

**Responses to Significant Comments on the  
2011 Proposed Rule on the  
National Ambient Air Quality Standards  
for Carbon Monoxide  
(February 11, 2011; 76 FR 8158)**

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## Table of Contents

Frequently Cited Documents .....	ii
I. INTRODUCTION .....	1
II. RESPONSES TO SIGNIFICANT COMMENTS ON PROPOSED RULEMAKING FOR CARBON MONOXIDE NAAQS .....	2
A. Comments on Primary Standards.....	2
1. Support for Proposed Decision to Retain the Current Standards.....	2
2. Comments Recommending Revision of the Current Standards .....	3
3. Comments on Evidence-based Considerations.....	4
4. Comments on Exposure and Risk Considerations.....	15
5. Additional Comments on the Interpretation of Scientific Evidence.....	24
6. Additional Comments on the Exposure and Risk Assessment.....	37
B. Comment on Consideration of a Secondary Standard .....	40
C. Comments Related to Monitoring.....	41
1. Sampling and Analysis Methods .....	41
2. Near-Roadway Monitors.....	44
3. Other Locations.....	48
4. Other Monitoring Comments.....	50
III. RESPONSES TO SIGNIFICANT COMMENTS RELATED TO IMPLEMENTATION OF STANDARDS .....	52
A. DESIGNATIONS .....	52
B. OTHER.....	52
IV. RESPONSES TO SIGNIFICANT COMMENTS RELATED TO EXCEPTIONAL EVENTS .....	55
V. RESPONSES TO LEGAL, ADMINISTRATIVE, AND PROCEDURAL ISSUES AND MISPLACED COMMENTS .....	55
VI. REFERENCES .....	59
APPENDIX A .....	63

## Frequently Cited Documents

The following documents are frequently cited throughout this response to comments document, often by means of the short names listed below:

Preamble to the final rule:

Preamble to the Final Rule on the Review of the National Ambient Air Quality Standards for Carbon Monoxide: Final Rule. To be published in the *Federal Register* in August or September, 2011.

Proposal:

National Ambient Air Quality Standards for Ozone: Proposed Rule. 76 FR 8158, February 11, 2011.

2010 Integrated Science Assessment (ISA):

U.S. Environmental Protection Agency (2010a) Integrated Science Assessment for Carbon Monoxide (Final). Washington, DC, EPA/600/R-09/019F. Available online at: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=218686>

Risk and Exposure Assessment (REA):

U.S. Environmental Protection Agency (2010b) Quantitative Risk and Exposure Assessment for Carbon Monoxide - Amended. July 2010. Office of Air Quality Planning and Standards, Research Triangle Park, NC. EPA Report no. EPA-452/R-10/009. Available online at: <http://www.epa.gov/ttn/naaqs/standards/co/data/CO-REA-Amended-July2010.pdf>

Policy Assessment (PA):

U.S. Environmental Protection Agency (2010c) Policy Assessment for the Review of the Carbon Monoxide National Ambient Air Quality Standards. October 2007. Office of Air Quality Planning and Standards, Research Triangle Park, NC. EPA report no. EPA-452/R-10-007. Available online at: <http://www.epa.gov/ttn/naaqs/standards/co/data/20101022copafinal.pdf>

# **Responses to Significant Comments on the 2011 Proposed Rule on the National Ambient Air Quality Standards for Carbon Monoxide**

## **I. INTRODUCTION**

This document, together with the preamble to the final rule on the review of the national ambient air quality standards (NAAQS) for carbon monoxide (CO), presents the responses of the Environmental Protection Agency (EPA) to some of the public comments received on the 2011 CO NAAQS proposal notice (76 FR 8158). All significant issues raised in timely public comments have been addressed. Where comments were submitted after the close of the public comment period, EPA responded to the extent practicable.

Comments were received from two organizations of state and local air agencies (National Association of Clean Air Agencies [NACAA], and Northeast States for Coordinated Air Use Management [NESCAUM]), approximately 12 State and local government agencies, and a council of local governments (Southeast Michigan Council of Governments [SEMCOG]); the American Thoracic Society and approximately 10 environmental or public health organizations or coalitions; three industry organizations (Alliance of Automobile Manufacturers [AAM], American Petroleum Institute [API], and American Electric Power Service Corporation [AEPSC]); an organization of state highway officials (American Association of State Highway and Transportation Officials [AASHTO]); several individuals and a group of approximately 100 individuals.

This response-to-comments document does not generally cross-reference each response to the commenter(s) who raised the particular issue involved, although commenters are identified in some cases where they provided particularly detailed comments that were used to frame the overall response on an issue.

The responses presented in this document are intended to augment the responses to comments that appear in the preamble to the final rule or to address comments not discussed in the preamble to the final rule. Although portions of the preamble to the final rule are paraphrased in this document where useful to add clarity to responses, the preamble itself remains the definitive statement of the rationale for the revisions to the standards adopted in the final rule.

In many instances, particular responses presented in this document include cross references to responses on related issues that are located either in the preamble to the CO NAAQS final rule, or in this 2011 Response to Comments document. All issues on which the Administrator is taking final action in the CO NAAQS final rule are addressed in the CO NAAQS rulemaking record.

Accordingly, this Response to Comments document, together with the preamble to the CO NAAQS final rule and the information contained in the Integrated Science Assessment (EPA, 2010a), the Risk and Exposure Assessment (EPA, 2010b) and the Policy Assessment (EPA, 2010c), and the Notice of Proposed Rulemaking should be considered collectively as EPA's response to all of the significant comments submitted on EPA's 2011 CO NAAQS proposed rule. This document incorporates directly or by reference the significant public comments addressed in the preamble to the CO NAAQS final rule as well as other significant public comments that were submitted on the 2011 proposed rule.

Consistent with the final decisions presented in the notice of final rulemaking, comments on the CO standards are addressed in sections II.A and II.B. Comments on monitoring are addressed below in section II.C. Comments on implementation are addressed in III. Comments on exceptional events are addressed in section IV. Section V includes responses to legal, administrative, procedural, or misplaced comments.

## **II. RESPONSES TO SIGNIFICANT COMMENTS ON PROPOSED RULEMAKING FOR CARBON MONOXIDE NAAQS**

### **A. Comments on Primary Standards**

General comments based on relevant factors that either support or oppose retention of the current CO primary standards are addressed in section II.B of the preamble to the final rule and/or in sections II.A.1 and II.A.2 of this document below. Additional comments about the health effects evidence and the REA are addressed in sections II.A.3-5 below.

#### ***1. Support for the Proposed Decision to Retain the Current Standards***

All of the state and local environmental agencies or governments that provided comments on the Administrator's proposed conclusion that the current CO standards provide the requisite protection of public health with an adequate margin of safety concurred with the proposed decision. Additionally three industry commenters also expressed agreement with EPA's proposal to retain the current standards, which they also viewed as providing the requisite level of public health protection. In support of this view, these commenters variously stated that:

- the current evidence indicates current standards are protective for the sensitive group of people with heart disease;
- the proposed conclusions give appropriate weight to epidemiological studies;
- the REA estimates of occurrences of carboxyhemoglobin (COHb) levels above 2% COHb in the at-risk populations are materially unchanged since last review, and;
- some aspects of the exposure and dose assessment lead the REA results to provide an overstatement of risk (further discussed in II.A.4.below) .

These comments received in support of retaining the current standards are generally addressed in Section II.B.3 of the preamble to the final rule. We additionally note here that EPA does not agree with commenters' characterization of the REA results as an overstatement of health risk as discussed in section II.A.4 below.

## ***2. Comments Recommending Revision of the Current Standards***

Comments received on the proposal from several organizations and individuals asserted that the evidence indicated the occurrence of health effects occurring at conditions below the current CO standards and that revisions should be made to the standards. Among those recommending revisions to the current standards were joint comments submitted from the American Lung Association, the American Thoracic Society, the Environmental Defense Fund (ALA et al); joint comments submitted from Physicians for Social Responsibility and Albert Donnay (PSR et al), signed by 27 other organizations and several hundred individuals; joint comments submitted from Center for Biological Diversity, Communities for a Better Environment, WildEarth Guardians, Coalition for a Safe Environment, and Alaska Center for the Environment (CBD et al); individual comments from Albert Donnay (Donnay) and a petition signed by 130 individuals. These various commenters recommended a range of lower levels for revised 1-hour and 8-hour standards with consideration of a revised form of 99<sup>th</sup> percentile. The recommended levels were at or below the lowest part of the range identified in the Policy Assessment. In supporting adoption of more stringent NAAQS for CO, these commenters generally stated that they supported comments provided by CASAC on the draft Policy Assessment which indicated a preference for a lower standard and recommended greater emphasis be given to epidemiological studies. The commenters also variously stated that:

- the available epidemiological studies provide evidence of effects at levels below the current NAAQS;
- epidemiological studies indicate that the current standards do not provide protection for all sensitive populations, including specifically fetuses, neonates and children; and;
- epidemiological studies provide evidence indicating that current standards do not provide protection against chronic CO exposures.

The NESCAUM also offered the view that a lower standard may be appropriate, “perhaps based on an alternate indicator”, noting CASAC’s preference, but recognized that “at this time the available epidemiological studies do not clearly indicate a specific level for the one or eight-hour standard”.

Comments received that recommended revising the current standards are addressed in section II.B.3 of the preamble to the final rule. Specific aspects to some of these comments are additionally discussed below.

### **3. Comments on Evidence-based Considerations**

- (1) *Comment:* In support of their view that the current standards fail to protect public health with an adequate margin of safety, one commenter (ALA et al) summarized findings for a number of studies of associations of respiratory endpoints with ambient CO concentrations, describing them as providing evidence of harm from CO exposure below the current standards. Two commenters (ALA et al and CBD et al) indicated that the Clean Air Act compelled EPA to revise standards in light of the epidemiological evidence, regardless of uncertainties.

*Response:* In addressing this comment EPA notes that it is important to consider both the extent to which the evidence supports a causal relationship between ambient CO exposures and respiratory effects, as well as the extent to which there is evidence pertinent to such effects under air quality conditions in which the current standards are met. With regard to the latter point and focusing on the epidemiological evidence, it is the studies involving air quality conditions in which the current standards were met that are most informative in evaluating the adequacy of the standards (PA, p. 2-30). Yet the commenter provides no evidence that the studies they cite, some of which are conducted outside the U.S., focused on conditions that meet the current U.S. CO standards. And, when considering the publicly available information on attainment and non-attainment of the current standards in the study locations for the time periods relevant to the U.S. studies cited by the commenters, it can be documented that the current standards were met throughout the period of study in only two study areas (<http://www.epa.gov/airtrends/reports.html>).

Further, as described in the ISA, EPA has determined the body of evidence for short-term exposure and respiratory morbidity to be only suggestive of a causal relationship (ISA, section 5.5.5.1). This conclusion was reached due to a lack of evidence on mechanism or mode of action that might lend biological plausibility to such a relationship for the low ambient concentrations of CO observed in epidemiological studies. Additionally, the inability to sufficiently rule out the role of chance, bias and confounding in the epidemiological associations observed contributed to the “suggestive” causal determination. EPA further determined that the evidence is inadequate to infer a causal relationship between long-term exposure to ambient CO and respiratory morbidity (ISA, section 5.5.5.2). Both of these determinations were reviewed and endorsed by CASAC in their January 2010 letter to the Administrator (Brain and Samet, 2010a), with CASAC additionally stating that the evidence of a potential causal relationship between short-term CO exposure and adverse respiratory outcomes “borders between suggestive and inadequate” (Brain and Samet, 2010a).

As noted in the ISA, PA, the proposal notice and advice received from CASAC, there are several aspects to the epidemiological evidence for CO that complicate

its interpretation with regard to ambient concentrations of CO that might be eliciting the reported health outcomes. In particular, a major challenge relates to the difficulty in determining the extent to which ambient CO is independently associated with health effects or if CO at ambient levels is acting as a surrogate for the effects of another traffic-related pollutant or mixture of pollutants (e.g., PA, pp. 2-36 to 2-39). As noted in the ISA in interpreting the epidemiological evidence, “the limited amount of evidence from studies that examined the effect of gaseous pollutants on CO-respiratory morbidity risk estimates in two-pollutant models, specifically NO<sub>2</sub>, 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 limits interpretation of the results observed in the epidemiologic studies evaluated” (ISA, p. 5-100). The ISA further noted that a “key uncertainty in interpreting the epidemiologic studies evaluated is the biological mechanism(s) that could explain the effect of CO on respiratory health” (ISA, p. 5-100). CASAC also acknowledged the potential for co-pollutants to serve as confounders to be “particularly problematic for CO” and the need to give consideration to the possibility of CO serving as a surrogate for a mixture of pollutants associated to fossil fuel combustion (Brain and Samet, 2010a).

After considering the evidence, together with these areas of uncertainty, the Administrator concluded in the final rule that the epidemiological evidence does not lead her to identify a need for any greater protection than that provided by the current standards.

EPA also disagrees with commenters (including ALA et al and CBD et al) who state that even if the evidence of adverse effects at and below the current standard is uncertain, there is sufficient evidence to warrant revision of the standards to provide an adequate margin of safety against adverse health effects. EPA agrees that section 109 is precautionary in nature, and, as discussed in the preamble (e.g., section I), the standard is intended to protect against risk associated with pollution at levels below those at which human health effects can be said to occur with reasonable scientific certainty. Thus, in selecting primary standards that provide an adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that have been demonstrated to be harmful but also to prevent lower pollutant levels that may pose an unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree. At the same time, the Clean Air Act (CAA) does not require the Administrator to establish a primary NAAQS at a zero-risk level. Rather, EPA’s task is to establish standards that are neither more nor less stringent than necessary.

Accordingly, EPA disagrees with the view expressed in one comment that “the CAA requires that the EPA act to protect public health as soon as there is any data suggesting health effects from a pollutant” (CBD et al at p. 5) as well as the view that the information available in this review necessitates stronger standards to provide a margin of safety. An approach that based the standard on the existence of “any data suggesting health effects,” absent a careful weighing of the evidence

and risks, may well result in standards more stringent than necessary to protect public health with an adequate margin of safety. In evaluating the air quality criteria and public comments, the Administrator has not required certainty as to the occurrence of adverse health effects but rather has made judgments about how to consider the range and magnitude of uncertainties that are inherent in the information and analyses. For the reasons explained above and in the preamble, the Administrator has concluded that the current standards are requisite to protect public health with an adequate margin of safety.

- (2) *Comment:* In support of their view that EPA's proposed retention of the current standards would not be protective of sensitive populations, two commenters (PSR et al, Donnay) argued that the CO-associated risks identified in epidemiological studies of birth defects, lower birth weight, asthma and neonatal respiratory mortality indicate that the health risks for fetuses, infants and children are much higher than risks reported in adults. The commenters characterized the risk for birth defects and neonatal respiratory mortality to be as high as one or two orders of magnitude greater than those faced by adults. Additionally, one commenter, in citing three studies of CO poisoning and cardiovascular damage in children (Donnay at p. 16) suggested that, based on such studies, EPA should incorporate a larger margin of safety in the final rule. Another commenter (CBD et al) indicated that the EPA did not appropriately consider epidemiological evidence on negative birth and developmental outcomes, and also stated that the Clean Air Act compelled EPA to revise standards in light of this evidence.

*Response:* As an initial matter EPA notes that, in considering the adequacy of the current standards, it is important to consider both the extent to which the evidence supports a causal relationship between ambient CO exposures and adverse health effects, as well as the extent to which there is evidence pertinent to such effects under air quality conditions in which the current standards are met. With regard to the latter point, and focusing on the epidemiological evidence, it is the studies involving air quality conditions in which the current standards were met that are most informative in evaluating the adequacy of the standards (PA, p. 2-30). Yet, of the six epidemiological studies cited by the commenters (e.g., PSR et al at pp. 8-9), all three of the U.S. studies (Ritz et al., 2002, 2006; Maisonet et al., 2001), as well as a fourth study that was performed in Brazil, included conditions when the current CO 8-hour standard was exceeded in those study areas (<http://www.epa.gov/airtrends/reports.html>; Conceicao et al., 2001). Sufficient information to assess the air quality conditions in relation to the U.S. NAAQS for CO is not available for the other two studies cited (performed in Taiwan and Seoul, Korea). We additionally note that one of these latter two studies focuses on assessing associations between respiratory effects and long-term concentrations of ambient CO; EPA has concluded that the available evidence is inadequate to infer a causal relationship for long-term exposure and respiratory morbidity (ISA, p. 5-101). In light of this information, EPA disagrees with the

commenters suggestion that these studies provide evidence of a lack of protection afforded by the current standards.<sup>1</sup>

The commenters further emphasize their view that the magnitude of the risks of birth defects and neonatal mortality associated with ambient CO suggested by the cited studies are greater than the risk faced by adults in response to similar increases in ambient CO, and that EPA should consequently give greater weight to evidence regarding birth defects and neonatal mortality. The commenters' view appears to be based on their comparison of effect estimates from studies finding associations for these different types of health outcomes with various measures of ambient CO. EPA notes, however, that such a comparison of effect estimates for health outcomes reported in studies of adults, such as cardiovascular outcomes, to those from the studies of developmental and neonatal outcomes cited by the commenters is inappropriate and misleading with regard to the difference in magnitude of risks potentially posed to exposed populations by ambient CO. Such an isolated comparison fails to consider critical differences between the two types of analyses and observed risks. Such differences include differences in the ambient air metric associated with the effect estimate, differences in the form of the effect estimates across some studies, and the fact that effect estimates are estimates of an increase in prevalence of specific outcomes, relative to the underlying prevalence of the health outcomes being examined.<sup>2</sup>

Contrary to the commenters' assertion as to a lack of appropriate consideration of birth and developmental outcomes, EPA has fully assessed the evidence regarding relationships between birth and developmental outcomes and exposure to ambient CO, including the studies cited by the commenters (ISA, section 5.4). Further, in reaching a decision regarding the adequacy of the current CO standards, the Administrator considered this assessment, as well as uncertainties and limitations of the evidence (preamble to final rule, section II.B.3). EPA's assessment of the body of evidence for the health outcomes emphasized by the commenter, including that for birth outcomes and developmental effects, concluded that the evidence indicates a potential for susceptibility during prenatal and neonatal periods, but that the evidence is only "suggestive" of a causal relationship with ambient CO (ISA, sections 2.5.3 and 2.6.1). Specifically, the ISA notes that evidence is lacking on mechanism or mode of action that might lend biological plausibility to a causal relationship between birth outcomes and developmental effects and the low ambient concentrations of CO observed in epidemiological studies (ISA, p. 5-80). Additionally, the inability to sufficiently rule out the role of chance, bias and confounding in the epidemiological associations observed contributed to the "suggestive" causal determination (ISA, section 5.4.3, Table 1-2). Thus, we recognize much greater uncertainty associated with a relationship

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<sup>1</sup> See comment response 4, below, for further discussion of the evidence for adverse health effects from chronic low level exposure to ambient CO.

