United States
Environmental Protection
Agency

Office of Health and
Environmental Assessment
Washington DC 20460

EPA/600/8-90/045A
March 1990
External Review Draft

Research and Development

EPA

Air Quality Criteria for Carbon Monoxide

Draft

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1. SUMMARY AND CONCLUSIONS

Carbon monoxide (CO) is a colorless, odorless gas. It is a trace constituent of the troposphere, produced by both natural processes and human activities. The major source of CO in urban areas is incompletely combusted fuels; two-thirds of total emissions are attributed to vehicle exhaust. The principal effect on humans inhaling CO-contaminated air is reduced transport of oxygen by the blood stream, a consequence of CO displacing oxygen in hemoglobin.

The Global Cycle of Carbon Monoxide

Limited data on global trends in tropospheric CO concentrations indicate a 1 to 2% annual increase over the last several decades. Global background concentrations fall in the range of 50 to 120 ppb; higher levels are found in the northern hemisphere, lower levels in the southern hemisphere. Average background concentrations fluctuate seasonally; higher levels occur in the winter months, lower levels in the summer months. About 60% of the CO in the non-urban troposphere is attributed to human activities, both directly from combustion processes, and indirectly through the oxidation of hydrocarbons and ammonia that, in turn, arise from agricultural activities, landfills, etc. Atmospheric reactions involving CO can produce O_3 in the troposphere. Other reactions may deplete concentrations of the hydroxyl radical ($OH^{\bullet}$), a key participant in the global removal cycles of many other natural and anthropogenic trace gases, thus possibly contributing to changes in atmospheric chemistry and, ultimately, global climate change.

Measurement Methods for Carbon Monoxide

The non-dispersive infrared (NDIR) optical transmission technique, the technique on which the EPA designated reference analytical method is based, is the only technique being used for compliance monitoring of CO. One category of NDIR monitor, the gas filter correlation (GFC) monitor, is currently the single most widely used NDIR-type analyzer for fixed-site monitoring stations. In general, NDIR monitors have significant advantages including small size, good sensitivity and specificity for CO, and reliability of operation under

typical network monitoring conditions. An associated recorder compiles and stores hourly averages for subsequent computer storage and analysis.

The recent development of small, portable electrochemical monitors has made possible the measurement of CO concentrations incurred by individuals as they move through numerous diverse indoor and outdoor microenvironments that cannot be monitored by fixed-site ambient stations. Such measurements show that some individuals can receive exposures significantly higher than would be inferred from a simple interpretation of data from local fixed-site stations.

Ambient Sources, Emissions and Concentrations of Carbon Monoxide

Current air quality standards define 1-hour and 8-hour average concentrations that should not be exceeded more than once per year. The 1-hour standard of 35 ppm is almost never exceeded in data reported from fixed-site monitoring stations. Concentrations of CO exceeding the 8-hour standard of 9 ppm have declined over the 10-year period 1979 to 1988 from an average of about ten per station per year to about two per year (U.S. Environmental Protection Agency, 1990). This decline reflects the efficacy of emission control systems on newer vehicles. In 1979, vehicular emissions of CO accounted for about 72% of total U. S. emissions; in 1988, it was 67%. During this same period, there was a 33% increase in highway vehicle miles traveled. The other categories of CO emissions are other fuel combustion sources, such as steam boilers (12%), industrial processes (8%), Solid waste disposal (3%), and miscellaneous other sources (10%).

Indoor Sources, Emissions, and Concentrations of Carbon Monoxide

EPA's mandate is to monitor and regulate pollutants in the ambient, i.e. outdoor, air; however, the great majority of people spend most of their time indoors, one place or another. A realistic assessment of ambient exposure to CO, therefore, must be set in the context of total exposure, a major component of which is exposure while indoors.

Indoor concentrations of CO are a function of outdoor concentrations, indoor sources, infiltration, ventilation and air mixing between and within rooms. In residences without sources, average CO concentrations are approximately equal to average outdoor levels.

Proximity to outdoor sources (e.g., heavily traveled roadways, attached garages, or parking garages) can have a major impact on indoor CO concentrations.

The extensive total personal CO exposure studies conducted by EPA in Washington, DC and Denver, CO (Akland et al., 1985; Whitmore et al., 1984; Hartwell et al., 1984; Johnson, 1984) have shown that the highest CO concentrations occur in indoor microenvironments associated with transportation sources. Concentrations in these environments frequently were found to exceed 9 ppm. Studies targeted toward specific indoor microenvironments have also identified the indoor commuting microenvironment as one in which CO concentrations frequently exceed 9 ppm and occasionally exceed 35 ppm. Similar concentrations have been reported in special environments or accompanying unusual occurrences (indoor ice skating rinks, offices where emissions from parking garages migrate indoors, etc.).

Unvented gas and kerosene space heaters that are used for substantial periods of time appear to be the major contributors to residential CO concentrations. Peak concentrations of CO in such residences often exceed an 8-hour average of 9 ppm and a 1-hour average of 35 ppm. One extensive study (Koontz and Nagda, 1988) of unvented gas space heaters indicated that 12 % of the homes had 15-hour average CO concentrations greater than 8 ppm; the highest recorded concentration was 36.6 ppm.

Intermittent sources such as gas cooking ranges can result in high peak CO concentrations (in excess of 9 ppm), while long-term average concentrations (i.e., 24 hours) associated with gas ranges are on the order of 1 ppm. The contribution of tobacco combustion to indoor CO levels is variable. One study suggested that its contribution to residential CO concentrations was on the order of 1 ppm; another study showed no significant increase.

Very limited data on CO levels in residences with wood burning stoves or fireplaces indicate non-airtight stoves can contribute substantially to residential CO concentrations; airtight stoves can contribute small increases. The available data indicate that fireplaces do not contribute measurably to average indoor concentrations. No information is available on residences with leaky flues or on the impact of attached garages.

The available data on the spatial and temporal variability of indoor CO concentrations as a function of microenvironments and associated sources are not adequate to assess exposures

in these environments. These indoor microenvironments represent the most important CO exposures for the majority of individuals and as such need to be better characterized.

Population Exposure to Carbon Monoxide

The current NAAQS for CO (9 ppm for 8 hours, 35 ppm for 1 hour) are designed to protect against actual and potential human exposures in outdoor air that would cause adverse health effects. Compliance with the NAAQS is determined by measurements taken at fixed-site ambient monitors, the use of which is intended to provide some measure of the general level of exposure of the population represented by the CO monitors. Results of both exposure monitoring in the field, and modeling studies, summarized in this document indicate that individual personal exposure does not directly correlate with CO concentrations determined by using fixed-site monitors alone. This observation is due to the mobility of people and to the spatial and temporal variability of CO concentrations. While failing to show a correlation between individual personal monitor exposures and simultaneous nearest fixed-site monitor concentrations, studies do suggest that aggregate personal exposures are lower on days of lower ambient CO levels as determined by the fixed-site monitors and higher on days of higher ambient levels.

A unique feature of carbon monoxide exposure is that there is a biological marker of the dose that the individual has received: the blood level of CO. This level may be calculated by measuring blood carboxyhemoglobin (COHb) or by measuring CO in exhaled breath.

The use of CO-Oximeters to measure low levels of COHb can provide useful information regarding mean values, provided a reference technique is used to properly calibrate the instrument. It has been shown, however, that the range of values obtained with this optical method will be greater than that obtained with a reference method. For example, in a group of subjects with cardiovascular disease, the standard deviation of the percent COHb values for non-smoking, resting subjects was 2 to 2.5 times greater for the CO-Oximeter values than for the gas chromatograph values on paired samples (Allred et al., 1989b). Therefore, the potential exists with the CO-Oximeter for having an incorrect absolute value for COHb as well as an incorrectly broadened range of values.

In addition, it is not clear exactly how sensitive the CO-Oximeter techniques are to small changes in COHb at the low end of the CO dissociation curve. Allred et al. (1989b)

have noted that the interference from changing O_2 saturation can have a very significant influence on the apparent COHb reading in a sample. The interaction between hemoglobin species was also reported by Dennis and Valeri (1980). This suggests nonlinearity or a disproportionality in the absorption spectrum of these two species of hemoglobin. It is also a potential source of considerable error in the estimation of COHb by optical methods.

The measurement of exhaled breath has the advantages of ease, speed, precision, and greater subject acceptance than measurement of blood COHb. However, the accuracy of the breath measurement procedure and the validity of the Haldane relationship between breath and blood at low environmental CO concentrations remains in question. There appears to be a clear research need to validate the breath method at low CO exposures. In view of the possible problems with the CO-Oximeter, such validation should be done using gas chromatography for the blood COHb measurements.

Cigarette consumption represents a special case of CO exposure; for the smoker it almost always dominates over personal exposure from other sources. Studies by Radford and Drizd (1982) show that COHb levels of cigarette smokers average 4% while those of nonsmokers average 1%. Therefore, this document focuses on environmental exposure of nonsmokers to CO.

People encounter CO in a variety of environments that include travelling in motor vehicles, working at their jobs, visiting urban locations associated with combustion sources, or cooking over a gas range. Studies of human exposure have shown that among these settings the motor vehicle is the most important for regularly encountered elevations of CO. Studies by Flachsbart et al. (1987) indicated that CO exposures while commuting in Washington, D.C. average 9 to 14 ppm at the same time that fixed station monitors record concentrations of 2.7 to 3.1 ppm. Similar studies conducted by EPA in Denver and Washington, D.C., have demonstrated that the motor vehicle interior has the highest average CO concentrations (averaging 7 to 10 ppm) of all microenvironments (Johnson, 1984). In these studies, 8% of all commuters experienced 8-hour exposures greater than 9 ppm while only 1% of noncommuters received exposures over that level. Furthermore, commuting exposures have been shown to be highly variable with some commuters breathing CO in excess of 25 ppm.

Another important setting for CO exposure is the workplace. In general, exposures at work exceed CO exposures during nonwork periods, apart from commuting to and from work. Average concentrations may be elevated during this period since workplaces are often located in congested areas that have higher background CO concentrations than do many residential neighborhoods. Occupational and nonoccupational exposures may overlay one another and result in a higher concentration of CO in the blood. Certain occupations also increase the risk of high CO exposure (e.g., those occupations involved directly with vehicle driving, maintenance, and parking). Occupational groups exposed to CO by vehicle exhaust include auto mechanics; parking garage and gas station attendants; bus, truck or taxi drivers; police; and warehouse workers. Other industrial processes produce CO directly or as a by-product, including steel production, coke ovens, carbon black production, and petroleum refining. Firefighters, cooks, and construction workers also may be exposed at work to higher CO levels. Occupational exposure in industries or setting with CO production also represent some of the highest individual exposures observed in field monitoring studies. For example, in EPA's CO exposure study in Washington, DC, of the approximately 4% (29 of 712) of subjects working in jobs classified as having a high potential for CO exposure, seven subjects (or approximately 25%) experienced 8-hour CO exposures in excess of 9 ppm.

The highest indoor nonoccupational CO exposures are associated with combustion sources and include enclosed parking garages, service stations, restaurants and stores. The lowest indoor CO concentrations are found in homes, churches, and health care facilities. EPA's Denver Study showed that passive cigarette smoke is associated with increasing a nonsmoker's exposure by an average of about 1.5 ppm and that use of a gas range is associated with about 2.5 ppm increase at home. Other sources which may contribute to CO in the home include combustion space heaters and wood burning stoves.

As noted above, people encounter different and often higher exposures than predicted from fixed-site monitoring data because of the highly localized nature of CO sources. For example, during the winter sampling period, 10% of Denver volunteers and 4% of Washington, DC volunteers recorded personal exposures in excess of 9 ppm for 8 hours. Breath measurements from the Washington volunteers indicated that as much as 9% of the population could have experienced a 9 ppm, 8-hour average. In contrast, during the entire winter period of 1982-1983, the two ambient CO monitors in Washington reported only one

exceedance of the 9-ppm level. In another study, using data from analyses of COHb in blood, Wallace and Ziegenfus (1985) report that CO in blood is uncorrelated with CO measured by ambient monitors. These findings point out the necessity of having personal CO measurements to augment fixed-site ambient monitoring data when total human exposure is to be evaluated. Data from these field studies can be used to construct and test models of human exposure that account for time and activity patterns known to affect exposure to CO. Models developed to date tend to underpredict the variability of CO exposures observed in field studies and have not been able to successfully predict individual exposures. The models may be modified and adjusted using information from field monitoring studies in order to capture the observed distribution of CO exposures, including the higher exposures found in the tail of the exposure distribution. The models also are useful for evaluating alternative pollutant control strategies.

Pharmacokinetics and Mechanisms of Action of Carbon Monoxide

This section of the document reviews the basic relationships of O_2 and CO with Hb and other O_2 binding proteins, outlines the fundamentals of CO uptake and elimination from blood and extravascular space, examines the mechanisms of CO toxicity, and evaluates the models of COHb formation.

The exchange of CO between the atmosphere (airway opening) and RBC is controlled by physical (mass transport, diffusion) and physiological (alveolar ventilation, cardiac output, etc.) processes. The final step of the competitive binding between CO and O_2 to Hb to form COHb and O_2Hb, respectively, is a complex sequence of reversible reactions, the kinetics of which are still not fully understood. The toxic effects of CO are due to its high affinity for Hb. The presence of CO reduces O_2-carrying capacity of blood and impairs release of O_2 from O_2Hb to extravascular tissues. Brain and heart tissues are particularly sensitive to the resultant drop in PO_2 and CO hypoxia. Because of tight binding of CO to Hb, the elimination half-time is quite long. This might lead to accumulation of COHb and even relatively low concentrations of CO might produce substantial blood levels of COHb.

The rate of rise of blood COHb levels as well as the time to equilibrium saturation depends on the inhaled concentration of CO, alveolar ventilation, lung diffusion, cardiac

output, and duration of exposure. These factors have been integrated into many empirical and mathematical models of COHb formation under static and dynamic conditions.

The best all around model for COHb prediction is still the equation developed by Coburn, Forster, and Kane (1965). The linear solution is useful for examining air pollution data leading to relatively low COHb levels, whereas the nonlinear solution shows good predictive power even for high CO exposures. The two regression models might be useful only when the conditions of application closely approximate those under which the parameters were estimated.

It is important to remember that almost all of the available modeling studies assumed a constant rate of CO uptake and elimination, which is rarely true. A number of physiological factors, particularly changes in ventilation, will affect both rates. The predicted COHb values also will differ from individual to individual due to smoking, age, or lung disease. There does not appear to be a single optimal averaging time period for ambient CO; however, the shorter the period the greater the precision. In general, the averaging time period should be well within the [COHb] half-life, which decreases with increased activity.

Although the principal cause of CO toxicity is tissue hypoxia due to CO binding to Hb, certain physiological aspects of CO exposure are not explained well by decreases in intracellular PO_2 related to the presence of COHb. For many years, it has been known that CO is distributed to extravascular sites such as skeletal muscle (Coburn et al., 1971; Coburn et al., 1973) and that 10 to 50% of the total body store of CO may be extravascular (Luomanmaki and Coburn, 1969). Furthermore, extravascular CO is metabolized slowly to CO_2 *in vivo* (Fenn, 1970). Consequently, secondary mechanisms of CO toxicity related to intracellular uptake of CO have been the focus of a great deal of research interest. CO binding to many intracellular compounds has been well documented both *in vitro* and *in vivo*; however, it is still uncertain whether or not intracellular uptake of CO in the presence of Hb is sufficient to cause either acute organ system dysfunction or long-term health effects. The virtual absence of sensitive techniques capable of assessing intracellular CO binding under physiological conditions has resulted in a variety of indirect approaches to the problem as well as many negative studies.

Current knowledge pertaining to intracellular CO-binding proteins suggests that the most likely ones to be inhibited functionally at relevant levels of COHb are myoglobin (Mb), found

predominantly in heart and skeletal muscle, and cytochrome oxidase. The physiological significance of CO uptake by Mb is uncertain at this time but sufficient concentrations of carboxymyoglobin (COMb) could potentially limit maximal O_2 uptake of exercising muscle. Although there is suggestive evidence for significant binding of CO to cytochrome oxidase in heart and brain tissue, it is unlikely that any significant CO binding would occur at low COHb levels. Therefore, further research is needed to determine if secondary, intracellular mechanisms will occur at exposure concentrations found in ambient air.

Health Effects of Carbon Monoxide

Concerns about the potential health effects of exposure to carbon monoxide have been addressed in extensive studies with various animal species as subjects. Under varied experimental protocols, considerable information has been obtained on the toxicity of CO, its direct effects on the blood and other tissues, and the manifestations of these effects in the form of changes in organ function. Many of these studies, however, have been conducted at extremely high levels of CO (i.e., levels not found in ambient air). Although severe effects from exposure to these high levels of CO are not directly germane to the problems from exposure to current ambient levels of CO, they can provide valuable information about potential effects of accidental exposure to CO, particularly those exposures occurring indoors.

Acute Pulmonary Effects

Currently available studies on the effects of CO exposures producing COHb concentrations of up to 39% fail to find any consistent effects on lung parenchyma and vasculature (Hugod, 1980; Fisher et al., 1969) or on alveolar macrophages (Chen et al., 1982; Weissbecker et al., 1969). The lack of significant changes in lung tissue is consistent with the lack of histologic changes in the pulmonary and coronary arteries. Alveolar epithelial permeability to ^{51}Cr-EDTA increased in rabbits (Fein et al., 1980) exposed to high concentrations of CO (63% COHb), and increased capillary endothelial permeability to ^{131}I-labeled human serum albumin was reported in early human studies (Parving, 1972) following acute, high-level CO exposure (23% COHb); however, no accumulation of lung water was found in dogs (Halebian et al., 1984a,b) with COHb levels of 59% and no edema was found in the lungs of rats chronically exposed to CO concentrations as high as 1300 ppm (Penney

et al., 1988). In addition, no changes in diffusing capacity of the lung were found in dogs with COHb levels up to 18% (Fisher et al., 1969). It is unlikely, therefore, that CO has any direct effect on lung tissue except at extremely high concentrations. The capillary endothelial and alveolar epithelial edema found with high levels of CO exposure in victims of CO poisoning may be secondary to cardiac failure produced by myocardial hypoxia (Fisher et al., 1969) or may be due to acute cerebral anoxia (Naeije et al., 1980).

Ventilatory responses to CO are related to the CO concentration as well as to the experimental conditions and the animal species being studied. In conscious goats (Chapman et al., 1980; Doblar et al., 1977; Santiago and Edelman, 1976) and cats (Gautier and Bonora, 1983), after an initial depression, ventilation suddenly increases, particularly at high CO concentrations (>2000 ppm). This response may result from the direct effects of hypoxia (and possibly central acidosis) and/or a specific CNS effect of CO. No effects on ventilation and perfusion distribution were found, however, in dogs exposed to 1% CO for 10 min, resulting in COHb levels of 59% (Robinson et al., 1985). At very high concentrations of CO (COHb >60%) total pulmonary resistance, measured indirectly by tracheal pressure, was reported to increase (Mordelet-Dambrine et al., 1978; Mordelet-Dambrine and Stupfel, 1979).

Human studies on the pulmonary function effects of CO are complicated by the lack of adequate exposure information, the small number of subjects studied, and the short exposures explored. Occupational or accidental exposure to the products of combustion and pyrolysis, particularly indoors, may lead to acute decrements in lung function if the COHb levels are >17% (Sheppard et al., 1986) but not at concentrations <2% (Evans et al., 1988; Hagberg et al., 1985; Cooper and Alberti, 1984). It is difficult, however, to separate the potential effects of CO from those due to other respiratory irritants in the smoke and exhaust. Community population studies on CO in ambient air have not found any relationships with pulmonary function, symptomatology, and disease (Lebowitz et al., 1987; Robertson and Lebowitz, 1984; Lutz, 1983).

Cardiovascular Effects

The 1984 Addendum to the 1979 Air Quality Criteria Document for Carbon Monoxide (U.S. Environmental Protection Agency, 1984) reported what appears to be a linear relationship between level of COHb and decrements in human exercise performance,

measured as maximal O_2 uptake. Exercise performance consistently decreases at a blood level of about 5.0% COHb in young, healthy, nonsmoking individuals (Klein et al., 1980; Stewart et al., 1978; Weiser et al., 1978). Some studies have even observed a decrease in performance at levels as low as 2.3 to 4.3% COHb (Horvath et al., 1975; Drinkwater et al., 1974; Raven et al., 1974a); however, this decrease is so small as to be of concern mainly for competing athletes rather than for ordinary people conducting the activities of daily life. Cigarette smoking has a similar effect on cardiorespiratory response to exercise in nonathletic human subjects indicating a reduced ability for sustained work (Hirsch et al., 1985; Klausen et al., 1983).

Since the 1979 Air Quality Criteria Document (U.S. Environmental Protection Agency, 1979), several important studies appearing in the literature have expanded the cardiovascular data base. Adverse effects in patients with reproducible exercise-induced angina (Allred et al., 1989a,b) have been noted with postexposure COHb levels (CO-Oximeter measurement) as low as 3.2% (corresponding to an increase of 2.0% from baseline). Sheps et al. (1987) also found a similar effect in a group of patients with angina at COHb levels of 3.8% (representing an increase of 2.2% from baseline). Kleinman et al. (1989) studied subjects with angina and found an effect at 3% COHb representing an increase of 1.5% from baseline. Thus, the lowest observed adverse effect level in patients with stable angina is somewhere between 3 and 4% COHb (CO-Oximeter measurement), representing an increase from baseline of from 1.5 to 2.2%. Effects on silent ischemia episodes, which represent the majority of episodes in these patients, have not been studied.

Exposure sufficient to achieve 6% COHb recently has been shown to adversely affect exercise-related arrhythmia in patients with coronary artery disease (Sheps et al., 1989). This finding combined with the epidemiologic work of Stern et al. (1988) in tunnel workers is suggestive but not conclusive that CO exposure may provide an increased risk of sudden death from arrhythmia in patients with coronary artery disease.

There is also strong evidence from both theoretical considerations and experimental studies in animals that carbon monoxide can adversely affect the cardiovascular system. Results from animal studies suggest that inhaled CO can cause disturbances in cardiac rhythm and conduction in healthy as well as cardiac-impaired animals. The lowest observed effect level varies, depending upon the exposure regime used and species tested. Values reported in

the literature for 6 to 24 week exposures range from 2.6 to 12.0% COHb (50 and 100 ppm CO) in dogs to 12.4% (100 ppm CO) in monkeys. For shorter duration exposures of 0.6 to 16 h, disturbances in cardiac rhythm were found at 4.9 to 17.0% COHb (500 ppm CO) in dogs and 9.3% COHb (100 ppm CO) in monkeys. Results from animal studies also indicate that inhaled CO can increase hemoglobin concentration and hematocrit ratio at COHb levels of 9.26% (100 ppm CO). Small increases in hemoglobin and hematocrit probably represent a compensation for the reduction in oxygen transport caused by CO. At higher CO concentrations, excessive increases in hemoglobin and hematocrit may impose an additional workload on the heart and compromise blood flow to the tissues. For example, cardiomegaly has been reported in adult animals at COHb levels of 12% (200 ppm CO). The oxygen transport system of the fetus, however, is especially sensitive to CO inhaled by the mother, and may be affected by CO at concentrations as low as 60 ppm.

There is conflicting evidence that CO exposure will enhance development of atherosclerosis in laboratory animals; and most studies show no measurable effect. Similarly, the possibility that CO will promote significant changes in lipid metabolism that might accelerate atherosclerosis is suggested in only a few studies. Any such effect must be subtle at most. Finally, CO probably inhibits rather than promotes platelet aggregation. Except for the studies by Rogers et al. (1980, 1988) on baboons, the CO exposures used in the studies on atherosclerosis created COHb levels of 7% or higher; sometimes much higher. While occupational exposures in some workplace situations might regularly lead to COHb levels of 10% or more, such high exposure levels are almost never encountered in the nonoccupationally exposed general public. In this general population, exposures are rarely as much as 25 to 50 ppm, and COHb levels typically are below 3% in nonsmokers. When examined in this context, this document therefore, provides little data to indicate that an atherogenic effect of exposure would be likely to occur in human populations at commonly encountered levels of ambient CO.

Cerebrovascular and Behavioral Effects

The data reviewed in this document indicate that carbon monoxide hypoxia increases cerebral blood flow, even at very low exposure levels. Cerebral O_2 consumption is well maintained until levels of COHb reach upwards of 30%. The overall responses of the

cerebrovasculature are similar in the fetus, newborn, and adult animal; however, the mechanism of the increase in cerebral blood flow is still unclear. In fact, several mechanisms working simultaneously to increase cerebral blood flow appear likely and these may involve metabolic and neural aspects as well as the oxyhemoglobin dissociation curve, tissue O_2 levels, and even a histotoxic effect of CO. These potential mechanisms of CO-induced alterations in the cerebral circulation need to be investigated further. The interaction of CO with cyanide (additive and synergistic) on the cerebral vasculature is clear, however the interaction of CO with other agents and their combined effects on brain blood vessels is unknown. This also is true for the long term (chronic) effects of CO alone, or in combination with other agents in low- or high-dose levels on the cerebral vasculature. Finally, under normal circumstances the brain can increase its blood flow or its O_2 extraction in order to compensate for a reduced O_2 environment. Whether these compensatory mechanisms continue to operate successfully in a variety of conditions where the brain, or its vasculature are compromised (i.e., stroke, head injury, atherosclerosis, hypertension) is unknown and requires further investigation.

Behaviors that require sustained attention and/or sustained performance are most sensitive to disruption by COHb. Therefore, the group of studies of tracking, vigilance, and continuous performance offer the most consistent and defensible evidence of COHb effects on behavior. The results across studies is, however, far from consistent. Further examination of the three areas seems appropriate.

Compensatory tracking was studied by two groups of investigators using virtually identical task parameters and equipment (Putz et al., 1976, 1979; Benignus et al., 1987, 1989). Both of the studies by Putz et al. (1976, 1979) found significant and moderately large effects of 5% COHb. Benignus et al. (1987) reported similar but smaller significant effects in a nearly identical experiment to Putz et al. (1976). However, in a dose-effects study including another direct replication group, Benignus et al. (1989a) found no significant effects, even for COHb levels of 17%. In the latter study, the means were nearly doseordinal but too small to be statistically significant. It is particularly puzzling why the latter study, using a large number of subjects on an identical task, should find no significant effects for even 17% COHb when three other studies found effects at lower levels. Three other double-blind tracking studies of various methods found no effects of COHb levels of 12% or greater.

There is a similar disunity among studies on the effects of COHb on vigilance. Because of the many failed attempts at direct replication, the conclusions seem weaker than for tracking.

Of the five double-blind experiments in which continuous performance was measured, three were mentioned earlier in the discussion of tracking. In these studies (direct replications), continuous performance was measured simultaneously with tracking (Putz et al., 1976, 1979; Benignus et al., 1987). The latter of the three found no effects. A small study reported continuous performance effects that were disordinal in COHb (O'Donnell et al., 1971). The remaining study (Benignus et al., 1977) used a different task and obtained no COHb effects.

As discussed above, a proportional vasodilation occurs in the brain in response to COHb elevation. This vasodilation is sufficient, on the average, to keep the cerebral O_2 consumption from being reduced even though the COHb has reduced the blood's O_2-carrying capacity 20 to 30% and the presence of COHb has shifted the oxyhemoglobin dissociation curve to the left. The cerebral vasodilation may be viewed, teleologically, as a closed-loop compensatory mechanism to assure adequate oxygenation of the brain in the presence of elevated COHb. If the cerebral vasodilation is adequate in any individual and if the vasodilation is homogeneous for all cerebral tissue, then that individual should not be behaviorally impaired by COHb elevation. This statement assumes that the sole mechanism for CO toxicity is the hypoxic effect of COHb.

