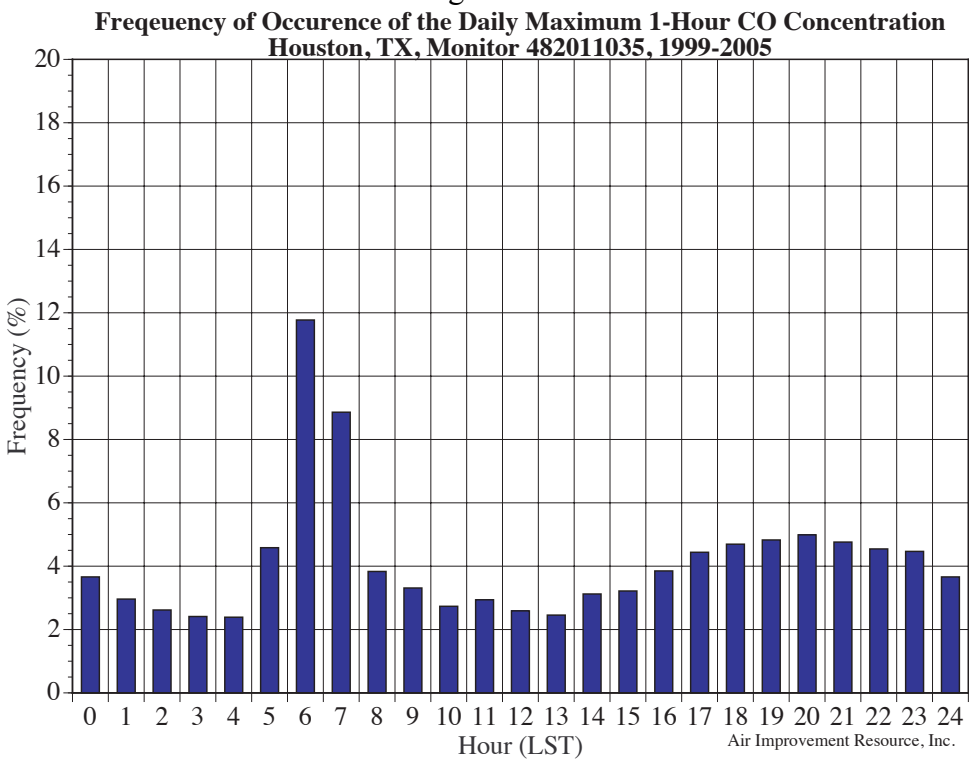


Figure 2E

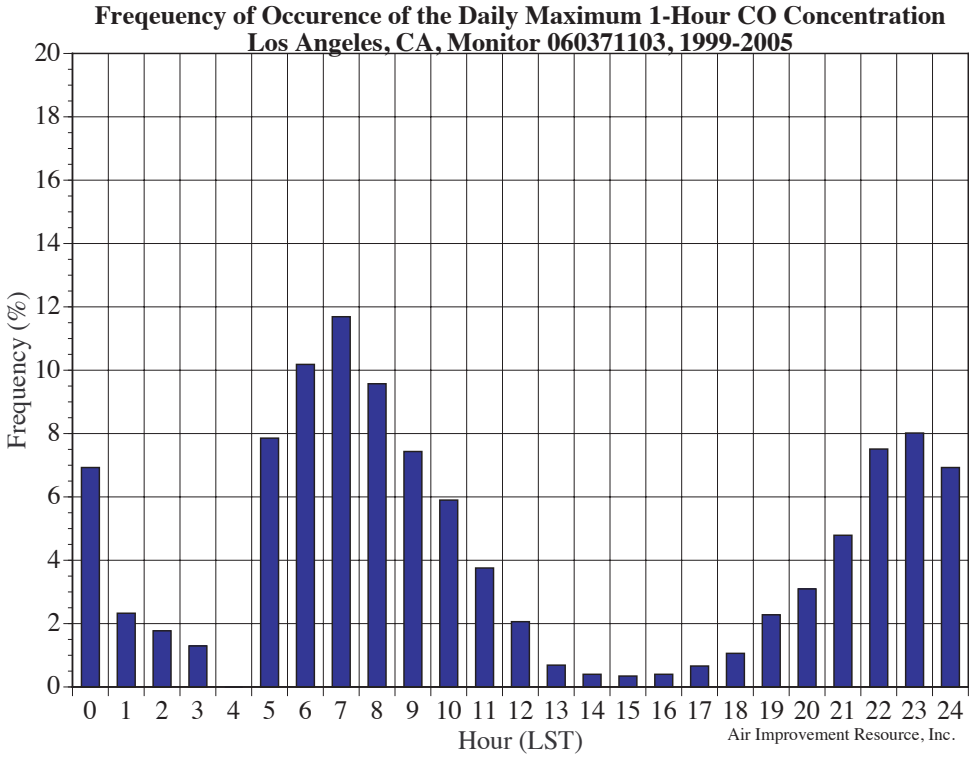


Figure 2F

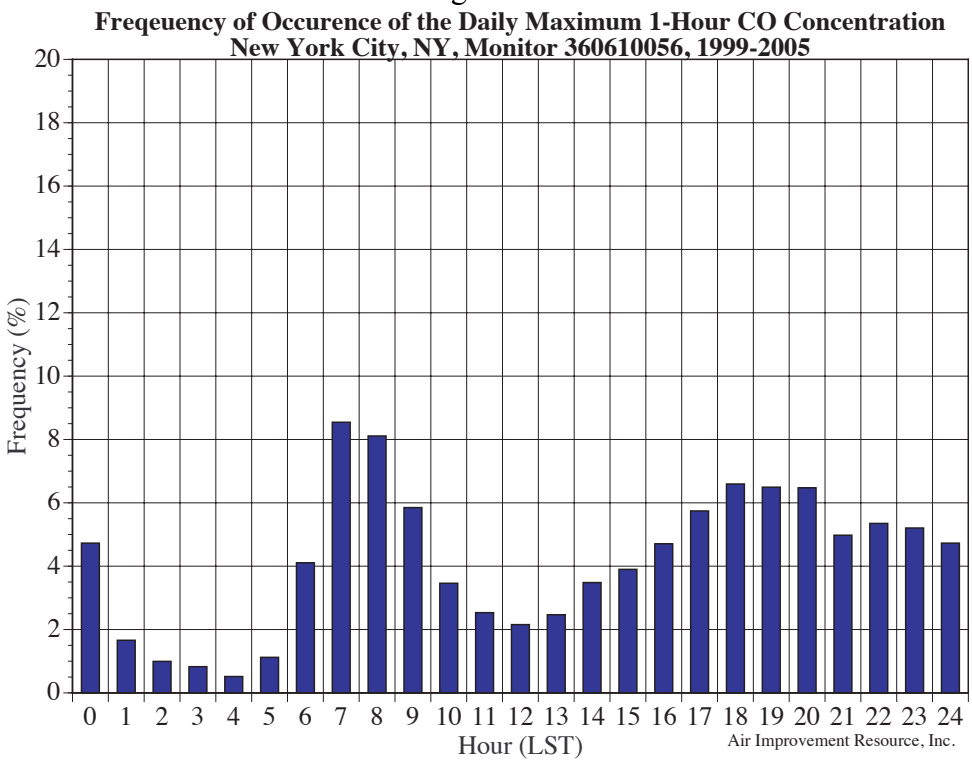


Figure 2G

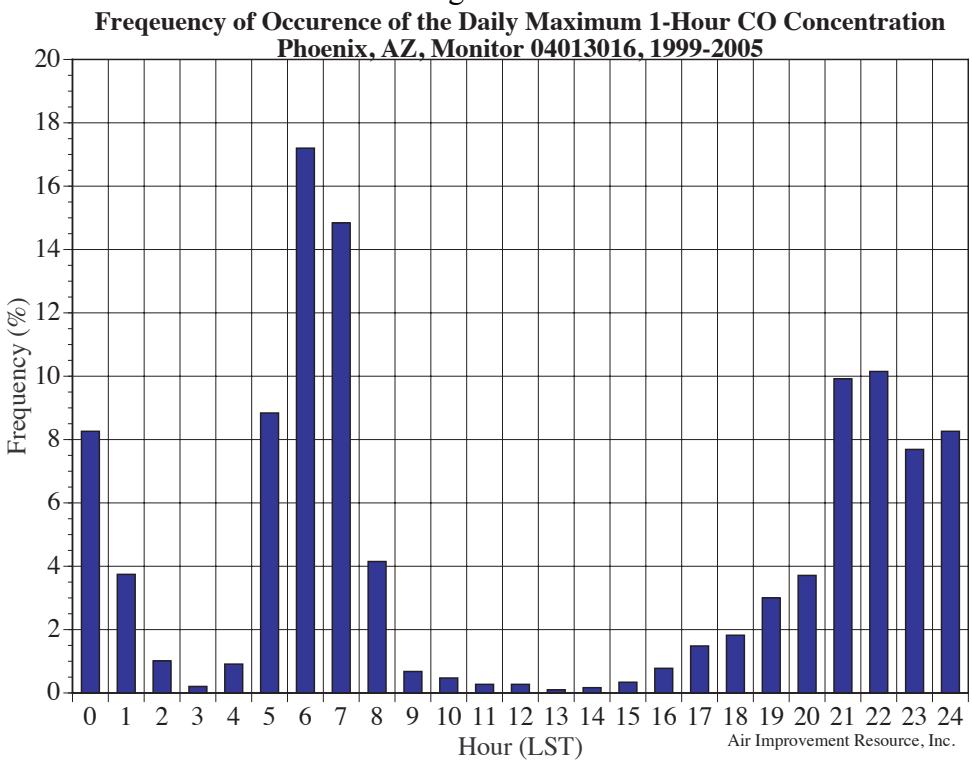


Figure 2H

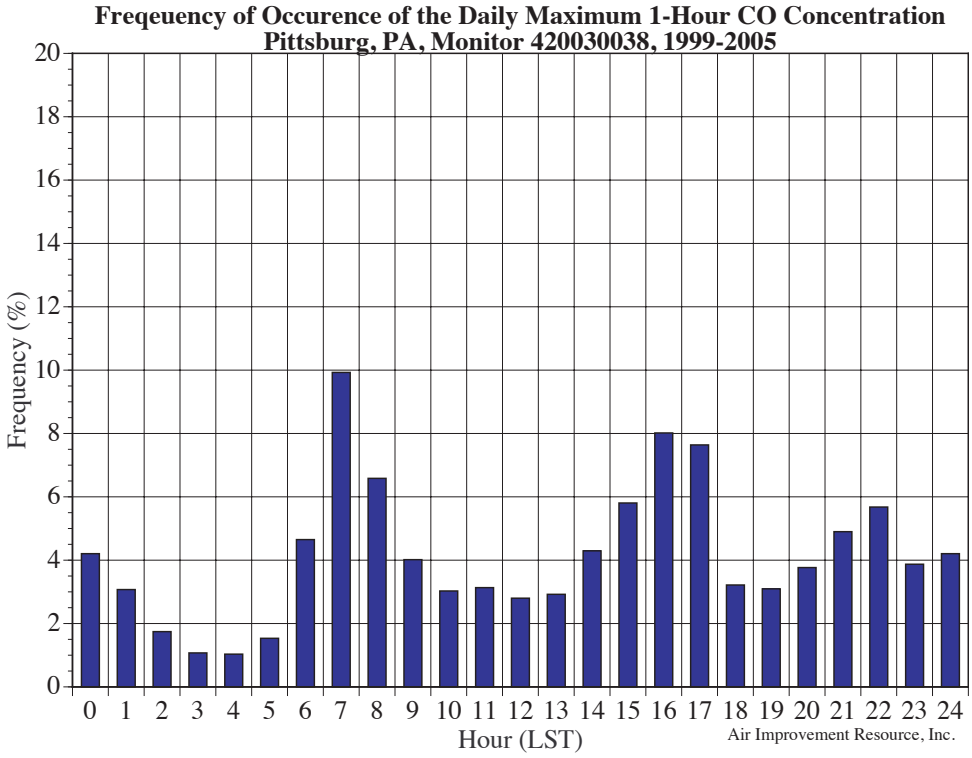


Figure 2I

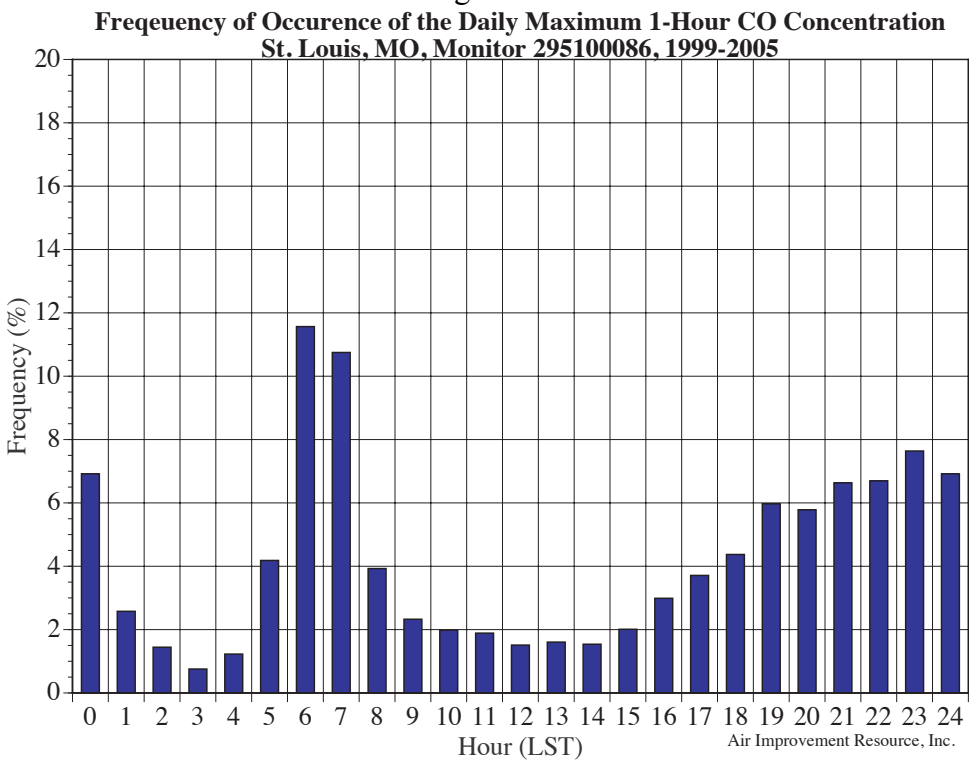


Figure 2J

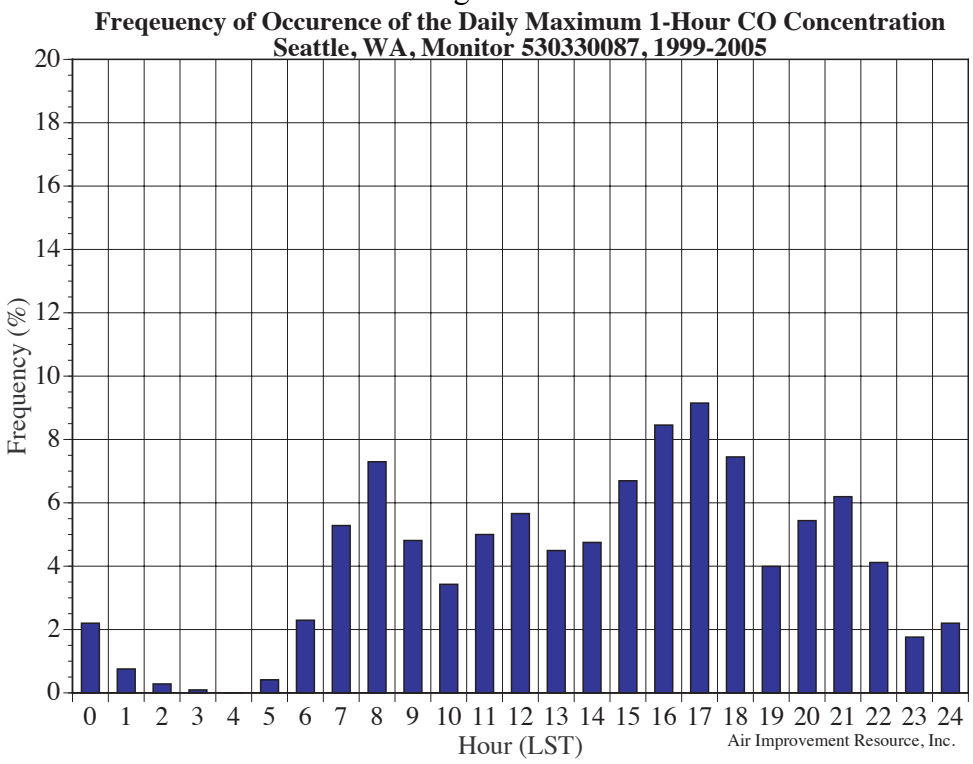


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Table 1. Percentage of time the daily 1-hour maximum CO concentration occurs during different time intervals

City	6 to 8	16 to 18	19 to 21	22 to 24	16 to 21	16 to 24	19 to 24
Atlanta	36.5	10.2	13.5	15.5	23.7	39.2	29
Boston	17.5	21.4	20.7	7.5	42.1	49.6	28.2
Denver	34.5	11.7	22.7	15.1	34.4	49.5	37.8
Houston	24.5	13	14.6	12.7	27.6	40.3	27.3
LA	31.4	2.1	10.2	22.4	12.3	34.7	32.6
NY	20.8	17	17.9	15.3	34.9	50.2	33.2
Phoenix	36.2	4.1	16.6	26.1	20.7	46.8	42.7
Pittsburgh	21.2	18.9	11.8	13.8	30.7	44.5	25.6
St Louis	26.2	11.1	18.4	21.3	29.5	50.8	39.7
Seattle	14.9	25.1	15.6	8.1	40.7	48.8	23.7

Health effects induced by CO exposures are due to the CO binding with a number of heme-containing compounds, mainly the hemoglobin, in the bloodstream. This is not an instantaneous process and depends on many factors. This process is described in the ISA:[10]

> The flow of CO between the blood and alveolar air or tissues is controlled by diffusion down the pCO gradient. The uptake of CO is governed not only by this CO pressure differential, but also by physiological factors, such as minute ventilation and lung diffusing capacity, that can, in turn, be affected by conditions such as exercise, age, and health. …Altitude also increases the endogenous production of CO through upregulation of HO-1. CO is considered a second messenger and is endogenously produced from the catabolism of heme proteins by enzymes such as HO-1. A number of diseases and conditions affect endogenous CO production, possibly causing a higher endogenous COHb level. Finally, CO is removed from the body by expiration or oxidation to CO_2.