<sup>2</sup> With regard to the consideration of prevalence, for example, a 10% increase for a more prevalent outcome, such as cardiovascular disease events, would translate to a much higher impact (in terms of size of the population affected) than for more rare outcomes, such as birth outcomes.

between ambient CO concentrations and these health outcomes as compared to a relationship with cardiovascular effects. As discussed in the previous response, EPA recognizes that the NAAQS are intended to provide protection against risk associated with pollution at levels below those at which human health effects can be said to occur with reasonable scientific certainty, but does not believe that the NAAQS should be set based on “any data suggesting health effects,” absent a careful weighing of the evidence and risks.

With regard to the three studies of CO poisoning and cardiovascular damage cited by one commenter (Donnay at p. 16), EPA notes that these studies involve COHb levels many times higher than the lowest COHb levels assessed in the study of coronary artery disease (CAD) patients by Allred et al (1989), which EPA has weighed heavily in this review of the CO NAAQS. Consequently, EPA disagrees that these studies – or the larger evidence base as a whole- provides a basis for a larger margin of safety than that represented by the decision described in the preamble to the final rule. Further, contrary to the assertion by commenter that EPA considers adults to be more sensitive than children, EPA has concluded, based primarily on the controlled human exposure studies of CAD patients that people with heart disease, such as CAD, regardless of age, are particularly susceptible to ambient CO exposures.

For the reasons described above and in the preamble, based on consideration of all of the currently available evidence, EPA considers the current standards to provide the requisite protection, including an adequate margin of safety, to potentially susceptible populations or lifestages, including pregnant women and infants, as well as to the widely recognized at-risk population of people with heart disease.

- (3) *Comment:* One commenter (Donnay) stated that EPA should conclude that there is biological plausibility for causal relationships between ambient CO exposure and a range of noncardiovascular health outcomes. In support of this view, the commenter stated that evidence of (a) organ and pathway effects at acute CO poisoning levels, as well as, (b) the role of CO in important physiologic pathways, also provides support for concluding that CO affects the same organs and pathways at much lower ambient CO exposure levels (i.e., those which exist in recent epidemiological studies). As a result the commenter states that EPA should conclude causal relationships exist between ambient CO exposure and infant mortality, adverse birth outcomes, childhood respiratory or immune system morbidity, adult mortality, and adult morbidity for a range of organ systems beyond the cardiovascular system and that there is evidence of such effects based on which EPA should revise the current NAAQS.

*Response:* As an initial matter, EPA notes our use of a consistent and transparent basis for the framework we use to evaluate the causal nature of air pollution-induced health effects (ISA, section 1.6). This framework establishes uniform

language concerning causality and brings specificity to the findings. The standardized language employed in the framework was drawn from across the federal government and wider scientific community, especially from the recent National Academy of Sciences, Institute of Medicine document, *Improving the Presumptive Disability Decision-Making Process for Veterans* (NAS, 2008) the most recent comprehensive work on evaluating causality. Under this framework, EPA has determined the separate bodies of evidence for birth outcomes and developmental effects, short-term exposure and respiratory morbidity, and short-term exposure and mortality to each be only suggestive of a causal relationship with ambient CO exposures (ISA, sections 5.4.3, 5.5.5.1, and 5.6.5.1). These determinations were reviewed and endorsed by CASAC in their January 2010 letter to the Administrator (Brain and Samet, 2010a), although we additionally note CASAC's comments that the association for short-term CO exposure and adverse respiratory outcomes "borders between suggestive and inadequate" (Brain and Samet, 2010a, p. 12). Based on EPA's provisional consideration of the additional epidemiological studies cited by the commenter, in the context of the findings of the ISA, EPA concludes that the new information and findings do not materially change any of the broad scientific conclusions made in the 2010 CO ISA and thus do not warrant reopening the air quality criteria review.

In considering the body of evidence for each of these outcomes, EPA disagrees with the commenter's view that CO poisoning studies (e.g., studies involving accidental exposures to very high concentrations of nonambient CO resulting in very high COHb levels) address uncertainties with regard to the biological plausibility for CO effects at lower exposures. Rather, EPA deliberately excluded studies involving CO poisoning (including the more than 100 publications cited by the commenter) from this review, judging them to be "not directly relevant to ambient exposures" (ISA, pp. 1-6 and 1-7). Such high-level CO exposures described in clinical reports are extremely unlikely to be experienced under ambient exposure conditions, as demonstrated in the REA. In addition, the types of adverse effects (including severe neurological impairment and death) observed at very high COHb levels have not been demonstrated following CO or COHb concentrations associated with ambient exposure (ISA, section 5.3).

The commenter also states that CO effects at the other end of the spectrum from CO poisoning – i.e., effects of endogenous CO – inform our consideration of the biological plausibility of a causal role for carbon monoxide in the identified health outcomes. The available literature on the topic of endogenous CO is vast. In fact, the commenter cites 144 reviews of endogenous CO and heme oxygenase. The EPA is aware of the literature on which these many reviews are based, and has included two timely review articles in on this topic in the ISA.<sup>3</sup> The important role played by endogenous CO in physiologic pathways and the potential for exogenous CO to influence these functions is described in the ISA:

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<sup>3</sup> Review articles are generally not included in the ISA. Rather than bring forward new information in the form of original research or new analyses, these articles typically present summaries or interpretations of existing studies.

- “CO is a ubiquitous cell signaling molecule with numerous physiological functions.” [ISA, p. 5-12]
- “A key issue in understanding the biological effects of environmentally-relevant exposures to CO is whether the resulting partial pressures of CO (pCO) in cells and tissue can initiate cell signaling which is normally mediated by endogenously generated CO or perturb signaling which is normally mediated by other signaling molecules such as NO.” [ISA, p. 5-9]

Some recent animal *in vivo* and *in vitro* studies demonstrate exogenous CO effects on signaling pathways and tissue and cellular levels of CO under certain conditions (ISA, tables 5-1 and 5-2). Little is known however regarding kinetics or compartmentalization of CO pools. Further, there is uncertainty in extrapolating cell signaling results to adverse health outcomes as recognized in the ISA: “Whether or not environmentally-relevant exposures to CO lead to adverse health effects through altered cell signaling is an open question for which there are no definitive answers at this time” (ISA, p. 5-12). As a result of these considerations, the biological plausibility for causal relationships between ambient CO exposure and a range of noncardiovascular health outcomes is not firmly established. More evidence is required to definitively link altered cell signaling with adverse health outcomes following environmentally-relevant CO exposures.

In summary, EPA does not find the issues raised by the commenter to support a conclusion that relevant ambient concentrations of CO are causally related to a broad range of health effects, and further disagrees with the commenter that there is cause for concern for such health effects under conditions when the current standards are met. For the reasons described in response to comments (1) and (2) above, and in the preamble, based on consideration of all of the currently available evidence, EPA considers the current standards to provide the requisite protection, including an adequate margin of safety, to potentially susceptible populations or lifestages, including pregnant women and infants, as well as to the widely recognized at-risk population of people with heart disease.

- (4) *Comment:* Two commenters (PSR et al; Donnay) stated that EPA should be concerned regarding chronic exposures to CO and that the evidence indicates that the current standards do not afford protection against chronic exposures. In arguing that a range of health effects (to neurological, respiratory and cardiopulmonary systems) reported to be associated with CO poisoning conditions are relevant to much lower ambient CO concentrations, the second commenter (Donnay) additionally stated that “EPA should err on the side of caution in establishing the CO NAAQS by making the reasonable assumption that chronic or repeated low level CO exposures may increase the risk of these outcomes.” Talking points provided by this commenter in written testimony accompanying their oral testimony stated that “...chronic low-level CO exposures

result in more severe and persistent CO illnesses than single high level acute exposures.” (Donnay written testimony February 28, 2011, p. 5).

*Response:* EPA disagrees with the commenter that it is a “reasonable assumption that chronic or repeated low level CO exposures may increase the risk” of a range of outcomes associated with CO poisoning conditions. Additional statements made by this commenter implied to be relevant to chronic CO exposures are that low CO exposures result in a slower, more gradual uptake into the blood stream than higher CO exposures, providing a longer period during which CO “free in plasma” (i.e., not bound to hemoglobin) is available for distribution into tissues. As an initial matter, EPA notes that, due to the strong affinity of hemoglobin (Hb) for CO, there is very little free CO occurring in plasma, with less than 1% of total body CO appearing as dissolved CO in body fluids (ISA, p. 4-12). In support of the commenter’s view that chronic low CO exposures result in greater uptake into tissues, the commenter cites a small study involving 7 individuals where control subjects appeared to have higher CO uptake into muscle tissue compared to CO-exposed subjects (ISA, p. 4-16). However, this study, in which direct measures of tissue CO were not reported, is in contrast with evidence from a study which directly measured CO liberated from tissues and demonstrated that tissue CO increased with increasing COHb level (ISA, Table 4-2, p. 4-16), which is consistent with the prevailing theory on CO pharmacokinetics. Thus, while EPA agrees with the commenter that the equilibrium between inhaled CO and blood COHb is approached more slowly at lower COHb levels compared to elevated COHb, a slower rate of uptake does not indicate greater total CO uptake. Rather, the rate and amount of uptake into tissue compartments is controlled by the blood to tissue CO pressure differential, which is greater at higher COHb levels. Thus, consistent with the lack of chronic effects observed in the CO evidence base (discussed below), the body of evidence does not support the commenter’s contention of increased uptake over time at low CO concentrations.

EPA considered the evidence currently available on cardiovascular and respiratory morbidity and long-term (chronic) CO exposures and determined that the evidence was inadequate to determine that a causal relationship exists at relevant ambient CO exposures (ISA, pp. 2-6 and 2-9). EPA further considered the currently available evidence with regard to neurological morbidity and long-term (chronic) CO exposures, concluding that the evidence was only suggestive of a causal relationship with relevant ambient exposures. This conclusion is based on a lack of evidence, such as that which might come from mechanistic studies, that might lend biological plausibility to epidemiological study results and the inability to sufficiently rule out the role of chance, bias and confounding in the epidemiological associations observed (ISA, pp. 2-7, 1-14). Further, our conclusion regarding the evidence on chronic exposures to CO in relation to mortality indicates “...that there is not likely to be a causal relationship between relevant long-term exposures to CO and mortality” (ISA, p. 2-10). During this review, CASAC endorsed EPA’s conclusions regarding chronic exposures to ambient CO (Brain and Samet, 2010a, pp. 12, 16). Thus, EPA’s judgment is that

the current body of evidence does not support the commenter's view that the current standards fail to provide adequate public health protection against chronic exposures to ambient CO.

- (5) *Comment:* One commenter (Donnay) stated that the ISA and other documents developed in this review do not reflect the latest scientific knowledge useful in identifying ambient CO effects as required by the Clean Air Act. This commenter identified a number of studies not discussed in the ISA which he describes as relevant. Another commenter (ALA et al) also identified two studies not discussed in the ISA as relevant. Donnay further questioned EPA's procedure for reviewing the relevant CO literature in preparation of the ISA, questioning "whether EPA conducted a sufficiently comprehensive literature review", providing a list of articles, some of which were published prior to the cut-off date for the ISA and some published subsequently (Donnay, p. 8).

*Response:* EPA disagrees with the comment that the ISA does not reflect the latest scientific knowledge on effects of ambient CO. Rather, EPA considers the ISA to represent a thorough review of the latest scientific knowledge pertaining to the effects of ambient CO, consistent with the requirements of CAA section 108. In their review of the second draft ISA, CASAC agreed, stating that the "CO ISA will be adequate for rulemaking with the incorporation of changes in response to the Panel's major comments and recommendations" (Brain and Samet, 2010a).

As to the comprehensiveness of the literature review conducted by EPA, as described in section 1.3 of the ISA, EPA scientists and collaborators conducted comprehensive literature searches in multiple health and atmospheric science disciplines to identify original peer-reviewed research published since the last CO NAAQS review. These searches focused on articles published between 1999 and May 2009, the cutoff date for articles to be included in the ISA. Researchers screened the large body of search results to identify potentially relevant articles to be considered in preparing the ISA. In addition to these broad searches, targeted searches were conducted using search strategies such as review of pre-publication tables of contents of relevant journals, searches on specific topics, and citation mapping to find papers citing known articles. Additional articles were identified by the public and CASAC during external review of two drafts of the ISA and other review documents.

EPA notes that, in contrast to Air Quality Criteria Documents prepared during previous reviews, which were more encyclopedic reviews of the scientific literature, ISAs developed under the current NAAQS process are intended to present a "concise evaluation and synthesis of the most policy relevant science (ISA, p. 1-1). CASAC has endorsed this approach during the CO NAAQS review (Brain and Samet, 2009; Brain and Samet, 2010a). Policy-relevant questions critical to the review were identified prior to preparation of the first draft CO ISA through a kickoff workshop held January 28-29, 2008 (73 FR 2490) and described in the Integrated Review Plan (USEPA, 2008), a draft of which was the subject of

a consultation with CASAC (73 FR 12998; Henderson, 2008). These policy-relevant questions, presented on page 1-1 of the CO ISA, formed the basis for EPA's consideration of the scientific evidence. In considering the available CO literature, topics such as those raised by commenters (e.g., very high concentration exposures in humans and animals) were not found to be informative to assessment of the health effects of ambient CO or to the policy-relevant questions for this review (ISA, pp. 1-6, 1-7). Thus, these topics were not extensively discussed in the ISA.

EPA has considered the articles identified by commenters and determined that many of them were not included in the ISA as they fall outside the scope of the ISA document as they were not found to be informative to assessment of the health effects of ambient CO or to the policy-relevant questions for this review (ISA, pp. 1-6, 1-7). Studies listed by commenters that fall within the scope of the ISA (listed in Appendix A), including recent studies published after the cutoff date for inclusion, have been provisionally considered in topic-specific comments elsewhere in this document. Based on this provisional consideration, we conclude that the information provided by these studies does not materially change the conclusions reached in the ISA. Accordingly, as discussed in section I.C of the preamble, EPA is not re-opening the air quality criteria for this review to further consider these studies.

- (6) *Comment:* One commenter (Donnay) questions how EPA can rely on consideration of the lowest tested COHb level in Allred et al (1989) study in judging the standards to provide adequate public health protection when EPA has stated that this study provided no evidence of threshold. This commenter claims EPA has no scientific or legal basis for their consideration of the Allred results for this purpose, which the commenter claims to suggest a “reckless and wanton disregard for public health” (Donnay, p. 2). The commenter additionally describes statements or actions of the World Health Organization (WHO), U.S. Agency for Toxic Substances and Disease Registry (ATSDR), and U.S. National Academies of Science, National Research Council (NRC) as indicating that evidence is lacking to inform EPA's decision regarding a CO NAAQS that protects public health with an adequate margin of safety.

*Response:* EPA first notes that, as discussed in section I.A of both the proposal and final notice, the Clean Air Act does not require that the NAAQS be established at a zero-risk level, but rather at a level that reduces risk sufficiently so as to protect public health with an adequate margin of safety. In setting primary standards that are “requisite” to provide this degree of public health protection, the Supreme Court has affirmed that EPA's task is to establish standards that are neither more nor less stringent than necessary for this purpose. Accordingly, a lack of evidence for a threshold effect level for exercise-induced myocardial ischemia resulting from CO exposure does not mean that there is no

standard level that would be protective of public health with an adequate margin of safety.

As noted in section I.A. of the final rule, in addressing the Clean Air Act requirement for an adequate margin of safety, the EPA considers such factors as the nature and severity of the health effects involved, the size of the sensitive population(s) at risk, and the kind and degree of the uncertainties that must be addressed. The selection of any particular approach to providing an adequate margin of safety is a policy choice left specifically to the Administrator's judgment. For example, in considering the controlled human exposure studies that describe the effect of short-term CO exposure on exercise-induced myocardial ischemia in coronary artery disease patients, as described in section II.B.3 of the final rule, the Administrator considered the nature and severity of the health effects involved, as well as the kind and degree of the uncertainties in those studies as well as in the exposure and dose assessment. Based on such considerations, as well as those concerning the rest of the evidence, as discussed in section II.B.3 of the final rule, the Administrator judged the current standards to provide the requisite public health protection against effects of concern.

With regard to the commenter's reference to a WHO publication, we note the citation is to an article by D. Schwela (2000) in which WHO publications are reviewed. As the commenter notes, the summary for CO in this article, states that "[a]mbient CO may have even more serious health consequences than does COHb formation and at lower levels than that mediated through elevated COHb levels". Although somewhat unclear, this statement may be intended to reference the potential for effects of CO unrelated to COHb-mediated decreased oxygen delivery to tissues. EPA has considered the evidence that exogenous CO may initiate or alter cell signaling, as described in section 5.1.3 of the ISA. These mechanisms are likely to involve the binding of CO to reduced iron in heme proteins other than Hb with subsequent alteration of heme protein function. COHb may play a role in these processes by delivering CO to cells and tissues (ISA, p. 5-9), however, the role of these effects in producing health outcomes, as well as whether these effects occur in response to CO exposures relevant to those associated with ambient air is still uncertain (ISA, p. 5-12). The ATSDR report cited by the commenter points to a similar mechanistic pathway: "given the physiological role of endogenous CO..., any exogenous source of CO exposure" has "the potential for producing potentially adverse effects." The ISA states that ambient CO has the potential to alter cell signaling processes which may result in downstream health effects but notes that this is an area of uncertainty, stating that "[w]hether or not environmentally-relevant exposures to CO lead to adverse health effects through altered cell signaling is an open question for which there are not definitive answers at this time" (ISA, p. 5-12). Thus, EPA assessed the evidence for these pathways in the ISA, and Administrator took into consideration the possibility of adverse health effects together with the uncertainties, and concluded that the current standards provide the requisite protection, with an adequate margin of safety.