The agreement between the behavioral literature and the compensatory mechanism hypothesis is noteworthy. According to the compensatory mechanism data, O_2 consumption in the brain does not begin to decrease until COHb exceeds 20 to 30%. Data from behavioral studies in laboratory animals demonstrate that significant effects in schedule-controlled behavior do not occur below 20 to 30% COHb. Behavioral effects in healthy humans have not been clearly demonstrated below 20 to 30% COHb. It seems unwise, however, to totally ignore the evidence suggesting effects below these levels. Even if effects are small or occasional, they might be important to the performance of critical tasks in some individuals.

Some of the differences among studies of the effect of COHb on the behavior of humans are due apparently to technical problems in the execution of experiments, because single-blind or nonblind experiments tend to yield a much higher rate of significant effects than do double-blind studies. Even when non-double-blind experiments are eliminated from

consideration, however, a substantial amount of disparity remains among results of studies. It is possible that such residual disagreement is due to the action of an unsuspected variable that is not being controlled across experiments.

If the compensatory CNS blood flow hypothesis has validity, it is possible that there exist groups that are at higher risk to COHb elevation than the usual subjects who were studied in the behavioral experiments. Disease or injury might either impair the compensatory mechanism or reduce the non-exposed O_2 delivery. Aging increases the probability of such injury and disease. It also is possible that there exist individual differences with regard to COHb sensitivity and/or compensatory mechanisms. Too little is known about the compensatory process to make conjectures, but the matters seem important to investigate.

The literature on the behavioral effects of COHb elevation has grown considerably since the last Criteria Document was written (U.S. Environmental Protection Agency, 1979). It seems safe to state that the effect of the new information did not increase the certainty about COHb effects. Unless some key piece of information is uncovered by new research, there does not seem to be much hope of gaining clarification in the conflicting findings. The solution to the puzzle would seem to lie in the conduct of more research into mechanisms of action of CO rather than in further attempts to show reliable behavioral effects. The latter approach, which has not been successful in the past, should be resumed only when mechanisms of toxicity are understood better. More findings of behavioral effects of COHb would not appreciably alter the conclusions of this document unless future studies were to show an unusual unanimity.

Developmental Toxicity

The data reviewed in this document provide strong evidence that CO exposures of 150 to 200 ppm produce reductions in birthweight, cardiomegaly, delays in behavioral development, and disruption in cognitive function in laboratory animals of several species. Isolated experiments suggest that some of these effects may be present at doses as low as 60 to 65 ppm maintained throughout gestation. The current data from human children suggesting a link between environmental CO exposures and sudden infant death syndrome (SIDS) are weak, but further study should be encouraged. Human data from cases of accidental high

dose CO exposures are difficult to use in identifying a lowest observed effect level (LOEL) or a no observed effects level (NOEL) for this agent because of the small numbers of cases reviewed and problems in documenting levels of exposure. However, such data if systematically gathered and reported could be useful in identifying possible ages of special sensitivity to CO and cofactors or other risk factors that might identify sensitive subpopulations.

Other Systemic Effects of Carbon Monoxide

Laboratory animal studies reviewed in the previous criteria document (U.S. Environmental Protection Agency, 1979) and again in this document suggest that enzyme metabolism and the P-450-mediated metabolism of xenobiotic compounds may be affected by CO exposure (Montgomery and Rubin, 1971; Kustov et al., 1972; Pankow and Ponsold, 1972, 1974; Martynjuk and Dacenko, 1973; Swiecicki, 1973; Pankow et al., 1974; Roth and Rubin, 1976a,b). Most of the authors have concluded, however, that effects on metabolism at low COHb levels (≤15%) are attributable entirely to tissue hypoxia produced by increased levels of COHb because they are no greater than the effects produced by comparable levels of hypoxic hypoxia. At higher levels of exposure, where COHb concentrations exceed 15 to 20%, there may be direct inhibitory effects of CO on the activity of mixed-function oxidases but more basic research is needed. The decreases in xenobiotic metabolism shown with CO exposure might be important to individuals receiving treatment with drugs.

The effects of CO on tissue metabolism noted above may partially explain the body weight changes associated with exposure to high concentrations of CO. Short-term exposure to 250-1000 ppm for 24 h was reported previously to cause weight loss in laboratory rats (Koob et al., 1974) but no significant body weight effects were reported in long-term exposure studies in laboratory animals at CO concentrations ranging from 50 ppm for 3 mo to 3000 ppm for 300 days (Theodore et al., 1971; Musselman et al., 1959; Campbell, 1934; Stupfel and Bouley, 1970).

Inhalation of high levels of CO, leading to COHb concentrations greater than 10 to 15%, have been reported to cause a number of systemic effects in laboratory animals as well as effects in humans suffering from acute CO poisoning. Tissues of highly active oxygen metabolism, such as heart, brain, liver, kidney, and muscle, may be particularly sensitive to

CO poisoning. The impairment of function in the heart and brain caused by CO exposure is well known and has been described above. Other systemic effects of CO poisoning are not as well known and are, therefore, less certain. There are reports in the literature of effects on liver (Katsumata et al., 1980), kidney (Kuska et al., 1980), and bone (Zebro et al., 1983). Results from one additional study in adult guinea pigs suggest that immune capacity in the lung and spleen was affected by intermittent exposure to high levels of CO for 3 to 4 weeks (Snella and Rylander, 1979). It generally is agreed that these systemic effects are caused by the severe tissue damage occurring during acute CO poisoning due to (1) ischemia resulting from the formation of COHb, (2) inhibition of O_2 release from HbO_2, (3) inhibition of cellular cytochrome function (e.g., cytochrome oxidases), and (4) metabolic acidosis.

Adaptation

The only evidence for short- or long-term COHb compensation in man is indirect. Experimental animal data indicate that COHb levels produce physiological responses that tend to offset other deleterious effects of CO exposure. Such responses are (1) increased coronary blood flow, (2) increased cerebral blood flow, (3) increased hemoglobin through increased hemopoiesis, and (4) increased O_2 consumption in muscle.

Short-term compensatory responses in blood flow or O_2 consumption may not be complete or might even be lacking in certain persons. For example, from laboratory animal studies it is known that coronary blood flow is increased with COHb, and from human clinical studies it is known that subjects with ischemic heart disease respond to the lowest levels of COHb (5%, or less). The implication is that in some cases of cardiac impairment, the short-term compensatory mechanism is impaired.

From neurobehavioral studies, it is apparent that decrements due to CO have not occurred consistently in all subjects, or even in the same studies, and have not demonstrated a dose-response relationship with increasing COHb levels. The implication from this data suggests that there might be some threshold or time lag in a compensatory mechanism such as increased cerebral blood flow. Without direct physiological evidence in either laboratory animals or, preferably humans, this concept only can be hypothesized. The observed results from the neurobehavioral studies could be explained by differences or problems in experimental protocols or due to possible nonrandom sampling.

The idea of a threshold or a time lag in compensatory mechanisms should not be rejected entirely, however. There simply is no direct evidence. Studies need to be performed to (1) measure cerebral blood flow and tissue PO_2 with low COHb levels at various ambient concentrations of CO to determine early and low level effects accurately, and (2) design behavioral studies where threshold effects or time lags are factors in the experimental protocols that can be explicitly studied.

The mechanism by which long-term adaptation would occur, if it could be demonstrated in humans, is assumed to be an increased Hb concentration via a several-day increase in hemopoiesis. This alteration in Hb production has been demonstrated repeatedly in animal studies but no recent studies have been conducted indicating or suggesting that some adaptational benefit has or would occur. Furthermore, even if the Hb increase is a signature of adaptation, it has not been demonstrated to occur at low ambient concentrations of CO. The human studies of the 1940s have not been replicated, so the question of adaptation remains unresolved.

Combined Exposure of Carbon Monoxide with Other Pollutants, Drugs, and Environmental Factors

High Altitude Effects

While there are many studies comparing and contrasting inhaling CO with exposure to altitude, there are relatively few reports on the effects of inhaling CO at altitude. There are data to support the possibility that the effects of these two hypoxia episodes are at least additive. These data were obtained at CO concentrations that are too high to have much meaning for regulatory concerns. There also are data that indicate decrements in visual sensitivity and flicker-fusion frequency in subjects exposed to CO (COHb = 5 to 10%) at higher altitudes. These data, however, are somewhat controversial.

There are even fewer studies of the long-term effects of CO at high altitude. These studies generally indicate few changes at CO concentrations below 100 ppm and altitudes below 4572 m (15,000 ft). A provocative study by McDonagh et al. (1986) suggests that the increase in ventricular capillarity seen with altitude exposure may be blocked by CO. The fetus may be particularly sensitive to the effects of CO at altitude; this is especially true with the high levels of CO associated with maternal smoking.

Carbon Monoxide Interaction with Drugs

There remains little direct information on the possible enhancement of CO toxicity by concomitant drug use or abuse; however, there are some data suggesting cause for concern. There is some evidence that interactions of drug effects with CO exposure can occur in both directions, that is, CO toxicity may be enhanced by drug use and the toxic or other effects of drugs may be altered by CO exposure. Nearly all the published data that are available on CO combinations with drugs concern psychoactive drugs.

The use and abuse of psychoactive drugs and alcohol is ubiquitous in society. Because of CO's effects on brain functioning, interactions between CO and psychoactive drugs could be anticipated. Unfortunately, very little systematic research has addressed this question. In addition, very little of the research that has been done has utilized models for expected effects for treatment combinations. Thus, often it is not possible to assess whether the combined effects of drugs and CO exposure are additive or differ from additivity. It is important to recognize that even additive effects of combinations can be of clinical significance, especially when the individual is unaware of the combined hazard.

Combined Exposure of Carbon Monoxide with Other Air Pollutants and Environmental Factors

Much of the data concerning the combined effects of CO and other pollutants found in the ambient air are based on animal experiments. Only a few human studies are available. Early studies in healthy human subjects by Hackney et al. (1975a,b), Raven et al. (1974a,b), Gliner et al. (1975), and Drinkwater et al. (1974) on common air pollutants such as NO_2, O_3, or PAN and more recent work on CO + O_3 by DeLucia et al. (1983) failed to show any interaction from combined exposure.

In animal studies, no interaction was observed following combined exposure of CO and pollutants such as HCN, NO_2, SO_2, or PbClBr (Hugod, 1979; Busey, 1972; Murray et al., 1978). However, an additive effect was observed following combined exposure of high levels of CO + NO (Groll-Knapp et al., 1988), and a synergistic effect was observed after combined exposure to CO and O_3 (Murphy, 1964).

Toxicological interactions of combustion products, primarily CO, CO_2, and HCN, from indoor and outdoor fires, have shown a synergistic effect following CO + CO_2 exposure (Rodkey and Collison, 1979; Levin et al., 1987a) and an additive effect with CO + HCN

(Levin et al., 1987b). Additional studies are needed, however, to evaluate the effects of CO under conditions of hypoxic hypoxia.

Finally, laboratory animal studies (Yang et al., 1988; Fechter et al., 1988; Young et al., 1987) suggest that the combination of environmental factors such as heat stress and noise may be important determinants of health effects occurring in combination with exposure to CO. Of the effects described, the one potentially most relevant to typical human exposures is a greater decrement in exercise performance seen when heat stress is combined with 50 ppm CO (Drinkwater et al., 1974; Raven et al., 1974a,b; Gliner et al., 1975).

Environmental Tobacco Smoke

Although tobacco smoke is another source of CO for smokers as well as nonsmokers, it is also a source of other chemicals with which environmental CO levels could interact. Available data strongly suggest that acute and chronic CO exposure attributed to tobacco smoke can affect the cardiopulmonary system, but the potential interaction of CO with other products of tobacco smoke confounds the results. In addition, it is not clear if incremental increases in COHb caused by environmental exposure would actually be additive to chronically elevated COHb levels due to tobacco smoke, because some physiological adaptation may take place. There is, therefore, a need for further research to describe these relationships better.

Evaluation of Subpopulations Potentially At Risk to Carbon Monoxide Exposure

Most of the information on the human health effects of carbon monoxide discussed in this document has concentrated on two carefully defined population groups – young healthy, predominantly male adults and patients with diagnosed coronary artery disease. On the basis of the known effects described, patients with reproducible exercise-induced angina appear to be best established as a sensitive group within the general population that is at increased risk for experiencing health effects (i.e., decreased exercise duration due to exacerbation of cardiovascular symptoms) of concern at ambient or near-ambient CO-exposure concentrations that result in COHb levels of $\leq 5\%$. A smaller sensitive group of healthy individuals experience decreased exercise duration at similar levels of CO exposure, but only during short-term maximal exercise. Decrements in exercise duration in the healthy population,

therefore, would be mainly of concern to competing athletes rather than for nonathletic people carrying out the common activities of daily life.

It is known, however, from both theoretical work and from experimental research in laboratory animals that certain other groups in the population are at potential risk to exposure from CO. Another purpose of this document is to explore the potential effects of CO in population groups that have not been studied adequately, but which could be expected to be susceptible to CO because of underlying physiological status either due to gender differences, aging, preexisting disease, or because of the use of medications or alterations in their environment. These probable risk groups include (1) fetuses and young infants; (2) pregnant women; (3) the elderly, especially those with compromised cardiopulmonary or cerebrovascular functions; (4) individuals with obstructed coronary arteries, but not yet manifesting overt symptomatology of coronary artery disease; (5) individuals with congestive heart failure; (6) individuals with peripheral vascular or cerebrovascular disease; (7) individuals with hematological diseases (e.g., anemia) that affect oxygen-carrying capacity or transport in the blood; (8) individuals with genetically unusual forms of hemoglobin associated with reduced oxygen-carrying capacity; (9) individuals with chronic obstructive lung diseases; (10) individuals using medicinal or recreational drugs having CNS depressant properties; (11) individuals exposed to other pollutants (e.g., methylene chloride) that increase endogenous formation of CO; and (12) individuals who have not been adapted to high altitude and are exposed to a combination of high altitude and CO. Unfortunately, little empirical evidence currently is available by which to specify health effects associated with ambient or near-ambient CO exposures in these probable risk groups.

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Most of the scientific information selected for review and comment in this document comes from the more recent literature published since completion of the previous criteria document (U.S. Environmental Protection Agency, 1979). Some of the these newer studies were reviewed briefly in the addendum to that document (U.S. Environmental Protection Agency, 1984a). Emphasis has been placed on studies conducted at or near CO concentrations found in ambient air. Other studies, however, were included if they contained unique data, such as the documentation of a previously unreported effect or a mechanism of an effect; or if they were multiple-concentration studies designed to provide exposure-response relationships relevant to total human exposure to CO. Studies that were presented in the previous criteria document and whose data are still considered relevant are summarized in tables or reviewed briefly in the text. Older studies were considered for discussion in the document if they were (1) judged to be significant because of their usefulness in deriving the current NAAQS, (2) open to reinterpretation because of newer data, or (3) potentially useful in deriving revised standards for CO. Generally, only published information that has undergone scientific peer review is included in this criteria document. Some newer studies not published in the open literature but meeting high standards of scientific reporting also are included.

2.2 LEGISLATIVE HISTORY OF NAAQS

Two sections of the Clean Air Act (CAA) govern the establishment, review, and revision of NAAQS. Section 108 (U.S. Code, 1982) directs the Administrator of the U.S. EPA to identify pollutants that reasonably may be anticipated to endanger public health or welfare and to issue air quality criteria for them. These air quality criteria are to reflect the latest scientific information useful in indicating the kind and extent of all identifiable effects on public health or welfare that may be expected from the presence of the pollutant in ambient air.

Section 109(a) of the CAA (U.S. Code, 1982) directs the Administrator of EPA to propose and promulgate primary and secondary NAAQS for pollutants identified under Section 108. Section 109(b)(1) defines a primary standard as one the attainment and maintenance of which in the judgment of the Administrator, based on the criteria and

allowing for an adequate margin of safety, is requisite to protect the public health. The secondary standard, as defined in Section 109(b)(2), must specify a level of air quality the attainment and maintenance of which in the judgment of the Administrator, based on the criteria, is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of the pollutant in ambient air. Section 109(d) of the CAA (U.S. Code, 1982) requires periodic review and, if appropriate, revision of existing criteria and standards. If, in the Administrator's judgment, the Agency's review and revision of criteria make appropriate the proposal of new or revised standards, such standards are to be revised and promulgated in accordance with Section 109(b). Alternately, the Administrator may find that revision of the standards is inappropriate and may conclude the review by leaving the existing standards unchanged.

In keeping with the requirements of the CAA, the Environmental Criteria and Assessment Office of EPA's Office of Health and Environmental Assessment has started to review and revise once again the criteria for CO. New data on the health and air quality aspects of CO exposure have become available since completion of the previous Air Quality Criteria Document (U.S. Environmental Protection Agency, 1979) and an addendum to that document (U.S. Environmental Protection Agency, 1984a).

2.3 REGULATORY BACKGROUND FOR CARBON MONOXIDE NAAQS*

On April 30, 1971, EPA promulgated identical primary and secondary NAAQS for CO at levels of 9 ppm for an 8-h average and 35 ppm for a 1-h average, not to be exceeded more than once per year. The scientific basis for the primary standard, as described in the first criteria document (National Air Pollution Control Administration, 1970), was a study suggesting that low levels of CO exposure resulting in carboxyhemoglobin (COHb) concentrations of 2 to 3% were associated with neurobehavioral effects in exposed subjects (Beard and Wertheim, 1967).

*This text is excerpted and adapted from "Review of the National Ambient Air Quality Standards for Carbon Monoxide; Final Rule" (Federal Register, 1985).

In accordance with Sections 108 and 109 of the CAA, EPA has reviewed and revised the criteria upon which the existing NAAQS for CO (Table 2-1) are based. On August 18, 1980, EPA proposed certain changes in the standards (Federal Register, 1980) based on scientific evidence reported in the revised criteria document for CO (U.S. Environmental Protection Agency, 1979). Such evidence indicated that the Beard and Wertheim (1967) study was no longer considered to be a sound scientific basis for the standard. Additional medical evidence accumulated since 1970, however, indicated that aggravation of angina pectoris and other cardiovascular diseases would occur at COHb levels as low as 2.7 to 2.9%. The proposed changes included (1) retaining the 8-h primary standard level of 9 ppm, (2) revising the 1-h primary standard level from 35 ppm to 25 ppm, (3) revoking the existing secondary CO standards (because no adverse welfare effects have been reported at or near ambient CO levels), (4) changing the form of the primary standards from deterministic to statistical, and (5) adopting a daily interpretation for exceedances of the primary standards, so that exceedances would be determined on the basis of the number of days on which the 8- or 1-h average concentrations are above the standard levels.

The 1980 proposal was based in part on health studies conducted by Dr. Wilbert Aronow. In March of 1983 EPA learned that the Food and Drug Administration (FDA) had raised serious questions regarding the technical adequacy of several studies conducted by Dr. Aronow on experimental drugs, leading FDA to reject use of the Aronow drug study data. Therefore, EPA convened an expert committee to examine the Aronow CO studies before any final decisions were made on the NAAQS for CO. The committee concluded that EPA should not rely on Dr. Aronow's data due to concerns regarding the research, which substantially limited the validity and usefulness of the results.

An addendum to the 1979 criteria document for CO (U.S. Environmental Protection Agency, 1984a) reevaluated the scientific data concerning health effects associated with exposure to CO at or near ambient exposure levels in light of the committee recommendations and taking into account new findings reported beyond those previously reviewed. (These data are summarized in the following section.) On September 13, 1985, EPA issued a final notice (Federal Register, 1985) announcing retention of the existing primary NAAQS for CO and rescinding the secondary NAAQS for CO.

TABLE 2-1. NATIONAL AMBIENT AIR QUALITY STANDARDS FOR CARBON MONOXIDE

Date of Promulgation	Primary NAAQS	Averaging Time
September 13, 1985	9 ppm[a] (10 mg/m^3)	8-h[b]
	35 ppm[a] (40 mg/m^3)	1-h[b]

[a] 1 ppm = 1.145 mg/m^3, 1 mg/m^3 = 0.873 ppm @ 25°C, 760 mm Hg.
[b] Not to be exceeded more than once per year.

See glossary of terms and symbols for abbreviations and acronyms.

2.4 SCIENTIFIC BACKGROUND FOR THE CURRENT CARBON MONOXIDE NAAQS

The following is a summary of the scientific basis for the current CO NAAQS. These key points were derived from a revised evaluation of the health effects of CO that was released as an addendum (U.S. Environmental Protection Agency, 1984a) to the previous air quality criteria document for CO (U.S. Environmental Protection Agency, 1979).

2.4.1 Mechanisms of Action

The binding of CO to hemoglobin, producing COHb and decreasing the oxygen-carrying capacity of blood, appears to be the principal mechanism of action underlying the induction of toxic effects of low-level CO exposures. The precise mechanisms by which toxic effects are induced via COHb formation are not understood fully, but likely include the induction of a hypoxic state in many tissues of diverse organ systems. Alternative or secondary mechanisms of CO-induced toxicity (besides COHb) have been hypothesized, but none have been demonstrated to operate at relatively low (near-ambient) CO-exposure levels. Blood COHb levels, then, currently are accepted as representing a useful physiological marker by which to estimate internal CO burdens due to the combined contribution of (1) endogenously derived CO and (2) exogenously derived CO resulting from exposure to external sources of CO. COHb levels likely to result from particular patterns (concentrations, durations, etc.) of external CO exposure can be estimated reasonably well from equations developed by Coburn et al. (1965) as demonstrated in Figure 2-1.

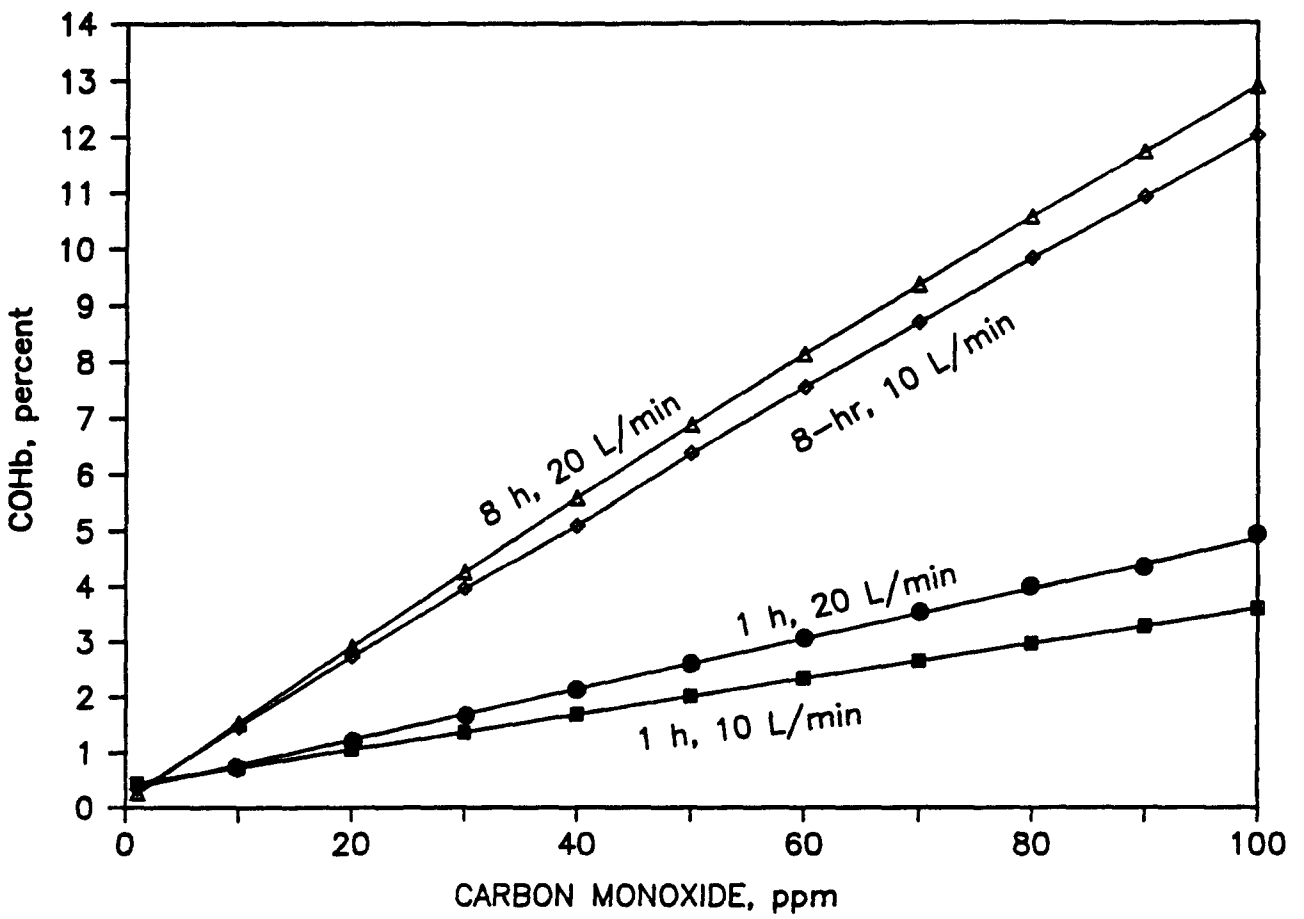

Figure 2-1. Relationship between carbon monoxide exposure and carboxyhemoglobin levels in the blood. Predicted COHb levels resulting from 1- and 8-h exposures to carbon monoxide at rest (10 L/min) and with light exercise (20 L/min) are based on the Coburn-Forster-Kane equation (Coburn et al., 1965) using the following assumed parameters for nonsmoking adults: altitude = 0 ft; initial COHb level = 0.5%; Haldane constant = 218; blood volume = 5.5 L; hemoglobin level = 15 g/100 ml; lung diffusivity = 30 ml/torr/min; endogenous rate = 0.007 ml/min. See glossary of terms and symbols for abbreviations and acronyms.

2.4.2 Carbon Monoxide Exposure Levels

Evaluation of human CO-exposure situations indicates that occupational exposures in some workplaces or exposures in homes with faulty combustion appliances can exceed 100 ppm CO, often leading to COHb levels of 10% or more with continued exposure. In contrast, such high exposure levels are encountered much less commonly by the general public exposed under ambient conditions. More frequently, exposures to less than 25 to 50 ppm CO for any extended period of time occur among the general population and, at the low exercise levels usually engaged in under such circumstances, the resulting COHb levels most typically remain 2 to 3% among nonsmokers. Those levels can be compared to the physiologic norm for nonsmokers, which is estimated to be in the range of 0.3 to 0.7% COHb. Baseline COHb concentrations in smokers, however, average 4% with a usual range of 3 to 8%, reflecting absorption of CO from inhaled smoke.

2.4.3 Health Effects of Low-Level Carbon Monoxide Exposures

Four types of health effects reported or hypothesized to be associated with CO exposures (especially those producing COHb levels below 10%) were evaluated in the last review of the CO NAAQS (U.S. Environmental Protection Agency, 1984a): (1) cardiovascular effects, (2) neurobehavioral effects, (3) fibrinolysis effects, and (4) perinatal effects. Data available at that time (Table 2-2) demonstrated an association between cardiovascular and neurobehavioral effects at relatively low-level CO exposures. Much less clear evidence existed to indicate that other types of health effects were associated with low-level CO exposures.

