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CARBON MONOXIDE

David B. Coultas, M.D.
William E. Lambert, Ph.D.

Carbon monoxide (CO) is a colorless, odorless gas produced by incomplete combustion of carbonaceous fuels such as wood, gasoline, and natural gas (National Research Council [NRC] 1977). Inhalation of CO, because of its marked affinity for hemoglobin, impairs oxygen transport and often manifests as adverse effects in the cardiovascular system and in the central nervous system. The severity of the health effects increases with the level and duration of exposure to CO.

Exposure to CO may be from outdoor and indoor sources with levels of exposure that vary widely from low concentrations with subtle effects to higher levels and acute poisoning. Although only few data are available on the overall public health impact of CO, it is a public health concern because of its many sources. In the United States, CO is a leading cause of death from poisoning (U.S. Department of Health and Human Services [DHHS] 1987), with an estimated 1,800 accidental deaths annually (U.S. Public Health Service [PHS] 1982). Many of these deaths have been associated with extreme exposures in indoor residential settings caused by faulty or improperly vented combustion appliances. The health effects of low-level exposures to CO are also considered an important public health problem because of the large population at risk.

In this chapter we review exposure to CO as an indoor air pollutant. However, since health data based directly on indoor exposures are limited, we have included information from outdoor exposures or experimental exposures which reflects levels of CO that may be found indoors. The pathophysiology of CO is presented in the first section. This is followed by a description of the sources and levels of exposure to CO. Finally, manifestations of CO intoxication and the health effects of exposures to low levels of CO are reviewed.

PATHOPHYSIOLOGY OF CO EXPOSURE

In its acute toxic action, CO can be conceptualized as an antimetabolite of oxygen. Inhaled CO binds strongly to hemoglobin in the pulmonary capillary bed; the resulting complex is called carboxyhemoglobin (COHb). The rate of absorption of CO is dependent on ventilatory volume, the hemoglobin content of the blood, the rate of diffusion across the alveolar membrane, the mean pulmonary capillary oxygen tension, and COHb levels in the pulmonary capillaries (Coburn, Forster, and Kane 1965). CO binds to hemoglobin with more than two hundred times the affinity of oxygen, thus effectively outcompeting oxygen for available binding sites on the heme groups. The health consequences of this binding are twofold. First, the oxygen-carrying capacity of the blood is directly reduced; and second, CO bound to one heme subunit induces an allosteric change that slows the dissociation of oxygen bound to any of the three other heme sites on the hemoglobin protein (Stryer 1975). Thus, the absolute oxygen-carrying capacity is reduced by displacement, and lower oxygen tensions are required to release oxygen bound to the hemoglobin (Figure 8.1). This leftward shift of the oxyhemoglobin dissociation curve is physiologically significant and explains the hypoxic differential between simple anemia and the equivalent percentage of COHb (Roughton and Darling 1944; Collier 1976).

In addition to the leftward shift of the oxyhemoglobin dissociation curve, several additional mechanisms of toxicity have been postulated. Ultimately, each is based upon competitive binding interactions and includes the binding of CO to heme proteins including myoglobin, cytochrome oxidase, tryptophan deoxygenase, and tryptophan catalase (Coburn 1979). For example, CO bound to myoglobin in the cardiac muscle could impair oxygen delivery to intracellular contractile processes. In the heart, the marked oxygen gradient from coronary blood to myocardial cells and the low tissue and intracellular oxygen tensions may promote significant CO binding even at relatively low blood COHb levels (Wittenberg 1970); however, experimental data are incomplete. The brain and spinal cord, another sensitive organ system, may be affected similarly.

Within the mitochondria, CO bound to cytochrome oxidase can be expected to interfere with electron transport. Flavoprotein prosthetic groups of the cytochrome enzymes contain iron in a porphyrin configuration that resembles hemoglobin. CO bound to cytochrome oxidase, the terminal oxidase in the system, would prevent the phosphorylation of adenosine diphosphate (ADP). Coburn (1979) observed that increased metabolism may reduce intracellular oxygen tensions and thereby promote CO binding although the affinity of CO for cytochrome oxidase is low at typical physiologic oxygen tensions. Although theoretically plausible, the experimental evidence to support this hypothesis remains limited.

It has been postulated that chronic exposure to CO may accelerate atherosclerotic processes by affecting cholesterol uptake in the arterial wall. Results from animal studies and *in vitro* data are conflicting (Astrup, Kjeldsen, and Wanstrup 1970; Theodore, O'Donnell, and Back 1971; Sarma et al. 1975; Armitage, Davies