The kinetics of the process are illustrated in Figure 4-4 of the ISA.[11] This figure shows that exposure to increased CO concentrations causes the carboxyhemoglobin (COHb) to immediately begin rising and this rise continues as long as the high exposure persists. The rate of rise as well as the absolute value of the rise is a function of the ambient CO concentration. At an exposure to 50 ppm the rate is rapid and the absolute value is on the order of 0.8 % over the 1-hour exposure illustrated in Figure 4-4. At an exposure to 10 ppm CO, the rate of rise is much slower and the absolute rise is less than 0.2%. However at an exposure to 2 ppm CO, which is more representative of today's ambient exposures, both the rate of rise and the incremental COHb increase are nearly imperceptible. In any event, a lag will exist between the onset of the exposure and the maximum COHb level and the onset of any cardiac symptoms.

Besides the lag between exposure and symptoms, Stieb et al., 2000[12] have identified a lag between the onset of symptoms and the time of arrival in the emergency department. Among the cardiac admissions, only 50% are admitted on the same day as the onset of any symptoms and the average time between onset and the same-day admission is 19 hours. About 20% wait one to three days while the remainder will wait longer. When the symptoms are finally perceived by the patient as warranting an emergency room visit, it still takes an average of 5 hours to be admitted.

Both the kinetics of COHb formation and the documentation that there is a lag between the onset of symptoms and the emergency department admissions clearly indicates that an evening exposure to a CO concentration that will cause a serious cardiac event will result in an increase in emergency admissions on the next calendar day. Consequently, the lack of a relationship between CO and admissions at lag one (the day after exposure) is not

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[10] ISA, *supra* note 3, at pages 4-33 to 4-34.
[11] ISA, *supra* note 3, at page 4-11.
[12] Stieb, D.M. et al, (2000). Beyond administrative data: Characterizing cardiorespiratory disease episodes among patients visiting the emergency department. Canadian J. of Public Health. 91: 107-112.

consistent with a causal relationship. This applies not only to Bell et al. but also to all of the other studies cited by EPA that identify positive associations at only same day lags.

