Policy Assessment for the Review of the Carbon Monoxide National Ambient Air Quality Standards

External Review Draft

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U.S. Environmental Protection Agency
Office of Air Quality Planning and Standards
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1 INTRODUCTION

1.1 PURPOSE

The U.S. Environmental Protection Agency (EPA) is presently conducting a review of the carbon monoxide (CO) national ambient air quality standards (NAAQS). The overall plan and schedule for this review were presented in the *Plan for Review of the National Ambient Air Quality Standards for Carbon Monoxide* (IRP; USEPA, 2008b).[1] The IRP identified key policy-relevant issues to be addressed in this review as a series of questions that frame our consideration of whether the current NAAQS for CO should be retained or revised.

This Policy Assessment (PA), prepared by staff in EPA's Office of Air Quality Planning and Standards (OAQPS), is intended to help "bridge the gap" between the relevant scientific information and assessments and the judgments required of the EPA Administrator in determining whether, and if so, how it is appropriate to revise the NAAQS for CO. This draft PA presents factors relevant to EPA's review of the current primary (health-based) standards and consideration of a secondary (welfare-based) standard. It focuses on both evidence- and risk-based information in evaluating the adequacy of the current CO NAAQS and in identifying potential alternative standards for consideration. In this draft PA, we consider the scientific and technical information available in this review as assessed in the *Integrated Science Assessment for Carbon Monoxide* (henceforth referred to as the ISA, USEPA, 2010a), prepared by EPA's National Center for Environmental Assessment (NCEA), and the *Risk and Exposure Assessment to Support the Review of the Carbon Monoxide Primary National Ambient Air Quality Standards: Second External Review Draft* (henceforth referred to as the draft Risk and Exposure Assessment document or draft REA, USEPA, 2010b). In so doing, we focus on information that is most pertinent to evaluating the basic elements of NAAQS: indicator,[2] averaging time, form,[3] and level. These elements, which together serve to define each standard, must be considered collectively in evaluating the health and welfare protection afforded by the PM standards.

While this draft PA should be of use to all parties interested in the CO NAAQS review, it is written with an expectation that the reader has some familiarity with the technical discussions contained in the ISA (USEPA, 2010a) and the second draft REA (USEPA, 2010b).

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[1] As described below in section 1.2.3, the schedule for this review is governed by a court order.

[2] The "indicator" of a standard defines the chemical species or mixture that is to be measured in determining whether an area attains the standard.

[3] The "form" of a standard defines the air quality statistic that is to be compared to the level of the standard in determining whether an area attains the standard.

1.2 BACKGROUND

1.2.1 Legislative requirements

Two sections of the Clean Air Act (Act) govern the establishment and revision of the NAAQS. Section 108 (42 U.S.C. 7408) directs the Administrator to identify certain pollutants that meet specified criteria, including emissions which "may reasonably be anticipated to endanger public health and welfare" and whose presence "in the ambient air results from numerous or diverse mobile or stationary sources" and to issue air quality criteria for them. Air quality criteria are to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in ambient air . . ."

Section 109 (42 U.S.C. 7409) directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants listed under section 108. Section 109(b)(1) defines a primary standard as one "the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health."[4] A secondary standard, as defined in Section 109(b)(2), must "specify a level of air quality the attainment and maintenance of which, in the judgment of the Administrator, based on such criteria, is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air."[5]

The requirement that primary standards include an adequate margin of safety was intended to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting. It was also intended to provide a reasonable degree of protection against hazards that research has not yet identified. Lead Industries Association v. EPA, 647 F.2d 1130, 1154 (D.C. Cir 1980), cert. denied, 449 U.S. 1042 (1980); American Petroleum Institute v. Costle, 665 F.2d 1176, 1186 (D.C. Cir. 1981), cert. denied, 455 U.S. 1034 (1982). Both kinds of uncertainties are components of the 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 include an adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that have been

[4] The legislative history of section 109 indicates that a primary standard is to be set at the "maximum permissible ambient air level…which will protect the health of any [sensitive] group of the population," and that for this purpose "reference should be made to a representative sample of persons comprising the sensitive group rather than a single person in such group." S. Rep. No.91-1196, 91st Cong., Sess. 10 (1970)

[5] Welfare effects as defined in section 302(h) (42U.S.C. 7602(h)) include, but are not limited to, "effects in soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effect on economic values on personal comfort and well-being."

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.

In selecting a 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. Lead Industries Association v. EPA, supra, 647 F.2d at 1161-62.

In setting standards that are "requisite" to protect public health and welfare, as provided in section 109(b), EPA's task is to establish standards that are neither more nor less stringent than necessary for these purposes. In so doing, EPA may not consider the costs of implementing the standards. See generally Whitman v. American Trucking Associations, 531 U.S. 457, 465-472, 475-76 (2001).

Section 109(b)(1) of the Act requires that "not later than December 31, 1980, and at 5-year intervals thereafter, the Administrator shall complete a thorough review of the criteria published under section 108 and the national ambient air quality standards . . . and shall make such revisions in such criteria and standards and promulgate such new standards as may be appropriate . . . ." Section 109(d)(2) requires that an independent scientific review committee "shall complete a review of the criteria . . . and the national primary and secondary ambient air quality standards . . . and shall recommend to the Administrator any new . . . standards and revisions of existing criteria and standards as may be appropriate . . . ." Since the early 1980's, this independent review function has been performed by the Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board.

1.2.2 Previous Reviews

EPA initially established NAAQS for CO, under section 109 of the Act, on April 30, 1971. The primary standards were established to protect against the occurrence of carboxyhemoglobin levels in human blood associated with health effects of concern. The standards were set at 9 parts per million (ppm), as an 8-hour average and 35 ppm, as a 1-hour average, neither to be exceeded more than once per year (36 FR 8186). In the 1971 decision, the Administrator judged that attainment of these standards would provide protection of public health with an adequate margin of safety and would also protect against known and anticipated adverse effects on public welfare, and accordingly setting the secondary (welfare-based) standards identical to the primary (health-based) standards.

In 1985, EPA concluded its first periodic review of the criteria and standards for CO (50 FR 37484). In that review, EPA updated the scientific criteria upon which the initial CO standards were based through the publication of the 1979 *Air Quality Criteria Document for*

Carbon Monoxide (AQCD; USEPA, 1979a) and prepared a Staff Paper (USEPA, 1979b), which, along with the 1979 AQCD, served as the basis for the development of the notice of proposed rulemaking which was published on August 18, 1980 (45 FR 55066). Delays due to uncertainties regarding the scientific basis for the final decision resulted in EPA's announcing a second public comment period (47 FR 26407). Following substantial reexamination of the scientific data, EPA prepared an Addendum to the 1979 AQCD (USEPA, 1984a) and an updated Staff Paper (USEPA, 1984b). Following review by CASAC (McClellan, 1991, 1992), EPA announced its decision not to revise the existing primary standard and to revoke the secondary standard for CO on September 13, 1985, due to a lack of evidence of direct effects on public welfare at ambient concentrations (50 FR 37484).[6]

On August 1, 1994, EPA concluded its second periodic review of the criteria and standards for CO by deciding that revisions to the CO NAAQS were not warranted at that time (59 FR 38906). This decision reflected EPA's review of relevant scientific information assembled since the last review, as contained in the 1991 AQCD (USEPA, 1991) and the 1992 Staff Paper (USEPA, 1992). Thus, the primary standards were retained at 9 parts per million (ppm), 8-hr average and 35 ppm, 1-hr average, neither to be exceeded more than once per year (59 FR 38906).

The next periodic review was initiated in 1997, and a workshop was held in September 1998 to review and discuss material to be contained in the AQCD. On June 9, 1999, CASAC held a public meeting to review the first draft AQCD and to provide a consultation on a draft exposure analysis methodology document. Comments from CASAC Panel members and the public on the AQCD were considered in a second draft AQCD, which was reviewed at a CASAC meeting, held on November 18, 1999. After revision of the second draft AQCD, the final 2000 AQCD (U.S. EPA, 2000) was released in August 2000. EPA put this review on hold when Congress requested that the National Research Council (NRC) review the impact of meteorology and topography on ambient CO concentrations in high altitude and extreme cold regions of the U.S. In response, the NRC convened the Committee on Carbon Monoxide Episodes in Meteorological and Topographical Problem Areas, which focused on Fairbanks, Alaska as a case-study. A final report, "Managing Carbon Monoxide Pollution in Meteorological and Topographical Problem Areas," was published in 2003 (NRC, 2003) and offered a wide range of recommendations regarding management of CO air pollution, cold start emissions standards, oxygenated fuels, and CO monitoring. Following completion of this NRC report, EPA did not conduct rulemaking to complete the review.

[6] EPA concluded in 1985 that "no standards appear to be requisite to protect the public welfare from any known or anticipated adverse effects from ambient CO exposures" (50 FR 37494).

1.2.3 The Current Review

On September 13, 2007, EPA issued a call for information from the public (72 FR 52369) requesting the submission of recent scientific information on specified topics. A workshop was held on January 28–29, 2008 (73 FR 2490) to discuss policy-relevant scientific and technical information to inform EPA's planning for the CO NAAQS review. Following the workshop, a draft IRP (USEPA, 2008a) was made available in March 2008 for public comment and was discussed by the CASAC via a publicly accessible teleconference consultation on April 8, 2008 (73 FR 12998). EPA made the final IRP available in August 2008 (USEPA, 2008b).

In preparing the CO ISA, NCEA held an authors' teleconference in November 2008 with invited scientific experts to discuss preliminary draft materials prepared as part of the ongoing development of the CO ISA and its supplementary Annexes. The first draft ISA (USEPA, 2009a) for CO was made available for public review on March 12, 2009 (74 FR 10734) and reviewed by CASAC at a meeting held on May 12-13, 2009 (74 FR 15265). A second draft ISA (USEPA, 2009b) was released for CASAC and public review on September 23, 2009 (74 FR 48536), and it was reviewed by CASAC at a meeting held on November 16-17, 2009 (74 FR 54042). The final ISA was released in January 2010 (USEPA, 2010a).

In preparing the REA, OAQPS first released a draft planning document, the draft Scope and Methods Plan, for consultation with CASAC and public review at the CASAC meeting held on May 12-13, 2009. Taking into consideration CASAC and public comments on the draft Plan, OAQPS staff conducted a risk/exposure assessment, and released for CASAC review and public comment a first draft REA (USEPA, 2009c), which was reviewed at the CASAC meeting held on November 16-17, 2009. A second draft REA was released for CASAC review and public comment in February 2010, and will be reviewed at an upcoming CASAC meeting scheduled for March 22-23, 2010. Drawing from information in the final CO ISA and the second draft REA, this draft PA is now being released for CASAC review and public comment at the same meeting.

The schedule for completion of this review is governed by a court order resolving a lawsuit filed in March 2003 by a group of plaintiffs representing two regional environmental organizations.[7] The court order that governs this review, entered by the court on November 14, 2008, provides that EPA will meet the following schedule in completing this review: a final risk/exposure assessment is to be completed by May 28, 2010 and notices of proposed and final rulemaking are to be signed by October 28, 2010 and May 13, 2011, respectively

[7] The lawsuit alleged that EPA had failed to perform its mandatory duty, under section 109(d)(1), of completing the current review within the period provided by statute. American Lung Association v. Whitman (No. 1:03CV00778, D.D.C. 2003).

1.3 CURRENT AIR QUALITY

This section provides a general overview of the current air quality conditions to provide context for this consideration of the current standards for carbon monoxide. A more comprehensive discussion of air quality information is provided in the ISA (ISA, sections 3.2 and 3.4), and a more detailed discussion of aspects particularly relevant to the exposure assessment is provided in the second draft REA (REA, chapter 3).

1.3.1 Sources to ambient air

Carbon monoxide in ambient air is formed primarily by the incomplete combustion of carbon-containing fuels and by photochemical reactions in the atmosphere. As a result of the combustion conditions, CO emissions from large fossil-fueled power plants are typically very low because optimized fuel consumption conditions make boiler combustion highly efficient. In contrast, internal combustion engines used in many mobile sources have widely varying operating conditions. Therefore, higher and more varying CO formation results from the operation of these mobile sources (ISA, section 3.2). In the National Emissions Inventory for 2002, CO emissions from on-road vehicles accounted for approximately half of the total CO emissions by individual source sectors in the U.S. (ISA, Figure 3-1.[8] As with previous reviews of the CO NAAQS, mobile sources continue to be a significant source sector for CO in ambient air.

As discussed in the ISA, the spatial and temporal patterns of ambient CO concentrations are heavily influenced by the patterns associated with mobile source emissions (ISA, chapter 3). In metropolitan areas of the U.S., due to their relatively greater motor vehicle density, the contribution from mobile sources has been estimated to be as high as 75% of all ambient CO emissions in the 2002 National Emissions Inventory (ISA, p. 3-2). For example, emissions in urban Denver County, Colorado originating from on-road mobile sources are estimated to be about 71% of total CO emissions (ISA, section 3.2), compared with 20% for rural Garfield County, Colorado[9] (ISA, section 3, Figure 3-6). When considering all mobile sources nationwide (non-road and on-road combined), the contribution to total ambient CO emissions

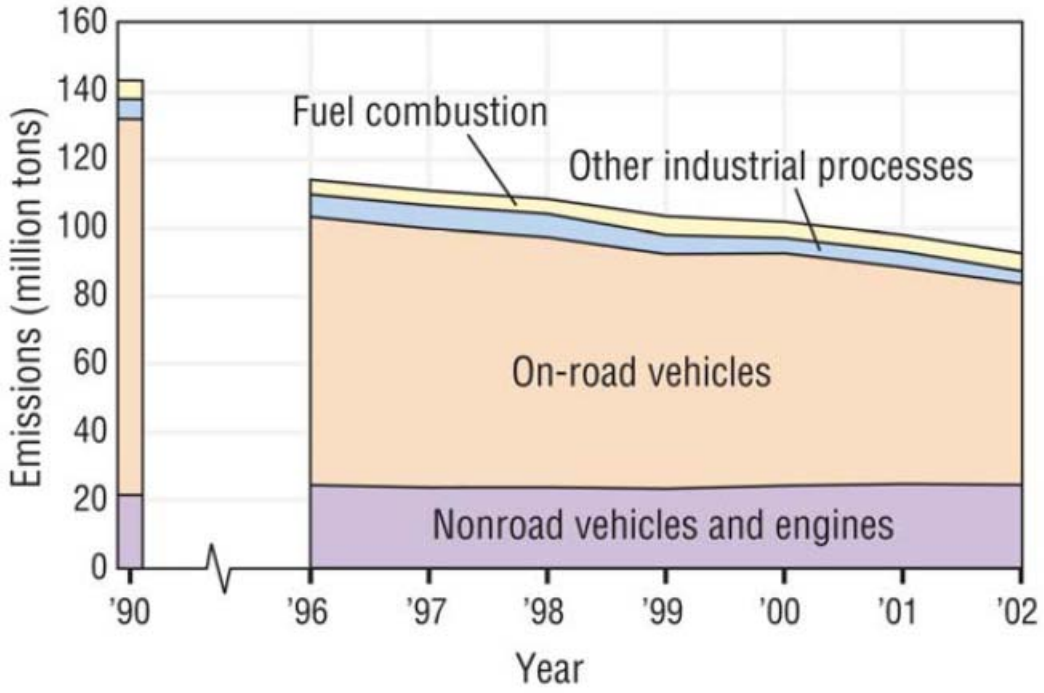
[8] EPA compiles CO emissions estimates for the U.S. in the National Emissions Inventory (NEI). The 2002 NEI provides the most recent publicly available CO emissions estimates for the U.S. that meet EPA's data quality assurance objectives. Estimates come from various sources and different data sources use different data collection methods, most of which are based on engineering calculations and estimates rather than measurements. Although these estimates are generated using well-established approaches, uncertainties are inherent in the emission factors and models used to represent sources for which emissions have not been directly measured. Uncertainties vary by source category, season and region (ISA, section 3.2.1).

[9] The 2002 National Emissions Inventory estimate for on-road emissions in Garfield is 20,000 tons, and the total emissions from all sources is estimated to be 98,831 (99K) tons. Thus, in this example the on-road vehicles accounts for 20.2% of the total emissions (ISA, section 3, figure 3-6).

nationally is over 80%. Again using Denver County as an example, all mobile sources are estimated to contribute about 98% of total CO emissions.

National-scale anthropogenic CO emissions have decreased 35% between 1990 and 2002 (Figure 1-1). Nearly all the national-level CO reductions since 1990 are the result of emission reductions in on-road vehicles (ISA, Figure 3.-2).

Figure 1-1. Trends in anthropogenic CO emissions in the U.S. by source category for 1990 and 1996-2002. Source: U.S. EPA (2008c)



1.3.2 Ambient Monitoring Network

Ambient CO concentrations are measured by monitoring networks that are operated by state and local monitoring agencies in the U.S., and are funded in part by the EPA. The main network providing ambient data for use in comparison to the NAAQS is the State and Local Air Monitoring Stations (SLAMS) network. CO monitors are typically sited to reflect one of the following spatial scales:

- Microscale: Data represent concentrations within a 100 m radius of the monitor. For CO, microscale monitors are sited 2 – 10 m from a roadway. Measurements are intended to represent the near-road or street canyon environment.
- Middle scale: Data represent concentrations averaged over areas defined by 100 – 500 m radii. Measurements are intended to represent several city blocks.

- Neighborhood scale: Data represent concentrations averaged over areas defined by 0.5 – 4.0 km radii. Measurements are intended to represent extended portions of a city.

In addition to monitoring required for determining compliance with the NAAQS, the EPA is currently in the process of implementing plans for a new network of multi-pollutant stations called NCore that is intended to meet multiple monitoring objectives (ISA, p. 3-21). The complete NCore network, required to be fully implemented by January 1, 2011, will consist of approximately 63 urban and 20 rural stations and will include some existing SLAMS sites that have been modified to include additional measurements. The majority of NCore stations will be sited, however, to represent neighborhood, urban, and regional scales, consistent with the NCore network design objective of representing exposure expected across urban and rural areas in locations that are not dominated by local sources.

To promote uniform enforcement of the air quality standards set forth under the CAA, EPA has established federal reference methods (FRMs) for ambient air sample collection and analysis. Measurements for determinations of NAAQS compliance must be made with FRMs or methods designated as equivalent (federal equivalent methods, FEMs). Given the levels of the CO NAAQS (35 ppm, 1-hour; 9 ppm, 8-hour), a lower detectable limit (LDL) on the order of 1.0 ppm is well below the NAAQS levels and is therefore sufficient for demonstration of compliance.[10] More than 95% of monitors in use during 2005-2007 have LDL of 0.5 ppm (ISA, Appendix A, Table A-8). With ambient CO levels now routinely near or below 1 ppm, however, a large percentage of the measurements are below the LDL of conventional monitors, contributing greater uncertainty in a larger portion of the distribution of monitoring data (ISA, section 3.4.1). For example, more than half of the dataset of nationally reported hourly data for 2005-2007 analyzed in the ISA fell below the reported LDL of 0.5 ppm (ISA, p. 3-56). To reduce the uncertainty at these lower concentrations, a new generation of ambient CO monitors has been designed that provides improved sensitivity for measurements at or below the typical ambient CO levels measured in most urban and all rural locations. The number of active monitors employing such sensitive methods is increasing, primarily in association with the implementation of the NCore network.[11] The extent to which these more sensitive monitors become integrated into non-NCore SLAMS stations, however, will depend on the availability of funding for states to replace existing legacy CO monitors as well as the possibility that

[10] Among the 13 approved FRMs in use in the SLAMS network for which data were reported to EPA's Air Quality System (AQS) between 2005 and 2009, nine are "legacy" methods with a federal method detection limit (MDL) listed as 0.5 ppm.

[11] For example, four approved FRMs are newer, more sensitive methods with a federal MDL of 0.02 ppm and a growing body of ambient data from more sensitive CO instruments is becoming available. Testing performed by EPA on several such CO monitors in 2005 and 2006 demonstrated MDLs of approximately 0.017 – 0.018 ppm (17 – 18 ppb), slightly below the stated LDL of 0.02 – 0.04 ppm (ISA, section 3.4.1).

monitoring requirements for CO might either encourage or require such technological improvements.

1.3.3 Ambient Monitoring Concentrations

Nearly 400 ambient monitoring stations report continuous hourly averages of CO concentrations across the U.S. None of monitoring sites with extensive records[12] for 2007 in 243 counties reported a second-highest 1-hour CO concentration above 35 ppm, the level of the current 1-hour NAAQS, while sites in two counties reported second-highest 1-hour CO concentrations between 15.1 and 35.0 ppm. Sites in five counties reported second-highest 8-hour CO concentration of 5.0 ppm or higher (ISA, section 3.5.1.1).

For the most recent period for which air quality status relative to the CO NAAQS has been analyzed (2007-2008), all areas of the U.S. meet both CO NAAQS.[13] In the previous two periods (2005-2006 and 2006-2007), one area, (Jefferson County, Alabama) has failed to meet the 8-hour standard. Further, one area of the country is designated in non-attainment with the CO NAAQS, however, air quality in that area currently meets the standards.

The current levels of ambient CO across the U.S. reflect the steady declines in ambient concentrations that have occurred over the past several years. Both the 2nd highest 1-hour and 8-hour concentrations have significantly declined since the last review (Figures 1-2 and 1-3). At the set of sites across the U.S. that have been continuously monitored since 1990 the average 2nd highest 8-hour and 1-hour concentrations have declined by nearly 70%.