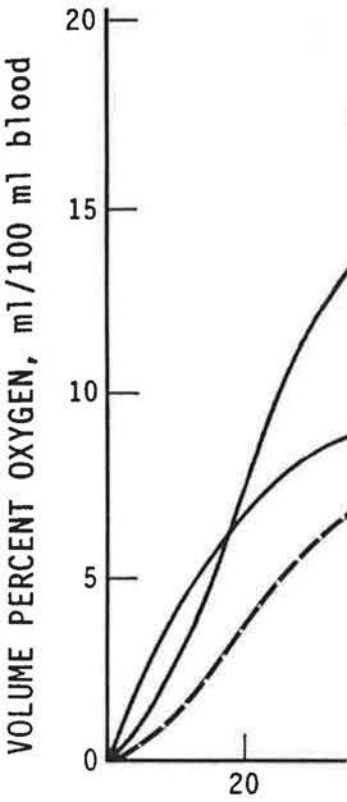

Figure 8.1. Oxyhemoglobin dissociati
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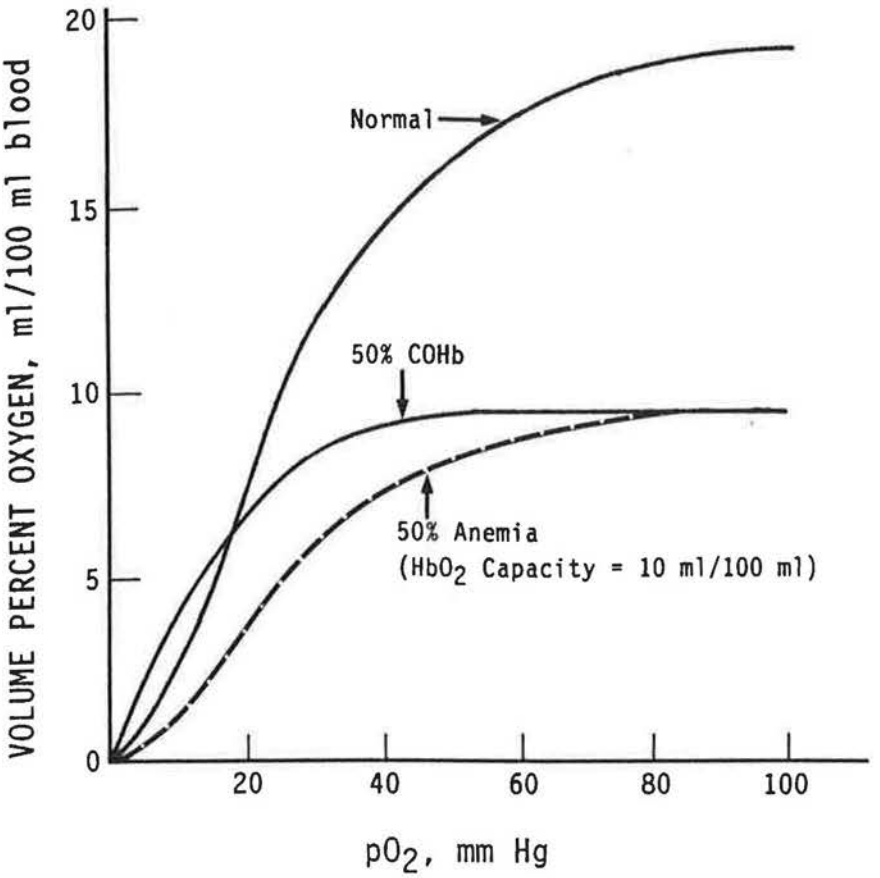

Figure 8.1. Oxyhemoglobin dissociation curves of normal human blood, of blood containing 50 percent COHb, and of blood with a 50 percent normal hemoglobin concentration due to anemia. *Source:* Reprinted from *Carbon Monoxide*, 1977, with permission from the National Academy of Sciences, Washington, D.C. (NRC, 1977).

and Turner 1976). Confident interpretation of this research is hampered by the high CO exposures and high dietary cholesterol employed in the animal studies and the methodologic difficulties in quantifying morphologic changes in the vessel walls. Limited evidence suggests that CO may accelerate clot lysis time (El-Attar and Sairo 1968) and may increase platelet activity and coagulation (Haft 1979). These alterations in the fibrinolytic system imply that CO could potentially increase risk for thromboembolism in the heart or brain.

SOURCES AND LEVELS OF EXPOSURE

There are many opportunities for exposure to CO in indoor environments because of the combustion sources placed or used in these settings. Approximately 47 percent of residences in the United States have gas ranges (U.S. Bureau of the Census 1983), a typically unvented source of combustion emissions. Another important unvented source is the kerosene or gas space heater, used in approximately seven percent of U.S. households (Cooper and Alberti 1984). Vented gas appliances, such as furnaces, water heaters, and clothes dryers, can emit CO into the indoor environment if not properly installed or maintained (Wharton et al. 1989). Similarly, improper use of charcoal cookers, wood-burning stoves or fireplaces, and gasoline engines can inject CO and other pollutants into the indoors. Intensive tobacco smoking in indoor locations may also result in CO buildup. The concentrations resulting from these sources are usually far below those that cause acute poisoning; however, the exposures may still be high enough to affect the blood, heart, and nervous systems adversely. In this section, poisonings and high-level exposure situations are discussed followed by presentation of low-level urban exposures in indoor settings.

ACUTE EXPOSURES AND POISONINGS

Investigations into the cause of poisoning accidents provide a *post facto* measure of the CO exposures experienced by the victims. Caplan et al. (1986) reported indoor residential CO concentrations ranging from 100 to 400 ppm. Invariably, evidence of a malfunctioning combustion appliance or tampering and misuse was discovered. Use of a gas range or oven for space heating may result in elevated indoor CO levels (Sterling, Dimich, and Kobayashi 1981) and predict symptomatic CO poisoning (Heckerling et al. 1987).

The U.S. Consumer Product Safety Commission (U.S. CPSC) estimates that 7.6 million unvented gas space heaters are in use in the United States, and directly attributes seventy deaths during 1980 to CO exposures resulting from the use of these heating devices in confined spaces (CPSC 1980). Although no measurements of the CO levels in these accidents were reported, it is known that kerosene space heater emissions are capable of increasing indoor CO concentrations to levels exceeding the eight-hour 9 ppm national primary ambient air quality standard (Cooper and Alberti 1984).