Heterogeneity of Results

Nationwide multi-city air pollution epidemiology studies in the U.S. are based on the template developed in National Morbidity, Mortality, and Air Pollution Study (NMMAPS).[13] Under this template, the results for individual cities grouped by geographic region were presented for each pollutant. This revealed the city-to-city variations in the associations and the heterogeneity of results by geographic region.

Unfortunately, Bell et al. do not present their individual city results so a geographical analysis is not possible. However, Figures IIa-d in their online-only Data Supplement show plots of the percent increase in the risk of total CVD hospital admissions per 1 ppm increase in same day 1-hour maximum CO for the individual counties with and without adjustments for co-pollutants. What these reveal is that for subsets of the counties that had concurrent measurements of nitrogen dioxide (NO_2), $PM_{2.5}$ or elemental carbon (EC), there was considerable heterogeneity among the risk estimates. The individual county estimates for the CO alone analysis (in counties that had data for both CO and NO_2) ranged from -1% to +4% with approximately 12% of the counties exhibiting a negative risk. With an adjustment for NO_2, 23% of the counties show a negative risk and the range of risks is -2.5 to +4. When the CO estimates are adjusted for $PM_{2.5}$, the range becomes -1.3 to +3.2 with 15% of the counties showing a negative risk. When an adjustment is applied for both NO_2 and $PM_{2.5}$, 24% of the CO risks become negative and the range becomes -2.1 to 4.3. Finally when they adjust for EC, 28% of the counties exhibit a negative risk and the range of risk estimates increases to -28% to +12. These wide ranges of estimates are not plausible, and the negative results for many counties imply a protective effect for CO. Unfortunately, Bell et al. did not include 95% confidence intervals, as is customary with multi-city studies,[14] so it is not possible to determine how many of the individual county estimates are statistically significant. However, based on NMMAPS, few would be expected to be statistically significant.