2.4.3.1 Cardiovascular Effects

In regard to cardiovascular effects, decreased oxygen uptake and resultant decreased work capacity under maximal exercise conditions clearly have been shown to occur in healthy young adults starting at 5.0% COHb; and several studies observed small decreases in work capacity at COHb levels as low as 2.3 to 4.3%. These cardiovascular effects may have health implications for the general population in terms of potential curtailment of certain physically demanding occupational or recreational activities under circumstances of sufficiently high CO-exposure. However, of greater concern at more typical ambient CO-exposure levels were

TABLE 2-2. LOWEST OBSERVED EFFECT LEVELS FOR HUMAN HEALTH EFFECTS ASSOCIATED WITH LOW-LEVEL CARBON MONOXIDE EXPOSURE

Effects	COHb concentration, percent[a]	References
Statistically significant decreased (3-7%) work time to exhaustion in exercising, young, healthy men	2.3-4.3	Horvath et al. (1975) Drinkwater et al. (1974)
Statistically significant decreased exercise capacity (i.e., shortened duration of exercise before onset of pain) in patients with angina pectoris and increased duration of angina attacks	2.9-4.5	Anderson et al. (1973)
No statistically significant vigilance decrements after exposure to CO	Below 5	Haider et al. (1976) Winneke (1974) Christensen et al. (1977) Benignus et al. (1977) Putz et al. (1976)
Statistically significant decreased maximal oxygen consumption and exercise time during strenuous exercise in young, healthy men	5-5.5	Klein et al. (1980) Stewart et al. (1978) Weiser et al. (1978)
Statistically significant diminution of visual perception, manual dexterity, ability to learn, or performance in complex sensorimotor tasks (such as driving)	5-17	Bender et al. (1971) Schulte (1973) O'Donnell et al. (1971) McFarland et al. (1944) McFarland (1973) Putz et al. (1976) Salvatore (1974) Wright et al. (1973) Rockwell and Weir (1975) Rummo and Sarlanis (1974) Putz et al. (1979) Putz (1979)
Statistically significant decreased maximal oxygen consumption during strenuous exercise in young, healthy men	7-20	Ekblom and Huot (1972) Pirnay et al. (1971) Vogel and Gleser (1972)

[a]The physiologic norm (i.e., COHb levels resulting from the normal catabolism of hemoglobin and other heme-containing materials) has been estimated to be in the range of 0.3 to 0.7% (Coburn et al., 1963). See glossary of terms and symbols for abbreviations and acronyms.

Source: U.S. Environmental Protection Agency (1984b).

certain cardiovascular effects (i.e., aggravation of angina symptoms during exercise) likely to occur in a smaller, but sizeable, segment of the general population. This group, chronic angina patients, is presently viewed as the most sensitive risk group for CO-exposure effects, based on evidence for aggravation of angina occurring in patients at COHb levels of 2.9 to 4.5%. Such aggravation of angina is thought to represent an adverse health effect for several reasons articulated in the 1980 proposal preamble (Federal Register, 1980), and the Clean Air Scientific Advisory Committee (CASAC) concurred with EPA's judgment on this matter. Dose-response relationships for cardiovascular effects in coronary artery disease patients remain to be defined more conclusively, and the possibility cannot be ruled out at this time that such effects may occur at levels below 2.9% COHb (as hinted at by the results of the now-questioned Aronow studies). Therefore, new studies published since the last review cycle are evaluated in this revised criteria document to determine the effects of CO on aggravation of angina at levels in the range of 2 to 6% COHb.

2.4.3.2 Neurobehavioral Effects

No reliable evidence demonstrating decrements in neurobehavioral function in healthy, young adults has been reported at COHb levels below 5%. Results of studies conducted at or above 5% COHb are equivocal. Much of the research at 5% COHb did not show any effect even when behaviors similar to those affected in other studies at higher COHb levels were involved. However, investigators failing to find CO decrements at 5% or higher COHb levels may have utilized tests not sufficiently sensitive to reliably detect small effects of CO. From the empirical evidence, then, it can be said that COHb levels ≥5% do produce decrements in neurobehavioral function. It cannot be said confidently, however, that COHb levels lower than 5% would be without effect. One important point made in the 1979 criteria document should be reiterated here. Only young, healthy adults have been studied using demonstrably sensitive tests and COHb levels at 5% or greater. The question of groups at special risk for neurobehavioral effects of CO, therefore, has not been explored. Of special note are those individuals who are taking drugs that have primary or secondary depressant effects which would be expected to exacerbate CO-related neurobehavioral decrements. Other groups at possibly increased risk for CO-induced neurobehavioral effects are the aged and ill, but these groups have not been evaluated for such risk.

2.4.3.3 Other Health Effects

Only relatively weak evidence points toward possible CO effects on fibrinolytic activity, generally only at rather high CO-exposure levels. Similarly, whereas certain data also suggest that perinatal effects (e.g., reduced birth weight, slowed postnatal development, Sudden Infant Death Syndrome) are associated with CO exposure, insufficient evidence presently exists by which to either qualitatively confirm such an association in humans or to establish any pertinent exposure-effect relationships.

2.5 CRITICAL ISSUES IN REVIEW OF THE NAAQS FOR CARBON MONOXIDE

Based on the scientific evidence currently evaluated in air quality criteria documents (U.S. Environmental Protection Agency, 1979, 1984a), potentially adverse health effects of CO have been demonstrated to occur at COHb levels in the range of 2.3 to 20% (see Table 2-2). However, several critical issues have developed during the current review of the scientific criteria for CO air quality standards that will need to be resolved in order to determine the extent to which adverse effects are occurring in the population, particularly at the lower COHb levels of greatest interest to standard-setting (≤5 percent). The following section will focus on specific issues pertaining to (1) exposure assessment in the general population, including the measurement of CO in ambient air and in blood; (2) mechanisms of action of CO; (3) health effects from exposure to CO; and (4) groups of individuals considered to be at greatest risk to CO at ambient or near-ambient exposure levels.

2.5.1 Exposure Assessment in the Population

The 1986 and 1987 trends in ambient air quality reported by EPA (U.S. Environmental Protection Agency, 1988, 1989a) summarize fixed-site monitoring data for carbon monoxide but only focus on 8-h averages. The rationale for this approach is that the 8-h standard (9 ppm) is typically the controlling standard and the 1-h standard (35 ppm) rarely is exceeded. For example, in 1987 there were only four exceedances of the 1-h standard for the entire United States and in each case the 8-h standard was exceeded by a greater percentage on that day. In 1988, only two areas (Denver, CO, and Steubenville, OH) exceeded the 1-h CO

standard, while 44 areas failed to meet the 8-h standard (U.S. Environmental Protection Agency, 1989b).

Ambient CO-concentration data from fixed-site monitors alone will not necessarily give a good estimate of potential total exposure to the population, based on experience from the Denver and Washington, DC human-exposure field studies using personal monitors. It is estimated that over 10% of the residents in Denver and 4% of the residents in Washington, DC, were exposed to CO levels above 9 ppm for 8 h during the winter of 1982-83 (Akland et al., 1985). The effects of personal activity, indoor sources, and time spent commuting contribute greatly to an individual's total exposure to CO. Available 1-h CO concentrations taken at fixed-site monitors in these field studies did not correlate well ($0.14 \leq r \leq 0.27$) with measurements made by personal monitors.

The best available study for determining relevant exposure to the most susceptible target population, that is, individuals with ischemic heart disease (IHD), is the work of Lambert and Colome (1988). A total of 36 nonsmoking men with IHD were followed during personal-exposure monitoring. A wide range of peak exposures to CO were measured. The highest CO exposures were found while the subjects were commuting and when the subjects were near internal combustion engines. For example, CO exposures on freeways in Los Angeles averaged 10 to 12 ppm. The average personal exposure for all time spent in automobiles was 8.6 ppm with a maximum 1-min average of 239 ppm. Concentrations of CO, averaging 7.9 ppm, also were found in parking lots, parking structures, service stations, and motor repair facilities. Residential CO exposure was much lower, averaging 2.0 ppm. In typical outdoor residential activities, transient peaks as high as 134 ppm were observed for woodcutting with a gas-powered chain saw and 226 ppm for gardening activity where a two-stroke, gasoline-powered engine was utilized. Exposures under these conditions would be expected, based on equations developed by Coburn et al. (1965), to cause COHb levels in excess of 2.5%.

The best indicator of exposure to CO continues to be the direct measurement of COHb in blood. There are, however, several issues regarding measurement techniques for COHb that have been raised during the current review of the CO air quality criteria. For many years, routine clinical laboratory measurements of COHb commonly have been made using the IL 182 and it successor, the IL 282 CO-Oximeter (Instrumentation Laboratory, Inc., Lexington, MA) which is a spectrophotometric instrument. Optical methods of COHb

measurement, however, are limited in sensitivity, particularly in the range of 0 to 5% where the lowest observed health effects associated with CO exposure have been described. Other, more sensitive techniques require the release of CO from hemoglobin into a gas phase that can be detected directly. One method for COHb measurement that has become more widely used in laboratory settings is gas chromatography. Recent efforts to compare COHb measurement by spectrophotometry versus gas chromatography have indicated that the high correlation over a wide range of concentrations (0 to >20%) becomes much worse at COHb levels <5% because of an apparent instrument offset or potential error. Thus, there has been concern about the relative accuracy and precision of the COHb measurements at levels that are of particular concern to the CO NAAQS review. Further, ongoing work is needed in order to determine (1) which method should be used to accurately quantify low levels of COHb; (2) if there is a scientifically acceptable way to compare COHb measurements made by different instruments across different laboratories; and (3) the relationship of measured COHb values to those derived from modeling efforts based on actual CO exposures in the general population.

Most "real-life" exposures to CO are to concentrations that vary with time and those exposures are experienced by people with differing physiological attributes and at varying exercise levels. Direct measurements of COHb are not readily available in the general population exposed to CO under these conditions. Mathematical models, therefore, have been developed to predict COHb levels from known CO exposures under a variety of circumstances. The most used model for COHb formation is still the Coburn-Forster-Kane equation (CFKE) developed by Coburn et al. (1965). The COHb levels predicted by this equation generally have been accepted as the best available estimates of COHb levels likely to result from varying CO concentrations, exposure durations, and exercise levels. Further research, however, is needed to evaluate the predictive capabilities of the CFKE in individuals exposed to low concentrations of CO leading to COHb levels of less than 10%. Of particular interest is the variation of predicted COHb in a population whose pattern of CO exposure involves frequent concentration variations. In addition, the CFKE needs to be evaluated for applicability to CO-susceptible subjects, such as patients with cardiovascular or pulmonary disease. Clinical evaluation of CO uptake by these individuals should be considered.

Epidemiology studies have suggested the possibility that increased mortality from heart attacks and increased cardiovascular complaints may be associated with elevated ambient concentrations of CO. Unfortunately, due to inadequate characterization of exposure as well as other limitations, inconclusive results have been obtained from existing studies. The availability of both personal-exposure monitors for CO and ambulatory EKG monitoring techniques have made it possible to design epidemiology studies to determine whether ambient CO exposures are related to serious or irreversible cardiovascular effects. It would be desirable, therefore, to obtain CO exposure data on CO-susceptible individuals in order to characterize their risk from elevated levels of COHb. Potentially susceptible individuals include infants, the elderly, and patients with known cardiovascular diseases.

2.5.2 Mechanisms of Action of Carbon Monoxide

The accepted mechanisms of action underlying the potentially toxic effects of low-level CO exposure continue to be the decreased oxygen-carrying capacity of blood and subsequent interference of oxygen release at the tissue level that is caused by the binding of CO with hemoglobin, producing COHb (Figure 2-2). The resulting impaired delivery of oxygen can interfere with cellular respiration and cause tissue hypoxia.

Review of the newer information on mechanisms of action of CO has focused on the possibility that secondary mechanisms that also can impair cellular respiration may be occurring at relatively low (near-ambient) CO-exposure levels. Approximately 10 to 50% of the total-body burden of CO can be distributed to extravascular sites, suggesting that intracellular uptake of CO may contribute to CO-induced toxicity. It is uncertain, however, if intracellular uptake of CO occurs at low levels of COHb or if it would be likely to contribute to the physiological effects of CO.

Carbon monoxide will bind to intracellular hemoproteins such as myoglobin (Mb), cytochrome oxidase, mixed function oxidases (e.g., cytochrome P-450), tryptophan oxygenase, and dopamine hydroxylase. Binding to CO would be favorable under conditions of low intracellular partial pressure of oxygen (PO_2), particularly in brain and myocardial tissue where intracellular PO_2 decreases with increasing COHb levels. The most likely hemoproteins to be inhibited functionally at relevant levels of COHb are Mb, found predominantly in heart and skeletal muscle, and cytochrome oxidase. The physiological

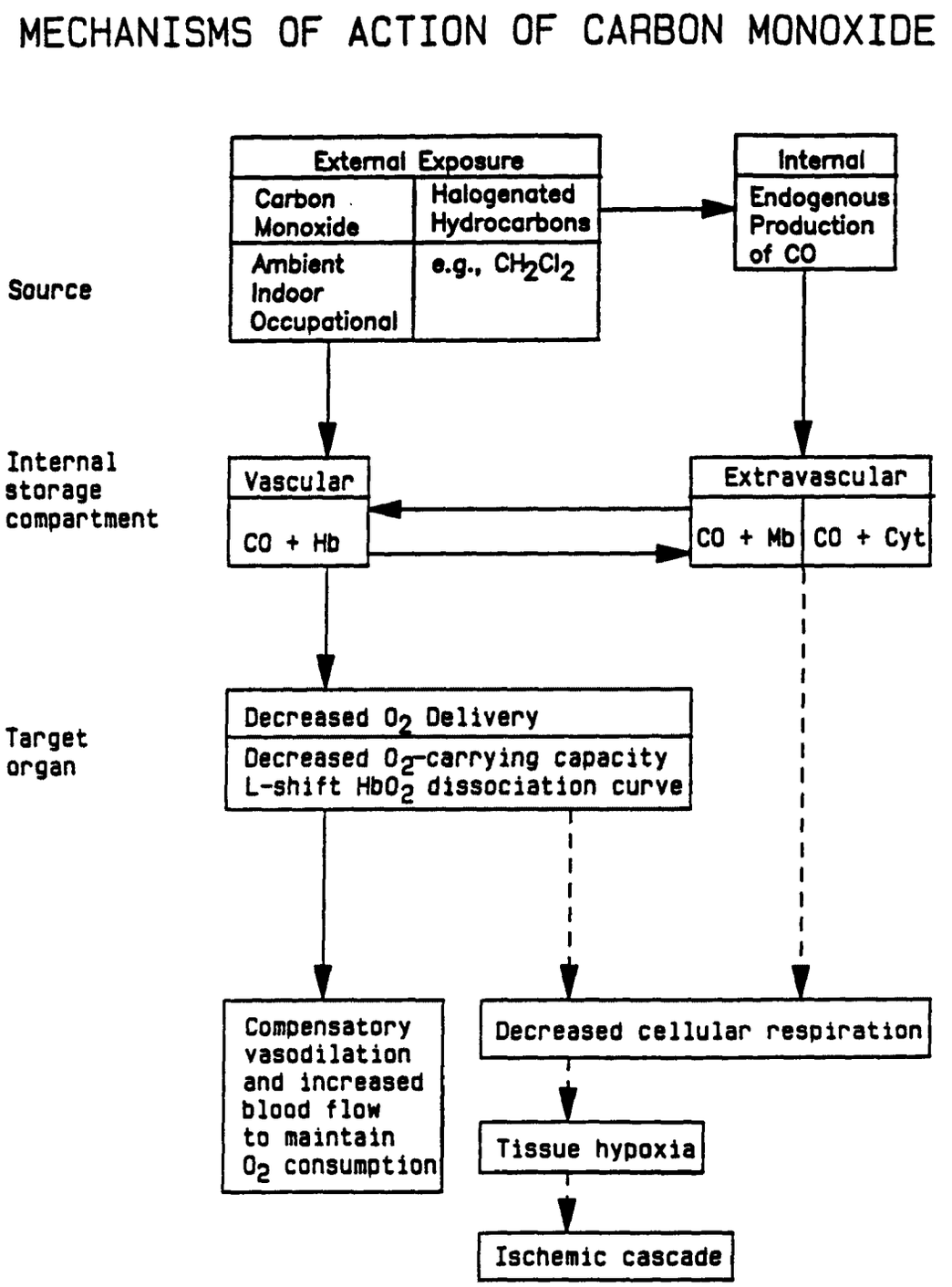

Figure 2-2. Currently accepted or proposed mechanisms of action of carbon monoxide resulting from external exposure sources can interfere with cellular respiration and cause tissue hypoxia (see text for details). See glossary of terms and symbols for abbreviations and acronyms.

significance of CO uptake by Mb is uncertain at this time but sufficient concentrations of carboxymyoglobin (COMb) could potentially limit maximal oxygen uptake of exercising muscle. Although there is suggestive evidence for significant binding of CO to cytochrome oxidase in heart and brain tissue, it is unlikely that any significant CO binding would occur at low COHb levels. Therefore, further research still is needed to determine if secondary, intracellular mechanisms will occur at exposure concentrations found in ambient air.

2.5.3 Health Effects from Exposure to Carbon Monoxide

2.5.3.1 Effects on the Cardiovascular System

Scientific support for the current NAAQS for CO is based primarily on studies of patients with stable angina pectoris (chest pain) from coronary artery disease. Although it is assumed that the development of angina reflects adverse effects of CO on myocardial metabolism, more specific research supporting the validity of this assumption is needed. For example, little is known about the reproducibility or reoccurrence of this disease. Time to onset of angina and the duration of angina are measurable outcomes that need to be defined more precisely. Research also is needed on more objective measures of myocardial ischemia, such as continuous EKG tracing for ST depression and arrhythmias, and on measurement of ventricular function using a gamma camera or thallium scan.

In view of questions concerning the validity of angina studies by Aronow et al. reviewed in the previous criteria document, additional data were clearly needed in order to (1) provide more reliable dose-response information in individuals with stable angina, (2) allow a better determination of the level of COHb necessary to cause adverse effects in the sensitive population, and (3) ultimately set an appropriate level for the CO NAAQS. In response to this need, additional studies recently have been completed by a number of independent laboratories to identify the relationship between COHb and aggravation of preexisting chronic heart disease. Four of these studies now have been published (Sheps et al., 1987; Adams et al., 1988; Kleinman et al., 1989; Allred et al., 1989). Collectively, all four studies provide new information on the likelihood that patients exposed to CO will experience angina earlier during exercise when compared to clean air exposure. Levels of COHb across the studies range from 2.9 to 5.9%, as measured by the spectrophotometric method (CO-Oximeter). An evaluation of these data is provided in this document as part of the overall

review of the scientific basis for the CO NAAQS. Any potential differences in the results between these studies primarily will be due to either the patient population studied or to the experimental design of the study itself.

Heart attack is the leading cause of death in the United States. In 1985 alone, over 540,000 deaths were attributed to coronary artery disease and over 4.8 million people alive at that time were estimated to have a history of heart attack, angina, or both (American Heart Association, 1988). Today that estimate may be as high as 6 to 7 million individuals inflicted with coronary artery disease. A major question that will become important in the evaluation of all the clinical studies involving subjects with coronary heart disease is whether the study population is representative of this broad group of patients with angina and, therefore, is applicable to the subpopulation of potentially susceptible individuals that are exposed routinely to ambient levels of CO. The possibility of studying the effects of CO in a more representative group of patients with coronary heart disease should be investigated. Recent changes in the treatment of coronary artery disease indicate that the sensitive subpopulation of angina patients may be changing from one of untreated patients to one of angina patients who have had coronary artery bypass or balloon angioplasty. The susceptibility of this new population to CO may not be the same. In addition, there is a greater likelihood of increased risk to CO exposure in a virtually unknown group of individuals who have silent ischemia (no symptomatic episodes of chest pain).

Additional research is needed to determine dose-response relationships for the acute effects of CO in other potentially susceptible groups. Patients with arteriosclerosis of the arteries of the lower limbs who develop intermittent claudication are analogous to patients with angina and could be studied in a similar manner. Research is needed to determine dose-response relationships for cardiovascular effects in individuals with ventricular arrhythmias. Patients with anemia may be susceptible to increased levels of COHb, because CO would further reduce the already compromised arterial oxygen content of the blood. Patients with chronic obstructive pulmonary disease and those with congestive heart failure also should be studied to determine if they are at increased risk to low levels of CO exposure.

Other cardiovascular effects of low-level CO exposure, particularly with prolonged or chronic exposure, have not been demonstrated. Previous studies on laboratory animals that were reviewed in the last criteria document failed to clearly link CO exposure with

atherogenesis and the development of arteriosclerosis. Newer data published since then still fail to prove conclusively an atherogenic effect of exposure to low concentrations of CO despite strong evidence from epidemiology studies showing an association between cigarette smoke and increased risk for arteriosclerosis. Other components of cigarette smoke (e.g., nicotine) as well as other risk factors (e.g., diet) also may promote atherogenesis, making it difficult to attribute the atherogenic effects of cigarette smoke to CO alone.

2.5.3.2 Neurobehavioral Effects

Neurobehavioral effects of CO exposure, such as changes in (1) hand-eye coordination (compensatory tracking), (2) detection of infrequent events (vigilance), and (3) visual system sensitivity have been reported in healthy young adults at COHb levels as low as 5%. These effects at low CO-exposure concentrations, however, have been very small and somewhat controversial. The newer data on neurobehavioral effects of CO discussed in this document apparently have provided little help in resolving this controversy. Nevertheless, the potential consequences of a lapse of coordination, vigilance, and visual sensitivity in the performance of critical tasks by operators of machinery such as public transportation vehicles could be serious. Therefore, additional research is necessary to provide a better understanding of the mechanisms of action of CO and compensatory changes in the vascular bed that may act to maintain an adequate oxygen supply to the brain.

Certain subgroups of the population are at increased risk from the neural and behavioral effects of elevated COHb. For example, any condition that would reduce oxygen supply to the brain also would potentially exacerbate the effects of CO exposure. A very large subgroup that is known to have a reduced oxygen supply to the brain is the aged. Therefore, it is important to determine COHb dose-response functions for neurobehavioral variables in older subjects. Other conditions that might reduce oxygen supply to the brain include certain cerebrovascular, cardiovascular, and pulmonary disease states mentioned above.

Another large subgroup that may be at increased risk from neurobehavioral effects of CO exposure are those people who take prescription or over–the– counter medications such as antihistamines, sedatives, antipsychotics, antiseizure drugs, antiemetics, and analgesics, that reduce alertness or motor abilities. The effects of ethanol, caffeine, nicotine, and other nonprescription drugs should not be overlooked. Such individuals already would be affected

behaviorally so that any further impairment due to elevated COHb might have serious consequences.

2.5.3.3 Perinatal Effects

The fetus and newborn infant are theoretically susceptible to CO exposure for several reasons. Fetal circulation is likely to have a higher COHb level than the maternal circulation due to differences in uptake and elimination of CO from fetal hemoglobin. Since the fetus also has a lower oxygen tension in the blood than adults, any further drop in fetal oxygen tension due to the presence of COHb could have a potentially serious effect. The newborn infant with a comparatively high rate of oxygen consumption and lower hemoglobin blood oxygen transport capacity than most adults also would be potentially susceptible to the hypoxic effects of increased COHb. Newer data from laboratory animal studies on the developmental toxicity of CO suggest that prolonged exposure to high levels (> 100 ppm) of CO during gestation may produce a reduction in birthweight, cardiomegaly, and delayed behavioral development. Human data are scant and more difficult to evaluate, but further research is warranted. Therefore, additional studies are needed in order to determine if chronic exposure to CO, particularly at low, near-ambient levels, can compromise the already marginal conditions existing in the fetus and newborn infant.

The effects of CO on maternal-fetal relationships are not understood well. In addition to fetuses and newborn infants, pregnant women also represent a susceptible group because pregnancy is associated with increased alveolar ventilation and an increased rate of oxygen consumption that serves to increase the rate of CO uptake from inspired air. Perhaps a more important factor is that pregnant women experience hemodilution due to the disproportionate increase in plasma volume as compared to erythrocyte volume. This group, therefore, should be studied to evaluate the effects of CO exposure and elevated COHb levels.

2.5.4 Population Groups at Greatest Risk for Ambient CO Exposure Effects

Angina patients or others with obstructed coronary arteries, but not yet manifesting overt symptomatology of coronary artery disease, appear to be best established as a sensitive group within the general population that is at increased risk for experiencing health effects (i.e.,

exacerbation of cardiovascular symptoms) of concern at ambient or near-ambient CO-exposure levels. Several other probable risk groups were identified: (1) fetuses and young infants; (2) pregnant women; (3) the elderly, especially those with compromised cardiopulmonary or cerebrovascular functions; (4) individuals with obstructed coronary arteries, but not yet manifesting overt symptomatology of coronary artery disease; (5) individuals with congestive heart failure; (6) individuals with peripheral vascular or cerebrovascular disease; (7) individuals with hematological diseases (e.g., anemia) that affect oxygen-carrying capacity or transport in the blood; (8) individuals with genetically unusual forms of hemoglobin associated with reduced oxygen-carrying capacity; (9) individuals with chronic obstructive lung diseases; (10) individuals using medicinal or recreational drugs having central nervous system (CNS) depressant properties; (11) individuals exposed to other pollutants (e.g., methylene chloride) that increase endogenous formation of CO; and (12) individuals who have not been adapted to high altitude and are exposed to a combination of high altitude and CO. However, little empirical evidence currently is available by which to specify health effects associated with ambient or near-ambient CO exposures in these probable risk groups.

2.6 CARBON MONOXIDE POISONING

The majority of this document deals with the relatively low concentrations of CO that induce effects in humans at or near the lower margin of detection by current medical technology. Yet, the health effects associated with exposure to this pollutant range from the more subtle cardiovascular and neurobehavioral effects at low-ambient concentrations, as identified in the preceding sections, to unconsciousness and death after prolonged chronic exposure or after acute exposure to high concentrations of carbon monoxide. The morbidity and mortality resulting from the latter exposures are described briefly here to complete the picture of CO exposure in present-day society.

Carbon monoxide is responsible for more than half of the fatal poisonings that are reported in the United States each year (National Safety Council, 1982). At sublethal levels, CO poisoning occurs in a small but important fraction of the population. Certain conditions exist in both the indoor and outdoor ambient environments that cause a small percentage of

the population to become exposed to dangerous levels of CO. Outdoors, concentrations of CO are highest near intersections, in congested traffic, near exhaust gases from internal combustion engines and from industrial combustion sources, and in poorly ventilated areas such as parking garages and tunnels. Indoors, CO concentrations in the workplace or in homes that have faulty appliances or downdrafts and backdrafts have been measured in excess of 100 ppm, resulting in COHb levels of greater than 10% for 8 h of exposure. In addition, CO is found in the smoke produced by all types of fires. Of the 6000 deaths from burns in the United States each year, more than half are related to inhalation injuries where victims die from CO poisoning, hypoxia, and smoke inhalation (Heimbach and Waeckerle, 1988).

Carbon monoxide poisoning is not new, although more attention to this problem has been addressed recently in the scientific literature as well as in the popular media. The first scientific studies of the hypoxic effects of CO were described by Claude Bernard (1865). The attachment of CO to hemoglobin, producing carboxyhemoglobin, was evaluated by Douglas et al. (1912), providing the necessary tools for studying man's response to CO. During the next half century, numerous studies were conducted with the principal emphasis being on high concentrations of COHb. Carbon monoxide poisoning as an occupational hazard (Grut, 1949) received the greatest attention due to the increased use of natural gas and the potential for leakage of exhaust fumes in homes and industry. Other sources of CO have become more important and more insidious. The clinical picture of CO poisoning, as described by Grut (1949), relate primarily to the alterations in cardiac and central nervous system function due to the extreme hypoxia induced.