The elevated indoor CO concentrations causing poisonings may be expected to occur more often in the cold seasons when heating sources are in use and homes are kept closed to prevent heat loss. Indeed, CO poisonings in Korean residences were strongly correlated with ambient temperature, a surrogate measure of heating (Kim 1985). Many Korean homes are heated by a traditional system of charcoal briquets placed in pails beneath the flooring of the house. Carbon monoxide concentrations have not been reported for Korean homes. In the United States, poisonings associated with space heating are expected to occur more frequently in the winter. However, summertime poisonings associated with exposures in con-

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LOW-LEVEL URBAN EXPOSURES

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Stores and service esta
Restaurants
Outdoor
Near active roadways
Away from roadways, pa
In transit
In vehicle
Walking or on bicycle

Soruce: Adapted from Akland e

fined spaces can occur. These poisonings can be caused by the use of gas-fueled campstoves, lamps, and lanterns, radiant heaters, and electric generators in or near tents and recreational vehicles (New Mexico Environmental Improvement Agency 1977; Hopkinson, Pearce, and Oliver 1980). Spengler and Cohen (1985) estimated that CO levels as high as 100 ppm could accumulate in tents during gas campstove use.

LOW-LEVEL URBAN EXPOSURES

Substantial data are available on exposures of urban dwellers to CO in the course of their daily activities. The locations generally making the largest contributions to personal exposure are the auto and residence, but industrial buildings and commercial, institutional, and public buildings are frequent contributors. Early attempts at exposure assessment focused largely on vehicular and occupational exposures, but recent advances in instrumentation for exposure monitoring have facilitated monitoring large numbers of urban residents from population-based samples. Using this type of instrumentation, the U.S. Environmental Protection Agency has conducted studies of personal exposure of five hundred residents of Denver, Colorado, and of Washington, D.C. (Table 8.1) (Akland et al. 1985).

Exposures occurring in automobiles and outdoor settings provide an important reference against which indoor exposures may be compared. In fact, personal monitoring studies indicate that in the total daily exposure profile of urban residents, the highest exposures occur during commuting and when near active internal combustion engines (Akland et al. 1985). In-transit exposures average 5 ppm, and residents of Washington, D.C., and Denver were observed to spend an average of two hours per day in an automobile or bus or on a bicycle. Peak

Table 8.1 Range of Mean Concentrations Observed in Major Urban Environments in the Denver, Colorado, and Washington, D.C., CO Exposure Studies

Environmental Setting	Mean CO Concentration (ppm)
Indoor	
Residential	1.2–1.7
Public buildings	
Park garages and automobile service facilities	10.4–18.8
Stores and service establishments	2.5–3.0
Restaurants	2.1–4.2
Outdoor	
Near active roadways	2.6–3.8
Away from roadways, parks	<1.0
In transit	
In vehicle	3.6–8.0
Walking or on bicycle	2.4–4.2

Soruce: Adapted from Akland et al. (1985), with permission.

exposures of automobile occupants in heavy traffic may attain 50 ppm and average 10–12 ppm (Cortese and Spengler 1976; Flachsbart et al. 1987). Outdoor exposures to CO experienced near roadways and parking areas average 3–4 ppm (Hartwell et al. 1984).

Indoor exposures in residences and public places are generally low (Table 8.1). In the absence of indoor sources, mean indoor CO levels are usually equal to outdoor concentrations. If strong indoor sources are present, however, indoor levels can be severalfold higher than those outside the building. Because CO is an essentially nonreactive gas, removal by ventilation to outside air is the usual route of elimination from the indoor environment. Therefore, in buildings with low ventilation rates, CO may be retained near occupants for extended periods. Residential exposures in Washington, D.C., and Denver during the winter of 1982–83 averaged less than 2 ppm (Hartwell et al. 1984; Johnson 1984; Akland et al. 1985). In Washington, D.C., no significant difference was observed between mean CO levels in residences with an unvented gas stove and in residences with no gas stove when mean levels were integrated over total time spent indoors in the residence (Akland et al. 1985). However, mean personal exposure during cooking activities with a gas stove was higher than those experienced with an electric range and averaged 3 ppm (Hartwell et al. 1984). Similarly, mean hourly CO levels in the kitchens and living rooms of Dutch homes in which unvented gas stoves and infusion water heaters were in use ranged from 1 to 40 ppm, with mean levels of 1–3 ppm (Lebret 1985); however, anecdotal accounts of exposures experienced during the use of gas stoves for space heating describe indoor concentrations ranging from 25 to 50 ppm (Coburn 1979). In general, cigarette smoking contributes little to indoor CO levels (Sterling, Dimich, and Kobayashi 1982; Lebret 1985).