Summary of comments on Bell et al., 2009

The diurnal CO concentration patterns that are observed in U.S. cities indicate that a high frequency of peak 1-hour maximum CO concentrations occur in the evening hours up to midnight. If CVD hospital admissions are caused by these peaks, there should be some carryover effect of CO exposure on hospital admissions into the next day. Both the kinetics of COHb formation and the documentation that there is a lag between the onset of symptoms and the emergency department admissions clearly indicate that an evening exposure to a CO concentration that will cause a serious cardiac event will result in an

[13] Samet J.M., Zeger S.L., Dominici F., Curriero F., Coursac I., Dockery D.W., Schwartz J., and Zanobetti A. (2000). The National Morbidity, Mortality, and Air Pollution Study Part II: Morbidity and Mortality from Air Pollution in the United States, Health Effect Institute, Number 94, Part II.
[14] Ibid.

increase in emergency admissions on the next calendar day. The Bell et al. study does not see such a carryover effect. The only statistically significant relationship they report between daily 1-hour maximum CO and CVD admissions is for the same day as the exposure. In fact, for 4 of the 6 CVD endpoints they studied including total CVD admissions, the 1-day lag relationship was negative, and in no case was it statistically significant. The lack of a next day relationship does not support the relationship on the same day as being causal.

Further the heterogeneity of the individual county risk estimates, including many that are negative, and the authors' failure to report the statistical significance of the individual county estimates raises doubts concerning the applicability of a single pooled risk estimate to the entire U.S.

3.2 General Comments on Epidemiology

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.

Model selection uncertainty is not fully acknowledged in the ISA

In interpreting the epidemiological evidence for cardiovascular morbidity, the draft downplays major 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.[15]

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 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).[16]

Smith et al. note that Lumley and Sheppard, 2000[17] 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. [18] 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"[19] 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[20] 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

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

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

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

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

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

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

external sources regarding the appropriate degrees of freedom to use. Such information, however, simply does not exist.

There are examples in the literature showing that the choice of the smoothing algorithm can change the results substantially. Klemm and Mason, 2003[21] showed that the degree of association of coarse PM with mortality was substantially affected by the choice of temporal smoothing algorithm. Using the data from the Schwartz, Dockery and Neas, 1996 analysis of six Eastern cities, Klemm and Mason showed that with a greater number of degrees of freedom, the association for fine PM was substantially reduced and the association for coarse PM became zero or negative. Klemm et al., 2004[22] in an analysis of fine and coarse PM and other air pollutants in Atlanta showed that are "substantial differences in terms of mean effects and statistical significance depending on the number of knots used to smooth time." Klemm et al., 2004 conclude that:

> Results can differ significantly across model specifications. We believe it is very important to consider a comprehensive set of models in future analyses, and the results of all analyses should be presented and considered in subsequent inferences.

With regard to uncertainty due to model selection, the Koop and Tole, 2004[23] 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. 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

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[21] Klemm RJ; Mason R. (2003). Replication of reanalysis of Harvard Six-City mortality study. in Health Effects Institute Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health, pp.165-172.

[22] Klemm RJ; Lipfert FW; Wyzga RE; Gust C. (2004). Daily mortality and air pollution in Atlanta: two years of data from ARIES. Inhal Toxicol, 16 Suppl 1: 131-141.

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

intervals were arrived at by a number of prior model specification searches, eliminating some worse fitting models, the true interval may well be wider."[24]

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 first draft CO ISA was essentially silent on this issue (and any changes in the relevant science). The second draft does acknowledge the model selection issue with regard to mortality and respiratory morbidity, noting for example:

> The majority of this literature does not report results of extended analyses to examine the potential influence of model selection, effect modifiers, or confounders on the association between CO and respiratory morbidity. The lack of copollutant models, specifically, has contributed to the inability to disentangle the effects attributed to CO from the larger complex air pollution mix (particularly motor vehicle emissions), and this creates uncertainty in interpreting the results observed in the epidemiologic studies evaluated.[25]

These cautions apply equally to cardiovascular morbidity and other health endpoints. The final ISA must acknowledge and address the uncertainty due to model selection as it affects the interpretation of epidemiological result for all the health endpoints evaluated.

Publication bias is acknowledged in Chapter 1 but then not discussed in the integrative synthesis

Publication bias is another major issue in interpreting air pollution epidemiology. The commentary by Goodman concerning meta-analyses is particularly insightful.[26] 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[27] concluded that "taken together, the meta-analyses provide evidence of a disturbingly large publication bias and model selection bias."

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[24] U. S. Environmental Protection Agency. (2004). Air Quality Criteria for Particulate Matter, Volume I. EPA/600/P-99/002aF; Volume II,.EPA/600/P-99/002bF. page 8-226.
[25] ISA, *supra* note 3, at pages 2-13, 5-143, and 5-144.
[26] Goodman S. (2005). The Methodologic Ozone Effect. Epidemiology. 16: 430-435.
[27] Report of a Working Conference. (2007). Critical Considerations in Evaluating Scientific Evidence of Health Effects of Ambient Ozone. Rochester, New York. June 2007.

Similarly, Anderson et al., 2005[28] 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-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[29] that the summary of health effects evidence is vulnerable to the errors of publication bias and multiple testing. The only reference in the first draft CO ISA to publication bias was found on page 5-120 in a discussion of the multi-city studies. In the second draft the following paragraph was added to Chapter 1.

> Publication bias is a source of uncertainty regarding the magnitude of health risk estimates. It is well understood that studies reporting non-null findings are more likely to be published than reports of null findings, and publication bias can also result in overestimation of effect estimate sizes (Ioannidis, 2008). For example, effect estimates from single-city epidemiologic studies have been found to be generally larger than those from multicity studies (Anderson et al., 2005). Although publication bias commonly exists for many research areas, it may be present to a lesser degree for epidemiologic studies on CO. In general, epidemiologic studies have focused on the effects of PM, and CO was largely considered as a potentially confounding copollutant of PM; thus, CO effect estimates may have been presented in these studies regardless of the statistical significance of the results.[30]

Although EPA suggests that publication bias may be present to a lesser degree in epidemiologic studies on CO, the rationale offered to support the contention ignores the fact that many studies evaluated CO within a suite of air pollutants and some other studies focused on CO.

The ramifications of publication bias in environmental epidemiology are substantial. Ioannidis, 2005[31] points out that the smaller the effect sizes in a scientific field, the less likely the research findings are to be true. He notes that if the true effect sizes are very small in a scientific field, this field is likely to be plagued by almost ubiquitous false

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[28] Anderson H; Atkinson R; Peacock J; Sweeting M; Marston L. (2005). Ambient Particulate Matter and Health Effects: Publication Bias in Studies of Short-Term Associations. Epidemiology. 16: 155-163.

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

[30] ISA, *supra* note 3, at page 1-22.

[31] Ioannidis J. (2005). Why most published research findings are false. PLoS Med. 2(8): e124.

positive claims. Ioannidis indicates that the greater the flexibility in designs, definitions, outcomes, and analytical modes in a scientific field, the less likely the research findings are to be true. He points out that flexibility increases the potential for transforming what would be "negative" results into "positive" results, introducing bias. Although Ioannidis addresses general issues in scientific research, the concerns and cautions he draws attention to apply directly to air pollution epidemiology where effect sizes are very small and model selection uncertainty provides the flexibility that can introduce a positive bias in the results.

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, not only in the introduction.

The pattern of acute associations is remarkably similar for all the criteria pollutants

Another issue that needs to be acknowledged and discussed in the final ISA 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. There are two aspects of the patterns that merit consideration. The first is that there is a similar pattern of results for each of the criteria pollutants in the published literature. The second is that, in systematic analyses such as multi-city studies, not only is the pattern similar for each of the criteria pollutants, but the range of associations is very wide, from positive to negative. There are important implications from each of these patterns.