Mortality from carbon monoxide exposure is high. In 1985, 1365 deaths due to CO exposure were reported in England and Wales (Meredith and Vale, 1988). In the United States, more than 3800 people die annually from CO (accidental and intentional), and more than 10,000 individuals seek medical attention or miss at least one day of work because of a sublethal exposure (U.S. Centers for Disease Control, 1982). The per capita mortality and morbidity statistics for CO are surprisingly similar for the Scandinavian countries and for Canada, as well. However, not all instances of CO poisoning are reported and complete up-to-date data are difficult to obtain. Often the individuals suffering from CO poisoning are unaware of their exposure because symptoms are similar to those associated with the flu or with clinical depression. This may result in a significant number of misdiagnoses by medical

professionals (Heckerling et al., 1988, 1987; Kirkpatrick, 1987; Dolan et al., 1987; Barrett et al., 1985; Fisher and Rubin, 1982; Grace and Platt, 1981). The precise number of individuals who have suffered from CO intoxication, therefore, is not known but it is certainly larger than the mortality figures indicate. Nonetheless, the reported literature available for review indicates the seriousness of this problem.

The symptoms, signs, and prognosis of acute poisoning correlates poorly with the level of COHb measured at the time of arrival at the hospital (Meredith and Vale, 1988). Carboxyhemoglobin levels below 10% usually are not associated with symptoms. At the higher COHb saturations of 10 to 30%, neurological symptoms of CO poisoning can occur, such as headache, dizziness, weakness, nausea, confusion, disorientation, and visual disturbances. Exertional dyspnea, increases in pulse and respiratory rates, and syncope are observed with continuous exposure producing COHb levels in excess of 30 to 50%. When COHb levels are higher than 50%, coma, convulsions, and cardiorespiratory arrest may occur.

Different individuals experience very different clinical manifestations of CO poisoning and, therefore, have different outcomes even under similar exposure conditions. Norkool and Kirkpatrick (1985) found that COHb levels in individuals who had never lost consciousness ranged from 5 to 47%. In individuals who were found unconscious but regained consciousness at hospital arrival, the range was 10 to 64%; for those remaining unconscious, COHb levels varied from 1 to 53%. These data clearly indicate that COHb saturations correlate poorly with clinical status and, furthermore, have little prognostic significance.

The level of CO in the tissues may have an equal or greater impact on the clinical status of the patient than the blood level of CO (Broome et al., 1988). For example a short exposure to CO at high ambient concentrations may allow insufficient time for significant increases in tissue levels of CO to occur. The syncope observed in these individuals may be the result of simple hypoxia with rapid recovery despite high COHb levels. A prolonged exposure to low concentrations of CO prior to hospital arrival may allow sufficient uptake of CO by tissues to inhibit the function of intracellular compounds such as myoglobin. This effect, in combination with hypoxia, may cause irreversible central nervous system or cardiac damage.

Patients with CO poisoning respond to treatment with 100% oxygen (Pace et al., 1950). If available, treatment with hyperbaric oxygen (HBO) at 2.5 to 3 times atmospheric pressure for 90 min is preferable (Myers, 1986), but the precise conditions requiring treatment have been a topic of debate in the literature (Thom and Keim, 1989; Roy et al., 1989; Raphael et al., 1989; Brown et al., 1989; James, 1989; Van Hoesen et al., 1989; Broome et al., 1988; Norkool and Kirkpatrick, 1985; Mathieu et al., 1985). It has been suggested that if COHb is above 25%, HBO treatment should be initiated (Norkool and Kirkpatrick, 1985), although treatment plans based on specific COHb saturations is not well founded (Thom and Keim, 1989). Most hyperbaric centers treat patients with CO intoxication when they manifest loss of consciousness or other neurological signs and symptoms (excluding headace) regardless of the COHb saturation at presentation (Piantadosi, 1990). The halftime elimination of CO while breathing air is approximately 320 min; when breathing 100% oxygen it is 80 min, and when breathing oxygen at 3 atmospheres it is 23 min (Penney et al., 1983; Myers et al., 1985).

Successful removal of CO from the blood does not ensure an uneventful recovery with no further clinical signs or symptoms. Neurological problems may develop insidiously weeks after recovery from the acute episode of CO poisoning (Meredith and Vale, 1988). These problems include intellectual deterioration; memory impairment; and cerebral, cerebellar, and mid-brain damage. Up to two-fifths of patients develop memory impairment and a third suffer late deterioration of personality. Arrhythmias are a common complication of CO poisoning. Conduction defects also are found, possibly from cardiomyopathies, but the precise mechanisms by which these occur are not understood. Other systemic complications, such as skeletal muscle necrosis, renal failure, blood dyscrasias, pulmonary edema, and hemorrhage in various tissues also can occur as a result of CO poisoning.

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3. PROPERTIES AND PRINCIPLES OF FORMATION OF CARBON MONOXIDE

3.1 INTRODUCTION

Carbon monoxide was first discovered to be a minor constituent of the earth's atmosphere by Migeotte (1949) in 1948. While taking measurements of the solar spectrum, he observed a strong absorption band in the infrared region at 4.7 μm, which he attributed to CO (Lagemann et al., 1947). On the twin bases of the belief that the solar contribution to that band was negligible and his observation of a strong day-to-day variability in absorption, Migeotte concluded that an appreciable amount of CO was present in the terrestrial atmosphere of Columbus, Ohio. In the 1950s many more observations (Benesch et al., 1953; Faith et al., 1959; Locke and Herzberg, 1953; Migeotte and Neven, 1952; Robbins et al., 1968; Sie et al., 1976) of CO were made, with measured concentrations ranging from 0.08 to 100 ppm. On the basis of these and other measurements available in 1963, Junge (1963) stated that CO appeared to be the most abundant trace gas, other than carbon dioxide, in the atmosphere. The studies of Sie et al. (1976) indicated higher mixing ratios near the ground than in the upper atmosphere, implying a source in the biosphere, but Junge emphasized that knowledge of the sources and sinks of atmospheric CO was extremely poor. It was not until the late 1960s that concerted efforts were made to determine the various production and destruction mechanisms for CO in the atmosphere.

Even far from human habitation, carbon monoxide occurs in air at an average background concentration of 0.05 mg/m^3, primarily as a result of natural processes such as forest fires and the oxidation of methane. Much higher concentrations occur in cities from technological sources such as automobiles and the production of heat and power. Carbon monoxide emissions are increased when the fuel is burned in an incomplete or inefficient way. The physical and chemical properties of CO suggest that its atmospheric removal occurs primarily by reaction of CO with hydroxyl ($OH^{\bullet}$) radicals.

The remainder of this chapter focuses on the physical properties and formation principles of CO that contribute to its release into the atmosphere. In Chapter 4, other source and sink estimates as well as the global cycle of CO are described; in Chapter 6, the various factors that determine the technological emission source strengths are discussed.

3.2 PHYSICAL PROPERTIES

Carbon monoxide is a tasteless, odorless, colorless diatomic molecule that exists as a gas in the earth's atmosphere. Radiation in the visible and near ultraviolet regions of the electromagnetic spectrum is not absorbed by CO, although the molecule does have weak absorption bands between 125 and 155 nm. It absorbs radiation in the infrared region corresponding to the vibrational excitation of its electronic ground state. Carbon monoxide has a low electric dipole moment (0.10 debye), short interatomic distance (1.23Å), and high heat of formation from atoms, or bond strength (2072 kJ/mol). These observations suggest that the molecule is a resonance hybrid of three structures (Perry et al., 1977), all of which contribute nearly equally to the normal ground state. General physical properties of CO are given in Table 3–1.

3.3 GASEOUS CHEMICAL REACTIONS OF CARBON MONOXIDE

In the atmosphere, carbon monoxide reacts with $OH^{\bullet}$ radicals to produce carbon dioxide and (CO_2) hydrogen ($H^{\bullet}$) atoms.

$$OH^{\bullet} + CO \rightarrow CO_2 + H^{\bullet} \qquad (3\text{-}1)$$

The $H^{\bullet}$ atoms formed in this process react very rapidly with oxygen (O_2) to produce hydroperoxyl radicals ($HO_2^{\bullet}$).

$$H^{\bullet} + O_2\ (+M) \rightarrow HO_2^{\bullet}\ (+M) \qquad (3\text{-}2)$$

The liberated $HO_2^{\bullet}$ radicals can react with nitric oxide (NO) to form nitrogen dioxide (NO_2) and regenerate $OH^{\bullet}$ radicals.

$$HO_2^{\bullet} + NO \rightarrow NO_2 + OH^{\bullet} \qquad (3\text{-}3)$$

TABLE 3-1. PHYSICAL PROPERTIES OF CARBON MONOXIDE[a]

Molecular weight	28.01
Critical point	-140°C at 34.5 atm
Melting point	-199°C
Boiling point	-191.5°C
Density	
at 0°C, 1 atm	1.250 g/L
at 25°C, 1 atm	1.145 g/L
Specific gravity relative to air	0.967
Solubility in water[b]	
at 0°C	3.54 mL/100 mL (44.3 ppmm)[c]
at 20°C	2.32 mL/100 mL (29.0 ppmm)
at 25°C	2.14 mL/100 mL (26.8 ppmm)
Explosive limits in air	12.5-74.2%
Fundamental vibration transition	2,143.3 cm^{-1}
	$CO(X^1\Sigma_g^+, v^1 = 1 Ev''O)(4.67\ \mu m)$
Conversion factors	
at 0°C, 1 atm	1 mg/m^3 = 0.800 ppm[d] 1 ppm = 1.250 mg/m^3
at 25°C, 1 atm	1 mg/m^3 = 0.873 ppm 1 ppm = 1.145 mg/m^3

[a] National Research Council (1977).
[b] Volume of carbon monoxide is at 0°C, 1 atm (atmospheric pressure at sea level = 760 torr).
[c] Parts per million by mass (ppmm = $\mu g/g$).
[d] Parts per million by volume (ppm = mg/L).
[*] See glossary of terms and symbols for abbreviations and acronyms.

The photolysis of NO_2 leads to the formation of ozone (O_3); hence, CO can contribute to the production of photochemical smog in the lower troposphere. Other radicals besides $OH^{\bullet}$ also can react with CO.

$$CO + HO_2^{\bullet} \rightarrow CO_2 + OH^{\bullet} \quad (3\text{-}4)$$

$$CO + NO_3^{\bullet} \rightarrow CO_2 + NO_2 \quad (3\text{-}5)$$

$$CO + CH_3O_2^{\bullet} \rightarrow \text{product} \quad (3\text{-}6)$$

The rates of these reactions, however, are so slow that their contribution to the overall chemistry occurring in the atmosphere is expected to be very slight. Hampson and Garvin (1978), in their review of chemical kinetics data, recommended a rate constant of $< 10^{-19}$ cm^3 $molecule^{-1}$ s^{-1} for reaction (3-4). DeMore et al. (1987), based on their analysis of rate data, suggested a rate constant of $< 4.0 \times 10^{-19}$ cm^3 $molecule^{-1}$ s^{-1} for reaction (3-5) and Heicklen (1973) recommended a value of 4×10^{-17} for reaction (3-6). In contrast, the rate constant for the CO + $OH^{\bullet}$ reaction is of the order of 10^{-13} cm^3 $molecule^{-1}$ s^{-1}, a factor of at least 10^4 to 10^6 greater than other known reactions between CO and atmospheric constituents. Thus, the reaction with $OH^{\bullet}$ is the only reaction involving CO that is expected to be of any consequence in the atmosphere.

The reaction of CO with $OH^{\bullet}$ is one of the most studied of all atmospheric reactions. Table 3-2 summarizes the results obtained in a few of these studies. More complete reviews of the kinetics of this reaction can be found in Hampson and Garvin (1978), Baulch et al. (1980), and DeMore et al. (1987). As seen in Table 3-2, the rate constants obtained in the late 1960s and early 1970s agreed fairly well and led the National Bureau of Standards (Hampson and Garvin, 1975) to recommend a value of 1.4×10^{-13} cm^3 $molecule^{-1}$ s^{-1} for the rate constant. At that time there did not appear to be either a substantial temperature or pressure dependency for this reaction. In the mid 1970s, however, Cox et al. (1976) studied the reaction at 700 torr using a mixture of N_2 and O_2 as the diluent gas. They obtained a rate constant of 2.7×10^{-13} cm^3 $molecule^{-1}$ s^{-1} and suggested that the reaction might be subject to a pressure effect. At approximately the same time, Sie et al. (1976) studied the CO + $OH^{\bullet}$ reaction as a function of pressure. When molecular hydrogen was used as the diluent gas, they found that the rate constant increased from 0.9×10^{-13} cm^3 $molecule^{-1}$ s^{-1} at a pressure

TABLE 3-2. REPORTED ROOM TEMPERATURE RATE CONSTANTS FOR THE REACTION OF OH• RADICALS WITH CO

Reference	Pressure (torr)	Diluent	Rate constant x 10^{-13} (cm^3 $molecule^{-1}$ s^{-1})
No observed pressure dependence			
Greiner (1969)	100	He	1.4 ± 0.2
Stuhl and Niki (1972)	20	He	1.3 ± 0.2
Westenberg and deHaas (1973)	1-3	He or Ar	1.3
Smith and Zellner (1973)	10-20	He or N_2O + H_2	1.4
Howard and Evenson (1974)	0.3-6	He, Ar, or N_2	1.6 ± 0.2
Davis et al. (1974)	20	He or N_2	1.6
Gordon and Mulac (1975)	730	Ar	1.5 ± 0.1
Atkinson et al. (1976)	25-650	Ar	1.5 ± 0.2
Pressure dependence observed*			
Cox et al. (1976)	700	N_2 + O_2	2.7 ± 0.2
Sie et al. (1976)	20-700	H_2	3.3 ± 0.2
Perry et al. (1977)	25-600	SF_6	3.4 ± 0.3
Chan et al. (1977)	100-700	Air	3.0 ± 0.2
Biermann et al. (1978)	25-750	N_2	2.8 ± 0.3
Paraskevopoulos and Irwin (1984)	20-700	N_2	2.2 ± 0.1
DeMore (1984)	200-730	N_2	2.1 ± 0.4
Hofzumahaus and Stuhl (1984)	20-700	N_2	2.3 ± 0.2
Hynes et al. (1986)	50-700	N_2	2.1 ± 0.2
Niki et al. (1984)	700	Air	2.4 ± 0.1
Hynes et al. (1986)	50-700	Air	2.3 ± 0.2

* Rate constants listed are the values obtained at the highest pressure used in each study.

See glossary of terms and symbols for abbreviations and acronyms.

of 20 torr to 3.3×10^{-13} cm^3 $molecule^{-1}$ s^{-1} at 700 torr. When argon was used as the diluent gas, however, the rate of the reaction was found to be insensitive to pressure changes. Subsequent research has supported this finding. In general, it appears that there is no pressure effect if noble gases (for example, helium or argon) are used as the carrier gas, but when other gases are used, such as N_2 or O_2, which are more representative of the atmosphere, the CO + $OH^{\bullet}$ reaction rate exhibits a strong pressure dependency. Table 3-2 summarizes the more recent pressure dependency studies. In all cases, the rate constant listed for the pressure dependent studies is the value obtained at the highest pressure used in each study. Excellent agreement is noted for the studies conducted in 1984 and later years.

The National Aeronautics and Space Administration (NASA) Data Evaluation Panel (DeMore, 1987) recently examined the kinetics data for the CO + $OH^{\bullet}$ reaction. They first analyzed all of the direct, low-pressure determinations to derive a zero pressure value for the rate constant. They then performed a weighted squares analysis of all the pressure-dependent data obtained since 1984 and fitted it to the expression

$$K = K^{\circ} \times (1 + CP_{atm}) \tag{3-7}$$

where

K° = zero pressure value for the rate constant,

c = constant,

P = pressure in atmospheres.

They found that the data were best fit using the expression

$$K = (1.50 \pm 0.45) \times 10^{-13} (1 + 0.6P_{atm}) \tag{3-8}$$

At a pressure of 760 torr, this corresponds to a rate constant of $2.4 \pm 0.7 \times 10^{-13}$ cm^3 $molecule^{-1}$ s^{-1}, independent of temperature. Thus, the rate constant at atmospheric pressure is substantially larger than the value that previously had been assumed for this reaction. The larger value has led to important changes in our understanding of the global CO cycle. This point is discussed in more detail in Chapter 4.

3.4 PRINCIPLES OF FORMATION BY SOURCE CATEGORY

Carbon monoxide is produced at the earth's surface during the combustion of fuels and in the atmosphere during the oxidation of anthropogenic and biogenic hydrocarbons. The role of man-made and natural hydrocarbons in CO production is discussed in Chapter 6 and only production of CO from combustion sources is addressed here.

The burning of any carbonaceous fuel produces two primary products: CO_2 and CO. The production of CO_2 predominates when the air or oxygen supply is in excess of the stoichiometric needs for complete combustion. If burning occurs under fuel-rich conditions, with less air or oxygen than is needed, CO will be produced in abundance. Most of the CO and CO_2 formed in past years simply was emitted into the atmosphere.

In recent years, concerted efforts have been made to reduce concentrations of potentially harmful materials in ambient air. Today, the CO in urban air originates almost entirely from local combustion processes. The background concentration of CO contributes less than 0.23 mg/m^3 (0.20 ppm) to the ambient air concentration at a given urban location. As a result of natural processes such as forest fires, oxidation of methane, and biological activity, the background level of CO is estimated to be about 0.05 mg/m^3 (0.04 ppm) (Seiler and Junge, 1970). See Chapter 4 for a discussion of global background concentrations.

Considerable effort has been made to reduce emissions of CO and other pollutants to the atmosphere. Since the automobile engine is recognized to be the major source of CO in most urban areas, special attention is given to the control of automotive emissions. Generally the approach has been technological: reduction of CO emissions to the atmosphere either by improving the efficiency of the combustion processes, thereby increasing the yield of CO_2 and decreasing the yield of CO; or by applying secondary catalytic combustion reactors to the waste gas stream to convert CO to CO_2.

The development and application of control technology to reduce emissions of CO from combustion processes generally have been successful and are continuing to receive deserved attention. The reduction of CO emissions from 7.0 to 3.4 g/mi, scheduled for the 1981 model year, was delayed two years, reflecting in part the apparent difficulty encountered by the automobile industry in developing and supplying the required control technology. The CO emission limit for light-duty vehicles (LDVs) at low altitude has been 3.4 g/mi since 1983; since 1984, this limit applied to LDVs at all altitudes.

Table 3-3 shows the automobile emissions control schedules that have resulted from the 1970 Clean Air Act and subsequent amendments, notably the 1977 and 1981 CAA Amendments.

The problems encountered in mass producing and marketing effective control technology for automobile engines are complex because a number of simultaneous requirements are involved (i.e., control of multiple air pollutants, fuel economy and efficiency, durability and quality control of components, and maintenance). Emission factor program testing conducted by EPA during the 1980s indicates that the durability of emission control systems continues to present a problem for in-use vehicles intended to comply with the 1983 and later requirement that CO emissions be limited to not more than 3.4 g/mi through the 50,000-mile, useful-life compliance period. (CO emissions are less than 3.4 g/mi for new, low-mileage automobiles.)

The following subsections present a brief discussion of the general principles and mechanisms of CO formation and control of emissions associated with the many combustion processes. The processes commonly are classified in two broad types, mobile sources and stationary sources, because this division generally does separate distinct types of major combustion devices. Control techniques for CO emissions from mobile and stationary sources are detailed in two National Air Pollution Control Administration publications (National Air Pollution Control Administration, 1970a,b).

3.4.1 General Combustion Processes

Incomplete combustion of carbon-containing compounds creates varying amounts of CO. The chemical and physical processes that occur during combustion are complex because they depend not only on the type of carbon compound reacting with oxygen but also on the conditions existing in the combustion chamber (Mellor, 1972; Pauling, 1960). Despite the complexity of the combustion process, certain general principles regarding the formation of CO from the combustion of hydrocarbon fuels are accepted widely.

Gaseous or liquid hydrocarbon fuel reacts with molecular oxygen in a chain of reactions that result in CO. Carbon monoxide then reacts with $OH^{\bullet}$ radicals to form CO_2. The second reaction is approximately ten times slower than the first. In coal combustion, too, the reaction of carbon and oxygen to form CO is one of the primary reactions, and a large

TABLE 3-3. SUMMARY OF LIGHT-DUTY VEHICLE (LDV) EMISSIONS STANDARDS[1]

Year	Test Procedure[2]	Hydro-carbons	Carbon Monoxide	Oxides of Nitrogen	Particu-lates[3]	Evaporative Hydrocarbons[4]
			Gasoline-fueled LDVs			
Prior to controls	7-mode	850 ppm	3.4 %	1000 ppm	-	-
	7-mode	11 g/mi	80 g/mi	4 g/mi	-	-
	CVS-75	8.8 g/mi	87.0 g/mi	3.6 g/mi	-	-
1968-69	7-mode					
	50-100 CID	410 ppm	2.3 %	-	-	-
	101-140 CID	350 ppm	2.0 %	-	-	-
	> 140 CID	275 ppm	1.5 %	-	-	-
1970	7-mode	2.2 g/mi	23 g/mi	-	-	-
1971	7-mode	2.2 g/mi	23 g/mi	-	-	6.0 g/test[5]
1972	CVS-72	3.4 g/mi	39 g/mi	-	-	2.0 g/test
1973-74	CVS-72	3.4 g/mi	39 g/mi	-	-	2.0 g/test
			Gasoline-fueled and diesel LDVs			
1975-76	CVS-75	1.5 g/mi	15 g/mi	3.1 g/mi	-	2.0 g/test
1977[6]	CVS-75	1.5 g/mi	15 g/mi	2.0 g/mi	-	2.0 g/test
1978-79	CVS-75	1.5 g/mi	15 g/mi	2.0 g/mi	-	6.0 g/test
1980	CVS-75	0.41 g/mi	7.0 g/mi	2.0 g/mi	-	6.0 g/test
1981	CVS-75	0.41 g/mi	3.4 g/mi[7]	1.0 g/mi[8,9]	-	2.0 g/test
1982[10]	CVS-75	0.41 g/mi (0.57)	3.4 g/mi[7] (7.8)[11]	1.0 g/mi[8,9] (1.0)[8,9]	0.60 g/mi (-)	2.0 g/test (2.6)
1983[10]	CVS-75	0.41 g/mi (0.57)	3.4 g/mi (7.8)	1.0 g/mi[8] (1.0)[8]	0.60 g/mi (0.60)	2.0 g/test (2.6)
1984-86[12]	CVS-75	0.41 g/mi	3.4 g/mi	1.0 g/mi[8]	0.60 g/mi	2.0 g/test
1987 & later[12]	CVS-75	0.42 g/mi (0.41)	3.4 g/mi (3.4)	1.0 g/mi (1.0)	0.20 g/mi[13] (0.20)[13]	2.0 g/test (2.0)

TABLE 3-3. (cont'd) SUMMARY OF LIGHT-DUTY VEHICLE (LDV) EMISSIONS STANDARDS

[1] Standards do not apply to LDVs with engines less than 50 CID from 1968 through 1974.

[2] Different test procedures, which vary in stringency, have been used since the early years of emission control. The appearance that the standards were relaxed from 1971 to 1972 is incorrect; the 1972 standards actually are more stringent because of the 1972 test procedure.

[3] Applies only to diesel LDVs.

[4] Evaporative emissions determined by carbon-trap method through 1977, SHED procedure beginning in 1978. Applies only to gasoline-fueled LDVs.

[5] Evaporative standard does not apply to off-road utility LDVs for 1971.

[6] LDVs sold in specified high-altitude counties are required to meet these standards at high altitude.

[7] Carbon monoxide standard is waived to 7.0 g/mi for 1981-82 for certain LDVs.

[8] Oxides of nitrogen standard is waived to 7.0 g/mi for 1981-82 for certain LDVs.

[9] Oxides of nitrogen standard for 1981-82 is 2.0 g/mi for American Motors Corporation LDVs.

[10] Standards in parentheses apply to LDVs sold in specified high-altitude counties.

[11] LDVs eligible for a carbon monoxide waiver to 7.0 g/mi at low altitude are eligible for a waiver to 11 g/mi at high altitude.

[12] The same numerical standards apply to LDVs sold in high-altitude areas. Exemptions from compliance at high-altitude are provided for qualifying low-performance vehicles.

[13] Emissions averaging may be used to meet this standard, provided that emissions from LDVs produced for sale in California or in designated high-altitude areas may be averaged only within each of those areas.

CID - cubic inch displacement
CVS-72 - constant volume sample cold start test
CVS-75 - constant volume sample test including cold and hot starts
g/mi - grams per mile
ppm - parts per million
7-mode - 137 second driving cycle test
SHED - sealed housing for evaporative determination

Source: AP-42 Supplement (1989); (in press)

fraction of carbon atoms go through the monoxide form. Again, the reaction of monoxide to dioxide is much slower.

Four basic variables control the concentration of CO in the combustion of all hydrocarbon gases. These are (1) O_2 concentration, (2) flame temperature, (3) gas residence time at high temperatures, and (4) combustion chamber turbulence. Oxygen concentration affects the formation of both CO and CO_2 because O_2 is required in the initial reactions with the fuel molecule and in the formation of the $OH^{\bullet}$ radical. As the availability of O_2 increases, more complete conversion of monoxide to dioxide results. Flame and gas temperatures affect both the formation of monoxide and the conversion of monoxide to dioxide because both reaction rates increase exponentially with increasing temperature. Also, the $OH^{\bullet}$ radical concentration in the combustion chamber is very temperature-dependent. The conversion of CO to CO_2 also is enhanced by longer residence time, because this is a relatively slow reaction in comparison with CO formation. Increased gas turbulence in the combustion zones increases the actual reaction rates by increasing the mixing of the reactants and assisting the relatively slower gaseous diffusion process, thereby resulting in more complete combustion.

3.4.2 Combustion Engines

Mobile Combustion Engines--Most mobile sources of CO are internal combustion engines of two types: (1) gasoline-fueled, spark-ignition, reciprocating engines (carbureted or fuel-injected); and (2) diesel-fueled reciprocating engines. The CO emitted from any given engine is the product of the following factors: (1) the concentration of CO in the exhaust gases, (2) the flow rate of exhaust gases, and (3) the duration of operation.

Internal Combustion Engines (Gasoline-Fueled, Spark-Ignition Engines)--Exhaust concentrations of CO increase with lower (richer) air-to-fuel (A/F) ratios, and decrease with higher (leaner) A/F ratios, but remain relatively constant with ratios above the stoichiometric ratio of about 15:1 (Hagen and Holiday, 1964). The behavior of gasoline automobile engines before and after the installation of pollutant control devices differs considerably. Depending on the mode of driving, the average uncontrolled engine operates at A/F ratios ranging from about 11:1 to a point slightly above the stoichiometric ratio. During the idling mode, at low speeds with light load (such as low-speed cruise), during the full-open throttle mode until speed picks up, and during deceleration, the A/F ratio is low in uncontrolled cars and CO

emissions are high. At higher speed cruise and during moderate acceleration, the reverse is true. Cars with exhaust controls generally remain much closer to stoichiometric A/F ratios in all modes, and thus the CO emissions are kept lower. The relationship between CO concentrations in engine exhaust and A/F ratios is shown in Figure 3-1. The exhaust flow rate increases with increasing engine power output.

The decrease in available oxygen with increasing altitude has the effect of enriching the A/F mixture and increasing CO emissions from carbureted engines. Fuel-injected gasoline engines, which predominate in the vehicle fleet today, have more closely controlled A/F ratios and are designed and certified to comply with applicable emission standards regardless of elevation (U.S. Environmental Protection Agency, 1983).

Correlations between total emissions of CO in grams per vehicle mile and average route speed show a decrease in emissions with increasing average speed (Simonaitis and Heicklen, 1972; Stuhl and Niki, 1972; U.S. Environmental Protection Agency, 1985). During low speed conditions (below 32 km/h or 20 mi/h average route speed), the greater emissions per unit of distance traveled are attributable to (1) an increased frequency of acceleration, deceleration, and idling encountered in heavy traffic; and (2) the consequent increase in the operating time per mile driven.