[12] During the period 2005-2007, 291 out of 376 monitors sited in 243 different counties, cities or municipalities, met the following dataset completeness criteria: 75% of the hours in a day, 75% of days in a calendar quarter and 3 complete quarters for 3 years (ISA, section 3.4.2.2). An exception was made for monitors in U.S. EPA Region 10 for which two rather than three complete quarters were considered to meet the criteria (ISA, p. 3-20).

[13] The air quality status in areas monitored relative to the CO NAAQS is provided at http://www.epa.gov/air/airtrends/values.html.

Figure 1-2. Trends in CO concentration (second maximum 8-hour average) in the U.S., 1990-2008. The white line indicates average across the sites; ninety percent of sites have concentrations below the top line, while ten percent of sites have concentrations below the bottom line.

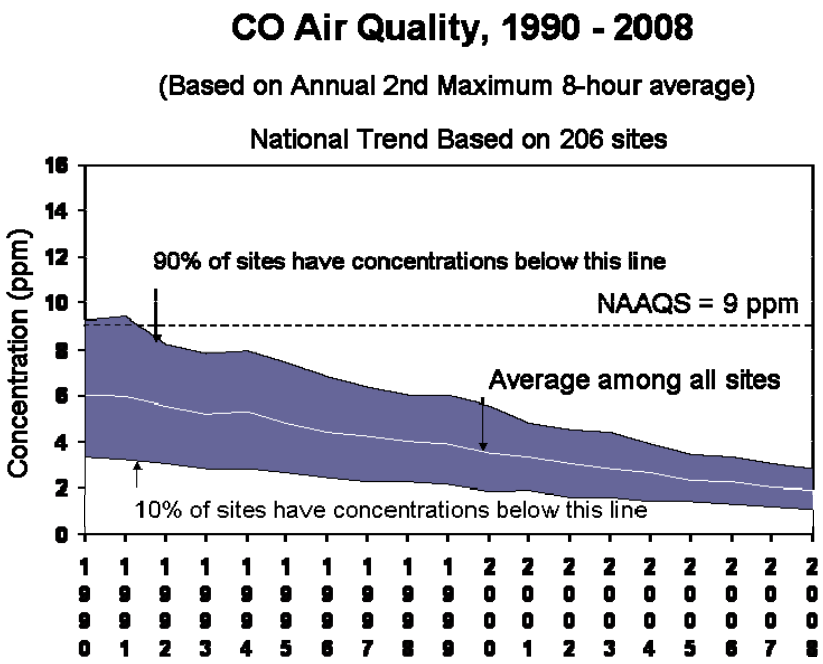
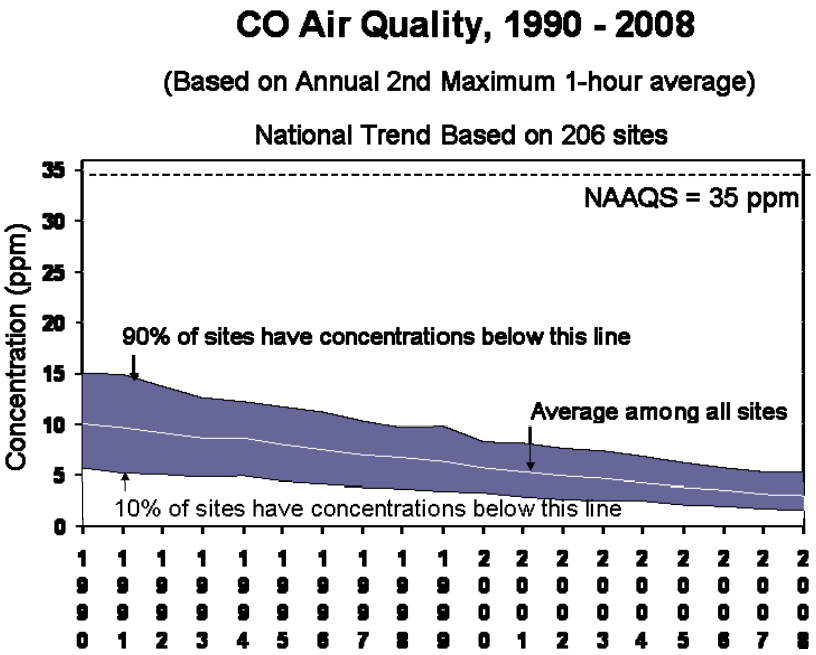


Figure 1-3. Trends in CO concentration (second maximum 1-hour average) in the U.S., 1990-2008. The white line indicates average across the sites; ninety percent of sites have concentrations below the top line, while ten percent of sites have concentrations below the bottom line.



1.4 GENERAL APPROACH AND ORGANIZATION OF THE DOCUMENT

This draft PA includes staff's evaluation of the policy implications of the scientific evidence reviewed in the ISA and the results of quantitative analyses based on that evidence. Taken together, this information informs initial staff conclusions and the identification of a range of policy options for consideration in addressing public health and welfare effects associated with ambient CO.

Following this introductory chapter, chapter 2 focuses on review of the primary standards for CO, presenting background information on the rationale for previous reviews and the approach followed in the current review. Chapter 2 discusses the adequacy of the current standards, taking into account evidence- and risk-based considerations, and includes initial staff conclusions on adequacy. Chapter 2 also discusses potential alternative standards for consideration, focusing on indicator, averaging time, form, and level, and includes initial staff conclusions on alternative standards for consideration. Finally, chapter 3 discusses information relevant to staff's consideration of a secondary standard for CO.

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2 REVIEW OF THE PRIMARY STANDARDS FOR CARBON MONOXIDE

This chapter presents initial staff conclusions for consideration in deciding whether the existing primary standards for carbon monoxide (CO) should be revised and, if so, what revisions are appropriate. The current primary CO standards include a 1-hour and an 8-hour standard to protect public health from exposure to CO. In initially evaluating the current primary NAAQS we have reviewed, and as appropriate, updated, a series of key policy-relevant issues initially presented in the *Plan for Review of the National Ambient Air Quality Standards for Carbon Monoxide* (USEPA, 2008a, section 3.1). The answers to these policy-relevant questions will inform decisions on whether, and if so, how to revise the primary standards for CO.

Following a background section regarding considerations in the previous review, the discussion in this chapter focuses on two central issues related to: (1) the adequacy of the current CO standards and (2) what potential alternative standards, if any, should be considered in this review. Within each of these broad areas, a series of questions are addressed. The four basic elements of the NAAQS (e.g., indicator, averaging time, level, and form) will be considered collectively in evaluating the health protection afforded by the current or any alternative standards considered.

2.1 APPROACH

For the purposes of this draft Policy Assessment (PA), staff has drawn from EPA's assessment and integrated synthesis of the scientific evidence presented in the *Integrated Science Assessment for Carbon Monoxide* (USEPA, 2010a; henceforth referred to as the ISA) and 2000 *Air Quality Criteria Document for Carbon Monoxide* (USEPA, 2000; henceforth referred to as the 2000 AQCD) and on the analyses presented in the second draft Risk and Exposure Assessment (USEPA, 2010b; henceforth referred to as the draft REA). The evidence-based discussions presented in this chapter draw upon evidence from epidemiologic studies, controlled human exposure studies, and toxicological studies evaluating short- or long-term exposures to CO, as discussed in chapter 5 of the ISA, with supporting information related to dosimetry and potential mode of action evidence as presented in chapters 4 and 5 of the ISA, respectively, as well as the integration of evidence across disciplines presented in chapter 2 of the ISA. The exposure/risk-based discussions have drawn from the quantitative health analyses for CO presented in the draft REA. Together the evidence-based and risk-based considerations have informed our conclusions related to the adequacy of the current CO standards and alternative standards that are supported by the currently available scientific evidence.

In presenting a range of primary standard options for consideration, we note that the final decision is largely a public health policy judgment. A final decision must draw upon scientific information and analyses about health effects and risks, as well as judgments about how to deal with the range of uncertainties that are inherent in the scientific evidence and analyses. Our approach to informing these judgments, discussed more fully below, is based on the recognition that the available health effects evidence generally reflects a continuum, consisting of ambient levels at which scientists generally agree that health effects are likely to occur, through lower levels at which the likelihood and magnitude of the response become increasingly uncertain. This approach is consistent with the requirements of the NAAQS provisions of the Act and with how EPA and the courts have historically interpreted the Act. These provisions require the Administrator to establish primary standards that, in the Administrator's judgment, are requisite to protect public health with an adequate margin of safely. In so doing, the Administrator seeks to establish standards that are neither more nor less stringent than necessary for this purpose. The Act does not require that primary standards be set at a zero-risk level, but rather at a level that avoids unacceptable risks to public health.

This section includes background information on the approach used in the previous review of the CO standards (section 2.1.1) and also a discussion of the approach for the current review (section 2.1.2).

2.1.1 Approach Used in the Previous Review

The current primary standards for CO are set at 9 parts per million (ppm) as an 8-hour average and 35 ppm as a 1-hour average, neither to be exceeded more than once per year. These standards were initially set in 1971to protect against the occurrence of carboxyhemoglobin (COHb) levels that may be associated with effects of concern (36 FR 8186). Reviews of these standards in the 1980s and early 1990s, respectively, identified additional evidence regarding ambient CO, COHb levels and health effects (USEPA, 1984a, 1984b; USEPA, 1991; USEPA, 1992; McClellan, 1991,1992). Assessment of the evidence in those reviews led the EPA to retain the existing standards without revision (59 FR 38906).

The 1994 decision to retain the primary standards without revision was based on the evidence published through 1990 and reviewed in the 1991 AQCD (USEPA, 1991), the 1992 Staff Paper assessment of the policy-relevant information contained in the AQCD and the quantitative exposure assessment (USEPA, 1992), and the advice and recommendations of CASAC (McClellan 1991, 1992). At that time, as at the time of the prior NAAQS review (50 FR 37484), COHb levels in blood were recognized as the most useful estimates of exogenous CO exposures and to serve as the best biomarker of CO toxicity for ambient-level exposures to

CO. Consequently, COHb levels were used as the indicator of health effects in the identification of health effect levels of concern for CO (59 FR 38909).

In reviewing the standards in 1994 the Administrator first recognized the need to determine the COHb levels of concern "taking into account a large and diverse health effects database". The more uncertain and less quantifiable evidence was taken into account to identify the lower end of this range to provide an adequate margin of safety for effects of clear concern. To consider ambient CO concentrations likely to result in COHb levels of concern, a model solution to the Coburn-Forster-Kane (CFK) differential equations was employed in the analysis of CO exposures expected to occur under air quality scenarios related to just meeting the current 8-hour CO NAAQS, the controlling standard (USEPA, 1992).[1] Key considerations in this approach are described below

Carboxyhemoglobin Levels of Concern and Margin of Safety

The assessment of the science that was presented in the 1991 AQCD (USEPA, 1991) indicated that CO is associated with effects in the cardiovascular system, central nervous system (CNS), and the developing fetus. Additionally, factors recognized as having potential interaction with CO that may alter health effects included exposures to other pollutants, some drugs and some environmental factors, such as altitude. Cardiovascular effects of CO, as measured by decreased time to onset of angina and to onset of significant electrocardiogram (ECG) ST-segment depression[2] were judged by the Administrator to be "the health effects of greater concern, which clearly had been associated with CO exposures at levels observed in ambient air" (59 FR 38913).

Based on the consistent findings of response in patients with coronary artery disease[3] across the controlled human exposure evidence (Adams et al., 1988; Allred et al., 1989a, 1989b, 1991; Anderson et al., 1973; Kleinman et al., 1989, 1998; Sheps et al., 1987) and discussions of adverse health consequences in the 1991 AQCD and the 1992 Staff Paper, at the CASAC

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[1] Air quality analyses of CO levels in the U.S. consistently demonstrate that attainment of the 8-hour standard results in 1-hour maximum concentrations well below the corresponding 1-hour standard.

[2] The ST-segment is a portion of the electrocardiogram, depression of which is an indication of insufficient oxygen supply to the heart muscle tissue (myocardial ischemia). Myocardial ischemia can result in chest pain (angina pectoris) or such characteristic changes in ECGs or both. In individuals with coronary artery disease, it tends to occur at specific levels of exercise. The duration of exercise required to demonstrate chest pain and/or a 1-mm change in the ST segment of the ECG were key measurements in the multicenter study by Allred et al (1989a, 1989b, 1991).

[3] Coronary artery disease (CAD), often also called coronary heart disease or ischemic heart disease is a category of cardiovascular disease associated with narrowed heart arteries. Individuals with this disease have myocardial ischemia, which occurs when the heart muscle receives insufficient oxygen delivered by the blood. Exercise-induced angina pectoris (chest pain) occurs in many of them. Among all patients with diagnosed CAD, the predominant type of ischemia, as identified by ST segment depression, is asymptomatic (i.e., silent). Patients who experience angina typically have additional ischemic episodes that are asymptomatic (2000 AQCD, section 7.7.2.1). In addition to such chronic conditions, CAD can include myocardial infarction (ISA, p. 5-24).

meetings and in the July 1991 CASAC letter, the Administrator concluded that "CO exposures resulting in COHb levels of 2.9-3.0 percent (CO-Ox) or higher in persons with heart disease have the potential to increase the risk of decreased time to onset of angina pain and ST-segment depression" (59 FR 38913).[4] Two of the five key studies were given particular emphasis in the 1991 AQCD to indicate the basis for conclusions regarding lowest observed-effect levels of COHb in patients with exercise-induced ischemia, in terms of measured COHb and its representation in terms of increase from baseline COHb on the order of 1.5 to 2.2% (USEPA, 1991, pp. 1-11 to 1-12; Allred et al., 1989a, 1989b, 1991; Anderson et al., 1973).

While EPA and CASAC recognized the existence of a range of views among health professionals on the clinical significance of the responses observed in the clinical studies, CASAC noted that the dominant view was that they should be considered "adverse or harbinger of adverse effect" (McClellan, 1991) and EPA recognized that it was "important that standards be set to appropriately reduce the risk of ambient exposures which produce COHb levels that could induce such potentially adverse effects" (59 FR 38913) as those occurring at COHb levels of 2.9-3.0% (CO-oximeter) (59 FR 38913; USEPA, 1991, p. 1-12; USEPA, 1992, pp. 20-22). In further considering additional results from the controlled human exposure evidence as well as other aspects of the available evidence and uncertainties regarding modeling estimates of COHb formation and human exposure to COHb levels in the population associated with attainment of a given CO NAAQS, the Administrator recognized the need to extend the range of COHb levels for consideration in evaluating whether the current CO standards provide an adequate margin of safety to those falling between 2.0 to 2.9 (59 FR 38913). Factors considered in recognizing this margin of safety included the following (59 FR 38913).

- Uncertainty associated with the clinical importance of cardiovascular effects associated with exposures to CO that resulted in COHb levels of 2 to 3 percent. Although recognizing the possibility that there is no threshold for these effects even at lower COHb levels, the health significance of the small changes in ST-segment depression observed was considered somewhat minor.
- Findings of short-term reduction in maximal work capacity measured in trained athletes exposed to CO at levels resulting in COHb levels of 2.3 to 7 percent.
- The potential that the most sensitive individuals have not been studied, the limited information regarding the effects of ambient CO in the developing fetus, and concern about visitors to high altitudes, individuals with anemia or respiratory disease, or the elderly.

[4] Based on matched measurements available for CO-Ox and gas chromatography in this range, staff note that CO-oximetry measurements of 2.9 to 3.0 percent COHb appear to correspond to GC measurements on the order of 2% (Allred et al., 1991).

- Potential for short term peak CO exposures to be responsible for impairments (impairment of visual perception, sensorimotor performance, vigilance or other CNS effects) which could be a matter of concern for complex activities such as driving a car, although these effects had not been demonstrated to be caused by CO concentrations in ambient air.
- Concern based on limited evidence for individuals exposed to CO concurrently with drugs (e.g., alcohol), during heat stress, or co-exposure to other pollutants.
- Large uncertainties remaining regarding modeling COHb formation and estimating human exposure to CO which could lead to overestimation of COHb levels in the population associated with attainment of a given CO NAAQS.
- Uncertainty associated with COHb measurements made using CO-Ox which may not reflect COHb levels in angina patients studied, thereby creating uncertainty in establishing a lowest effects level for CO.

Based on these considerations of the evidence, the Administrator identified a range of COHb levels of concern extending from 2.9% at the upper end down to 2% at the lower end and concluded that "evaluation of the adequacy of the current standard should focus on reducing the number of individuals with cardiovascular disease from being exposed to CO levels in the ambient air that would result in COHb levels of 2.1 percent." She additionally concluded that standards that "protect against COHb levels at the lower end of the range should provide an adequate margin of safety against effects of uncertain occurrence, as well as those of clear concern that have been associated with COHb levels in the upper-end of the range" (59 FR 48914).

Estimation of Population Exposures

To estimate CO exposures and resulting COHb levels that might be expected under air quality conditions that just met the current standards, an analysis of exposure and associated internal dose in terms of COHb levels in the population of interest in the city of Denver, Colorado was performed (59 FR 38906; USEPA, 1992). That analysis indicated that if the 9 ppm 8-hour standard were just met, the proportion of the nonsmoking population with cardiovascular disease experiencing a daily maximum 8-hour exposure at or above 9 ppm for 8 hours decreased by an order of magnitude or more as compared to the proportion under then-existing CO levels, down to less than 0.1 percent of the total person-days in that population. More specifically, upon meeting the 8-hour standard, EPA estimated that less than 0.1% of the nonsmoking cardiovascular-disease population would experience a COHb level greater than or equal to 2.1%. A smaller percentage of the at-risk population was estimated to exceed higher

COHb levels.[5] Based on these estimates, the Administrator concluded that "relatively few people of the cardiovascular sensitive population group analyzed will experience COHb levels ≥ 2.1 percent when exposed to CO levels in absence of indoor sources". The analysis also took into account that certain indoor sources (e.g., passive smoking, gas stove usage) contributed to total CO exposure and EPA recognized that such sources may be of concern for such high risk groups as individuals with cardiovascular disease, pregnant women, and their unborn children but concluded that "the contribution of indoor sources cannot be effectively mitigated by ambient air quality standards" (59 FR38914).

Decision Regarding Adequacy of the Standards

Based on consideration of the evidence and the quantitative results of the exposure assessment, the Administrator concluded that revisions of the current primary standards for CO were not appropriate at that time (59 FR 38914). The Administrator additionally concluded that both averaging times for the primary standards, 1-hour and 8-hour, be retained. The 1-hour and 8-hour averaging times were first chosen when EPA promulgated the primary NAAQS for CO in 1971. The selection of the 8-hour averaging time was based on the following: (a) most individuals' COHb levels appeared to approach equilibrium after 8 hours of exposure, (b) the 8-hour time period corresponded to the blocks of time when people were often exposed in a particular location or activity (e.g., working or sleeping), and (c) judgment that this provided a good indicator for tracking continuous exposures during any 24-hour period. The 1-hour averaging time was selected as better representing a time period of interest to short-term CO exposure and providing protection from effects which might be encountered from very short duration peak exposures in the urban environment (59 FR 38914).

2.1.2 Approach for the Current Review

To evaluate whether it is appropriate to consider retaining the current primary CO standards, or whether consideration of revisions is appropriate, we adopted an approach in this review that builds upon the general approach used in the last review and reflects the broader body of evidence and information now available. As summarized above, the Administrator's decisions in the previous review were based on an integration of information on health effects associated with exposure to ambient CO; expert judgment on the adversity of such effects on individuals; and policy judgments as to when the standard is requisite to protect public health with an adequate margin of safety, which were informed by air quality and related analyses,

[5] In the 1992 assessment, the person-days (number of persons multiplied by the number of days per year exposed) and person-hours (number of persons multiplied by the number of hours per year exposed) were the reported exposure metrics. Upon meeting the 8-hour standard, it was estimated that less than 0.1% of the total person-days simulated for the nonsmoking cardiovascular-disease population were associated with a maximum COHb level greater than or equal to 2.1% (USEPA, 1992; Johnson et al., 1992).

quantitative exposure and risk assessments when possible, and qualitative assessment of impacts that could not be quantified.

In conducting this assessment, we draw on the current evidence and quantitative assessments of exposure pertaining to the public health risk of ambient CO. In considering the scientific and technical information, we consider both the information available at the time of the last review and information newly available since the last review, including the current ISA and the 2000 AQCD (USEPA, 2010; USEPA, 2000), as well as current and preceding quantitative exposure/risk assessments (USEPA 2010b). As was the case at the time of the last review, the best characterized health effect associated with CO levels of concern is hypoxia (reduced oxygen availability) induced by increased COHb levels in blood (ISA, section 5.1.2). Accordingly, CO is of particular concern for those with impaired cardiovascular systems, and the most compelling evidence of cardiovascular effects is that from a series of controlled human exposure studies among exercising individuals with coronary heart disease (CHD) also referred to as coronary artery disease (CAD) (ISA, sections 5.2.4 and 5.2.6). Additionally available in this review are a number of epidemiological studies that investigated the association of cardiovascular disease-related health outcomes with concentrations of CO at ambient monitors. To inform our review of the ambient standards, we performed a quantitative exposure and dose modeling analysis that estimated COHb levels associated with different air quality conditions in simulated at-risk populations in two U.S. cities. Thus, in developing conclusions in this review as discussed in sections 2.2 and 2.3 below, we have taken into account both evidence-based and exposure/risk-based considerations framed by a series of key policy-relevant questions.