As EPA has considered each criteria pollutant in turn, single-pollutant model results have been used to estimate the strength and consistency of association. 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 acute health effects caused by the pollutant under consideration. Single-pollutant associations are plotted in the draft CO ISA[32] to implicate CO as causing cardiovascular hospital admissions. In a similar manner, single-pollutant associations with PM,[33] ozone, [34] NO_2,[35] and SO_2[36] have been used recently as evidence of cardiovascular hospital admissions associated with these pollutants. Visual inspection of the figures referenced below reveals a remarkably similar pattern. The associations selected from the literature are generally small and positive but there is an occasional negative association and a few strongly positive associations. If there are multi-city studies, only the combined association is

[32] ISA, *supra* note 3, at pages 2-21, 5-37, and 5-46.
[33] U. S. EPA. (2009). Second External Review Draft Integrated Science Assessment for Particulate Matter. EPA 600/R-08/139B. Pages 6-98, 6-103, and 6-109.
[34] U. S. EPA. (2006). Air Quality Criteria for Ozone and Related Photochemical Oxidants. EPA 600/R-05/004aF. February 2006. Page 7-81.
[35] U. S. EPA. (2008). Integrated Science Assessment for Nitrogen Oxides: Health Criteria. EPA 600/R-08/071. July 2008. Pages 3-47 and 3-48.
[36] U. S. EPA. (2008). Integrated Science Assessment for Sulfur Oxides: Health Criteria. EPA 600/R-08/047F. September 2008. Page 3-40.

shown. The individual-city associations in multi-city studies are not shown. Where there are multiple lags, the result for the lag with the strongest association is shown.
In AIR comments on the first draft CO ISA[37] we provided another example – where EPA has used figures displaying the data to implicate four different pollutants in respiratory morbidity. Those figures are also remarkably similar.

There is additional evidence for similar acute pollutant associations for all the criteria pollutants. Stieb et al.[38] 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 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 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.

The similar patterns raise two issues. First, claiming health effects for each pollutant based on single-pollutant models raises the issue of double-, triple-, or even quadruple-counting of health effects. Second, as the air quality standard for each pollutant is reviewed in turn, the current practice of compiling all the strongest specific single-pollutant associations for that pollutant results in a false appearance of strength and 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.

In systematic analyses, there is not only a similar pattern for each of the criteria pollutants, but the magnitude of the associations cover a wide range from negative to positive. A remarkably 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.[39] While there are some inverse or negative air

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[37] Heuss and Wolff (2009), *supra* note 2, at page 7.
[38] Stieb D; Judek S; Burnett R. (2002). 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; Stieb et al., (2003). J. Air & Waste Management Association. 53: 258-261.
[39] 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

pollution associations reported in the literature (implying an unlikely protective effect from exposure to the pollutant), the NMMAPS study shows that there are actually many more "negative" associations in the multi-city data than reported in the single-city literature. For example, Dominici et al.[40] acknowledge that the city-specific maximum likelihood estimates from their study of the 88 largest U. S. cities range from - 4 % to + 4 % per 10 $\mu g/m^3$ increase in PM_{10}.

An implausibly wide range, from strongly positive to strongly negative, is present in all multi-city studies that report the individual-city associations. The Bell et al., 2009 study of CO and cardiovascular admissions discussed in detail above is one example. The Medina-Ramon et al., 2006[41] study of respiratory hospital admissions in 36 U. S. cities is another example. Medina-Ramon et al. show that a 10 $\mu g/m^3$ increase in PM10 is associated with anywhere from a 10 % increase to a 10 % decrease in chronic obstructive pulmonary disease (COPD) admissions in individual cities in a single-pollutant model. For pneumonia admissions, the ranges were almost as wide. In addition, they show that a 0.010 ppm increase in ozone is associated with anywhere from a 10 % increase to a 10 % decrease in COPD admissions in individual cities.

The presence of such a wide range in multi-city studies indicates that there are a substantial number of false positives and false negatives in the individual-city 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 tend to be reported in 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 individual-city data than heretofore thought.

Additional evidence for substantial stochastic variation comes from a Health Effects Institute study[42] that evaluated coherence between the time-series associations of mortality and hospital admissions in 14 cities. That study found little or no coherence between the PM_{10} mortality and morbidity associations and, importantly, found little or no correlation between the time series of health event counts (mortality and hospital admissions) in the various cities. As in other multi-city studies, the individual associations for mortality and morbidity covered a wide range from positive to negative.

There is also evidence for substantial stochastic variability and similar patterns from a systematic analysis of one city. When the statistical issues with the General Additive

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that was evaluated. This data was also provided to EPA and CASAC during the PM review process; Heuss J. (2003). Comments on the 4th Draft Criteria Document for Particulate Matter. AIR, Inc. comments prepared for the Alliance of Automobile Manufacturers. August 20, 2003.

[40] Dominici F. et al. (2003). National Maps of the Effects of Particulate Matter on Mortality: Exploring Geographic Variation. Environmental Health Perspectives. 111: 39-43.

[41] Medina-Ramon M; Zanobetti A; Schwartz J. (2006). The effect of ozone and PM-10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: A national multi-city study. Am. J. Epidemiol. 163: 579-588.

[42] Health Effects Institute. (2005). Dominici F. et al. Health Effects Institute Research Report 94, Part IV.

Model (GAM) were raised, Ito[43] systematically re-analyzed the 1220 separate air pollution mortality and morbidity associations that were included in the original Lippmann et al., 2000 study of Detroit. Comparing the results using the General Linear Model (GLM) to those with the suspect GAM shows a wide range of negative and positive excess risks (associations) in Detroit when a large number of pollutants, lags and morbidity and mortality endpoints were considered. All the combinations of pollutant, lag and health outcome evaluated in the original Lippmann study were considered plausible candidates for air pollution health effects. Ito showed in separate figures that the wide range of associations occurred for each pollutant. Although the focus in the original Lippmann study, like most published literature, was on the positive associations, Ito's plots show that there are many negative associations in the data.

Given the substantial stochastic variation in acute time series data, the EPA needs to acknowledge and consider the wide range of associations with regard to both biological plausibility and the limitations on the use of time series and other epidemiological studies to set ambient standards. 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."[44] The ISA needs to acknowledge the stochastic variability in time series 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.

3.3 Comments on Weight of Evidence Regarding Cardiovascular Morbidity

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 2000 CD also presents and discusses a substantial body of studies that report CO associations with cardiovascular hospital admissions in single pollutant model. The

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[43] Ito K. (2003). Associations of Particulate Matter Components with Daily Mortality and Morbidity in Detroit, Michigan. Health Effects Institute, Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health. at 143-156.

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

Executive Summary summarized 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 heterogenous 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.[45]

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.[46] The observed associations of ambient CO with heart disease exacerbation are described as having some biological plausibility and being of potential public health concern.[47] 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.[48] A point is also made that modeled effects estimates for single pollutants are likely to be inaccurate.[49] Finally, the 2000 CD notes[50] 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.

All of the issues that led to the conclusion in the 2000 CD that the epidemiological associations should be interpreted with caution are still relevant and should be discussed in a balanced fashion in the final ISA.

The draft ISA, in its current form, does not provide a balanced discussion of the weight of evidence regarding cardiovascular health effects. The ISA indicates:

> …the epidemiologic evidence for cardiovascular morbidity summarized in this assessment indicates that CO associations generally remain robust in copollutant models (see Figure 5-6 and Figure 5-7), which, combined with the consistency of effects observed across studies, the coherence of epidemiologic health outcomes

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[45] U. S. EPA (2000), *supra* note 5, at page E-6.
[46] Id. at pages 6-4 and 6-5.
[47] Id. at pages 6-7.
[48] Id. at pages 6-4 and 6-10.
[49] Id. at page 6-21.
[50] Id. at page 6-8.

> with effects observed in controlled human exposure studies, and the emerging evidence on the potential role for cell signaling effects at low tissue CO concentrations, supports an independent effect of short-term CO exposure on cardiovascular morbidity. This combined evidence supports a determination that the relationship between CO and cardiovascular morbidity is likely causal, while still recognizing that CO is a component of a mixture of combustion-related pollutants.[51]

There are several reasons why this line of argument over-states the current state-of-science. Each will be discussed in turn.

Consistency of effects observed across studies

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.[52] 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.

As noted above, the range in individual-city results in multi-city time series studies of hospital admissions 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 the Figures in the ISA. If the full range of individual-city results were shown in the Figures, it would be apparent that the draft ISA could not appropriately claim consistency in these data.