The CO and the unburned hydrocarbon exhaust emissions from an uncontrolled engine result from incomplete combustion of the fuel-air mixture. Emission control on new vehicles is being achieved by engine modifications, improvements in engine design, and changes in engine operating conditions. Substantial reductions in CO and other pollutant emissions result from consideration of design and operating factors such as leaner, uniform mixing of fuel and air during carburetion, controlled heating of intake air, increased idle speed, retarded spark timing, improved cylinder head design, exhaust thermal reactors, oxidizing and reducing catalysts, secondary air systems, exhaust recycle systems, electronic fuel injection, A/F ratio feedback controls, and modified ignition systems (National Research Council, 1973).

Internal Combustion Engines (Diesel Engines)--Diesel engines in use are primarily the heavy-duty type that power trucks and buses. Diesel engines allow more complete combustion and use less volatile fuels than do spark-ignition engines. The operating principles are

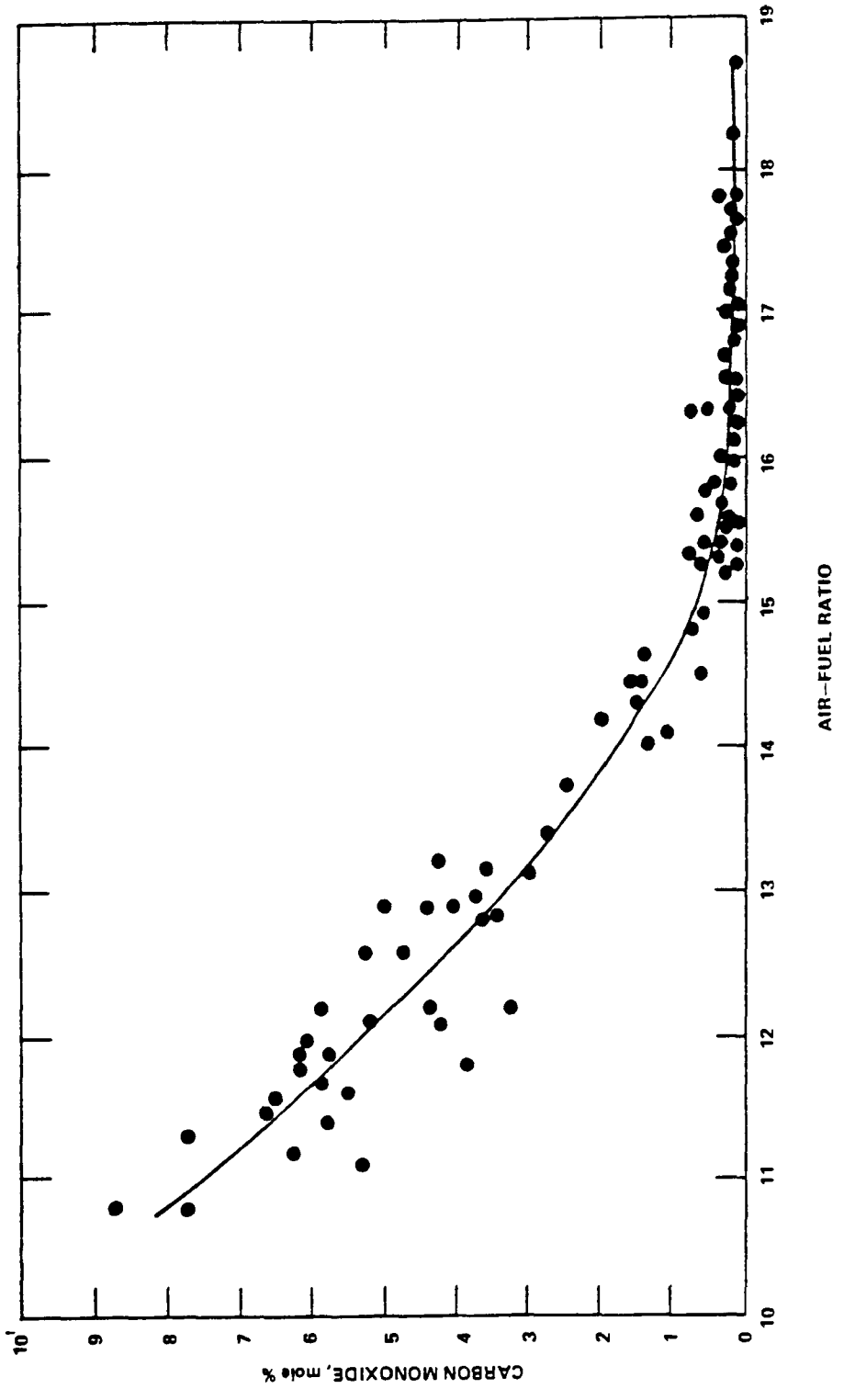

Figure 3-1. Effect of air-fuel ratio on exhaust gas carbon monoxide concentrations from three gasoline-fueled test engines.

Source: Hagen and Holiday, 1964.

significantly different from those of the gasoline engine. In diesel combustion, CO concentrations in the exhaust are relatively low because high temperature and large excesses of oxygen are involved in normal operation. The exhaust emissions from diesel engines have the same general composition as gasoline engine emissions, though the concentrations of different pollutants vary considerably. For example, the diesel emits larger quantities of nitrogen oxides (NO_x) and polycyclic organic particulates than gasoline engines; it emits less CO.

Stationary Combustion Sources (Steam Boilers)--This section refers to fuel-burning installations such as coal-, gas-, or oil-fired heating or power generating plants (external combustion boilers).

In these combustion systems, the formation of CO is lowest at a ratio near or slightly above the stoichiometric ratio of air to fuel. At lower than stoichiometric A/F ratios, high CO concentrations reflect the relatively low O_2 concentration and the possibility of poor reactant mixing from low turbulence. These two factors can increase emissions even though flame temperatures and residence time are high. At higher than stoichiometric A/F ratios, increased CO emissions result from decreased flame temperatures and shorter residence time. These two factors remain predominant even when O_2 concentrations and turbulence increase. Minimal CO emissions and maximum thermal efficiency, therefore, require combustor designs that provide high turbulence, sufficient residence time, high temperatures, and near stoichiometric A/F ratios. Combustor design dictates the actual approach to that minimum.

The measurement of CO in effluent gas is used as an indication of improper and inefficient operating practice for any given combustor, or of inefficient combustion.

3.4.3 Other Sources

There are numerous industrial activities that result in the emission of CO at one or more stages of the process (Walsh and Nussbaum, 1978). Manufacturing pig iron can produce as much as 700 to 1,050 kg CO/metric ton of pig iron. Other methods of producing iron and steel can produce CO at a rate of 9 to 118.5 kg/metric ton. However, most of the CO generated is normally recovered and used as fuel. Conditions such as "slips", abrupt collapses of cavities in the coke-ore mixture, can cause instantaneous emissions of CO that

temporarily exceed the capacity of the control equipment. Slips have been reduced greatly with modern equipment. Grey-iron foundries can produce 72.5 kg CO/metric ton of product, but an efficient afterburner can reduce the CO emission to 4.5 kg/metric ton.

Charcoal production results in CO emissions of 160 kg/metric ton with or without the installation of chemical recovery equipment. Emissions from carbon black manufacture can range from 5 to 3,200 kg CO/metric ton depending on the efficiency and quality of the emission control systems.

Some chemical processes such as phthalic anhydride production give off as little as 6 kg CO/metric ton with proper controls or as much as 200 kg CO/metric ton if no controls are installed. There are numerous other chemical processes that produce relatively small CO emissions per metric ton of product, such as sulfate pulping for paper at 1 to 30 kg CO/metric ton; lime manufacturing normally runs 1 to 4 kg CO/metric ton; and CO from adipic acid production is zero or slight with proper controls. Other industrial chemical processes that cause CO emissions are the manufacture of terephthalic acid and the synthesis of methanol and higher alcohols. As a rule, most industries find it economically desirable to install suitable controls to reduce CO emissions.

Even though some of these CO emission rates seem excessively high, they are, in fact, only a small part of the total pollutant load. Mention of these industries is made to emphasize the concern for localized pollution problems when accidents occur or proper controls are not used.

While the estimated CO emissions resulting from forest wildfires in the United States for 1971 was 4×10^6 metric tons, the estimated total industrial process CO emission of the U.S. for 1971 was 10.3×10^6 metric tons.

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4. THE GLOBAL CYCLE OF CARBON MONOXIDE: TRENDS AND MASS BALANCE

4.1 INTRODUCTION

In the troposphere CO may control the removal, and therefore the concentrations, of $OH^{\bullet}$ radicals (Crutzen, 1974; Khalil and Rasmussen, 1985; Levine et al., 1985; Sze, 1977; Thompson and Cicerone, 1986). The chemical reactions of CO also may produce substantial amounts of O_3 in the troposphere (Conrad and Seiler, 1982; Fishman and Crutzen, 1978; Fishman et al., 1980; Fishman and Seiler, 1983; Seiler and Fishman, 1981). If the concentrations of CO increase, O_3 may increase; concomitantly, $OH^{\bullet}$ may be depleted thus affecting the global cycles of many natural and anthropogenic trace gases that are removed from the atmosphere by reacting with $OH^{\bullet}$. Therefore increasing CO may indirectly affect the global climate and contribute to widespread changes in atmospheric chemistry.

The purpose of this chapter is to review the present understanding of the sources and sinks of CO and the resulting global distributions and trends. The first section is a review of the global sources and sinks and the estimated atmospheric lifetime of CO. The next section deals with the global distribution of CO resulting from the sources and sinks, including variations with seasons, altitude, and latitude. Next, there is an analysis of the current evidence for global trends that reflect an imbalance of the sources and sinks probably caused by steadily increasing emissions from anthropogenic sources. The chapter is concluded with a summary.

4.2 GLOBAL SOURCES, SINKS, AND LIFETIME

The mass balance of a trace gas in the atmosphere can be described as a balance between the rate of change of the global burden added to the annual rate of loss on the one side and balanced by the global emissions on the other side (d concentration/dt + loss rate = source emissions). In steady state the atmospheric lifetime (τ) is the ratio of the global burden to the loss rate. The global burden is the total number of molecules of a trace gas in the atmosphere or its total mass. The concentration of a trace gas can vary (dC/dt is not 0)

when either the loss rate or the emissions vary cyclically in time representing seasonal variations or vary over a long time often representing trends of human industrial activities and increasing population. For CO both types of trends exist. There are large seasonal cycles mostly driven by seasonal variations in the loss rate but also affected by seasonal variations of emissions, and there are indications of long-term trends probably caused by increasing anthropogenic emissions.

It appears that the largest sources of CO in the global atmosphere are combustion processes and the oxidation of hydrocarbons. CO is produced in the atmosphere by reactions of $OH^{\bullet}$ with methane (CH_4) and other hydrocarbons, both man-made and natural, and also from the reactions of alkenes with O_3 and of isoprene and terpenes with both $OH^{\bullet}$ and O_3. Most of the CO is removed from the atmosphere by reacting with tropospheric $OH^{\bullet}$ radicals.

4.2.1 Sources

Carbon monoxide comes from both natural and anthropogenic processes. About half of the CO is released at the earth's surface while the rest is produced in the atmosphere. Many papers on the global sources of CO have been published over the last 15 years; whether most of the CO in the atmosphere is from human activities or from natural processes has been debated for nearly as long. Before 1970 it was believed that CO in the troposphere was almost all man-made (Jaffe, 1968, 1973). Later, based on the theory that oxidation of CH_4 produces large amounts of CO, it was suggested that much of the CO in the non-urban troposphere was of natural origin (Levy, 1971, 1973; McConnell et al., 1971; National Research Council, 1977; Weinstock and Niki, 1972; Wofsy, 1976; Wofsy et al., 1972). However, this view was controversial (Newell, 1977; Stevens et al., 1972). At that time, it commonly was believed that CH_4 came from natural processes, although the existing tabulation of the sources suggested otherwise (Ehhalt and Schmidt, 1978). Even now the source of CO from the oxidation of CH_4 often is regarded as natural as opposed to the direct emissions of CO from combustion processes. However, there is good evidence that about half the CH_4 in the atmosphere is from human activities, particularly rice paddies, cattle, urban areas, landfills, and other sources (Khalil and Rasmussen, 1983). Therefore, regardless of how much CO is estimated to come from the oxidation of CH_4 about half of it could be considered to come indirectly from anthropogenic activities. In recent years the estimates of

the average level of $OH^{\bullet}$ radicals have been revised downward so that the production of CO from CH_4 and other hydrocarbons no longer is thought to be the dominant source (Hameed and Stewart, 1979; Logan et al., 1981; Pinto et al., 1983).

The recent budgets that take into account previously published data, suggest that human activities are responsible for about 60% of the CO in the non-urban troposphere while natural processes account for the remaining 40%. It also appears that combustion processes directly produce about 40% of the annual emissions of CO (Jaffe, 1968, 1973; Robinson and Robbins, 1969, 1970; Swinnerton et al., 1971), while oxidation of hydrocarbons make up most of the remainder (Greenberg et al., 1985; Hanst et al., 1980; Rasmussen and Went, 1965; Went, 1960, 1966; Zimmerman et al., 1978) (about 50%) along with other sources such as the oceans (Bauer et al., 1980; DeMore et al., 1985; Lamontagne et al., 1971; Logan et al., 1981; Linnenbom et al., 1973; Liss and Slater, 1974; National Research Council, 1977; Seiler, 1974; Seiler and Junge, 1970; Seiler and Schmidt, 1974; Swinnerton et al., 1969, 1974) and vegetation (Bauer et al., 1980; Bidwell and Fraser, 1972; DeMore et al., 1985; Krall and Tolbert, 1957; Logan et al., 1981; National Research Council, 1977; Seiler, 1974; Seiler and Giehl, 1977; Seiler et al., 1978; Seiler and Junge, 1970; Siegel et al., 1962; Wilks, 1959). Some of the hydrocarbons that eventually end up as CO also are produced by combustion processes constituting an indirect source of CO from combustion. These conclusions are summarized in Table 4-1 which is adapted from the 1981 budget of Logan et al. (1981) in which most of the previous work was incorporated (Logan et al., 1981; World Meteorological Organization, 1986), including the CO budget of Seiler (1974). The total emissions of CO are about 2,600 Tg/year. Other budgets by Volz et al. (1981) and by Seiler and Conrad (1987) are reviewed by Warneck (1988). Global emissions between 2,000 and 3,000 Tg/year are consistent with these budgets.

4.2.2 Sinks

It is believed that reaction with $OH^{\bullet}$ radicals is the major sink for removing CO from the atmosphere. The cycle of $OH^{\bullet}$ itself cannot be uncoupled from the cycles of CO, CH_4, water (H_2O), and O_3. In the troposphere $OH^{\bullet}$ radicals are produced by the photolysis of O_3 ($h\upsilon + O_3 \longrightarrow O(^1D) + O_2$) followed by the reaction of the excited oxygen atoms with H_2O

TABLE 4-1. SOURCES OF CARBON MONOXIDE
(Teragrams per year)

		Anthropogenic	Natural	Global	Range
I.	Directly from Combustion				
	Fossil Fuels	500	--	500	400 - 1,000
	Forest Clearing	400	--	400	200 - 800
	Savanna Burning	200	--	200	100 - 400
	Wood Burning	50	--	50	25 - 150
	Forest Fires	--	30	30	10 - 50
II.	Oxidation of Hydrocarbons				
	Methane	300	300	600	400 - 1,000
	Non-methane HCs	90	600	690	300 - 1,400
III.	Other Sources				
	Plants	--	100	100	50 - 200
	Oceans	--	40	40	20 - 80
TOTALS (Rounded)		1,500	1,100	2,600	2,000 - 3,000

Notes:

1. Table adapted from Logan et al. (1981) and revisions reported by World Meteorological Organization (1986). All estimates are in Tg/year of CO. Tg/year = megatons/year = 10^{12} g/year.

2. All estimates are expressed to one significant figure. The sums are rounded to two significant digits.

3. Half the production of CO from the oxidation of CH_4 is attributed to anthropogenic sources and the other half to natural sources based on the budget of CH_4 from Khalil and Rasmussen (1984c).

vapor to produce two hydroxyl radicals ($O(1D) + H_2O \longrightarrow OH^{\bullet} + OH^{\bullet}$). The production of $OH^{\bullet}$ radicals is balanced by their removal principally by reactions with CO and CH_4. On a global scale CO removes many more $OH^{\bullet}$ radicals than CH_4, however CH_4 becomes more important in the southern hemisphere where there is much less CO than in the northern hemisphere but the amount of CH_4 is only slightly less.

The amount of CO that is removed by reactions with $OH^{\bullet}$ radicals can be estimated by calculating the loss as $= K_{eff}[OH^{\bullet}]_{ave}[CO]_{ave}$. The reaction rate constant of $CO + OH^{\bullet}$ is $K = (1.5 \times 10^{-13})(1 + 0.6\ P_{atm})$ cm^3/molecules-s (DeMore et al., 1987). K_{eff} describes the effective reaction rate constant taking into account the decreasing atmospheric pressure and decreasing CO concentrations with height. Estimating K_{eff} to be 2×10^{-13} cm^3/molecules-s and taking $[OH^{\bullet}]_{ave}$ to be 8×10^5 molecules/cm^3 and $[CO]_{ave}$ to be 90 ppbv, the annual loss of CO from reactions with $OH^{\bullet}$ is about 2,200 Tg/year. The values adopted for $[OH^{\bullet}]_{ave}$ and $[CO]_{ave}$ are discussed in more detail later in this chapter.

Uptake of CO by soils has been documented and may amount to about 250 Tg/year or about 10% of the total emitted into the atmosphere (Bartholomew and Alexander, 1981; Ingersoll et al., 1974; Inman et al., 1971; Seiler and Schmidt, 1974), although arid soils may release CO into the atmosphere (Conrad and Seiler, 1982). Another 100 Tg (5%) or so are probably removed annually in the stratosphere (Seiler, 1974).

4.2.3 Atmospheric Lifetime

Based on the global sources and sinks described above, the average atmospheric lifetime of CO can be calculated to be about 2 months with a range of between 1 and 4 months which reflects the uncertainty in the annual emissions of CO (τ = C/S). The lifetime, however, can vary enormously with latitude and season compared to its global average value. During winters at high and middle latitudes CO has a lifetime of more than a year but during summers at mid latitudes the lifetime may be closer to the average global lifetime of about 2 months. Moreover, in the tropics the average lifetime of CO is probably about 1 month. These calculated variations reflect the seasonal cycles of $OH^{\bullet}$ at various latitudes.

4.2.4 Latitudinal Distribution of Sources

When the sources, sinks, transport, and observed concentrations are combined into a mass balance model it is possible to calculate any one of these four components if the others are known. In the case of CO, the sources can be estimated assuming that the sinks ($OH^{\bullet}$ reaction and soils), transport, and concentrations are known. The latitudinal distribution of sources can be described in a one-dimensional model as follows:

$$S(\mu,t) = \varepsilon(\mu) \left\{ \frac{\partial}{\partial \mu} + \tau^{-1}(\mu,t) - \frac{1}{H(\mu)\varepsilon(\mu)} \frac{\partial}{\partial \mu} (1-\mu^2) \frac{K(\mu,t)}{R^2} H(\mu) \frac{\partial}{\partial \mu} \right\} C(\mu,t) \qquad (4\text{-}1)$$

where

C = tropospheric mixing ratio
K = zonally and height averaged transport coefficient
τ = the lifetime
S = emissions
ε = a factor to account for the lower concentrations of CO in the stratosphere
H = a factor to account for the variation of the tropopause height with latitude
μ = the sine of latitude
R = the radius of the earth

This model is similar to that described by Czeplak and Junge (1974) and Fink and Klais (1978). A time-averaged version was applied to the CO budget by Hameed and Stewart (1979) and a somewhat modified and time-dependant version shown above was applied by Khalil and Rasmussen (1988c) to derive the latitudinal distribution of CO shown in Figure 4–1. Calculations by Khalil and Rasmussen (1988c) also suggest that emissions are higher in spring and summer compared with the other seasons, particularly in the middle northern latitudes. This is expected for two reasons: (1) oxidation of CH_4 and other hydrocarbons is faster during the summer because of the seasonal variation of $OH^{\bullet}$, and (2) other direct emissions are also greater during spring and summer.

From Figure 4-1 the emissions from the northern and southern tropical latitudes sum up to 480 Tg/year and 330 Tg/year, respectively; from the northern and southern middle latitudes the emissions are 960 Tg/year and 210 Tg/year; from the Arctic some 50 Tg are emitted each year and some 10 Tg/year come from the Antarctic. The largest fluxes of CO are from the industrial band of latitudes between 30° to 50° North. From this region some 620 Tg/year are emitted representing about 30% of the total emissions of 2050 Tg/year. The model does not distinguish between the anthropogenic or natural sources nor does it distinguish between direct emissions and photochemical production of CO from the oxidation of hydrocarbons. Much of estimated fluxes from the mid-northern latitudes and from tropical regions are likely to be of anthropogenic origin. The latitudinal distribution in Figure 4-1 is compatible with the estimate (Table 4-1) that about 60% of the total emissions are from anthropogenic activities.

4.2.5 Uncertainties and Consistencies

The first consistency one notes is that the total emissions of CO estimated from the various sources are balanced by the estimated removal of CO. The approximate balance between sources and sinks is expected because the trends, to be discussed later, are only about 4 to 8 Tg/year compared to the total global emission rate of more than 2000 Tg/year. On the other hand, there are many uncertainties in the sources and sinks.

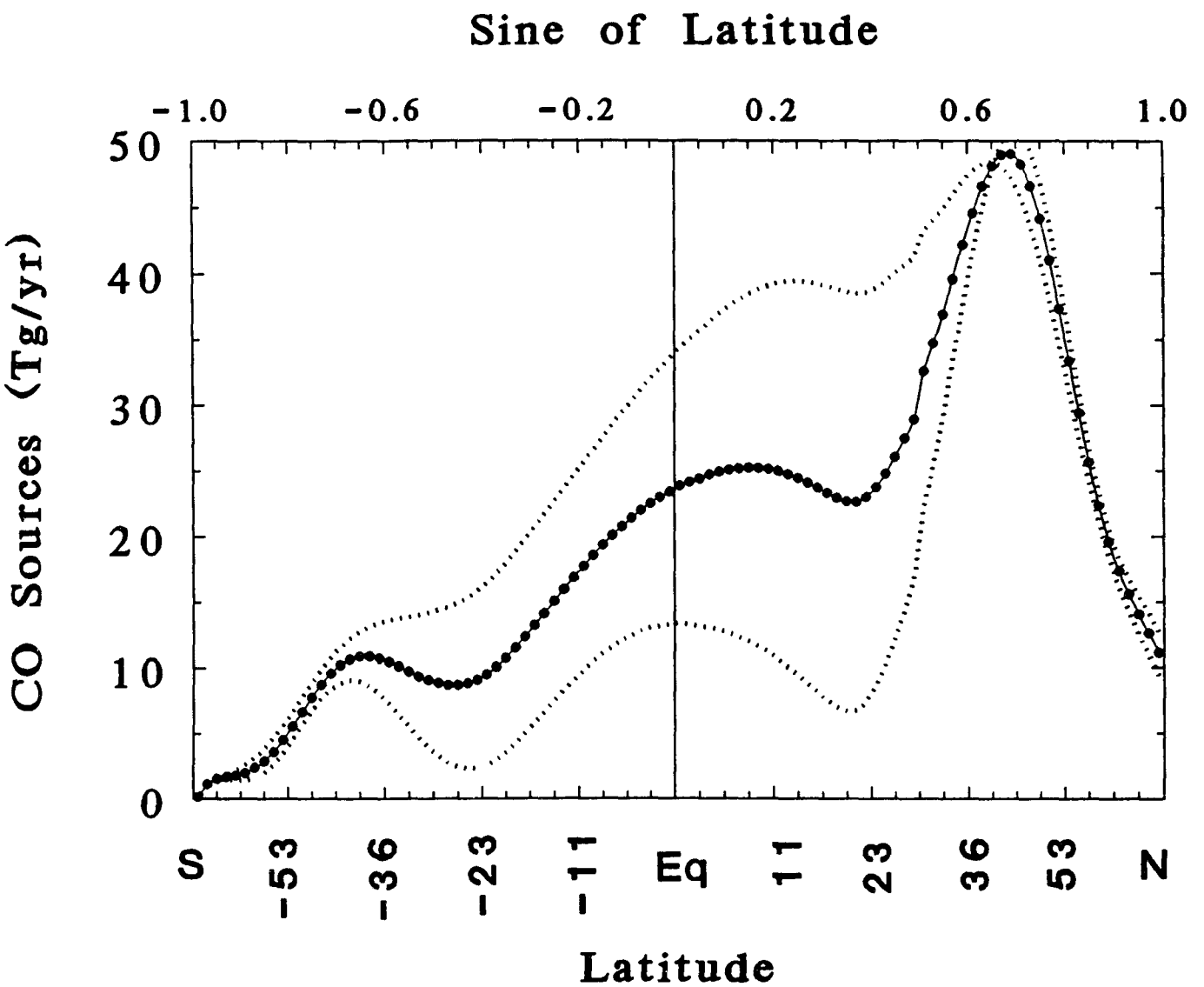

Figure 4-1. The estimated sources of CO as a function of latitude. The sources are in teragrams per year in each latitude band 0.02 units in sine of latitude. The solid lines are estimates of uncertainties as $OH^{\cdot}$ concentrations and the rate of dispersion are varied simultaneously so that the maximum values of each of these parameters are twice the minimum values.

Source: Khalil and Rasmussen (1988c).

There are large uncertainties in the estimates of emissions from individual sources as expressed in Table 4-1. In most cases the stated uncertainty is a qualitative expression of the likely range of emissions and it cannot be interpreted statistically. Therefore the resulting uncertainty in the total emissions, obtained by adding up the uncertainties in individual sources, appears to be large.

There are two difficulties in improving the estimates of CO from individual sources. First, although many critical experiments to determine the production and emissions of CO from individual sources are yet to be done, there is a limit to the accuracy with which laboratory data can be extrapolated to the global scale. Second, the cycle of CO may be so intimately tied up with the cycles of hydrocarbons that accurate global estimates of CO emissions may not be possible until the cycles of the hydrocarbons are better understood.

Whereas the global distribution and seasonal variations of $OH^{\bullet}$ can be calculated, there are no direct measurements of $OH^{\bullet}$ that can be used to estimate the removal of CO. The effective average concentration of $OH^{\bullet}$ that acts on trace gases can be estimated indirectly from the cycles of other trace gases with known global emissions. Therefore the total emissions of CO are constrained by the budgets of other trace gases even though the estimates of emissions from individual sources may remain uncertain. The most notable constraint may be the budget of methylchloroform (CH_3CCl_3). Methylchloroform is a degreasing solvent that has been emitted into the atmosphere in substantial quantities for more than 20 years. It is thought to be removed principally by reacting with $OH^{\bullet}$ radicals and to a lesser extent by photodissociation in the stratosphere. Because industry records on CH_3CCl_3 production and sales have been kept for a long time, it can be used to estimate the average amount of $OH^{\bullet}$ radicals needed to explain the observed concentrations compared to the emissions. The accuracy of the source estimates of CH_3CCl_3 is improved by the patterns of its uses; most of it tends to be released shortly after purchase, so that large unknown or unquantified reservoirs probably do not exist. The recent budgets of CH_3CCl_3 suggest that on an average there are about 8×10^5 molecules of $OH^{\bullet}$ per cubic centimeter although significant uncertainties remain (see for example Khalil and Rasmussen, 1984c; Prinn et al., 1987). This is the value used earlier in estimating the loss of CO from reaction with $OH^{\bullet}$. The same average value of $OH^{\bullet}$ also explains the CH_4 concentrations compared to estimated sources, lending more support to the accuracy of the estimated $OH^{\bullet}$ concentrations. Neither of these constraints is very

stringent; however, if the total global emissions of CO from all sources are much different from the estimated 2600 Tg/year then revisions of the budgets of both CH_4 and CH_3CCl_3 may be required.

