

**CARBON MONOXIDE:  
EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS  
WITH RESPECT TO PROTECTION OF CHILDREN**

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## **A. INTRODUCTION**

Carbon monoxide (CO) is a toxic gas to which children are exposed in a many different types of environment, including the home, in vehicles, while out-of-doors and in their schools. This report will first examine studies that have been part of the scientific basis for the establishment of California's CO air quality standard. Although many of these articles deal with adults rather than children, the mechanisms of action and injury are by and large similar. Next, recently published articles that examine the issue of whether children's exposures or their health responses to CO are different from those of adults will be examined. Finally, these data will be integrated to provide an appraisal of possible differences in responses between children and adults at given environmental levels of CO.

### **A.1. Background**

CO competes with oxygen (O<sub>2</sub>) for binding sites on the heme portion of the hemoglobin (Hb) molecules in red blood cells to form carboxyhemoglobin (COHb). Most of the documented health effects of CO derive from its ability to reduce oxygen delivery to metabolizing tissues, most notably the heart and the central nervous system (CNS).

**A.1.1. State Standards:** The Air Resources Board (ARB) is required by Section 3906(b) of the Health and Safety Code to adopt ambient air quality standards to protect public health and welfare. The health-based ambient air standards specify concentrations and averaging times chosen to prevent adverse effects with consideration to providing protection to sensitive population groups. The ARB adopted a standard of 20 ppm averaged over 8 hours in 1969. The standard was revised in 1970 to 10 ppm averaged over 12 hours and 40 ppm averaged over 1 hour. When the U.S. EPA, in 1971, promulgated national health standards of 9 ppm averaged over 8 hours and 35 ppm averaged over 1 hour, ARB staff proposed changing the state

ambient air quality standards to match. In 1975 the ARB requested that the California Department of Health Services (DHS) consider the potential increased health risks of exposure to CO at high altitude. DHS responded by recommending a more stringent standard (6 ppm CO averaged over 8 hours) for regions of the state 4,000 or more feet above sea level. In 1982, the DHS developed ambient air quality standards for CO based on its recommendation that “a target concentration of 2.5% COHb serve as a basis for the air quality standard for CO.” A mathematical model was used to estimate the ambient concentrations to which individuals might be exposed that would lead to the target 2.5% COHb. The model calculations lead to the adoption of the current standards (9 ppm CO averaged over 8 hours and 20 ppm averaged over 1 hour). The current California ambient air CO standards are more stringent than the national standards, and California is unique in the US in having a more stringent standard for high altitude areas.

**A.1.2. U.S. Federal Standards:** The National Ambient Air Quality Standards (NAAQS) for CO were promulgated by the Environmental Protection Agency (EPA) in 1971 at levels of 9 ppm ( $10 \text{ mg/m}^3$ ) for an 8 h average and 35 ppm ( $40 \text{ mg/m}^3$ ) for a 1 h average, not to be exceeded more than once per year. (Primary and secondary standards were established at identical levels). The 1970 CO criteria document (National Air Pollution Control Administration, 1970) cited as the standard's scientific basis a study which indicated that subjects exposed to low levels of CO, resulting in COHb concentrations of 2 to 3% of saturation exhibited neurobehavioral effects (Beard and Wertheim, 1967). A revised CO criteria document (U.S. Environmental Protection Agency, 1979) concluded that it was unlikely that significant, and repeatable, neurobehavioral effects occurred at COHb concentrations below 5%. However, reports that aggravation of angina pectoris, and other symptoms of

myocardial ischemia, occurred in men with chronic cardiovascular disease, exposed to low levels of CO resulting in COHb concentrations of about 2.7% (Aronow and Isbell, 1973; Aronow et al., 1972; Anderson et al., 1973), lead EPA to retain the 8 h 9 ppm primary standard level and to reduce the 1 h primary standard from 35 to 25 ppm. (EPA also revoked the secondary CO standards because no adverse welfare effects had been reported at near-ambient levels). Later, concerns regarding the validity of data on which the proposed reduction in the 1 h standard was based caused EPA to decide to retain the 1 h 35 ppm standard.

The 1984 addendum to the 1979 CO criteria document (U.S. Environmental Protection Agency, 1984) reviewed four effects associated with low level CO exposure: cardiovascular, neurobehavioral, fibrinolytic, and perinatal. Dose response data provided by controlled human studies allowed the following conclusions to be drawn:

- a) Cardiovascular effects. Among those with chronic cardiovascular disease, a shortening of time to onset of angina was observed at COHb concentrations of 2.9-4.5%. A decrement in maximum aerobic capacity was observed in healthy adults at COHb concentrations at and above 5%. Patients with chronic lung disease demonstrated a decrease in walking distance when COHb concentrations were increased from 1.1-5.4% to 9.6-14/9%.
- b) Neurobehavioral effects. Decrements in vigilance, visual perception, manual dexterity, and performance of complex sensorimotor tasks were observed at, and above, 5% COHb.
- c) Effects on Fibrinolysis. Although evidence existed linking CO exposure to fibrinolytic mechanisms, controlled human studies did not demonstrate consistent effects of carbon monoxide exposure on coagulation

parameters.

- d) Perinatal effects. While there were some epidemiological associations between CO exposure and perinatal effects, such as low birth weight, slowed post-natal development and incidences of sudden infant death syndrome (SIDS), the available data were not sufficient to establish causal relationships.

In September 1985, EPA issued a final notice that announced the retention of the existing 8 h 9 ppm and 1 h 35 ppm primary NAAQS for CO and the rescinding of the secondary NAAQS for CO.

The EPA completed the most recent CO criteria document in 1991 and this chapter reviews the health-based literature that has been published since the December 1991 criteria document. Addendum (U.S. Environmental Protection Agency, 1991) including controlled human clinical exposures and population based studies. There have also been inhalation studies using laboratory animal models. These studies have provided important insights into the possible mechanisms of toxic action of CO, in addition to those related to hypoxia, and illuminate effects not currently identified in human studies, or which might not be amenable to controlled human experimentation, such as perinatal and developmental effects. The existing NAAQS for CO were retained, and are the current US standards.