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. The Bell et al., 2009 study demonstrates this pattern for CO. With from 25 to 40 percent of the associations in various multi-city studies being negative, it is impossible to characterize the data as consistent.

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[51] ISA, *supra* note 3, at page 2-24.

[52] 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.

Robustness in co-pollutant models

The draft ISA refers to Figures 5-6 and 5-7 to make the point that CO associations generally remain robust in co-pollutant models. However, the criterion for what constitutes robust in the text, that the association remains positive in co-pollutant models, is weak. The supplemental on-line material included in the Bell et al., 2009 paper provides a great deal more information on this issue. Bell et al. report on the impact of co-pollutant models on the combined CO association in their paper, but the plots in the supplemental material show a wide divergence in co-pollutant associations in individual cities. For example, for two-pollutant models with NO_2, the combined CO association was more than halved. In a three pollutant model with NO_2 and $PM_{2.5}$ the combined CO association was more than halved. In the scatter plots, Figures IIa through IId, it is apparent that the individual–city CO associations vary much more widely, with some being increased but with many more being reduced substantially. For example, Figure IIa from Bell et al., 2009 is re-produced below as Figure 3.

Figure 3 – Figure IIa from Bell et al.

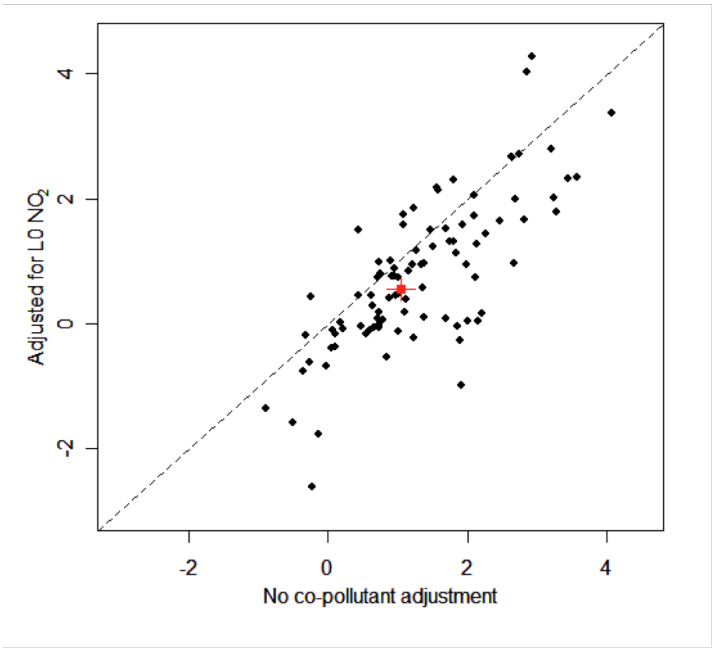

Fig. IIa. With and without adjustment by same day NO_2

If all the co-pollutant and multi-pollutant results in Bell et al. were added to Figures 5-6 and 5-7 of the ISA, the extremely wide variability of CO associations in co-pollutant models would be apparent, and robustness could not be claimed.

Evidence for independent CO effect

The draft ISA focuses on single-pollutant associations for CO. However, Klemm et al., 2004 note:

> It is axiomatic that effects attributed to a given pollutant based on a single-pollutant regression will include effects from any other pollutants with which the given pollutant may be correlated. Thus, single-pollutant regressions may be a useful screening tool but cannot provide valid judgments as to the relative importance of a given pollutant.[53]

In order to investigate the role of CO in the presence of other air pollutants, most of the studies cited in the ISA 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[54] reported associations with CO and other pollutants and indicated that they may be surrogates for the air pollution mix. Linn et al., 2000 reported associations with CO and other pollutants and implicated the mix of primary pollutants, not CO per se. 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 Sarnat et al, 2009 study of circulatory admissions reported similar associations for the four pollutants evaluated in the study.

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

[53] Klemm et al., 2004, *supr*a note 22.

[54] Papers cited in the text by author and date without a footnote are references included in the draft ISA or draft REA.

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[55] in the first draft ISA is for a multi-city study of congestive heart failure admissions and PM that did 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.

The ISA documents the correlation between CO and other pollutants. It also indicates that the correlation complicates the quantitative interpretation of effect estimates to determine the relative extent to which CO at ambient concentrations is independently associated with cardiovascular or other effects, and the extent to which CO acts as a marker for the effects of another combustion-related pollutant or mix of pollutants.[56]

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."[57]

Given this difficulty, along with the understanding that model selection uncertainty and publication bias exaggerate the strength and consistency of association, the epidemiologic studies in the ISA do not provide support for an independent effect of CO on cardiovascular morbidity. In contrast, the controlled human studies do show strong evidence of independent effects of CO on cardiac function above COHb levels of 2 %.

Emerging evidence for potential role of CO in cell signaling

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

[55] The Wellenius et al., 2006b reference in the first draft ISA was 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.
[56] ISA, *supra* note 3, at page 2-23.
[57] ISA, *supra* note 3, at page 5-57.

pathophysiology was not yet well understood.

Section 5.1.3 of the draft ISA summarizes the information on non-hypoxic mechanisms 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 provides less information concerning important new findings that exposure to exogenous CO may have beneficial or protective effects. 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 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. 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. 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. [58] 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.

The Durante et al., 2006 review referenced in the ISA also notes that both endogenously

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

derived and exogenously applied CO may exert important protection against thrombosis. 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 delineate the biology and potential applications of this often misunderstood 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 multiple heme-based signaling pathways due to its nonspecific nature.[59]

This view is one-sided. It should be replaced by a statement acknowledging the growing body of information indicating that CO can have beneficial effects through non-hypoxic mechanisms. In the NOx ISA, the fact that nitric oxide (NO), another signaling molecule, is used therapeutically is cited as strong evidence for the lack of toxicity of NO.[60] The growing evidence that CO can have beneficial effects through non-hypoxic mechanisms argues against the view that extremely low exposures to CO can be causing or contributing to cardiovascular morbidity through non-hypoxic mechanisms.

Coherence with effects in controlled studies

Coherence is one of the factors evaluated in the ISA. It is considered because an inference of causality from epidemiologic associations may be strengthened by other lines of evidence (e.g., clinical and animal studies) that support a cause-and-effect interpretation of the association. The draft claims that the controlled human exposure studies are coherent with findings of recent epidemiologic studies conducted since the 2000 CO Criteria Document 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). Although the controlled human studies do demonstrate effects on the cardiovascular system, interpreting the epidemiological evidence as causal is even more

[59] ISA, *supra* note 3, at page 5-17.
[60] NOx ISA, *supra* note 35, at page 3-45.

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 CO provides anti-inflammatory and cytoprotective benefits through non-hypoxic mechanisms, 3) a similar pattern of epidemiologic 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 magnitude and consistency of the epidemiological associations.

4.0 REA Comments

As noted in the Introduction, the first draft 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). The distribution of CO and COHb in the target population was evaluated for two CO concentration levels. The first represented current "as is " air quality. The second represented CO air quality adjusted to simulate just meeting the current CO NAAQS. In the second draft, EPA plans to include additional CO concentration levels designed to simulate alternative CO NAAQS.

