

Chapter 2. Integrative Overview

The subsequent chapters of this ISA present the most policy-relevant information related to this review of the NAAQS for CO, including a synthesis of the evidence presented in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)), along with the assessment of more recent studies. This chapter integrates important findings from the disciplines evaluated in this current assessment of the CO scientific literature, which includes the atmospheric sciences, ambient air data analyses, climate forcing effects, exposure assessment, dosimetry, and health effects research (animal toxicological studies, controlled human exposure studies, and epidemiologic studies). The EPA framework for causal determinations described in Chapter 1 has been applied to the body of evidence evaluated in this assessment in order to characterize the relationship between exposure to CO at relevant concentrations and health effects. The EPA framework applied here employs a five-level hierarchy that classifies the weight of evidence for causation:

- Causal relationship
- Likely to be a causal relationship
- Suggestive of a causal relationship
- Inadequate to infer a causal relationship
- Not likely to be a causal relationship

This evaluation led to causal determinations for several health outcome categories and characterization of the magnitude of the response, including responses in susceptible populations, over a range of relevant concentrations. This integration of evidence also provides a basis for characterizing the concentration-response relationships of CO and adverse health outcomes for the U.S. population, given the current state of knowledge.

This chapter summarizes and integrates the newly available scientific evidence that best informs consideration of the policy-relevant questions that frame this assessment, which are presented in Chapter 1. Section 2.1 discusses the trends in ambient concentrations and sources of CO. Section 2.2 provides an overview of climate forcing related directly and indirectly to CO. Section 2.3 provides a brief summary of factors influencing personal exposure to ambient CO. Section 2.4 summarizes CO dosimetry and pharmacokinetics and describes what is known regarding the modes of action of CO. Section 2.5 integrates the evidence from studies that examined health effects related to short- and long-term exposure to CO and discusses important uncertainties identified in the interpretation of the scientific evidence. Section 2.6 summarizes policy-relevant considerations associated with exposure to CO including evidence of effects in potentially susceptible populations and information on the shape of the concentration-response function. Finally, Section 2.7 presents an integrated summary of the health effects of CO, reports the levels at which effects are observed and discusses important uncertainties to consider in the interpretation of the scientific evidence.

2.1. Ambient CO Sources and Concentrations

CO is formed by incomplete combustion of carbon-containing fuels and by photochemical reactions in the atmosphere. Nationally, on-road mobile sources constituted more than half of total CO emissions in 2002, or ~61 of ~117 million tons (MT) of total CO emissions, based on the most recent publicly available data meeting data quality objectives from EPA's National Emissions

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

Inventory (NEI). In metropolitan areas in the U.S., as much as 75% of all CO emissions result from on-road vehicle exhaust. The majority of these on-road CO emissions are derived from gasoline-powered vehicles. When emissions from incomplete combustion of fuels powering nonroad mobile sources, such as farm and construction equipment, lawnmowers, boats, ships, snowmobiles, and aircraft, are included, all mobile sources accounted for ~80% of total CO emissions in the U.S. in 2002. Other primary sources of CO include wildfires, controlled vegetation burning, residential biomass combustion, and industrial processes. While CO emissions from nonroad mobile sources, wild fires, and industry have remained fairly constant, on-road mobile source CO emissions have decreased by roughly 5% per year since the early 1990s. Secondary sources of CO include the oxidation of both anthropogenic and biogenic hydrocarbons, such as methane and isoprene and other carbon containing species including aldehydes and alcohols. During summer when biogenic emissions are at their peak, secondary sources of CO are estimated to be a significant fraction of total U.S. sources; however, secondary sources are dispersed over the entire country, while direct emissions are concentrated near primary sources, such as on-road mobile sources, which are mainly in urban areas. 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, and these uncertainties vary by source category, season, and region.

Significant reductions in ambient CO concentrations and in the number of NAAQS exceedances have been observed over the past 25 yr, a continuation of trends documented in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)). Nationwide ambient CO data from the EPA Air Quality System (AQS) for the years 2005-2007 show that the median 1-h daily maximum (max) concentration across the U.S. was 0.7 ppm; the mean was 0.9 ppm; the 95th percentile was 2.4 ppm; and the 99th percentile was 3.8 ppm. Roughly one-third of the 1-h daily max data fell below the limit of detection (LOD) for the majority of CO monitors reporting to AQS. The median 8-h daily max ambient CO concentration for the years 2005-2007 was 0.5 ppm; the mean was 0.7 ppm; the 95th percentile was 1.7 ppm; and the 99th percentile was 2.6 ppm. Half of the 8-h daily max concentrations fell below the LOD for the majority of CO monitors in the field. The current CO NAAQS are 35 ppm (1-h avg) and 9 ppm (8-h avg), not to be exceeded more than once per year. During the years 2005-2007, 1-h and 8-h CO concentrations did not exceed the NAAQS level more than once per year at any monitoring site. Moreover, in these 3 yr, a 1-h avg concentration in excess of 35 ppm was reported only once (39 ppm), and there were only 7 reported 8-h avg values nationwide in excess of 9 ppm in all 3 yr. Seasonally divided box plots of data from 2005-2007 compiled for spatially diverse urban metropolitan areas illustrate the tendency for higher median CO concentrations and wider variations in concentrations in the winter and fall compared with the spring and summer (Section 3.5).

Policy-relevant background (PRB) concentrations include contributions from natural sources everywhere in the world and from anthropogenic sources outside the U.S., Canada, and Mexico. PRB concentrations of CO were estimated for this assessment using data for the years 2005-2007 collected at 12 remote sites in the U.S. which are part of the National Oceanic and Atmospheric Administration's (NOAA) Global Monitoring Division (GMD) and are not part of the EPA national regulatory network. The 3-yr avg CO PRB averaged ~0.13 ppm in Alaska, ~0.10 ppm in Hawaii, and ~0.13 ppm over the contiguous U.S. (CONUS). The analysis for North American PRB in this assessment was made by segregating the three Alaska sites based on their high latitude and the two Hawaii sites based on their distance from the continent, and then treating the remaining seven sites as being more representative of the CONUS PRB. Note that these seven sites are affected by anthropogenic emissions in North America to varying degrees.

2.2. Climate Forcing Effects

Recent data do not alter the current well-established understanding of the role of urban and regional CO in continental- and global-scale chemistry outlined in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)) and subsequently confirmed in the recent global assessments of climate change by the Intergovernmental Panel on Climate Change (IPCC, 2001, [156587](#); IPCC, 2007, [092765](#)). CO is a weak direct contributor to radiative forcing (RF) and greenhouse warming. Sinha and Toumi (1996, [193747](#)) estimated the direct RF of CO computed for all-sky conditions at the tropopause to be

0.024 W/m² based on an assumed change in CO mean global concentrations from 25 to 100 ppb since preindustrial times. The direct RF attributed to CO over this time frame is ~1.5% of the direct RF for CO₂ estimated by the IPCC (Forster et al., 2007, [092936](#)).