There are other sources and sinks of CO, believed to be of lesser importance on a global scale, which are reviewed in the previous EPA criteria document on CO (Chan et al., 1977; Swinnerton et al., 1971).

4.3 GLOBAL DISTRIBUTIONS

Atmospheric concentrations and thus the global distribution generally are the most accurately known components of a global mass balance of a trace gas because direct atmospheric measurements can be taken (Dianov-Klokov and Yurganov, 1981; Ehhalt and Schmidt, 1978; Fraser et al., 1986; Heidt et al., 1980; Hoell et al., 1984; Khalil and Rasmussen, 1988a,b; Pratt and Falconer, 1979; Rasmussen and Khalil, 1982; Reichle et al., 1982; Seiler, 1974; Seiler and Fishman, 1981; Wilkness et al., 1973). Much has been learned about the global distribution of CO over the last decade. The experiments leading to the present understanding range from systematic global observations at ground level for the last 8 to 10 years reported by Khalil and Rasmussen (Khalil and Rasmussen, 1988a,b) and Seiler (Seiler, 1974; Seiler and Junge, 1970), to finding the instantaneous global distribution of CO from remote-sensing instruments on board NASA's space shuttle as reported by Reichle et al. (1982, 1989a).

4.3.1 Seasonal Variations

The seasonal variations of CO are well established (Dianov-Klokov and Yurganov, 1981; Fraser et al., 1986; Khalil and Rasmussen, 1988b; Seiler et al., 1984). High concentrations are observed during the winters in each hemisphere and lowest concentrations are seen in late summer. The amplitude of the cycle is largest at high northern latitudes and diminishes as one moves towards the equator until it is reversed in the southern hemisphere reflecting the reversal of the seasons. The seasonal variations are small in the equatorial region. These patterns are expected from the seasonal variations of $OH^{\bullet}$ concentrations. At mid and high latitudes, diminished solar radiation, water vapor, and O_3 during winters cause

the concentrations of $OH^{\bullet}$ to be much lower than during summer. The removal of CO is slowed down and its concentrations build up. In summer the opposite effect exists causing the large seasonal variations of CO. These variations are apparent in the observed global seasonal cycles shown in Figure 4-2a.

On the hemispherical scale the seasonal variation of CO is approximately proportional to the concentration. Therefore, because there is much more CO in the northern hemisphere than in the southern hemisphere, the decline of concentrations during the summer of the northern hemisphere is not balanced by the rise of concentrations in the southern hemisphere. This causes a global seasonal variation. The total amount of CO in the earth's atmosphere undergoes a remarkably large seasonal variation with highest global burden during northern winters and lowest during northern summers. This feature is shown in Figure 4–2b.

4.3.2 Latitudinal Variation

The global seasonal variation of CO in the earth's atmosphere also creates a seasonal variation in the latitudinal distribution (Khalil and Rasmussen, 1988a,b; Newell et al., 1974; Reichle et al., 1982, 1986; Seiler, 1974). During northern winters, CO levels are at their highest in the northern hemisphere whereas southern hemisphere concentrations are at a minimum. The interhemispheric gradient, defined as the ratio of the amount of CO in the northern and southern hemisphere, is at its maximum of about 3.2 during northern hemisphere winters and falls to about 1.8 during northern hemisphere summers, which is about half of the winter value. The average latitudinal gradient is about 2.5, which means that on an average there is about 2.5 times as much CO in the northern hemisphere as in the southern hemisphere. Earlier data on the latitudinal variations did not account for the seasonal variations.

4.3.3 Variations with Altitude

In the northern hemisphere troposphere, the concentrations of CO generally decline with altitude but in the southern hemisphere the vertical gradient may be reversed due to the transport of CO from the northern hemisphere into the southern hemisphere. Above the tropopause concentrations decline rapidly so that there is very little CO between 20 km and

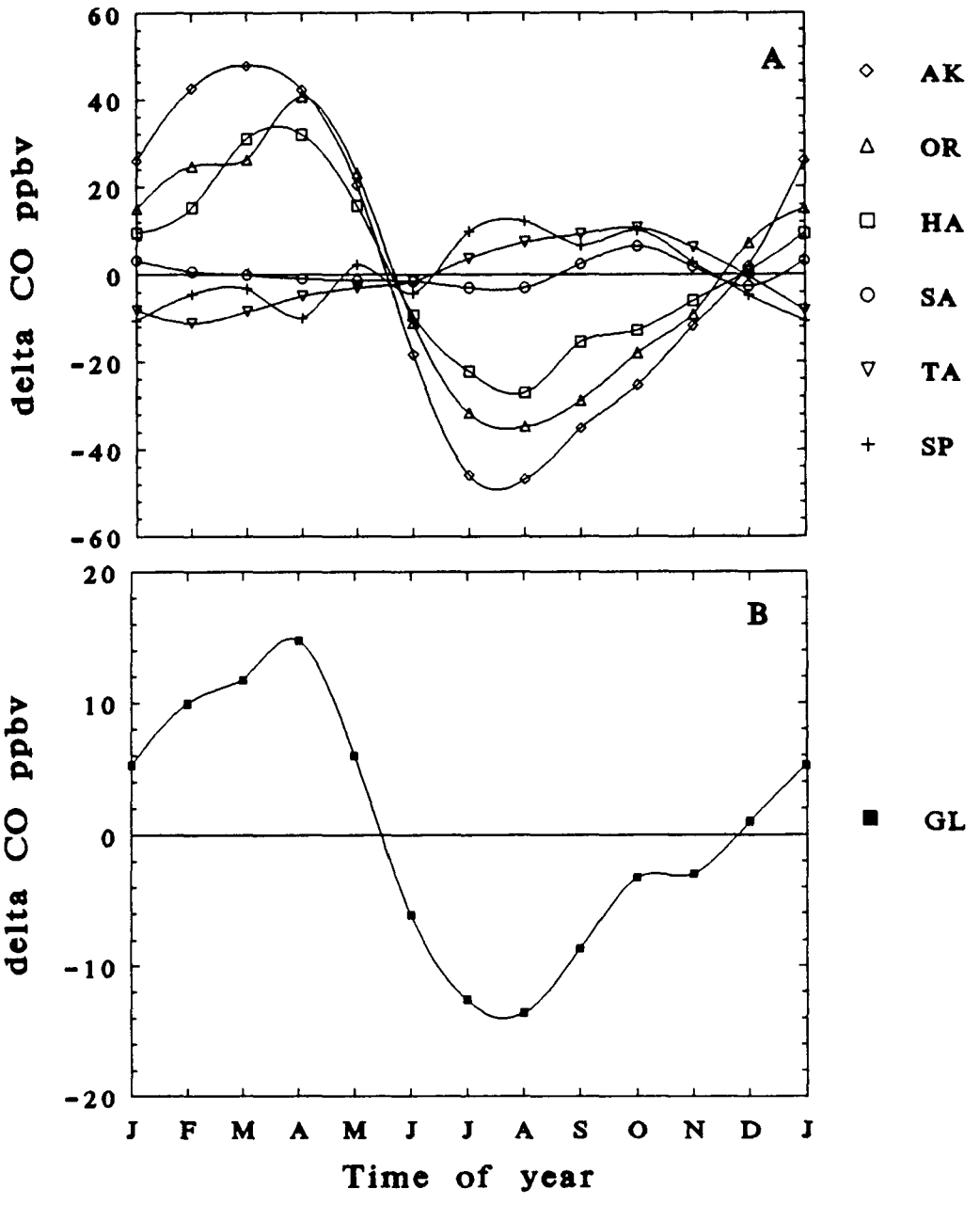

Figure 4-2. The global seasonal variations of CO. Figure 4-2a shows the seasonal cycle at 6 sites in polar, middle, and tropical latitudes of both hemispheres (AK = Alaska, OR = Oregon, HA = Hawaii, SA = Samoa, TA = Tasmania, SP = South Pole). Figure 4-2b shows the seasonal variation of the global burden of atmospheric CO. The atmospheric content of CO is much higher during northern hemisphere winters compared to summers.

Sources: Khalil and Rasmussen (1988b).

40 km; at still higher altitudes the mixing ratio may increase again (Fabian et al., 1981; Seiler and Junge, 1969; Seiler and Warneck, 1972).

4.3.4 Other Variations

The concentration of CO generally is higher over populated continental areas compared to the air over oceans, even though oceans release CO into the atmosphere. Other regions, such as tropical forests also may be a source of isoprene and other hydrocarbons that may form CO in the atmosphere. Such sources produce shifting patterns of high CO concentrations over regional and perhaps even larger spatial scales. Concentrations are representative of the middle troposphere and were measured during the 1984 flights of the space shuttle and reported by Reichle et al. (1989a). Eventually, CO in the lower troposphere may be measured from space using the techniques described by Reichle et al. (1989b). The new method uses gas correlation filter radiometry at 2.3 μm in addition to the 4.67 μm line used earlier to obtain mid-tropospheric concentrations of CO.

Occasionally in some locations significant diurnal variations of CO also may occur. For instance, diurnal variations have been observed over some parts of the oceans with high concentrations during the day and low concentrations at night. Because similar patterns also exist in the surface sea water, the diurnal variations in the air can be explained by emissions from the oceans.

Finally, after the repeating cycles and other trends are subtracted, considerable random fluctuations still remain in time series of measurements. These fluctuations reflect the short lifetime of CO and the vicinity of the sources and complicate the detection of long-term trends (see Figure 4-3).

4.4 GLOBAL TRENDS

Because some 60% of the global emissions of CO are believed to come from anthropogenic sources with increasing emissions, it stands to reason that the global

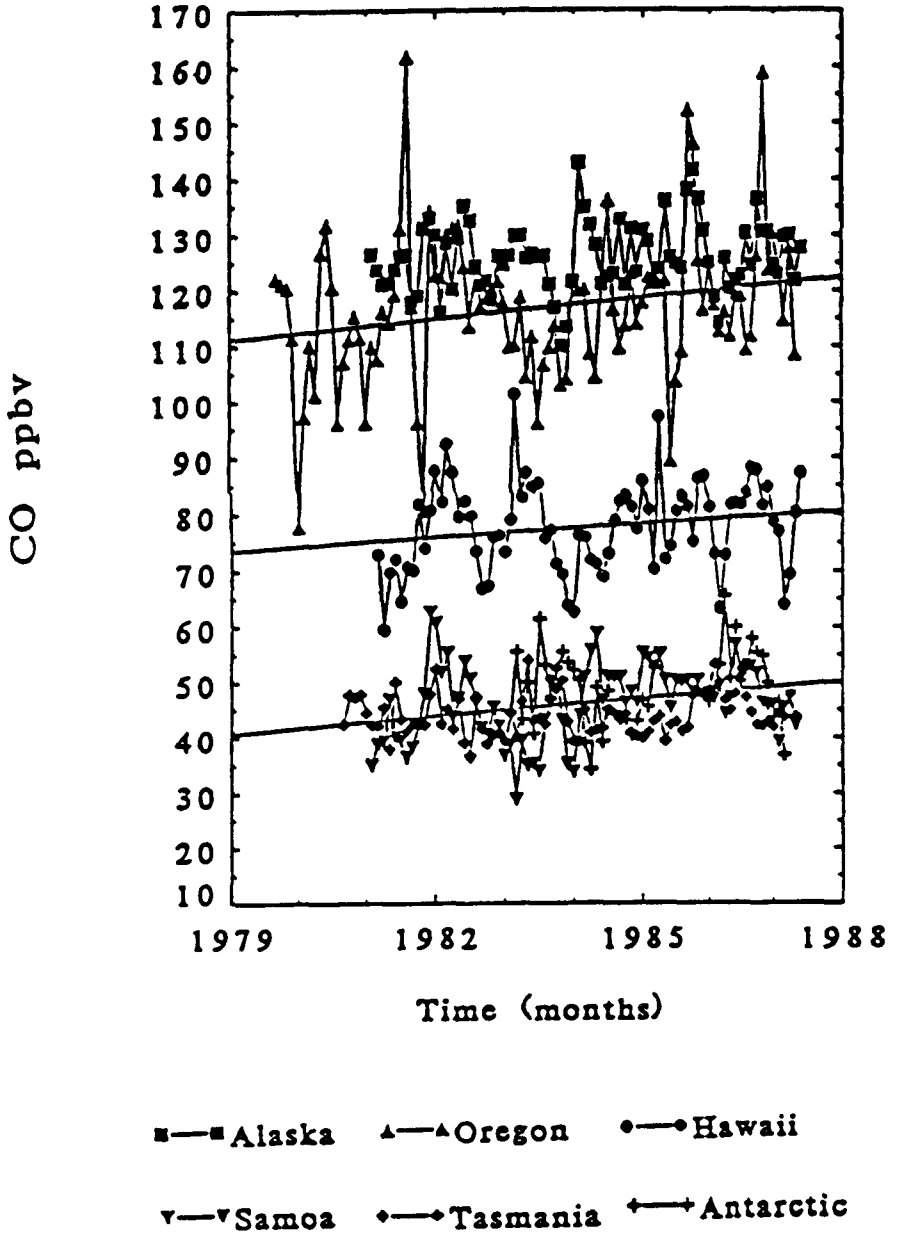

Figure 4-3. The global concentrations and trends of CO. The seasonal cycles have been subtracted from the time series of measurements at various latitudes ranging from inside the Arctic Circle to the South Pole. The latitudinal variation of CO also is apparent in the figure.

Sources: Khalil and Rasmussen (1988a).

concentration of CO should be increasing. At present, there are several independent pieces of evidence for an increasing trend although none are definitive. First, direct atmospheric observations reported by Khalil and Rasmussen (1984a) showed a detectable trend at Cape Meares in Oregon between 1979 and 1982. Over these 3 years the rate of increase was about 5%/year. Subsequent data from the same site showed that the rate was not sustained for long and a much smaller trend of a somewhat less than 2%/year emerged over the longer period of 1970 to 1987 (Khalil and Rasmussen, 1988a). Similar data from other sites distributed worldwide now show that there is evidence for a global increase of about 1% per year as shown in Figure 4-3 (Khalil and Rasmussen, 1988a). This is the only study in which trends from different parts of the world are evaluated. It shows that the trends are strongest in the mid-northern latitudes where most of the sources are located and become smaller and weaker in the southern hemisphere. At the mid-southern latitude site the trends persist but are not statistically significant (Khalil and Rasmussen, 1988a). Second, Rinsland and Levine (1985) have reported estimates of CO concentrations from spectroscopic plates from Europe that show that between 1950 and 1984 CO increased at about 2% per year. Finally, spectroscopic measurements of CO taken by Dvoryashina et al. and Dianov-Klokov et al. in the Soviet Union also suggest an increase of about 2%/year between 1974 and 1982 (Dianov-Klokov et al., 1978; Dianov-Klokov and Yurganov, 1981; Dvoryashina et al., 1982, 1984; Khalil and Rasmussen, 1988a; Khalil and Rasmussen, 1984b).

There is good evidence that the concentrations of CO are increasing in the non-urban troposphere, however the rate of increase still is not well known and may vary considerably over time. The random variability is so large and the trends so small that there are just enough data to detect the increase but not enough to estimate the long-term rate of increase with confidence. Such increases of tropospheric CO can cause a reduction of $OH^{\bullet}$ concentrations and thus reduce the oxidizing capacity of the atmosphere causing other trace gases, including CH_4, to build up more rapidly in the atmosphere and reach higher levels. This occurrence could add to the greenhouse effect and deplete the stratospheric O_3 layer. In the troposphere, increased CO in the presence of NO_x also could result in an increase of O_3 concentrations.

All the studies show increases of 1 to 2% per year over the last several decades. These trends and the sources shown in Table 4-1 suggest that the anthropogenic sources, both direct

and indirect, probably were very small until this century. Therefore, the average CO concentration may have doubled over the last 50 years or so. This change could be a significant contributing factor to increasing levels of O_3 in the non-urban troposphere. Because the influence of CO on tropospheric O_3 is not understood fully, the role of increasing CO on tropospheric O_3 also remains uncertain.

4.5 SUMMARY

The annual global emissions of CO are estimated to be about 2600 $\pm$ 600 Tg, of which about 60% are from human activities including combustion of fossil fuels and oxidation of hydrocarbons including CH_4. The remaining 40% of the emissions are from natural processes, mostly from the oxidation of hydrocarbons, but also from plants and the oceans. Almost all the CO emitted into the atmosphere each year is removed by reactions with $OH^{\bullet}$ radicals (85%), by soils (10%), and by diffusion into the stratosphere. There is a small imbalance between annual emissions and removal causing an increase of about 1% per year. It is very likely that the imbalance is due to increasing emissions from anthropogenic activities. The average concentration of CO is about 90 ppbv, which amounts to about 400 Tg in the atmosphere and the average lifetime is about 2 mo. This view of the global cycle of CO is consistent with the present estimates of average $OH^{\bullet}$ concentrations and the budgets of other trace gases including CH_4 and CH_3CCl_3.

There are large remaining uncertainties that in the future may upset the apparently cohesive present budget of CO. Although the patterns of the global distribution are becoming established, there still are uncertainties about the absolute concentrations. Estimates of emissions from individual sources are very uncertain, however the total annual emissions are likely to be more accurate.

There are just sufficient data on the trends to suggest that CO is increasing, but the rates are not certain. However, if the present view of the global cycle of CO is correct, then it is likely that, in time, increasing levels of CO will contribute to widespread changes in atmospheric chemistry and the global climate.

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5. MEASUREMENT METHODS FOR CARBON MONOXIDE

5.1 INTRODUCTION

To promote uniform enforcement of the air quality standards set forth under the Clean Air Act as amended (U.S. Senate Committee, 1977), the EPA has established provisions under which analytical methods can be designated as "reference" or "equivalent" methods (Code of Federal Regulations, 1977a). A reference method or equivalent method for air quality measurements is required for acceptance of measurement data. An "equivalent method" for monitoring CO can be so designated when the method is shown to produce results equivalent to the approved reference monitoring method based on absorption of infrared radiation from a nondispersed beam.

EPA-designated reference methods are automated, continuous methods utilizing the nondispersive infrared (NDIR) technique, which generally is accepted as being the most reliable method for the measurement of CO in ambient air. The official EPA reference methods are described in Code of Federal Regulations, 1988. Eleven reference methods for CO have been designated for use in determining compliance and all methods employ the NDIR technique (Code of Federal Regulations, 1988). Before a particular NDIR instrument can be used in a reference method, it must be designated by the EPA as approved in terms of manufacturer, model number, components, operating range, etc. Several NDIR instruments have been so designated (Code of Federal Regulations, 1988), including the gas filter correlation (GFC) technique which was developed through EPA-sponsored research (Burch et al., 1976). No equivalent methods that use a principle other than NDIR have as of January 1988 been designated for measuring CO in ambient air. The performance specifications for automated CO analyzers are shown in Table 5-1 (Code of Federal Regulations, 1977a).

The normal full scale operating range for reference methods is 0 to 50 ppm (0 to 58 mg/m^3). Some instruments offer higher ranges, typically 0 to 100 ppm (0 to 116 mg/m^3) or lower ranges such as 0 to 20 ppm (0 to 23 mg/m^3). A narrower range up to 1 ppm may be needed to measure background levels in unpolluted atmospheres. Higher ranges up to 1000 ppm (1150 mg/m^3) are used to measure CO concentrations in vehicular tunnels and parking garages.

5.1.1 Overview of Techniques for Measurement of Ambient Carbon Monoxide

There have been several excellent reviews on the measurement of CO in the atmosphere (National Research Council, 1977; Driscoll and Berger, 1971; Harrison, 1975; American Industrial Hygiene Association, 1972; Leithe, 1971; Repp, 1977; Schnakenberg, 1976; Stevens and Herget, 1974; National Air Pollution Control Association, 1970; National Institute for Occupational Safety and Health, 1972; Verdin, 1973). The nondispersive infrared (NDIR) method is discussed widely in the literature (Dailey and Fertig, 1977; Houben, 1976; McKee and Childers, 1972; McKee et al., 1973; Perez et al., 1975; Pierce and Collins, 1971; Schunck, 1976; Scott, 1975; Smith and Nelson, 1973; Smith, 1969, and Luft, 1975). Currently, the most commonly-used measurement technique is the type of NDIR method referred to as gas filter correlation (Acton et al., 1973; Bartle and Hall, 1977; Burch and Gryvnak, 1974; Burch et al., 1976; Chaney and McClenny, 1977; Goldstein et al., 1976; Gryvanak and Burch, 1976a,b; Herget et al., 1976; Ward and Zwick, 1975). This technique was developed to a commercial prototype stage through EPA sponsored research (Burch et al., 1976).

The NDIR method is an automated, continuous method that generally is accepted as being the most reliable method for the measurement of CO in ambient air. NDIR analyzers are based on the specific absorption of infrared radiation by the CO molecule (Feldstein, 1967). Most commercially available analyzers incorporate a gas filter to minimize interferences from other gases; they operate at atmospheric pressure and the most sensitive analyzers are able to detect minimum CO concentrations of about 0.05 mg/m^3. Interferences due to CO_2 and water vapor can be dealt with so as not to affect the data quality. NDIR analyzers with Luft type detectors are relatively insensitive to flow rate, require no wet chemicals, are sensitive over wide concentration ranges, and have short response times. NDIR analyzers of the newer GFC type have overcome zero and span problems and minor problems due to vibrations.

A more sensitive method for measuring low, background levels is gas chromatography (Bergman et al., 1975; Bruner et al., 1973; Dagnall et al., 1973; Porter and Volman, 1962; Feldstein, 1967; Smith et al., 1975a; Swinnerton et al., 1968; Tesarik and Krejci, 1974). This technique is an automated, semicontinuous method where CO is separated from water,

TABLE 5-1. PERFORMANCE SPECIFICATIONS FOR AUTOMATED ANALYTICAL METHODS FOR CARBON MONOXIDE (CODE OF FEDERAL REGULATIONS, 1977a)

Range	0 to 57 mg/m^3 (0 to 50 ppm)
Noise	0.6 mg/m^3 (0.50 ppm)
Lower detectable limit	1.2 mg/m^3 (1.0 ppm)
Interference equivalent	
Each interfering substance	$\pm$1.2 mg/m^3 ($\pm$1.0 ppm)
Total interfering substances	1.7 mg/m^3 (1.5 ppm)
Zero drift	
12 h	$\pm$1.2 mg/m^3 ($\pm$1.0 ppm)
24 h	$\pm$1.2 mg/m^3 ($\pm$1.0 ppm)
Span drift, 24 h	
20% of upper range limit	$\pm$10.0%
80% of upper range limit	$\pm$ 2.5%
Lag time	10 min
Rise time	5 min
Fall time	5 min
Precision	
20% of upper range limit	0.6 mg/m^3 (0.5 ppm)
80% of upper range limit	0.6 mg/m^3 (0.5 ppm)

Definitions:

Range: Nominal minimum and maximum concentrations that a method is capable of measuring.
Noise: The standard deviation about the mean of short duration deviations in output that are not caused by input concentration changes.
Lower detectable limit: The minimum pollutant concentration that produces a signal of twice the noise level.
Interference equivalent: Positive or negative response caused by a substance other than the one being measured.
Zero drift: The change in response to zero pollutant concentration during continuous unadjusted operation.
Span drift: The percent change in response to an upscale pollutant concentration during continuous unadjusted operation.
Lag time: The time interval between a step change in input concentration and the first observable corresponding change in response.
Rise time: The time interval between initial response and 95% of final response.
Fall time: The time interval between initial response to a step decrease in concentration and 95% of final response.
Precision: Variation about the mean of repeated measurements of the same pollutant concentration expressed as one standard deviation about the mean.

CO_2, and hydrocarbons other than methane by a stripper column. Carbon monoxide and CH_4 then are separated on an analytical column and the CO is passed through a catalytic reduction tube where it is converted to CH_4. The CO (converted to CH_4) passes through a flame ionization detector (FID), and the resulting signal is proportional to the concentration of CO in the air. This method has been used throughout the world. It has no known interferences and can be used to measure levels from 0.03 to 50 mg/m^3. These analyzers are expensive and require continuous attendance by a highly trained operator to produce valid results. For high levels, a useful technique is catalytic oxidation of the CO by Hopcalite or other catalysts (Stetter and Blurton, 1976), either with temperature-rise sensors (Naumann, 1975; Poli et al., 1976; Schnakenberg, 1976) or with electrochemical sensors (Bay et al., 1974, 1972; Bergman et al., 1975; Dempsey et al., 1975; Repp, 1977; Schnakenberg, 1975).

Other analytical schemes used for CO in air include dual–isotope infrared fluorescence, another technique derived from NDIR (Link et al., 1971; McClatchie, 1972; McClatchie et al., 1972); reaction with hot mercuric oxide to give elemental mercury vapor (Beckman et al., 1948; McCullough et al., 1947; Mueller, 1954; Palanos, 1972; Robbins et al., 1968); reaction with heated iodine pentoxide to give elemental iodine (Adams and Simmons, 1951; Moore et al., 1973; Newton and Morss, 1974; van Dijk and Falkenburg, 1976; Vol'berg and Pochina, 1974); and color reactions (Allen and Root, 1955; Bell et al., 1975; Feldstein, 1965; Jones, 1977; Lambert and Wiens, 1974; Levaggi and Feldstein, 1964; Ray et al., 1975; Simonescu et al., 1975; Smith et al., 1975b), as with palladium salts or the silver salt of *p*-sulfamoylbenzoate. Many of these methods are described in Section 5.3, Measurement in Ambient Air. A classical procedure for many decades was to use gasometric apparatus such as the Orsat or Haldane (Cormack, 1972), in which the CO present in a gas sample is absorbed by cuprous chloride solution and the decrease in volume or pressure is measured. This method, however, is not sensitive enough for trace amounts.

Microwave rotational spectroscopy is an analytical technique with high specificity (Hrubesh, 1973; Morgan and Morris, 1977). Other possible ways to determine CO include chemiluminescent reaction with ozone (v. Heusden and Hoogeveen, 1976), X–ray excited optical fluorescence (Goldstein et al., 1974), radiorelease of ^{85}Kr from the kryptonates of mercuric oxide or iodine pentoxide (I_2O_5) (Goodman, 1972; Naoum et al., 1974), and

utilization of narrow-band infrared laser sources (Chaney et al., 1979; Optical Society of America, 1975; Golden and Yeung, 1975).

5.1.2 Calibration Requirements

Whichever method or instrument is used, it is essential that the results be validated by frequent calibration with samples of known composition similar to the unknowns (Commins et al., 1977; Goldstein, 1977; National Bureau of Standards, 1975). Chemical analyses can be relied on only after the analyst has achieved acceptable accuracy in the analysis of such standard samples through an audit program.

5.2 PREPARATION OF STANDARD REFERENCE MATERIALS

5.2.1 Gas Standards

A set of reliable gas standards for CO in air, certified at levels of approximately 12, 23, and 46 mg/cm^3 (10, 20, and 40 ppm) is obtainable from the National Institute of Standards and Technology (formerly National Bureau of Standards), Washington, DC (National Bureau of Standards, 1975). These Standard Reference Materials (SRMs) are supplied as compressed gas (at about 1700 psi) in high-strength aluminum cylinders containing 31 ft^3 of gas at dry standard temperature and pressure and are accurate to better than 1% of the stated values. Because of the time and effort required in their preparation, SRMs are not intended for use as daily working standards, but rather as primary standards against which transfer standards can be calibrated.