EPA used the Air Pollutants Exposure Model (APEX) in the analysis. The REA describes the APEX model as follows:

> APEX estimates human exposure to criteria and toxic air pollutants at the local, urban, or consolidated metropolitan area levels using a stochastic, "microenvironmental" approach. The model randomly selects data for a sample of hypothetical individuals from an actual population database and simulates each hypothetical individual's movements through time and space (e.g., indoors at home, inside vehicles) to estimate his or her exposure to a pollutant. APEX can account for travel to and from work locations (i.e., commuting) and provide estimates of exposures at both home and work locations for individuals who work away from home.[61]

The current version of APEX (Version 4.3) was also recently used to estimate ozone, nitrogen dioxide, and sulfur dioxide exposures in the NAAQS reviews of these pollutants. For CO, EPA applied APEX in a simplified form compared to the modeling approach used in prior CO NAAQS reviews. The REA notes that EPA implemented a much-simplified, screening-level approach focused on a single monitor and an exposure situation of particular interest for ambient CO based on the input from CASAC that:

> The current ambient monitoring network is not well designed to characterize spatial and temporal variability in ambient concentrations. Thus it does not adequately support detailed assessments of human exposure or air quality modeling such as for photochemical oxidants.[62]

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[61] REA, *supra* note 4, at page 5-1.

[62] Brain JD and Samet JM (2009). Letter to EPA Administrator Lisa Jackson: Clean Air Scientific Advisory Committee's (CASAC) Peer Review of the Agency's 1st Draft Carbon Monoxide Integrated Science Assessment. EPA-CASAC-09-011. June 24, 2009.

Based on these concerns, EPA staff decided not to perform a detailed exposure analysis involving multiple monitors and multiple microenvironments, as has been done in the past. In particular, EPA chose one monitor in each area to represent the ambient concentrations throughout the area. In both areas, the monitor chosen was the monitor that has consistently reported the highest CO concentrations in the area. In addition, EPA chose to model only two broadly-defined microenvironments, "in-vehicle" and "all others." Finally, EPA chose to evaluate two exposure scenarios for each study area -- one (Scenario A) in which all microenvironmental concentrations are set equal to the ambient concentrations measured at the single fixed-site monitor and the other (Scenario B) in which the in-vehicle microenvironment is set equal to twice the ambient monitor concentrations.

The draft REA recognizes that these simplifications contribute to limitations and uncertainties in the interpretation of the results and explicitly seeks CASAC and public comment on the analysis. In the following several major concerns with the analysis are detailed.

Even accepting CASAC's view concerning the adequacy of the monitoring network, EPA's simplifications make the problem worse, not better.

EPA rationalizes the decision to collapse the APEX model application for the REA down to one monitor and only two microenvironments on the CASAC comments noted above. However, the CASAC comments were addressing the question of whether a central-site monitor concentration is a good indicator for the ambient component of personal CO exposure not the nature or extent of the REA. Individual CASAC panelists provided separate input on the Scope and Methods Plan for the REA in a consultation. That input does not address the change EPA made to the planned analysis.

The CASAC panel indicated that "the current monitoring network is adequate to demonstrate compliance with the NAAQS, but substantial improvement could be achieved in coverage and detection limits to better quantify ambient CO concentrations, sources, and exposure."[63] Thus, CASAC was calling for additional monitoring to determine the spatial and temporal variation of CO concentrations and exposures so as to be able to adequately test exposure models. A related concern raised by CASAC, as noted above, is that a large proportion of the reported concentrations are below the conventional instrument detection limit of 1 ppm at many sites.

Not only did EPA miss-interpret the intent of the CASAC comments, but the simplifications make the problem worse not better. CASAC is concerned that there is not enough data to characterize CO exposures and EPA, by using only one monitor to characterize an entire area, leaves out information that can be used to characterize the distribution of exposures and COHb levels. Whereas the APEX model is designed to simulate the movement of groups of people through time and space and account for their activities and breathing rates, the simplifications EPA has imposed makes the assumption

[63] Id. at page 10.

that the entire population of cardiac patients lives out its life at the location of the CO monitor EPA chose in Scenario A. For Scenario B, EPA adds the assumption that the CO exposure for the time spent in vehicles is at twice the CO concentration at the monitor.

These assumptions are entirely unrealistic and defeat the purpose of using a detailed model to account for activity and movement of the subject population. They also bias the CO and COHb levels high.

The choice of CO monitors in Denver and Los Angeles biases the results high

The monitoring sites EPA chose to represent CO exposures in the two study areas are clearly worst-case situations. For Denver, EPA chose the CAMP site, as it is commonly referred to. The acronym CAMP comes from the Continuous Air Monitoring Program instituted by the predecessor agency to the U. S. EPA in the 1960s. Thus, CO monitoring has been conducted at this site for over 40 years. The site is located on a triangular-shaped traffic island at the intersection where a major diagonal arterial road, Broadway, intersects Stout and 21st Streets. The REA indicates that this site was chosen because it appears to best represent the highest population density in Denver County. The site is described in the REA as a micro-scale site, within 6 meters from a roadway having 17,200 vehicles/day traffic volume, 7 meters from a road with 10,000 vehicles/day, and 16 meters from a road with 1,000 vehicles/day. As shown in Figure 3-1 of the REA, the site routinely reports the highest CO concentrations among the CO monitoring sites in Denver.

For Los Angeles, EPA chose the Lynwood site. The CO concentrations measured at Lynwood are consistently higher by almost a factor two than the CO concentrations measured at other sites in the Los Angeles Basin as shown in Figure 3-2 of the REA. The Lynwood monitor is described as a middle scale monitor that is near a major arterial road (Long Beach Blvd.), and 350 m from a major freeway (the I-105).

It is inappropriate to assume that the entire population of adults with coronary artery disease resides at these specific locations in Denver and Los Angeles, respectively. In fact, 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.[64] 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. Since the NRC study was sponsored by EPA, the Agency was aware of the unique nature of these sites. While it would be appropriate to include these sites along with others in evaluating CO and COHb in Denver and Los Angeles, it is inappropriate to rely solely on the highest monitoring site to represent the population over the entire area. By not including the full range of monitoring sites in the

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

chosen areas, EPA has also made any attempt to extrapolate the results to a national analysis of CO and COHb exposure problematic.

One of the concerns raised in the REA is that the number of monitoring sites in each area has decreased since the last CO review. The REA notes that the number of monitors decreased from nine to three or four (depending on the year considered) in Denver and from 21 to 12 in Los Angeles. However, the CO monitors that have been dropped by local and state agencies tend to be monitors that reported only low levels of CO or that were thought to be redundant.

The treatment of in-vehicle exposures is also simplistic and biases the results for Scenario B high

CASAC has expressed the concern that "Relying only on EPA's fixed monitoring network CO measurements may underestimate CO exposures for specific vulnerable populations such as individuals residing near heavily trafficked roads and who commute to work on a daily basis."[65] Therefore, it is appropriate to include microenvironments for being in vehicles and outside near the road. Indeed EPA's previous CO exposure analyses and APEX include such microenvironments. The draft REA, however, takes a step backward in how these exposures are modeled. By compressing the analysis down to two microenvironments and utilizing only the CO measured at a microscale site in Denver, the REA overestimates the CO concentrations in-vehicles throughout Denver.

For example, as shown in Tables 6-5 and 6-6 of the REA, the range of 1-hour ambient CO concentrations in the "as-is" case for Denver in 2006 is 0 to 6.4 ppm. This means that the range of in-vehicle concentrations in the model is 0 to 12.8 ppm. For the "just meets the standard" case, the range of 1-hour ambient CO concentrations is 0 to 24.2 ppm so the range of in-vehicle CO concentrations is 0 to 48.4 ppm. There is no data indicating that the in-vehicle concentrations in the U. S. relevant to either case approach the upper end of the ranges used in the model.

The U. S in-vehicle measurements reported in the ISA (that would correspond to ambient concentrations at or below the current standard) are very much below either the 24 or 48 ppm (1-hour average) upper limit. 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 REA based the choice of a multiplicative factor of two primarily on the Shikiya et al., 1989 study of Los Angeles commuting exposures that reports data gathered in 1987.

[65] Brain JD and Samet JM (2009), *supra* note 62, at page 2.

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.