More importantly, CO can indirectly cause increased RF because it reacts with tropospheric OH and thus can increase the lifetime of trace gases in the atmosphere including the GHGs CH₄ and O₃. Additionally, the major pathway for removal of CO from the atmosphere is reaction with OH to produce CO₂. CH₄, O₃, and CO₂ absorb infrared radiation from the Earth's surface and contribute to the greenhouse effect. Indirect RF attributed to 1750-2005 emissions of CO through changes in concentration of the GHGs O₃, CH₄, and CO₂ was estimated by Forster et al. (2007, [092936](#)) to be ~0.2 W/m², or ~12% of the direct RF of CO₂ (Figure 3-7). The future direct and indirect integrated RF for year 2000 emissions of CO was estimated to be ~0.2 W/m²·yr with ~50% uncertainty over both 20-yr and 100-yr time horizons (Figure 3-8). The RF related to short-lived CO is ~25% of that for CO₂ for a 20-yr time horizon but only ~7% of that for longer-lived CO₂ over a 100-yr horizon. Overall, the evidence reviewed in this assessment is sufficient to conclude that **a causal relationship exists between current atmospheric concentrations of CO and effects on climate.**

2.3. Exposure to Ambient CO

Very few recent exposure assessment studies involve ambient CO concentration data. The studies of personal exposure to ambient CO presented here generally found that the largest percentage of time in which an individual is exposed to ambient CO occurs indoors but that the highest ambient CO exposure levels occur in transit. In-vehicle CO concentrations are typically reported to be between 2 and 5 times higher than ambient concentrations, although peak in-vehicle concentrations more than an order of magnitude higher than corresponding ambient monitor concentrations have also been reported. Among commuters, exposures were higher for those traveling in automobiles in comparison with those traveling on buses and motorbikes and with those cycling or walking. Ambient CO exposure in automobiles has been demonstrated to vary with vehicle ventilation settings, and a very small portion of that exposure is thought to come from the vehicle in which the exposed person travels. High near-road CO concentrations can be important for those living in the near-road environment because virtually all of ambient CO infiltrates indoors. Hence, indoor exposure to ambient CO is determined by the CO concentration outside the building. CO concentration in the near-road environment has been shown to decrease sharply with downwind distance from a highway, wind direction, and emission source strength (e.g., number of vehicles on a highway); natural and urban topography also influence localized ambient CO concentrations.

Recent exposure assessment studies support one of the main conclusions of the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)), that central site ambient CO monitors may overestimate or underestimate individuals' personal exposure to ambient CO because ambient CO concentration is spatially variable, particularly when analyzing exposures in the near-road environment. Exposure error may occur when the ambient CO concentration measured at the central site monitor is used as an ambient exposure surrogate and differs from the actual ambient CO concentration outside a subject's residence and/or worksite. For example, measurement at a "hot spot" could skew community exposure estimates upwards, and likewise measurement at a location with few CO sources could skew exposure estimates downwards. Correlations across CO monitors can vary widely within and between cities across the U.S. as a function of natural and urban topography, meteorology, source strength and proximity to sources. Typically, intersampler correlation ranges from 0.35 to 0.65 for monitors sited at different scales within a metropolitan area, although it can be greater than 0.8 in some areas.

Health effects estimates from time-series epidemiologic studies are not biased by spatial variability in CO concentrations if concentrations at different locations are correlated in time. Exposure assessment in epidemiologic studies is also complicated by the existence of CO in multipollutant mixtures emitted by combustion processes, making it difficult to quantify the health effects related specifically to CO exposure compared with those related to another combustion-related pollutant or mix of pollutants. In most circumstances, exposure error tends to bias a health effect estimate downward (Sheppard et al., 2005, [079176](#); Zeger et al., 2000, [001949](#)). Spatial and temporal variability not fully captured by ambient monitors and correlation of CO with copollutants

are examples of sources of uncertainty that could widen confidence intervals of health effects estimates.

2.4. Dosimetry, Pharmacokinetics, and Mode of Action

2.4.1. Dosimetry and Pharmacokinetics

Upon inhalation, CO elicits various health effects by binding to and altering the function of a number of heme-containing molecules, mainly hemoglobin (Hb). The formation of COHb reduces the oxygen (O₂)-carrying capacity of blood and impairs the release of O₂ from oxyhemoglobin (O₂Hb) to the tissues. The 2000 CO AQCD (U.S. EPA, 2000, [000907](#)) has a detailed description of the well-established Coburn-Forster-Kane (CFK) equation, which has been used for many years to model COHb formation. Since then, models have been developed that include myoglobin (Mb) and extravascular storage compartments, as well as other dynamics of physiology relevant to CO uptake and elimination. These models have indicated that CO has a biphasic elimination curve, due to initial washout from the blood followed by a slower flux from the tissues. The flow of CO between the blood and alveolar air or tissues is controlled by diffusion down the pCO gradient. The uptake of CO is governed not only by this CO pressure differential but also by physiological parameters, such as minute ventilation and lung diffusing capacity that can, in turn, be affected by factors such as exercise, age, and medical conditions (e.g., obstructive lung disease). Susceptible populations, such as health-compromised individuals, are at a greater risk from COHb-induced health effects due to altered CO kinetics, compromised cardiopulmonary processes, and increased baseline hypoxia levels. Altitude also may have a substantial effect on the kinetics of COHb formation, especially for visitors to high-altitude areas. Compensatory mechanisms, such as increased cardiac output, combat the decrease in barometric pressure. Altitude also increases the endogenous production of CO through upregulation of heme oxygenase (HO). CO is considered a second messenger and is endogenously produced from the catabolism of heme proteins by enzymes such as HO-1 (the inducible form of heme oxygenase) and through endogenous lipid peroxidation. Finally, CO is removed from the body by expiration and oxidation to CO₂.

2.4.2. Mode of Action

The diverse effects of CO are dependent upon concentration, duration of exposure, and the cell types and tissues involved. Responses to CO are not necessarily due to a single process and may instead be mediated by a combination of effects including COHb-mediated hypoxic stress and other mechanisms such as free radical production and the initiation of cell signaling. However, binding of CO to reduced iron in heme proteins with subsequent alteration of heme protein function is the common mechanism underlying the biological responses to CO (see Section 5.1).

As discussed in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)), the most well-known pathophysiological effect of CO is tissue hypoxia caused by binding of CO to Hb. Not only does the formation of COHb reduce the O₂-carrying capacity of blood, but it also impairs the release of O₂ from O₂Hb. Compensatory alterations in hemodynamics, such as vasodilation and increased cardiac output, protect against tissue hypoxia. Depending on the extent of CO exposure, these compensatory changes may be effective in people with a healthy cardiovascular system. However, hemodynamic responses following CO exposure may be insufficient in people with decrements in cardiovascular function, resulting in health effects, as described in Section 5.2. Binding of CO to Mb, as discussed in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)) and in Section 4.3.2.3, can also impair the delivery of O₂ to tissues. Mb has a high affinity for CO, about 25 times that of O₂; however, pathophysiological effects are seen only after high-dose exposures to CO, resulting in COMb concentrations far above baseline levels.

Nonhypoxic mechanisms underlying the biological effects of CO have been the subject of recent research since the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)). Most of these mechanisms are related to CO's ability to bind heme-containing proteins other than Hb and Mb. These mechanisms, which may be interrelated, include alteration in nitric oxide (NO) signaling, inhibition of

cytochrome *c* oxidase, heme loss from proteins, disruption of iron homeostasis, alteration in cellular redox status, alteration in ion channel activity and modulation of protein kinase pathways. CO is a ubiquitous cell signaling molecule with numerous physiological functions. The endogenous generation and release of CO from heme by HO-1 and HO-2 is tightly controlled, as is any homeostatic process. However, exogenously-applied CO has the capacity to disrupt multiple heme-based signaling pathways due to its nonspecific nature. Only a limited amount of information is available regarding the impact of exogenous CO on tissue and cellular levels of CO and on signaling pathways. However, recent animal studies demonstrated increased tissue CO levels and biological responses following exposure to 50 ppm CO. Whether or not environmentally-relevant exposures to CO lead to adverse health effects through altered cell signaling is an open question for which there are no definitive answers at this time. However, experiments demonstrating oxidative/nitrosative stress, inflammation, mitochondrial alterations and endothelial dysfunction at concentrations of CO within one or two orders of magnitude higher than ambient concentrations suggest a potential role for such mechanisms in pathophysiological responses. Furthermore, prolonged increases in endogenous CO resulting from chronic diseases may provide a basis for the enhanced sensitivity of susceptible populations to CO-mediated health effects such as is seen in individuals with coronary artery disease.

2.5. Health Effects

This assessment reviewed health effects evidence regarding the effect of CO on several categories of health outcomes. Table 2-1 presents the overall conclusions of the ISA regarding the presence of a causal relationship between short-term (i.e., hours, days, or weeks) or long-term (i.e., months or years) exposure to relevant CO concentrations (defined in Chapter 1 as generally within one or two orders of magnitude of ambient CO concentrations) and health outcome categories. Summaries of the evidence supporting each causal determination and considerations relevant to application of the causal framework are provided in the following subsections.