2.2 ADEQUACY OF THE CURRENT STANDARD

In considering the adequacy of the current CO standards, the overarching question we consider is:

- **Does the currently available scientific evidence- and exposure/risk-based information, as reflected in the ISA and draft REA, support or call into question the adequacy of the protection afforded by the current CO standards?**

To assist us in interpreting the currently available scientific evidence and the results of recent quantitative exposure/risk analyses to address this question, we have focused on a series of more specific questions, posed within sections 2.2.1 and 2.2.2 below. In considering the scientific and technical information, we consider both the information available at the time of the last review and information newly available since the last review which has been critically analyzed and characterized in the 2000 AQCD and more recently in the ISA.

2.2.1 Evidence-based Considerations

In considering the evidence with regard to the issue of adequacy of the current standard, we address a series of questions beginning with the health effects associated with CO exposure, followed by the use of COHb levels as the indicator of CO exposures and biomarker for characterizing the potential for health effects associated with exposures to ambient CO, and then the identification of the populations most susceptible to the effects of CO. We next consider the evidence regarding the levels of CO in ambient air associated with health effects and the important uncertainties associated with the evidence.

- **Does the current evidence alter our conclusions from the previous review regarding the health effects associated with exposure to CO?**

The current evidence continues to support our conclusions from the previous review regarding key health effects associated with CO exposure. The best characterized effect of CO continues to be related to the binding of CO to blood Hb to form increased levels of COHb (ISA, sections 4.1 and 5.1.2) and the primary focus is on associated cardiovascular effects (ISA, section 5.2). In the scientific assessment for the current review, a likely causal relationship is judged to exist between relevant CO exposures[6] and cardiovascular effects (ISA, section 2.5.1) which is similar to conclusions in the last review. The evidence for effects on the central nervous system, birth outcomes and developmental effects, and respiratory effects, while in some cases expanded from that which was available at the time of the last review, is judged to be suggestive of a causal relationship with relevant CO exposures (ISA, section 2.5). These overall findings, additional details of which are described below, are consistent with and extend in some ways conclusions drawn from the health effects evidence in the last review.

The long-standing body of evidence that has established many aspects of the biological effects of CO continues to contribute to our understanding of the health effects of ambient CO. Upon inhalation, CO diffuses through the respiratory zone (alveoli) to the blood where it binds to Hb, forming COHb. This binding to reduced iron in heme proteins and the alteration of their function is the common mechanism underlying biological responses to CO. Accordingly, inhaled CO elicits various health effects through binding to, and associated alteration of the function of, a number of heme-containing molecules, mainly Hb (see e.g., ISA, section 4.1). The best characterized health effect associated with CO levels of concern is hypoxia (reduced O_2 availability) induced by increased COHb levels in blood and decreased oxygen availability to critical tissues and organs, specifically the heart (ISA, section 5.1.2). Thus, people with a cardiovascular disease that affects their ability to compensate for this effect (e.g., through

[6] Relevant CO exposures are defined in the ISA as "generally within one or two orders of magnitude of ambient CO concentrations" (ISA, section 2.5).

vasodilation or increased cardiac output) are a key population at risk from CO exposures.[7] The dose metric most commonly used as a bioindicator of exposure and health risk from CO is the level of COHb in the blood (USEPA, 1991; 2002; 2010a).

The body of health effects evidence for CO has grown considerably since the previous review with the addition of numerous epidemiological and toxicological studies (ISA; 2000 AQCD). This evidence provides additional detail and support to our prior understanding of CO effects and population susceptibility. For example, the currently available evidence expands on potential nonhypoxic mechanisms for CO effects, although the importance of such mechanisms at environmentally-relevant CO exposures is unclear. Most notably, the current evidence includes much expanded epidemiological evidence that provides support for previous conclusions regarding cardiovascular disease-related susceptibility and indications of air quality conditions that may be associated with ambient CO-related risk.

In the most recent analysis of the health evidence EPA has developed a framework to characterize the evidence as to likelihood of causal relationships between exposure to ambient CO and specific health effects (ISA, chapter 1). The clearest evidence is available for cardiovascular effects, such that the major conclusion drawn in the ISA regarding the critical analysis of all available data on health effects of CO including the clinical and epidemiological evidence is that "Given the consistent and coherent evidence from epidemiologic and human clinical studies, along with biological plausibility provided by CO's role in limiting O_2 availability, it is concluded that a causal relationship is likely to exist between relevant[8] short-term CO exposures and cardiovascular morbidity" (ISA, p. 2-6, section 2.5.1). The evidence is judged suggestive of causal relationships between relevant short- and long-term CO exposures and CNS effects, birth outcomes and developmental effects following long-term exposure, respiratory morbidity following short-term exposure, and mortality following short-term exposure (ISA, section 2.5, Table 2-1). It was concluded that there is not likely to be a causal relationship between relevant long-term CO exposures and mortality (ISA, Table 2-1).

Similar to the previous review, results from controlled human exposure studies of individuals with coronary artery disease (Adams et al., 1988; Allred et al., 1989a, 1989b, 1991; Anderson et al., 1973; Kleinman et al., 1989, 1998; Sheps et al., 1987;) are the "most compelling evidence of CO-induced effects on the cardiovascular system" (ISA, Section 5.2). Additionally,

[7] As described in discussing susceptibility below, cardiovascular disease comprises many types of medical disorders, including heart disease (e.g., CHD), cerebrovascular disease (e.g., stroke), hypertension (high blood pressure), and peripheral vascular diseases and heart disease patients often have markedly reduced circulatory capacity and reduced ability to compensate for increased circulatory demands during exercise and other stress (2000 AQCD, p. 7-7).

[8] Relevant CO exposures are defined in the ISA as "generally within one or two orders of magnitude of ambient CO concentrations" (ISA, section 2.5).

the use of an internal dose metric, COHb, adds to the strength of the findings in these controlled exposure studies. As a group, these studies demonstrate the role of CO in increasing the susceptibility of people with CAD to incidents of exercise-associated myocardial ischemia.

Among these controlled human exposure studies, the ISA places principal emphasis on the study of coronary artery disease patients by Allred et al. (1989a, 1989b, 1991) which was key to considerations from the previous review for the following reasons: 1) dose-response relationships was observed; 2) effects were observed at the lowest COHb levels tested (mean of 2-2.4% COHb following experimental CO exposure), providing no evidence of a threshold; 3) objective measures of myocardial ischemia (ST-segment depression) were assessed, as well as the subjective measure of decreased time to induction of angina; 4) measurements were taken both by gas chromatography (GC), which provides a more accurate measurement of COHb blood levels[9], and by CO-Ox; 5) a large number of subjects were used; 6) a strict subject selection protocol was employed to include only CAD patients with reproducible exercise-induced angina.; and 7) the study was conducted at multiple laboratories around the U.S. This study evaluated changes in time to exercise-induced onset of markers of myocardial ischemia resulting from two short CO exposures targeted to result in mean study subject COHb levels of 2% and 4%, respectively (ISA, section 5.2.4). In this study, subjects (n=63) on three separate occasions underwent an initial graded exercise treadmill test, followed by 50 to 70-minute exposures under resting conditions to room air CO concentrations or CO concentrations targeted for each subject to achieve blood COHb levels of 2% and 4%. The exposures were to average CO concentrations of 0.7 ppm (room air concentration range 0-2 ppm), 117 ppm (range 42-202 ppm) and 253 ppm (range 143-357 ppm). After the 50- to 70-min exposures, subjects underwent a second graded exercise treadmill test, and the percent change in time to onset of angina and time to ST endpoint between the first and second exercise tests was determined. For the two CO exposures, the average post-exposure COHb concentrations were reported as 2.4% and 4.7%, and the subsequent post-exercise average COHb concentrations were reported as 2.0% and 3.9%.[10]

[9] As stated in the ISA, the gas chromatographic technique for measuring COHb levels "is known to be more accurate than spectrophotometric measurements, particularly for samples containing COHb concentrations < 5%" (ISA, p. 5-41). CO-oximetry is a spectrophotometric method commonly used to rapidly provide approximate concentrations of COHb during controlled exposures (ISA, p. 5-41). At the low concentrations of COHb (<5%) more relevant to exposures to ambient CO, co-oximeters are reported to overestimate COHb levels compared to GC measurements, while at higher concentrations, this method is reported to produce underestimates (ISA, p.4-18).

[10] While the COHb blood level for each subject during the exercise tests was intermediate between the post-exposure and subsequent post-exercise measurements (e.g., mean 2.0-2.4% and 3.9-4.7%), the study authors noted that the measurements at the end of the exercise test represented the COHb concentrations at the approximate time of onset of myocardial ischemia as indicated by angina and ST segment changes. The corresponding ranges of CO-Ox measurements for the two exposures were 2.7-3.2% and 4.7-5.6%. In this document, we refer to the GC-measured mean of 2.0% or 2.0-2.4% for the COHb levels resulting from the lower experimental CO exposure.

Relative to clean-air exposure that resulted in a mean COHb level of 0.6% (post-exercise), exposure to CO resulting in post-exercise mean COHb concentrations of 2.0% and 3.9% were observed to decrease the exercise time required to induce ST-segment depression by 5.1 ($p=0.01$) and 12.1% ($p<0.001$), respectively. These changes were well correlated with the onset of exercise-induced angina, the time to which was shortened by 4.2% ($p=0.027$) and 7.1% ($p=0.002$), respectively, for the two experimental CO exposures (Allred et al., 1989a, 1989b, 1991).[11] As at the time of the last review, while ST-segment depression is recognized as an indicator of myocardial ischemia, the exact physiological significance of the observed changes is unclear (ISA, p. 5-48).

No human clinical studies have been specifically designed to evaluate the effect of controlled short-term exposures to CO resulting in COHb levels lower than a study mean of 2% (ISA, section 5.2.6). However, an important finding of the multi-laboratory study was the dose-response relationship (discussed further in addressing a subsequent question below) observed between COHb and the markers of myocardial ischemia, with effects observed at the lowest increases in COHb tested, without evidence of a measurable threshold effect. As reported by the authors, the results comparing "the effects of increasing COHb from baseline levels (0.6%) to 2 and 3.9% COHb showed that each produced further changes in objective ECG measures of ischemia" implying that "small increments in COHb could adversely affect myocardial function and produce ischemia" (Allred et al., 1989b; Allred et al., 1991).

The epidemiological evidence has expanded considerably since the last review including numerous additional studies that are coherent with the evidence on markers of myocardial ischemia from controlled human studies of CAD patients (ISA, section 2.7). The most recent series of epidemiological studies have evaluated the associations between ambient concentrations of multiple pollutants (i.e. $PM_{2.5}$, NO_2, SO_2, O_3 and CO) at fixed-site monitors and increases in emergency department visits and hospital admissions for specific cardiovascular health outcomes including ischemic heart disease (IHD), myocardial infarction (MI), congestive heart failure (CHF), and cardiovascular diseases (CVD) as a whole (Bell et al., 2009; Koken et al., 2003; Linn et al., 2000; Mann et al., 2002; Metzger et al., 2004; Peel et al., 2007; Symons et al., 2006; Tolbert et al., 2007; Wellenius et al., 2005). As noted by the ISA, "[s]tudies of hospital admissions and ED visits for IHD provide the strongest [epidemiological] evidence of ambient CO being associated with adverse CVD outcomes" (ISA, p. 5-40, section 5.2.3; Linn et al., 2000;

[11] Another indicator measured in the study was the combination of heart rate and systolic blood pressure which provides a clinical index of the work of the heart and myocardial oxygen consumption, since heart rate and blood pressure are major determinants of myocardial oxygen consumption (Allred et al., 1991). A decrease in oxygen to the myocardium would be expected to be paralleled by ischemia at lower heart rate and systolic blood pressure. This heart rate-systolic blood pressure indicator at the time to ST-endpoint was decreased by 4.4% at the 3.9% COHb dose level and by a nonstatistically-significant, smaller amount at the 2.0% COHb dose level.

Mann et al., 2002;Metzger et al., 2004; Peel et al., 2007). With regard to studies for other measures of cardiovascular morbidity, the ISA notes that "[t]hough not as consistent as the IHD effects, the effects for all CVD hospital admissions (which include IHD admissions) and CHF hospital admissions also provide evidence for an association of cardiovascular outcomes and ambient CO concentrations" (ISA, section 5.2.3; Bell et al., 2009; Tolbert et al., 2007).[12]

The geographic areas in the studies for IHD and all CVD outcomes (which is inclusive of IHD) include Atlanta, urban areas of California and a group of 126 urban counties (Table 2-1 below; ISA, Figure 2-1). In these studies, different multiple-year periods were assessed and the air quality statistics analyzed varied from 1 hour to 24 hours. Together the individual study periods spanned the period from 1988 through 2005. Further, the studies encompass a range of air quality conditions, such that during the time periods of study for these outcomes, only the three Atlanta studies (Metzger et al., 2004; Peel et al., 2007; Tolbert et al., 2007) (and the studies of CHF in Pittsburgh and Baltimore)[13] did not include years in which ambient CO concentrations exceeded the 8-hour standard (Table 2-1).

[12] As summarized further in response to a subsequent question below, the ISA notes the difficulty in determining from this group of studies on cardiovascular disease outcomes the extent to which CO is independently associated with CVD outcomes as compared to CO as a marker for the effects of another traffic-related pollutant or mix of pollutants, although the ISA concludes that the evidence provides support for a direct effect of short-term ambient CO exposure on CVD morbidity (ISA, pp. 5-40 to 5-41).

[13] The study by Symons et al (2006) in Baltimore focused on an 8-month period from April to December, 2002 (ISA, pp. 5-31, 5-32, C-21).

Table 2-1. Information from U.S. epidemiological studies of hospital admissions for ischemic heart disease (ISA, Figure 5-2), cardiovascular disease (ISA, Figure 5-5) and congestive heart failure (ISA, Figure 5-4) and on air quality during the study periods.

Study Reference	Study Area	Study Time Period	Health Outcome	Risk Estimate (confidence interval) *Estimates are standardized within averaging times.*[1]	Air Quality Metric Analyzed with Health Outcome	CO concentration in study areas, in terms of air quality metric analyzed (ppm)		Range of design values (ppm) for study areas during study period	
						Mean or median (study)	99th percentile (AQS)	1-hour	8-hour
U.S. studies of hospital admissions for coronary heart disease (drawn from ISA, Figure 5-2).									
Metzger et al., 2004	Atlanta	1993-2000	IHD	1.016 (0.999-1.034)	1-hr daily max	1.5[2]	5.5 - 5.9	4.3 -16.3	3.2 - 5.3
Peel et al., 2007	Atlanta	1993-2000	IHD		1-hr daily max	1.8	5.5 - 5.9	4.3 -16.3	3.2 - 5.3
Mann et al., 2002	CA	1988-1995	IHD	1.0136 (1.0053-1.0220)	8-hr daily max	2.07	1.3 - 15.9	16.5 - 32	11.6 - 23.4
Linn et al., 2000	CA	1992-1995	MI	1.02 (1.01-1.03)	24-hr average	1.5	1.1 - 8.3	16.5 - 25	11.6 -16.4
U.S. studies of hospital admissions for cardiovascular disease (drawn from ISA, Figure 5-5)									
Bell et al., 2009	126 urban counties	1999-2005	CVD 65+	1.0096 (1.0079-1.0112)	1-hr daily max	1.3[2]	1.2 - 22.1	17.5-33.5	8.8-24.3
Tolbert et al., 2007	Atlanta	1993-2004	CVD	1.017 (1.008-1.027)	1-hr daily max	1.6	5.3 - 5.4	3.5 -16.3	2.5 - 5.3
Linn et al., 2000	CA	1992-1995	CVD	1.012 (1.005-1.020)	24-hr average	1.5	1.1 - 8.3	16.5 - 25	11.6 -16.4
U.S. studies of hospital admissions for congestive heart failure (drawn from ISA, Figure 5-4)									
Linn et al., 2000	CA	1992-1995	CHF	1.012 (1.005-1.020)	24-hr average	1.5	1.1 - 8.3	16.5 – 25	11.6 -16.4
Mann et al., 2002	CA	1988-1995	IHD+CHF	1.0304 (1.0135-1.0475)	8-hr daily max	2.07	1.3 - 15.9	16.5-32	11.6-23.4
Symons et al., 2006	Baltimore	2002	CHF	1.08 (0.40-2.99)	8-hr daily max	0.4	2.3	4.4-9.6	2.6-3.0
Wellenius et al., 2005	Pittsburgh	1987-1999	CHF	1.0843 (1.0614-1.1078)	24-hr average	1.03	1.6-3.9	3.1-5.9	1.3-8.8
Metzger et al., 2004	Atlanta	1993-2000	CHF	1.01(0.99-1.03)	1-hr daily max	1.5[2]	5.5 - 5.9	4.3-16.3	3.2-5.3
Peel et al., 2007	Atlanta	1993-2000	CHF	1.019 (0.997-1.041)	1-hr daily max	1.8	5.5 - 5.9	4.3-16.3	3.2-5.3
Koken et al., 2003	Denver	1993-1997	CHF	1.181 (1.002-1.393)	24-hr average	0.9	1.3-2.0	8.2-18.2[3]	4.7-10.4[3]

Table legend. Information is from (a) studies that provide the strongest and most consistent weight of evidence from the epidemiological literature, and (b) additional supportive epidemiological studies. Presented are risk estimates (unadjusted for other pollutants) for hospital admissions for ischemic heart disease (IHD), myocardial infarction (MI), cardiovascular disease (CVD; Bell 2009 included only subjects 65 years old and above) outcomes, and congestive heart failure (CHF), with the study reported mean/median for the ambient CO concentration metric analyzed by the study authors. The 99 th percentile CO concentrations for the three studied metrics (1-, 8-hr daily max, or 24-hr average) were derived from AQS data for monitors in study areas during study time periods. Design values are CO concentrations in the statistical form of the standard; presented is the range of 2nd maximum 1-hour and 8-hour average concentrations at highest monitor in each study area across years (from AQS for the areas and time periods of the studies). [1]Estimates standardized for 1 ppm increase in CO concentration for 1-hour metric, 0.75 ppm for 8-hour metric and 0.5 ppm for 24-hour metric. Lag period (e.g., 0, 1, 0-1, 0-2) varies by study. [2]These values for Metzger et al., 2004 and Bell et al., 2009 are the median. [3]These design values reflect full year of data, inclusive of study months (July-Aug).

Additional epidemiological studies have been conducted on associations of ambient CO with other cardiovascular effects. For example, preliminary evidence of a link between exposure to CO and alteration of blood markers of coagulation and inflammation in individuals with CAD or CVD has been provided by a few well conducted and informative studies (ISA, Table 5-6; Delfino et al., 2008; Liao et al., 2005). As noted by the ISA, however, further studies are warranted to investigate the role of these markers in prothrombotic events and their possible contribution to the pathophysiology of CO-induced aggravation of ischemic heart disease (ISA, section 5.2.1.8). Other epidemiological studies (including field and or panel studies) also provide some evidence of a link between CO exposure and heart rate and heart rate variability (ISA, section 5.2.1.1). With regard to the two of three studies reporting a positive association with heart rate, the ISA concluded that "further research is warranted" to corroborate the results, while the larger number of studies for heart rate variability parameters is characterized as mixed (ISA, p. 5-15). Additionally, of the two studies of electrocardiogram changes indicative of ischemic events (ISA, section 5.2.1.2), one found no association and, in the other study, unlike the association with black carbon in that study, the association with CO did not remain significant in multipollutant models (ISA, p. 5-16). A limited number of epidemiological studies (Bell et al., 2009; Linn et al., 2000) have investigated hospital admissions for stroke (including both hemorrhagic and ischemic forms) and generally report small or no associations with ambient CO concentrations (ISA, section 5.2.1.9, Table 5-8 and Figure 5-3).

Our consideration of these epidemiological studies here reflects our understanding of CO mechanisms and effects which is informed by the long-standing body of evidence for CO summarized above. Figure 2-1 below presents a conceptual model of the pathway from CO exposures to these effects. Figure 2-2 separately shows elements of this conceptual model investigated in clinical studies in contrast to those in the epidemiological studies discussed above. More specifically, the clinical studies provide linkages between directly measured controlled short-term CO exposures and COHb levels in CAD patients and between those COHb levels and effects in that study group, specifically, markers of myocardial ischemia. In contrast, the epidemiological studies report associations between ambient CO concentrations at fixed-site monitors and cardiovascular-related health outcomes (i.e., hospital admissions and emergency room visits). However, our ability to integrate the evidence from these epidemiological studies with our knowledge of CO-related effects based on the clinical evidence is limited in a few aspects. Most particularly, we lack information on the actual CO exposures and associated internal COHb levels that may have elicited the population response observed in the epidemiological studies, including the extent to which the response may be driven by CO exposures other than the ambient CO concentrations. Moreover, it is also unknown how those unmeasured exposures relate to the exposure concentrations of the clinical studies (e.g., 1 hour at

approximately 50-200 ppm). We are also limited in our understanding of the specific relationship between the changes in indicators of myocardial ischemia observed in the controlled human exposure studies and the hospital admissions assessed in the epidemiological studies. In consideration of the epidemiological studies for cardiovascular outcomes in light of the larger body of evidence, the ISA notes that the "known role of CO in limiting O_2 availability lends biological plausibility to ischemia related health outcomes following CO exposure", providing coherence between the two sets of findings. The ISA additionally recognizes a lack of clarity as to whether "the small changes in COHb associated with ambient CO exposures results in substantially reduced O_2 delivery to tissues" (ISA, p. 5-48).