## **A.2. Principle Sources and Exposure Assessment**

**A.2.1. Sources:** Carbon monoxide is essentially ubiquitous in our environment. It is emitted from virtually all sources of incomplete combustion. Outdoor sources include gasoline and diesel engines and other combustion activities. Indoor sources include improperly adjusted gas and oil appliances (e.g. space heaters, water heaters, stoves, clothes dryers and ovens); and tobacco smoking (Darbool, et al., 1997; Clifford, et al., 1997; Hampson and Norkool, 1992). Because ambient CO concentrations show large temporal and spatial

variations, the exposure of individuals to CO is, therefore, also quite variable, and will depend upon the types of activities in which that individual is engaged and how long he or she is engaged in those activities (time - activity profiles). Other factors that are of importance are related to where the activity takes place (microenvironments e.g. indoors, at a shopping mall, outdoors, in a vehicle, at work or school, in a parking garage or even in a skating rink), (Viala, 1994; Levesque, et al., 1990; Dor, et al., 1995; Koushki, et al., 1992) and the proximity to CO sources.

**A.2.2. Exposure assessment and dosimetry:** In adults, the affinity of Hb for CO is about 220 to 250 times that for O<sub>2</sub> (Roughton, 1970). The formation of COHb by the binding of CO to circulating Hb thus reduces the oxygen-carrying capacity of blood. In addition, binding of CO to one of the four hemoglobin binding sites increases the O<sub>2</sub> affinity of the remaining binding sites, thus interfering with the release of O<sub>2</sub> at the tissue level. When O<sub>2</sub> content of blood [mL O<sub>2</sub> / mL blood] is plotted vs. O<sub>2</sub> partial pressure [mm Hg] in blood, the increased O<sub>2</sub> affinity is seen as the so-called leftward shift in the curve for blood partially loaded with CO (Longo, 1976). CO-induced tissue hypoxia is therefore a joint effect of the reduction in O<sub>2</sub> carrying capacity and the reduction of O<sub>2</sub> release at the tissue level. The brain and heart, under normal conditions, utilize larger fractions of the arterially delivered O<sub>2</sub> (about 75%) than do peripheral tissues and other organs (Ayers, et al., 1970), and are therefore the most sensitive targets for hypoxic effects following CO exposures. The potential for adverse health effects is increased under conditions of stress, such as increased activity levels, which increase O<sub>2</sub> demands at the tissue level. CO may also have a neurotransmitter function and may mediate changes in blood pressure. Children, acutely exposed to CO, present with acidosis and hypertension, among other symptoms (Meert et al., 1998).

The measure of biological dose that relates best to observed biological responses and deleterious health effects is the concentration of COHb expressed as a percentage of

available, active Hb, thus representing the percent of potential saturation of Hb. COHb can be measured directly in blood or estimated from the CO content of expired breath (Lambert, et al., 1988; Lee et al., 1994). When direct measurements cannot be made, COHb can be estimated from ambient air CO concentrations (Ott et al., 1988), indoor air CO concentrations and personal CO monitoring data (Wallace and Ott, 1982). This requires using pharmacokinetic and other models (Wallace and Ott, 1982; Forbes et al., 1945; Pace et al., 1946; Goldsmith et al., 1963; Coburn et al., 1965) that compute COHb from the concentration of inhaled CO, breathing rate and volume, blood volume, metabolic production of endogenous CO and rate of removal of CO. The Coburn-Forster-Kane (CFK) model (Coburn et al., 1965) has been widely used for this purpose. The CFK model has been experimentally verified for exposures at 25 to 5000 ppm, during rest and exercise (Peterson and Stewart, 1975; Tikuisis et al., 1987).

### **A.3. CO Toxicity and sensitive populations**

**A.3.1. Toxicology:** CO affects health by interfering with the systemic transport of oxygen to tissues (especially the heart and other muscles and brain tissue) (Costa and Amdur, 1996). The resulting impairment of O<sub>2</sub> delivery cause tissue hypoxia and interferes with cellular respiration. Direct intracellular uptake of CO could permit interactions with hemoproteins such as myoglobin, cytochrome oxidase and cytochrome P-450, and therefore interfere with electron transport processes and energy production at the cellular level (Brown and Piantidosi, 1992). Thus, in addition to observed physiological effects and cardiovascular effects, CO can modify electron transport in nerve cells resulting in behavioral, neurological and developmental toxicological consequences, and may itself play a role in neurotransmission.

Some data suggest a possible role of CO as an etiologic factor in development of atherosclerosis (Ramos et al., 1996) and can contribute to cardiac ischemia. Cardiac ishemia is a causative factor in cardiac arrhythmias, which can lead to sudden cardiac arrest and

myocardial infarctions. Thus, chronic exposure to elevated CO levels could potentially have long term consequences for the developing child.

The hemodynamic responses to CO have been reviewed by Penney (1988). Chronic CO exposures, at levels sufficient to raise COHb concentrations to greater than 10% can produce increased numbers of red blood cells (polycythemia), increased blood volume, and increased heart size (cardiomegaly). In addition, heart rate, stroke volume, and systolic blood pressure may be increased. Some of these effects have been seen in smokers. Other environmental factors, such as effects of other pollutants (both from conventional air pollution sources and from environmental tobacco smoke), interactions with drugs and medications, health and related factors (e.g. cardiovascular and respiratory diseases, anemia, or pregnancy), and exposures at high altitude are possible risk modifiers for the health effects of CO.

### **A.3.2. Mechanisms and human characteristics that increase risk**

#### (i) Heart diseases

Ischemic heart disease, or coronary artery disease, which is a leading cause of disability and death in industrialized nations (Levy and Feinleib, 1984), is a clinical disorder of the heart resulting from an imbalance between oxygen demand of myocardial tissue and oxygen delivery via the bloodstream. The ability of the heart to adjust to increases in myocardial O<sub>2</sub> demands resulting from increased activity, or to reductions in O<sub>2</sub> delivery by arterial blood due, for example, to COHb or reduced partial pressure in O<sub>2</sub> in inspired air, by increasing O<sub>2</sub> extraction, is limited, because the extraction rate in myocardial tissue is already high. Normally, coronary circulation responds to such increased O<sub>2</sub> demands by increasing blood flow. Individuals, including children, with blood flow insufficiencies may be at increased risk of CO effects, especially when exercising. If impedance of local coronary blood flow occurs during exercise, exercise-induced increased O<sub>2</sub> demands can force the myocardium to extract more O<sub>2</sub> (resulting in reduced coronary venous and tissue O<sub>2</sub>

tensions), which can lead to localized myocardial ischemia and possible tissue damage. Severe myocardial ischemia can lead to myocardial infarction (heart attack) and to abnormal

cardiac rhythms, or arrhythmias. The association of acute CO exposure to heart attacks has been described (Marius-Nunez, 1990).