5.2.2 Gravimetric Method

The gravimetric method used by NBS for preparing primary standards of CO (Hughes, 1975, 1976) is as follows. An empty gas cylinder is tared on an analytical balance; then 2 g of pure CO, weighed accurately to ± 2 mg, is added from a high-pressure tank. Next, 100 g of pure air (accurately weighed) is added from a pressure tank, and the concentration of CO is calculated from the sum of the respective weights added to the molecular weights of the two gases. Not only the average "molecular weight" of the air, but also the requisite careful check of purity, is obtained by mass spectrometry and gas chromatography analyses of the air

and the CO. Lower-concentration primary standards are prepared by serial dilutions (not more than a factor of 100 for each step) by the same technique.

The commercial suppliers of compressed gases are another source of air samples containing CO in the milligram per cubic meter or parts-per-million range. However, the nominal values for CO concentration supplied by the vendor should be verified by intercomparison with an SRM or other validated standard sample. A three-way intercomparison has been made among the NBS SRMs, commercial gas blends, and an extensive set of standard gas mixtures prepared by gravimetric blending at the Environmental Protection Agency (Paulsell, 1976). Results of the comparison showed that commercial gas blends are within $\pm 2\%$ of the true value represented by a primary standard. Another study on commercial blends (Elwood, 1976) found poorer accuracy. To achieve compatible results in sample analyses, different laboratories should interchange and compare their respective working standards frequently.

In making and using standards, many precautions are needed (Hughes, 1975): One deserves special mention. Large but unpredictable decreases in CO concentration occur within a few months in mixtures prepared in ordinary mild steel gas cylinders, as shown in Figure 5-1. This may be due to carbonyl formation or oxidation and CO to CO_2. The difficulty can be avoided by the use of gas cylinders made of stainless steel or aluminum. A special treatment for aluminum, which includes enhancement of the aluminum oxide surface layer, has been recommended (Wechter, 1976).

In addition to the set of SRMs for CO in air, another set of SRMs is available from NBS for CO in nitrogen. This second set covers concentrations from 10 to 957 ppm.

5.2.3 Volumetric Gas Dilution Methods

Standard samples of CO in air also can be prepared by volumetric gas dilution techniques. In a versatile system designed for this purpose (Hughes et al., 1973), air at a pressure of 10 to 100 psi is first purified and dried by passage through cartridges of charcoal and silica gel, then passed through a sintered metal filter into a flow control and flowmeter system. The CO (or a mixture of CO in air that is to be diluted further), also under pressure, is passed through a similar flow control and flowmeter system.

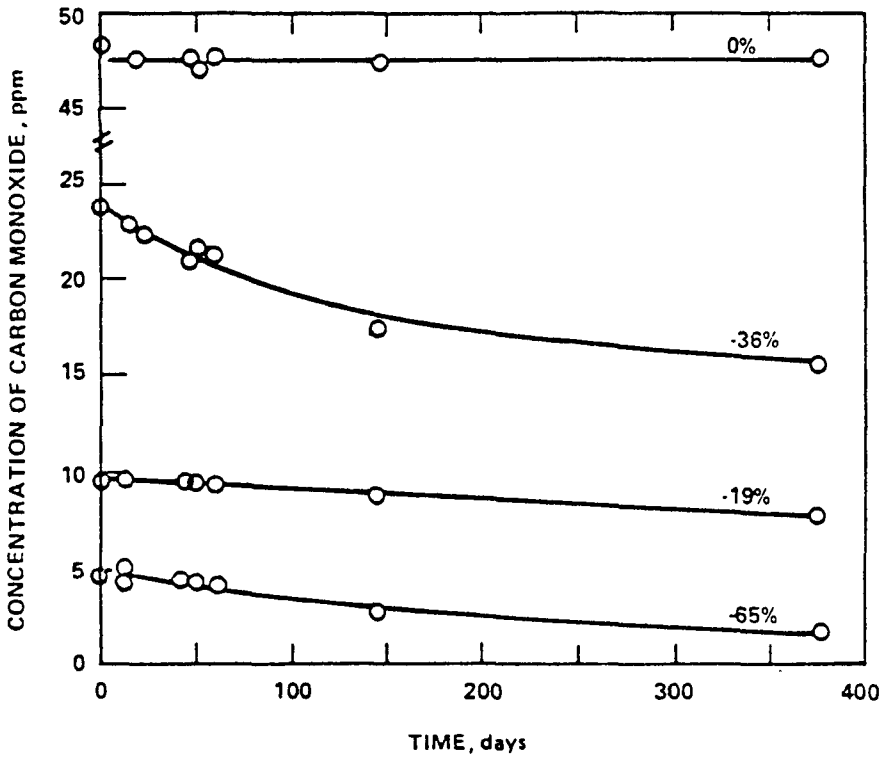


Figure 5-1. Loss of carbon monoxide with time in mild steel cylinders (Hughes, 1975).

Both gas streams are fed into a mixing chamber, which is designed to mix the gas streams rapidly and completely before passage into the sampling manifold from which the standard samples will be withdrawn. From the air flow rate, F_A, and the CO flow rate, F_{co}, the concentration of CO in the sample, C_{co}, is readily calculated by the expression

$$C_{co} = \frac{F_{co}}{F_{co} + F_A} \tag{5-1}$$

For samples prepared by dilution of a more concentrated bulk mixture, the concentration is given by

$$C_{co} = \frac{F_b}{F_b + F_A} (C_b) \tag{5-2}$$

where F_b and C_b are the values of flow rate and concentration of CO, respectively, for the bulk mixture.

5.2.4 Other Methods

Permeation tubes have been used for preparing standard mixtures of such pollutant gases as SO_2 and NO_2 (O'Keeffe and Ortman, 1966; Scaringelli et al., 1970). Permeation tubes are not used routinely in the United States for making CO standard samples. In the permeation tube techniques, a sample of the pure gas under pressure is allowed to diffuse through a calibrated partition at a defined rate into a diluent gas stream to give a standard sample of known composition.

Another possible way to liberate known amounts of CO into a diluent gas is by thermal decomposition of nickel tetracarbonyl. However, an attempt to use this as a gravimetric calibration source showed that the relation between CO output and weight loss of the $Ni(CO)_4$ is nonstoichiometric (Stedman et al., 1976).

5.3 MEASUREMENT IN AMBIENT AIR

Ambient CO monitoring is an expensive and time-consuming task, requiring skilled personnel and sophisticated analytical equipment. This section discusses several important

aspects of the continuous and intermittent measurement of CO in the atmosphere, including sampling techniques, sampling schedules, and recommended analytical methods for CO measurement.

5.3.1 Sampling System Components

Carbon monoxide monitoring requires a sample introduction system, an analyzer system, and a data recording system, as illustrated in Figure 5-2 (Smith and Nelson, 1973). While the "heart" of any air pollution monitoring system is the air pollution analyzer, Figure 5-2 shows that there is a considerable amount of supportive equipment necessary for continuous air monitoring.

A sample introduction system consists of a sampling probe, an intake manifold, tubing, and air movers. This system is needed to collect the air sample from the atmosphere and to transport it to the analyzer without altering the original concentration. It also may be used to introduce known gas concentrations in order to check periodically the reliability of the analyzer output. Construction materials for the sampling probe, intake manifold, and tubing should be tested to demonstrate that the test atmosphere composition or concentration is not altered significantly. It is recommended that sample introduction systems be fabricated from borosilicate glass or FEP Teflon® (Code of Federal Regulations, 1977b) if several pollutants are to be monitored. However, in monitoring for CO only, it has been reported (Wohlers et al., 1967) that no measurable pollutant losses were observed at the high (>1 L/min) sampling flow rates when sampling systems were constructed of tygon, polypropylene, polyvinylchloride, aluminum, or stainless steel piping. The sample introduction system should be constructed so that it presents no pressure drop to the analyzer. At low flow and low concentrations, such operation may require validation.

The analyzer system consists of the analyzer itself and any sample preconditioning components that may be necessary. Sample preconditioning might require a moisture control system to help minimize the false positive response of the analyzer (e.g., the NDIR analyzer) to water vapor, and a particulate filter to help protect the analyzer from clogging and possible chemical interference due to particulate buildup in the sample lines or analyzer inlet. The sample preconditioning system also may include a flow metering and flow control device to control the sampling rate to the analyzer. As for the analyzer, there are several analytical

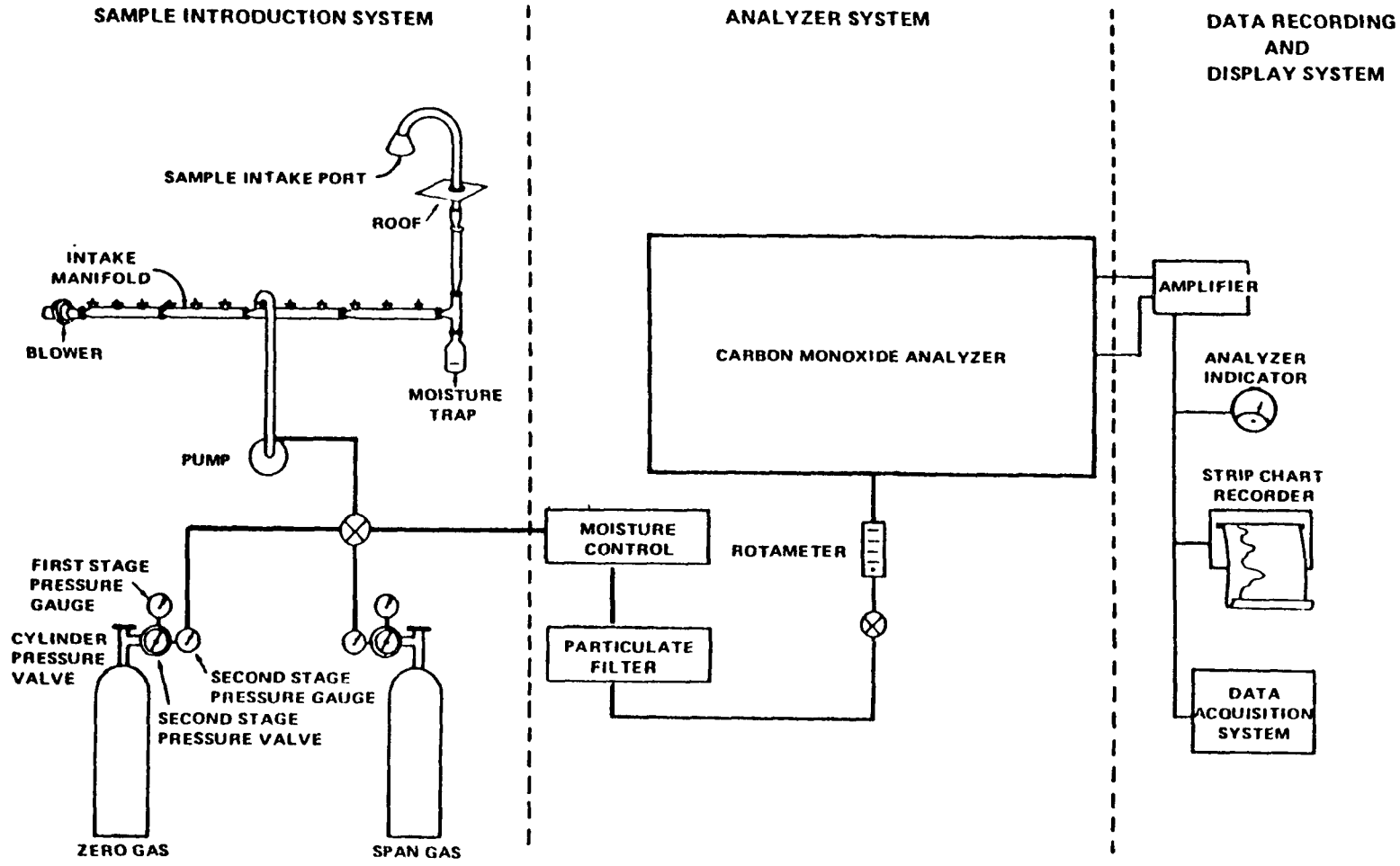


Figure 5-2. Carbon monoxide monitoring system (Smith and Nelson, 1973).

methods for the continuous measurement of CO. These are described in Section 5.3.4, Continuous Analysis.

A data recording system is needed to record the output of the analyzer. Data recording systems range from simple strip chart recorders to digital magnetic tape recorders to computerized telemetry systems that transfer data from remote stations to a central location via telephone lines or radio waves.

5.3.2 Quality Assurance Procedures for Sampling

The accuracy and validity of data collected from a CO monitoring system must be ensured through a quality assurance program. Such a program consists of procedures for calibration, operational and preventive maintenance, data handling, and auditing; and the procedures are documented fully in a quality assurance program manual maintained by the monitoring organization.

Calibration procedures consist of periodic multipoint primary calibration and secondary calibration, both of which are prescribed to minimize systematic error. Primary calibration involves the introduction of test atmospheres of known concentration to an instrument in its normal mode of operation for the purpose of producing a calibration curve.

A calibration curve is derived from the analyzer response obtained by introducing several successive test atmospheres of different known concentrations. One recommended method for generating CO test atmospheres is to use zero air (containing no CO) along with several known concentrations of CO in air or nitrogen contained in high-pressure gas cylinders and verified by NBS-certified SRMs wherever possible (Code of Federal Regulations, 1977a). The number of standard gas mixtures (cylinders) necessary to establish a calibration curve depends on the nature of the analyzer output. A multipoint calibration at five or six different CO concentrations covering the operating range of the analyzer is recommended by EPA (Code of Federal Regulations, 1977b; Federal Register, 1978). Alternatively, the multipoint calibration is accomplished by diluting a known high-concentration CO standard gas with zero gas in a calibrated flow dilution system.

Primary calibrations should be performed when the analyzer is first purchased and every 30 days thereafter (Smith and Nelson, 1973). Primary calibration also is recommended after the analyzer has had maintenance that could affect its response characteristics or when results

from auditing show that the desired performance standards are not being met (Smith and Nelson, 1973).

Secondary calibration consists of a zero and upscale span of the analyzer. This is recommended to be performed daily (Federal Register, 1978). If the analyzer response differs by more than 2% from the certified concentrations, then the analyzer is adjusted accordingly. Complete records of secondary calibrations should be kept to aid in data reduction and for use in auditing.

Operational and preventive maintenance procedures consist of operational checks to ensure proper operation of the analyzer and a preventive maintenance schedule necessary to prevent unexpected analyzer failure and the associated loss of data (PEDCo Environmental Specialists, Inc., 1971). Operational checks include checks of zero and span control settings, sample flow rate, gas cylinder pressures, sample cell pressure, shelter temperature, water vapor control, the particulate filter, the sample introduction system, the recording system, and the strip chart record. These checks may indicate the need for corrective/remedial action. They usually are performed in conjunction with secondary calibrations. In addition to operational checks, a routine schedule of preventive maintenance should be developed. Maintenance requirements for the analyzer usually are specified in the manufacturer's instrument manual. Routine maintenance of supportive equipment (i.e., the sample introduction system and the data recording system) also is required. This may include sample line filter changes, water vapor control changes, sample line cleaning, leak checks, and chart paper supply changes.

Data handling procedures consist of data generation, reduction, validation, recording, and analysis and interpretation. Data generation is the process of generating raw, unprocessed, and unvalidated observations as recorded on a strip chart record. Data reduction is the conversion, by use of calibration records, of raw data to concentration units. Data validation involves final screening of data before recording. Then, questionable data "flagged" by the monitoring technician are reviewed with the aid of daily calibration and operation records to assess their validity. Specific criteria for data selection and several instrument checks are available (Smith and Nelson, 1973). Data recording involves recording in a standard format for data storage, interchange of data with other agencies, and/or data analysis. Data analysis and interpretation usually include a mathematical or statistical analysis

of air quality data and a subsequent effort to interpret results in terms of exposure patterns, meteorological conditions, characteristics of emission sources, and geographic and topographic conditions.

Auditing procedures consist of several quality control checks and subsequent error analyses to estimate the accuracy and precision of air quality measurements. The quality control checks for CO include a data processing check, a control sample check, and a water vapor interference check, which should be performed by a qualified individual independent of the regular operator. The error analysis is a statistical evaluation of the accuracy and precision of air quality data. Guidelines have been published by EPA (Smith and Nelson, 1973) for calculating an overall bias and standard deviation of errors associated with data processing, measurement of control samples, and water vapor interference, from which the accuracy and precision of CO measurements can be determined. Since January 1, 1983, all state and local agencies submitting data to EPA must provide estimates of accuracy and precision of the CO measurements based on primary and secondary calibration records (Federal Register, 1978). The precision and accuracy audit results through 1985 indicate that the 95% national probability limits for precision are $\pm 9\%$ and the 95% national probability limits for accuracy are within $\pm 1.5\%$ for all audit levels from 3 to 8 ppm to 80 to 90 ppm. The results for CO are better than comparable results for the other pollutants with national air quality standards (Rhodes and Evans, 1987).

5.3.3 Sampling Schedules

Carbon monoxide concentrations in the atmosphere exhibit large temporal variations due to changes in the time and rate that CO is emitted by different sources and due to changes in meteorological conditions that govern the amounts of transport and dilution that take place. During a one-year period an urban CO station may monitor hourly concentrations of CO ranging from 0 to as high as 50 mg/m^3 (45 ppm). The NAAQS for CO are based on the second highest one- and eight-hour average concentrations; violations represent extreme events when compared to the 8760 hours that constitute a year. In order to measure the highest two values from the distribution of 8760 hourly values, the "best" sampling schedule to employ is continuous monitoring 24 hours per day, 365 days per year. Even so, continuous monitors rarely operate for long periods without data losses due to malfunctions,

upsets, and routine maintenance. Data losses of 5 to 10% (438 to 876 hours per year) are not uncommon. Consequently, the data must be interpreted in terms of the "likelihood" that the NAAQS were attained or violated. Statistical methods can be employed to interpret the results (Garbarz et al., 1977; Larsen, 1971).

Compliance with one- and eight-hour NAAQS requires continuous monitoring. Statistically valid sampling could be performed on random or systematic schedules, however, if annual averages or relative concentration levels were of importance. Most investigations of various sampling schedules have been conducted for particulate air pollution data (Hunt, 1972; Ott and Mage, 1975; Phinney and Newman, 1972), but the same schedules also could be used for CO monitoring. However, most instruments do not perform reliably in intermittent sampling.

5.3.4 Continuous Analysis

5.3.4.1 Nondispersive Infrared Photometry

Carbon monoxide has a characteristic infrared absorption near 4.6 μm: The absorption of infrared radiation by the CO molecule therefore can be used to measure CO concentration in the presence of other gases. The NDIR method is based on this principle.

Nondispersive infrared systems have several advantages. They are not sensitive to flow rate, they require no wet chemicals, they are reasonably independent of ambient air temperature changes, they are sensitive over wide concentration ranges, and they have short response times. Further, NDIR systems may be operated by nontechnical personnel. NDIR analyzers using Luft-type detectors were widely used in the 1970s while GFC analyzers are most commonly used now in documenting compliance with ambient air standards.

NDIR Using Luft-Type Detectors

The Luft-type detector is the primary distinguishing feature for the type of NDIR monitor that was widely used in the 1970s. This type of analyzer contains a hot filament source of infrared radiation, a rotating sector (chopper), a sample cell, and reference cell, and a detector. The reference cell contains a non-infrared-absorbing gas, while the sample cell is continuously flushed with the sample atmosphere. The detector consists of a two-compartment gas cell (both filled with CO under pressure) separated by a diaphragm whose

movement causes a change of electrical capacitance in an external circuit and ultimately an amplified electrical signal suitable for input to a servo-type recorder.

During analyzer operation a mechanical chopper alternately exposes the reference and sample cells to the infrared sources. At the frequency imposed by the chopper, infrared energy passes unattended through the reference cell to one compartment of the detector cell. Transmission through the sample cell is adjusted with no CO present so that the two beams are matched. Subsequently, when sample is introduced into the sample cell, infrared energy is attenuated by CO absorption, causing an imbalance in the energy reaching the two compartments of the detector cell. These unequal amounts of infrared energy differentially heat the absorbing gas in the detector cell and the resulting pressure difference inside the cells causes movement of the diaphragm that forms their common wall. A signal is generated at the chopping frequency with an amplitude related to the concentration of CO in the sample. This in turn produces the electrical signal previously discussed.

Because water vapor is the principal interfering substance in determining CO by NDIR techniques, a moisture control or compensation system is particularly important. Water vapor can be removed by absorption using in-line drying agents or by removal of condensate in a cooled inlet line. Alternatively, the water vapor concentration can be measured independently and its contribution subtracted from the total signal.

Gas–Filter Correlation Spectroscopy

A GFC monitor (Burch et al., 1976) is in essence a modern NDIR monitor. It has all the advantages of an NDIR instrument and the additional advantages of smaller size, no interference from CO_2, and very small interference from water vapor. It is not sensitive to flow rate, requires no wet chemicals, has a very fast response, and is relatively independent of normal ambient temperature changes.

A top view of the GFC monitor is presented schematically in Figure 5-3A, showing the components of the optical path for CO detection. During operation, sample air is continuously pushed through the sample cell. Radiation from the source is directed by optical transfer elements through the two main optical subsystems: the rotating gas filter (designated as correlation cell in Figure 5-3A) and the optical multipass (sample) cell. The beam exits the sample cell through interference filter FC, which limits the spectral passband to a few of the

strongest CO absorption lines in the 4.6-μm region. Detection of the transmitted radiation occurs at the infrared detector, C.

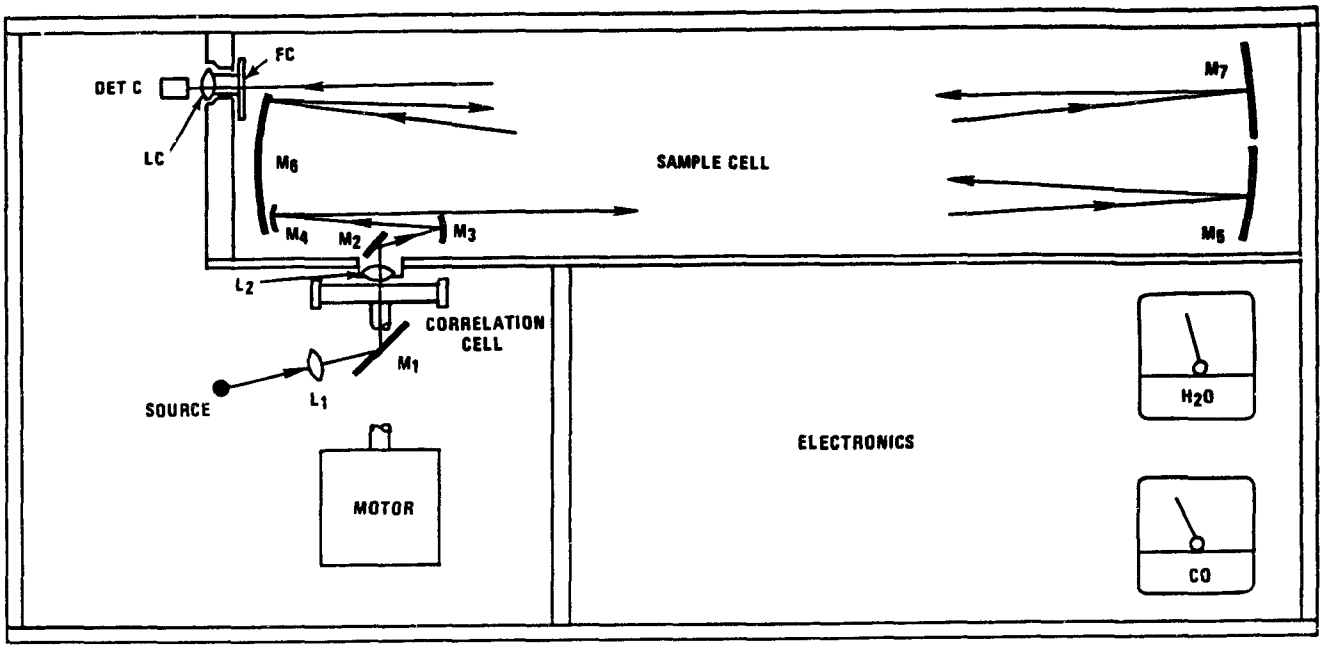
Although the passbound of filter FC is chosen to minimize interference from other gases, some residual H_2O interference occurs. This residual interference is not significant at criteria pollutant levels, but can be corrected by independent measurement of H_2O in the same cell.

The gas correlation cell is constructed with two compartments (Figure 5-3B): one compartment (gas cell 1) is filled with one-half atmosphere of CO, and the other compartment (gas cell 2) is filled with pure N_2. Radiation transmitted through cell 1 is completely attenuated at spectral positions where CO absorbs strongly. The radiation transmitted by cell 2 is reduced by coating the exit window of the cell with a neutral attenuator. In this way, the amounts of radiation transmitted by the two cells are made approximately equal in the spectral passband that reached detector C through filter FC.

In operation, radiation passes alternately through the two cells as they are rotated by a synchronous motor drive. This establishes a signal modulation frequency. Transmission to the detector is constant if no absorption by the ambient sample occurs. If CO is present in the sample, the radiation transmitted through cell 1 is not appreciably changed, while that through cell 2 is changed. This imbalance is linearly related to CO concentration for small concentrations. Other gas species absorb the radiation transmitted by cells 1 and 2 in approximately equal amounts since their absorption structure does not correlate with that of CO.

Superimposed on the entrance window of the cell is a typical light chopper pattern (Figure 5-3B) that creates a carrier frequency 12 times the signal modulation frequency, i.e., a carrier frequency of 400 Hz. The detector output from the CO channel is fed to two phase-sensitive amplifiers that separate the detector response at the signal frequency from the detector response at the reference (carrier) frequency. The signal due to CO is divided by the reference signal to substantially reduce many of the causes of sensitivity change, such as accumulation of material on optical components and variation in detector sensitivity.

A



B

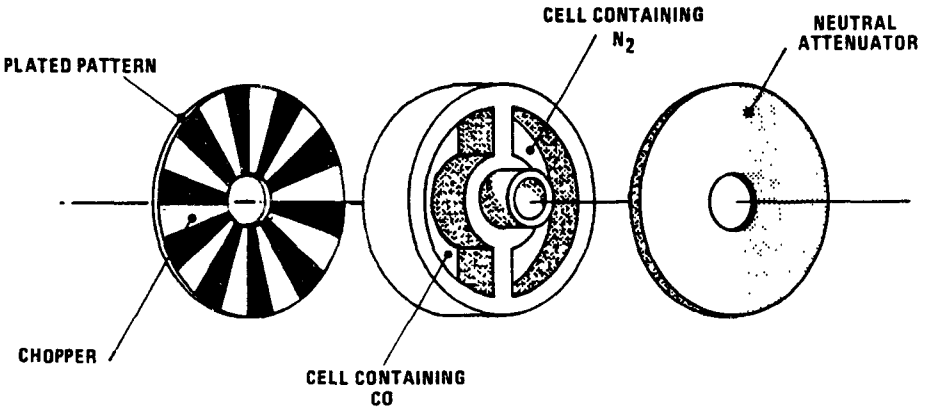


Figure 5-3. Schematic diagram of gas filter correlation (GFC) monitor for CO. A: Optical layout (M denotes mirror reflector; L denotes lens); B: Detail of correlation cell.

Source: Chaney and McClenny (1977).