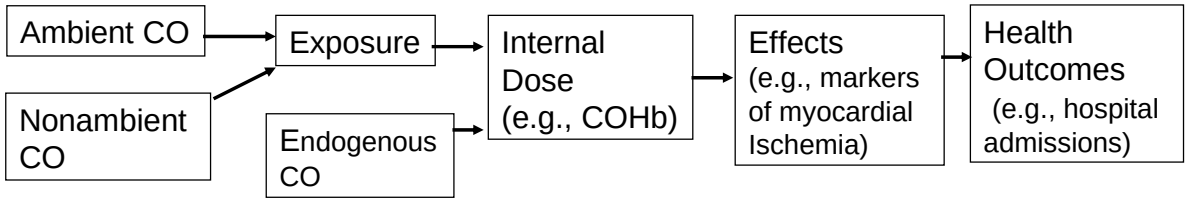

Figure 2-1. A conceptual model of CO source-to-health outcome pathway.

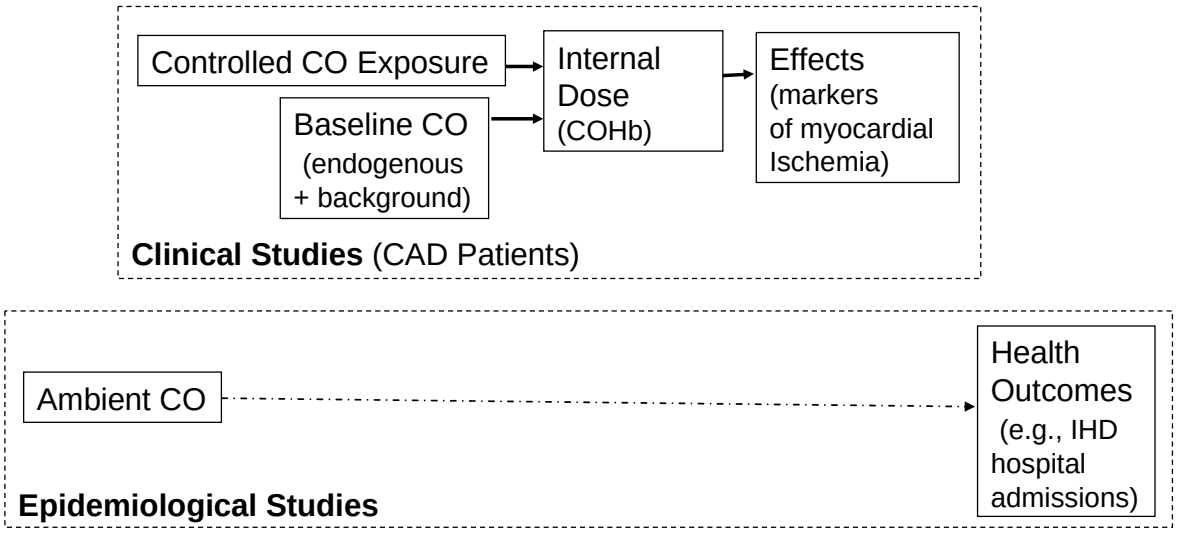

Figure 2-2. Components of CO source-to-outcome conceptual model measured in controlled human exposure and epidemiological studies discussed in this document.

Toxicological evidence presented in the current review provides further evidence of the effects of CO in the cardiovascular system (e.g., aortic injury, microvascular permeability, vascular remodeling, ventricular hypertrophy) occurring at laboratory animal CO exposure levels ranging from 35 to 200 ppm (ISA, section 5.2.5).

At the time of the last review, there was evidence for effects other than cardiovascular morbidity, including neurological, respiratory and developmental effects. With regard to neurological effects, acute exposures to CO have long been known to induce CNS effects such as those observed with CO poisoning, although limited equivocal evidence available at the time of the last review included indications of some neurobehavioral effects to result from CO exposures resulting in a range of 5-20% COHb (2000 AQCD, section 6.3.2). No additional clinical or epidemiological studies are now available that investigated such effects of CO at ambient levels (ISA, section 5.3). With regard to potential effects of CO on birth outcomes and developmental effects, the currently available evidence includes limited but suggestive epidemiologic evidence for a CO-induced effect on preterm-birth, birth defects, decrease in birth weight, other measures of fetal growth, and infant mortality (ISA, section 5.4.3). The available animal toxicological studies provide some support and coherence for these birth and developmental outcomes, although a clear understanding of the mechanisms underlying potential reproductive and developmental effects is still lacking (ISA, section 2.5.3). There is limited evidence of an association between short-term exposure to CO and respiratory-related outcomes, although only preliminary evidence is available regarding a mechanism that could provide plausibility for CO-induced effects. Thus, while there is some additional evidence on neurological, respiratory and developmental effects, it remains limited.

In summary, rather than altering our conclusions from the previous review, the current evidence provides continued support and some additional strength to our previous conclusions regarding the health effects associated with exposure to CO and continues to indicate cardiovascular effects, particularly effects related to the role of CO in limiting oxygen availability, as those of greatest concern at low exposures.

- **Does the current evidence continue to support a focus on COHb levels as the most useful indicator of CO exposures and the best biomarker to characterize potential for health effects associated with exposures to ambient CO? Or does the current evidence provide support for a focus on alternate dose indicators to characterize potential for health effects?**

As discussed in both the 2000 AQCD (USEPA, 2000) and the ISA, the best characterized mechanism of action of CO is tissue hypoxia caused by binding of CO to hemoglobin to form COHb. Increasing levels of COHb with subsequent decrease in oxygen availability for organs and tissues are of concern in people with pre-existing heart disease who have compromised

compensatory mechanisms (e.g., arteries unable to vasodilate, reduced capacity to increase cardiac output) such as those affected with coronary heart disease. The integrative review of health effects of CO indicates that "the clearest evidence indicates that individuals with coronary artery disease are most susceptible to an increase in CO-induced health effects" (ISA, section 5.7.8) and the evidence, including that from clinical studies described in addressing the previous question (regarding health effects associated with exposure to CO), continues to support levels of COHb as the most useful indicator of CO exposure that is related to the health effects of CO of major concern.

Alternative mechanisms of CO-induced effects primarily associated with CO's ability to bind heme-containing proteins other than hemoglobin and myoglobin, and involving a wide range of cellular tissues and CO concentrations, have been described in the 2000 AQCD (USEPA, 2000, section 5.8) and in the ISA (ISA, section 5.1.3). The ISA notes that collectively the older toxicological studies demonstrated that exposure to high concentrations of CO resulted in altered functions of heme proteins other than myoglobin and hemoglobin which have the potential to interfere with basic cell and molecular processes that could lead to dysfunction and/or disease. More recent toxicological studies described in the ISA, conducted at CO exposure levels ranging from 35 to 100 ppm have provided evidence of non-hypoxic mechanisms involving binding of CO to reduced iron in heme proteins by which CO may be causing cellular injury or toxicity (ISA, section 2.5). The ISA notes that these mechanisms may or may not be interrelated and include alteration of nitric oxide signaling, inhibition of cytochrome C oxidase, heme loss from protein, disruption of iron homeostasis and alteration of cellular redox status. Less understood mechanisms noted in the ISA are alteration in ion channel activity and modulation of protein kinases signaling pathways. The ISA notes that "CO may be responsible for a continuum of effects from cell signaling to adaptive responses to cellular injury, depending on intracellular concentrations of CO, heme proteins and molecules which modulate CO binding to heme proteins" (ISA, section 5.1.3.3).

Although there is evidence of additional biomarkers potentially associated with effects of CO, new research is needed to further understand these biomarkers and their linkage to CO-induced effects in at-risk populations. Therefore, the evidence indicates that COHb continues to be the most useful and well supported indicator of CO exposures and the best biomarker to characterize the potential for health effects associated with exposures to ambient CO.

- **Does the current evidence alter our understanding of populations that are particularly susceptible to CO exposures? Is there new evidence that suggest additional susceptible populations that should be given increased focus in this review?**

The term susceptibility has been used to recognize populations that have a greater likelihood of experiencing effects related to ambient CO exposure (ISA, section 5.7). Thus, susceptible populations are at greater risk of CO effects and are referred to as *at-risk* in the discussion here. This increased likelihood of response to CO can potentially result from many factors, including pre-existing medical disorders or disease state, lifestage, gender, lifestyle or increased exposures (ISA, section 5.7).

The current evidence, while much expanded in a number of ways, continues to support our conclusions from the previous review regarding the key and best-characterized at-risk population for exposure to ambient CO. Based on the evidence from clinical studies also considered in the last review, with which the now much-expanded epidemiological evidence base is coherent, the population with pre-existing cardiovascular disease associated with limitation in oxygen availability continues to be the best characterized population at risk of adverse CO-induced effects, with coronary artery disease (CAD) recognized as "the most important susceptibility characteristic for increased risk due to CO exposure" (ISA, section 2.6.1). An important factor determining the increased susceptibility of this population is their inability to compensate for the reduction in oxygen levels due to an already compromised cardiovascular system. Individuals with a healthy cardiovascular system (i.e., with healthy coronary arteries) have operative physiologic compensatory mechanisms (e.g., increased blood flow and oxygen extraction) for CO-induced hypoxia and are unlikely to be at increased risk of CO-induced effects (ISA, p. 2-10).[14] In addition, the high oxygen consumption of the heart, together with the inability to compensate for the hypoxic effects of CO make the cardiac muscle of a person suffering with coronary artery disease a critical target for the hypoxic effects of CO.

In the current review, recognition of susceptibility of the population with pre-existing cardiovascular disease, such as CAD, is supported by the expanded epidemiological database, which includes a number of studies reporting significant increases in hospital admissions for IHD, angina and MI in relation to CO exposures (ISA, section 2.7). Further support is provided by epidemiologic studies (Mann et al., 2002; and Peel et al., 2007) of increased hospital admissions and emergency department visits for IHD among individuals with secondary

[14] The other well-studied individuals at the time of the last review were healthy male adults that experienced decreased exercise duration at similar COHb levels during short term maximal exercise. This population was of lesser concern since it represented a smaller sensitive group, and potentially limited to individuals that would engage in vigorous exercise such as competing athletes (1991 AQCD, section 10.3.2).

diagnoses for other cardiovascular outcomes including arrhythmia and congestive heart failure (ISA, section 5.7), and toxicological studies reporting altered cardiac outcomes in animal models of cardiovascular disease (ISA, section 5.2.1.9).

Cardiovascular disease comprises many types of medical disorders, including heart disease, cerebrovascular disease (e.g., stroke), hypertension (high blood pressure), and peripheral vascular diseases. Heart disease, in turn, comprises several types of disorders, including ischemic heart disease (CHD or CAD, myocardial infarction, angina), congestive heart failure, and disturbances in cardiac rhythm (2000 AQCD, section 7.7.2.1). Types of cardiovascular disease other than those discussed above may also contribute to increased susceptibility to the adverse effects of low levels of CO (ISA, section 5.7.1.1). For example, some evidence with regard to other types of cardiovascular disease such as congestive heart failure, arrhythmia, and non-specific cardiovascular disease, although more limited for peripheral vascular and cerebrovascular disease, indicates that "the continuous nature of the progression of CAD and its close relationship with other forms of cardiovascular disease suggest that a larger population than just those individuals with a prior diagnosis of CAD may be susceptible to health effects from CO exposure" (ISA, p. 5-117).

Although there was little experimental data available at the time of the last review to adequately characterize specific health effects of CO at ambient levels for other potentially at-risk populations, several other populations were identified as being potentially more at risk of CO-induced effects due to a number of factors. These factors include pre-existing diseases that could inherently decrease oxygen availability to tissues, lifestage vulnerabilities (e.g., fetuses, the elderly), gender, lifestyle, medications or alterations in the environment (e.g., increased altitude). This is consistent with the ISA conclusions in the current review which recognize other populations that may be potentially susceptible to the effects of CO as continuing to include: those with other pre-existing diseases that may have already limited O_2 availability or increased COHb production or levels, such as people with obstructive lung diseases, diabetes and anemia; older adults and fetuses during critical phases of development; commuters and those living near heavily traveled roadways; visitors to high-altitude locations; and people ingesting medications and other substances that enhance endogenous or metabolic CO production.

Preliminary evidence from epidemiological, controlled human exposure, and toxicological studies indicate that people with obstructive lung disease (e.g., COPD patients with underlying hypoxia, asthmatics) may be a potentially susceptible population (ISA, section 5.7.1.2). Overall, the few available epidemiological studies have reported weak, positive associations between ambient CO and CVD hospital admissions for individuals with underlying COPD. Additionally, a controlled human exposure study of individuals with COPD reported that two patients experienced COPD exacerbation and a slight anti-inflammatory effect during

CO exposures of 100-125 ppm for 2 hours (ISA, section 5.5.1.2). Other epidemiological studies (ISA, section 5.5.2.2) have reported weak associations in asthmatics, which constitute another population that can experience exercise-induced airflow limitation. Preliminary evidence was also shown in one animal toxicological study (Ghio et al., 2008), indicating mild pulmonary inflammation upon exposure to 50 ppm CO.

With regard to other potentially at-risk populations, there is also limited epidemiological data showing associations between CO exposures and diabetes (ISA, section 5.7.1.3). Epidemiologic studies (Pereira Filho et al., 2008; Zanobetti and Schwartz, 2001) provide suggestive evidence that CVD patients with diabetes may be at greater risk of emergency department visits and hospital admissions than those without diabetes (ISA, section 5.7.1.3). Inferences may also be drawn from results from panel studies for individuals with metabolic syndrome[15] that observed associations between short-term exposures to CO and changes in heart rate variability parameters (ISA, section 5.2.1.1) and from a toxicological study providing evidence of vascular dysfunction associated with increases in endogenous CO in an animal model of metabolic syndrome (ISA, section 5.7.1.3). People with anemia who have reduced oxygen-carrying capacity and/or higher baseline COHb levels are an additional population considered to be potentially susceptible to the hypoxic effects of CO. However, there are no controlled human studies or epidemiological studies that have specifically examined the CO-related health effects in individuals with anemia (ISA, section 2.6.1, p. 2-11).

Older adults (65+) have been considered as a potentially susceptible population to the effects of CO, primarily due to the increased prevalence of cardiovascular disease among this population when compared to all age groups or lifestages. There is limited epidemiologic evidence showing associations between short-term exposure to CO and increases in IHD or myocardial infarction (MI) hospital admissions among older adults as compared to all age groups or younger adults. The combination of this limited epidemiological data and the fact that older adults have a higher prevalence of CAD than the general population, indicates that older adults are a potentially susceptible population for increased health effects due to CO exposure (ISA, section 5.7.2.1).

The developing fetus has been a population considered to be at potential risk of CO-induced effects due to the higher affinity of their hemoglobin for CO when compared to that of adults. Limited evidence indicates an association of CO exposure during early pregnancy with pre-term births and birth defects (ISA, p. 2-8). Toxicological studies reporting effects in laboratory animals including decrements in birth weight, reduced prenatal growth, and effects on the heart provide support to the epidemiological evidence.

[15] These patients share risk factors with diabetics; see ISA section 5.7.1.3.

Gender has also been considered as a possible source for susceptibility. However, the evidence is inconclusive based on the limited epidemiological data, and the gender-specific variability in CO endogenous production (ISA, section 5.7.3). Increased altitude and physical activity through their effect on CO uptake and elimination has also been considered to potentially influence susceptibility. For example, residents of low altitudes visiting high altitudes, especially the elderly and those with CAD (Leaf and Kleinman, 1996; Kleinman et al., 1998), may be at greater risk from added effects of ambient CO than adapted residents (ISA, p. 2-12). Other less certain susceptibility factors have been considered, such as those pertaining to the taking of medications that may alter CO production (ISA, p. 2-12). Lastly, people experiencing increased CO exposures, such as those spending relatively greater amounts of time in microenvironments with relatively higher levels of ambient CO have been considered to be potentially at risk to CO-induced effects (ISA, section 5.7.6).

As we recognize the potential susceptibility of the populations identified above, we also note the lack of information on specific COHb levels that may be associated with health effects in these other groups as well as a way to relate the specific evidence available for the CAD population to these other populations.

In summary, the current evidence continues to support the identification of people with cardiovascular disease as having susceptibility to CO-induced health effects (ISA, 2-12), with those having CAD as the best characterized population with increased susceptibility to CO-induced health effects (ISA, sections 5.7.1.1 and 5.7.8). An important susceptibility consideration for this population is the inability to compensate for CO-induced hypoxia since individuals with CAD have an already compromised cardiovascular system. Included in this susceptible population are those with angina pectoris (cardiac chest pain), those who have experienced a heart attack, and those with silent ischemia or undiagnosed IHD (AHA, 2003). People with other cardiovascular diseases, particularly heart diseases, are also at risk of CO-induced health effects. We also recognize other populations potentially susceptible to CO-induced effects, most particularly those with other pre-existing diseases that may have already limited oxygen availability, increased COHb levels, or increased endogenous CO production, such as people with obstructive lung diseases, diabetes and anemia; however, information characterizing susceptibility is limited.

- **Does the current evidence alter our conclusions from the previous review regarding the levels of CO in ambient air associated with health effects?**

At the time of the last review, EPA's conclusions regarding concentrations of CO in ambient air that might be associated with risk of health effects were drawn from the combined consideration of the evidence of COHb levels for which cardiovascular effects of concern had been reported and the results of an exposure and dose modeling assessment (59 FR 38906). As described in more detail in section 2.1.1 above, the key effects judged to be associated with CO exposures resulting from concentrations observed in ambient air were cardiovascular effects, as measured by decreased time to onset of exercise-induced angina and to onset of ECG ST-segment depression (59 FR 38913).

Levels of COHb that have been associated with different types of effects in clinical studies are summarized in Table 2-2 below. At the time of the last review, decreases in time to onset of exercise-induced angina (a symptom of myocardial ischemia) had been documented in multiple studies at post-exposure COHb levels ranging from 2.9 to 5.9% (CO-Ox), which represented incremental increases of 1.5-4.4% COHb from baseline (Adams et al., 1988; Allred et al., 1989a, 1989b, 1991; Anderson et al., 1973; Kleinman et al., 1989, 1998; Sheps et al., 1987). The matched measurements available from Allred et al. (1989a, 1989b, 1991) of CO-Ox and gas chromatography, the method generally recognized to be the more accurate for COHb levels below 5% (ISA, section 5.2.4), indicate that CO-Ox measurements of 2.9 to 3.0% COHb generally correspond to GC measurements on the order of 2-2.4%.[16] Other groups for which clinical studies have reported CO-related effects at slightly higher COHb levels include effects in subjects with cardiac arrhythmias and effects on exercise duration and maximal aerobic capacity in healthy adults. Among the studies of myocardial ischemia indicators in patients with CAD, the two studies involving the lowest experimental CO exposures (which resulted in average increases in COHb of about 1.5% over pre-exposure baseline) were Anderson et al. (1973)[17] and the more recent Allred et al. (1989a, 1989b, 1991) to which we give primary attention in this review (discussed in more detail above). Neither study provided evidence of a measurable threshold at the lowest experimental CO exposures and associated COHb levels assessed (mean of 2.0-2.4% COHb, GC). Allred et al. (1989a, 1989b, 1991) further reported a dose-response relationship between the increased COHb levels and the response of the assessed indicators of myocardial ischemia (Allred et al., 1989a, 1989b, 1991). While this evidence informed our

[16] In the lower CO exposure group, the post-exposure mean COHb was 3.21% by CO-Ox and 2.38% by GC, while the post-exercise mean COHb was 2.65% by CO-Ox and 2.00% by GC (Allred et al., 1989a, 1989b, 1991).

[17] The study by Anderson et al. (1973) did not use GC to measure COHb levels, and reported reduced exercise duration due to increased chest pain at CO exposures resulting in 2.9% COHb (CO-Ox), representing a 1.6% increase in average COHb levels over baseline.

conclusions regarding COHb levels associated with health effects, the CO exposure concentrations employed in the studies to achieve these COHb levels were substantially above ambient concentrations. Thus, an exposure and dose assessment was performed to consider the COHb levels that might be attained as a result of exposures to ambient CO allowed under the current NAAQS, as described in section 2.1.1 above.

Since the time of the last review, there have been no new controlled human exposure studies specifically designed to evaluate the effects of CO exposure in susceptible populations at COHb levels below 2%. Thus, similar to the last review, the multilaboratory study by Allred et al.(1989a, 1989b, 1991) continues to be the study that has evaluated cardiovascular effects of greatest concern (i.e., reduced time to exercise-induced myocardial ischemia as indicated by ECG ST-segment changes and angina) at the lowest tested COHb levels (ISA, section 2.7). This is currently considered the most rigorous and well designed study, presenting the most sensitive analysis methods (GC used in addition to CO-Ox) to quantify COHb blood levels. Key findings from that study with regard to levels of CO associated with health effects include the following:

- Increases in COHb to mean levels of 2.0% and 3.9% from baseline (0.6%) significantly reduced exercise time required to induce markers of myocardial ischemia in CAD patients.[18]
- The associated dose-response relationship between incremental changes in COHb and change in time to myocardial ischemia in CAD patients indicates a 1.9% and 3.9% reduction in time to onset of exercise-induced angina and ST-segment change, respectively, per 1% increase in COHb concentration without evidence of a measurable threshold.

Since the last review, there have been numerous improvements to the exposure and COHb models that we employ to estimate exposure and dose for the current review. The results of modeling using these improved tools in the current review and our conclusions based on it with regard to the expectation for COHb levels of concern to occur in the at-risk population under differing air quality conditions are described in section 2.2.2 below.

[18] Relative to baseline (0.6% mean COHb), mean COHb levels of 2.0-2.4% and 3.9-4.7% were associated with decreases in time to onset of exercise-induced ST-segment changes of 5.1% ($p=0.01$) and 12.1%($p<0.001$), respectively. Similarly, the time to onset of exercise-induced angina was shortened by 4.2% ($p=0.027$) and 7.1% ($p=0.002$) for these two mean levels of COHb (Allred et al., 1989a, 1989b.1991).