(ii) Anemia and other blood disorders

Individuals with reduced blood hemoglobin concentrations, or with abnormal hemoglobin, will have reduced O<sub>2</sub> carrying capacity in blood. In addition, disease processes that result in increased destruction of red blood cells (hemolysis) and accelerated breakdown of hemoproteins accelerate endogenous production of CO (Berk, et al., 1974; Solanki et al., 1988), resulting in higher COHb concentrations than in normal individuals. For example, patients with hemolytic anemia have COHb concentrations 2 to 3 times those seen in normal individuals (Coburn et al., 1966).

(iii) Chronic lung diseases

Chronic lung diseases such as chronic bronchitis, emphysema and chronic obstructive pulmonary disease (COPD) are characterized by impairment of the lung's ability to transfer O<sub>2</sub> to the bloodstream because diseased regions of the lung are poorly ventilated and blood circulating through these regions will therefore receive less O<sub>2</sub> (so-called ventilation-perfusion mismatch) (West, 1987). Exertional stress often produces a perception of difficulty in breathing, or breathlessness (dyspnea) in these individuals. Although exercise increases ventilatory drive, they have a limited ventilatory capacity with which to respond (Sue et al., 1988). Reduction of blood O<sub>2</sub> delivery capacity due to formation of COHb could exacerbate symptoms and further reduce exercise tolerance in these individuals. Children with severe inflammatory lung diseases (e.g. frequent episodes of asthma) have been shown to have higher concentrations of CO in exhaled breath ( $2.17 \pm .021$ ), and thus presumably higher COHb concentrations, than healthy children ( $1.01 \pm 0.12$ ) (Uasuf et al., 1999). Thus, it might require less exposure to CO for them to reach a target COHb concentration of 2.5% for a given exposure time. The source of this excess CO is due to increased activity of a metabolic protein, heme oxygenase in individuals with asthma. Children with other lung inflammatory

problems (such as cystic fibrosis or possibly infections) might also have increased exhaled CO levels. Using an adaptation of the Coburn equation the average 8 hr ambient concentration required to achieve a COHb level of 2.5% for children with different baseline levels of COHb was calculated. As shown in Figure 1, as baseline COHb concentration increased, the amount of inhaled CO required to raise the blood level to 2.5% was decreased.

#### (iv) Pregnant women and fetuses

CO induces a strong leftward shift in the O<sub>2</sub>Hb saturation curve (Grote et al., 1994). This may be significant for fetuses because the O<sub>2</sub> tension in their arterial blood is low (20 to 30 mm Hg) compared to adult values (100 mm Hg) and because fetal Hb has a higher O<sub>2</sub> affinity than does maternal Hb (Longo, 1976). In pregnant women, O<sub>2</sub> consumption is increased 15 to 25% and hemoglobin concentration may be simultaneously reduced, which can lower the O<sub>2</sub> carrying capacity of their blood (Pernoll et al., 1975) and reduce O<sub>2</sub> delivery to the developing fetus. CO exposure will further reduce O<sub>2</sub> delivery. Fortunately, fetal blood has higher Hb concentrations than does maternal blood (Hellman and Pritchard, 1971). There is, however, little information on the affinity of fetal hemoglobin for CO or its effect on oxygen dissociation in the fetus, and there were no relevant data on human fetuses retrieved after an extensive literature search.

#### (v) Children

Children have greater activity levels and smaller body masses than adults. Physiologically, children have larger metabolic demands and consequently greater oxygen uptake demands than do adults, on a per unit mass basis. Children should therefore experience higher levels of CO uptake than will adults for the same average exposure concentration. However, since intensity of health effects are likely to be a function of COHb concentration, it is important to consider whether or not the increased CO uptake in children will translate to an elevated COHb. This was addressed, using the Coburn equation (which was used by DHS to estimate the CO levels for adults to achieve 2.5% COHb for 1 hr and 8 hr

exposures) to make similar estimates for children. The estimates provided are for a child with body mass of 35 kg (as compared to a 70 kg adult). The model parameters for an adult breathing at a ventilation rate of 10 LPM were adjusted to match the condition that an 8 hr exposure to 9 ppm CO would increase blood COHb from a baseline level of 0.5% to a level of 2.5% COHb. Child-specific parameters (ventilation rate [ $V_A$ ], adjusted for body mass and rate of diffusion of CO across the lung boundary) were substituted into the model. The model was then run to estimate a 1 hr exposure level that would result in a 2.5% COHb level in an adult and a child. The resulting calculations are shown in Table 1. The model predicts that a child requires lower ambient exposures to CO to achieve 2.5% COHb than an adult under comparable environmental conditions. There are little data comparing CO uptake or binding between children and adults. The model estimates use the same values for children and adults.

**Table 1. Children require lower ambient exposures to CO to reach COHb concentrations of 2.5%. The estimated values use resting ventilation rates of 6 LPM for children and 10 LPM for adults which are scaled to body masses of 35 kg and 70 kg, respectively.**

Exposure Duration	Child, Rest ( $V_A = 6$ LPM)	Adult, Rest ( $V_A = 10$ LPM)
	Ambient CO (ppm)	
1 hr Average	26	33.5
8 hr Average	8.4	9.3

## **A.4. HEALTH EFFECTS OF CO**

### **A.4.1. Population-based studies**

#### (vi) Acute exposures and their effects

Most of the population-based studies in the literature relating to the health effects of CO in humans have been concerned with exposures to combustion and pyrolysis products from sources such as tobacco, fires, motor vehicle exhaust, home appliances fueled with wood (Pierson et al., 1989), gas or kerosene, and small engines. The individuals in these studies are therefore exposed to variable, and usually unmeasured, concentrations of CO and also to high concentrations of other combustion products. Exposures to CO in occupational settings represent another substantial exposure classification, but such exposures are also often accompanied by exposures to other contaminants as well.