Exposures to CO in public buildings averaged 2–4 ppm in the Washington, D.C., and Denver studies (Akland et al. 1985). Highest mean personal exposures were observed in indoor parking garage locations and averaged 10–18 ppm. Average personal exposures in restaurants averaged 2–4 ppm, and stores and shopping malls averaged 2–3 ppm. Higher indoor levels, averaging 12 ppm and exceeding the eight-hour federal standard of 9 ppm, have been measured in a Honolulu shopping mall with an attached garage (Flachsbart and Brown 1985); this result has important implications for employees and shoppers who spend long periods of time in malls of this architectural design. Some office building settings have been associated with chronically high CO levels. Workers in an underground office located on the same level as an enclosed parking garage experienced mean exposures in the range of 12–22 ppm, with peak exposures to 34 ppm (Wallace 1983). Proper use of garage fans and closure of fire doors leading to the parking garage lowered office concentrations to 5 ppm. Thus, indoor CO levels may accumulate if ventilation systems are operated at low flow rates to reduce energy costs.

Indoor exposures to CO, included under the larger classification of urban exposure, may also be evaluated in terms of the resulting COHb levels. As part of the

1976–80 National Health and I
blood samples were analyzed for
graphic and personal characteris
COHb concentration in never sm
urban areas was 1.25 percent.
levels greater than 2.5 percent;
identified. Children aged three to
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1976–80 National Health and Nutrition Examination Survey, more than 8,000 blood samples were analyzed for COHb content and classified according to demographic and personal characteristics (Radford and Drizd 1982). Wintertime mean COHb concentration in never smokers aged twelve to seventy-four years living in urban areas was 1.25 percent. More than 4 percent of nonsmoking adults had levels greater than 2.5 percent; however, the source of exposure could not be identified. Children aged three to eleven years, considered to represent a group not exposed from occupational sources and personal tobacco use, had mean COHb levels of 1.01 percent during the winter months; however, their exposures during transportation may be lower than those of adults. Wintertime COHb levels were substantially higher in the three- to eleven-year-old subgroup than in the adult group; 3.3 percent of the children had a COHb level in excess of 2.5 percent. These results, when extrapolated to the nonsmoking adult population, indicate that 3–4 percent of the population may be exposed during the winter to CO levels exceeding the 9 ppm eight-hour and the 35 ppm one-hour standard assigned to keep COHb levels from rising above 1.5 percent.

Only two studies relate specific indoor exposures with COHb levels. In each study, COHb levels were estimated by measuring CO concentrations in samples of end-expired breath. This methodology is reviewed by Lambert, Colome, and Wojciechowski (1988). In Dutch homes, Verhoeff et al. (1983) observed a small but significant increase in breath CO after occupants used infusion water heaters. Wallace (1983) observed increases in breath CO levels of office workers exposed to motor vehicle exhaust.

HEALTH EFFECTS OF EXPOSURE

The health effects of CO have been described through clinical observations of patients with CO intoxication and experimental and epidemiologic investigations of persons exposed to low levels of CO. The health effects of CO vary with the level of COHb (Table 8.2) and range from nonspecific symptoms, headache, dizziness, and fatigue, to death (Winter and Miller 1976). CO poisoning, resulting in death, has been recognized since the nineteenth century (Winter and Miller 1976), but the adverse consequences of exposure to low levels of CO have only recently received attention.

Because of the adverse effects of CO on oxygen delivery to tissues, individuals with a need for high oxygen consumption or who have preexisting disorders of oxygen delivery may be highly sensitive to the effects of CO (Table 8.3). These considerations related to oxygen delivery suggest that the developing fetus (Longo 1977), the growing child (Zimmerman and Truxal 1981), and maximally exercising persons may be particularly susceptible to the effects of hypoxia from CO. Other groups that may be unusually sensitive to the adverse consequences of CO include those with chronic hypoxemia, cardiovascular disease, and hemoglobin abnormalities.

Table 8.2 Health Effects Associated with Different Carboxyhemoglobin Levels

COHb (%)	Symptoms
10	No appreciable effect except shortness of breath on vigorous exertion; possible tightness across the forehead; dilatation of cutaneous blood vessels
20	Shortness of breath on moderate exertion; occasional headache with throbbing in temples
30	Decided headache; irritable; easily fatigued; judgment disturbed; possible dizziness; dimness of vision
40–50	Headache; confusion; collapse; fainting on exertion
60–70	Unconsciousness; intermittent convulsions; respiratory failure; death if exposure is continued for long
80	Rapidly fatal

Source: Winter and Miller (1976), reprinted with the permission of the American Medical Association.

Table 8.3 Conditions That Potentially Increase Susceptibility to Adverse Effects of CO

Fetal development
Children
Chronic hypoxemia
High altitude
Chronic lung disease
Right-to-left shunts
Impaired cardiac output
Cardiomyopathy
Valvular heart disease
Vascular disease
Atherosclerotic heart disease
Cerebrovascular disease
Peripheral vascular disease
Hemoglobin abnormalities
Anemia
Hemoglobinopathy

CO INTOXICATION

Intoxication from CO may be acute or chronic, depending upon concentration and duration of exposure. Generally, clinically apparent problems with acute exposures appear at COHb levels of 10 percent or greater (Table 8.2). However, the severity of symptoms may not correlate well with COHb levels (Sokal and Kralkowska 1985, Kirkpatrick 1987). Furthermore, because of its nonspecific picture, intoxication may be frequently overlooked (Dolan 1985; Barret, Danel, and Faure 1985).

To determine the frequency of misdiagnosis of CO poisoning, Barret, Danel, and Faure (1985) reviewed records from 340 patients with CO poisoning admitted

to a toxicology service in Fra
were initially misdiagnosed.
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Unexplained
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Unexplained

[a]May vary dep
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to a toxicology service in France. Between 1975 and 1977, 30 percent of patients were initially misdiagnosed. The initial diagnoses included food poisoning, neuropsychiatric problems, cardiac disorders, and other intoxications. Food poisoning was the most frequent incorrect diagnosis.