Table 2-1. Causal determinations for health effects categories.

Outcome Category	Exposure Period	Causality Determination
Cardiovascular morbidity	Short-term	Likely to be a causal relationship
	Long-term	Inadequate to infer a causal relationship
Central nervous system effects	Short- and long-term	Suggestive of a causal relationship
Birth outcomes and Developmental effects	Long-term	Suggestive of a causal relationship
Respiratory morbidity	Short-term	Suggestive of a causal relationship
	Long-term	Inadequate to infer a causal relationship
Mortality	Short-term	Suggestive of a causal relationship
	Long-term	Not likely to be a causal relationship

2.5.1. Cardiovascular Morbidity

The most compelling evidence of a CO-induced effect on the cardiovascular system at COHb levels relevant to the current NAAQS comes from a series of controlled human exposure studies among individuals with coronary artery disease (CAD) (Section 5.2). These studies, described in the 1991 (U.S. EPA, 1991, [017643](#)) and 2000 (U.S. EPA, 2000, [000907](#)) CO AQCDs, demonstrate consistent decreases in the time to onset of exercise-induced angina and ST-segment changes following CO exposures resulting in COHb levels of 2-6% (Section 5.2.4). No human clinical studies have been designed to evaluate the effect of controlled exposures to CO resulting in COHb concentrations lower than 2%. Human clinical studies published since the 2000 CO AQCD

(U.S. EPA, 2000, [000907](#)) have reported no association between CO and ST-segment changes or arrhythmia; however, none of these studies included individuals with diagnosed heart disease.

While the exact physiological significance of the observed ST-segment changes among individuals with CAD is unclear, ST-segment depression is a known indicator of myocardial ischemia. It is also important to note that the individuals with CAD who participated in these controlled exposure studies may not be representative of the most sensitive individuals in the population. It is conceivable that the most sensitive individuals respond to levels of COHb lower than those evaluated in controlled human exposure studies. Variability in activity patterns and severity of disease among individuals with CAD is likely to influence the critical level of COHb which leads to adverse cardiovascular effects.

The degree of ambient CO exposure which leads to attainment of critical levels of COHb will also vary between individuals. Although endogenous COHb is generally <1% in healthy individuals, higher endogenous COHb levels are observed in individuals with certain medical conditions. Nonambient exposures to CO, such as exposure to environmental tobacco smoke (ETS), may increase COHb above endogenous levels, depending on the gradient of pCO. Ambient exposures may cause a further increase in COHb. Modeling results described in Chapter 4 indicate that increases of ~1% COHb are possible with exposures of several ppm CO depending on exposure duration and exercise level.

Findings of epidemiologic studies conducted since the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)) are coherent with results of the controlled human exposure studies. These recent studies observed associations between ambient CO concentration and emergency department (ED) visits and hospital admissions (HAs) for ischemic heart disease (IHD), congestive heart failure (CHF) and cardiovascular diseases (CVD) as a whole and were conducted in locations where the mean 24-h avg CO concentrations ranged from 0.5 ppm to 9.4 ppm (Table 5-7). All but one of these studies that evaluated CAD outcomes (IHD, MI, angina) reported positive associations (Figure 5-2). Although CO is often considered a marker for the effects of another traffic-related pollutant or mix of pollutants, 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. These studies add to findings reported in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)) that demonstrated associations between short-term variations in ambient CO concentrations and exacerbation of heart disease.

The known role of CO in limiting O₂ availability lends biological plausibility to ischemia-related health outcomes following CO exposure. However, it is not clear whether the small changes in COHb associated with ambient CO exposures result in substantially reduced O₂ delivery to tissues. Recent toxicological studies suggest that CO may also act through other mechanisms by initiating or disrupting cellular signaling. Studies in healthy animals demonstrated oxidative injury and inflammation in response to 50-100 ppm CO, while studies in animal models of disease demonstrated exacerbation of cardiomyopathy and increased vascular remodeling in response to 50 ppm CO. Further investigations will be useful in determining whether altered cell signaling contributes to adverse health effects following ambient CO exposure.

Given the consistent and coherent evidence from epidemiologic and human clinical studies, along with biological plausibility provided by CO's role in limiting O₂ availability, it is concluded that **a causal relationship is likely to exist between relevant short-term exposures to CO and cardiovascular morbidity.**

Only two epidemiologic studies were identified that investigated the relationship between long-term exposure to CO and cardiovascular effects, and the results of these studies provide very limited evidence of an association (Section 5.2.2). Considering the lack of evidence from controlled human exposure studies and the very limited evidence from toxicological studies on cardiovascular effects following long-term exposure to CO, the available evidence is **inadequate to conclude that a causal relationship exists between relevant long-term exposures to CO and cardiovascular morbidity.**

2.5.2. Central Nervous System Effects

Exposure to high levels of CO has long been known to adversely affect central nervous system (CNS) function, with symptoms following acute CO poisoning including headache, dizziness,

cognitive difficulties, disorientation, and coma. However, the relationship between ambient levels of CO and neurological function is less clear and has not been evaluated in epidemiologic studies. Studies of controlled human exposures to CO discussed in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)) reported inconsistent neural and behavioral effects following exposures resulting in COHb concentrations of 5-20%. No new human clinical studies have evaluated central nervous system or behavioral effects of exposure to CO. At ambient-level exposures, healthy adults may be protected against CO-induced neurological impairment owing to compensatory responses including increased cardiac output and cerebral blood flow. However, these compensatory mechanisms are likely impaired among certain potentially susceptible groups including individuals with reduced cardiovascular function.

Toxicological studies that were not discussed in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)) employed rodent models to show that CO exposure during the in utero or perinatal period can adversely affect adult outcomes, including behavior, neuronal myelination, neurotransmitter levels or function, and the auditory system (discussed in Section 5.3). In utero CO exposure, including both intermittent and continuous exposure, has been shown to impair multiple behavioral outcomes in offspring (75-150 ppm). In utero CO exposure (75 and 150 ppm) was associated with significant myelination decrements and neurotransmitter effects (up to 200 ppm). Finally, perinatal CO exposure has been shown to affect the developing auditory system of rodents, inducing permanent changes into adulthood (12.5-100 ppm), some of which appear to be reactive oxygen species mediated. Considering the combined evidence from controlled human exposure and toxicological studies, the evidence is **suggestive of a causal relationship between relevant short- and long-term exposures to CO and central nervous system effects.**

2.5.3. Birth Outcomes and Developmental Effects

The most compelling evidence for a CO-induced effect on birth and developmental outcomes is for preterm birth (PTB) and cardiac birth defects. These outcomes were not addressed in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)), which included only two studies that examined the effect of ambient CO on low birth weight (LBW). Since then, a number of studies have been conducted looking at varied outcomes, including PTB, birth defects, fetal growth (including LBW), and infant mortality.

There is limited epidemiologic evidence that CO during early pregnancy (e.g., first month and first trimester) is associated with an increased risk of PTB. The only U.S. studies to investigate the PTB outcome were conducted in California, and these reported consistent positive associations with CO exposure during early pregnancy when exposures were assigned from monitors within close proximity of the mother's residential address. Additional studies conducted outside of the U.S. provide supportive, though less consistent, evidence of an association between CO concentration and PTB.

Very few epidemiologic studies have examined the effects of CO on birth defects. Two of these studies found maternal exposure to CO to be associated with an increased risk of cardiac birth defects. Human clinical studies also demonstrated the heart as a target for CO effects (Section 5.2). Animal toxicological studies provide additional evidence for cardiac effects with reported transient cardiomegaly at birth after continuous in utero CO exposure (60, 125, 250 and 500 ppm CO) and delayed myocardial electrophysiological maturation (150 ppm CO). Toxicological studies have also shown that continuous in utero CO exposure (250 ppm) induced teratogenicity in rodent offspring in a dose-dependent manner that was further affected by dietary protein (65 ppm CO) or zinc manipulation (500 ppm CO). Toxicological studies of CO exposure over the duration of gestation have shown skeletal alterations (7 h/day, CO 250 ppm) or limb deformities (24 h/day, CO 180 ppm) in prenatally exposed offspring.