Table 2-2. Carboxyhemoglobin levels and reported effects in CAD patients and healthy adults.

Study Population	Effect	%COHb (mean)		%COHb, increase over baseline	Study
		GC	CO-Ox		
Patients with coronary artery disease*	Reduction in time to exercise-induced onset of myocardial ischemia - 5.1% decrease in time to ST- segment change, 4.2% decrease in time to angina - 12.1% decrease in time to ST- segment change, 7.1% decrease in time to angina	2.0-2.4 3.9-4.7	2.7-3.2 4.7-5.6	1.4-1.7 3.3-4.0	Allred et al., 1989a, 1989b, 1991
	Reduction in exercise duration prior to angina and/or ST segment changes	NA**	2.8-5.2	1.5-4.2	Adams et al., 1988; Anderson et al., 1973; Kleinman et al., 1989; Kleinman et al., 1998; Sheps et al., 1987
	Exercise-induced arrhythmia	NA	6		Sheps et. al., 1990, 1991
Healthy adults	Reduction in exercise duration and maximal aerobic capacity	NA	3-20		Drinkwater et al., 1974; Ekblom and Huot, 1972; Horvath, 1975; Raven et al., 1974a, 1974b
	Equivocal behavioral effects (hand eye coordination, vigilance, continuous performance of critical tasks)	NA	5		Benignus et. al., 1987, 1990a, 1990b; Putz et. al., 1976, 1979

* All studies involved subjects with reproducible exercise-induced angina.
** NA = not available.

Since the time of the last review, a number of additional epidemiological studies have been conducted of health outcome associations with different ambient CO metrics (e.g., ISA, section 5.2). The majority of these epidemiological studies, conducted in selected urban areas of the U.S. or Canada, were designed to evaluate the effects of multiple pollutants (i.e. $PM_{2.5}$, NO_2, SO_2, O_3 and CO). As discussed above, a number of these studies have reported associations between concentrations of CO measured at fixed-site ambient monitors and cardiovascular endpoints other than stroke, particularly hospitalizations and emergency department visits for specific cardiovascular health outcomes including ischemic heart disease (IHD), congestive heart failure (CHF) and cardiovascular diseases (CVD) as a whole (Bell et al., 2009; Koken et al., 2003; Linn et al., 2000; Mann et al., 2002; Metzger et al., 2004; Peel et al., 2007; Symons et al.,

2006; Tolbert et al., 2007; Wellenius et al., 2005). In general, these studies report positive associations and a number of these associations are statistically significant (ISA, sections 5.2.3 and 5.2.1.9; Table 2-1 above).

In considering these epidemiological studies in the case of CO, we recognize that there is coherence between the available clinical and epidemiological evidence with regard to the health effects of CO in the cardiovascular system (primarily for ischemic related events). As noted above, however, we also recognize several gaps between the two lines of evidence which complicate their integration, particularly with regard to ambient exposures and ambient concentrations associated with health effects of concern. As discussed in the ISA, the epidemiological studies reported associations with emergency department visits and/or hospital admissions for IHD and other cardiovascular disease-related outcomes that are plausibly related to the effects on physiological indicators of myocardial ischemia (e.g., ST-segment changes) demonstrated in the controlled human exposure studies, providing coherence between the two sets of findings. However, there is appreciable uncertainty with regard to the specific relationship between these two types of measures of cardiovascular morbidity. Furthermore, the clinical studies document relationships between controlled elevated exposures to CO and specific levels of an internal dose metric, COHb, which elicited specific responses in CAD patients. This informs our interpretation of the associations we observe in the epidemiological studies, although COHb has not been monitored in the epidemiological studies and the personal CO exposure concentrations eliciting the outcomes observed, including the contributions from ambient and nonambient CO, are unknown (as illustrated in Figure 2-2 above).[19] Further, to achieve their experimental target levels of COHb, the clinical studies used short (approximately 1-hour) exposures to concentrations of CO that were substantially higher than current commonly occurring ambient concentrations (ISA, section 2.7). The relationship of the clinical exposure concentrations to exposure concentrations occurring in the populations studied in the epidemiological studies is unknown, but the clinical exposures may be higher. For example, individual exposure concentrations for the lower clinical exposure ranged from 42 to 202 ppm (Allred et al., 1989b). Experimental studies have not been conducted at COHb levels that might be elicited in response to exposures to lower CO concentrations such as those within the ranges of current maximum ambient concentrations (ISA, section 2.7) or closer to personal exposure concentrations more commonly expected currently (e.g., ISA, Figure 3-45). Gaps in our understanding of the role of nonambient CO exposures and their contribution to COHb levels

[19] As recognized in the ISA in consideration of the epidemiological studies, the known role of CO in limiting O_2 availability lends biological plausibility to ischemia-related health outcomes following CO exposures, although "it is not clear whether the small changes in COHb associated with ambient CO exposures results in substantially reduced O_2 delivery to tissues" (ISA, p. 5-48).

also complicates our ability to disentangle ambient concentrations that may be related to health effects.

In considering these epidemiological studies in the case of CO, we recognize several uncertainties that complicate the quantitative interpretation with regard to ambient concentrations that might be eliciting the reported health outcomes. These uncertainties relate to conclusions regarding CO as the pollutant eliciting the effect reported in these studies and to our understanding of the ambient CO concentrations (and total concentrations) to which study subjects demonstrating effects are exposed.

- With regard to the first, a major uncertainty relates to the difficulty in determining the extent to which ambient CO is independently associated with cardiovascular effects or if CO at ambient levels is acting as a surrogate for the effects of another traffic-related pollutant or mixture of pollutants (ISA, section 5.2.3). As noted in the ISA, in interpreting the epidemiological evidence for cardiovascular morbidity "[i]t is difficult to determine from this group of studies the extent to which CO is independently associated with CVD outcomes or if CO is a marker for the effects of another traffic-related pollutant or mix of pollutants. On-road vehicle exhaust emissions are a nearly ubiquitous source of combustion pollutant mixtures that include CO and can be an important contributor to CO in near-road locations" (ISA, p. 5-40 – 5-41). We also note CASAC's recognition of the potential for co-pollutants to pose confounding 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 fossil- fuel-combustion-related pollutants (Brain and Samet, 2010).
- To identify the CO-specific effect, and assess and control for potential confounding of CO-associated health effects by other pollutants for which measurements are available, two-pollutant regression models are a commonly used statistical method (ISA, section 1.6.3). Although CO associations may, in some studies, be slightly attenuated in models adjusting for one other combustion-related pollutant, they generally remain robust (Figures 5-6 and 5-7). However, there are several statistical issues influencing results generated using multi-pollutant models, such as models that force all pollutants to follow the same lag structure, the inclusion of correlated but noncausal variables, and the potential omission of etiologically relevant co-pollutants. Although data for co-pollutant modeling are available for some of the other criteria pollutants, data are not available for additional combustion-related pollutants, which may or may not include all pollutants that elicit the health effects (ISA, section 2.5.1). In light of the uncertainty (referenced in discussion of the question below) regarding the biological plausibility of CO-related effects at low ambient concentrations, it is possible that the CO risk estimates ascribed to measured ambient CO levels in epidemiological studies is instead another pollutant that is highly correlated with CO, but was not measured.
- With regard to the second, the presence of exposure error and/or measurement error from reliance on fixed-site ambient CO monitors, a large portion of which are measuring CO concentrations at or below detection limits can result in the over or underestimation of the effects of the poorly measured pollutant. This limitation can add uncertainty to the association between ambient concentrations of CO and health

effects estimates (ISA, p. 3-91) and constrain their interpretation with regard to CO exposure levels (Brain and Samet, 2010).

We have considered here the epidemiological studies in the U.S. for ischemia-related outcomes. In Table 2-2, we focused on the U.S. studies of CHD hospital admissions for CHD (i.e., IHD and MI), that provided the strongest and most consistent weight of evidence (ISA, Figure 5-2, pp. 5-24 to 5-26). In Table 2-3, we present the U.S. studies for the broader category of all CVD hospital admissions that also contributed to the ISA's causality determination (ISA, Figure 5-5, pp. 5-33 to 5-36). In focusing on these studies, we did not include studies of associations with CHF, a chronic condition for which there are multiple causes and for which the evidence is less clear.[20] We have focused here on studies for IHD, MI and all CVD outcomes (which are inclusive of IHD), which we consider to be key due to the more direct conceptual linkages that can be drawn between the these outcomes and the myocardial ischemia effects of the CAD clinical studies.

Of particular interest in addressing the question posed here is information pertaining to CO concentrations in ambient air that meet the current standard. While, the full set of these epidemiological studies, including those reporting associations with ambient CO concentrations under conditions when the current standards were not met, provide support to the previous evidence regarding cardiovascular effects of CO, it is the studies involving air quality conditions in which the current standards were met that are most informative within the context of considering the adequacy of the current standards.[21] Accordingly, in considering these epidemiological studies, we have considered the air quality conditions during the periods of study.

The areas of focus across these studies of IHD and CVD outcomes (inclusive of IHD) include Atlanta, urban areas of California and a group of 126 urban counties[22] and the multi-year time periods for these studies together span the period from 1988 through 2005 (Tables 2-3 and 2-4 below). During the time periods of study, only the three Atlanta studies (Metzger et al., 2004; Peel et al., 2007; Tolbert et al., 2007) did not include years in which ambient CO concentrations exceeded the 8-hour standard (Tables 2-3 and 2-4). Based on data reported to AQS for the general areas studied, ambient CO concentrations during a portion of the time periods studied in the other three of these analyses exceeded the level of the current 8-hour NAAQS (Bell et al., 2007; Linn et al., 2000; Mann et al., 2002). Among these three studies, all

[20] We note that two of the studies listed in Tables 2-3 and 2-4 also reported positive associations with CHF (ISA, pp. 5-31 to 5-33). Additionally, there are three other studies of CHF associations shown in Table 2-1 above, two of which were statistically significant, with one of those with significant results focused on an area in which the current 8-hour standard was just met (Koken et al., 2003; Symons et al., 2006; Wellenius et al., 2005).

[21] As at the time of the last review, the 8-hour standard continues to be the controlling standard.

[22] The 126 counties span some 40 states, including the District of Columbia.

of which reported statistically significant risk estimates, the highest 8-hour design values ranged from 11.6-23.4 ppm, as compared to the 8-hour standard of 9 ppm.[23] In the Atlanta area, which was the focus for the other three studies (Peel et al., 2007; Metzger et al., 2004; Tolbert et al., 2007), the second highest non-overlapping 8-hour average CO concentration in a year (i.e., the design value for the 8-hour standard) ranged from 3.2 up to 5.3 ppm over the combined 12 years of study. One of these three studies (Tolbert et al., 2007) reported a statistically significant risk estimate for cardiovascular hospital visits associated with CO concentrations, while the other two did not. In the Atlanta area during the period studied, the 99th percentile daily maximum 8-hour CO concentration in a year ranged up to 4.9 ppm, while the yearly 99th percentile daily maximum 1-hour CO concentration ranged up 7.9 ppm. The studies in which CO concentrations exceeded the current NAAQS during some portion of the study period accordingly are less informative to our overarching question regarding the adequacy of the protection afforded by the current standard. We note that studies reporting associations with IHD or total CVD outcomes for which air quality data reported to AQS do not indicate that the current 8-hour standard was exceeded during the study period are limited to those for Atlanta.

[23] Staff also note that the national-scale study of 126 urban counties by Bell et al. (2009) included a subset analysis that evaluated associations for all cardiovascular outcomes, adjusted for NO_2, after restricting the dataset to days with a 1-hour daily maximum CO concentration less than 35 ppm, which is the level of the 1-h standard although its form is the 2nd maximum in a year. This subset analysis found a statistically significant effect estimate identical to the estimated risk with the full data set. Further subset analyses by Bell et al. in this study using data below cutoff values of 1-10 ppm all found positive, statistically significant associations (with adjustment for NO_2), although confidence intervals increased at the lower cutoff values and the proportion of values near and below the limit of detection grew larger.

Table 2-3. Air quality information for key U.S. epidemiological studies of hospital admissions for coronary heart disease (ISA, Figure 5-2).

Study	Area	Study Period	Health Outcome	1-hour Daily Maximum (ppm)		8-hour Daily Maximum (ppm)		24-hour Average (ppm)		Design Values (ppm) for Study Areas During Study Period	
				Mean	99th percentile	Mean	99th percentile	Mean	99th percentile	1-hour	8-hour
Metzger et al., 2004	Atlanta	1993-2000	IHD	1.5*[1]	5.5-5.9						3.2-5.3
Peel et al., 2007	Atlanta	1993-2000	IHD	1.8*	5.5-5.9						3.2-5.3
	Atlanta Air Quality Data (from 3 monitors in 20 counties)	1993			6.1				2.4	6.5	4.9
		1994			6.3-6.6				2.7-3.3	7.1	5.3
		1995			5.8-7.9				2.4-3.2	16.3	5.2
		1996			5.3-6.1				2.0-2.7	6.6	3.8
		1997			5-5.4	4.4	3.1-4.2		2.3-2.4	5.8	4.3
		1998			4.8-4.9	4.3-4.9			2.1-2.4	5	4.1
		1999			4.9-5.4	4.3-4.9			2.0-2.3	6.3	4.1
		2000			4.9-5.4	3.5-3.6			1.5-1.8	4.6	3.2
Mann et al., 2002	CA	1988-1995	IHD		2 - 22	2.07*	1.3-15.9			16.5-32	11.6-23.4
	California Air Quality Data (from 31 monitors in 4 counties)	1988			4.0-31.0	2.8-3.9			1.2-10.9	32	23.4
		1989			2.0-22.0	3-3.8			1.7-6.9	28	18.3
		1990			4.0-22.0	3.0-3.8			1.3-7.8	23	15.9
		1991			2.0-21				2.0-8.7	29	15.7
		1992			2.0-21.0	1.4-14.6			1.0-9.6	25	16.4
		1993			2.0-19.0	2.0-10.1			1.1-8.0	20	13.8
		1994			2.1-14.5	1.6-11.7			1.1-8.9	20.8	16
		1995			1.5-11.6	2-10.7			1.0-7.6	16.5	11.6
Linn et al., 2000	CA	1992-1995	MI			1.0-8.1		1.5*	1.1-8.3	16.5-25	11.6-16.4

Table legend. This table presents information from key studies finding associations with coronary heart disease (ISA, section 5.2.3, Figure 5-2). The health outcomes evaluated include hospital admissions for ischemic heart disease (IHD) and myocardial infarction (MI). The 99th percentile (in ppm) of the CO concentration for the specific study metrics (i.e.,1-, 8-hour daily maximum, or 24-hour average) were derived from AQS data for monitors in the study areas during the study period. Design values are values of CO concentration in the statistical form of the standard; presented here is the range of 2nd highest 1-hour and 8-hour average concentrations per year at the highest monitor in each study area (obtained from the AQS database for the areas and time periods of the studies).

* Risk estimates and CO concentrations for the study metric as reported by the study authors.

[1]This value for Metzger et al. (2004) is the median.

Table 2-4. Air quality information for key U.S. epidemiological studies of hospital admissions for CVD (ISA, Figure 5-5).

Study	Area	Study Period	Health Outcome	1-hour Daily Maximum (ppm)		8-hour Daily Maximum (ppm)		24-hour Average (ppm)		Design Values (ppm) for Study Areas During Study Period	
				mean	99th percentile	mean	99th percentile	mean	99th percentile	1-hour	8-hour
Bell et al., 2009	126 urban counties	1999-2005	CVD 65+	1.3*	1.2-22.1						8.8-24.3
Tolbert et al., 2007	Atlanta	1993-2004	CVD	1.6*	5.3-5.4					3.5-16.3	2.5-5.3
	Atlanta Air Quality Data (3 monitors in 20 counties)	For 1993-2000, see Table 2-2 above									
		2001			3.8-4.1		2.4-3.0		1.8-1.9	5.3	4.1
		2002			4.2-4.3		2.2-2.5		1.5-1.6	4.6	3.6
		2003					2-2.1		1.2-1.7	3.5	2.5
		2004					2			4.6	2.5
Linn et al., 2000	CA	1992-1995	CVD	2.6-3.3				1.5*	1.1-8.3	16.5-25	11.6-16.4

Table legend. This table presents information from key studies finding associations with CVD (ISA , section 5.2.3, Figure 5-5). The health outcomes evaluated in these studies include hospital admissions for cardiovascular disease (CVD; Bell et al (2009) only included subjects 65 years old and above), with the associated risk estimates, unadjusted for other pollutants. The 99th percentile (in ppm) of the CO concentration for the specific study metrics (i.e.,1-, 8-hour daily maximum, or 24-hour average) were derived from AQS data for monitors in the study areas during the study period. Design values are values of CO concentration in the statistical form of the standard; presented here is the range of 2nd highest 1-hour and 8-hour average concentrations per year at the highest monitor in each study area (obtained from the AQS database for the areas and time periods of the studies).

* CO concentrations for the study metric as reported by the study authors.

In summary, although there is no new evidence regarding lower COHb levels associated with effects, the evidence is much expanded with regard to epidemiological[24] analyses of ambient monitor concentrations, which observed associations between specific and overall cardiovascular-related outcomes and ambient CO measurements. With regard to extending our understanding of effects occurring below levels of CO observed in the clinical studies, however, the epidemiological evidence for CO is somewhat limited. The epidemiological evidence lacks measurements of COHb or personal exposure concentrations that would facilitate integration with the clinical data. Furthermore, as discussed above, the full epidemiological evidence base for IHD outcomes or CVD outcomes as a whole includes a number of studies involving conditions in which the current standard was not met. Though these studies are informative to consideration of the relationship of health effects to the full range of ambient CO concentrations, they are less useful to informing our conclusions regarding adequacy of the current standards. Consideration of the smaller set of studies under conditions where the current standards were met is considered to better inform our consideration of the adequacy of the standards or conditions of lower ambient concentrations. Among the few studies for IHD or CVD outcomes under conditions where the current standards were met, one study reported statistical significance for IHD or CVD outcomes, and all of these studies are limited to a single study area (i.e. Atlanta). These limitations lessen the weight we give these studies for our purposes here in making interpretations with regard to ambient concentrations of CO that may be eliciting health outcomes, particularly in light of the availability of strong evidence from controlled human exposure studies. Therefore, with regard to this question of CO concentrations we have primarily focused our consideration of the epidemiological studies on the extent to which this evidence is consistent with and generally supportive of conclusions drawn from the combined consideration of the controlled human exposure evidence with estimates from the exposure and dose assessment (section 2.2.2 below). As in the previous review, we believe the integration of the controlled human exposure evidence with the exposure and dose estimates will be most important to informing conclusions regarding ambient CO concentrations of public health concern.

- **To what extent have important uncertainties identified in the last review been reduced and/or have new uncertainties emerged?**

Since the time of the last review, some important uncertainties have been reduced, some still remain and others associated with newly available evidence have been identified. A range

[24] Few epidemiological studies that had investigated the relationship between CO exposure and ischemic heart disease were available at the time of the last review (USEPA, 1991, section 10.3.3).

of important uncertainties were identified in a number of areas at the time of the last review (59 FR 38913, USEPA, 1992), including:

- The adverse nature and significance of the small changes in ST-segment depression identified at the lowest COHb levels investigated in the controlled human exposure studies, and the magnitude of risk associated with such changes for specific health outcomes, such as myocardial infarction, or of slight but cumulative myocardial damage, among other possibilities.
- The extent to which COHb measurements made using CO-Ox do not reflect COHb levels in angina patients studied and the potential for as yet unidentified health effects at COHb levels below 2%.
- The potential for short-term peak CO exposures to contribute to CNS effects which might affect individual's performance of complex activities such as driving a car or to contribute to other effects of concern.
- Effects of ambient CO on potentially susceptible populations other than those with cardiovascular disease, including the developing fetus.
- Modeling of COHb formation associated with exposures to ambient CO under different air quality conditions, including those associated with attainment of different NAAQS.

As discussed below, some of these uncertainties have been reduced, while some still remain.

The CO-induced effects considered of concern at the time of the last review were reduced time to exercise-induced angina and ST-segment depression in patients suffering from coronary artery disease as a result of increases in COHb associated with short CO exposures. These effects had been well documented in multiple studies, and it was recognized that the majority of cardiologists at the time believed that recurrent exercise-induced angina was associated with substantial risk of precipitating myocardial infarction, fatal arrhythmia, or slight but cumulative myocardial damage (USEPA, 1992, p. 22; 59 FR 38911; Basan, 1990; 1991 AQCD). As at the time of the last review, although ST-segment depression is a recognized indicator of myocardial ischemia, the exact physiological significance of the observed changes among individuals with CAD is unclear (ISA, p. 48).

In interpreting the study results at the time of the last review, EPA recognized uncertainty in the COHb measurements made using CO-Ox and associated uncertainty in establishing a lowest effects level for CO (USEPA, 1992, p. 31). A multicenter then-recent study (Allred et al., 1989a, 1989b, 1991) was of great importance at that time for several reasons including the large number of subjects used, the rigorous protocol used for subject selection, the use of the most accurate method to measure blood COHb levels and the finding of a dose-response relationship between COHb levels and the ischemic events evaluated in the study. This study reported changes in post-exercise ST-segment depression and reduced time to onset of exercise-induced angina as a result of increases in COHb from a mean baseline of 0.6% to mean levels of 2% and

3.9% (ISA, section 5.2.4; (Allred et al., 1989a,1989b, 1991). In the current review of the evidence related to cardiovascular effects associated with CO exposure, the we place primary emphasis on the findings of Allred et al. (1989a, 1989b, 1991) recognizing the superior quality of the study, both in terms of the rigorous study design as well as the sensitivity of the analytical methods used in determining COHb concentrations (ISA, Section 2.7). No additional clinical studies are available that evaluate responses to lower COHb levels in the cardiovascular-disease population, and uncertainties still remain in determining specific and quantitative relationships between the CO-induced effects in these studies and the increased risk of specific health outcomes. Further, with regard to then unidentified effects at lower COHb levels, no studies have identified other effects on the CAD population or on other populations at lower exposures (ISA, sections 5.2.2).