The clinical history and physical examination may suggest the diagnosis of CO intoxication (Table 8.4). However, because the presenting problems of CO poisoning are nonspecific, only a high index of suspicion will result in the correct diagnosis (Hopkinson, Pearce, and Oliver 1980; Heckerling et al. 1987; Kirkpatrick 1987). The history of a potential source of exposure (Heckerling et al. 1987) or the finding of retinal hemorrhages (Kelley and Sophocleus 1978) may provide the first clues to the correct diagnosis. Furthermore, the identification of an index case of CO poisoning should alert the clinician to other potential cases (Wharton et al. 1989).

CO is currently the only air pollutant with a specific and clinically relevant biologic marker, COHb. However, the COHb level may not strongly predict the severity of intoxication, and the duration of exposure may be a better predictor (Sokal and Kralkowska 1985). In a study of thirty-nine patients with CO poisoning, Sokal and Kralkowska (1985) found that the mean duration of exposure was about nine hours among those with clinically severe poisoning, compared with five hours among those with mild to moderate poisoning. There were only slight differences in the COHb levels between the two groups of patients.

CO intoxication, especially with prolonged high levels of COHb, may affect every organ system (Table 8.5). Most complications of CO poisoning are a direct result of tissue hypoxia, and the presence of these complications may provide the first alert to the clinician of possible CO intoxication. For example, an unexplained

Table 8.4 Clinical Findings That Suggest the Possibility of CO Poisoning

History
Exposure to potential source of CO
Nonspecific symptoms (e.g., headache, dizziness, fatigue, nausea, vomiting)
Household members or co-workers with similar symptoms
Unexplained illness/death among household pets
Physical exam
Retinal hemorrhage
Unexplained coma
Unexplained cardiac arrhythmias
Laboratory
COHb $\geq 10\%$[a] in a nonsmoker
Unexplained lactic acidosis

[a]May vary depending upon the chronicity and level of exposure and on the time at which the specimen is drawn in relation to the exposure.

Table 8.5 Complications of CO Poisoning

Organ System	Complication
Cardiac	Myocardial ischemia, arrhythmias, angina
Pulmonary	Pulmonary edema, hemorrhage
Muscular	Myonecrosis, compartment syndrome
Renal	Myglobinuria, acute renal failure
Neurologic	Seizure, encephalopathy, cerebral edema
Ophthalmologic	Retinal hemorrhage, visual defect
Cutaneous	Erythema, listers, bullae
Vestibular/auditory	Vertigo, nystagmus, hearing loss, tinnitus
Hematologic	Thrombotic thrombocytopenic purpura
Fetal	Death, neurologic sequelae

[a]*Source*: Adapted from Zimmerman and Truxal (1981), with permission.

lactic acidosis strongly suggests CO poisoning (Sokal and Kralkowska 1985).

Although most patients with CO poisoning recover completely, some develop delayed neurologic complications. These problems, which include headache, memory loss, disorientation, hallucinations, apraxia, and aphasia, appear days to weeks after apparent recovery from an acute exposure (Werner et al. 1985). Among patients who develop these delayed neurologic problems, areas of brain necrosis have been demonstrated by magnetic resonance imaging (Horowitz, Kaplan, and Sarpel 1987).

The immediate therapeutic goal in CO poisoning is reversal of the tissue hypoxia (Winter and Miller 1976). As soon as the diagnosis is considered, 100 percent oxygen should be administered. This will increase the dissolved oxygen in plasma and shorten the half-life of COHb. For severe cases, hyperbaric oxygen treatment may be necessary.

LOW-LEVEL EXPOSURE

The health effects of low levels of CO exposure have been examined with two types of investigations: laboratory studies involving short-term exposure, and population studies. The major health outcomes that have been studied include effects on the fetus, on neurobehavioral mechanisms, and on exercise in normal subjects and in patients with coronary artery disease, peripheral vascular disease, and chronic lung disease. For all of these problems we primarily consider information on indoor exposures but include results based on outdoor exposures if indoor data are limited. Similarly, we review relevant data from animal studies only if human data are unavailable.

Effects on the Fetus Because of the adverse consequences of cigarette smoking on the fetus (U.S. Department of Health, Education, and Welfare [DHEW] 1979), researchers have hypothesized that CO may be the component of cigarette smoke which causes the adverse effects (Longo 1977). Animal experiments have been

conducted in an attempt to isolate
effects of CO on the fetus (Astru
Scott 1984).

In animal experiments, the e
cigarette smoking rather than exp
ments have involved exposures
levels of 4–18 percent (Astrup
Scott 1984). At the lowest level
pregnant rats from day 3 to day 2
4.8 percent. The animals were ki
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For humans, few data are avail
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Animal experiments have been

conducted in an attempt to isolate from the other components of tobacco smoke the effects of CO on the fetus (Astrup et al. 1972; Garvey and Longo 1978; Singh and Scott 1984).