Acute CO intoxication most commonly results in neurologic and/or myocardial injury, with approximately 10% of patients displaying delayed neurological sequelae (Thom and Keim, 1989). Parkinsonism, which can be viewed as an outcome of some neuropathological lesions, has been associated with exposures to certain neurotoxins, including CO (Bleeker, 1988). Some of the cases involve firefighters and it is not clear that CO alone is a causal factor. Marius-Nunez (1990) reported a case of an individual who suffered an acute myocardial infarction (shown by ECG and serum enzyme findings) after an acute CO exposure. This case was of interest because the patient's medical profile was negative for coronary heart disease risk factors and because a coronary angiogram performed one week after admission failed to show coronary obstructive lesions. A similar case was reported by Ebisuno et al. (1986) and the circumstances of both cases suggest that contributing factors to the CO-induced reduction in oxygen supply to the myocardium might include induction of coronary artery spasm, inadequate myocardial perfusion, and a direct toxic effect on myocardial mitochondria. CO has a role as a neurotransmitter (Cardell et al., 1998). Inhaled CO decreases total lung resistance and increases lung diffusing capacity for CO in a dose dependent manner (Akesson et al., 2000).

#### **A.4.2. Chronic exposures**

##### (vii) Cardiovascular effects

Kristensen (1989) examined the relationship between cardiovascular diseases and chronic occupation exposures, and concluded that CO exposure increases the acute risk of cardiovascular disease, at least transiently. Stern et al. (1988) performed a retrospective study of heart disease mortality in matched groups of 5,529 bridge and tunnel officers. The tunnel officers had significantly higher CO exposures than the bridge officers, and also had significantly elevated risks of coronary artery disease (61 deaths observed vs. 45 deaths expected). The risk declined after cessation of exposure, dissipating substantially after 5 years. Penney and Howley (1991) report that CO can enhance atherosclerosis in individuals with elevated serum cholesterol.

##### (viii) Effects on lung function

Individuals exposed to relatively high concentrations of CO in both indoor and outdoor environments may have lung function decreases. In most cases, however, causality is difficult to establish because, in addition to CO, these individuals were also exposed to high concentrations of other combustion products, many of which are respiratory system irritants.

In the study of tunnel and bridge officers, described earlier, lung functions, forced vital capacity (FVC) and forced expiration volume in 1 s ( $FEV_{1.0}$ ), were slightly reduced in tunnel vs. bridge officers (Evans et al., 1988). Exposures of adults to typical ambient concentrations of CO, both outdoors and indoors, have not been significantly associated with lung function decrements (Lebowitz et al., 1987). Pollutants related to automotive traffic, especially CO and nitrogen oxides, were associated with the prevalence of asthma in middle-school Taiwanese students (Guo et al., 1999; Lin et al., 1999). Physician consultations in London for lower respiratory diseases were significantly correlated with  $NO_2$  and CO levels in children, but not in adults (Hajat et al., 1999). Exposure of children with mild asthma to environmental tobacco smoke (that contains CO and other combustion products) resulted in

pulmonary function decrements, i.e. reduced FEV<sub>1.0</sub> (Magnusen et al., 1993).

(ix) Effects on pregnancy outcomes

A case-control study of the association between low birthweight infants and maternal CO exposures in approximately 1000 cases in Denver (Alderman et al., 1987) failed to detect a relationship between CO exposure (estimated from fixed-site outdoor monitoring data) during the last 3 months of pregnancy and lower birth weights. Mean CO levels ranged from 0.5 to 3.6 ppm at 8 monitoring locations in metropolitan Denver. The 5<sup>th</sup> and 95<sup>th</sup> percentile concentrations at the site with the highest (3.6 ppm) mean were 1.6 and 4.8 ppm, respectively. The odds ratio at the highest concentration site was 1.1 and the 95% confidence interval was 0.8-1.6). This study did not directly account for unmeasured sources of CO exposure, such as smoking, emissions from gas appliances and exposures to vehicular exhaust, which are limitations of the study design. A more extensive study of a cohort of 125,573 children born to women living in the Los Angeles area (1989-1993) found that exposure to ambient concentrations > 5.5 ppm (3 mo average) during the last trimester of pregnancy was associated with a significantly increased risk of low birthweight (odds ratio = 1.22; confidence interval =1.03-1.44) after adjustment for potential confounders (Ritz and Yu, 1999). Fetotoxicity has been demonstrated in laboratory animal studies. Altered brain neurochemical development and growth retardation have been demonstrated in rats exposed to CO *in utero* (Storm and Fechter, 1985; Leichter, 1993).

**A.4.3. Controlled human studies**

Several clinically based studies have been published which have provided a relatively coherent picture of the effects of CO on the cardiopulmonary system. Some of the key studies cited in the 1991 CO criteria document (EPA, 1991), as well as those published since then, are described below. None of these clinical studies involved children (for practical as well as ethical reasons) but are included in this report because they had a strong influence of the setting of the current CO standards.

### (x) Cardiovascular Effects

Individuals with ischemic heart disease have limited ability to compensate for increased myocardial oxygen demands during exercise, hence exercise testing is often used as a means for evaluating the severity of their cardiovascular impairment. Calvert et al. (1987) determined that four useful parameters of ischemia, measurable during exercise testing, were: ST segment depression (at least 1 mV of horizontal or downsloping depression of the ST segment of an electrocardiographic tracing persisting for 70 ms in 3 successive complexes); exercise-induced angina (chest pain during exercise, which is increased with effort and then resolves with rest - some individuals may experience pain in the jaw, neck, or shoulder areas); impaired work capacity (maximum work levels expressed as a percentage of nomographically predicted, normal values (Bruce et al., 1973); and an inadequate blood pressure response to exercise (blood pressure that falls on exercise or fails to rise more than 15 mm Hg at a work level of at least 40% of the predicted norm). These non-invasive parameters, taken in combination, can identify 85 to 90% of people with coronary artery disease (Calvert et al., 1987). Since CO exposure impairs myocardial O<sub>2</sub> delivery, CO exposure would be expected to worsen symptoms of ischemia in individuals with coronary artery disease. Therefore exercise tests of such individuals have been an important means of providing quantitative and dose-related estimates of the potential impact of CO on health.