The commenter also points to the NRC's decision to not establish an acute exposure guideline level (AEGL)<sup>4</sup> for "non-disabling" effects (an AEGL-1) for CO, implying that this is related to consideration of uncertainty regarding a threshold for effects. EPA notes, however, that that is not the basis for the NRC's decision. Rather, as the NRC report describes, an AEGL-1 value was not recommended because susceptible persons may experience more serious effects (usually the basis for AEGL-2) at concentrations that do not yet cause non-disabling effects (usually the basis for the AEGL-1) in the general population (NRC, 2010). Thus consistent with the NRC methodology for cases such as this (NRC, 2001, p. 41<sup>5</sup>), the NRC did not set an AEGL-1. EPA additionally notes that the data on which the NRC relied for their decisions was that which focused on effects observed in response to elevations in COHb (e.g., Allred et al., 1989). Thus, particularly given the widely differing purposes for AEGLs and NAAQS and the statutory framework for NAAQS, EPA does not believe that the NRC's conclusions regarding AEGLs for CO are inconsistent with the Administrator's judgment as to the degree of protection afforded by the current standards.

#### **4. Comments on Exposure and Risk Considerations**

Included in this section are comments concerning consideration of the quantitative exposure and health risk assessments in the decision on the adequacy of the standards, which are generally not discussed in the preamble to the final rule.

- (1) *Comment:* One industry commenter (AAM), in concurring with EPA that the current standards provide a high degree of protection for the COHb levels and associated health effects of concern, also identified aspects of the REA that in their view result in the risk being overstated in the upper tail of the COHb distribution.
  - The reduced number of monitoring sites from which ambient CO measurements were drawn for the Denver study area inappropriately biases the exposure concentration distribution upward through giving relatively

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<sup>4</sup> Acute exposure guideline levels are established by the AEGL committee of the NRC for use in emergency planning. As defined by the NRC, an AEGL-1 is the airborne concentration of a substance "above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure." An AEGL-2 is defined as the airborne concentration of a substance "above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape." [NRC, 2001]

<sup>5</sup> *In cases in which the biologic criteria for the AEGL-1 value would be close to, or exceed, the AEGL-2 value, the conclusion is reached that it is "not recommended" (NR) to develop AEGL-1 values. In these cases, "detectability" by itself would indicate that a serious situation exists. In instances in which the AEGL-1 value approaches or exceeds the AEGL-2 value, it may erroneously be believed that people experiencing mild irritation are not at risk when in fact they have already been exposed to extremely hazardous or possibly lethal concentrations.* [NRC, 2001, p. 41]

greater weight to a site (in traffic island) not representative of locations where people in the population spend their time.

- In-vehicle and near-roadway CO concentrations are overestimated; there is no evidence of 1-hour exposure concentrations as high as 60 parts per million (ppm) in vehicles in areas that meet the current CO standards, indicating that the ratio method used for this microenvironment in the REA produces overestimates of exposure concentration.
- The cities on which the REA focused are worst case situations with regard to ambient CO concentrations nationally.

*Response:* With regard to the first REA aspect cited, AAM contend that the four Denver monitors used in the current REA overestimate risk relative to that estimated in the 2000 probabilistic NAAQS Exposure Model (pNEM) analysis (Johnson et al., 2000) which used ambient CO concentrations from six monitors. Specifically AAM charges that the approach used in the REA “biases the distribution upward by overstating the number of people exposed to high CO concentrations.” EPA first notes that all four Denver monitors used in the current assessment were also used in the previous CO exposure and dose assessment conducted by Johnson et al. (2000) (see REA, Table 5-1). The two monitors that were not used in the current assessment but used in the prior assessment were located outside of the urban core of Denver.<sup>6</sup> Neither of these additional monitors reported CO measurements for 2006, the year selected to represent *as is* air quality in the REA. In developing the exposure modeling domain (described in REA sections 5.3 and 5.4), EPA staff elected to maintain consistency in the ambient monitors chosen for the current assessment and considering the multiple air quality scenarios evaluated rather than attempt to be consistent with the ambient monitors used in the prior 2000 assessment.

While use of the four Denver urban core monitors may result in a greater percent of the population at or above selected benchmarks when compared with that of a simulation conducted using the six monitors from the 2000 assessment (and assuming the added two monitors in the modeling domain have lower concentrations relative to the four monitors used and all other modeling parameters are identical), EPA staff note that the actual number of persons (and person-days) at or above a benchmark within the air districts defined by these four monitors (all other modeling parameters held constant) would likely not be different than if the simulation had covered a larger study area inclusive of the areas surrounding the other two monitors that are outside of the Denver urban core. This is because the simulated population residing within the census tracts and encompassed by the same air quality districts is identical.

The commenter additionally states that inclusion of the microscale site at the main intersection in Denver overstates the number of people exposed to high CO

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<sup>6</sup> The first monitor was ID 080050002 sited in Littleton, Colorado (Arapahoe County). The second monitor was actually an aggregation of CO concentrations from two closely sited Boulder, Colorado monitors: ID 080130010 and 080131001 (Johnson et al., 2000).

concentrations and the fraction of time exposed. EPA notes, however, that the evidence indicates and CASAC also concludes that there is a segment of the population that spend some of their time in proximity to locations such as the microscale, near-road site where short-term CO exposures may be elevated (REA, section 3.1.3). The importance of capturing near-road microenvironments in considering ambient CO exposures was emphasized multiple times over the course of this review in comments received from CASAC who raised concerns with regard to the ability of the existing CO monitoring network to provide for this aspect of CO population exposures.<sup>7</sup> Further, a simulation from which this monitor was omitted would lack representation of the large spatial variation in short-term concentrations that the evidence indicates generally occurs across an urban area as a result of the steep concentration gradients near roadway locations where it is formed.<sup>8</sup> Thus, EPA finds the use of the full set of monitors, including the microscale site to be appropriate.<sup>9</sup>

As an initial point of clarification with regard to the statement made in the 2<sup>nd</sup> comment by AAM, the modeling for conditions just meeting the current 8-hour standard did not use 1-hour in-vehicle concentrations approaching 60 ppm. As clearly stated in footnote *d* for the table referenced by AAM in making this statement (REA, table 6-9, p. 6-14), the microenvironmental CO concentrations presented are for exposure events that ranged in duration from 1 minute to 1 hour.<sup>10,11</sup> In fact, the highest concentration noted in this table (for the simulation of conditions just meeting the current standard in Denver), which is 63.4 ppm,

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<sup>7</sup> See, for example, CASAC letter of June 24, 2009, in which they stated that “[r]elying 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” and “[r]elevant microenvironments that are influenced by local factors, such as in-vehicles {sic} and in high proximity to roadways, are not well represented.”

<sup>8</sup> The other three monitors in the study area are more similar to each other with regard to concentrations in the upper end of the distribution of 1-hour concentrations than they are to the micro-scale site monitor identified by commenters (REA, Table 5-18).

<sup>9</sup> EPA also notes that if the micro-scale site was omitted for the simulation of conditions just meeting the current 8-hour standard, another of the three monitors would be identified as the design monitor and all monitor concentrations would be adjusted to the point where that design monitor just met the current 8-hour standard. As these remaining three monitors are more similar to each other with regard to concentrations in the upper end of the distribution of 1-hour concentrations than they are to the micro-scale site monitor identified by AAM (REA, Table 5-18), the adjusted ambient CO concentrations would be generally higher across the full study area if only those three monitors were included in a simulation. This would be expected to contribute to a larger number of occurrences of generally higher CO exposures and might also include a greater percent of the CHD population with COHb levels over 2% or higher benchmarks.

<sup>10</sup> REA Table 6-9, footnote *d* states “The mean, standard deviation, and percentiles (p) were calculated using all events regardless of event duration. Note that based on the activity pattern diaries used, the length of an event can range from 1 minute to 1 hour.”

<sup>11</sup> These event-level microenvironmental concentrations were generated from a model simulation designed to output minute-by-minute microenvironmental concentrations. As described in sections 5.10 and 6.1 of the REA, these microenvironmental concentration and ratio analyses were generated using a reduced model run of 5,000 persons per air quality scenario and within each study area due to the magnitude of the files generated and the time required to process each persons’ event-level data. The full exposure model runs used 50,000 simulated individuals and generated summary output data files only.

was estimated to occur for a single 2-minute exposure event and that event was in an outdoor microenvironment and not inside a vehicle (see REA, figure 6-3). We note though that most (about 95%) of the highest microenvironmental concentrations ( $\geq 20$  ppm) simulated in Denver were associated with the in-vehicle microenvironment (REA, Figure 6-3). The highest estimated in-vehicle concentration, 56.9 ppm (REA, Table 6-9), however, was associated with a 1-minute exposure event, not 1 hour.<sup>12</sup> In the simulation for the Los Angeles study area under conditions just meeting the current standard, maximum event-level microenvironmental concentrations (ranging from 1-minute to 1-hour in duration) were much lower than Denver and estimated to be at or above 30 ppm (REA, Table 6-12 and Figure 6-4), with most occurring inside vehicles. The maximum exposure concentration was 39.8 ppm (REA, Table 6-12) occurring for two exposure events with duration of 5 and 10 minutes, well short of the 1-hour duration stated by the commenter.

Further, EPA disagrees with the commenter's contention that there are no data supporting the magnitude of the in-vehicle exposure concentrations in the REA. As noted in the REA (p. 6-17), "estimated upper level concentrations [for both study areas] for the in-vehicle microenvironment are within the maximum measured peak level (one minute average) concentration reported by Rodes et al. (1998) of 67 ppm during rush hour commutes in Los Angeles (ISA, section 3.6.6.2)." The REA exposure concentrations are also consistent with the AAM statement that "both the Shikiya et al. and Rodes et al. studies report peak CO concentrations of the order of 50 ppm" (AAM comments at p. 5).

EPA notes that under conditions just meeting the current standard in the Denver and Los Angeles study areas, the maximum 1-hour microenvironmental concentrations were estimated from the 5,000-person simulations (see footnote 11 above) to be 37.1 ppm and 34.8 ppm, respectively, both of which occurred inside vehicles.<sup>13</sup> These event-level results developed from the 5,000-person simulations are consistent with the results reported for the full model simulations (REA, Tables 6-7 and 6-10) and what is specifically stated in the REA regarding maximum 1-hour exposure concentrations<sup>14</sup> in the Denver study area where the "highest 1-hour daily maximum exposure was estimated to be at or above 40 ppm (but below 60 ppm)" (REA, section 6.1.2, p. 6-11). Regarding the Los Angeles study area, the REA similarly states that "the range of the 1-hour daily maximum exposure distribution extends upward to 30 ppm, but less than 40 ppm."

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<sup>12</sup> The duration of the exposure event in these microenvironments was obtained from analyzing the APEX events file for this simulation; it is not specifically reported in the REA.

<sup>13</sup> These maximum 1-hour microenvironmental concentrations were not directly reported in the REA and are from the 5,000 person simulations, though they are consistent with the distribution of maximum 1-hour exposure concentrations that were reported in the REA for the full model runs.

<sup>14</sup> In the full model runs, the 1-hour exposure concentrations are summarized by time-averaging across all microenvironments persons inhabited within the clock hour. As such, the 1-hour exposure concentration could be comprised of a single microenvironmental concentration (duration of 60 minutes) or multiple microenvironments (durations of less than 60 minutes). Specific microenvironment information is not included in these hourly summary output files.

Therefore, assuming that most of the highest CO exposure concentrations occurred inside vehicles, estimated 1-hour maximum concentrations were reported in the REA as mostly less than 40 ppm for the in-vehicle microenvironment and not “approaching 60 ppm” as charged by AAM.

In their rationale for concluding the REA overestimated in-vehicle concentrations, AAM also stated that Rodes et al. (1998) “reported in-vehicle CO concentrations between 3 and 5.4 ppm for 2-hour measurements.” This refers to the range of mean values calculated in the Rodes et al. (1998) study, which, as they are mean concentrations over periods well longer than a few seconds, are more relevant to the mean of the simulated in-vehicle concentration reported in REA Table 6-9 rather than to maximum microenvironmental concentrations. In fact the mean in-vehicle concentration in REA Table 6-9 is 3.5 ppm, falling toward the lower end of the range quoted by AAM. Even considering this excellent agreement between the Rodes et al (1998) mean measured in-vehicle CO concentrations and the mean modeled concentrations reported in the REA, we note that the Rodes et al. (1998) study only included measurements for a few hours of the day, all occurring within a 9-day period in late September and early October 1997 in Los Angeles. In the REA, exposure concentrations are estimated for, at a minimum, 8,260 exposure events<sup>15</sup> of each simulated individual’s full year exposure profile. Throughout a year there are a variety of emission, meteorological, physical, and personal factors that influence ambient and exposure concentration variability captured by the model and likely not at all represented by the data typically reported in measurement studies. The ISA indicates that when considering four basic seasons of the year, the mean and maximum ambient CO concentrations are highest in winter for Los Angeles (ISA, Figure 3-22), a time period represented by the REA exposure simulations but not by the Rodes et al., (1998) study. Given that, it is very likely that the Rodes et al. (1998) study does not represent the upper percentiles of the in-vehicle concentration distribution occurring for that year of the study (1997), thus limiting its comparability with the REA in-vehicle estimates.

AAM further compares REA estimated upper percentile in-vehicle concentrations from simulations for air quality that just meets the current standard to measurements reported by Westerdahl et al. (2005), a comparison which EPA notes is inappropriate. This comparison is inappropriate because the Westerdahl et al. (2005) study was conducted in 2003, a year having ambient CO concentrations well below the current NAAQS. Median ambient 1-hour monitoring concentrations from that 2003 study ranged from 0.6 to 1.0 ppm (Westerdahl et al., 2005, Table 2) and are more comparable with the REA *as is* air quality scenario that employed 2006 Los Angeles ambient monitoring data in which median 1-hour concentrations ranged from 0.3 to 0.7 ppm (REA, Table 5-16).

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<sup>15</sup> As described in REA section 4.4.3.2, a person could be exposed for periods as short as 1 minute with a maximum duration of 1-hour, depending on the duration of the person’s activity performed or their time spent in a particular microenvironment.

AAM also argue that the ratio method used by EPA to estimate in-vehicle concentrations would tend to bias CO concentrations high, particularly in an urban area if ratios are generated from other less urbanized areas having low background concentrations. In such instances, AAM allege that the distribution of derived ratios would be higher than similar ratios generated in locations, such as urban areas, where background concentrations are typically higher. EPA responds, however, that the method used to estimate all microenvironmental concentrations (including in-vehicle) in the REA (which was derived from measurement studies conducted in Denver and Los Angeles, as described in the REA section 4.4.4.3.1) would tend to guard against the mismatching of high ratios with high ambient concentrations. The microenvironmental algorithm employs an exponential transformation of the ambient concentration (REA, sections 4.4.4.3 [pp. 4-19 to 4-20], 4.4.4.4 and 5.9.1 [pp. 5-27 to 5-29]) that effectively produces a “compression” effect in which the ratio of outdoor CO to ambient monitor CO tends to become smaller (on average) as the ambient monitor concentration increases (REA, p. 5-28). Section 5.10.2 of the REA discusses the relationship between estimated microenvironmental concentrations and their associated ambient monitor concentrations, and demonstrates that the phenomenon about which the commenter is concerned does not occur. For example, ratios derived in the REA of the estimated microenvironmental concentrations to the associated ambient concentrations (for the in-residence and in-vehicle microenvironments) illustrate an inverse relationship (REA, Figure 5-3), rather than the direct relationship that the commenter presumes. As stated in the REA, this demonstrates that the high ratios “that might have occurred when randomly sampling from the distributions used in Table 5-22 were effectively modified by the ambient concentration exponential adjustment (equation 4-11), thus controlling for extreme ratio and high concentration combinations in estimating the microenvironmental concentrations (REA, p. 5-35).”

As basis for the commenter’s statement that the study areas selected for assessment in the REA would be considered a “worst case” situation, they cite the discussion of ambient monitoring in these cities reported by the National Research Council (NRC, 2003). EPA notes, that the NRC report mentions these two cities among a list of eleven locations across the U.S.<sup>16</sup> that were identified as locations where NAAQS attainment “has been a particular challenge” because of a combination of conditions that may favor accumulation of CO emitted into the ambient air, and associated increases in CO concentrations, including meteorological, topographical, vehicle emission, and CO transport issues (NRC, 2003). The NRC report does not, however, identify Denver and Los Angeles as cities representing the worst cases among the eleven identified, nor does it refer to the individual “CAMP” and “Lynwood” monitors mentioned by AAM as reporting “worst case” CO concentrations. In fact, when considering the current

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<sup>16</sup> The nine other locations identified in Table 1-1 of NRC (2003) include: Birmingham, AL; Calexico, CA; Fairbanks, AK; Phoenix, AZ; Spokane, WA; Las Vegas, NV; Anchorage, AK; El Paso, TX; and Kalispell, MT.

8-hour CO NAAQS, the NRC report identifies a monitor in Birmingham Alabama (01-073-6004) as having the greatest number of exceedances during 1995-2001 (the period examined) of the 11 locations discussed (Table 1-1, NRC, 2003).

EPA does not consider the two study areas to represent “worst case” situations. As explained in the REA (section 5.3), study area selection criteria included “the prior analysis of these locations in CO NAAQS reviews, the areas having historically elevated CO concentrations, and the areas currently having some of the most complete ambient monitoring data available” (REA, p. 5-2). There are two benefits in using these two particular study areas for our exposure assessment. Minimal adjustment was needed to simulate the air quality scenario of just meeting the current standard, as CO monitoring concentrations had in the past been at levels just above and below the current CO standards in both of these locations, thus providing a more realistic simulation of such an air quality scenario, and previous CO exposure assessments had also focused on these areas. Further, the relationship between 1-hour and 8-hour average ambient CO concentrations, a characteristic EPA noted as influential in differences in the population occurrences of elevated end-of-hour COHb estimates for the datasets for these two locations for the just meeting the current standard simulations was described in the Policy Assessment (PA, p. 2-41). The ratios of 1-hour to 8-hour design values for the two study areas were not extreme among all U.S. counties in the most recent year for which data were available (2009). The ratio for the Los Angeles dataset corresponded to approximately the 25<sup>th</sup> percentile of U.S. counties in 2009 while the Denver dataset corresponds to the 75<sup>th</sup> percentile.