In animal experiments, the exposures have been designed to simulate active cigarette smoking rather than exposures to lower levels of CO. Most of the experiments have involved exposures to CO levels of 30–500 ppm, resulting in COHb levels of 4–18 percent (Astrup et al. 1972; Garvey and Longo 1978; Singh and Scott 1984). At the lowest level of 30 ppm, Garvey and Longo (1978) exposed pregnant rats from day 3 to day 20 of gestation, resulting in a mean COHb level of 4.8 percent. The animals were killed, and the percentage of successful pregnancies in the exposed group was 69 percent compared with 100 percent in the unexposed. Other investigators have shown lower birth weight and increased fetal and neonatal mortality at higher levels of exposure (Astrup et al. 1972; Singh and Scott 1984).

For humans, few data are available on fetal and neonatal morbidity and mortality from exposure to CO indoors or outdoors. Alderman, Baron, and Savitz (1987) conducted a case-control study of birth weight and maternal exposure to neighborhood CO during the last three months of gestation. The series included 998 low–birth weight infants (2,500 g or less) and 1,872 normal–birth weight infants from Denver. They used ambient CO levels from stationary monitors to categorize the mother's exposure. For the mothers whose CO exposures were considered most accurate, the odds ratio for having a low–birth weight baby was 1.5 (95 percent confidence interval, 0.7–3.5) for an ambient CO level of 3 ppm or greater compared with lower levels. This finding is limited by the lack of personal smoking histories and personal exposure measurements.

Neurobehavioral Effects To determine the effects of low levels of CO on the central nervous system, investigators have assessed effects in normal volunteers (Table 8.6), including effects on visual perception (Halperin et al. 1959; Hosko 1970; Stewart et al. 1970; Horvath, Dahms, and O'Hanlon 1971; Luria and McKay 1979), on auditory perception (Beard and Wertheim 1967; Wright and Shephard 1978), on manual dexterity (Stewart et al. 1970; McFarland 1973), and on vigilance (Benignus et al. 1977). The results from these investigations have been inconsistent (Benignus et al. 1977; Luria and McKay 1979). Potential reasons for the varied findings include small numbers of subjects and different study designs. Despite the inconsistent results, clinically important neurobehavioral effects in normal subjects are not a major concern with COHb levels below 10–20 percent.

Effects on Exercise Performance in Normal Subjects As in the studies of the neurobehavioral effects of CO, researchers have exposed normal volunteers to CO and then tested its influence on exercise performance (Table 8.7). At COHb levels of 5 percent or less, maximal exercise time and maximal oxygen consumption have generally decreased among healthy subjects compared with preexposure exercise

Table 8.7 Selected Experimental Studies of Normal Human Volunteers on the Effects of Low Levels of CO on Exercise Performance

Reference	Subjects/Exercise	Exposure	Mean COHb (%)	Findings
Chevalier, Krumholz, and Ross (1966)	10 nonsmokers, mean age 30 years; bicycle ergometer for 5 min with a mean $\dot{V}o_{2\,max}$ of 1.8 l/min	2.5–3.5 min of 0.5% CO	3.95 ± 1.87[a]	Oxygen debt and ratio of oxygen debt to total oxygen uptake increased 12.0 and 14%, respectively, compared with no exposure
Drinkwater et al. (1974)	20 normal males, 10 nonsmokers, and 10 smokers; treadmill exercise to exhaustion	Double-blind: Filtered air 50 ppm CO 0.27 ppm PAN[b] CO + PAN	2.5 ± 0.30	5% decrement in mean total walking time and 1.9% decrement in $\dot{V}o_{2\,max}$ for nonsmokers with CO exposure but no decrement among smokers
Aronow and Cassidy (1975)	9 males, 1 female, normal nonsmokers, with mean age 50.7; treadmill exercise to exhaustion	Double-blind, 100 ppm CO for 1 h	3.95 ± 0.49	Mean exercise time decreased 5%
Horvath et al. (1975)	4 healthy males, 24–33 years, 1 pipe smoker; treadmill exercise to exhaustion	Single-blind: Filtered air 75 ppm CO 100 ppm CO delivered by a bolus method or gradual increments on two occasions	3.18–3.35 4.25–4.30	Regardless of delivery mode, $\dot{V}o_{2\,max}$ decreased 4.9 and 7.0% at the low and high exposures, respectively
Weiser et al. (1978)	9 male nonsmokers, mean age 24.7 years; treadmill exercise to exhaustion at altitude of 1,610 m	Double-blind: Filtered air CO bolus and rebreathing to achieve 5% COHb	5.09 ± 0.11	With CO exposure, total exercise time decreased 3.8%, total work decreased 10.0%, and $\dot{V}o_{2\,max}$ decreased 3.5%
Horvath et al. (1988)	11 males and 12 women nonsmokers; exercised to maximal aerobic capacity at simulated altitudes of 55, 1,524, 2,134, and 3,048 m	Double-blind: 0 ppm CO 50 ppm CO 100 ppm CO 150 ppm CO	Not provided	CO and altitude at ≥2,134 m decreased $\dot{V}o_{2\,max}$, but COHb did not result in an additional decline at a given altitude

[a]Calculated COHb level from alveolar gas.
[b]PAN, peroxyacetyl nitrate.