Sheps et al. (1987) exposed 30 subjects with ischemic heart disease, aged 38 to 75 yr., to CO (100 ppm) or air, during a 3-day, randomized, double-blind protocol, to achieve an average post-exposure COHb concentration of 3.8% on the CO exposure day (COHb on the air exposure day averaged 1.5%). After exposure to either CO or air, subjects performed an exercise stress test. Exercise was continued until anginal pain required cessation of exercise, fatigue precluded further exercise, or blood pressure plateaued or decreased, despite the increase in workload. All of the subjects were non-smokers and had documented evidence of ischemic heart disease. The authors concluded that there were no clinically significant effects of low-level CO exposures at COHb

concentrations of 3.8%.

Adams et al. (1988) subsequently extended the above study to an average post-exposure COHb concentration of 5.9%, during exercise, using an identical protocol and 30 subjects (22 men, 8 women; mean age 58 yrs). The authors concluded that exposures to CO resulting in COHb concentrations of about 6% significantly impaired exercise performance in subjects with ischemic heart disease.

Kleinman et al. (1989) exposed 24 nonsmoking male subjects with stable angina and positive exercise tests to 100 ppm CO or air to achieve an average COHb concentration of 2.9%, during exercise, on the CO exposure day. Subjects ranged in age from 51 to 66 yr., with a mean age of 59 yr. All but one of the subjects had additional confirmation of ischemic heart disease. Subjects performed an incremental exercise test on a cycle ergometer until the point at which they could detect the onset of their typical anginal pain, and then stopped exercising. The time to onset of angina was decreased after CO exposure (5.9%;  $p = 0.046$ ) relative to air exposure. The duration of angina was longer after CO exposure compared to air exposure (8.3%), but this change was not statistically significant. Oxygen uptake at the angina point was slightly reduced after CO exposure compared to air exposure (2.2%;  $p = 0.04$ ), but the increase in oxygen uptake with increasing workload was similar on both exposure days. A subgroup of 11 subjects who, in addition to angina, exhibited arrhythmias or ST segment depressions during exercise, showed a greater reduction in time to angina after CO exposure, compared to air exposure (10.6%;  $p = 0.016$ ), than did the overall group. The time to significant ST segment depression was significantly reduced for the 8 subjects with this characteristic after CO exposure, compared to air exposure (19.1%;  $p = 0.044$ ). The number of subjects exhibiting exercise-induced ST segment depression identified in this study was small, however those subjects in whom angina preceded

detection of ST segment changes would not have been identified in the protocol used because exercise was stopped at the point of onset of angina.

The results of a multicenter CO exposure study, conducted in three different cities, have been reported by Allred et al. (1989) in which 63 men with documented coronary artery disease underwent exposure to air, 117 ppm CO or 253 ppm CO, on three separate days in a randomized, double-blind protocol, followed by an incremental treadmill exercise test. Average COHb concentrations of 2.2% and 4.3%, during exercise, were achieved on the two CO exposure days (2.0 and 3.9%, respectively, at the end of exercise). All of the subjects had objective evidence of coronary artery disease. On each of the exposure days, the subject performed a symptom-limited treadmill exercise test, was exposed to one of the three test atmospheres (clean air, 117 ppm CO or 253 ppm CO), and then performed a second exercise test at the target COHb concentration (~2% or ~4%). The time to onset of angina was significantly reduced by CO exposure, in a dose-dependent manner (4.2% at ~2% COHb,  $p = 0.054$ ; 7.1% at ~4% COHb,  $p = 0.004$ ). The time to onset of 1 mV ST segment depression was also reduced by CO in a dose-dependent manner (5.1% at 2% COHb,  $p = 0.02$ ; 12.1% at 4% COHb,  $p = 0.0001$ ) compared to the clean air exposure. There was a decrease of approximately  $3.9 \pm 0.6$  percent in time to ST depression for every 1% increase in COHb ( $p = 0.0001$ ). There was a significant correlation between the percent change in the time to onset of angina and the time to onset of ST depression of 1 mV ( $p = 0.0001$ ).

There is some evidence that a level of hypoxia that can result in myocardial ischemia and reversible angina, can also lead to arrhythmias (Kerin et al., 1979; Carboni, 1987; Dahms et al., 1993). Hinderliter et al. (1989) exposed 10 subjects, with ischemic heart disease and no ventricular ectopy at baseline, to air, 100 ppm CO, and 200 ppm CO; COHb concentrations averaged 4% and 6% on the two respective CO exposure days. The exposures were randomized and double-blinded. Following exposure, each subject performed a symptom-limited supine exercise test;

ambulatory electrocardiograms were obtained prior to exposure, during exposure, during exercise, and over a 5-h post-exercise period. The ECG's were analyzed for the frequency and severity of arrhythmias. Eight of the ten subjects demonstrated evidence of ischemia on one or more of the exposure days (angina, 1 mV ST-segment depression, or abnormal ejection fraction response). There were no CO-related increases in the frequency of premature ventricular beats and no multiple arrhythmias occurred. The authors concluded that low-level CO exposure (4 to 6% COHB) was not arrhythmogenic in patients with coronary artery disease and no ventricular ectopy at baseline.

However, researchers from this same team (Sheps et al., 1990), reported on a larger study population (41 subjects) with some evidence of ventricular ectopy, exposed to air, 100 ppm CO, and 200 ppm CO in a similar protocol to that described above. The frequency of single ventricular premature depolarizations (VPD's) per h increased ( $p < 0.03$ ) from  $127 \pm 28$  (mean  $\pm$  SD) after the air exposure to  $168 \pm 38$  after exposure to achieve a COHb concentration of 6%. During exercise, the frequency of multiple VPD's per h increased approximately 3-fold at 6% COHb, compared to air exposure ( $p < 0.02$ ). No significant differences in these parameters occurred after exposures that achieved COHb concentrations of 4%, compared to air exposures. The subjects who exhibited single VPD's with increased frequency after CO exposure were significantly older than the subjects who had no increased arrhythmias. The subjects who exhibited increased frequencies of multiple VPD's were older, exercised for longer durations, and had higher peak workloads during exercise, than those who did not have complex arrhythmias. Leaf and Kleinman have also reported evidence of effects of CO exposure on cardiac rhythm after relatively low CO exposures (3% COHb) in a small group of volunteers with coronary artery disease that exhibited abnormal rhythms on one or more exercise test (Leaf and Kleinman, 1996).