There is evidence of ambient CO exposure during pregnancy having a negative effect on fetal growth in epidemiologic studies. In general, the reviewed studies, summarized in Figures 5-7 through 5-9, reported small reductions in birth weight (ranging ~5-20 g). Several studies examined various combinations of birth weight, LBW, and small for gestational age (SGA)/intrauterine growth restriction (IUGR) and inconsistent results are reported across these metrics. It should be noted that having a measurable, even if small, change in a population is different than having an effect on a subset of susceptible births and increasing the risk of IUGR/LBW/SGA. It is difficult to conclude if CO is related to a small change in birth weight in all births across the population, or a marked effect

in some subset of births. Toxicology studies have found associations between CO exposure in laboratory animals and decrements in birth weight (90-600 ppm), as well as reduced prenatal growth (65-500 ppm CO).

In general, there is limited epidemiologic evidence that CO is associated with an increased risk of infant mortality during the neonatal or post-neonatal periods. In support of this limited evidence, animal toxicological studies provide some evidence that exogenous CO exposure to pups in utero significantly increased postnatal mortality (7 h/day and 24 h/day, 250 ppm CO; 24 h/day, 90 or 180 ppm CO) and prenatal mortality (7 h/day, 250 ppm CO).

Evidence exists for additional developmental outcomes which have been examined in toxicological studies but not epidemiologic or human clinical studies, including behavioral abnormalities, learning and memory deficits, locomotor effects, neurotransmitter changes, and changes in the auditory system. Structural aberrations of the cochlea involving neuronal activation (12.5, 25 and 50 ppm CO) and auditory related nerves (25 ppm CO) were seen in pups after neonatal CO exposure. Auditory functional testing using otoacoustic emissions testing (OAE at 50 ppm CO) and 8th cranial nerve action potential (AP) amplitude measurements (12, 25, 50, 100 ppm CO) in rodents exposed perinatally to CO showed auditory decrements at postnatal day (PND) 22 (OAE and AP) and permanent changes in AP into adulthood (50 ppm CO). Furthermore, exogenous CO may interact with or disrupt the normal physiological roles that endogenous CO plays in the body. There is evidence that CO plays a role in maintaining pregnancy, controlling vascular tone, regulating hormone balance, and sustaining normal ovarian follicular maturation.

Overall, there is limited, though positive, epidemiologic evidence for a CO-induced effect on PTB and birth defects, and weak evidence for a decrease in birth weight, other measures of fetal growth, and infant mortality. Animal toxicological studies provide support and coherence for these effects. Both hypoxic and nonhypoxic mechanisms have been proposed in the toxicological literature (Section 5.1), though a clear understanding of the mechanisms underlying reproductive and developmental effects is still lacking. Taking into consideration the positive evidence for some birth and developmental outcomes from epidemiologic studies and the resulting coherence for these associations in animal toxicological studies, the evidence is **suggestive of a causal relationship between relevant long-term exposures to CO and developmental effects and birth outcomes.**

2.5.4. Respiratory Morbidity

New epidemiologic studies, supported by the body of literature summarized in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)), provide evidence of positive associations between short-term exposure to CO and respiratory-related outcomes including pulmonary function, respiratory symptoms, medication use, hospital admissions, and ED visits. The majority of the studies evaluated have not conducted extensive analyses to examine the potential influence of model selection or effect modifiers on the association between CO and respiratory morbidity. A limited number of studies have examined the potential confounding effects of copollutants on CO risk estimates, and found that CO risk estimates were generally robust to the inclusion of O₃, SO₂, and PM in two-pollutant models, but were slightly attenuated in models with NO₂. However, the limited amount of evidence from studies that have examined the effect of gaseous pollutants on CO-respiratory morbidity risk estimates in two-pollutant models, specifically NO₂, has contributed to the inability to disentangle the effects attributed to CO from the larger complex air pollution mix (particularly motor vehicle emissions), and this limits interpretation of the results observed in the epidemiologic studies evaluated. A key uncertainty in interpreting the epidemiologic studies evaluated is the biological mechanism(s) that could explain the effect of CO on respiratory health. Animal toxicological studies, however, provide some evidence that short-term exposure to CO (50-100 ppm) can cause oxidative injury and inflammation and alter pulmonary vascular remodeling. Controlled human exposure studies have not extensively examined the effect of short-term exposure to CO on respiratory morbidity, with a very limited number of studies reporting inconsistent effects of CO on pulmonary function. Although these controlled human exposure studies do not provide evidence to support CO-related respiratory health effects, epidemiologic studies show positive associations for CO-induced lung-related outcomes and animal toxicological studies demonstrate the potential for an underlying biological mechanism, which together provide evidence that is **suggestive of a causal relationship between relevant short-term exposures to CO and respiratory morbidity.**

Currently, only a few studies have been conducted that examine the association between long-term exposure to CO and respiratory morbidity, including allergy. Although some studies did observe associations between long-term exposure to CO and respiratory health outcomes, key uncertainties still exist. These uncertainties include: the lack of replication and validation studies to evaluate new methodologies (i.e., Deletion/Substitution/Addition (DSA) algorithm) that have been used to examine the association between long-term exposure to CO and respiratory health effects; whether the respiratory health effects observed in response to long-term exposure to CO can be explained by the proposed biological mechanisms; and the lack of copollutant analyses to disentangle the respiratory effects associated with CO due to its high correlation with NO₂ and other combustion-related pollutants. Overall, the evidence available is **inadequate to conclude that a causal relationship exists between relevant long-term exposures to CO and respiratory morbidity.**

2.5.5. Mortality

The recently available multicity studies, which consist of larger sample sizes, along with the single-city studies, evaluated reported associations that are generally consistent with the results of the studies evaluated in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)). However, to date the majority of the literature has not conducted extensive analyses to examine the potential influence of model selection, effect modifiers, or confounders on the association between CO and mortality.

The multicity studies reported comparable CO mortality risk estimates for total (nonaccidental) mortality, with the APHEA2 European multicity study showing slightly higher estimates for cardiovascular mortality in single-pollutant models. However, when examining potential confounding by copollutants, these studies consistently showed that although CO mortality risk estimates remained positive, they were reduced when NO₂ was included in the model. But this observation may not be “confounding” in the usual sense in that NO₂ may also be an indicator of other pollutants or pollution sources (e.g., traffic).

Of the studies evaluated, only the APHEA2 study focused specifically on the CO-mortality association and in the process examined: (1) model sensitivity; (2) the CO-mortality C-R relationship; and (3) potential effect modifiers of CO mortality risk estimates. The sensitivity analysis indicated an approximate 50-80% difference in CO risk estimates from a reasonable range of alternative models, which suggests that some model uncertainty likely influences the range of CO mortality risk estimates obtained in the studies evaluated. The examination of the CO-mortality concentration-response relationship found very weak evidence for a CO threshold at 0.5 mg/m³ (0.43 ppm). Finally, when examining a variety of city-specific variables to identify potential effect modifiers of the CO-mortality relationship, the APHEA2 study found that geographic region explained most of the heterogeneity in CO mortality risk estimates.

The results from the single-city studies are generally consistent with the multicity studies in that some evidence of a positive association was found for mortality upon short-term exposure to CO. However, the CO-mortality associations were often but not always attenuated when copollutants were included in the regression models. In addition, limited evidence was available to identify cause-specific mortality outcomes (e.g., cardiovascular causes of death) associated with short-term exposure to CO.