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Weiser et al. (1978)	9 male nonsmokers, mean age 24.7 years; treadmill exercise to exhaustion at altitude of 1,610 m	Double-blind: Filtered air CO bolus and rebreathing to achieve 5% COHb	5.09 ± 0.11	With CO exposure, total exercise time decreased 3.8%, total work decreased 10.0%, and $\dot{V}o_{2\,max}$ decreased 3.5%
Horvath et al. (1988)	11 males and 12 women nonsmokers; exercised to maximal aerobic capacity at simulated altitudes of 55, 1,524, 2,134, and 3,048 m	Double-blind: 0 ppm CO 50 ppm CO 100 ppm CO 150 ppm CO	Not provided	CO and altitude at ≥2,134 m decreased $\dot{V}o_{2\,max}$, but COHb did not result in an additional decline at a given altitude

[a]Calculated COHb level from alveolar gas.
[b]PAN, peroxyacetyl nitrate.

tests. Most exposures have been at sea level, but no additional decrements in exercise performance have been found with CO exposure at higher altitudes (Weiser et al. 1978; Horvath et al. 1988).

Experimental Studies of Effects on Patients with Cardiovascular and Peripheral Vascular Disease Since the early 1970s, numerous investigations studies have been conducted to examine the effects of exposure to low levels of CO on exercise tolerance in patients with vascular disease (Table 8.8). The results of most of these studies have indicated that patients with vascular disease have earlier onset of angina or claudication at COHb levels between about 2 and 5 percent. Although the validity of the investigations conducted by Aronow and his co-workers (1972, 1973, 1974, 1975; Aronow 1981) has been questioned (Budiansky 1983), subsequent investigations have obtained similar results to those reported by Aronow and his co-workers (Table 8.8).

Kleinman and Whittenberger (1989) reported that the exercise tolerance of twenty-four men with reproducible angina was reduced 5.8 percent, and maximal oxygen uptake was decreased 2.2 percent after exposure to 100 ppm for two hours. In a multicenter study (Warren et al. 1989), sixty-three men with reproducible angina and electrocardiographic (ECG) changes indicative of myocardial ischemia were studied at two levels of exposure sufficient to result in COHb levels of 2 and 4 percent. Relative to filtered air, mean time to onset of angina was reduced 4 and 7 percent, respectively. ECG changes preceded angina, and the time to onset of ST segment depression was reduced by 5 and 12 percent, respectively.

Effects on Patients with Chronic Lung Disease The available literature concerning the effects of CO on patients with chronic obstructive lung disease is limited and does not provide definite conclusions (Aronow, Ferlinz, and Glauser 1977; Calverley, Leggett, and Flenley 1981). Calverley, Leggett, and Flenley (1981) studied fifteen patients with severe chronic obstructive pulmonary disease, mean FEV_1 of 0.56 liters, and measured the distances walked during a series of twelve-minute walks after breathing air, 2 liters of oxygen, air, and 0.02 percent CO per minute; and 2 liters of oxygen and 0.02 percent CO per minute. The mean increase in COHb was 9.2 percent, which resulted in a mean decrease of 43 m in the walking distance after breathing air and CO. However, since the CO exposures were always last, the decrease in exercise time may have resulted from fatigue.

Epidemiologic Studies of Effects on Patients with Cardiorespiratory Disease Several investigations have been conducted to examine the relationship between ambient CO levels and cardiorespiratory effects (Cohen, Deane, and Goldsmith 1969; Hexter and Goldsmith 1971; Kuller et al. 1975; Kurt, Mogielnicki, and Chandler 1978; Kurt et al. 1979). The health effects that have been examined have ranged from emergency room visits for dyspnea and nontraumatic chest pain to mortality from myocardial infarction. Most of these studies found an association between outdoor measurements of CO and adverse health outcomes.

Table 8.8 Selected Experimental Studies of the Effects of Low Levels of CO Exposure on Patients with Atherosclerotic Heart Disease

Reference	Subjects/Exposure	Exposure	Mean COHb (%)	Findings
Anderson et al. (1973)	10 males with stable angina, 5 were smokers, mean age 49.9 years, incremental treadmill exercise until onset of angina	Double-blind exposure to room air, 50 or 100 ppm CO for 4 h prior to exercise	50 ppm = 2.9 ± 0.70, 100 ppm = 4.5 ± 0.80	Mean time to onset of angina was reduced 15% with exposure to both concentrations of CO; duration of pain was prolonged with 100 ppm CO; ST segment depression appeared earlier and was deeper with CO exposure; no difference between smokers and nonsmokers
Aronow et al. (1972)	10 males with angina, 3 were smokers, mean age 48 years; bicycle ergometer exercise until onset of angina	Driven in an open car on Los Angeles freeway for 90 min during traffic; mean CO level in the car was 53 ± 6 ppm. On a second day subjects breathed compressed air during the drive	5.08 ± 1.19	Mean exercise time was decreased 75 s after exposure to freeway air, and decreased exercise time persisted for 2 h after the exposure compared with base line or while breathing compressed air
Aronow and Isbell (1973)	10 males with angina, nonsmokers; bicycle ergometer exercise until onset of angina	Double-blind exposure to air or 50 ppm CO for 2 hours	2.68 ± 0.15	Mean exercise time decreased 37 s with CO exposure compared with air
Aronow et al. (1974)	10 males with intermittent claudication, confirmed angiographically	Double-blind exposure to compressed air or 50 ppm CO for 2 h	2.8 ± 0.19	Mean exercise time decreased 30 s with CO exposure compared with air
Aronow (1981)	15 subjects with stable angina, 14 males, 1 female, nonsmokers; bicycle ergometer exercise until onset of angina	Double-blind exposure to air or 50 ppm CO for 1 h	2.02 ± 0.16	Mean exercise time was decreased 33 s with CO exposure compared with air
Sheps (1985)	30 subjects with ischemic heart disease, nonsmokers; type of exercise unknown	Double-blind exposure to air or 100 ppm CO on successive days	4.1 ± 0.10	No effect on time to onset of angina or change in cardiac function with CO exposure
Adams et al. (1987)	30 subjects with ischemic heart disease; type of exercise unknown	Double-blind exposure to air or CO	5.9 ± 0.10	Mean exercise duration decreased 41 s with CO exposure compared with air; angina only occurred with CO exposure; left ventricular ejection frac-