- (2) *Comment:* Comments from one individual (Donnay) stated that the Coburn-Foster-Kane (CFK) model used by the Agency is in error and should not be used to estimate COHb. Specifically, in using selected results of a comparison of CFK model estimates to experimental COHb measurements published by Benignus et al. (1994), Mr. Donnay suggests the range of predicted error in the CFK model is “almost the 2% threshold upon which EPA’s entire risk and exposure assessment modeling is based” (Donnay, p. 4).

*Response:* In considering this comment, EPA first notes that there are occasions where the CFK model may either over or underestimate % COHb in an individual’s blood (this is referred to here as model or prediction error). In general, the frequency and magnitude of prediction errors in any model are commonly linked to the model’s ability to represent the most, if not all, influential variables that affect variability in the estimated values. Such occasions of CFK model prediction error, which are described in the 2000 *Air Quality Criteria for Carbon Monoxide* (AQCD) (USEPA, 2000, pp. 5-14 to 5-15), can include specific minutes within a CO exposure time series, particularly those associated with substantial CO exposures, and such occasions are the focus of the commenter’s statements on this issue. However, EPA disagrees with the commenter’s limited interpretation of the published findings by Benignus et al.

(1994), which evaluated CFK model predictions against experimental measurements. The commenter did not fully consider the intent of the Benignus et al. (1994) research and study design, its many findings and conclusions, conclusions drawn from other publications that evaluated the CFK model, and thus, the relevance of Benignus et al. (1994) to the CFK modeling done in the REA.

As an initial matter, by claiming that CFK predictions are in error by “almost the 2% threshold in % COHb” which is a benchmark used in the REA, the commenter is inappropriately citing a Benignus et al (1994) result for a single maximum underestimation by the CFK model of 3.8% in one participant at one time point, and implying that this study indicates that an underestimation of the same absolute value of the percentage COHb is likely in the REA. Notwithstanding the likely lower prediction error for the much lower exposures which are the focus of the REA, discussed in more detail below, EPA notes that model prediction error from the Benignus et al (1994) paper is more appropriately considered in terms of the percentage of the total measured (or predicted) value that is represented by the absolute difference in values between the measured and predicted values. For example, in the study by Benignus et al. (1994), for which the total % COHb levels of the participants ranged from about 12 to 18% COHb, the underestimation of 3.8% cited by the commenter represented a maximum prediction error for that specific time point for that individual of about 20-30% of the individual’s absolute COHb level.<sup>17</sup> Thus, if it were the case that the individual time point errors for the higher CO exposures of Benignus et al. (1994) were predictive for the substantially lower exposures of the REA, this finding might indicate that the maximum prediction error for an REA prediction of 2% COHb could be as much as an increment of 0.6% COHb (i.e., 30% of 2% COHb).

Importantly, however, the CO exposures that are the focus of Benignus et al. (1994), and which are substantially higher than those in the REA, are associated with higher prediction errors on individual time points than occur for lower CO exposure scenarios. For example, as described in the 2000 AQCD, Hauck and Neuberger (1984) compared the 5-minute time series of COHb observations with CFK model predictions in four individuals, each exposed to varying CO concentrations, while at rest and performing moderate exercise (2000 AQCD, p. 5-14). While CO exposure concentrations in this study were still somewhat higher than those simulated in the REA (i.e., generally study participant were exposed to one hundred to hundreds of ppm), the resulting COHb time-series for a few subjects fell within the range of about 1% to 4% COHb (see Figures 2 and 4 of Hauck and Neuberger, 1984), consistent with the range of % COHb estimates reported in the REA (REA, Tables 6-18 and 6-19). As noted in the 2000 AQCD, “[t]he agreement between measured and predicted COHb under these varied

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<sup>17</sup> This can be calculated as the difference of the measured from predicted [3.8%] divided by the absolute measured value [which, while not explicitly reported is described by Figure 1 of Benignus et. al. (1994) to range from 12-18%).

conditions was very good”, with a mean difference of only 7.4% of the nominal (maximal predicted) value (2000 AQCD, p. 5-14).<sup>18</sup>

EPA further notes that, contrary to the commenter’s assertion, the study by Benignus et al. (1994) in fact finds the CFK model estimates of COHb to be generally consistent with actual measurements of vCOHb, providing support for our use of the CFK model. As shown in Table 2 of Benignus et al (1994), the averages of model predictions at all tested time periods were not statistically significantly different from the corresponding averages of venous COHb measurements ( $p > 0.80$ , see Table 2 of Benignus et al. 1994). This finding is particularly significant given the fact that the CO exposure concentrations investigated in Benignus et al. (1994) are much higher than those assessed in the REA. In Benignus et al. (1994), CO exposure concentrations were specifically selected to be so high and occur over such a short period of time that they would intentionally disrupt the concentration equilibrium that would normally exist between the venous and arterial blood flows within study subjects if exposed to lower CO concentrations. The administered CO exposure concentration to study subjects was 6,683 ppm occurring over period of about 5 minutes (Benignus et al., 1994). This is over one hundred times the maximum single CO exposure concentration estimated in the REA (i.e., 63.4 ppm for 2 minutes).<sup>19</sup>

Further, although not mentioned in Mr. Donnay’s characterization of Benignus et al. (1994), EPA notes the discussion by Benignus et al. (1994) that supports the CFK model assumption of a single well-mixed vascular compartment and the model’s accurate prediction of venous COHb at low CO exposure concentrations and for longer durations. For example, the paper states that when inspired CO “is low and exposure are long, as was the case during initial experiments (Coburn et al., 1965), these assumptions [of a single well mixed compartment] are valid and the CFKE accurately predicts mean peripheral venous HbCO” (Benignus et al., 1994, p. 1743). As discussed more fully in the response to comment II.A.5(1) below, in considering the lag between arterial and venous COHb, the paper further states that “arterial blood mean  $\Delta$ HbCO began to decline within 1 min of exposure cessation and progressively approach the mean venous value” and indicates that the equilibrium between venous and arterial COHb is reestablished within 3 minutes or less time (Benignus et al., 1994, p. 1743 and Figure 2). The

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<sup>18</sup> The absolute value of the mean percent deviation of % COHb (not total deviation in % COHb) in two persons experiencing this relevant range of %COHb across four experiments ranged from 5.4% to 14.1% (Table 3 of Hauck and Neuberger, 1984). Using this prediction error and the range of estimated % COHb experienced by the two study subjects, CFK model predictions could vary by an increment as little as  $\pm 0.05$ - $0.14\%$  COHb at  $1\%$ COHb or at most, an increment of  $\pm 0.22$ - $0.56\%$  COHb while at  $4\%$  COHb.

<sup>19</sup> For added context, EPA notes that over 99% of all exposure events simulated by APEX in the REA for the highest CO exposure simulations in the Denver and Los Angeles study areas (Tables 6-9 and 6-12) had CO concentrations below 13 ppm and well below 9 ppm, respectively. While the duration of exposure events simulated by APEX can be as short as 1 to 5 minutes, it is certainly not the case that short-term CO concentrations would reach thousands of ppm during any time or would vary by such extremes over such a short time period as that assessed in Benignus et al. (1994) (i.e. start at 0 ppm, increase to 6,700 ppm for 5 minutes, then decrease to 0 ppm for about 5 minutes).

CFK model assumption of equilibrium is also supported by several studies cited by Benignus et al. (1994) which involved COHb levels more similar in magnitude to those estimated in the REA and for which CFK model estimates are comparable to COHb measurements obtained from venous blood of study subjects. CFK model evaluation studies are discussed in depth in the 2000 AQCD. For example, based on experiments performed for 10 different CO exposure profiles at several exercise levels, the 2000 AQCD concluded that “the agreement between measured and predicted COHb under these varied conditions was very good” (2000 AQCD, p. 5-14).

## ***5. Additional Comments on Interpretation of Scientific Evidence***

Specific comments on the EPA’s interpretation of the scientific evidence not discussed in the preamble to the final rule are described and addressed in this section.

- (1) *Comment:* One commenter (Donnay) argued that the reliance on COHb for judging the effects of CO is inappropriate, stating that venous COHb is “not a consistent or meaningful biomarker of either CO dose or effect”. In support of this view, the commenter first states that “vCOHb is a unreliable measure of any recent CO exposure”, which “does not correlate consistently with the symptoms, severity or outcomes of CO poisoning” because, in the commenter’s view, “[venous COHb] always rises more slowly than [arterial COHb] in response to any level of exposure ... taking anywhere from 6 to more than 20 hours to reach equilibrium with arterial COHb” (Donnay, p. 4).

*Response:* The EPA disagrees with the commenter’s view that COHb should not be relied upon as a biomarker of CO exposure, dose, and effect. The EPA accepts that using the measurement and estimation of COHb has limitations in terms of interpretation of the immediate dose following CO inhalation (discussed in Section 4.2 of the ISA). However, COHb measured in venous blood remains the most extensively validated biomarker of CO exposure and effects, and is the metric used in published health outcome studies (ISA p. 4-1; ISA, section 5.2.4).

EPA agrees with the commenter that in response to changes in CO exposure conditions the evidence indicates there is a period where the arterial and venous COHb levels are not equivalent. EPA notes, however, such periods are quite short and, based on the relationship between magnitude of exposure and size of the disparity, any such disparity is expected to be small under exposure conditions associated with ambient CO. As discussed in the ISA (ISA, section 4.2.1), this disparity between venous COHb (vCOHb) and arterial COHb (aCOHb) was examined by Benignus et al. (1994). This study, also quoted by the commenter, concludes that “after rapid high concentration CO uptake (6,683 ppm CO) in resting adults, the CFKE-predicted group mean change in COHb became indistinguishable from the group mean observed change in COHb in peripheral venous blood within 2-5 min after the end of exposure”. Benignus et al. (1994) found that vCOHb and aCOHb equilibrated in less than 10 minutes in most

subjects exposed to high concentrations of CO, highlighting the short-lived nature of this inequality. Importantly, the a-vCOHb disparity was proportional to the COHb equilibrium level. Thus, although comparisons of arterial and venous COHb concentrations have not been investigated after ambient exposure to CO in a similar experimental manner as has been done for high concentration CO exposures, exposure to the much lower ambient levels of CO would be expected to result in a much smaller difference between venous and arterial COHb making the venous COHb an informative measure of arterial COHb and the distribution of CO among critical organs, such as the heart and brain.

- (2) *Comment:* Some commenters (Donnay, PSR et al) questioned EPA's reliance on the Allred et al. controlled human exposure study in evaluating the health effects of CO, with one commenter stating that the age of the study (conducted more than 20 years ago) precludes it from meeting the CAA requirements for EPA to rely on the latest scientific knowledge. The commenters also argue that the study population was small and only included non-smoking men, making the study "inappropriate for use as the primary basis for a national population standard" (PSR, p. 5) The commenters state that the study used exposure conditions significantly different from the low-level exposures experienced currently, and that the study results show high inter-individual variability, limiting their biological significance.

*Response:* EPA strongly disagrees with the assertion that older studies should, as a matter of course, be given less weight in evaluating the health effects of exposures to the criteria air pollutants, particularly in cases where these studies remain the definitive works available in the scientific literature. The study to which the commenter is referring (Allred et al., 1989) is a well conducted, extensively reviewed, multicenter investigation funded by the Health Effects Institute evaluating the effect of carbon monoxide on the induction of myocardial ischemia among a relatively large number of human subjects with coronary artery disease. The commenters are correct that the results of this study demonstrate considerable interindividual variability; however, it is important to note that even with this variability, the study was sufficiently powered to detect statistically significant CO-induced decreases in time to indicators of myocardial ischemia during exercise at both COHb concentrations (i.e., targeted COHb concentrations of 2% and 4%). As pointed out by the commenter, in order to achieve these COHb concentrations during a relatively short exposure period (~60 minutes), average exposure concentrations that were higher than typical 1-hour ambient CO exposure concentrations were used by necessity. Nonetheless, as is illustrated by the REA, the resulting COHb concentrations for the lower exposure conditions (which averaged 2-2.4% COHb<sup>20</sup>) fall within those that might occur in response to ambient CO exposures under conditions when the current 8-hour standard (the

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<sup>20</sup> The average COHb level immediately upon cessation of CO exposure conditions was 2.4% and the average across the subjects after exercise and at the time of response measurement was 2.0% (Allred et al., 1989).

controlling standard) is just met (e.g., PA, Table 2-4). Further, we note that the study was designed by an advisory committee appointed by HEI's Research Committee; three of the six advisory committee members were experts not affiliated with HEI. The overriding objective was to produce an independent, robust and high quality study that would be informative to the consideration of the occurrence of exercise-induced myocardial ischemia that might be associated with exposures that may occur under the current NAAQS (Allred et al. 1989, p. 81).

With respect to the commenters' view that EPA has placed undue emphasis on the findings of Allred et al. (1989), it is important to note the results of this study are supported by other similar controlled human exposure studies (see ISA, section 5.2.4). As described in the ISA and alluded to by the commenters, differences in experimental protocols and analytical methods across studies (Adams et al, 1988; Allred et al., 1989; Anderson et al. 1973; Kleinman et al., 1989; Kleinman et al., 1998) do not allow for an informative quantitative pooled or meta-analysis. Nonetheless, similar to Allred et al. (1989), these studies demonstrate decreases in the time to onset of angina among individuals with coronary artery disease following exposure to CO resulting in COHb concentrations between 3% and 6%. Further, a much larger body of epidemiologic studies of cardiovascular outcomes (described in section 5.2.1 of the ISA) is coherent with this line of evidence (ISA, section 5.2.6.1). In evaluating the health effects evidence for relevant exposures to CO, EPA has integrated evidence from across scientific disciplines, recognizing the strengths, limitations, and uncertainties associated with each study type, as well as each of the individual studies reviewed. EPA requested that CASAC comment on the interpretation of the evidence and the causal determination reached for short-term exposure to CO and cardiovascular morbidity as a part of the review of the second draft CO ISA. In their consensus response to the Agency's charge (Brain and Samet, 2010a), CASAC stated, "*The most compelling CO-related CVD results remain those from the 20+-year-old controlled human exposure studies ... More recent human epidemiology studies of morbidity at ambient CO levels, including data on hospital admissions, are consistent with and reinforce the observations from earlier controlled human studies.*" These statements provide strong support to the Agency's consideration of the study by Allred et al (1989) in the scientific evaluations and conclusions described in the ISA.

Thus, EPA concludes it is appropriate to place weight on the results of the study by Allred et al (1989) to inform our interpretation of dose estimates from the REA under conditions associated with just meeting the current standard. Such consideration of this study is consistent with the critical role of the study in providing quantitative evidence regarding health effects associated with short-term exposures to ambient CO in the ISA, and with the complexity of drawing quantitative conclusions from the epidemiological studies of cardiovascular outcomes recognized in the ISA and by CASAC (ISA, p. 2-14; PA, pp. 2-34 to 2-39; Brain and Samet, 2010a).

- (3) *Comment:* One commenter (PSR et al.) contends that the weight EPA gives to angina-related effects in patients with coronary artery disease (CAD) in considering the adequacy of the NAAQS is inappropriate. In support of this view, the commenter cites a CASAC comment regarding consideration of the epidemiological studies for various cardiovascular outcomes and potential uncertainty associated with identification of the population most susceptible to CO-induced effects, as well as the commenter's own comparison of effect estimates reported from epidemiological studies for various health outcomes.

*Response:* As an initial matter, EPA notes that we have not limited our focus in this review to angina (a symptom of myocardial ischemia, which does not occur in all individuals with myocardial ischemia). Rather, EPA has appropriately focused on ischemia-related effects in patients with CAD as the population group most sensitive to effects of ambient CO exposures (ISA, p. 2-10; 2000 AQCD, p. 4-3). The focus on ischemia-related effects is well-supported by the integrated evaluation of the evidence from controlled human exposure, toxicological and epidemiological evidence, rather than reliance on a singular outcome in the epidemiological evidence, as is implied by the commenter's statements. In fact, the CO ISA 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 CAD" (pg 5-47), which found decreased time to onset of exercise-induced angina and electrocardiogram changes indicative of myocardial ischemia. The findings from the epidemiological studies are coherent with this evidence, and the known role of CO in limiting O<sub>2</sub> availability lends biological plausibility to ischemia-related health outcomes following CO exposures. Because the most compelling evidence is from controlled human exposure studies among individuals with CAD, a view endorsed by CASAC (Brain and Samet 2010a, p. 12), the focus on ischemia-related effects in susceptible groups, including people with CAD and other types of heart disease is appropriate.

In comparing effect estimates, the comment cites a single effect estimate from a single study of hospital visits for angina and some higher effect estimates for individual studies of other cardiovascular endpoints (e.g., stroke and heart attack). In focusing on effect estimates from individual studies, they overlook the need for an integrated assessment of the evidence which is provided by the ISA. In this assessment, EPA concludes that the epidemiological studies of CAD outcomes are coherent with the results of the controlled human exposure studies and that, given this consistent and coherent evidence from epidemiological and human clinical studies, along with biological plausibility provided by CO's role in limiting oxygen availability, a causal relationship is likely to exist between relevant short-term exposures to CO and cardiovascular morbidity (ISA, p. 5-48). The commenter ignores the full range of epidemiological study results for ischemia-related outcomes. For example, Figure 5-2 of the ISA demonstrates that studies evaluating the association of CO concentrations and ischemia-related

outcomes (including ischemic heart disease, angina, and myocardial infarction) generally report increases in the number of hospital admissions for these outcomes, ranging in magnitude from approximately 1% to 20% (ISA, p. 5-27).

- (4) *Comment:* One commenter (Donnay) stated that studies of the associations of effects with exhaled CO (eCO) were ignored in the CO ISA, and that eCO is a more consistent biomarker than COHb of both exogenous CO exposure and elevated endogenous CO production. This commenter further stated that EPA should rely more on exhaled CO (instead of COHb) as key metric for assessing CO effects and exposure.