The evidence from the recent multi- and single-city studies suggests that an association between short-term exposure to CO and mortality exists, but limited evidence is available to evaluate cause-specific mortality outcomes associated with CO exposure. In addition, the attenuation of CO risk estimates which was often observed in copollutant models contributes to the uncertainty as to whether CO is acting alone or as an indicator for other combustion-related pollutants. Overall, the epidemiologic evidence is **suggestive of a causal relationship between relevant short-term exposures to CO and mortality.**

The evaluation of new epidemiologic studies conducted since the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)) that investigated the association between long-term exposure to CO and mortality consistently found null or negative mortality risk estimates. No such studies were discussed in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)). The reanalysis of the American Cancer Society (ACS) data by Jerrett et al. (2003, [087380](#)) found no association between long-term exposure to CO and mortality. Similar results were obtained in an updated analysis of the ACS data when using earlier (1980) CO data, but negative associations were found when using more recent (1982-1998) data.

These results were further confirmed in an extended analysis of the ACS data. The Women's Health Initiative (WHI) Study also found no association between CO and CVD events (including mortality) using the mortality data from recent years (1994-1998), while the series of Veterans Cohort studies found no association or a negative association between mean annual 95th percentile of hourly CO values and mortality. An additional study was identified that used a cross-sectional study design, which reported results for a study of U.S. counties that are generally consistent with the cohort studies: positive associations between long-term exposure to PM_{2.5} and SO₄²⁻ and mortality, and generally negative associations with CO. Overall, the consistent null and negative associations observed across epidemiologic studies which included cohort populations encompassing potentially susceptible populations (i.e., post-menopausal women and hypertensive men) combined with the lack of evidence for respiratory and cardiovascular morbidity outcomes following long-term exposure to CO; and the absence of a proposed mechanism to explain the progression to mortality following long-term exposure to CO provide supportive evidence that there is **not likely to be a causal relationship between relevant long-term exposures to CO and mortality.**

2.6. Policy-Relevant Considerations

2.6.1. Susceptible Populations

The examination of populations potentially at greater risk for health effects due to CO exposure is an important consideration in setting NAAQS to provide an adequate margin of safety for both the general population and sensitive populations (see Section 5.7 for a more detailed discussion). During the evaluation of the CO literature, numerous studies were identified that examined whether underlying factors increased the susceptibility of an individual to CO-related health effects. These types of studies were those that included stratified analyses, examined individuals with an underlying health condition, or used animal models of disease.

The most important susceptibility characteristic for increased risk due to CO exposure is CAD, also known as coronary heart disease (CHD). As discussed in Section 5.7, there were approximately 13.7 million individuals with CHD in the U.S. in 2007. Persons with a normal cardiovascular system can tolerate substantial concentrations of CO, if they vasodilate or increase cardiac output in response to the hypoxia produced by CO. In contrast, individuals unable to vasodilate in response to CO exposure may show evidence of ischemia at low concentrations of COHb. Many of the controlled human exposure studies have focused on individuals with CAD, and several studies have found that controlled exposures to CO resulting in COHb concentrations of 2-6% result in significant decreases in time to onset of exercise-induced angina or ST-segment changes in patients with stable angina. Epidemiologic studies found limited evidence for increased hospital admissions for ischemic heart disease (IHD) in individuals with secondary diagnoses of dysrhythmias or congestive heart failure (CHF). This combined evidence from controlled human exposure and epidemiologic studies indicates that individuals with underlying cardiovascular disease, particularly CAD, are a large population that is susceptible to increased health effects in response to exposure to ambient CO. Additional evidence for increased CO-induced cardiovascular effects is provided by toxicological studies that observed altered cardiac outcomes in animal models of cardiovascular disease.

Other medical conditions that have been linked to increased susceptibility to CO-induced health effects include COPD, diabetes, and anemia. Individuals with hypoxia resulting from COPD may be particularly sensitive to CO during submaximal exercise typical of normal daily activity. The results available from epidemiologic and controlled human exposure studies provide preliminary evidence that individuals with obstructive lung disease (e.g., COPD patients with underlying hypoxia, asthmatics) may be susceptible to cardiovascular or respiratory effects due to CO exposure. Diabetics are known to have elevated exhaled CO concentrations indicative of increased endogenous CO production rates. In addition, some recent epidemiologic studies provide preliminary evidence for increased associations between short-term CO exposure and ED visits and hospital admissions for cardiovascular disease (CVD) among diabetics compared to non-diabetics, as well as associations between short-term CO exposure and changes in HRV parameters among subjects with metabolic syndrome, but not among healthy subjects. Increased endogenous CO production and the potential

for higher baseline COHb concentrations in individuals with diabetes, combined with the limited epidemiologic evidence showing cardiovascular effects, suggests that diabetics are potentially susceptible to short-term exposure to CO. Individuals with various forms of anemia experience lowered hematocrit or produce altered forms of hemoglobin, resulting in decreased arterial O₂ content; in addition, individuals with hemolytic anemia exhibit increased endogenous CO production rates and COHb levels. This suggests that individuals with anemia who have diminished O₂-carrying capacity and/or high baseline COHb levels may be more susceptible to health effects due to ambient CO exposure, although no studies were identified that evaluated specific CO-related health effects in anemic individuals.

Aging alters physiological parameters that influence the uptake, distribution, and elimination of CO. The general impact of these changes over an individual's lifetime increases the time required for both loading and elimination of CO from the blood. As noted in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)), changes in metabolism that occur with age, particularly declining maximal oxygen uptake, may make the aging population susceptible to the effects of CO via impaired oxygen delivery to the tissues. Some epidemiologic studies reported increases in IHD or myocardial infarction (MI) HAs among older adults as compared to all-age groups or younger adults in response to short-term exposure to CO. Older adults represent a large and growing fraction of the U.S. population and have a higher prevalence of CAD and other cardiovascular conditions than the general population; combined with the limited evidence available from epidemiologic studies, this indicates that older adults are a potentially susceptible population for increased health effects due to CO.

During gestational exposure, fetal CO pharmacokinetics differ from maternal kinetics, in part because human fetal Hb has a higher CO affinity than adult Hb. At steady-state conditions, fetal COHb concentrations are up to 10-15% higher on a relative basis than maternal COHb levels, and these levels are maintained over a longer period since the half-life for fetal CO Hb is approximately twice that of maternal COHb (7.5 h versus 4 h). Some epidemiologic studies reported higher associations between short-term CO exposure and IHD or MI HAs among older adults as compared to all-age groups or younger adults. Epidemiologic studies provide some evidence that CO exposure during pregnancy is associated with changes in birth outcomes, including PTB, cardiac birth defects, reductions in birth weight, and infant mortality in the postneonatal period. Toxicological studies report effects in laboratory animals that lend biological plausibility to outcomes observed in epidemiologic studies, including decrements in birth weight, reduced prenatal growth, and effects on the heart. Toxicological evidence also exists for additional developmental outcomes which have not been examined in epidemiologic or human clinical studies, including behavioral abnormalities, learning and memory deficits, locomotor effects, neurotransmitter changes, and changes in the auditory system. This evidence suggests that critical developmental phases may be characterized by enhanced sensitivity to CO exposure.

COHb concentrations are generally higher in males than in females, and the COHb half-life is longer in healthy men than in women of the same age. However, women experience fluctuating COHb levels through the menstrual cycle due to variations in the endogenous CO-production rate. Only a limited number of epidemiologic studies have examined gender differences, and found some evidence for larger effects in males compared to females when examining the association between short-term CO exposure and IHD HAs. The limited epidemiologic evidence combined with known gender-related differences in endogenous CO production do not provide sufficient basis for determining whether CO disproportionately affects males or females.

Increased altitude induces a number of physiological changes as compensatory mechanisms to counteract the effects of decreased barometric pressure and the resulting altitude-induced hypobaric hypoxia (HH). These changes generally increase both CO uptake and elimination, with increased COHb levels observed in subjects at rest and decreased COHb observed in individuals exposed to CO during exercise. In addition, baseline COHb levels increase due to increased endogenous CO production. A controlled human exposure study observed an additive effect of CO exposure and simulated high altitude on the reduction in time to onset of angina among a group of individuals with CAD. Acclimatization occurs as the length of stay at high altitude increases, indicating that visitors to high-altitude locations may have an increased risk of health effects due to CO exposure and represent a potentially susceptible population.