	were smokers, mean age 48 years; bicycle ergometer exercise until onset of angina	Los Angeles freeway for 90 min during traffic; mean CO level in the car was 53 ± 6 ppm. On a second day subjects breathed compressed air during the drive		after exposure to freeway air, and decreased exercise time persisted for 2 h after the exposure compared with base line or while breathing compressed air
Aronow and Isbell (1973)	10 males with angina, nonsmokers; bicycle ergometer exercise until onset of angina	Double-blind exposure to air or 50 ppm CO for 2 hours	2.68 ± 0.15	Mean exercise time decreased 37 s with CO exposure compared with air
Aronow et al. (1974)	10 males with intermittent claudication, confirmed angiographically	Double-blind exposure to compressed air or 50 ppm CO for 2 h	2.8 ± 0.19	Mean exercise time decreased 30 s with CO exposure compared with air
Aronow (1981)	15 subjects with stable angina, 14 males, 1 female, nonsmokers; bicycle ergometer exercise until onset of angina	Double-blind exposure to air or 50 ppm CO for 1 h	2.02 ± 0.16	Mean exercise time was decreased 33 s with CO exposure compared with air
Sheps (1985)	30 subjects with ischemic heart disease, nonsmokers; type of exercise unknown	Double-blind exposure to air or 100 ppm CO on successive days	4.1 ± 0.10	No effect on time to onset of angina or change in cardiac function with CO exposure
Adams et al. (1987)	30 subjects with ischemic heart disease; type of exercise unknown	Double-blind exposure to air or CO	5.9 ± 0.10	Mean exercise duration decreased 41 s with CO exposure compared with air; angina only occurred with CO exposure; left ventricular ejection fraction with exercise was less after CO exposure
Kleinman and Whittenberger (1989)	24 males with reproducible angina	Double-blind exposure to filtered air or to 100 ppm CO	2.9 ± 0.30	Mean exercise time decreased 5.8% and maximal oxygen uptake decreased 2.2% with CO exposure relative to air
Warren et al. (1989)	63 males, ages 35–75 with stable angina; treadmill exercise until onset of angina	Double-blind exposure to air and two levels of CO to achieve COHb of 2.2 and 4.4%	2.0 ± 0.10 3.9 ± 0.10	4.2 and 7.1% trimmed mean decrease in time to onset of angina at low and high exposures, respectively; 5.1 and 12.1% trimmed mean decreases in time to development of ischemic ST segment changes

However, because the ambient measures of exposure used in these studies may not have been representative of personal exposure to CO (Ott and Flachsbart 1982; Akland et al. 1985), these results must be interpreted carefully. Furthermore, exposure misclassification would tend to bias risk estimates downward, making it more difficult to observe an effect.

In contrast to community studies, occupational settings may provide better estimates of exposure to CO. Increased mortality from arteriosclerotic heart disease has been documented in an occupational environment with exposure to elevated levels of CO in an enclosed space (Stern et al. 1988). Among 5,529 New York City bridge and tunnel officers employed between 1952 and 1981, the overall mortality ratio for arteriosclerotic heart disease was 35 percent higher among tunnel workers compared with bridge workers; the former having the higher exposures to CO. The mortality ratio was highest (1.88) for tunnel workers employed for ten or more years. Differences in smoking habits were not sufficient to explain the differences in mortality.

SUMMARY

Numerous and varied types of observations have documented the adverse health effects of CO. For low levels of CO the effects have largely been studied experimentally with small numbers of subjects. However, these experiments may not provide an accurate description of the free-living environment with variations in exposure, in activity level, and in severity of disease. Nevertheless, the available data demonstrate that levels of COHb greater than 2 percent, which may result from exposure indoors, impair exercise capacity of patients with cardiopulmonary disease and of normal subjects at maximum exercise capacity. Furthermore, CO may exacerbate ischemic symptoms in patients with cardiovascular disease and may contribute to excess mortality. Because nonspecific symptoms result from CO at low or high levels of exposure, a high index of suspicion is necessary to make the diagnosis and to prevent further exposure.

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Since the early 1970s, use of wo
1981 approximately 7 percent
major or supplementary source
(Annandale, Duxbury, and New
significantly degraded ambient
notably in towns and cities pr
Denver, Colorado (Lewis and
1980). Research on wood comb
wood use, has provided inventor
but data needed for understandi
still lacking. Few investigations
quality have been performed, a
exposure to wood smoke remain

Wood is composed primarily
conditions with complete comb
primary end products. Nitrogen
oxides are primarily from the c
during high temperature combu
sulfur in the wood. Incomplete c
such as particulates, organic co
and carbon monoxide (CO) (Qu
are highly variable and depend o
for combustion, size of fuel ch
content of the wood (Quraishi 1

DeAngelis and colleagues (19
stoves (one baffled and one no