In all of the above clinical studies of CO-related effects, subjects with coronary artery disease, were maintained on individualized regimens of medications, some of which might interact

with CO-induced responses, increasing the apparent variations in observed responses. Specifically, blockade of beta-adrenergic receptors (Melinyshyn et al., 1988) and alpha-adrenergic receptors (Villeneuve et al., 1986) were shown to modify hemodynamic responses to CO in animal studies. Examination of the potential influence of medications on observed responses to CO could provide additional insights on the possible mechanisms of action of CO in individuals with coronary artery disease.

A general conclusion is that the cardiological effects of CO are best understood as being due to a reduction in oxygen delivery. In Figure 2, data on reduction in time to angina from several of the recent studies are summarized as a function of % oxygen saturation of the blood. The effects increase linearly as % oxygen saturation is reduced (within the experimental limits). Also it is important to note that the studies which were conducted by different laboratories, in different areas and with different subject populations, fall along a common curve (within limits of experimental error).

(xi) Cardiopulmonary effects (lung function and exercise tolerance)

1) *Normal individuals*

Reduction of O<sub>2</sub> delivery could reduce the ability to perform work in healthy individuals. Studies of the cardiopulmonary effects of CO have demonstrated that maximal oxygen uptake during exercise ( $\dot{V}_{O_2}$  max) decreases linearly with increasing COHb concentrations ranging from 2.3% to 35% COHb, in normals. The linear relationship can be expressed as percent decrease in  $\dot{V}_{O_2}$  max = 0.91 [%COHb] + 2.2. The specific studies on which these findings are based have been extensively reviewed in the 1979 CO criteria document (U.S. Environmental Protection Agency, 1979), the 1984 addendum to that document (U.S. Environmental Protection Agency, 1984), Horvath (1981) and Shephard (1984). Changes in  $\dot{V}_{O_2}$  max are significant because they represent changes in an individual's maximal aerobic exercise (or work) capacity.

Horvath et al. (1988) exposed 23 subjects (11 male, 12 female) to 0, 50, 100 and 150 ppm CO, at 4 different altitudes (55, 1524, 2134 and 3048 m). Following exposure, each subject performed an incremental exercise test. COHb concentrations ranged from  $0.5 \pm 0.2$  to  $5.6 \pm 0.4$  percent of saturation after sea level exposures. The study showed a significant effect of increased altitude on decreased work performance and  $\dot{V}_{O_2}$  max. The female subjects appeared to be more resistant to the hypoxic effects of altitude than the male subjects. The rate of CO uptake (that is formation of COHb) decreased with increasing altitude, in part due to the reduced driving pressure of CO at altitude. While this might be a mechanism by which CO could directly affect cardiac myoglobin, evidence for direct cardiotoxicity of CO is still lacking. Horvath and Bedi (Horvath, S.M. and Bedi, J.F., 1989) have demonstrated that longer term, low level (9 ppm for 8 h) exposures at 2134 m results in lower COHb concentrations than the same exposure at 55 m, again suggesting slower CO uptake during altitude exposure. McGrath (1989), however, has reported that endogenous CO production is increased in rats chronically maintained at high altitudes (1000 m to 6000m), suggesting that high altitude residents have higher initial COHb concentrations and might therefore achieve 2% or greater COHb levels (the COHb level associated with the CO NAAQS) more quickly than sea level residents. It has been reported that unacclimated workers exposed to about 25 ppm CO at an altitude of 2.3 km above sea level exhibited significantly increased symptoms of headache, vertigo, fatigue, weakness, memory impairment, insomnia and heart palpitations compared to local residents (Song, 1993). The subjects in these human clinical studies of exercise tolerance have been relatively young and all were in good health. There is not sufficient information available to determine if relationships between CO exposure, altitude and COHb concentrations would be similar for individuals with coronary artery disease, chronic lung diseases, anemia's, or in pregnant women.

Kleinman and associates have demonstrated that hypoxia due to high altitude and CO exposure may cause additive effects on exercise tolerance, hemodynamic changes and cardiologic parameters (Kleinman et al., 1998). The subjects in this study were older men with confirmed coronary artery disease.

## 2) *Individuals with chronic obstructive pulmonary disease (COPD)*

Individuals with COPD usually have limited exercise tolerance because they have low ventilatory capacity, which can result in desaturation of arterial blood and hypoxemia (a relative deficiency of O<sub>2</sub> in the blood) and hypoxia (a relative deficiency of O<sub>2</sub> in some tissue) during exercise. Exercise performance in such individuals can be improved by providing supplemental O<sub>2</sub> (Lane et al., 1987). Reduced O<sub>2</sub> carrying capacity of blood due to formation of COHb could exacerbate this limitation, hence individuals with COPD could represent a potentially sensitive group. Aronow et al. (1977) exposed 10 men, aged 53 to 67 y to 100 ppm CO for 1 h, achieving increases in COHb from baseline concentrations of 1.4% to post-exposure concentrations of 4.1%. Mean exercise time was reduced by 33%. Calverley et al. (1981) exposed 6 smokers (who stopped smoking 12 h prior to testing) and 9 nonsmokers to 200 ppm CO for 20 to 30 min (increasing COHb concentrations to between 8 and 12% COHb above baseline COHb), and measured the distance each subject walked in a 12 min period. Significant decreases in walking distance were only seen in individuals with 12.3% COHb or greater. Some individuals with severe COPD, but without clinically apparent coronary artery disease, exhibit exercise-related cardiac arrhythmias. Cheong et al. (1990) reported that these arrhythmias were associated with arrhythmias at rest but were not related to the severity of pulmonary disease, O<sub>2</sub>Hb desaturation or ECG evidence of chronic lung disease. The Sheps et al. (1990) studies of exercise-related arrhythmias in CO-exposed subjects with coronary artery disease suggest that COPD subjects might be important to study, as well. Overall, the information available on individuals with COPD

are consistent with the hypothesis that they represent a population potentially at risk of CO-related health effects during sub-maximal exercise, as may occur during normal daily activities. The available data are however based on population group sizes that are too small and too diverse with respect to disease characteristics to draw firm conclusions.