Physiological changes associated with exercise tend to increase both uptake and elimination of CO. In a controlled human exposure study, healthy subjects exposed to CO and achieving COHb levels of ~5% observed a significant decrement in exercise duration and maximal effort capability

during heavy exercise. Due to the counterbalancing effects of increased COHb formation and elimination rates, it is unclear whether individuals engaging in light to moderate exercise represent a population potentially susceptible to ambient CO exposure.

CO concentrations on and adjacent to heavily traveled roadways are several times higher than concentrations measured at fixed-site monitors not located adjacent to roadways. In addition, studies of commuters have shown that commuting time is an important determinant of CO exposure for those traveling by car, bicycle, public transportation, and walking. Census data indicate that 17.9 million occupied homes nationwide (16.1%) are located within approximately 90 m of a freeway, railroad, or airport, and that 5.5 million U.S. workers (5%) commute 60 min or more to work in automobiles. This evidence for elevated on-road and near-road CO concentrations combined with residential and commuting data indicates that the large numbers of individuals who spend a substantial amount of time on or near heavily traveled roadways are an important population that is potentially susceptible to increased health risks due to ambient CO exposure.

Endogenous CO production can be altered by medications or other substances, including nicotinic acid, allyl-containing compounds (acetamids and barbiturates), diphenylhydantoin, progesterone, contraceptives, and statins. One epidemiologic study observed an association between short-term CO exposure and an increase in SDNN for CAD patients not taking beta blockers; however, this association did not persist in CAD patients taking beta blockers. Other compounds such as carbon disulfide and sulfur-containing chemicals (parathion and phenylthiourea) increase CO following metabolism by cytochrome p450s. The p450 system may also cause large increases in CO produced from the metabolic degradation of dihalomethanes such as methylene chloride. Minor sources of endogenous CO include the auto-oxidation of phenols, photo-oxidation of organic compounds, and lipid peroxidation of cell membrane lipids. Taken together, this evidence indicates that individuals ingesting medications and other substances that enhance endogenous or metabolic CO production represent a population that is potentially susceptible to increased health effects due to additional exposure to ambient CO.

Overall, the controlled human exposure, epidemiologic, and toxicological studies evaluated in this assessment provide evidence for increased susceptibility among multiple populations. Medical conditions that increase endogenous CO production rates may also contribute to increased susceptibility to health effects from ambient CO exposure. Although the weight of evidence varies depending on the factor being evaluated, the clearest evidence indicates that individuals with CAD are most susceptible to an increase in CO-induced health effects.

2.6.2. Concentration- and Dose-Response Relationships

Currently, very limited information is available in the human clinical and epidemiologic literature regarding the CO concentration- or dose-response (C-R, D-R) relationships and the potential existence of a CO threshold. Two human clinical studies described in the 1991 (U.S. EPA, 1991, [017643](#)) and 2000 (U.S. EPA, 2000, [000907](#)) CO AQCDs have evaluated the D-R relationship between percent COHb (a measure of internal dose of CO) and onset of exercise-induced angina among individuals with CAD. Anderson et al. (1973, [023134](#)) exposed 10 adult men with stable angina (5 smokers and 5 nonsmokers) for 4 h to CO concentrations of 50 and 100 ppm, which resulted in average COHb concentrations of 2.9% and 4.5%, respectively. Both exposures significantly decreased the time to onset of exercise-induced angina relative to room air control (1.6% COHb). However, there was no difference in response between the two exposure concentrations of CO. In a much larger study, 63 adults with stable angina were exposed for 1 h to 2 concentrations of CO (average exposure concentrations of 117 and 253 ppm) resulting in average COHb concentrations in the range of 2.0-2.4% and 3.9-4.7% (Allred et al., 1989, [013018](#); Allred et al., 1989, [012697](#); Allred et al., 1991, [011871](#)). Relative to control (average COHb 0.6-0.7%), COHb concentrations of 2.0-2.4% and 3.9-4.7% were observed to decrease the time required to induce ST-segment changes indicative of myocardial ischemia by 5.1% ($p = 0.01$) and 12.1% ($p < 0.001$), respectively. Increasing COHb concentration was similarly shown to decrease the time to onset of exercise-induced angina. As described in Allred et al. (1989, [013018](#); 1989, [012697](#); 1991, [011871](#)), the observed dose-response relationship was further evaluated by regressing the percent change in time to ST-segment change or time to angina on actual COHb concentration (0.2% - 5.1%) using the three exposures (air control and two CO exposures) for each subject. Regression analyses were conducted separately for each individual and the averages of the intercepts and slopes across subjects were reported. This analysis demonstrated statistically significant decreases in time to angina and

ST-segment change of approximately 1.9% and 3.9%, respectively, per 1% increase in COHb concentration, with no evidence of a measurable threshold. The findings of Allred et al. (1989, [013018](#); 1989, [012697](#); 1991, [011871](#)) provide evidence of a significant D-R relationship over a range of COHb concentrations relevant to the NAAQS. While several other laboratory studies have evaluated cardiovascular effects of CO exposure among adults with CAD, differences in study protocols and analytical methods do not allow for an informative pooled or quantitative meta-analysis of the D-R relationship across studies (Section 5.2.4).

Two studies in the epidemiologic literature attempted to examine the C-R relationship at the low end of CO concentrations through a threshold analysis. Samoli et al. (2007, [098420](#)) in their examination of the association between short-term exposure to CO and mortality conducted an ancillary analysis to examine the potential presence of a CO threshold. In this analysis the authors compared city-specific models to the threshold model, which consisted of thresholds at 0.5 mg/m³ (0.43 ppm) increments. Samoli et al. (2007, [098420](#)) then computed the deviance between the two models and summed the deviances for a given threshold over all cities. While the minimum deviance suggested a potential threshold of 0.43 ppm (the lowest threshold examined), the comparison with the linear no-threshold model indicated weak evidence (p-value > 0.9) for a threshold. However, determining the presence of a threshold at the very low range of CO concentrations (i.e., at 0.43 ppm) in this data set is challenging, because, in 7 of the 19 European cities examined, the lowest 10% of the CO distribution was at or above 2 mg/m³ (1.74 ppm). By only using the 12 cities in the analysis that had minimum CO concentrations approaching 0.5 mg/m³ (0.43 ppm), a limited number of observations were examined around the threshold of interest, which subsequently contributed to the inability to draw conclusions regarding the potential presence of a threshold with any certainty. In addition to the time-series analyses investigating the association of CO concentrations with hospital admissions due to CVD among Medicare enrollees, Bell et al. (2009, [193780](#)) performed subset analyses using datasets that included only days with CO levels below certain specified values, ranging from 1 to 10 ppm (in 1 ppm increments). When these various CO-limit values were evaluated, there were positive associations between cardiovascular health effects and CO concentrations at each level investigated in this study, thus providing no evidence for the existence of a threshold. The investigators also estimated an exposure-response curve allowing a nonlinear relationship between CO concentration and risk of CVD hospital admissions, and reported no evidence of departure from a linear exposure-response curve.