The last review recognized a variety of neurobehavioral effects associated with CO exposure, including changes in visual perception, hearing, motor performance and vigilance among other measures of neurobehavioral performance based on a series of studies conducted from the mid 1960's through the early 1990's (1991 AQCD). Since these effects were observed at exposures to CO resulting in COHb levels ranging from 5-20%, and were poorly understood at the time (1991 AQCD), the review focused on cardiovascular effects, which had been observed at COHb levels below 5% and consequently for which a focus would also provide adequate protection against potential adverse neurobehavioral effects. No new human clinical studies have evaluated CNS or behavioral effects of exposure to CO (ISA, section 5.3.1). However, given the drastic reduction in CO ambient concentrations, the occurrence of these effects in response to ambient CO would be expected to be rare within the current population. Thus, our uncertainty with regard to the potential for such effects to be associated with current ambient CO exposures is reduced.

At the time of the last review, the developing fetus was recognized as having the potential to be particularly vulnerable to the effects of CO exposures because human fetal development often occurs at or near critical tissue oxygenation levels (Longo, 1977; 59 FR 38911; USEPA, 1992, p. 25). The human data at the time of the last review consisted of a limited set of studies primarily considering the effects of maternal cigarette smoke in the developing fetus, many of them conducted at very high exposure levels (500-1000 ppm). The effects observed included spontaneous abortion and death due to decreased birth weight. Additional animal toxicological studies, also conducted at CO concentrations higher than the ambient CO levels at the time, provided suggestive evidence of fetal mortality, teratogenicity, reduced body weight, morphological changes, altered cardiovascular development and neurochemical changes. Since the last review, the epidemiologic and toxicological evidence of effects on birth and developmental outcomes has somewhat expanded, although the available evidence is still

considered limited with regard to effects on preterm birth, birth defects, decreases in birth weight, measures of fetal growth, and infant mortality. Although there are animal toxicological studies providing support and coherence for those effects, the understanding of the mechanisms underlying reproductive and developmental effects is still lacking (ISA, section 5.4.1). Thus, although the evidence continues to "suggest[s] that critical developmental phases may be characterized by enhanced sensitivity to CO exposure" (ISA, p. 2-11), evidence is still lacking on the potential for adverse effects on birth and developmental outcomes at CO exposures near those associated with current levels of ambient CO. As a result uncertainty still remains in this area.

Numerous improvements have been made over the last decade that have reduced the uncertainties associated with the models used to estimate COHb levels resulting from ambient CO exposures under different air quality conditions, including those associated with just meeting the current CO NAAQS (draft REA, section 4.3). This progression in exposure model development has led to the Agency's currently used model (APEX4.3) that has an enhanced capacity to estimate population CO exposures and more accurately predicts COHb levels in persons exposed to CO. Our application of APEX4.3 to the current situation, using updated data and new algorithms to estimate exposures and doses experienced by individuals, better represents the variability in population exposure and COHb dose levels. However, while APEX 4.3 is greatly improved when compared with previously used exposure models, its application is still limited with regard to data to inform our understanding of spatial relationships in ambient CO concentrations and within microenvironments of particular interest. Further information regarding model improvements and remaining exposure modeling uncertainties are described in section 2.2.2 below.

In the current review, we continue to recognize coronary artery disease as the most important susceptibility characteristic for increased risk due to CO exposure (ISA, p. 2-10). While a much expanded epidemiologic database inclusive of studies showing associations between ambient CO monitor concentrations and increases in emergency room visits and hospitalizations for ischemic heart disease events support this conclusion, a variety of associated uncertainties complicate the interpretation of these studies. Although CO associations generally remain robust in copollutant models (ISA, Figures 5-6 and 5-7, section 2.7), disentangling a CO-specific effect at low ambient concentrations from other pollutants remains of concern, particularly for the quantitative interpretation of these studies. The potential for CO to act as a surrogate for another combustion related pollutant included in a copollutant statistical model "complicates quantitative interpretation of the effect estimates reported in epidemiologic studies"

(Tolbert 2007; ISA, p. 2-16).[25] Moreover, as recognized by CASAC, "the problem of co-pollutants serving as potential confounders is particularly problematic for CO" and "a better understanding of the possible role of co-pollutants is relevant to regulation … on the health effects of CO" (Brain and Samet, 2010). Error in the assessment of personal CO exposure through the use of fixed site-monitors measuring CO levels at or below the limit of detection of the monitor is a new source of uncertainty since the prior review due to an overall decrease in ambient CO concentrations. This error may lead to an over or underestimation of CO health risk estimates. Thus, some uncertainties associated with the epidemiological evidence "complicate the quantitative interpretation of the epidemiologic findings, particularly regarding the biological plausibility of health effects occurring at COHb levels resulting from exposures to the ambient CO concentrations" assessed in these studies (ISA, p. 2-17).

In summary, some important uncertainties from the last review have been reduced, including those associated with concerns for ambient levels of CO to pose neurobehavioral risks. A variety of uncertainties still remain including the adverse nature and significance of the small changes in ST-segment depression identified at the lowest COHb levels investigated, and the magnitude of associated risk of specific health outcomes, as well as the potential for as yet unidentified health effects at COHb levels below 2%. Additionally, although the evidence base is somewhat expanded with regard to the potential for CO effects on the developing fetus, uncertainties remain with regard to this potential susceptibility. Our exposure and dose models have improved giving us increased confidence in their estimates. We additionally recognize that the expanded body of epidemiological evidence includes its own set of uncertainties which complicates its interpretation.

2.2.2 Exposure/Risk-based Considerations

Our consideration of the scientific evidence in the current review, as at the time of the last review (summarized in section 2.1.1 above), is informed by results from a quantitative analysis of estimated population exposure and resultant COHb levels. As in our consideration of the evidence in section 2.2.1 above, we have organized the discussion that follows here around a set of key questions to assist us in drawing from the draft assessment of CO exposure and resultant COHb levels for at-risk populations living in two cities under current air quality

[25] In interpreting the epidemiological evidence for cardiovascular morbidity the ISA notes that it "is difficult to determine from this group of studies the extent to which CO is independently associated with CVD outcomes or if CO is a marker for the effects of another traffic-related pollutant or mix of pollutants. On-road vehicle exhaust emissions are a nearly ubiquitous source of combustion pollutant mixtures that include CO and can be an important contributor to CO in near-road locations. Although this complicates the efforts to disentangle specific CO-related health effects, the evidence indicates that CO associations generally remain robust in copollutant models and supports a direct effect of short-term ambient CO exposure on CVD morbidity." (ISA, pp. 5-40 to 5-41).

conditions and conditions simulated to just meet the current CO standards. These questions are intended to inform consideration of the following overarching question.

Prior to addressing the series of questions below, we provide a description of the modeling tools used in and the design of the assessment, the magnitude of COHb levels. We then consider the question regarding the size of the simulated at-risk population estimated to experience COHb levels of interest, followed by the identification of key uncertainties associated with our assessment of exposure and dose with regard to drawing conclusions as to the adequacy of the protection afforded by the current CO standards. We then consider the exposure and dose estimates from the quantitative assessment with regard to implications as to the extent of the population provided protection from COHb levels of concern under the current standards to help inform judgments about the extent to which such estimates may be judged to be important from a public health perspective.

In the draft assessment conducted for this review, described in detail in the draft REA and summarized here, we have estimated CO exposure and associated COHb levels in simulated populations in two urban study areas in Denver and Los Angeles, in which current CO concentrations are below the current standards. We selected these areas because: (1) both cities have been included in prior CO NAAQS exposure assessments and thus serve as an important connection with past assessments; (2) historically, they have generally had the highest CO ambient concentrations among urban areas in the U.S.; and (3) Denver is at high altitude and represents an important risk scenario due to the potential increased susceptibility to CO exposure associated with high altitudes. In addition, of 10 urban areas across the U.S. selected for detailed analysis in the ISA and having monitors meeting a 75% completeness criteria, the two locations were ranked first (Los Angeles) and second (Denver) regarding the percentage of elderly population within 5, 10, and 15 km of monitor locations, and ranked first (Los Angeles) and fifth (Denver) regarding number of 1- and 8-hour daily maximum CO concentration measurements (ISA, section 3.5.1.1).

Estimates were developed for exposures associated with current "as is" conditions (2006 air quality) and also for higher ambient CO concentrations associated with air quality conditions simulated to just meet the current 8-hour standard.[26] In considering the adequacy of the current standard, it is important to note that over the last few years, the standard has been met throughout the country with few exceptions.[27] Although we consider it unlikely that air concentrations in many urban areas across the U.S. that are currently well below the current standard would

[26] As discussed elsewhere, the 8-hour standard is the controlling standard for CO.

[27] As described in section 1.3.3 above, in the most recent period analyzed (2007-2008), all areas of the U.S. met both CO NAAQS. In both of the previous periods (2005-2006 and 2006-2007), one area did not meet the 8-hour standard. Further, one area of the country is designated in non-attainment with the CO NAAQS although air quality in that area has met the standards in the past three periods.

increase to just meet the standard, we also recognize the potential for CO concentrations in some areas currently below the standard to increase to just meet the standard. Accordingly, we have simulated conditions of increased CO concentrations that just meet the current standard in the two study areas. In this scenario, we note there is uncertainty associated with simulating this hypothetical profile of higher CO concentrations that just meet the current standard.

The exposure and dose modeling, presented in detail in the draft REA, relied on EPA's Air Pollutant Exposure model (APEX4.3), which estimates human exposure using a stochastic, event-based microenvironmental approach. This model has a history of application, evaluation, and progressive model development in estimating human exposure and dose for several NAAQS reviews, including CO, O_3, NO_2, and SO_2. As mentioned above, we have made major changes to the exposure modeling approach used in the last CO review. The prior review relied on estimated population exposure and dose generated from pNEM, a model that 1) employed a cohort-based approach,[28] 2) relied on a limited set of activity pattern data (approximately 3,600 person-days) 3) used four broadly defined categories to estimate breathing rates (i.e., slow-sleeping, slow-awake, medium, and fast), and implemented a geodesic distance range methodology to approximate workplace commutes (Johnson et al., 1992; USEPA, 1992). Each of these approaches used by pNEM, while appropriate given the data available at the time would tend to limit the ability to accurately model the lower and upper tails of the population exposure distribution. In contrast, APEX4.3 includes new algorithms to 1) simulate activity sequences and exposure profiles for individuals, 2) estimate activity-specific minute-by-minute oxygen consumption and breathing rates, 3) address spatial variability in home and work-tract ambient concentrations for commuters, and 4) estimate event-based microenvironmental concentrations. APEX also uses additional data available from recent activity pattern surveys (CHAD now has about 34,000 person-days of data) and uses the most recent US census data to represent population demographics and home-to-workplace commutes. Modeling the prevalence of exposures or dose in a population of interest (such as individuals with coronary heart disease) has also been enhanced in APEX with the addition of output tables presenting statistics for identified subpopulations and age groups (or life stages), using the updated census population demographic data, and including options for approaches used to estimate microenvironmental concentration.

[28] When using the cohort approach, each cohort is assumed to contain persons with identical exposures during the specified exposure period. Thus, variability in exposure will be attributed to differences in how the cohorts are defined, not necessarily reflecting differences in how individuals might be exposed in a population. A total of 420 cohorts were used to estimate population exposure based on selected demographic information (11 groups using age, gender, work status), residential location, work location, and presence of indoor gas stoves (Johnson, et al., 1992; USEPA, 1992).

APEX probabilistically generates a sample of hypothetical individuals from an actual population database and simulates each individual's movements through time and space (e.g., indoors at home, inside vehicles) to estimate his or her exposure to a pollutant. Population characteristics are taken into account to represent the demographics of each study area. With regard to age and gender demographics for the simulated at-risk population (adults with diagnosed and undiagnosed CAD), we augmented estimates of the prevalence of CAD provided by the National Health Interview Survey with estimates of undiagnosed ischemia that were based on two assumptions: (1) there are 3.5 million persons in U.S. with undiagnosed IHD (drawn from an estimate by the American Heart Association) and (2) persons with undiagnosed IHD are distributed within the population in the same manner as persons with diagnosed IHD (draft REA, section 5.5.2). Based on exposure concentrations, minute-by-minute activity levels, and physiological characteristics of the simulated person (see draft REA, chapters 4 and 5), APEX estimates the level of COHb in the blood at the end of each hour based on solution to the nonlinear Coburn-Forster-Kane equation (draft REA, section 4.4.7).

APEX simulations performed for this review have focused on exposures to ambient CO occurring in eight microenvironments, with no additional contribution from indoor CO sources. We note that, where present, indoor sources, including gas stoves and tobacco smoke can also be important contributors to total CO exposure and may be of concern for at-risk populations. Some assessments performed previously have included modeling simulations both with and without certain indoor sources and these assessments provide context for the assessment of ambient CO exposure and dose. For example, a 2000 exposure/dose assessment indicated that the impact of such sources can be substantial on the portion of the population experiencing higher exposures and COHb levels (Johnson et al., 2000). In the last review it was noted that while these indoor sources were shown to contribute to total CO exposure they would not be effectively mitigated by setting more stringent ambient air quality standards (59 FR 38914). In the current review, model simulations have not included indoor sources.

As discussed in the previous section (Section 2.2.1), people with cardiovascular disease are the population of primary focus in this review. Further, based on the available evidence in the current review, coronary artery disease, also known as coronary heart disease is the "most important susceptibility characteristic for increased risk due to CO exposure" (ISA, p. 2-11). Controlled human exposure studies have provided specific quantitative COHb dose-response information for this specific population with regard to effects on markers of myocardial ischemia. In identifying COHb levels associated with specific effects for CAD patients, we have given primary focus to the multi-laboratory study in which COHb was analyzed by the more accurate GC method (Allred et al., 1989a, 1989b, 1991). Specifically, this study has documented reductions in times to exercise-induced change in the ST-segment of an electrocardiogram and to

exercise-induced onset of angina, observed in response to CO exposures involving subjects with pre-existing CAD, as described in section 2.2.1 above.

Studies have not been designed to evaluate similar effects at CO exposure eliciting COHb levels below this range. In addition, these studies do not address the fraction of the population experiencing a specified health effect at various dose levels. These aspects of the evidence contributed to EPA's conclusion that there are currently insufficient controlled human exposure data to support the development of quantitative dose-response relationships which would be required in order to conduct a quantitative risk assessment for this health endpoint, rather than a benchmark level approach. Further, based on the current evidence with regard to quantitative information of COHb levels and association with specific health effects, the primary target population for purposes of the quantitative assessment is adults with CHD (also known as ischemic heart disease IHD or CAD), both diagnosed and undiagnosed.[29] Evidence characterizing the nature of specific health effects of CO in other populations is limited and does not include specific COHb levels related to health effects in those groups. As a result, the quantitative assessment does not develop separate quantitative dose estimates for populations other than those with CAD.

We have reviewed COHb estimates developed in the draft REA for the simulated at-risk population with attention to both COHb in absolute terms and based on consideration of the contribution associated with ambient CO exposures. For purposes of the review of COHb in absolute terms, we identified benchmark levels of 1.5%, 2.0%, 2.5% and 3% COHb. Selection of this range of benchmark levels is based on consideration of the evidence from controlled human clinical studies of CAD patients (discussed in section 2.2.1 above). This range includes the range of COHb levels identified as levels of concern in the review completed in 1994 (2.0 to 2.9%) and the level given particular focus (2.1%), as described in section 2.1.1 above (USEPA, 1992; 59 FR 48914). The range of benchmark levels identified here extends below the lowest mean COHb level (e.g., 2.0% post-exercise in Allred et al., 1989b) resulting from controlled increased exposure to CO in the clinical evidence. The extension of this range reflects a number of considerations, including: (1) comments from the CASAC CO panel on the draft Analysis Plan (Brain, 2009); (2) consideration of the uncertainties regarding the actual COHb levels experienced in the controlled human exposure studies; (3) that these studies did not include individuals with most severe cardiovascular disease[30]; (4) the lack of studies that have evaluated

[29] As described in section1.2 above, this is the same population group that was the focus of the CO NAAQS exposure/dose assessments conducted previously (e.g., US EPA, 1992; Johnson et al., 2000).

[30] Although the CAD patients evaluated in the controlled human exposure study by Allred et al. (1989a, 1989b, 1991) are not necessarily representative of the most sensitive population, the level of disease in these individuals ranged from moderate to severe, with the majority either having a history of myocardial infarction or having ≥ 70% occlusion of one or more of the coronary arteries (ISA, p. 5-43).

effects of experimentally controlled short-term CO exposures resulting in mean COHb levels below 2.0-2.4%; and (5) the lack of evidence of a threshold at the increased COHb levels evaluated. We note that CASAC comments on the first draft REA recommended the addition of a benchmark at 1% COHb and we have presented results for this COHb level in the second draft REA. Given that this level overlaps with the upper part of the range of endogenous levels in healthy individuals as characterized in the ISA (ISA, p. 2-6) and is within the upper part of the range of baseline COHb levels in the study by Allred et al (1989b, Appendix B), however, we considered that it may not be appropriate to place weight on it as a potential health effects benchmark level and accordingly has not focused on dose estimates for it in the discussion below. Additionally, in considering contributions to COHb associated with ambient CO exposures, we recognize the findings of Allred et al (1989a, 1989b, 1991) with regard to a dose-response relationship for decreases in time to exercise-induced angina and ST-segment change per 1% increase in COHb concentration in persons with pre-existing CAD (ISA, section 5.2.4; Allred et al., 1989a, 1989b, 1991). In considering COHb estimates from the quantitative assessment below, we take note of estimates of endogenous COHb levels from the quantitative exposure and dose analysis which indicated that in the absence of external CO sources, approximately 1.5% of the simulated at-risk population in one of the two populations was estimated to experience maximum end-of-hour endogenous COHb levels at or above 1% (draft REA, section 6).

The benchmark levels identified are used to interpret COHb levels estimated to occur in the modeled population in response to exposures to ambient CO in different air quality scenarios in light of the evidence for cardiovascular effects in individuals with CHD when exposed to CO. Specifically, in considering the exposure and dose estimates with regard to consideration of the adequacy of the current standards here, we focus on estimates of the portion of this at-risk population estimated to experience maximum end-of-hour COHb levels above these benchmarks, and on information concerning the COHb increment above endogenous levels associated with ambient CO exposures.

- **What is the magnitude of at-risk population COHb levels estimated to occur in areas simulated to just meet the current CO standards? What portion of the at-risk population is estimated to experience maximum COHb levels above levels of potential health concern?**

In addressing this question, we consider the population COHb estimates provided by the draft REA (draft REA, section 6.2) and summarized in Tables 2-5 and 2-6 below. These tables include estimates associated with current "as is" conditions and conditions simulated to just meet the current standard. In considering these estimates, we particularly focus on the extent to which the current standards provide protection to the simulated at-risk population from COHb levels of

potential concern, by comparing the estimated levels in the population to the potential health effect benchmarks described above. As described above, the draft REA estimates of COHb reflect the impact of exposures to ambient CO in addition to individual endogenous levels (draft REA, section 6.4).

Under "as is" conditions in the two study areas, fewer than 0.1 % and 2% of the simulated at-risk population are estimated to experience an end-of-hour COHb concentration at or above 2% and 1.5%, respectively, with the results for the Los Angeles study area including slightly larger portions of the population above these benchmarks than that estimated for the Denver study area. Under conditions with higher ambient CO concentrations that just meet the current 8-hour standard, the portion of the simulated at-risk population estimated to experience these levels of COHb is greater. But for these simulations, the relationship between the two study areas is reversed with the Denver study area having higher COHb levels. In the Denver study area 3.4% of the simulated at-risk population is estimated to experience a maximum end-of-hour COHb level at or above 2%, while 19% of the population is estimated to experience a maximum COHb level at or above 1.5%. For the Los Angeles study area, less than 1% and 5% of the population was estimated to experience maximum end-of-hour COHb levels at or above 2% and 1.5%, respectively (Table 2-5).

Table 2-5. Portion of simulated at-risk population with maximum end-of-hour COHb levels at or above the indicated level under air quality conditions simulated to just meet the current standards and under "as is" (2006) conditions. COHb levels reflect endogenous levels and ambient CO exposures.