*Response:* The commenter provides a bibliography of additional references pertaining to eCO, some published after May 2009, the CO ISA reference date cut-off. The majority of the provided publications focus on the association of eCO with various diseases not resulting from CO exposure. EPA agrees that endogenous CO is increased by a number of diseases and health conditions (ISA, section 4.5) and that these diseases result in increased eCO (ISA, Figure 4-12). This is a result of up-regulation of heme oxygenase expression and activity and heme protein catabolism. However, these publications do not provide evidence of eCO as an indicator of CO exposure but instead as an indicator of inflammatory and oxidative health conditions that increase endogenous CO production and thus elimination. Based on EPA's provisional consideration of these studies, in the context of the findings of the ISA, EPA concludes that the new information and findings do not materially change any of the broad scientific conclusions regarding effects as to the relevance of eCO as a biomarker of CO exposure made in the 2010 CO ISA and thus do not warrant reopening the air quality criteria review.

The use of eCO as an indicator of clinical severity of disease is well documented (e.g., ISA, Figure 4-12, p. 4-25). However eCO has not been established as a biomarker of ambient air CO exposure. One study provided by the commenter elegantly describes the necessity of biomarker validation (Scherer, 2005) including understanding of specificity, sensitivity, population background levels, dose-response relationship, inter- and intra-individual variability, kinetics, confounding, and modifying factors. However, the use of eCO as a biomarker of ambient CO exposure has not been characterized with regard to these criteria. To date, evidence is lacking to fully characterize the response of eCO concentrations to inhaled CO concentrations and accordingly no quantitative models that describe this relationship are available, thus limiting the utility of eCO as a biomarker of exposure to ambient CO. As COHb has been used as the biomarker of CO exposure for decades the necessary validation of COHb as a biomarker has been conducted, including the development of multiple quantitative models describing its generation in response to CO exposure (see ISA, section 4.2).

Finally, as eCO has been the focus of recent research, whereas COHb has been used as a marker of CO dose for many years, health effects studies have not used eCO as the primary dose metric when investigating the relationship between exogenous CO exposure and biological responses including ischemia-related cardiovascular outcomes, birth outcomes, or other health effects. Therefore, EPA does not find adequate support in the scientific evidence for the use of eCO in assessing CO effects and exposure.

- (5) *Comment:* One commenter (Donnay) stated that EPA did not give adequate consideration to studies of effects other than COHb-mediated hypoxia, and the commenter provided a list of publications he states provide evidence of other measures of CO effects which should have been considered in this review, and which he considers to support his view that EPA should have focused less on COHb in this review.

*Response:* The 14 publications cited by the commenter on other measures of CO effects include 10 studies of CO poisoning or intoxication. As discussed above (response to comment II.B.3(3) above), these studies are outside the scope of the ISA (ISA, section 1.5) because EPA judged them to be “not directly relevant to ambient exposures” (ISA, pp. 1-6 and 1-7). The other four studies include one which describes a new method for measuring COHb, an animal study demonstrating the role of free radicals in ototoxicity resulting from noise plus CO exposure, a case report describing central nervous system effects thought to be associated with chronic CO exposure and an epidemiologic study describing an association of CO exposure with indices of atherosclerosis in barbecue workers. One of these latter two studies was published after the cutoff date for the ISA.

Based on EPA’s provisional consideration of these studies, in the context of the findings of the ISA, EPA concludes that the new information and findings do not materially change any of the broad scientific conclusions regarding effects associated with CO exposure made in the 2010 CO ISA and thus do not warrant reopening the air quality criteria review. Furthermore, as described in the response to comment (II.B.5(1) above), EPA believes that the ISA’s focus on COHb is appropriate, given that COHb has been extensively validated over many years, is well-correlated with other biomarkers, and is the basis for controlled human exposure studies investigating health effects of CO.

- (6) *Comment:* One commenter (Donnay) pointed EPA to consideration of a list of studies describing genetics and gene expression of heme oxygenase, by which endogenous CO is derived, including studies of associations between heme oxygenase genetic polymorphisms and susceptibility to coronary artery disease. In so doing, he stated that, as EPA cannot regulate endogenous CO, they should more tightly regulate exogenous CO exposures in order to reduce total risk.

*Response:* The EPA recognizes that there are numerous conditions and disease states where heme oxygenase (HO-1) is induced. As discussed in the ISA, the resulting excess endogenous CO may react intracellularly with heme proteins or diffuse into the blood according to the gradient of pCO in the cell/tissue and blood compartments (ISA, section 5.1.3.3). Short-term increases in HO-1 often represent adaptive responses to stress. Longer-term increases in HO-1 are sometimes associated with protective responses and sometimes with pathophysiologic responses. While it is possible that prolonged increases in endogenous CO production may result in less of a reserve capacity to handle additional intracellular CO resulting from exogenous exposures, there is no experimental evidence to support this mechanism.

Similarly, polymorphisms of the heme oxygenase gene promoter may result in inter-individual variation in endogenous CO levels. Since CO is a product of reactions catalyzed by heme oxygenase, altered expression of heme oxygenase could lead to more or less intracellular CO. Some studies, including some cited by the commenter, have linked lower HO-1 expression, which would lead to *lower* endogenous CO, to increased susceptibility to coronary artery disease (or adverse cardiovascular outcomes) in humans. These results are consistent with cytoprotective effects of CO demonstrated experimentally (see ISA, sSection 5.3.1.2). Based on EPA's provisional consideration of these studies, in the context of the findings of the ISA, EPA concludes that the new information and findings do not materially change any of the broad scientific conclusions regarding effects associated with CO exposure made in the 2010 CO ISA and thus do not warrant reopening the air quality criteria review. While these findings are intriguing and suggest that endogenous CO may play a role in susceptibility, other plausible mechanisms have not been ruled out. For example, iron and biliverdin, which are also products of heme oxygenase-catalyzed breakdown of heme and also bioactive, could mediate the cytoprotective effects. Conversely, iron and biliverdin could mediate pathophysiologic effects associated with increased HO-1.

Thus, while it is possible that prolonged increases in endogenous CO resulting from chronic diseases or deficits in endogenous CO resulting from genetic polymorphisms may provide a basis for the enhanced sensitivity of susceptible populations to CO-mediated health effects, additional studies are required to investigate the relationship between internal CO burden and associated health risk. As noted in the ISA, "CO may be responsible for a continuum of effects from cell signaling to adaptive responses to cellular injury..." (ISA, p. 5-11).

It should be noted that the commenter cited numerous studies of "genetics and gene expression of CO and its primary endogenous source" (Donnay, p. 8). Only a minority of these studies address genetic polymorphisms of heme oxygenase in humans. As described above, our provisional consideration of these studies concludes that the study findings do not materially change any of the conclusions made in the ISA regarding effects associated with CO exposure and thus do not

warrant reopening the air quality criteria review. The majority of the studies which were cited addressed other topics including the therapeutic effects of heme oxygenase achieved by transfection or gene therapy in animal models, the regulation of HO gene expression by cellular signaling pathways and the role of CO in regulating the expression of genes. These topics, while scientifically interesting, do not address the issue of susceptibility in human populations or the health effects of ambient CO exposure, and as such are outside the scope of the ISA.

- (7) *Comment:* One commenter (AAM) stated that the evidence on potentially beneficial effects of exposure to CO should be considered by the Administrator, additionally claiming the information in this area is relevant to the interpretation of the epidemiological results.

*Response:* As the commenter recognizes, studies on therapeutic or potentially beneficial aspects of CO application (e.g., anti-inflammatory response) are discussed in the ISA (ISA, section 5.1.3.2). Accordingly, such effects are part of the body of evidence considered by the Administrator during this review. The ISA notes, however, that dose-response relationships between CO and these types of effects remain unexplored and that it is “unclear how these effects may be related to environmentally-relevant exposures” (ISA, p. 5-7). For example, results of controlled human exposure studies, which evaluated the potential anti-inflammatory effects of exposure to 100-500 ppm CO, were mixed. One of the two studies reported no effect, and a second reported that two of the nineteen subjects experienced exacerbations of COPD. Thus, while some studies demonstrate the involvement of CO in potentially beneficial physiological processes, uncertainties regarding dose-response relationships, the link between these effects and environmentally relevant exposures, and the potential for concomitant adverse effects complicate the interpretation of this evidence with respect to health effects of CO in ambient air. While the commenter states that evidence on potentially beneficial effects of exposure to CO is relevant to the interpretation of epidemiological studies, we note that to the extent some beneficial effect is exerted by ambient CO, it would inherently be reflected in the studies.

CASAC agreed with EPA’s characterization of this evidence (Brain and Samet, 2010a, p. 13), saying that:

*There is a growing literature regarding possible therapeutic applications of CO at levels of ~250 ppm. These studies have been carried out in some animal models and in cell culture. CO is a pro-oxidant and has profound extended pro-inflammatory effects. However, in specific scenarios with distinct organ systems or specific cell types, CO may have short-term anti-inflammatory effects. Clinical trials thus far have not supported health benefits of CO administration. Further, there is no evidence that the hypothetical therapeutic results provide any insight into health*

*effects of acute or chronic ambient exposures in the general population, and especially in subpopulations susceptible to CO effects.*

Thus, EPA does not believe the current evidence regarding possible therapeutic aspects of CO is informative to judgments regarding the adequacy of the CO NAAQS.

- (8) *Comment:* One commenter (CBD et al) asserts that EPA, in judging the adequacy of the current standards, was not justified in giving less weight to the epidemiological evidence, claiming that this type of evidence is the only type available for noncardiovascular effects, and consequently, should be given weight. The commenter argues that EPA has given weight to the epidemiological studies for other criteria pollutants, such as PM, after considering and rejecting concerns about confounding from other pollutants, unlike its approach for CO, and that two CO measurement issues noted by EPA in the proposal would tend to only underestimate any existing effect of CO.

*Response:* As an initial matter, EPA notes that, contrary to the commenter's assertion, epidemiological studies are not the only type of study available on noncardiovascular effects of CO. For example, as noted in the ISA's summary of the long-standing database of CO toxicological studies on birth outcomes and developmental effects, "in utero or perinatal CO exposure in pregnant dams or pups affects outcomes in the offspring, including postnatal mortality, skeletal development, the ability of the developing fetus to tolerate maternal dietary manipulation, behavioral outcomes, neurotransmitters, brain development, the auditory system, myocardial development, and immune system development" (ISA, p. 5-63).<sup>21</sup> In considering whether exposures associated with CO in ambient air might be expected to elicit such effects, the 2000 AQCD went on to conclude that "it is unlikely that ambient levels of CO typically encountered by pregnant women would cause increased fetal risk" (2000 AQCD, p. 6-44). In considering the full evidence base in this review regarding the potential for ambient concentrations of CO to elicit birth and developmental effects, we concluded it was only suggestive of a causal relationship. In so concluding, we noted uncertainty regarding the biological plausibility of ambient CO eliciting the effects that were associated with ambient CO in epidemiological studies and the inability to sufficiently rule out the role of chance, bias and confounding in those studies, in addition to the limited extent of the evidence and the mixed findings for some outcomes (ISA, pp. 1-14, 5-79, 5-80), as described in the response to comment II.A.3(2).

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<sup>21</sup> The 2000 AQCD states that "[f]rom all of the laboratory animal studies, it is clear that severe, acute CO poisoning can be fetotoxic, although specification of maternal and fetal COHb levels is difficult" and that data reviewed in the 1991 AQCD "provide strong evidence that maternal CO exposures of 150 to 200 ppm, leading to approximately 15 to 25% COHb" produce a range of developmental effects with some isolated experiments suggesting that "some of these effects may be present at concentrations as low as 60 to 65 ppm (approximately 6 to 11% COHb) maintained throughout gestation" (2000 AQCD, p. 6-44).

Thus, in considering the epidemiological studies for noncardiovascular effects, such as developmental effects, we have recognized uncertainties of the CO evidence base related to biological plausibility of such effects being elicited by ambient concentrations of CO, and we have also taken note of the advice offered by CASAC regarding potential confounding (e.g., Brain and Samet, 2010a). In so doing, contrary to the commenter's assertion, EPA has considered issues of potential confounding in epidemiological studies using the same approach for CO as we have for other criteria pollutants. That approach includes the consideration of the full evidence base available for each pollutant for the array of health effects assessed. Accordingly, the Administrator's judgment as to the weight to give to epidemiological studies in judging the adequacy of the current CO standards takes into consideration the full evidence base for CO, which includes epidemiological studies but is comprised largely of non-epidemiological studies and which provides the basis for our understanding of CO mechanisms of action, toxicity, and health effects, as well as the spatial and temporal variability of ambient concentrations and exposures.

As noted above and elsewhere in this document, the evidence for the noncardiovascular effects cited by the commenter is "suggestive" of a causal relationship with ambient CO, yet evidence is generally lacking on mechanism or mode of action that might lend biological plausibility to associations of effects with low ambient concentrations observed in epidemiological studies. In light of this uncertainty, particularly careful attention must be paid to the possibility of confounding, and indeed CASAC commented that "the problem of co-pollutants serving as potential confounders is particularly problematic for CO" (Brain and Samet, 2010a). CASAC further stated that "consideration needs to be given to the possibility that in some situations CO may be a surrogate for exposure to a mix of pollutants generated by fossil fuel combustion" and "a better understanding of the possible role of co-pollutants is relevant to ... interpretation of epidemiologic studies on the health effects of CO" (Brain and Samet, 2010a). We recognize that, as the commenter notes, some study authors use statistical methods to adjust for multiple pollutant effects, typically through the use of two pollutant regression models (ISA, p. 1-11), and, in assessing the evidence in the ISA, we considered the results of such models. We also recognize, however, that, as also noted by CASAC, associations reported for CO may be related to the presence of other, etiologically-relevant pollutants that are correlated with CO yet absent from the analysis (PA, p. 2-37). We particularly recognize this potential in light of the understanding we draw from the larger CO evidence base and its various aspects, many of which differ from the evidence bases for other criteria pollutants, such as PM and NO<sub>2</sub> (e.g., PA, pp. 2-36 to 2-39; 76 FR 8177-8178).

Moreover, a central question for this review is what patterns of ambient CO concentrations might be expected to cause adverse health effects and whether the current standards provide requisite protection against such occurrences. Apart from uncertainty as to whether ambient CO exposure is causally related to

noncardiovascular health effects, the two ambient CO measurement issues described in section II.D.2(a) of the proposed rule complicate and contribute uncertainty to our interpretation of the epidemiological studies with regard to the specific ambient CO concentrations that may have elicited the reported health outcomes.<sup>22</sup> Thus, while we agree with the commenter's statement that uncertainty associated with the two CO measurement issues they cite could contribute to an underestimation of CO effect in the epidemiological studies, uncertainty in the size of effect estimates (e.g., change in health risk per unit of exposure metric) is not the uncertainty of primary concern for the central question posed above. Rather, the uncertainty of concern to this question is related to what might be concluded from the studies with regard to what, if any, specific ambient concentrations of CO may have elicited the observed health outcomes. The two measurement issues as well as the potential for confounding and the larger issue of biological plausibility at ambient CO concentrations, contribute to this uncertainty (PA, pp. 2-37 to 2-39; 76 FR 8177-8178).

In summary, we considered the epidemiological evidence in this review in light of the full evidence base for CO, just as we do for other criteria pollutants. In considering the extent to which associations of health outcomes with ambient CO concentrations in epidemiological studies inform judgments in this review as to the adequacy of the current NAAQS, we first consider the extent to which the full evidence base supports a conclusion that the relationship of the health outcomes with ambient concentrations may be causal. Factors contributing uncertainty to this conclusion for noncardiovascular health outcomes are discussed previously in this response and in responses to comments (1) and (2) of section II.A.3 above. Secondly, we consider whether the current standards were met during the study periods, and what might be concluded from the studies with regard to specific ambient concentrations eliciting the observed health outcomes.<sup>23</sup> In so doing, we have identified aspects of the CO evidence base which contribute uncertainty to and complicate our use of the epidemiological studies in this regard. In light of these uncertainties and complications, these studies have been less informative to the Administrator in drawing conclusions regarding the adequacy of the current

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<sup>22</sup> As described in the proposal (76 FR 8177-8178), the first of the two issues, the prevalence of ambient monitor measurements at or below detection limits, is a particular concern for the more recently available epidemiological studies in which ambient CO concentrations are much reduced from the past. The second issue relates to the use in the epidemiological studies of CO measurements from area-wide or central-site monitors which can obscure the significant spatial gradient that exists for CO with distance from source locations such as highly-trafficked roadways.

<sup>23</sup> As we note in the PA and proposal, it is the studies conducted under conditions when the current standards were met that are particularly informative to the consideration of the adequacy of the current standards, and the identification of such studies requires consideration of all elements of the standard beyond just the level. For example, even when concentration statistics reported in epidemiological studies (e.g., daily maximums at central site monitors, often averaged over multiple days) are below the levels of the current standards, CO levels stated in the form of the standards (e.g., second highest daily maximum 1-hour and 8-hour concentration at a specific location) may, and in many studies do, exceed one of the standards (e.g., PA, p. 2-32). The form is an integral part of a NAAQS and its stringency. Thus, it is important to consider not simply the value of the air quality statistic reported compared to NAAQS level, but whether the air quality met the NAAQS.

standards, than have other elements of the CO evidence base. Thus, the Administrator has fully considered and carefully weighed the available evidence, giving greater weight to those aspects more fully supported in making her judgment on the adequacy of the current standards to provide the requisite protection.

- (9) *Comment:* Comments from AAM state their view that little weight should be given to the epidemiological studies of CO based on several observations that they have previously brought to EPA's attention over the course of the review. Commenters additionally describe a recent study as suggesting that the epidemiological evidence relied on by EPA in the ISA is unsound.

*Response:* EPA carefully considered the epidemiological studies, in light of the full evidence base for CO. While EPA has recognized a variety of uncertainties related to interpretation of CO epidemiological studies, particularly with regard to ambient concentrations that may elicit effects (preamble to final rule, section II.B.2), we also recognize the coherence of the study results for ischemia-related outcomes with the results of controlled human exposure studies and the biological plausibility provided to these studies by the known role of CO in limiting oxygen availability (ISA, p. 5-48). These aspects of the full evidence base contribute to our conclusion that a causal relationship is likely to exist between relevant short-term exposures to CO and cardiovascular morbidity, a conclusion that has been favorably reviewed by the CASAC Panel, with the Panel concluding the 2010 ISA to be "adequate for rulemaking with the incorporation of changes in response to the Panel's major comments and recommendations" (Brain and Samet, 2010a).