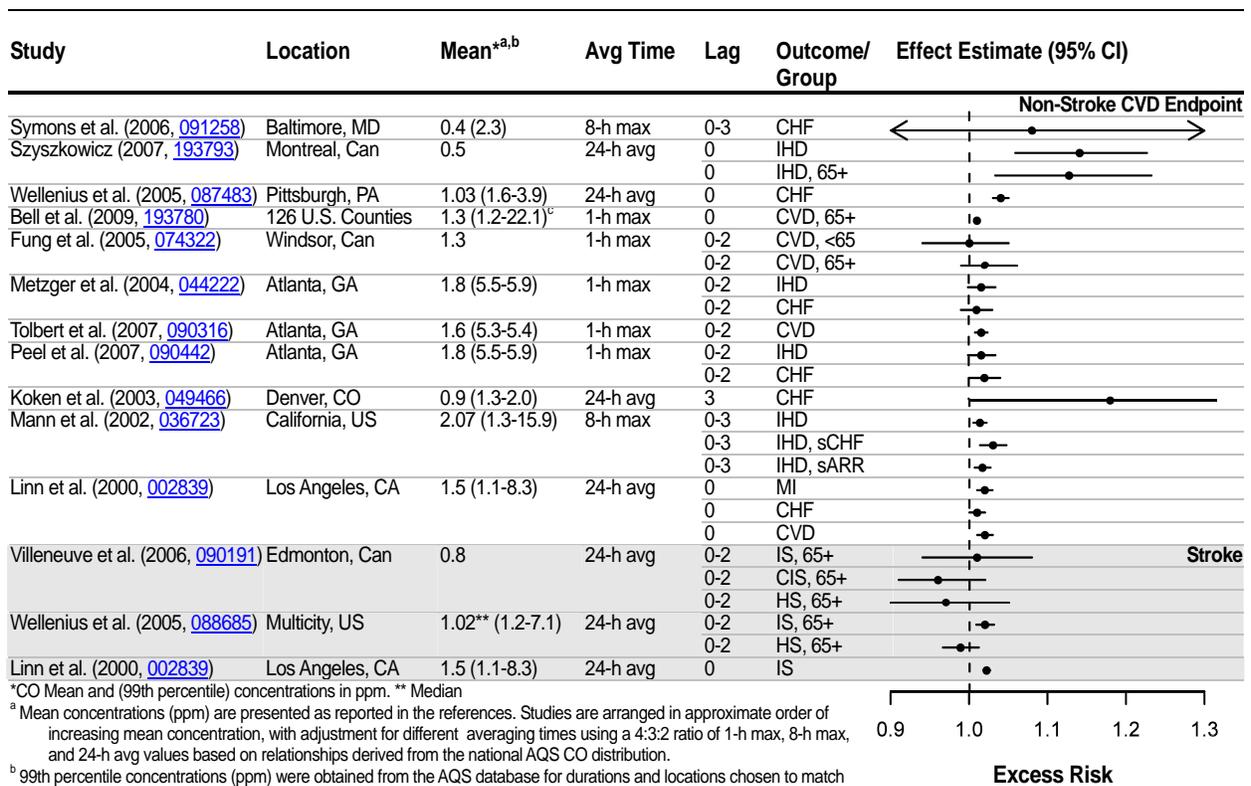
2.7. Integration of CO Health Effects

This section summarizes the main conclusions of this assessment regarding the health effects of CO and the concentrations at which those effects are observed. It also discusses important uncertainties that were considered in interpreting the health effects evidence. The clearest evidence for health effects associated with short-term exposure to CO is provided by studies of cardiovascular morbidity. The combined health effects evidence supports a likely causal relationship for this outcome. Controlled human exposure studies provide strong evidence of independent effects of CO on cardiac function, with effects being observed in patients with CAD following short-term CO exposures resulting in 2.0-2.4% COHb. Epidemiologic studies of ED visits and hospital admissions for ischemic heart disease report consistent positive associations with additional preliminary evidence for an increase in cardiovascular-related mortality provided by a multicity study. This epidemiologic evidence is coherent with ischemia-related effects observed in controlled human exposure studies. Recent toxicological evidence suggests that other mechanisms involving altered cellular signaling may play a role in cardiovascular disease outcomes following CO exposure.

Consistent decreases in time to onset of exercise-induced angina, along with ST-segment changes indicative of myocardial ischemia, were observed in individuals with CAD following controlled CO exposures resulting in COHb concentrations of 2-6%, with no evidence of a threshold at the lowest levels tested. Modeling results described in Chapter 4 indicated that increases of ~1% COHb are possible with exposures of several ppm CO, depending on exposure duration and exercise level. Baseline COHb levels are <1% in healthy individuals, with higher endogenous CO production observed in individuals with certain medical conditions. The volunteers who participated in these studies were diagnosed with moderate to severe CAD, although they may not be representative of the most sensitive individuals in the population. Variability in activity patterns and severity of

disease combined with daily fluctuations in baseline COHb levels may influence the critical level of increased COHb which leads to adverse cardiovascular effects in a particular individual. In addition, arterial COHb is transiently higher than venous COHb for several minutes following a rapid increase in inhaled CO concentration. Transient increases in ambient CO have the potential to elevate COHb to higher levels in the coronary arteries than in other vascular beds, possibly increasing heart CO levels and cardiovascular symptoms in diseased individuals. Quantification of the magnitude of effects at ambient concentrations from the results of controlled human exposure studies is difficult due to the gap between ambient concentrations and the higher concentrations used in these studies (i.e., experimental studies have not been conducted at levels within the range of current maximum ambient concentrations).

Epidemiologic studies consistently show associations between ambient CO concentrations and cardiovascular endpoints other than stroke, particularly hospitalizations and ED visits for ischemic heart disease, MI, and angina. These effects are robust to adjustment for copollutants. Since the heterogeneity of endpoints in these studies does not lend itself to a quantitative meta-analysis, a forest plot was used to summarize the results. Figure 2-1 presents unadjusted health effect estimates from U.S. and Canadian studies of short-term CO exposure and CVD hospitalizations, along with mean and 99th percentile concentrations during the study periods. Table 2-2 summarizes the range of mean and 99th percentile concentrations observed in the studies presented in Figure 2-1. This evidence for ischemia-related outcomes is coherent with effects observed in controlled human exposure studies, although uncertainty regarding the extent of reduced O₂ delivery to tissues following exposure to ambient CO concentrations contributes to the uncertainty in quantitative interpretation of effect estimates.



^aCO Mean and (99th percentile) concentrations in ppm. ^{**} Median

^a Mean concentrations (ppm) are presented as reported in the references. Studies are arranged in approximate order of increasing mean concentration, with adjustment for different averaging times using a 4:3:2 ratio of 1-h max, 8-h max, and 24-h avg values based on relationships derived from the national AQS CO distribution.

^b 99th percentile concentrations (ppm) were obtained from the AQS database for durations and locations chosen to match those of the U.S. studies. When multiple monitors were available at the study location, the range of monitor specific 99th percentile concentrations during the study period is presented. No 99th percentile data are presented for Canadian studies.

^c For the Bell et al. (2009, [193780](#)) study, the concentration statistics represent the 1999-2005 average of daily county-specific values. The central estimate is the median county-average across the U.S. The 99th percentile values represent the counties with the lowest and highest 99th percentile concentrations. Additional cause-specific effect estimates adjusted for NO₂ are presented in Section 5.2.1.

Figure 2-1. Excess risk estimates from epidemiologic studies of short-term CO exposure and CVD hospitalizations along with author-reported mean and AQS-derived 99th percentile CO concentrations. See the footnotes related to concentration data.

Table 2-2. Range of mean and 99th percentile concentrations (ppm) in US and Canadian studies of short-term CO exposure and CVD hospitalizations. See the notes in Figure 2-1 for sources of concentration data.

Metric	1-h daily max	8-h daily max	24-h avg
Mean	1.3-1.8	0.4-2.07	0.5-1.5
99th percentile	1.2-22.1	1.3-15.9	1.1-8.3

Additional studies provide evidence for associations between CO exposure and other health outcomes, including CNS effects, birth outcomes and developmental effects, respiratory effects, and mortality. Although inconsistent results were reported in controlled human exposure studies on neural and behavioral effects, toxicological studies in rodents found that perinatal exposure to CO can have a range of effects on the adult nervous system. This combined evidence is suggestive of a causal relationship between both short- and long-term CO exposure and CNS effects. Differences in fetal pharmacokinetics from those of the mother result in fetal COHb levels that are up to 10-15% higher than maternal COHb levels. Epidemiologic studies provide some evidence that CO exposure during pregnancy is associated with changes in birth outcomes, including increased risk of PTB, cardiac birth defects, small reductions in birth weight, and infant mortality in the postneonatal period. This evidence, in conjunction with developmental effects observed in toxicological studies, is suggestive of a causal relationship between long-term exposure to CO and birth and developmental effects.