(xii) Neurotoxicological and behavioral effects

The neurotoxic effects of relatively high level acute CO exposures have been well documented. Subtle neurotoxic effects associated with lower-level CO exposures may be underreported or not associated with CO exposure because the symptoms, which resemble those of a flu-like viral illness, may be misdiagnosed (Ilano and Raffin, 1990). Population based studies on the potential neurotoxicological and behavioral effects of chronic CO exposure at ambient concentrations have not been reported. However, clinical studies of CO-related sensory effects have evaluated several different parameters, under controlled laboratory conditions. A recent study by Hudnell and Benignus (1989) demonstrated, in a double-blind study, that visual function in healthy, young adult males, as defined by measurements of contrast threshold, luminance threshold, and time of cone/rod break, was not affected by COHb concentrations maintained at 17% for over 2 h. Von Restorff and Hebisch (1988) reported no changes in time to dark adaptation and sensitivity after adaptation, at COHb concentrations ranging from 9% to 17%. A large number of studies have investigated the effects of CO on several other behavioral parameters, however effects in general are only seen at COHb concentrations above 5%, and there are inconsistencies between the study results. Of the studies, other than those discussed above, published in 1984 and later, Bunnell and Horvath (1988) showed interactive effects of exercise and CO exposure (>7% COHb) on cognitive tasks, Insogna and Warren (1984) demonstrated a significant decrement in video game performance (targets tracked and destroyed) at 2.1 to 4.2% COHb. (Both of these were single blind studies with relatively small numbers of subjects - 15 and 9, respectively). Although many earlier studies had demonstrated significant changes in brain electrical activity,

Harbin et al. (1988) showed no changes in visually evoked response potentials in young (23 yr) and older (69 yr) subjects at 5.3% COHb. In general, neurotoxicity at COHb levels near 5% has not been convincingly demonstrated in normal healthy adults (Benignus et al., 1987).

(xiii) Fetal developmental and perinatal effects

There are both theoretical reasons and supporting experimental data which indicate that the fetus may be more susceptible to the effects of CO than the mother. Fetal Hb has greater affinities for CO and O<sub>2</sub> than does maternal Hb. The partial pressure of O<sub>2</sub> in fetal blood is about 20 to 30% of that in maternal blood, because of the greater O<sub>2</sub> affinity of fetal Hb. In addition, COHb shifts the O<sub>2</sub>Hb dissociation curve to the left in maternal blood, reducing the transfer of O<sub>2</sub> across the placenta from maternal to fetal circulation. As in adults, the nervous and cardiovascular systems of the fetus are the most sensitive to the effects of CO. For humans, information is available for women who smoked during pregnancy or were acutely exposed to CO, however most of the available reports do not characterize the relevant CO exposure levels, and can not, in general rule out toxic effects of co-contaminants. Acute CO exposure plays a role in fetal death (Caravati et al., 1988) and environmental exposures, as well as maternal smoking, has been linked to sudden infant death syndrome (SIDS) (Hoppenbrouwers et al., 1981). Neonatal mortality and low birthweights are more prevalent in children born in high altitude regions (Lichty et al., 1957; Grahn and Kratchman, 1963), suggesting a relation to high altitude hypoxia, and further suggesting that these effects seen in children born to women who smoke are possibly a result of CO-induced hypoxia. The study of Ritz and Yu (1999) described earlier support the hypothesis that elevated CO during the last trimester of pregnancy increases the risk of low birthweight.

High level maternal CO exposures may have significant neurotoxicological consequences for the fetus, but available data come from animal studies. Significant neurotoxic effects in prenatally exposed rats included disruption of neuronal proliferation and possible disruption of markers of neurochemical transmission (Fechter, 1987). Immune system changes have also been

noted in rats exposed to CO prenatally (Giustino et al., 1993).

(xiv) CO as a risk factor in cardiovascular disease development

Evidence from population-based studies indicates that workers exposed to CO in combination with other combustion products from automobile exhaust (Stern et al., 1988) and other workers, as well (Kristensen, 1989) have increased risk of development of atherosclerotic heart disease. Also, individuals hospitalized for myocardial infarction frequently exhibit higher COHb concentrations than individuals hospitalized for other reasons (Leikin and Vogel, 1986). Central to the development of atheromatous plaques is the deposition and retention of fibrinogen and lipids within the arterial wall. It is known that cigarette smoke increases the permeability of the arterial wall to fibrinogen. Allen et al. (1989) demonstrated in a canine model that both CO and nicotine in cigarette smoke might produce an atherogenic effect, but that they act via different mechanisms. CO increases arterial wall permeability and nicotine reduces clearance of deposited fibrinogen. Activation and dysfunction of blood platelets is also thought to be important in atherogenesis (Ross, 1986) and in cardiac related sudden deaths due to the platelets role in the initiation of thrombosis. Nowak et al. (1987) reported biochemical evidence that cigarette smoking induced both platelet and vascular dysfunctions in apparently healthy individuals. Platelet dysfunction may also be a contributory cause of thrombosis during pregnancy and may increase fetal mortality and morbidity among women who smoke (Davis et al., 1987). Abnormalities in platelet aggregation after CO exposure have been seen in animal models (Kalmaz et al., 1980) and may be linked to guanylate cyclase activation (Brune and Ullrich, 1987). Davis et al. (1989) exposed 10 healthy nonsmokers passively to cigarette smoke (in hospital corridors) resulting in a small increase in COHb concentration, from  $0.9\% \pm 0.3\%$  to  $1.3 \pm 0.6\%$ , before and after passive exposure, respectively. They showed evidence of changes in platelet aggregation and endothelial cell damage. The changes in endothelial cell counts (pre- to post-exposure) were significantly correlated to changes in COHb concentrations from before to after exposure, but plasma nicotine levels were not. The

contribution of carbon monoxide relative to other components of tobacco smoke in causing platelet dysfunction is not established.