In evaluating the epidemiological evidence in the ISA, EPA has considered comments provided by the commenter on the ISA, some of which are also reflected in this comment submitted on the proposal. Across the documents prepared for this review, EPA has carefully considered the evidence, including the epidemiological evidence, taking particular note of potential areas of uncertainty. For example, in drawing conclusions on the effects of ambient CO, EPA has not relied on any one individual study or small cluster of studies. Rather we consider the group of studies available for biologically plausible health outcomes, such as those related to ischemia following CO exposure (ISA, p. 5-48). In so doing, we find the full body of epidemiological studies of emergency room visits and hospital admissions for ischemic heart disease to be generally consistent with controlled human exposure and toxicological evidence of cardiovascular morbidity effects, as noted above. Further, EPA agrees with commenters that issues related to model specification for epidemiologic studies, such as selection of models and approaches to adjust for meteorological and temporal variables are important considerations. The CO ISA describes how these issues were carefully considered in selecting studies for inclusion in the ISA and in interpreting the results of the body of epidemiologic evidence (CO ISA, Figure 1-1 and accompanying text on p. 1-5). Furthermore, we recognize the phenomenon of publication bias as a potential source of uncertainty regarding the nature of the

association and the magnitude of health risk estimates. Specifically, it is well understood that studies reporting non-null findings are more likely to be published than reports of null findings, and, thus, publication bias can result in reporting of spurious associations and overestimating effects (Ioannidis, 2008). We do not agree, however, that publication bias limits the interpretation of published associations between CO and health effects.

Finally, EPA disagrees with the commenters' assertion that the recent study cited by the commenter (Koop et al., 2010) calls into question the epidemiological evidence for CO assessed in the ISA. EPA notes several aspects of the study by Koop et al. (2010) that limit its interpretation in light of the evidence base for CO. For example, the authors use monthly pollutant averages and monthly counts of hospital admissions, rather than daily data in their time-series analyses, which may overlook relationships in the shorter time-step data, which may have relevance to ambient CO. Among the health outcome categories assessed, the authors have omitted chronic obstructive pulmonary disease, a respiratory outcome that has been demonstrated to be associated with ambient concentrations of various air pollutants, while including tracheostomy malfunctions, an outcome unlikely to be associated with air pollution. Further, by focusing on hospital admissions, rather than physician visits or emergency department visits, it is likely that the authors missed all but the most severe cases of some diseases. While this study (Koop et al., 2010) was published after the ISA, EPA has provisionally considered it and concludes that it does not materially change any of the broad scientific conclusions regarding effects associated with CO exposure made in the 2010 CO ISA and thus does not warrant reopening the air quality criteria review.

- (10) *Comment:* Comments from NESCAUM stated that EPA should work toward a better understanding of the broad range of CO exposures, including those in vehicles, and the role of the CO NAAQS in addressing these exposures. They additionally state that current research suggests that in-cabin CO may be higher than ambient levels and may be a main route of CO exposure.

*Response:* EPA agrees that in-vehicle exposures are an important component of personal exposure to ambient CO, as indicated by evidence described in the ISA (ISA, section 3.6.6) as well as the REA results. The ISA summarizes the current evidence with regard to roadway-related results (ISA, sections 3.6.6 and 3.5.1.3). Further, the REA which also informs our understanding, found that time spent on or near motor vehicle activity (e.g., in vehicles, in garages) was a major contributor to higher CO exposures (e.g., REA, section 6.4). Lastly, we note the revisions to the CO monitoring network to include near-road monitors made in the final rule (preamble to final rule, section IV) is expected to help to improve our understanding of the gradients in ambient CO concentrations in the near-road environment which will in turn contribute to an improved understanding of roadway-related exposures.

## 6. Additional Comments on the Exposure and Health Risk Assessment

Comments related to the REA for CO that are not discussed in the preamble to the final rule (e.g., in sections II.B) are described and addressed in this section.

- (1) *Comment:* One public commenter (Thomas McCurdy) expressed concern with how alveolar ventilation rate ( $V_A$ )<sup>24</sup> is estimated by APEX and the resulting impact on estimating population COHb levels. In general, this commenter noted that the  $V_A$  to oxygen consumption rate ( $VO_2$ ) relationship is variable, both within and between individuals, and not constant as was assumed in the REA (i.e., a value of 19.63), particularly noting the existence of a non-linear relationship at high ventilation rates. The commenter further indicated their view that accurately estimating VA is important because it plays a large role in estimating COHb levels.

*Response:* EPA does not disagree with much of what the commenter states regarding the overall variability in the relationship between alveolar ventilation ( $V_A$ ) and oxygen consumption ( $VO_2$ ) rates. When modeling risk and exposure to any pollutant, there are always limits in representing the true variability of model input variables. This is a common occurrence due to the limited availability of input data that fully capture the influential characteristics (e.g., age, gender, activity level, health status/condition) driving the variability of many physiological variables used in the model, including the  $V_A/VO_2$  relationship. Given the time and resources available for this review, EPA did not perform a literature review to evaluate or improve the point estimate of 19.63 used in the current REA. We add that this value has been used to estimate  $V_A$  in prior CO exposure assessments (e.g., Johnson et al., 2000). Further, as described below, we have concluded that, given the relatively low influence of  $V_A$  on REA results, the current approach was adequate to our needs in estimating exposure and dose in this review.

In response to this comment, we first note that the limitations of the currently used relationship, particularly regarding the non-linear relationship of  $V_A$  to  $VO_2$ , was mentioned in the REA by EPA (and noted by the commenter), specifically “the point estimate of 19.63 used may not adequately represent the  $V_A$  to  $VO_2$  relationship at higher ventilation rates” (REA, p. 7-21). More specifically, we agree with the commenter’s statement that the  $V_A/VO_2$  relationship (if plotted as an x-y graph) can be “concave upward” (McCurdy, p. 2) at upper ventilation rates, hence this non-linearity in the  $V_A/VO_2$  relationship observed at upper ventilation rates would lead to underestimations in  $V_A$  if using a value of 19.63, and assuming this value is consistent with a ratio calculated while performing low exertion activities. In considering the  $V_A/VO_2$  ratios provided by the commenter

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<sup>24</sup> Alveolar ventilation *rate* is typically expressed as “ $\dot{V}_A$ ”, though the volume associated with alveolar ventilation is commonly expressed as  $V_A$ . For simplicity in the formatting in this document, the rate is expressed as  $V_A$  and represents the rate, not the volume. This was also conferred to how oxygen consumption rate is expressed here ( $VO_2$  is used); the accent over the “V” is not included.

(McCurdy, Table 1, p. 5), we note that the point estimate of 19.63 used in the REA falls within the range of these ratios, bounded by values of 17.33 and 26.69, representing resting and moderate activity levels, respectively. Based on this information alone,  $V_A$  for persons simulated in the REA while at rest or performing low exertion level activities may be slightly overestimated in using the value of 19.63, while for simulated persons performing at or above moderate exercise,  $V_A$  may be underestimated. Regarding one variable potentially affecting inter-personal variability,  $V_A/VO_2$  is stated by McCurdy to decrease “moderately or greater with age” based on limited  $V_A$  and  $VO_{2max}$ <sup>25</sup> data reported for females by Astrand (1960). This reported finding, if consistent in both genders and taken with the above remarks regarding the non-linear relationship observed while performing moderate to greater physical activities, suggests that there would likely be a lesser propensity to underestimate  $V_A$  in older persons than in younger persons.<sup>26</sup>

We disagree, however, with the commenter’s statement regarding the magnitude of importance of  $V_A$  in estimating COHb levels. Specifically Mr. McCurdy states that because  $V_A$  is used to estimate COHb levels, it “play[s] a large role in all conclusions regarding subsequent COHb distributions modeled”. Nowhere in Mr. McCurdy’s comments is provided evidence to indicate the magnitude of the role  $V_A$  plays in the calculation of COHb levels. In reviewing a published sensitivity analysis of variables input to the CFK model by McCartney (1990), it appears that  $V_A$  does not have a large influential role in the estimation of COHb level. In McCartney (1990), the sensitivity of COHb to changes in  $V_A$  (among other CFK equation variables) is evaluated across five work/activity levels, ranging from at rest ventilation to performing moderate exercise. McCartney (1990) reports “the effect of  $V_A$  on the equilibrium value of [COHb](t) is small (Figure 3 [of publication]) and would be zero in the absence of endogenously produced CO.” In our review of Figure 3 in McCartney (1990), we note also that there is a consistent trend of decreasing sensitivity of COHb level to  $V_A$  with increasing work level, with maximum sensitivity of equilibrium values of COHb to  $V_A$  observed while at rest (McCartney, 1990, Table V). This research suggests that when performing moderate or greater exercise, any inaccuracies in estimates of  $V_A$  would have even less of an influence on estimated COHb levels using the CFK model than when at lower activity levels.

In the REA, EPA staff indicated that the CO exposure concentration was one of the most important variables in estimating COHb levels. As noted in the REA, “most of the upper level exposure concentrations in this assessment are associated with time spent inside vehicles, where it is expected that the exertion level and breathing rate would be at a relatively low level” (REA, p. 7-21). The REA then concluded that “it may be that the point estimate [used to estimate  $V_A$  from  $VO_2$ ]

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<sup>25</sup> Maximal oxygen consumption rate ( $VO_{2max}$ ) or aerobic capacity is where oxygen consumption plateaus or increases only slightly with increasing exercise intensity (McArdle, 2001).

<sup>26</sup> Ischemia-related effects are more prevalent in older persons, and accordingly they are of greater importance for this assessment.

is appropriately used for these activities [i.e., driving a vehicle] and the estimated maximum end-of-hour COHb associated with the in-vehicle microenvironment may not be adversely affected” (REA, p. 7-21). As noted above regarding the range of  $V_A/VO_2$  ratios for low to moderate activity offered by McCurdy, driving a motor vehicle would be characterized as a relatively low exertion activity, generally supporting the value of 19.63 used to estimate  $V_A$  for simulated persons inhabiting this particular microenvironment.

There was limited time available to perform sensitivity analyses of the APEX modeling used in the REA given the review schedule, however EPA was able to perform three separate evaluations of input data used and their affect on COHb estimates (REA, section 7.2.2). The input variables for which sensitivity analyses were performed were chosen based on careful consideration of advice from CASAC (Brain, 2009; Brain and Samet, 2010b; Brain and Samet, 2010c), the situations being simulated and the model specifications and performance. These model sensitivity analyses included: the spatial representation of ambient CO concentrations (all ambient monitors versus design monitor CO concentrations only), at-risk prevalence rates used (base prevalence versus increased undiagnosed CHD prevalence such that women equaled that of males), and the hemoglobin content of blood (a base level versus anemic population). Of these three APEX model input variables, variability in the spatial representation of ambient CO concentrations contributed to the greatest amount of variability in percentage of persons at or above selected COHb levels (REA, Tables 7-5 through 7-8). This relative importance of ambient CO concentration and its influence on COHb levels was also indicated by McCartney (1990), with inspired CO concentration among one of the few input variables conferring nearly an equivalent factor of influence on equilibrium COHb values.<sup>27</sup>

Subsequent to completion of the REA, EPA performed additional analyses on the REA-generated APEX outputs to determine the magnitude of influence  $V_A$  and exposure concentrations have on estimated COHb levels using the event-level output data generated for the REA.<sup>28</sup> The results of an analysis of variance and multiple linear regression modeling indicate that the combination of endogenous COHb, real-time CO exposure concentrations, and CO exposure concentration

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<sup>27</sup> McCartney (1990) used fractional sensitivities to evaluate the influence of input variables in the CFK model, such that a value of unity (or 1) “means that an error in the selected variable propagates unattenuated to an error in calculated [COHb]( $\infty$ ).” Table V of McCartney (1990) indicates maximum sensitivity values for the nonlinear CFK equation, with inspired CO concentration ranked 4<sup>th</sup> highest and having a maximum fractional sensitivity of 0.92, while the  $V_A$  was ranked 11<sup>th</sup> having a maximum fractional sensitivity of 0.53.

<sup>28</sup> The additional analyses were performed using the 5,000 person APEX simulation event-level files generated in the REA for air quality just meeting the current standard and for both study areas. These files are described in Docket item EPA-HQ-OAR-2008-0015-0123. Data output to the APEX file and included in the analysis were end-of-event COHb, calculated endogenous end-of-event COHb from endogenous simulations, event CO exposure concentration, event  $V_A$ , event duration, hourly averaged CO exposure concentrations from hours 1, 2, and 3 prior to the event, and hourly average  $V_A$  from hours 1, 2, and 3 prior to the event.

lags from prior hours were the most important input variables in explaining variability in COHb levels. While  $V_A$  was a statistically significant explanatory variable in the statistical models, the overall contribution of variation in  $V_A$  to variability in COHb level was negligible in comparison with the exposure concentration variables and COHb resulting from endogenous CO production.

Therefore, the results of sensitivity analyses by McCartney (1990), as well as our own APEX model sensitivity analyses and output data evaluations, indicate that CO exposure concentration is a much more influential variable relative to that of  $V_A$  in estimating a person's COHb level. Thus, although the  $V_A$  approach used in the REA has recognized limitations (e.g., REA, p. 7-21), the potential magnitude of influence of this APEX input variable is smaller than other variables, such as the time series of CO exposure concentrations.

## **B. Comment on Consideration of a Secondary Standard**

General comments based on relevant factors that either support or oppose EPA's decision that a secondary standard for CO is not requisite to protect the public welfare from adverse effects associated with CO in ambient air are addressed in section II.C of the preamble to the final rule and/or in this section of this document below.

- (1) *Comment:* In testimony at the public hearing, one commenter (Gossage) stated that EPA's consideration of a secondary standard lacked review of CO-related "hazards to transportation" which is included in CAA definition of welfare effects. In response to a query regarding the types of such hazards related to CO, another commenter stated that there were studies of CO exposure effects on the ability of drivers to manage the hazards of driving at exposure ranges below the current one-hour standard, although references for such studies were not provided.

*Response:* EPA notes that it is not clear whether the neurological effects on drivers cited by the commenters fall within the meaning of "hazards to transportation" as that phrase is used in defining "welfare" for purposes of the NAAQS. Even assuming that these effects would constitute adverse effects on public welfare, as well as adverse effects on public health, EPA does not believe there is evidence in the air quality criteria of such effects associated with ambient concentrations of CO that would warrant establishment of a secondary standard (or revision of the primary standard), nor was such evidence provided by the commenter. EPA notes that the ISA characterized the evidence as only suggestive of a causal relationship between relevant short-term CO exposures and central nervous system (CNS) effects. The ISA further concluded that, while acute CO poisoning events (involving exposure to levels much higher than the NAAQS) have been known to adversely affect CNS function, controlled human exposures have provided limited and equivocal evidence for neurobehavioral effects resulting from somewhat lower levels of CO exposure. The lowest level evaluated in these studies, however, was associated with quite elevated COHb

levels, in the range from 5 to 20% (PA, p. 2-16). As indicated by the REA results, little if any occurrence of COHb levels over 4% are expected under conditions associated with just meeting the current 8-hour standard (PA, Table 2-4).

- (2) *Comment:* One commenter (CBD et al) stated that EPA should consider the role of CO in contributing to climate-related effects of ozone, objecting to EPA's conclusion that indirect effects of CO on climate that are attributable to ozone formation should be addressed through the ozone NAAQS.

*Response:* To the extent that indirect effects of CO on climate are attributable to ozone it would be more appropriate to address them in the review of the ozone NAAQS. The NAAQS for a criteria pollutant must be requisite to protect public health and welfare in accordance with the Clean Air Act, and EPA does not believe it necessary or appropriate to additionally consider the adverse effects attributable to one criteria pollutant in setting the standard for a different criteria pollutant which may also be a precursor to the first pollutant. For example, the NAAQS for oxides of nitrogen (long-recognized ozone precursors) are not set to establish requisite protection from the adverse effects of ozone.

## **C. Comments Related to Monitoring**

### ***1. Sampling and Analysis Methods***

Comments received (API) on the proposed revision to part 50 and part 53 generally indicated support for the general proposed changes to update and clarify the CO Federal reference method (FRM). The commenter also welcomed the general upgrading of the analyzer performance requirements and that new candidate CO Federal equivalent methods (FEM) analyzers will be required to meet them. Comments on specific aspects of the proposed changes are addressed below.

- (1) *Comment:* Part 50, appendix C – In section 4.2.1 (in the calibration procedure), EPA proposes to change the requirement for flow rate control and regulation to  $\pm 2\%$  from the existing  $\pm 1\%$  requirement. The commenter questioned whether this relaxation was intended or an oversight.

*Response:* This change is intended. In response to this comment, EPA has reconsidered this proposed change. However, it was again determined that the 1% requirement for flow rate control and regulation was unnecessarily stringent in comparison with the level of overall uncertainty tolerable in the calibration system and in the monitoring instrument. This change is commensurate with the flow rate measurement accuracy requirement of 2% (which is unchanged from the existing requirement) in the succeeding section 4.2.2.

- (2) *Comment:* Part 50, appendix C- The commenter suggested that the numerator in Formula 1 (of the calibration procedure) should contain either parentheses or a multiplication symbol to indicate that the two terms are to be multiplied.

*Response:* EPA has made a change in response to this comment. Although not mathematically necessary, the addition of a multiplication symbol in the numerator of the formula will help to clarify that the two terms are to be multiplied.

- (3) *Comment:* Part 50, appendix C – The commenter points out that in sections 4.4.5 and 4.4.6 (of the calibration procedure), no provision is made for connecting a data read-out device to the CO analyzer under calibration to facilitate monitoring of the analyzer readings. Use of the analyzer’s visual display may not accurately represent the way readings are routinely recorded.

*Response:* EPA has made a change in response to this comment. Typically, FRMs do not contain such a provision, since it seems quite obvious that such a device is necessary. However, the suggestion to include such an appropriate provision has merit and may help to improve the overall accuracy of the calibration. Section 4.4.3 has been revised to include a statement that the read-out device used should represent the way that the routine analyzer readings are recorded.