The use of a multiplicative factor to account for the increase in in-vehicle exposures due to roadway emissions is an oversimplification that can lead to erroneous results. EPA and others typically analyze the results from studies of roadway- and near-roadway pollutant concentrations in terms of the ratio of the contribution from the roadway to the background. The ratio of on-road increment to background varies substantially in these studies. 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 but the background is very low, applying that high ratio to an urban situation with a high background will substantially over-estimate the on-road increment. Thus, the ratio method can substantially overestimate on-road exposures and risk.

The concern that there may be high CO or other pollutant concentrations in-vehicles or near roadways under adverse meteorological conditions is not a new concern. 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.[66] 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.[67] 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.

The ISA acknowledges these effects noting that the influence of vehicle speed and start/stop activity is consistent with the turbulence research of Khare et al., 2005 and Gokhale and Khare, 2007 which indicates that an increase in traffic volume and vehicle movement acts to dilute the on-road concentration of CO.[68]

There is additional evidence in the literature that microscale monitoring will not identify

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[66] Cadle S; Chock D; Monson P; Heuss J. (1977). General Motors Sulfate Dispersion Experiment: Experimental Procedures and Results. J. Air Pollut. Control Assoc. 27: 33-38.
[67] Chock D. (1977). General Motors Sulfate Dispersion Experiment: Assessment of the EPA HIWAY Model. J. Air Pollut. Control Assoc. 27: 39-45.
[68] ISA, *supra* note 3, at page 3-105.

unmonitored "hot spots" of exposure to motor vehicle pollutants. The South Coast Air Quality Management District has carried out two studies that compared motor vehicle air toxic exposures at microscale sites in Los Angeles suspected of being unmonitored "hot spots" with exposures at current monitoring sites. In both cases, the exposures at the anticipated hot spots were similar to the exposures at the fixed neighborhood-scale monitoring sites.[69]

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 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.

The draft REA notes that the purpose of Scenario B is "to determine the magnitude of the change in exposure and COHb levels when incorporating a rough estimate of the greater exposure concentrations occurring inside motor vehicles."[70] However, by overstating both the ambient exposure for the subject population and the in-vehicle exposures, the REA significantly overestimates the resulting CO and COHb exposures . This is readily apparent in Table 6-8 where a small portion of the population experiences 1-hour CO concentrations above 40 ppm in the Scenario B and "meets current standard" case. As noted above, there is no experimental evidence for in-vehicle exposures of this magnitude in Denver or any other city that just meets the 8-hour CO NAAQS. As a result of the overestimation of CO, COHb is also overestimated.

Inspection of Table 6-9 also reveals that the entire subject population is estimated to experience the maximum concentration measured at the CAMP monitor in Scenario A. This occurs, obviously, because the entire subject population is assumed to be exposed to the concentrations at the traffic island CAMP site no matter where they might actually reside or work.

EPA acknowledges some of the biases in the REA

At various places in the REA, the Agency acknowledges many of the biases in the analysis. For example, one of the key observations from Chapter 5 is that "the single monitoring site selected in each location typically reported a higher range of CO concentrations when compared with other monitors in each area, and thus, when used as an input to an exposure model, is generally considered likely to generate conservative (i.e., higher) estimates of exposure for the large majority of the population."[71]

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[69] South Coast Air Quality Management District. (2000). Multiple Air Toxics Exposure Study. MATES II Final Report. March 2000; South Coast Air Quality Management District. (2008). Multiple Air Toxics Exposure Study. MATES III Final Report. January 2008.

[70] REA, *supra* note 4, at page 5-29.

[71] Id. at page 5-30.

The REA notes that the single site assumption "likely results in over-estimates of CO exposure and COHb levels for much of the population because CO peak hourly concentrations are typically somewhat lower indoors than outdoors due to consideration of air exchange (in the absence of indoor sources of CO)."[72]

One of the key observations in Chapter 6 is that "…the exposure and dose estimates for much of the simulated population represented by either scenario in this assessment are likely overestimated."[73]

The final key observation in Chapter 6 is that "given the considerations described above regarding the characterization of uncertainty and the tendency of the assessment approach to overestimate exposure and dose, staff finds the utility of this assessment for the purpose of considering the adequacy of the current standards to be limited."[74]

One of the reasons for the limited utility of the analysis arises from a comparison of the current draft REA with a similar assessment carried out in 2000. The only direct comparison available is for the "meets current standard" case. The REA notes that when compared to the current assessment, the 2000 assessment employed more monitors to represent ambient CO levels, differentially treated a much greater number of microenvironments, and encompassed larger study areas. There was also a major difference in the results of the two analyses. The REA indicates that "the estimated percent of persons with daily maximum end-of-hour COHb blood levels when using air quality adjusted to just meet the current standard in both Denver and Los Angeles was substantially greater in the current assessment when compared to that estimated in the 2000 assessment (e.g., a difference of a factor of 10 or more at the 2% COHb benchmark)."[75] There is also a factor of ten or more difference in the percent of persons with daily maximum end-of-hour COHb blood levels above 1.5 %. This is clear from the comparison in Tables 6-22 and 6-23. Thus, the REA acknowledges that the crude simplifications in the 2009 assessment resulted in an inflation of the upper percentiles of the COHb distribution by the order of a factor of ten or more.

Even with the biases, the REA demonstrates that the current CO standards are protective of public health

The REA concludes that fewer than 1% of the study population in each study area (< 0.2%) were estimated to experience a daily maximum end-of-hour COHB level at or above 2.0% under "as is" air quality conditions in either scenario A or B. In addition, the number of person-days at COHb levels of possible concern is extremely small when expressed as a fraction of the total person-days, and the number of person-days /person are less than one. This is shown for Denver in Tables 6-12, 13, and 14 and for Los Angeles in Tables 6-19, 20, and 21. Given the very conservative nature of the analysis

[72] Id. at page 5-29.
[73] Id. at page 6-43.
[74] Id. at page 6-43.
[75] Id. at page 6-43.

and the acknowledged inflation of the upper end of the distribution of COHb, this means that "as is" CO air quality is highly protective of public health.

Even in the "just meets standard" case, the number of person-days at COHb levels of possible concern are extremely small when expressed as a fraction of the total person-days. The REA indicates that the results for the two study areas differed appreciably for air quality adjusted to just meet the current standard. For these conditions, the estimates of percent of population experiencing a daily maximum end-of-hour COHb level at or above potential health benchmarks were substantially greater for the Denver study area (e.g., differing by a factor of 8 or more for the 2% COHb benchmark).[76] The higher COHb levels in Denver for scenario B are clearly caused by the erroneous assumption that 1-hour in-vehicle exposures are up to 48 ppm. The Denver results should, therefore, be disregarded. For Los Angeles, for scenario B, the portion of possible person-days greater than 2 % COHb is 0.0003, and the average number of person-days/person greater than 2 % COHb is 0.1. Thus, the REA estimates that the likelihood of a given CHD subject experiencing greater than 2 % COHb is the order of once every ten years in a location that just meets the current CO NAAQS, and the aggregate risk for all the CHD subjects is 0.0003 or 0.03 % of the possible person-days. Since this estimate is acknowledged to be a substantial overestimate, the REA demonstrates that the current CO NAAQS is protective of public health.

The final REA should evaluate the sensitivity of the results to more accurate assumptions

The draft REA is of limited utility, as acknowledged by staff. In order to provide useful information for the Administrator, EPA should either revert to the 2000 analysis or conduct the APEX exposure simulation including all the available monitoring sites. In the alternative, if time or resources are limited, EPA should carry out sensitivity analyses with more realistic assumptions (such as using an average of the CO monitors and using an additive factor for the in-vehicle exposure).

In addition, the results for person-days of exposure should be presented in tables both as total person-days and person-days as a fraction or percentage of total possible person days. For example, 1600 person-days in a year above a certain COHb threshold in Los Angeles (which has a CHD population of 160,000) is 1600 out of a total of 160,000 x 365 = 58,400,000 possible person-days, or 0.00003 (0.003 %).

[76] Id. at page 6-42.