Maximum end-of-hour COHb Level	Percentage (%) of Simulated At-risk Population			
	Just meeting current standards		"as is" conditions	
	Los Angeles	Denver	Los Angeles	Denver
≥ 3%	<0.1	0.2	0.0	0.0
≥ 2.5%	<0.1	0.6		
≥ 2%	0.5	3.4	<0.1	
≥ 1.5%	4.6	19.1	1.5	0.6
* <0.1 is used to represent nonzero estimates below 0.1%				

- **What are the key uncertainties associated with our exposure and dose estimates, including those of particular significance with regard to drawing conclusions as to the adequacy of the protection afforded by the current CO standards?**

In considering the uncertainties associated with the quantitative estimates of exposure and dose from the draft REA, we relied on an approach intended to identify and compare the relative impact that important sources of uncertainty may have on the estimated potential health effect endpoints (i.e., estimates of the maximum end-of-hour COHb levels in the simulated at-risk population). The approach used (as described in section 7.2 of the second draft REA) was developed using guidelines outlining how to conduct a qualitative uncertainty characterization (WHO, 2008) and applied in the most recent NO_2 (US EPA, 2008b) and SO_2 NAAQS reviews (US EPA, 2009). We employed the mainly qualitative approach given the extremely limited data available to inform probabilistic analyses. The qualitative approach used varies from that of WHO (2008) in that a greater focus of the characterization performed was placed on evaluating the direction and the magnitude of the uncertainty; that is, qualitatively rating how the source of uncertainty, in the presence of alternative information, may affect the estimated exposures and health risk results. In addition and consistent with the WHO (2008) guidance, we discuss the uncertainty in the knowledge-base (e.g., the accuracy of the data used, acknowledgement of data gaps) and decisions made where possible (e.g., selection of particular model forms), though qualitative ratings were assigned only to uncertainty regarding the knowledge-base.

In the characterization of uncertainty for the current analysis, we identified and evaluated fourteen separate sources of uncertainty associated with four main components of the assessment:

- Ambient monitor CO concentrations
  - database quality, spatial and temporal representation, and missing data substitution;
- Adjustment of air quality to simulate just meeting the current and potential alternative standards
  - historical data used, proportional approach used;
- APEX inputs and algorithms
  - population database, activity pattern database, longitudinal profile algorithm, meteorological data, micrenvironmental algorithm and input data, commuting algorithm, CHD prevalence, physiological factors; and,
- Potential health effects benchmark levels for the simulated at-risk population.

By comparing judgments made regarding the magnitude and direction of influence the identified sources have on estimated exposure concentrations and dose levels and the existing uncertainties in the knowledge-base, we identified six sources (i.e., the spatial and temporal representation, historical data used, activity pattern database, longitudinal profile algorithm, microenvironmental algorithm and input data, and physiological factors) that remain as the most important uncertainties in this assessment. Taking into consideration improvements in the model algorithms and data since the last review, and having identified and characterized these uncertainties here, we conclude that the estimates associated with the current analysis, at a minimum, better reflect the full distribution of exposures and dose as compared to results from the 1992 analysis. When considering the overall quality of the current exposure modeling approach, the algorithms, and input data used, alongside the identified limitations and uncertainties, we conclude that the quantitative assessment provides reasonable estimates of CO exposure and COHb dose for the simulated population the assessment is intended to represent (i.e., the population residing within the urban core of each study area). We note somewhat greater uncertainty in characterizing of the ends of the distribution of population exposures.

- **To what extent are the estimates of at-risk population COHb levels under conditions just meeting the current CO standards important from a public health perspective?**

In considering the public health implications of the quantitative dose estimates, we first note the size of the at-risk population simulated in the draft REA, people with CAD, both diagnosed and undiagnosed. This population is recognized as that most susceptible to increased risk of CO-induced health effects (ISA, sections 5.7.1.1 and 5.7.8). The 2007 estimate from the National Health Interview Survey (NHIS) performed by the U.S. Centers for Disease Control of the size of the U.S. population with coronary heart disease, angina pectoris (cardiac chest pain) or who have experienced a heart attack (ISA, Table 5-26) is 13.7 million people (ISA, pp.5-117). Further, there are estimated to be three to four million additional people with silent ischemia or undiagnosed IHD (AHA, 2003). In combination this represents a large population represented by the draft REA analyses and for which the COHb benchmarks described above (based on studies of CAD patients) are relevant, that is more susceptible to ambient CO exposure when compared to the general population (ISA, section 5.7).

As discussed above, the draft REA estimates that 0.5 percent of the Los Angeles and 3.4% of the Denver study CHD populations may experience maximum end-of-hour COHb levels of the same magnitude as the average COHb level resulting for the lower experimental exposure group in the study by Allred et al. (1989a, 1989b, 1991) which resulted in a statistically significant reduction in the time to exercise-induced markers of myocardial ischemia (angina and ECG ST-segment change) of 4-5% on average. While recognizing that the exposure resulting in

the 2% average COHb level associated with this result was significantly over background (e.g., approximately 1 hour at 50-200 ppm CO as compared to 0-2 ppm clinic air concentrations), we also note the dose-response relationship was summarized by the authors as indicating decreases of roughly 1.9% in time to exercise-induced angina and 3.9% in time to exercise-induced ST-segment change per 1% increase in COHb concentration in persons with pre-existing CAD, as discussed in section 2.2.1 above (ISA, section 5.2.4; Allred et al., 1989a,1989b, 1991).[31] As noted in the ISA, the physiological significance of the observed ST-segment changes among individuals with CAD is unclear and variability in severity of disease among individuals with CAD is likely to influence the critical level of COHb which leads to adverse cardiovascular effects (ISA, p. 2-6).

In addition to the population with diagnosed and undiagnosed CAD, we note implications with regard to risk to people with other forms of CVD, which we recognize as potentially susceptible (ISA, section 2.6.1). For example, NHIS estimates for 2007 indicate there are approximately 12 million additional people with other types of heart disease (ISA, Table 5-26). Within this broad group, implications are more significant for those included in this population for which their disease state affects their ability to compensate for the hypoxia-related effects of CO (ISA, section 4.4.4).

Other potentially susceptible populations to the effects of CO include people with chronic obstructive pulmonary disease, diabetes and anemia, as well as older adults and fetuses during critical phases of development (as discussed in section 2.2.1 above). In considering potential impacts on such populations, however, we recognize limitations in the evidence in informing us with regard to the specific effects of CO on these populations and, importantly, the exposures and associated COHb levels associated with such effects.

In summary, we recognize that conclusions regarding the extent to which the estimates of exposure and COHb associated with just meeting the current standard are important from a public health perspective depend in part on public health policy judgments about the significance of effects at the COHb benchmark levels considered and judgments about the level of public health protection with an adequate margin of safety. For example, we note that these estimates indicate that the current 8-hour standard limits substantially the percent of the population expected to experience maximum COHb levels at or above the higher benchmarks, while limiting much less so the percentage of the population with maximum COHb levels above the

[31] The dose-response relationship was derived as the average of the regressions of the individual study subject data for changes in time to onset of the monitored measures of ischemia across their range of COHb levels (from their baseline COHb to their two higher COHb levels resulting from the two experimental CO exposures). The clean-air exposure, post-exercise (baseline) COHb levels in the individual study subjects ranged from 0.2% to 1.1%, their post-exercise COHb levels for the lower experimental CO exposure ranged from 1.0 to 3.0% and their post-exercise COHb levels for the higher experimental CO exposure ranged from 2.3 to 5.1% (Allred et al., 1989b).

lowest benchmarks. Thus, we initially conclude that these estimates provide support for a range of views regarding the importance of these estimates form a public health perspective.

2.2.3 Initial Staff Conclusions on Adequacy of the Current Standards

In considering the adequacy of the current standard, staff gives great weight to the long-standing body of evidence for CO, augmented in some aspects since the last review, that has established: the common mechanism of CO health effects as involving binding to reduced iron in heme proteins and the alteration of their functioning; the important role of hypoxia (reduced oxygen availability) induced by increased COHb blood levels in eliciting health effects; the use of COHb as the bioindicator and dose metric for evaluating CO exposure and potential for health effects; and, people with cardiovascular disease as a key population at risk from low CO exposures (ISA; 2000 AQCD; 1991 AQCD). We additionally recognize the expansion of the epidemiological evidence that provides coherence with our conclusions regarding cardiovascular disease-related susceptibility and may (recognizing various uncertainties associated with the evidence in the particular case of CO) provide indications of air quality conditions associated with ambient CO-related risk, most particularly in areas during periods which included exceedance of the current 8-hour standard (ISA, section 5.2.1).

As at the time of the last review, we give weight to COHb estimates developed from modeling exposures to ambient CO under conditions simulated to just meet the current, controlling, 8-hour standard. These COHb estimates and the incremental contribution from ambient CO exposures are considered in light of the clinical studies. These estimates indicate that some 1-3 percent of the simulated at-risk population are expected to experience maximum COHb levels of a magnitude for which association has been demonstrated with markers of myocardial ischemia and larger portions of the population may experience maximum COHb levels at or above the lowest benchmark considered. Further, in considering public health significance of such estimates, while recognizing uncertainty in the clinical significance associated with the smaller effects observed at the lower COHb levels, we note the substantial size of the at-risk population in the U.S. and the existence of other potentially susceptible populations for which evidence is more limited.

In summary, we draw initial conclusions with regard to the adequacy of the current standard from both the evidence and from the exposure and dose assessment, in light of related limitations and uncertainties. We initially conclude that the combined consideration of the body of evidence and the quantitative exposure and dose estimates provide support for a standard at least as protective as the current standard. Further, we recognize that conclusions regarding the adequacy of the current standard depend in part on public health policy judgments about the significance of effects at the COHb benchmark levels considered and judgments about the level

of public health protection with an adequate margin of safety. Thus, we initially conclude that the combined consideration of the evidence and quantitative estimates described above may be viewed as providing support for either retaining or revising the current 8-hour standard.

The extent to which the current standard is judged to be adequate or not depends on a variety of factors, inclusive of technical considerations, science policy judgments and public health policy judgments. These include public health policy judgments on the appropriate COHb benchmark levels on which to place weight; judgments on the clinical significance of the effects that have been observed at those levels; uncertainty associated with interpretation of the epidemiological evidence as providing information on ambient CO as distinct from information on the mixture of pollutants associated with traffic, and the weight to place on the epidemiological studies for purposes of considering adequacy of the current standards, given that few are available (in one city) during periods under air quality conditions that did not exceed the current standard; and the weight to place on the results of the draft exposure assessment relative to those from past assessments, recognizing the implementation of a new modeling approach and input data.

Staff's initial conclusions with regard to elements of revised primary standards for CO that may be appropriate to consider are discussed in the following sections. These conclusions are drawn from consideration focused on the 8-hour standard in recognition of its role in controlling ambient air quality conditions for CO. We give more specific consideration to each of the two CO primary standards in the discussion of alternative standards in section 2.3 below.

2.3 CONSIDERATION OF ALTERNATIVE STANDARDS

To the extent that the information available in this review suggests that revision of the current standards is appropriate to consider, staff has considered whether the available body of evidence supports consideration of options that are different from the current standard, as articulated by the following overarching question:

- **To what extent does the currently available scientific evidence- and exposure/risk-based information, as reflected in the ISA and draft REA, support consideration of alternatives to the current CO standards to provide increased protection from ambient CO exposures?**

To assist us in interpreting the currently available scientific evidence and the results of recent quantitative exposure/risk analyses to address this question, we have focused on a series of more specific questions in sections 2.3.1 and 2.3.2 below. In considering the scientific and technical information, we consider both the information available at the time of the last review and information newly available since the last review which has been critically analyzed and characterized in the 2000 AQCD and more recently in the ISA. Specifically, we consider how

the currently available scientific evidence informs decisions regarding the basic elements of the NAAQS: indicator, averaging time, level and form. Considerations with regard to indicator and averaging time are presented in sections 2.3.1 and 2.3.2. Form and level are discussed in section 2.3.3.

2.3.1 Indicator

The indicator for carbon monoxide is carbon monoxide as measured by the federal reference methods and equivalent methods. Unlike several other criteria pollutants, there are not multiple compounds or size fractions of carbon monoxide. Federal reference methods are available that can effectively measure carbon monoxide, and thus we have not identified any basis for considering an indicator other than carbon monoxide for the standard.

2.3.2 Averaging Time

In considering potential alternative averaging times other than the current 1- and 8-hour averaging times, we consider the following question:

- **Do health effects evidence and air quality/exposure assessments provide support for considering different exposure indices or averaging times?**

The averaging times for the current standards are 1-hour (35 ppm) and 8-hours (9 ppm). These averaging times were first chosen when EPA promulgated the primary NAAQS for CO in 1971 (36 FR 8186), and were retained in subsequent reviews (1980, 45 FR 55066; 1985, 50 FR 37485; and 1994, 59 FR 38906).

The 8-hour averaging time was selected primarily based on the rationale that most individuals achieve steady-state blood levels of COHb after approximately 8 hours of continuous CO exposure (USEPA, 1979; AQCD 2000, section 7.4; ISA, section 4.3.2.2). Another consideration was that the 8-hour time-frame represented a good basis for tracking continuous exposures during any 24-hour period, recognizing that people may be exposed in approximately 8-hour blocks of time (e.g., working or sleeping).

The 1-hour averaging time primarily reflected consideration of the potential impact of exposures of 1 hour or shorter, such as very short duration peak exposures in urban environments (59 FR 38914). Much of the health evidence, however, is linked to exposures of 1 hour or longer, such as the controlled human studies demonstrating aggravation of myocardial ischemia after exposure of individuals with coronary artery disease to CO for approximately 1-2 hours. Further, based on consideration of air quality data patterns it was recognized that attainment of the 8-hour standard would tend to also limit short-term peaks to levels below those of concern (45 FR 55077).

In considering whether the information available in this review supports consideration for different averaging times for the CO standards, we note that the available information is generally consistent with and supportive of the conclusions reached in the previous reviews to retain the 1- and 8-hour averaging times.

- Controlled human exposure studies, with which epidemiological evidence is coherent, provide the clearest evidence of short-term CO-induced effects and reflect exposures of 1-2 hours (ISA, sections 5.2, 5.2.6.1).
- Epidemiological studies provide evidence based on analyses of 1-, 8-, and 24-hour averaging times (ISA, section 5.2.6).
- Most individuals would be expected to achieve steady-state levels of blood COHb after 6-8 hours of continuous exposure to a fixed CO concentration. Therefore, 8 hours may reasonably be considered closely representative of longer continuous exposures (2000 AQCD, section 7.4).
- The 1-hour averaging time is considered to provide protection from the occurrence of shorter term peak exposure concentrations of ambient CO that may be encountered in some environments, and from COHb levels that may result from such exposures (2000 AQCD, section 7.4; ISA, section 2.4.1).

Taken together, we initially conclude that the information available in the current review continues to support the 1- and 8-hour averaging times and does not provide information that would lead to consideration of standards with alternative averaging times.

2.3.3 Form and Level

In considering potential alternative forms and levels for the standards, we focused primarily on form and level for the 8-hour standard, while also considering form and level for the 1-hour standard. In so doing, we addressed the following overarching question:

- **What is the range of alternative levels and forms for the standard that are supported by the health effects evidence and air quality/exposure assessments, and what are the uncertainties and limitations in that health effects evidence and air quality/exposure assessments?**

In this section, we focus on general considerations with regard to form in section 2.3.2.1. We then address specific considerations for both level and form in section 2.3.2.2, first with regard to the 8-hour standard and then with regard to the 1-hour standard.

2.3.3.1 Potential Alternative Forms

When evaluating alternative forms in conjunction with specific levels, staff considers the adequacy of the public health protection provided by the combination of level and form to be the foremost consideration. In addition, we recognize that it is preferable to have a form that is reasonably stable and relatively insulated from the impacts of extreme meteorological events or

other rare, transitory impacts on air quality. A standard set with a high degree of instability could have the effect of reducing public health protection because shifts in and out of attainment could disrupt an area's ongoing implementation plans and associated control programs.

Therefore, consistent with recent reviews of the O_3, PM and NO_2 NAAQS, we have focused here on a concentration-based form (as compared with an expected or allowable exceedance-based form) and are considering this with regard to an average over 3 years. As noted in the review of the O_3 NAAQS (USEPA, 2007), concentration-based forms[32] may better reflect pollutant-associated health risks than forms based on expected exceedances because concentration-based forms give proportionally greater weight to periods of time when pollutant concentrations are well above the level of the standard than to times when the concentrations are just above the standard, while an expected exceedance form would give the same weight to periods of time with concentrations that just exceed the standard as to times when concentrations greatly exceed the standard. Concentration-based forms also provide greater regulatory stability than a form based on allowing only a single expected exceedance.

In considering specific concentration-based forms on which to focus the current review, we have initially considered such forms as have been considered in other NAAQS reviews, including the 98th and 99th percentile forms averaged over three years, which were considered in the most recent PM and NO_2 NAAQS reviews (USEPA, 2005; USEPA, 2008b).[33] We note that a 99th percentile form for an 8-hour daily maximum standard would correspond to the fourth highest daily maximum 8-hour average concentration in a year. We have initially considered that a 98th percentile form or forms of 99th percentile or fourth highest daily maximum would provide appropriate balances between limiting peak CO concentrations and providing a stable regulatory target.

When considering results of the second draft REA as they relate to standard form, we note that a decision on form must be made in conjunction with selection of a particular standard level. The primary emphasis in such a decision will be on the level of public health protection provided by the combination of form and level. The current form of both the 8-hour and 1-hour standards is a maximum, not to be exceeded more than once per year. In the section below we consider the results of the second draft REA for different combinations of level with both a 99th percentile concentration-based form and the current "exceeded only once per year" form.

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[32] The term "concentration-based" forms is used here to refer to forms based on a concentration associated with a targeted point on the distribution of pollutant concentrations, as distinguished from a "not to be exceeded" or "to be exceeded no more than x times in a year' form.

[33] Given the limited time frame for this review, only one alternative form (for the 8-hour and 1-hour standards) has been evaluated in the REA, such that we do not have the results of the quantitative assessment in terms of a 98th percentile form available to us at this time.

2.3.3.2 Potential Alternative Levels

In considering potential alternative standard levels with regard to their potential to provide greater protection than that afforded by the current standard against CO-related adverse health effects, we have taken into account scientific evidence from both experimental and epidemiologic studies, as well as the uncertainties and limitations in that evidence, and the quantitative estimates of exposure and dose provided by the second draft REA. We note that the scientific evidence and quantitative assessment can provide insights into alternative standard levels only within the context of specific averaging times and forms. Therefore, this section considers the evidence and quantitative analysis as they relate to alternative levels particular to different forms and averaging times. The primary focus of staff's initial considerations in this draft Policy Assessment is on the 8-hour standard because it has long been the controlling standard for air quality.

As an initial matter, we recognize that indoor sources of CO can be important determinants of population exposures to CO and to population distributions of COHb including maximum COHb levels. For some portions of the population these sources may be the primary influences on external exposure-related COHb levels. However, we take note of the conclusions drawn in the previous review that the contribution of indoor sources to individual exposures and associated COHb levels cannot be effectively mitigated by ambient air quality standards (e.g., 59 FR 38914) and so focus here on COHb levels resulting from ambient CO exposures. At the same time, we additionally recognize people whose exposures to nonambient CO result in elevated COHb levels, and particularly those whose COHb levels may be appreciably influenced by additional ambient CO exposures. Findings of previous quantitative assessments in which some indoor sources were represented (e.g., gas stoves and tobacco smoke), however, indicated that indoor source contributions to population maximum COHb levels were substantial in comparison to ambient contributions. While we are limited with regard to information regarding CO emissions from indoor sources today and how they may differ from the time of the 2000 assessment, we note that ambient contributions have notably declined and indoor source contributions from some sources may also have declined. Thus, we have no firm basis to conclude a different role for indoor sources today with regard to contribution to population CO exposure and COHb levels.

We believe that the integration of the health effects evidence with the exposure and dose estimates will be particularly important to informing conclusions regarding standard levels and forms considered to provide protection of public health with an adequate margin of safety. With regard to the scientific evidence, as discussed in section 2.2.1 above, we have given principal emphasis to findings of the multilaboratory controlled human exposure study of individuals with pre-existing CAD (Allred et al., 1989a, 1989b, 1991). In this study, controlled experimental

exposures to CO that resulted in a post-exercise study mean COHb level as low as 2.0% relative to clean-air exposures that resulted in a mean COHb level of 0.6% (post-exercise) were associated with myocardial ischemia-related effects (including, specifically, reduced time to exercise-induced angina and ST-segment change). A dose-response analysis of the study subject specific data, in which individual regressions of study subject responses at baseline COHb and at the two increased COHb levels were averaged, indicated decreases of roughly 1.9% in time to exercise-induced angina and 3.9% in time to exercise-induced ST-segment change per 1% increase in COHb concentration, with no evidence of a measurable threshold at the controlled exposures evaluated (ISA, section 5.2.4; Allred et al., 1989a, 1989b, 1991). For our purposes here, we additionally have considered the epidemiological studies with regard to the extent to which this evidence is consistent with and generally supportive of conclusions drawn from the combined consideration of the controlled human exposure evidence with estimates from the exposure and dose assessment. We take note of the epidemiological studies showing positive associations with IHD and CHD health outcomes described in section 2.2.1 above, three of which were based in a study area in which the current standard was met, the association for one of which was statistically significant. In our consideration of the evidence, we recognize CASAC advice with regard to aspects of the epidemiological evidence that are particularly problematic for CO and the weight to be given to the well-conducted clinical studies (Brain and Samet, 2010).

In considering health risk implications for the simulated at-risk population associated with dose estimates from the quantitative exposure/dose assessment we compared the estimates to potential health effects benchmark levels of 1.5%, 2.0%, 2.5% and 3% COHb (as described in section 2.2.2 above). In considering the population estimates of maximum end-of-hour COHb levels from the draft REA for the purposes of considering the level for the 8-hour standard that provides appropriate public health protection, we have focused on the results in terms of percentage of simulated at-risk population in each study area estimated to experience maximum end-of-hour COHb levels below each of the two lower potential health effects benchmarks and an intermediate COHb level. Based on analysis of the air quality data used in the draft REA to identify the equivalent levels for alternative forms, the five different air quality conditions simulated for each of the two study areas provide information on an array of alternative levels for the current and an alternative form (Table 2-6).