#### **A.5. SUMMARY AND CONCLUSIONS**

The current CO ambient air standards are designed to protect susceptible individuals from exposures that would result in COHb concentrations of 2.5% and above. Occupational standards are designed to protect workers from concentrations of 5% COHb (U.S. Department of Health, Education and Welfare, 1972). Studies of individuals with coronary artery disease, and residents of New York, NY, Denver, CO, Washington, DC and Los Angeles, CA suggest that susceptible individuals frequently exceed 2% COHb in cities that frequently exceed NAAQS or California standards. Control of exposures is difficult because the sources of CO are widespread, the distribution of ambient CO is very non-uniform, and because emissions from unregulated sources, especially indoors, probably contribute substantially to individual CO doses.

The current state and federal standards were based largely on data from susceptible adult populations. This review suggests that there are specific concerns for children.

Convincing documentation for effects of CO on children and other potentially susceptible individuals at ambient exposure levels is becoming available. The most extensive body of evidence of CO effects on pregnant women, fetuses and neonates comes from the literature on smoking and from acute, high-level accidental CO exposures. In most cases actual CO exposures are poorly, if at all, documented and the contribution of co-pollutants to the observed effects cannot be assessed. Animal studies demonstrating developmental changes and associations between environmental CO and SIDS indicate that risks to pregnant women, fetuses and neonates may be important. The recent human epidemiology study by Ritz and Yu (1999), which was discussed earlier, show significant low birthweights to children

born of women exposed at CO levels below the current standard (5.5 ppm and above).

Differences in body mass, activity levels and CO uptake may make children more at risk than adults. There are associations between CO exposure and asthma prevalence, but these could be confounded because in most instances CO is covariable with other products of combustion. One might also hypothesize that children with asthma or other inflammatory lung diseases could require lower exposures to CO to reach target concentrations of 2.5% COHb because their baseline COHb levels might be elevated.

It would seem from this review that both occupational and ambient standards are placed at the limits at which significant effects are seen, albeit in sensitive adults. The available information on the role of CO in the development of effects on children, including possible increased severity of asthma, low birthweight and a possible role in infant mortality suggests that children may be an important susceptible population. There are however several important gaps in our basic knowledge of the physiology and effects of disease states on baseline COHb in children and on the affinity of fetal and children's hemoglobin for CO. In addition, new, well-controlled population studies, with accurate estimates of CO exposure history are needed. Careful clinical studies with children to determine uptake and retention of CO and how these change with age would be extremely helpful.

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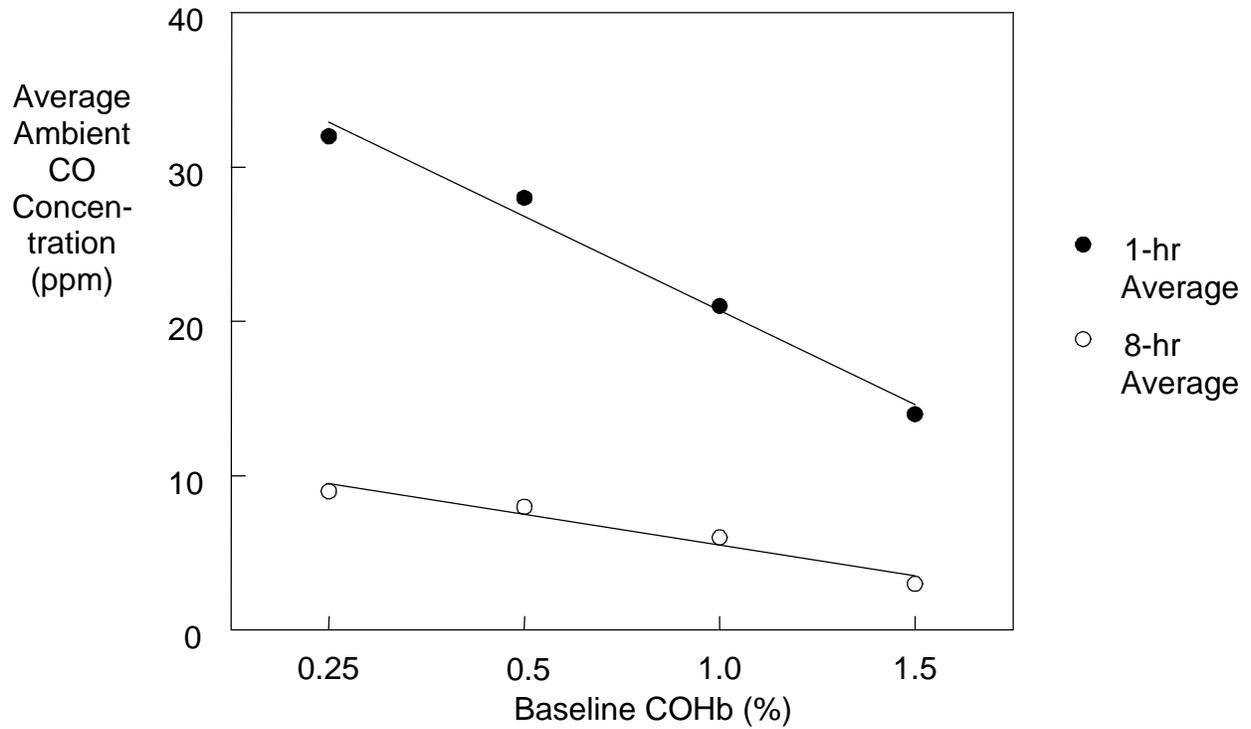
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Figure 1. Increasing baseline COHb will reduce the time-weighted average CO concentration required to reach 2.5% COHb after a given exposure.



**Figure 2. Reduction in Time to Angina (TTA) Following CO Exposure in Subjects with Coronary Artery Disease. Linear regression shows that TTA is reduced in a dose-dependent Manner. Values shown are mean  $\pm$  SE.**