- (4) *Comment:* Part 53, subpart B – The commenter stated they could not review the complete set of analyzer performance data that EPA cited as a basis for the proposed new FRM and FEM analyzer performance requirements because the cited reference (a spreadsheet of analyzer manufacturers’ published performance data for various analyzers) did not include the performance data from FRM applications received by EPA that were also used by EPA for this purpose.

*Response:* In addition to the performance data included in the referenced spreadsheet, EPA also used data from recent CO FRM applications that EPA has received and processed under part 53. These latter data could not be included in the referenced spreadsheet because the applications and all data they contain are identified by their respective applicants as confidential business information (CBI). EPA must treat data identified as CBI in accordance with 40 CFR part 2, which restricts its public release pending a final determination of its status as CBI. Any person seeking to review data for which a claim of CBI has been made may file a request under the Freedom of Information Act and 40 CFR part 2.

- (5) *Comment:* Part 53, subpart B – The commenter stated that EPA did not provide or cite data to support its conclusion that the existing performance limit requirement for the “total of all interferences” is redundant with the individual interferent limits for modern CO analyzers and the proposed withdrawal of this total interference limit requirement.

*Response:* In response to this comment, EPA has re-examined the efficacy of the existing total interference limit requirement for CO analyzers and has again determined that it is not necessary. All CO analyzers in monitoring use today are FRMs, which use an infrared absorption measurement principle. For these analyzers, only 2 interferents are listed in Table B-3 of 40 CFR part 53, and the analyzers' responses to those interferences are typically well controlled. Even for other potential measurement principles listed in Table B-3 – none of which are represented in currently available CO analyzers – only a few interferences are listed, and they are quite unlikely to be all simultaneously elevated at typical CO monitoring sites. Thus, the limit for total interferences is of minimal efficacy, and therefore EPA believes it can be eliminated. For analyzers opting to meet the proposed new lower measurement range, the individual interference limit is reduced to ½ of the limit for the standard measurement range, again rendering the need for a total interference limit unnecessary.

- (6) *Comment:* Part 53, subpart B – Similarly, the commenter states that EPA did not cite or provide data to support the proposed withdrawal of the existing limit requirement for span drift determined at a concentration of 20 % of the upper range limit (URL). The commenter contends that this requirement is important because 20 % of the standard range of 50 ppm is 10 ppm, which is close to existing (and proposed) 8-hour NAAQS for CO and is closer to the 1-hour NAAQS than the 80% URL drift limit. Accordingly, the commenter suggests withdrawing the 80% URL drift limit instead of the 20 % URL limit.

*Response:* EPA does not agree that the 80% URL drift limit should be withdrawn in place of the 20% URL limit. The purpose of the span drift limit is not to directly assess measurement error at a particular, mid-scale concentration level. That is the purpose of the 1-point quality control check for CO monitors described in Section 3.2.1 of appendix A of 40 CFR part 58. FRM and FEM CO analyzers have a measurement response function that is well defined and typically very nearly linear with respect to the input CO concentration. For the purpose of analyzer performance testing, this linear input/output functional characteristic is best described by its zero point and its slope, because these parameters are generally subject to change (drift) independently. Thus, zero drift (change in the zero point) and span drift (change in the slope) are tested separately. Zero drift is, of course, measured at zero concentration, and span drift is most accurately measured at a concentration near the URL. The span drift test at 80% URL (when the zero drift is within the specified requirement) adequately determines any change in the slope parameter. The currently specified test at 20% URL serves little, if any, purpose in regard to determining change in the slope and can therefore be withdrawn.

- (7) *Comment:* Part 53, subpart B - The commenter notes that new FRM and FEM analyzers would be subject to the new, more stringent requirements, but existing FRM analyzers, which have been approved based on the existing, less stringent requirements, would continue to be approved. EPA noted that most commercially

available CO analyzers already meet the proposed new performance requirements so it is unlikely that new analyzer that are approved under the proposed new requirements would cost more, and thus there would be no economic impact on monitoring agencies. The commenter interpreted that statement to mean that EPA is more concerned about cost than data quality. The commenter further suggested that existing FRM analyzers approved under the existing performance requirements may provide data quality inferior to that of analyzers approved under the proposed new requirements and that older analyzers may be unacceptable for some applications that demand higher performance or higher data quality. A “tiered” approach was suggested to handle this situation.

*Response:* In proposing more stringent performance requirements for approval of new FRM and FEM analyzers, EPA noted that the performance of analyzers approved under the existing performance requirements was fully adequate for most routine compliance monitoring applications, and that the proposed new requirements were largely to bring the base FRM and FEM performance requirements up to date and more commensurate with the performance of modern commercially available CO analyzers. The commenter indicated that these changes were “long overdue and welcome.” Since all currently designated FEM analyzers already meet the proposed new requirements, there would likely be no increase in cost for new analyzers that would be approved under the new requirements. Thus, EPA was merely pointing out that the new requirements were unlikely to impose a resultant economic impact on monitoring agencies. EPA considers such impacts when proposing rule changes. More importantly, this means that routine CO monitoring data quality currently being obtained is already of the higher level portended by the proposed new performance requirements. However, EPA did recognize that some special CO monitoring applications do require a higher level of performance than that required for routine applications. Therefore, EPA is, in fact, proposing a “tiered” approach by proposing optional, more stringent performance requirements for analyzers having a more sensitive, “lower range” available for such applications. Applicants would be able to elect to have such lower ranges approved as part of their FRM or FEM designation.

## ***2. Near-Roadway Monitors***

- (1) *Comment:* Two commenters objected to the use of a near-road network for judging compliance with the NAAQS (Indiana Department of Environmental Management [IN DEM], South Carolina Department of Health and Environmental Control [SC DHEC]). One commenter (IN DEM) indicated their view that roadside monitors did not provide a measurement that was “representative of ambient air quality everywhere in a city or county”. The second commenter, in addition to stating that data from this monitoring network were not appropriate for use in judging an area’s status in comparison to a NAAQS, further stated that such monitoring “does not provide a mechanism to add further protection to the general population or susceptible individuals” (SC DHEC).

*Response:* The EPA notes that monitoring near roads for peak CO concentrations for compliance with the NAAQS is not a new concept, and has been in practice since the 1970s. The Agency believes that this final rule is updating the same intent that was originally presented in monitoring regulations introduced in the May 1979 (44 FR 27571). Similarly, the data produced at near-road monitoring stations would likely be treated as data from existing CO monitors near-roads, in downtown areas, or urban street canyons have been. EPA disagrees with commenters regarding the protection provided by this monitoring. As discussed in the final rule, people who spend time on or around major roads (e.g., because they live there, go to school there, or commute in vehicles on major roads) can be exposed to elevated concentrations of ambient CO. Accordingly, monitoring in these locations does provide further protection to the general population and susceptible individuals who are exposed in these areas, and is appropriate for judging compliance with the NAAQS regardless of whether such monitoring is indicative of concentrations found throughout an urban area.

- (2) *Comment:* The NYS DEC commented that CO monitors, due to collocation with near-road NO<sub>2</sub> monitors, will be located in a range up to 50 meters from target road segments. The commenter stated that “data from these sites cannot adequately characterize near-road emissions nor would the data be comparable from one site or city to another.” The commenter goes on to state that the “final NO<sub>2</sub> and proposed CO regulations have preceded an understanding of how these data will be used for anything other than for research.”

*Response:* The EPA understands the potential influence that monitor placement relatively nearer or further from a target road can have on resultant measured pollutant concentrations. However, the Agency believes that on the whole, near-road monitors will be representative of exposures that can occur in the near-road environment. Further, the EPA recognizes the existence of a gradient in the near-road environment within which, based on a number of physical factors, pollutant concentrations decrease with increasing distance away from the source road. That was the rationale behind requiring near-road NO<sub>2</sub> sites within which CO monitors are required to be collocated, to have monitor probes “...be as near as practicable to the outside nearest edge of the traffic lanes of the target road segment; but shall not be located at a distance greater than 50 meters, in the horizontal, from outside nearest edge of the traffic lanes of the target road segment” (40 CFR part 58, appendix E, section 6.4(a)). The intent is to measure the peak concentrations that are occurring in the near-road environment for a given urban area by being as close as practicable to target roads. EPA agrees that this data may be helpful to support research on near-road air quality and public health, which is one of the primary objectives for ambient monitoring networks. However, EPA believes this data is also useful and necessary for ensuring that near-road ambient air quality meets the NAAQS.

- (3) *Comment:* The TCEQ commented that in Texas, frontage roads are included with the central line traffic counts. They stated that “the EPA’s interpretation that the access road through lanes in Texas are not traffic lanes is incorrect...” and that the EPA needs to modify the interpretation to match conformity, National Environmental Policy Act (NEPA), and storm water reviews.

*Response:* In this rulemaking, the EPA has not taken a stance on the interpretation of how frontage roads are included in central line traffic counts. The regulation requiring near-road monitoring only references a ‘target’ road segment. In Texas’ case where frontage roads are included as part of a road segment, regardless of the physical configuration of that road, the outside edge of that road, whether it be frontage road or not, is the location from where measurements can appropriately be made to determine if a monitoring site is meeting siting criteria. Further, the EPA notes that siting criteria do not preclude the placement of a monitoring station in open space (not traffic lanes) within a road segment (e.g., between frontage lanes and so-called ‘through lanes’ if such a site is safely accessible and can meet siting criteria for probe placement in the vertical plane, and with respect to obstructions.

- (4) *Comment:* Some commenters (e.g., New York Department of Environmental Conservation [NYS DEC], NESCAUM, Texas Commission on Environmental Quality [TCEQ], AAM) expressed concern that near-road sites may not provide information representative of general population exposure, which one commenter claims is a primary monitoring objective. The AAM recommended that population exposure be included in siting and network design requirements, stating that at any new sites, there should be “human exposure to the ambient air for time periods corresponding to the 1-hour or 8-hour CO NAAQS.”

*Response:* As an initial matter, EPA notes that as summarized in section IV.B.1 of the final rule, 40 CFR part 58, appendix D specifies three basic objectives for the design of ambient air monitoring networks: a) provide air pollution data to the general public in a timely manner; b) support compliance with ambient air quality standards and emissions strategy development; and, c) provide support for air pollution research studies. As described in the preamble to the final rule, the near-road monitoring requirement will assist particularly with regard to the second objective. The EPA notes that, as described in the ISA and consistent with findings of the REA, elevated short-term exposures to ambient CO are associated with near-roadway locations and other locations of motor vehicle activity. The REA results indicated that key contributors to highest ambient CO human exposures are in-vehicle and near-vehicle microenvironments (e.g., REA, Figure 6-4). While many vehicle-associated exposures may be shorter than 8 hours, the 8-hour standard, as the controlling standard, provides control of shorter-term elevations in concentration which also influence people’s CO exposures and associated COHb levels. Thus, siting monitors in near-roadway locations will

help ensure compliance with the NAAQS and protection of the public from elevations in roadway-associated ambient CO concentrations of concern.

- (5) *Comment:* Several commenters (e.g., AASHTO and New York State Department of Transportation [NYSDOT]) recommended that state and local air monitoring agencies be required to cooperate with state and local transportation agencies on the placement of near-road monitors

*Response:* The EPA is not in a position to require state and local air agencies to cooperate or collaborate with their state or local transportation agencies in the implementation of required near-road monitoring sites by rule. However, the EPA strongly encourages air monitoring agencies to work with their respective transportation counterparts, and believes that air monitoring agencies are already inclined to do so. Further, the EPA believes that many candidate near-road monitoring stations will be in right-of-way locations, within which air agencies will have to work with transportation agencies to negotiate access and ensure safety for the travelling public, air monitoring staff, and the associated monitoring infrastructure.

- (6) *Comment:* Several commenters (e.g., AAM, NACAA) suggested that required near-road monitors should be phased in over a period of time. For example, NACAA cited a CASAC statement that there are benefits from implementing near-road monitors in stages, e.g., over a three year period.

*Response:* EPA agrees with these commenters that phasing in the implementation of near-road CO monitors is warranted. Accordingly, in the final rule, EPA has required near-road CO monitors within CBSAs having populations of 2.5 million or more persons to be implemented by January 1, 2015, while those CBSAs having 1 million or more persons, but less than 2.5 million, are required to be operational by January 1, 2017. EPA intends to review the experience of states with the first round of near-road CO monitors and the data produced by such monitors and consider whether adjustments to the network requirements are warranted.

- (7) *Comment:* A number of commenters (e.g., AASHTO, IN DEM, NYSDOT) expressed concern regarding safety for the public and air agency workers at monitoring stations in the near-road environment.

*Response:* The EPA recognizes safety as a top priority in the implementation of any near-road monitoring sites. This is evident in the preamble to the final rule promulgating the requirements for near-road NO<sub>2</sub> monitors. By requiring CO monitors to be collocated with near-road NO<sub>2</sub> monitors, network implementation issues such as safety will effectively be handled as the near-road NO<sub>2</sub> network is

installed. In an effort to support state and local air agencies in the implementation of near-road NO<sub>2</sub> sites, the EPA is collaborating with U.S. Department of Transportation, Federal Highway Administration and several state Departments of Transportation (DOTs) (e.g., Florida & Texas), along with partner state and local air agencies, to provide technical assistance on near-road site implementation to the air monitoring community. Safety is a key subject in that assistance, with topics covering issues of right-of-way access, the use of safety features such as guardrails or recognition of ‘clear zones’, and how to engage DOTs or other transportation agencies to ensure safety of the travelling public, air monitoring staff, and air monitoring infrastructure at near-road monitoring sites. Further, monitoring by roads for CO is not a new concept to states and local air agencies. They have been monitoring near roads, mainly in downtown areas and in urban street canyons, since the late 1970s. The EPA believes that state and local air agencies are very aware of safety issues, in part based on existing experience, and the Agency is confident that state and local air agencies will be able to safely implement near-road monitoring sites through the use of the technical assistance to be provided and by working with their respective partner transportation agencies as necessary.

### 3. Other Locations

- (1) *Comment:* One commenter (Safe Air for Everyone) noted that agricultural burning can have a significant impact on populations in and around agricultural areas. Particularly, the commenter state stated that “EPA should be monitoring the impacts of CO on agriculturally burned lands to protect citizens since crop residue burning occurs in all 50 states.”

*Response:* In the preamble to the final rule, the EPA notes that a nationally applicable network design may not always account for all locations in every area where monitors may be warranted. The Agency believes that a minimum monitoring requirement to assess agricultural burning is not practical in a nationally applied network design. However, in this final rule, the Agency has given EPA Regional Administrators the discretion to require monitoring above the minimum requirements as necessary to address situations where minimum monitoring requirements are not sufficient to meet monitoring objectives. The EPA believes that the assessment of agricultural burning may be another example of a situation where the EPA Regional Administrators may work with state and local air monitoring agencies to consider deploying monitoring resources to assess air pollution. In addition to the Regional Administrator authority, state and local agencies can also deploy pollutant analyzers on a temporary basis, as special purpose monitors, to explore potential pollution issues in areas where problems are suspected due to agricultural burning. The Agency believes these two flexible approaches (with respect to location and duration) are appropriate to assess impacts of agricultural burning in lieu of nationally applied minimum monitoring requirements near these sources.

- (2) *Comment:* NACAA stated that “EPA should also take this opportunity to reevaluate the existing CO monitoring network and eliminate sites that are redundant or no longer necessary so that resource can be transferred to higher priority areas.” The commenter goes on to state that “providing clear guidance and support for the divestment of unnecessary monitors is essential to allow state and local agencies to best focus limited resources, and is a necessary prerequisite to the relocation of existing CO monitors for inclusion in the near roadway network.”

*Response:* The Agency agrees with the commenter that the removal or relocation of redundant sites or those that are likely no longer necessary is desirable. The EPA will continue to work with state and local agencies to shut-down or relocate these monitors that meet the criteria of 40 CFR 58.14 as they are identified and proposed for modification. EPA will also consider revisions to maintenance plans where monitors are currently required but otherwise meet the criteria of 40 CFR 58.14.

- (3) *Comment:* API suggested that EPA require any CO monitors recording peak values that are greater than or equal to 80% of NAAQS be retained.

*Response:* Existing monitoring sites are not allowed to be shut-down unless they meet certain criterion with respect to their data. These rules by which a monitor can be considered for shut-down are maintained in 40 CFR Part 58, 58.14 *System Modification*. Among the criteria under which monitors are eligible to be shut down is if there is less than a 10% probability that the monitor will record an ambient concentration in excess of 80% of the NAAQS over the succeeding three years, and the monitor is not needed under the maintenance plan.<sup>29</sup> Further, as is noted in the preamble to the final rule, before any monitor can be shut-down, the state or local air agency must also receive EPA Regional Administrator approval. Accordingly EPA does not believe an additional requirement to retain CO monitors recording peak values above 80% of the NAAQS is necessary or appropriate.

- (4) *Comment:* AASHTO asked for clarification on whether, or where, NCore sites in areas where near-road monitor would also be required; and for clarification on

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<sup>29</sup> Other criteria include: (1) where a monitor has consistently measured lower concentrations than another monitor for the same pollutant in the same county (or portion of a county within a distinct attainment area, nonattainment area, or maintenance area, as applicable) during the previous five years under certain circumstances; and (2) where a monitor has not measured violations of the applicable NAAQS in the previous five years, and the approved SIP provides for a specific, reproducible approach to representing the air quality of the affected county in the absence of actual monitoring data. See 40 CFR 58.14(c).

whether NCore sites would provide background data for conformity and NEPA related issues.

*Response:* NCore site information is maintained by the EPA and available to the public through several different mediums. One resource is EPA's AirExplorer, which is an on-line tool that can be used to generate maps, data graphs, and data tables. AirExplorer is located at: <http://www.epa.gov/airexplorer>. Another resource is EPA's Air Quality System (AQS) database.

NCore sites, which represent area-wide pollutant concentrations by nature, are already operational throughout the country. As noted in section IV.B.2.e of the preamble to the final rule, upon analysis of existing NCore stations and all other area-wide CO monitors operating nationwide, the EPA believes that there are only four CBSAs that do not already have an area-wide monitor where near-road CO monitors are required by the final rule. The EPA's view is that generally area-wide monitors (e.g. those at sites with a spatial scale of neighborhood, urban, or regional) are likely appropriate to consider as being representative of broader urban or background concentrations, depending on their individual location. However, specific guidance on modeling for conformity and NEPA analyses is beyond the scope of this rulemaking.