In considering the estimates provided by the draft REA (summarized in Table 2-6 below), we note that differences between the two study areas with regard to the simulated at-risk population distributions of maximum end-of-hour COHb levels (noted in the section 6.2 of the draft REA) lead to differences in the proportion of the population protected from maximum end-of-hour COHb levels at or above the potential health effect benchmarks being considered here.

For example, the percentage of the simulated at-risk population estimated to experience maximum COHb levels below 2% is 99.5% or greater in the Los Angeles study area for all simulated levels for either form, while the percentage of the simulated population in Denver estimated to experience maximum end-of-hour COHb levels below 2% is less than 99% (approximately 96.6%) for the highest alternative standard level simulated for either form. Alternatively, the percentage of the simulated population estimated to experience maximum COHb levels below 1.5% is more than 95% in the Los Angeles study area and more than 80% in the Denver study area for all simulated levels for either form. Further, the percentage of the simulated at-risk population estimated to experience maximum COHb levels below an intermediate COHb level of 1.8%, is more than 99% in the Los Angeles study area and more than 98% in the Denver study area for all simulated levels for either form.

Table 2-6. Portion of simulated at-risk population with maximum end-of-hour COHb levels below the indicated COHb level under alternative levels for the 8-hour standard for the current form and a 99th percentile daily maximum form.

Form	Level	< 2 percent COHb		< 1.8 percent COHb		< 1.5 percent COHb	
		Los Angeles	Denver	Los Angeles	Denver	Los Angeles	Denver
Second Highest Non-overlapping 8-hour Concentration	**9.4**	99.5	96.6			95.4	80.9
	6.5	99.9	99.2	99.7	98.1	98.6	92.9
	5.7	99.9		99.8		99.1	
	5.6	99.9*	99.6	99.6*	98.9	98.5*	95.8
	5.4	99.9	99.6	99.8	99.2	99.4	96.2
	3.1		100.0*		100.0*		99.4*
99th Percentile of 8-hour Daily Maximum Concentration	**8.2**	99.5				95.4	
	7.2		96.6				80.9
	5.7	99.9		99.7		98.6	
	5.1	99.9*		99.6*		98.5*	
	5.0	99.9	99.2	99.8	98.1	99.1	92.9
	4.7	99.9		99.8		99.4	
	4.3		99.6		98.9		95.8
	4.1		99.6		99.2		96.2
	2.8		100.0*		100.0*		99.4*

* Asterisks indicate simulations based on "as is" (2006) air quality conditions.

Taking into account the differences between the simulated at-risk populations in the two study areas, recognizing considerations regarding maximum COHb benchmarks of 1.5 to 2% and above, and being mindful of the support provided by the epidemiological studies, we consider the draft REA estimates of maximum end-of-hour COHb levels with regard to level of protection

estimated to be provided by the different alternative levels for the 8-hour standard (Table 2-6 below). In further considering the weight to place on this information, we are mindful of several key aspects of the evidence (described in more detail in section 2.2.1 above):

- Uncertainty in the clinical significance of the effects observed in the controlled human exposure studies of CAD patients.
- The lack of evidence for a measurable threshold effect for the effects observed in the human clinical studies and the lack of studies that have evaluated effects of experimentally controlled short-term CO exposures of individuals with CAD that resulted in study mean COHb levels below 2%.
- Uncertainty associated with interpretation of COHb levels estimated in the quantitative assessment to result from simulated CO exposure concentrations much lower than the experimental CO exposure concentrations used in the controlled human studies to increase subject COHb levels to COHb study targets.
- The lack of studies of COHb levels associated with health effects in other potentially susceptible populations.
- Limitations associated with the epidemiological studies for CO which complicate our use for quantitative purposes.

Staff find that identification of the range of alternative standards that may be appropriate to consider differs based on the weight placed on different aspects of the evidence and on different aspects of the quantitative dose estimates, as well as on public health policy decisions regarding the significance of the effects considered, the appropriate COHb benchmark on which to focus in considering maximum end-of-hour COHb levels, and the targeted proportion of the at-risk population. For example, focusing on the 2.0% COHb benchmark and considering a target for the at-risk population of 95 or 96% across the two study areas would indicate support for retaining the current level of the 8-hour standard. That is, the draft REA results in Table 2-6 indicate that under the current standard, the maximum end-of-hour COHb levels for at least 96% of the at-risk populations in the two study areas would be expected to fall below the 2% benchmark.[34] Alternatively, consideration of a higher population target of 99% while focusing on the 2% COHb benchmark, would lead to consideration of a level of approximately 5 to 6 ppm, as would a population target of 98% below the 1.8% COHb benchmark, while a focus on a COHb benchmark of 1.5% with a target of 95% for the at-risk population would indicate support for consideration of a level somewhat below 5 ppm. On the other hand, consideration of a target level of 99% in combination with a focus on the 1.5% COHb benchmark would indicate support for a somewhat lower level, of about 3 ppm.

[34] Results are not currently available from the second draft REA for the percentage of the simulated at-risk population with end-of-hour COHb levels below 1.8%.

Thus, we note that placing weight on the exposure assessment results for the population target of 95% or 96% for a benchmark level of 2% COHb, in combination with a recognition of limitations in the epidemiological evidence for CO with regard to its use in drawing quantitative conclusions regarding a level for the standard, would provide a basis for considering retaining the current 8-hour standard. Alternatively, placing weight on the three epidemiological studies for the location in which the current standard was met, the association in one of which statistically significant, and consideration of the ambient CO concentrations in that study (Atlanta, 99th percentile 8-hour daily maximum ranging up to 4.9 ppm during the study period) would lead to consideration of the lower part of the range identified above.

While the focus in this draft Policy Assessment is on consideration of the controlling 8-hour standard, we have also considered the rationale for the existing 1-hour standard as generally providing protection from effects that might result from short peak exposures over this shorter exposure duration (as described in section 2.3.1 above). We find value in retaining this standard for that purpose, recognizing that it may provide such protection independent from the type of protection provided by the 8-hour standard.

We note that the results of the quantitative exposure/dose analysis also provides estimates for the ten model simulations (described in the draft REA) in terms of potential alternative levels for a 1-hour standard either of current form or a revised 99th percentile daily maximum form (Table 2-7 below). These estimates indicate the extent to which levels for the 1-hour standard that are appreciably lower than the current level might influence population maximum end-of-hour COHb levels in the situation where the 8-hour standard was of a magnitude such that it no longer was the controlling force for ambient CO concentrations. From these estimates it can be seen that an appreciable reduction in the level for the 1-hour standard would be required to achieve an impact on population COHb levels comparable to those achieved by the current 8-hour standard or levels only somewhat lower. For example, to achieve a similar distribution of expected COHb levels as the current 8-hour standard, the results from the draft REA indicate that a level of approximately 15 ppm would be required for the 1-hour standards, either in terms of the current form or of a 99th percentile daily maximum form (Table 2-7 below).

Table 2-7. Portion of simulated at-risk population with maximum end-of-hour COHb levels below the indicated COHb level under alternative levels for the 1-hour standard for the current form and a 99th percentile daily maximum form.

Form	Level	< 2 percent COHb		< 1.8 percent COHb		< 1.5 percent COHb	
		Los Angeles	Denver	Los Angeles	Denver	Los Angeles	Denver
Second Highest 1-hour concentration	**16.2**		96.6	100.0			80.9
	11.8	99.5				95.4	
	11.2		99.2		98.1		92.9
	9.7		99.6		98.9		95.8
	9.3		99.6		99.2		96.2
	8.2	99.9*		99.6*		98.5*	
	8.1	99.9		99.7		98.6	
	7.2	99.9		99.8		99.1	
	6.8	99.9		99.8		99.4	
	4.6		100.0*		100.0*		99.4*
99th percentile of 1-hour Daily Maximum Concentration	**13.3**		96.6				80.9
	11.6	99.5				95.4	
	9.2		99.2		98.1		92.9
	8.0	99.9	99.6	99.7	98.9	98.6	95.8
	7.7		99.6		99.2		96.2
	7.4	99.9*		99.6*		98.5*	
	7.1	99.9		99.8		99.1	
	6.7	99.9		99.8		99.4	
	4.5		100.0*		100.0*		99.4*

* Asterisks indicate simulations based on "as is" (2006) air quality conditions.

With regard to the current 1-hour standard, staff has identified several policy options in this draft Policy Assessment that may be appropriate to consider. First, we note that the current 1-hour standard may be considered to provide protection from effects which might be encountered from infrequent, very short duration peak ambient concentrations. With regard to such a purpose for the 1-hour standard independent of a focus on COHb levels as illustrated in Table 2-7 above, we have not identified information that might provide for an alternative level and form. Alternatively, while recognizing that the 8-hour standard has traditionally been the controlling standard, we have also considered alternative levels for the 1-hour standard drawing from the results of the draft REA in similar manner to the discussion above for the 8-hour standard. In considering the alternatives for public health policy judgments identified above for the 8-hour standard, we note the results of the draft REA with regard to alternative levels for the

1-hour standard might be concluded to indicate support for a range from approximately 15 ppm at the upper end to approximately 5 ppm at the lower end, combined with a 99th percentile form.

Further, in light of the role of the 8-hour standard as the controlling standard, and depending on judgments made regarding additional protection that may be provided by the 1-hour standard from infrequent, very short duration peak ambient concentrations, we note that it may also be appropriate to consider revoking the 1-hour standard in conjunction with revision of the 8-hour standard to provide increased protection from maximum COHb levels that may result from ambient CO concentrations.

2.3.4 Initial Staff Conclusions on Alternative Standards

Initial staff conclusions for consideration in making decisions on the primary standards for CO, together with supporting conclusions from sections 2.2.3 and 2.3.2 above, are briefly summarized below. In drawing these initial conclusions, we are mindful that the Act requires standards to be set that, in the Administrator's judgment, are requisite to protect public health with an adequate margin of safety, such that the standards are to be neither more nor less stringent than necessary. Thus, the Act does not require that NAAQS be set at zero-risk levels, but rather at levels that avoid unacceptable risks to public health.

(1) Staff initially concludes that the combined consideration of the body of evidence and the quantitative exposure and dose estimates provide support for standards at least as protective as the current suite of standards to provide appropriate public health protection for susceptible populations, including most particularly individuals with cardiovascular disease, against effects of CO in exacerbating conditions of reduced oxygen availability to the heart.

(2) Staff also initially concludes that, depending on public health policy judgments about protecting public health with an adequate margin of safety, the information available in this review supports consideration of either retaining or revising the current suite of standards, with any such revisions focused on providing increased public health protection.

(3) With regard to the indicator for the CO standards, staff initially concludes that it is appropriate to continue to use measurements of CO in accordance with federal reference methods as the indicator to address effects associated with exposure to CO.

(4) With regard to the current 8-hour standard, staff initially concludes that it is appropriate to consider the following range of policy options:

   a. Retaining the 8-hour averaging time.

   b. Retaining or revising the level of the standard, with consideration given to levels within the range from the current level of 9 ppm at the upper end to

approximately 3 ppm at the lower end to provide protection from maximum COHb levels that may result from ambient CO exposures.

c. In conjunction with consideration of revising the level, it is also appropriate to consider revising the form of the standard to a 99th percentile or fourth-highest daily maximum form, including consideration of such a form that is the average of this concentration across three years.

(5) With regard to the current 1-hour standard, staff initially concludes that it is appropriate to consider the following range of policy options:

a. Retaining the current 1-hour standard to provide protection from effects which might be encountered from infrequent, very short duration peak ambient concentrations.

b. Revising the standard, with consideration given to levels within the range from approximately 15 ppm at the upper end to approximately 5 ppm at the lower end, combined with a 99th percentile or fourth-highest daily maximum form, to provide protection from maximum COHb levels that may result from ambient CO exposures. Consideration of a revised level for the 1-hour standard within this range would be intended to provide the same protection as revision of the 8-hour standard within the range identified in item (4)b above.

c. In conjunction with consideration of revising the level of the 8-hour standard to a lower level, it is also appropriate to consider revoking the 1-hour standard in recognition of the increased protection provided by a revised 8-hour standard from maximum COHb levels that may result from ambient CO exposures.

2.4 KEY UNCERTAINTIES AND AREAS FOR FUTURE RESEARCH AND DATA COLLECTION

Staff believes it is important to highlight key uncertainties associated with establishing ambient standards for CO. Such key uncertainties and recommendations for health-related research, model development, and data gathering are outlined below. In some cases, research in these areas can go beyond aiding standard setting to aiding in the development of more efficient and effective control strategies. We note, however, that a full set of research recommendations to meet standards implementation and strategy development needs is beyond the scope of this discussion. We have initially identified the following key uncertainties, research questions and data gaps that have been highlighted in this review of the health-based primary standards.

- A critical aspect of our consideration of the evidence and the quantitative dose estimates is our interpretation of the controlled human clinical studies. Expansion of

this evidence base in several areas would reduce uncertainty in our interpretation for purposes of risk characterization.

  - Additional information relevant to health effects of short-term increases in CO exposure resulting in COHb levels below 2% in individuals with CAD.
  - Additional research to clarify the clinical significance of the sensitive markers of myocardial ischemia observed in controlled human exposure studies of CAD patients.
  - Research to reduce uncertainty associated with interpretation of COHb levels estimated in the quantitative assessment to result from simulated CO exposure concentrations much lower than the experimental CO exposure concentrations used in the controlled human studies to increase subject COHb levels to COHb study targets.

- Existing clinical data correlates CO-induced effects (i.e., cardiovascular ischemia observed at specific COHb levels) to COHb levels resulting from short-term, high CO exposure concentrations. However, there is lack of studies evaluating effects of CO, in terms of COHb levels, at lower ambient concentrations and/or longer term exposures periods.

- Further research to characterize CO effects for other potentially susceptibility populations, including populations with preexisting diseases other than CAD that limit O_2 availability, such as anemia and obstructive respiratory diseases; populations at certain lifestages (i.e., older adults and fetuses at critical stages of development); populations with elevated baseline COHb due to increased CO production, such as individuals with diabetes;, and visitors to high altitude.

- Our interpretation of the epidemiological evidence for CO would benefit from a better understanding of the possible role of co-pollutants.

- Our future assessments would benefit from research on studies evaluating effects of CO linked to biomarkers other than COHb and research on mechanisms of CO-induced effects other that those associated with limiting O_2 availability at ambient CO levels.

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3 CONSIDERATION OF A SECONDARY STANDARD FOR CO

This chapter focuses on the key policy-relevant issues related to the review of welfare-related effects of CO. Under Section 109(b) of the Clean Air Act, a secondary standard is to be established at a level "requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of the pollutant in ambient air." Section 302(h) of the Act defines effects on welfare in part as "effects on soils, water, crops, vegetation, man-made materials, animals, weather, visibility, and climate."

Specifically, this chapter first summarizes the history of EPA's consideration of secondary standards for CO. Considerations is then given to the evidence currently available for welfare effects to inform decisions in this review as to whether, and if so how, to establish secondary standards for CO based on public welfare considerations. Initial staff conclusions are based on the assessment and integrative synthesis of the scientific evidence presented in the ISA (USEPA, 2010), building on the evidence described in the 2000 AQCD (USEPA, 2000).

3.1 CONSIDERATION IN PREVIOUS REVIEWS

With the establishment of the first NAAQS for CO in 1971, secondary standards were set identical to the primary standards. CO was not shown to produce detrimental effects on certain higher plants at levels below 100 ppm. The only significant welfare effect identified for CO levels possibly approaching those in ambient air was inhibition of nitrogen fixation by microorganisms in the root nodules of legumes associated with CO levels of 100 ppm for one month (National Air Pollution Control Administration, 1970). In the first review of the CO NAAQS, the threshold level for plant effects was recognized to occur well above ambient CO levels, such that vegetation damage as a result of CO in ambient air was concluded to be very unlikely (50 FR 37494). As a result, EPA concluded that the evidence did not support maintaining a secondary standard for CO, as welfare-related effects had not been documented to occur at ambient concentrations (50 FR 37494). Bsed on that conclusion, EPA rescinded the secondary standard. In the most recent review of CO, which was completed in 1994, EPA again concluded there was insufficient evidence of welfare effects occurring at or near ambient levels to support setting a secondary NAAQS (59 FR 38906). That review did not consider climate-related effects.

3.2 CONSIDERATION OF EVIDENCE AVAILABLE IN THE CURRENT REVIEW

To evaluate whether consideration of establishment of a secondary standard for CO is appropriate, we adopted an approach in this review that builds upon the general approach used in

the last review and reflects the broader body of evidence and information now available. In developing conclusions in this review below, staff has taken into account the following overarching question:

- **Does the currently available scientific information provide support for considering the establishment of a secondary standard for CO?**

In considering this overarching question, we first note that the extensive literature search performed for the current review did not identify any evidence of ecological effects of CO unrelated to climate-related effects, at or near ambient levels (ISA, section 1.3 p. 1-3). However, ambient CO has been associated with welfare effects related to climate (ISA, section 3.3). Climate-related effects of CO were considered for the first time in the 2000 AQCD. The greater focus on climate in the current ISA relative to the 2000 AQCD reflects comments from CASAC and increased attention to the role of CO in climate forcing (Brain and Samet, 2009). Based on the current evidence, the ISA has concluded that "a causal relationship exists between current atmospheric concentrations of CO and effects on climate" (ISA, section 2.2). Accordingly, the following discussion focuses on climate-related effects of CO in addressing the question posed above.

Recently available information does not alter the current well-established understanding of the role of urban and regional CO in continental and global-scale chemistry, as outlined in the 2000 AQCD. CO is a weak direct contributor to greenhouse warming. The most significant effects on climate result indirectly from CO chemistry, related to the role of CO as a major atmospheric sink for hydroxyl groups (OH). Increased concentrations of CO can lead to increased concentrations of other gases whose loss processes also involve OH chemistry. Some of these gases, such as methane (CH_4) and ozone (O_3), contribute to the greenhouse effect directly while others deplete stratospheric O_3 (ISA, section 3.3 p. 3-11).

Advances in modeling and measurement have improved our understanding of the relative contribution of CO to climate forcing. This link between ambient CO and climate is based on both direct radiative forcing (RF) of CO estimated at 0.024 W/m^2 by Sinha and Toumi (1996) and indirect effects of CO on climate through CH_4, O_3 and carbon dioxide (CO_2) (Forster et al. 2007). The combined RF for these indirect effects of CO was estimated by the Intergovernmental Panel on Climate Change (IPCC) to be ~0.2 W/m^2 over the period 1750-2005 (Forster et al., 2007) with more than one-half of the forcing attributed to O_3 formation.

Ambient CO, by itself, does not significantly absorb the Earth's longwave radiation and warm the atmosphere and surface (ISA, section 2.2). Rather, the effects of CO emissions on climate are felt indirectly because emissions of CO lead to increased ambient concentrations of two important greenhouse gases, CH_4 and O_3. This increase results in contributions to RF that are significant (Forster et al. 2007). However, it is highly problematic to evaluate the indirect

effects of CO on climate due to the spatial heterogeneity in its emissions and concentrations and due to the localized chemical interdependencies involving CO, CH_4, and O_3, which also depend on levels of NOx. (ISA section 3.3).

Most climate model simulations are based on global scale scenarios and have a high degree of uncertainty associated with short-lived climate forcers such as CO (ISA, section 3.3. p. 3-16). These models may fail to consider the local variations in climate forcing due to emissions sources and local meteorological patterns (ISA, section 3.3 p. 3-16).

With regard to time period, ambient CO emissions vary on an hourly basis and exhibit seasonal and weekday/weekend fluctuations (ISA, section 3.5). This episodic emission pattern, coupled with the relatively short atmospheric lifetime of CO, has limited the ability to characterize welfare-related exposures to this pollutant. CO is classified as a short-lived climate forcing agent, prompting CO emission reductions to be considered as a possible strategy to mitigate effects of global warming. It is possible to compute individual contributions to RF of CO from separate emissions sectors, although uncertainty in these estimates has not been quantified (ISA, section 3.3 p. 3-13).

Additional sources of uncertainty in the current assessment include the chemical interdependencies of CO and other climate forcing pollutants and the complexity of CO atmospheric chemistry (ISA, section 3.2.2). Measurement of and techniques for assessing climate forcing are improving, but estimates of RF still have ~50% uncertainty (ISA, section 3.3, p. 3-13). Large regional variations in CO concentrations also contribute to the uncertainties in the RF from CO and other trace gases (ISA, section 2.2 p. 3-12).

3.3 STAFF CONCLUSIONS FOR THE CURRENT REVIEW

In considering whether the currently available scientific information indicates the need for a secondary standard for CO, we have reached the following initial conclusions:

(1) With respect to non-climate welfare effects, including ecological effects and impacts to vegetation, there is no currently available scientific information that supports a CO secondary standard.

(2) With respect to climate-related effects, we note that there is evidence of climate forcing effects associated with CO (ISA, sections 2.2 and 3.3). There are weak direct, and stronger, but primarily highly variable, indirect continental and regional climate forcing effects from CO. However, the available information provides no basis for estimating how localized changes in the temporal, spatial and composition patterns of ambient CO likely to occur across the US with (or without) a secondary standard

would affect local, regional, or nationwide changes in climate. For these reasons, it is currently not feasible to conduct an analysis for the purpose of considering a CO secondary standard based on climate considerations. Moreover, more than half of the indirect forcing effects of CO have been estimated to occur through O_3 formation, and effects of O_3 are more appropriately considered in the context of the review of the O_3 NAAQS, rather than in this CO NAAQS review. Based on these considerations, staff initially concludes there is insufficient information at this time to support the consideration of a secondary NAAQS based on CO effects on climate processes.

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