Evidence regarding the effect of short-term exposure to CO on respiratory morbidity is suggestive of a causal relationship, based on associations observed in epidemiologic studies and animal toxicological studies which indicate the potential for an underlying biological mechanism, while the evidence on long-term exposure and respiratory morbidity is inadequate to infer the presence of a causal relationship.

An evaluation of epidemiologic studies that examined the effect of short-term exposure to CO on mortality provides evidence that is suggestive of a causal relationship. Epidemiologic studies that examined mortality and long-term exposure to CO reported consistent null associations, which, combined with the lack of respiratory and cardiovascular morbidity or a proposed biological mechanism for mortality following long-term exposure, indicate that there is not likely to be a causal relationship between long-term exposure to CO and mortality.

Issues such as exposure error and isolation of the independent effect of CO as a component of a complex air-pollutant mixture contribute to uncertainty in interpreting the results of epidemiologic studies. Studies published since the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)) have provided insight regarding the nature and magnitude of these uncertainties. Exposures in near-road and on-road microenvironments are likely to be higher than concentrations measured at community-oriented regulatory monitors, which may result in over- or underestimation of the magnitude of ambient exposure for some individuals. Individuals who are susceptible to CO-induced health effects, such as those with CAD, may be at additional risk when experiencing elevated on-road CO concentrations. However, as discussed in Section 2.3 and in more detail in Section 3.6, spatial variability in absolute concentration will not introduce error into time-series epidemiologic studies if the concentrations are correlated in time. A recent study by Sarnat et al. (2009, [180084](#)) found that associations between CO and cardiovascular ED visits were similar when based on different monitors within an urban center, regardless of monitor location or distance to population, while an association was not observed when using a rural monitor outside the urban area. This may have been related to the similarity of driving patterns and peak rush-hour times in the urban center as compared to the area around the rural monitor, where the temporal driving patterns were different. Simulations of ambient and nonambient exposures to a nonreactive pollutant indicated that nonambient exposure has no effect on the association between ambient exposure and health outcomes for the case where ambient and nonambient concentrations are independent, although variability is introduced. Nonambient exposure to CO is not expected to be temporally correlated with ambient CO concentrations, and therefore nonambient CO will not act as a confounder in epidemiologic associations with ambient CO. Exposure error is not likely to affect the magnitude of the population-averaged effect estimates observed in epidemiologic studies, although it would tend to widen the confidence intervals.

Epidemiologic studies consider the effects of CO as a component of a complex mixture of air pollutants that varies across space and time, with moderate to high correlations observed between CO concentrations and those of other combustion-related pollutants. On-road vehicle exhaust emissions are a nearly ubiquitous source of combustion pollutant mixtures that include CO, NO₂, and PM_{2.5}, and these emissions are the most important contributor to ambient CO in near-road locations. Correlations between CO and NO₂ reported in epidemiologic studies of short-term exposure to CO generally ranged from 0.3 to 0.86, with correlations reported in US studies ranging from 0.55 to 0.86. Correlations between CO and PM_{2.5} reported in all studies ranged from 0.17 to 0.74, with correlations in US studies ranging from 0.43 to 0.62. This complicates the quantitative interpretation of effect estimates in these studies to apportion the relative extent to which CO at ambient concentrations is independently associated with cardiovascular or other effects, and the extent to which CO acts as a marker for the effects of another combustion-related pollutant or mix of pollutants.

As summarized in Tolbert et al. (2007, [090316](#)), when toxicological or controlled human exposure studies of two correlated pollutants provide evidence that each exerts an independent health effect, two-pollutant models may be appropriate to adjust the effect estimate for each pollutant for confounding by the other pollutant. PM_{2.5} and NO₂ have each been linked to cardiovascular health effects in epidemiologic studies. In two-pollutant models in which one of the pollutants is linked to the measured outcome and the other is a surrogate for the first pollutant, the copollutant model can help identify which is the better predictor of the effect, particularly if the etiologically linked pollutant is measured with more error than the second pollutant. Uncertainty is introduced in the size of the effect estimate and the portion of the effect size represented by each of the coefficients in the model by correlation between the two pollutants and by differential exposure measurement error. Since the spatial variability of CO is a larger contributor to measurement error than for other more homogeneously distributed pollutants such as PM_{2.5}, robustness of CO effect estimates indicates that CO is the better predictor of effects in copollutant models. Although this complicates quantitative interpretation of the effect estimates reported in epidemiologic studies, the epidemiologic evidence for cardiovascular morbidity summarized in this assessment indicates that CO associations generally remain robust in copollutant models (Figure 5-6 and Figure 5-7), which, combined with the consistency of effects observed across studies, the coherence of epidemiologic health outcomes with effects observed in controlled human exposure studies, and the emerging evidence on the potential role for cell signaling effects at low tissue CO concentrations, supports an independent effect of short-term CO exposure on cardiovascular morbidity. This combined evidence supports a determination that the relationship between CO and cardiovascular morbidity is likely causal, while still recognizing that CO is a component of a mixture of combustion-related pollutants.

Evidence from controlled human exposure and epidemiologic studies indicates that individuals with underlying CVD, specifically CAD, are an important susceptible population at increased risk of health effects due to ambient CO. Potentially susceptible populations include those with other underlying diseases, including anemia, obstructive lung disease, or diabetes; older adults and fetuses during critical phases of development; commuters and those living near heavily traveled roadways; visitors to high-altitude locations; and individuals ingesting medications and other substances that enhance endogenous or metabolic CO production. Limited evidence is available from controlled human exposure studies of CAD patients indicating a statistically significant inverse relationship between COHb concentration and time to ST segment change or time to exercise-induced angina. Epidemiologic analyses investigating the exposure-response relationship for mortality and cardiovascular morbidity did not find evidence for a departure from linearity or a threshold for CO effects.

The new evidence reviewed in this ISA builds upon the health-effects evidence summarized in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)), with many new epidemiologic studies adding to the body of evidence showing associations between acute cardiovascular effects and CO measured at ambient monitors. Controlled human exposure studies reviewed both in this ISA and the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)) show definitive evidence of cardiovascular effects among individuals with CAD following short-term CO exposure, resulting in COHb concentrations as low as 2.0-2.4%. Emerging toxicological evidence points to the potential role for CO in modes of action not directly related to COHb's role in O₂ delivery. In evaluating the several epidemiologic studies available at the time that reported associations between ambient CO and cardiovascular effects, the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)) considered those findings to be inconclusive for multiple reasons, including: questions regarding the consistency of the results among studies; the ability of

community fixed-site monitors to represent spatially variable ambient CO concentrations and personal exposures; the small expected increase in COHb due to ambient CO concentrations; the lack of biological plausibility for health effects to occur at such COHb levels, even in diseased individuals; the potentially greater impact of non-ambient exposure on COHb; and the possibility that ambient CO is serving as a surrogate for a mixture of combustion-related pollutants. Some of these uncertainties remain and complicate the quantitative interpretation of the epidemiologic findings, particularly regarding the biological plausibility of health effects occurring at COHb levels resulting from exposures to ambient CO concentrations measured at AQS monitors. New research summarized in this assessment reduces several of the other uncertainties noted in the 2000 CO AQCD (U.S. EPA, 2000, [000907](#)) and demonstrates the lack of influence of nonambient exposure on effect estimates in epidemiologic studies, the consistency of epidemiologic study results, their robustness in copollutant models, and the coherence of ischemia-related outcomes with evidence from controlled human exposure studies. This consistent and coherent evidence from epidemiologic and human clinical studies, along with biological plausibility provided by the role of CO in limiting O₂ availability, is sufficient to conclude that a causal relationship is likely to exist between relevant short-term CO exposures and cardiovascular morbidity.

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

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