#### **4. Other Monitoring Comments**

- (1) *Comment:* Multiple commenters (e.g., NACAA, IN DEM, North Carolina Division of Air Quality [NCDAQ], SC DHEC, Wisconsin Department of Natural Resources [WIDNR]), stated that the EPA needs to provide full funding for any new monitoring requirements.

*Response:* The EPA notes that it has historically provided full or partial funding for the cost of installing and operating monitors used to satisfy minimum monitoring requirements, and the agency expects to follow this precedent for required monitoring associated with this rulemaking. EPA understands the financial hardship many state and local agencies are currently enduring, and will continue to identify sources of funding and work with air monitoring agencies to move funds to states and support the implementation of all required monitoring. The Agency also notes that it expects states will be in a position to relocate existing CO monitors to satisfy the new minimum monitoring requirements. The Agency believes that in some cases, states may lower operating costs by shutting down some existing individual CO sites, while moving those monitors to the near-road sites required and implemented as part of the NO<sub>2</sub> rulemaking.

- (2) *Comment:* Several commenters (e.g., NACAA and NESCAUM) suggested that EPA should support and/or facilitate the introduction of trace level instruments into the state and local air monitoring networks while phasing out older monitors.

*Response:* The EPA agrees that when possible the introduction of more sensitive “trace-level” instrumentation into the SLAMS network is desirable. The EPA did not require the use of such instruments in this rulemaking because the required monitors are expected to be in locations of highest ambient CO concentrations. However, as state and local air agencies replace their inventory of gas analyzers, the Agency strongly encourages the adoption of trace-level instrumentation instead of standard sensitivity or traditional analyzers.

- (3) *Comment:* NACAA suggested that there is a need to provide traffic cameras at near-road CO sites.

*Response:* The EPA did not propose or promulgate any requirement for state and local air agencies to install traffic cameras at near-road monitoring sites. The Agency agrees that traffic information would be very valuable in characterizing CO data (and other pollutant data) collected at the near-road site. In the site selection process for near-road monitoring sites the EPA is encouraging air monitoring agencies to place some additional consideration on near-road locations where utilities or other transportation agency infrastructure, such as traffic counters and/or cameras, are located. If an air agency does not place a near-road site at a location with or near a traffic counter and/or camera, the Agency encourages those state and local air agencies to consider if a traffic counter and/or camera is financially feasible and implementable at their site, which may be identified during the near-road site selection process, and/or by engaging their respective transportation agency.

- (4) *Comment:* EPA received comments suggesting that near-road monitoring sites should be multipollutant monitoring sites, monitoring for pollutants such as air toxics, elemental carbon, organic carbon, and black carbon.

*Response:* The EPA has envisioned that near-road monitoring stations would be multipollutant monitoring sites. This concept fits with the Agency paradigm to promote multipollutant monitoring wherever possible. Multipollutant monitoring is viewed by the EPA as a means to broaden the understanding of air quality conditions and pollutant interactions, furthering the capability to evaluate air quality models, develop emission control strategies, and support research, including health studies. With that, the EPA agrees that the monitoring of other pollutants such as air toxics or black carbon, for example, is encouraged whenever feasible for state and local air agencies. The requirement of such monitoring in the near-road environment, other than for CO, is outside the scope of this rulemaking.

- (5) *Comment:* It was suggested that the EPA should not claim that there are not significant costs associated with the proposed monitoring network requirements.

*Response:* With the expectation that only approximately 52 (based on recent 2010 Census counts) CO monitors are being required with this rulemaking, the EPA believes that in almost all cases, state and local air monitoring agencies will be in a position to move existing monitors or put monitors back into service at required near-road sites. The costs of installing the near-road monitoring site infrastructure are to be borne by the implementation of near-road NO<sub>2</sub> sites. EPA recognizes that moving a CO monitor does have some associated costs but does not believe the costs associated with the monitoring requirements will be significant.

### **III. RESPONSES TO SIGNIFICANT COMMENTS RELATED TO IMPLEMENTATION OF STANDARDS**

#### **A. Designations**

- (1) *Comment:* Several commenters (including state transportation agencies, AAM, AASHTO, AEPSC and SEMCOG) commented on, and sought clarification of, issues related to designation of nonattainment areas that could occur in the future following changes in the monitoring network. For example, several commenters raised questions about whether such nonattainment areas would be large, or very localized.

*Response:* EPA is not revising the CO NAAQS. Accordingly, EPA will not be undertaking the designation process set forth in CAA section 107(d)(1). EPA has no knowledge as to whether the new monitoring network will produce air quality data such that the Administrator will deem it appropriate to initiate the redesignation process. EPA also notes that the CAA and judicial decisions make clear that the economic and technical feasibility of attaining ambient standards are not to be considered in setting or revising NAAQS (although such factors may be considered in the development of State plans to implement the standards). Accordingly, EPA believes it is unnecessary and would be premature to address in this action issues as to the scope of potential nonattainment areas or the process or factors to be considered if the Administrator finds it appropriate to initiate redesignations.

#### **B. Other**

- (1) *Comment:* Several commenters, including NESCAUM, state that there are many CO monitoring sites currently required by maintenance plans that are no longer needed. These sites have consistently measured levels of CO well below the current NAAQS, and they represent a resource drain in light of state budget constraints. States associated with NESCAUM urge EPA to develop a procedure that would allow states to shut down those sites earlier than the dates of existing agreements, as appropriate. This could be achieved using a simple approach,

possibly based on existing design value data being below a chosen threshold. Given that the nature of the agreements varies widely from state to state and across EPA regions, it is desirable to have a consistent national approach to the expeditious closing of these sites.

*Response:* The EPA currently provides a process for the shutting down of monitors which is provided at 40 CFR 58.14, titled “system modification.” In order for a monitor to be shut down, a state, or where appropriate a local, agency must develop and implement a plan and schedule to modify the monitoring network that complies with the findings of the network assessments required every 5 years by section 58.10(e). The state, or local agency, is then required to consult with the appropriate EPA Regional Administrator during the development of the schedule to modify the monitoring program, and is required to make the plan and schedule available to the public for 30 days prior to submission to the EPA Regional Administrator.

Plans containing modifications to NCore Stations or PAMS Stations are required to be submitted to the EPA Administrator. The Regional Administrator is required to provide an opportunity for public comment and is required to approve or disapprove submitted plans and schedules within 120 days. 40 CFR 58.14(c) provides that a State, or where appropriate a local, agency’s requests for a SLAMS monitor station discontinuation, subject to review of the Regional Administrator, will be approved if any of the following criteria are met and if the requirements of appendix D of 40 CFR 58 continue to be met. Other requests for discontinuation may also be approved on a cases-by-case basis if discontinuance of the affected monitor does not compromise data collection needed for implementation of a NAAQS and if the requirements of appendix D of 40 CFR 58 continue to be met.

More specifically, as it relates to the shutting down of monitors in maintenance areas, 40 CFR 58.14(c)(1) states the following: “Any PM<sub>2.5</sub>, O<sub>3</sub>, CO, PM<sub>10</sub>, SO<sub>2</sub>, Pb, or NO<sub>2</sub>, SLAMS monitor which has shown attainment during the previous five years, that has a probability of less than 10 percent of exceeding 80 percent of the applicable NAAQS during the next three years based on the levels, trends, and variability observed in the past, and which is not specifically required by an attainment plan or maintenance plan. In a nonattainment or maintenance area, if the most recent attainment or maintenance plan adopted by the state and approved by the EPA contains a contingency measure to be triggered by an air quality concentration and the monitor to be discontinued is the only SLAMS monitor operating in the nonattainment or maintenance area, the monitor may not be discontinued.”

EPA is willing to work with States to identify reasonable approaches to demonstrating that a monitor meets the criteria of 40 CFR 58.14(c)(1), and to consider revisions to maintenance plans that currently require monitors that otherwise meet those criteria.

- (2) *Comment:* Two state agencies (IN DEM and SC DHEC) submitted comments stating that if violations are measured by a roadside monitor, states do not possess the necessary authority to implement the required controls to establish attainment or meet their obligations for state implementation plan development. The commenters stated that a significant percentage of vehicles that travel major urban roadways are registered outside of the state and are regulated at the federal level. Transportation control measures could be implemented to reduce congestion and vehicle miles traveled, but only at the local level and would not achieve substantial reductions in CO. Commenters further state that, until U.S. EPA petitions Congress for the necessary revisions to the Clean Air Act, granting authority to states to have control over mobile sources, a means to develop an attainment strategy for roadside CO and NO<sub>2</sub> must be established.

*Response:* As noted above, EPA is not revising the CO NAAQS. Accordingly, EPA will not be undertaking the designation process set forth in CAA section 107(d)(1), or requiring SIP submissions pursuant to CAA section 110. EPA has no knowledge as to whether the new monitoring network will produce air quality data such that the Administrator will deem it appropriate to initiate the redesignation process.

EPA agrees that it is a federal responsibility to implement regulations that reduce emissions from new light- and heavy-duty motor vehicles. However, if it becomes necessary to achieve additional reductions in ambient CO, states have authority that can be used to reduce emissions from in-use light- and heavy-duty vehicles. For example, CAA section 177 allows states to adopt California's standards that apply to new motor vehicles or new motor vehicle engines. States can also implement programs to retrofit older heavy-duty diesel vehicles to reduce their CO emissions. States can also implement regulations to reduce or eliminate long-duration idling of heavy-duty diesel vehicles. They can implement an inspection and maintenance program for light-duty vehicles. Additionally, states can implement a wide range of programs to improve transportation efficiency (e.g., working with freight shippers).

It is EPA's belief that a number of states have already achieved reductions in CO emissions from on-road sources. EPA anticipates that if an area were to be designated nonattainment for the CO NAAQS, the state would evaluate a variety of control measures to reduce emissions from mobile sources (which include nonroad engines), as well as other sources that are contributing to the nonattainment problem.

If any areas are designated nonattainment at some point in the future, EPA expects that each state with a designated CO nonattainment area would develop a SIP that brings the area into attainment by the applicable deadline and that each state would evaluate the potential for controlling emissions from all sources that are contributing to the nonattainment problem.

#### **IV. RESPONSES TO SIGNIFICANT COMMENTS RELATED TO EXCEPTIONAL EVENTS**

- (1) *Comment:* Several state departments of transportation (including those from New York, Texas, Virginia, and Washington) and the American Association of State Highway and Transportation Officials commented that the proposed monitoring requirements for near-road CO monitors would result in “hotspot” monitoring rather than monitoring of background concentration levels and that the Exceptional Events Rule should, therefore, be revised to recognize temporary traffic-related activities, such as construction and traffic congestion caused by accidents, as potential exceptional events.

*Response:* The Exceptional Events Rule (EER) and the accompanying preamble (72 FR 13560, March 22, 2007) created a regulatory process containing definitions, procedural requirements, requirements for state demonstrations, and criteria for EPA approval for the exclusion of air quality data from regulatory decisions under the EER. EPA believes that these criteria and procedures sufficiently address any exceptional events claim that may arise for the CO NAAQS, and that additions or modifications to the EER, specific to CO, are not needed. EPA further recognizes that temporary traffic-related activities or conditions could be potential exceptional events, and, therefore, created a data flag (i.e., Qualifier Code and Qualifier Description) in the Air Quality System (AQS) for “unique traffic disruption.” EPA believes that the general rule criteria and specific AQS flagging mechanisms provide sufficient flexibility to identify and address near-road exceptional events.

In addition, EPA has developed draft implementation guidance products, available by request at [EEGuidanceComments@epa.gov](mailto:EEGuidanceComments@epa.gov), that clarify the criteria on which exclusion of event-affected data depend, describe the administrative process and associated timing for submittal and review of demonstrations, and provide answers to frequently asked questions, including questions regarding temporary activities and “hot-spot” (i.e., microscale) monitors.

#### **V. RESPONSES TO LEGAL, ADMINISTRATIVE, AND PROCEDURAL ISSUES AND MISPLACED COMMENTS**

- (1) *Comment:* Two commenters (PSR et al and Donnay) suggest that the rule be found subject to Executive Order 13045 (62 FR 19885, April 23, 1997), concerning the protection of children from environmental health and safety risks.

*Response:* EPA found that the proposed rule was not subject to E.O. 13045 because it was not “economically significant” as defined in E.O. 12866, and because the Agency does not believe the environmental health or safety risks addressed by this action present a disproportionate risk to children. Likewise,

EPA finds that the final rule is not subject to EO 13045 for the same reasons. EPA notes that a rule must be “economically significant” to be subject to EO 13045. Accordingly, the fact that the rule is not economically significant is a sufficient reason why it is not subject to EO 13045. However, EPA has carefully considered the risks from ambient CO for children. For the reasons discussed in the preamble (section II.B) and elsewhere in this document (e.g., see responses to comments at II.A.3(1), II.A.3(2) and II.A.5(8)), EPA disagrees with the commenters’ view that there is evidence establishing that a range of health effects, including developmental and respiratory effects, are occurring as a result of exposures to CO in ambient air at or below the current standards, or that children are at a disproportionate risk from adverse health effects from ambient CO. EPA believes the current CO NAAQS provide the requisite protection for children, with an adequate margin of safety.

- (2) *Comment:* Some comments stated that EPA failed to properly characterize CASAC's advice and to comply with its obligation under the CAA to respond to comments from CASAC.

*Response:* EPA believes the preamble to the proposed and final rules and this Response to Comments document fairly and adequately characterize CASAC's advice and that it has fully complied with its obligations under CAA section 307(d)(3) to "summarize and provide a reference to any pertinent findings, recommendations, and comments by [CASAC] and, if the proposal differs in any important respect from any of these recommendations, an explanation of the reasons for such differences."

EPA has explained in the preamble to the proposed and final rules that CASAC expressed a "preference" for a lower standard, stating that “[i]f the epidemiological evidence is given additional weight, the conclusion could be drawn that health effects are occurring at levels below the current standard, which would support the tightening of the current standard” and further advised that "revisions that result in lowering the standard should be considered" (see e.g., 76 FR 8183). However, EPA disagrees with the comment that "[i]t is evident ... that the CASAC believes the current standards are likely to be inadequate" (CBD et al, p. 7). The CASAC Panel explained its views at greater length in its response to charge questions on the draft Policy Assessment (Brain and Samet, 2010d, p. 12):

*While there have been no new controlled human exposures designed to examine effects of CO at COHb levels below 2%, there have been numerous improvements to the exposure and COHb dosimetry models employed to provide exposure and risk estimates. The Staff analysis indicates that some of the uncertainties identified in previous reviews of the standard have been reduced. Based on their overall analysis, they conclude that the body of evidence and the quantitative exposure and dose estimates provide support for a standard at least as*

*protective as the current standards. I.e. the data provide support for retaining or revising the current 8-hr standard.*

*Overall the Panel agrees with this conclusion. If the epidemiological evidence is given additional weight, the conclusion could be drawn that health effects are occurring at levels below the current standard, which would support the tightening of the current standard. The PA should include an analysis the number of exceedances that would have occurred if the standard had been based on the epidemiological data."*

Based on this statement, and others, from CASAC, EPA explained in the proposed notice that "the Administrator considers the advice of CASAC, including both their overall agreement with the Policy Assessment conclusion that the current evidence and quantitative exposure and dose estimates provide support for retaining the current standard, as well as their view that in light of the epidemiological studies, revisions to lower the standards should be considered and their preference for a lower standard" (76 FR 8183). EPA believes this, and other statements in the proposed and final notices, and this Response to Comments document, fairly and adequately summarize CASAC's advice. Moreover, EPA believes it has acted consistent with CASAC's advice in considering a lower standard. Ultimately, after giving a balanced assessment of the various lines of evidence, including further consideration of the epidemiological evidence, and its associated uncertainties (also noted by CASAC), the Administrator concluded that the current standards are requisite to protect public health with adequate margin of safety. Even if, for the sake of argument (despite CASAC's explicit recognition that the evidence supports either retaining or revising the standard), this conclusion were considered to differ in an important respect with the advice of CASAC, EPA has fully explained the basis for the Administrator's conclusion.

- (3) *Comment:* Two commenters stated that the Office of Management and Budget "classifies the CO NAAQS as a 'major' and 'economically significant' rule" (PSR at 10; Donnay at 60), and that therefore EPA is required to publish a Regulatory Impact Analysis (RIA), as EPA did during the last review. Another commenter (NYSDOT at 4) suggested that "if there are changes to CO attainment and nonattainment designations as a result of near-road monitors, those impacts and added costs should be fully evaluated and accounted for in this rule-making effort in accordance with Executive Order 13563."

*Response:* As noted in Section V of the preamble, under Executive Order 12866 (58 FR 51735, October 4, 1993), this action is a "significant regulatory action" because it was deemed to "raise novel legal or policy issues." Accordingly, EPA submitted this action to the Office of Management and Budget (OMB) for review under Executive Orders 12866 and 13563 (76 FR 3821, January 21, 2011). However, this action is not an "economically significant action" within the

meaning of section 3(f)(1) of EO 12866, and therefore section 6(a)(3)(C) of EO 12866 does not apply to this rulemaking and EPA was not required to prepare an RIA, which includes, to the extent feasible, a quantification of the costs and benefits of the rulemaking. Likewise, this rule is not a “major rule” for purposes of the Congressional Review Act.

As noted above, EPA has no knowledge as to whether the new monitoring network will produce air quality data such that the Administrator will deem it appropriate to initiate the redesignation process. However, EPA notes that the CAA and judicial decisions make clear that the economic and technical feasibility of attaining ambient standards are not to be considered in setting or revising NAAQS (although such factors may be considered in the development of State plans to implement the standards). EPA acknowledges that we could have prepared an RIA, even though an RIA was not required under EO 12866 and EO 13563. However, in light of the facts that EPA was not proposing to change the standard, that evidence is limited on current ambient concentrations near roads, and that any RIA would be irrelevant to a decision whether to change the standard, as well as EPA’s limited resources for preparing RIAs, EPA chose not to prepare an RIA for this action.

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**Appendix A.** Studies cited by public commenters that were not included in the 2010 CO ISA (e.g., published after document closure). These studies were provisionally considered by EPA, as discussed in section I.C of the preamble to the final rule and in this document.

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