5.3.4.2 Gas Chromatography - Flame Ionization

In this type of system, CO is separated from other trace gases by gas chromatography and catalytically converted to CH_4 prior to detection. A gas sampling valve, a back flush valve, a precolumn, a gas chromatographic column, a catalytic reactor, and an FID comprise the gas chromatography-flame ionization system. In operation, measured volumes of air are delivered 4 to 12 times per hour to a hydrogen FID that measures the total hydrocarbon content (THC). A portion of the same air sample, injected into a hydrogen carrier gas stream, is passed through the precolumn where it is separated from water, CO_2, and hydrocarbons other than CH_4. Methane then is separated from CO on a second gas chromatographic column. The CH_4, which is eluted first, is unchanged after passing through a catalytic reduction tube into the FID. The CO eluted into a catalytic reduction tube is reduced to CH_4 before passing through the FID (Porter and Volman, 1962). Between analyses the precolumn is flushed out. Nonmethane hydrocarbon concentrations also can be determined by subtracting the CH_4 value from the total hydrocarbon (TH) value.

There are two possible modes of operation. One of these is a complete chromatographic analysis showing the continuous output from the detector for each sample injection. In the other, the system is programmed for both automatic zero and span settings to display selected elution peaks as bar graphs. The peak height is then the measure of the concentration. The first operation is referred to as the chromatographic or "spectro" mode and the second as the barographic or "normal" mode.

Because measuring CO entails only small increases in cost, instrument complexity, and analysis time, these instruments customarily are used to measure three pollutants: CH_4, THs, and CO.

The instrumental sensitivity for each of these three components is 0.023 mg/m^3 (0.02 ppm). The lowest full-scale range available is usually 2.3 mg/m^3 (2 ppm) to 5.7 mg/m^3 (5 ppm), although at least one instrument has a 1.2 mg/m^3 (1 ppm) range. Because of the complexity of these instruments, continuous maintenance by skilled technicians is required to minimize downtime. This maintenance requirement may be considered a possible disadvantage of the system. Depending on the frequency of analysis and the temporal variability of CO, the representativeness over short averaging times may not be accurate (Chaney and McClenny, 1977).

5.3.4.3 Other Analyzers

Controlled-Potential Electrochemical Analysis

Carbon monoxide is measured by means of the current produced in aqueous solution by its electro-oxidation by an electro-catalytically active noble metal. The concentration of CO reaching the electrode is controlled by its rate of diffusion through a membrane. This is dependent on its concentration in the sampled atmosphere (Bay et al., 1974; 1972). Proper selection of both the membrane and such cell characteristics as the nature of the electrodes, the electrode potential, and the solution make the technique selective for various pollutants. A similar technique has been reported by Yamate and Inoue (1973).

The generated current is linearly proportional to the CO concentration from 0 to 115 mg/m^3 (0 to 100 ppm). A sensitivity of 1.2 mg/m^3 (1 ppm) and a 10-s response time (to reach 90% of full scale) are claimed for currently available commercial instruments.

Acetylene and ethylene are the chief interfering substances: one part acetylene responds as 11 parts CO, and one part ethylene as 0.25 part CO. For hydrogen, ammonia, hydrogen sulfide, NO, NO_2, SO_2, natural gas, and gasoline vapor, interference is less than 0.03 part CO per one part interfering substance.

Galvanic Analyzer

Galvanic cells employed in the manner described by Hersch (1966; 1964) can be used to measure atmospheric CO continuously. When an air stream containing CO is passed into a chamber packed with I_2O_5 and heated to 150°C, the following reaction takes place:

$$5CO + I_2O_5 \longrightarrow 5CO_2 + I_2 \qquad (5\text{-}3)$$

The liberated iodine is absorbed by an electrolyte and transferred to the cathode of a galvanic cell. At the cathode, the iodine is reduced and the resulting current is measured by a galvanometer. Instruments with this detection system have been used successfully to measure CO levels in traffic along freeways (Haagen-Smit, 1966).

Mercaptans, hydrogen sulfide, hydrogen, olefins, acetylenes, and water vapor interfere. Water may be removed by sampling through a drying column; hydrogen, hydrogen sulfide,

acetylene, and olefin interferences can be minimized by sampling through an absorption tube containing mercuric sulfate on silica gel.

Coulometric Analyzer

A coulometric method employing a modified Hersch-type cell has been used for continuous measurement of CO in ambient air (Dubois et al., 1966). The reaction of I_2O_5 with CO liberates iodine, which then is passed into a Ditte cell, and the current generated is measured by an electrometer-recorder combination. Interferences are the same as those discussed above for the galvanic analyzer.

This technique may be used for a minimum detectable concentration of 1.2 mg/m^3 (1 ppm) with good reproducibility and accuracy if flow rates and temperatures are controlled well. This method requires careful column preparation and use of filters to remove interferences. Its relatively slow response time may be an added disadvantage in some work.

Mercury Replacement

Mercury vapor formed by the reduction of mercuric oxide (HgO) by CO is detected photometrically by its absorption of ultraviolet light at 253.7 nm. The reaction involved is as follows:

$$CO + HgO \xrightarrow{(210^\circ C)} CO_2 + Hg \qquad (5\text{-}4)$$

This is potentially a much more sensitive method than infrared absorption because the oscillator strength of Hg at 253.7 nm is 2000 times greater than that of CO at 4.6 μm. Hydrogen and hydrocarbons also reduce HgO to Hg, and there is some thermal decomposition of the oxide. Operation of the detector at constant temperature results in a regular background concentration of Hg from thermal decomposition. The instrument is portable and can analyze CO concentrations of 0.025 to 12 mg/m^3 (0.020 to 10.0 ppm). Changes of 0.002 mg/m^3 (0.002 ppm) are detectable. For this reason, this instrument has been used to determine global CO levels. McCullough et al. (1947) and Beckman et al. (1948) recommended a detector operating temperature of 175°C to minimize hydrogen interference. A commercial instrument employing these principles was made and used during the middle

1950s (Mueller, 1954). The technique recently has been used for measuring background CO concentrations. Robbins et al. (1968) have described an instrument in which the HgO chamber is operated at 210°C, and the amount of hydrogen interference is assessed by periodic introduction of a tube of silver oxide into the intake air stream. At room temperature silver oxide quantitatively oxidizes CO, but not hydrogen. Thus, the baseline hydrogen concentration can be determined. Additional minor improvements are discussed by Seiler and Junge (1970), who gave the detection limit for CO as 0.003 mg/m^3 (0.003 ppm).

More recently, Palanos (1972) described a less sensitive model of this instrument intended for use in urban monitoring. It has a range of 0 to 23 mg/m^3 (20 ppm), a sensitivity of about 0.58 mg/m^3 (0.5 ppm), and a span and zero drift of less than 2% per day. As in other similar instruments, specificity is achieved by removal of the potentially interfering substances (which is less than 10%) other than hydrogen.

With all of these instruments, a constant geophysical hydrogen concentration is assumed. In unpolluted atmospheres, the hydrogen concentration is roughly 46.5 $\mu g/m^3$ (0.56 ppm). However, the automobile not only is a source of CO but also of hydrogen. Therefore, if this technique is used in polluted areas, it will be necessary to measure the hydrogen concentration frequently.

Dual Isotope Fluorescence

This instrumental method utilizes the slight difference in the infrared spectra of isotopes. The sample is alternately illuminated with the characteristic infrared wavelengths of carbon monoxide-16 ($^{12}C^{16}O$) and carbon monoxide-18 ($^{12}C^{18}O$). The CO in the sample that has the normal isotope ratio, nearly 100% $^{12}C^{16}O$, absorbs only the $^{12}C^{16}O$ wavelengths. Therefore, there is a cyclic variation in the intensity of the fluorescent light that is dependent on the $^{12}C^{16}O$ content of the sample (Link et al., 1971; McClatchie, 1972; McClatchie et al., 1972).

Full-scale ranges of 0 to 23 mg/m^3 (0 to 20 ppm) and up to 0 to 230 mg/m^3 (0 to 200 ppm) with a claimed sensitivity of 0.23 mg/m^3 (0.2 ppm) are available in this instrument. The response time (to reach 90% of full scale) is 25 s, but a 1-s response time also is available. An advantage of this technique is that it minimizes the effects of interfering substances.

Catalytic Combustion – Thermal Detection

Determination of CO by this method is based on measuring the temperature rise resulting from catalytic oxidation of the CO in the sample air.

The sample air is pumped first into a furnace that brings it to a preset, regulated temperature and then over the catalyst bed in the furnace. A thermopile assembly measures the temperature difference between the air leaving the catalyst bed and the air entering it. The output of the thermopile, which is calibrated with known concentrations of CO in air, is read on a strip chart recorder as parts of CO per million parts of air. The sensitivity is about 1.2 mg/m^3 (1 ppm). Most HCs are oxidized by the same catalyst, and will interfere unless removed. These systems are widely used in enclosed spaces; their applicability for ambient air monitoring is limited because they function best at high CO concentrations.

Second-Derivative Spectrometry

A second-derivative spectrometer processes the transmission-versus-wavelength function of an ordinary spectrometer to produce an output signal proportional to the second derivative of this function. Ultraviolet light of continuous wavelength is collected and focused onto an oscillating entrance slit of a grating spectrometer. When the grating orientation is changed slowly, a slowly scanning center wavelength with sinusoidal wavelength modulation is created in the existing light by the oscillating entrance slit. This radiation passes through a gas sample and is detected with a photomultiplier tube. The signal then is electronically processed to produce a second-derivative spectrum (Lawrence Berkeley Laboratory, 1973). This method has the advantage that it can be used to measure other pollutants as well as CO.

Fourier–Transform Spectroscopy

Fourier-transform spectroscopy is an extremely powerful infrared spectroscopic technique (Bell, 1972) that has developed in the past 20 years and has been applied in the last 10 years to air pollution measurement problems (Hanst et al., 1973; Lawrence Berkeley Laboratory, 1973). The advantage of this technique over a standard grating or prism spectrometer is that it has a higher throughput, which means that the available energy is used more effectively and that a much higher resolving power is obtainable. In air pollution measurements individual absorption lines can be resolved.

A special advantage for air pollution measurements is that all the data required to reconstruct the entire absorption spectrum are acquired at the same time. The spectrum as a function of wavelength is generated by a built-in computer. This means that several gases can be measured simultaneously. Several commercial instruments now are available with resolutions of 0.06/cm or better. These instruments are capable of clearly defining the spectrum of any gaseous pollutant, including CO and currently are being used for special air pollution studies.

5.3.5 Intermittent Analysis

Intermittent samples may be collected in the field and later analyzed in the laboratory by the continuous analyzing techniques described above. Sample containers may be rigid (glass cylinders or stainless steel tanks) or they may be nonrigid (plastic bags). Because of location or cost, intermittent sampling at times may be the only practical method for air monitoring. Samples can be taken over a few minutes or accumulated intermittently to obtain, after analysis, either "spot" or "integrated" results. Additional techniques for analyzing intermittent samples are described below.

5.3.5.1 Colorimetric Analysis

Colored Silver Sol Method

Carbon monoxide reacts in an alkaline solution with the silver salt of *p*-sulfamoyl-benzoate to form a colored silver sol. Concentrations of 12 to 23,000 mg/m^3 (10 to 20,000 ppm) CO may be measured by this method (Ciuhandu, 1958, 1957, 1955; Ciuhandu and Krall, 1960; Ciuhandu et al., 1965; Levaggi and Feldstein, 1964). The method has been modified to determine CO concentrations in incinerator effluents. Samples are collected in an evacuated flask and reacted. The absorbance of the resulting colloidal solution is measured spectrophotometrically. Acetylene and formaldehyde interfere, but can be removed by passing the sample through mercuric sulfate on silica gel. Carbon monoxide concentrations of 5.8 to 20,700 mg/m^3 (5 to 18,000 ppm) may be measured with an accuracy of 90 to 100% of the true value.

National Bureau of Standards Colorimetric Indicating Gel

An NBS colorimetric-indicating gel (incorporating palladium and molybdenum salts) has been devised to measure CO in the laboratory and in the field (Shepherd, 1947; Shepherd et al., 1955). The laboratory method involves colorimetric comparison with freshly prepared indicating gels exposed to known concentrations of CO. The method has an accuracy range of 5 to 10% of the amount of CO involved, and the minimum detectable concentration is 1.2 mg/m^3 (1 ppm). This technique requires relatively simple and inexpensive equipment; however, oxidizing and reducing gases interfere, and the preparation of the indicator tube is a tedious and time-consuming task.

Length-of-Stain Indicator Tube

An indicator tube that uses potassium palladosulfite is a commonly employed manual method (Silverman and Gardner, 1965). Carbon monoxide reacts with the contents of the tube and produces a discoloration.

The length of discoloration is an exponential function of the CO concentration. This method and other indicator tube manual methods are estimated to be accurate to within $\pm 25\%$ of the amount present, particularly at CO concentrations of about 115 mg/m^3 (100 ppm). Such indicator tube manual methods have been used frequently in air pollution studies. Ramsey (1966) used the technique to measure CO at traffic intersections, and Brice and Roesler (1966) estimated CO concentrations with an accuracy of $\pm 15\%$ by means of color-shade detector tubes.

Colorimetric techniques and length-of-stain discoloration methods are recommended for use only when other physicochemical monitoring systems are not available. They may be used in the field for gross mapping where accuracy is not required and may possibly be of great value during emergencies.

Frontal Analysis

Air is passed over an adsorbent until equilibrium is established between the concentration of CO in the air and the concentration of CO on the adsorbent. The CO then is eluted with hydrogen, reduced to CH_4 on a nickel catalyst at 250°C, and determined by flame ionization as CH_4.

Concentrations of CO as low as 0.12 mg/m^3 (0.10 ppm) can be measured. This method does not give instantaneous concentrations, but does give averages over a six-minute or longer sampling period (Dubois and Monkman, 1972; 1970).

5.4 MEASUREMENT USING PERSONAL MONITORS

Until the 1960s, most of the data available on ambient CO concentrations came from fixed monitoring stations operated routinely in urban areas. The accepted measurement technique was by NDIR spectrometry, but the instruments were large and cumbersome, often requiring vibration-free, air-conditioned enclosures. Without a portable, convenient monitor for CO, it was extremely difficult to measure CO concentrations accurately in the microenvironments that people usually visited. In the late 1960s, studies were initiated to investigate the CO concentrations within vehicles (Brice and Roesler, 1966; Lynn et al., 1967). In 1971, an investigator walked on congested downtown streets alongside pedestrians to measure their exposures (Ott, 1971). With a portable pump, the investigator filled sampling bags in various locations, then transported them to the laboratory where the contents were analyzed by NDIR spectrometry.

In the early 1970s, portable electrochemical monitors about the size of a shoe box became available. Using the Ecolyzer monitor, CO concentrations were measured in traffic in Boston, MA. (Cortese and Spengler, 1976). In the late 1970s, smaller personal monitors using electrochemical sensing systems became available and were deployed in specialized field surveys involving a few people (Jabara et al., 1980).

As CO monitors continued to evolve, they were used in studies of indoor microenvironments. Many of the microenvironmental CO data on indoor concentrations were collected as an integral part of multipollutant indoor health or dosage studies in homes, offices, or rooms (Berglund et al., 1982; Hoffman et al., 1984; Hugod, 1984), or as more narrowly focused multipollutant exposure field studies in homes (Quackenboss et al., 1984; Koontz and Nagda, 1984; Traynor et al., 1984) and in buildings (Konopinski, 1984; Malaspina et al., 1984; Clarkson, 1984).

Although the CO personal monitors evolved rapidly, they were not used in large-scale field surveys of indoor microenvironments until the early 1980s. Personal monitors have

been used in studies of CO concentrations in sustained-use vehicles (Ziskind et al., 1981) and in passenger compartments of vehicles traveling on highways (Ott and Willits, 1981; Flachsbart and Ah Yo, 1986).

Ultimately, small personal exposure monitors were developed that could measure CO concentrations continuously over time and store the readings automatically on internal digital memories (Ott et al., 1986). These small personal exposure monitors (PEMs) made possible the large-scale CO human exposure field studies in Denver, CO, and Washington, DC, in the winter of 1982-1983 (Akland et al., 1985). The PEM employed in these studies uses an aqueous solid polymer ion exchange material as the electrolyte in which CO is converted to CO_2 by an electrochemical reaction at a noble metal electrode, thereby generating an electrical current. The signal (current) is proportional to the quantity of CO present in the gas stream, and the continuous electrical signal is recorded in internal memory. A small pump operates continuously to send air into the sensing cell, and chemical filters in the intake stream remove interfering chemicals, such as ethanol. The pump operates on batteries for up to 40 h with a precision of 2 ppm, with zero and span checks required before and after field service. Other studies have employed the CO detector and combined it with small computers such as the HP-41CV to enhance the utility of the detector for studying factors that affect CO concentration variability (Fitz-Simons and Sauls, 1984). These monitors proved effective in generating 24–h CO exposure profiles on more than 1600 persons. By breaking up the profiles into the microenvironments visited by these people, it was possible to develop CO concentration readings on more than 40 indoor and in-transit microenvironments (see Chapter 8).

Detector tubes also can be used in studies where high concentrations occur (above 5 mg/m^3) or long exposure times are possible and only cumulative exposures are required. Air is drawn through specifically manufactured tubes containing an absorbent impregnated with a chemical reagent that changes color if CO is present (Jacobs, 1949). The length of the stain produced in the tube after exposure is read on a chart to give the concentration of CO. Unfortunately, interferences also may produce color changes, unless additional precautions are taken to filter out particles and to absorb interfering gases such as oxides of nitrogen, SO_2, HCs, ammonia, hydrogen sulfide, and water vapor. Techniques such as the detector tube, may have the greatest utility to the researcher by providing inexpensive approximate value for

screening purposes, which would require confirmation found about some predetermined "action" level.

5.5 REFERENCES

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6. AMBIENT CARBON MONOXIDE SOURCES, EMISSIONS, AND CONCENTRATIONS

6.1 ESTIMATING NATIONAL EMISSION FACTORS

The national carbon monoxide emission estimates presented herein are taken from two U.S. Environmental Protection Agency (EPA) reports: National Air Quality and Emissions Trends Report, 1988 (U.S. Environmental Protection Agency, 1990a) and National Air Pollutant Emission Estimates, 1940-1988 (U.S. Environmental Protection Agency, 1990b). These data are most useful as indicators of overall emission trends, since national totals or averages are not the best guide for estimating or predicting specific trends in local areas. The emission data represent calculated estimates based on standard emission inventory procedures developed by the Office of Air Quality Planning and Standards of the U.S. Environmental Protection Agency (1990b). These procedures either estimate the emissions directly or estimate the magnitude of other variables that can then be related to emissions. For CO, these indicators include fuel consumption, vehicle population, vehicle miles traveled (VMT), sales of new vehicles, tons of refuse burned, raw materials processed, etc., which are then multiplied by the appropriate CO emission factor(s) to obtain the CO emission estimate(s). It should be noted that emission factors have specific limitations and applicability. Emission factors, in general, are not precise indicators of emissions from a single source; rather, they are quantitative estimates of the average rate of pollutant released as a result of some activity. They are most valid when applied to a large number of sources and processes. Emission factors thus relate quantity of pollutants emitted to indicators such as those noted above, and are EPA's approach for determining national estimates of emissions from various source categories.

6.2 EMISSION SOURCES AND EMISSION FACTORS BY SOURCE CATEGORY

Emission source categories, as presented in Table 6-1, are divided into five individual categories: transportation, stationary source fuel combustion, industrial processes, solid waste

TABLE 6-1. CARBON MONOXIDE NATIONAL EMISSION ESTIMATES (TERAGRAMS/YEAR)

Source Category	1970	1975	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988
Transportation													
Highway Vehicles	65.3	57.2	55.6	51.9	48.7	48.0	45.9	45.9	43.5	40.7	37.5	36.0	34.1
Aircraft	0.9	0.9	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.1	1.1	1.1	1.1
Railroads	0.3	0.2	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Vessels	1.2	1.4	1.5	1.4	1.4	1.4	1.4	1.4	1.7	1.4	1.5	1.6	1.6
Other-Off Highway	6.8	5.4	4.8	4.5	4.7	4.7	4.4	3.9	4.2	4.5	4.4	4.4	4.2
Transportation Total	74.4	65.0	63.1	59.1	56.1	55.4	52.9	52.4	50.6	47.9	44.6	43.2	41.2
Stationary Source Fuel Combustion													
Electric Utilities	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Industrial	0.7	0.7	0.8	0.7	0.7	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Commercial-Institutional	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Residential	3.5	3.3	4.8	5.7	6.4	6.7	7.3	7.2	7.3	6.5	6.6	6.6	6.6
Fuel Combustion Total	4.5	4.3	5.9	6.7	7.4	7.7	8.2	8.2	8.3	7.4	7.5	7.6	7.6
Industrial Processes	8.9	6.9	7.2	7.1	6.3	5.9	4.3	4.3	4.7	4.4	4.3	4.5	4.7
Solid Waste Disposal													
Incineration	2.7	1.8	1.4	1.3	1.2	1.2	1.1	1.0	1.0	1.1	0.9	0.9	0.9
Open Burning	3.7	1.3	1.1	1.0	1.0	0.9	0.9	0.9	0.9	0.9	0.8	0.8	0.8
Solid Waste Total	6.4	3.1	2.5	2.3	2.2	2.1	2.0	1.9	1.9	2.0	1.7	1.7	1.7
Miscellaneous													
Forest Fires	5.1	4.0	5.0	5.8	6.9	5.8	4.3	7.1	5.7	4.7	4.4	6.5	5.4
Other Burning	2.1	0.8	0.7	0.7	0.7	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Miscellaneous Organic Solvent	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Miscellaneous Total	7.2	4.8	5.7	6.5	7.6	6.4	4.9	7.7	6.3	5.3	5.0	7.1	6.0
Total of All Sources	101.4	84.1	84.4	81.7	79.6	77.4	72.4	74.5	71.8	67.0	63.1	64.1	61.2

Source: U.S. Environmental Protection Agency (1990b).

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disposal, and miscellaneous. The methodology used in the generation of emission estimates for the individual source categories is summarized below.

6.2.1 Transportation Sources

Transportation sources include emissions from all mobile sources including highway and other off-highway motor vehicles. Highway motor vehicles include passenger cars, trucks, buses and motorcycles. Off-highway vehicles include aircraft, railroads, vessels, and miscellaneous engines such as farm equipment, industrial and construction machinery, lawnmowers, and snowmobiles.

6.2.1.1 Motor Vehicles

Emission estimates from gasoline- and diesel-powered motor vehicles are based upon vehicle-mile tabulations and emission factors. Eight vehicle categories are considered; light duty gasoline (mostly passenger cars), light duty diesel passenger cars, light duty gasoline trucks (weighing less than 6000 pounds) light duty gasoline trucks (weighing 6001 to 8500 pounds), light duty diesel trucks, heavy duty gasoline trucks and buses, and heavy duty diesel trucks and buses, and motorcycles. The emission factors used are based on EPA's MOBILE4 mobile source emission factor model, which uses the latest available data to estimate average in-use emissions from highway vehicles (U.S. Environmental Protection Agency, 1989a,b). The MOBILE4 model, developed by the EPA Office of Mobile Sources, was used to calculate emission factors for each year. The emission factors are weighted to consider the approximate amount of motor vehicle travel in low- and high-altitude areas to obtain overall national average emission factors. For each area a representative average annual temperature (low altitude average annual temperature = 57°F, high altitude = 54°F, California = 65°F), together with national averages for motor vehicle registration distributions and annual mileage accumulation rates by age and hot/cold start vehicle operation percentages were used to calculate the emission factors. Average speed is taken into account according to the published distribution of vehicle-miles travelled (VMT) (U.S. Department of Transportation, 1988). The published VMT are divided into three road categories corresponding to roads with assumed average speeds of 55 miles per hour for

interstates and other primary highways, 45 miles per hour for rural roads, and 19.6 miles per hour for urban streets.

6.2.1.2 Aircraft

Aircraft emissions are based on emission factors and aircraft activity statistics reported by the Federal Aviation Administration (1988). Emissions are based on the number of landing-takeoff (LTO) cycles. Any emissions in cruise mode, which is defined to be above 3000 feet (1000 meters) are ignored. Average emission factors for each year, which take into account the national mix of aircraft types for general aviation, military, and commercial aircraft, are used to compute the emissions.

6.2.1.3 Railroads

The Department of Energy reports consumption of diesel fuel and residual fuel oil by railroads (U.S. Department of Energy, 1988a). Average emission factors applicable to diesel fuel consumption were used to calculate emissions.

6.2.1.4 Vessels

Vessel use of diesel fuel, residual oil, and coal is reported by the Department of Energy (U.S. Department of Energy, 1988a,b). Gasoline use is based on national boat and motor registrations, coupled with a use factor (gallons/motor/year) (U.S. Environmental Protection Agency, 1973) and marine gasoline sales (U.S. Department of Transportation, 1988). Emission factors from AP-42 are used to compute emissions (U.S. Environmental Protection Agency, 1985).

6.2.1.5 Nonhighway Use of Motor Fuels

Gasoline and diesel fuel are consumed by off-highway vehicles in substantial quantities. The fuel consumption is divided into several categories including farm tractors, other farm machinery, construction equipment, industrial machinery, snowmobiles, and small general utility engines such as lawnmowers and snowthrowers. Fuel use is estimated for each category from estimated equipment population and an annual use factor of gallons per unit per year (Hare and Springer, 1974), together with reported off–highway diesel fuel deliveries

(U.S. Department of Energy, 1988a) and off-highway gasoline sales (U.S. Department of Transportation, 1988).

6.2.2 Stationary Source Fuel Combustion

Stationary combustion equipment, such as coal-, gas-, or oil-fired heating or power generating plants, generate CO as a result of improper or inefficient operating practices or of inefficient combustion techniques. The specific emission factors for stationary fuel combustors vary according to the type and size of the installation and the fuel used, as well as the mode of operation. The EPA compilation of air pollutant emission factors provides emission data obtained from source tests, material balance studies, engineering estimates, etc., for the various common emission categories. For example, coal-fired electricity-generating plants report coal use to the Department of Energy (U.S. Department of Energy, 1988b,c). Distillate oil, residual oil, kerosene, and natural gas consumed by stationary combustors are also reported by user category to the U.S. Department of Energy (1988a, 1989a,b). Average emission factors from AP-42 (U.S. Environmental Protection Agency, 1985) were used to calculate the emission estimates. The consumption of wood in residential wood stoves has likewise been estimated by the U.S. Department of Energy (1982, 1984).

6.2.3 Industrial Processes

In addition to fuel combustion, certain other industrial processes generate and emit varying quantities of CO into the air. The lack of published national data on production, type of equipment, and controls, as well as an absence of emission factors, makes it impossible to include estimates of emissions from all industrial process sources.

Production data for industries that produce the great majority of emissions were derived from literature data. Generally, the Minerals Yearbook, (U.S. Department of the Interior, 1987) published by the Bureau of Mines, and Current Industrial Reports, (U.S. Department of Commerce, annual) published by the Bureau of the Census, provide adequate data for most industries. Average emission factors were applied to production data to obtain emissions. Control efficiencies applicable to various processes were estimated on the basis of published reports and from NEDS data (U.S. Environmental Protection Agency, 1971).

6.2.4 Solid Waste Disposal

Solid waste CO emissions result from the combustion of wastes in municipal and other incinerators, and also from the open burning of domestic and municipal refuse. Specific emission estimates for the various waste combustion procedures in use were taken from a study conducted in 1968 concerning solid waste collection and disposal practices (U.S. Department of Health, Education, and Welfare, 1968). Results of this study indicate that the average collection rate of solid waste is about 5.5 pounds per capita per day in the United States. It has been stated that a conservative estimate of the total generation rate is 10 pounds per capita per day. The results of this survey were updated based on data reported in NEDS and used to estimate, by disposal method, the quantities of solid waste generated (NEDS, National Emissions Data System, n.d.). Average emission factors were applied to these totals to obtain estimates of total emissions from the disposal of solid wastes.

6.2.5 Miscellaneous Combustion Sources

Miscellaneous CO emissions results from the burning of forest and agricultural materials, smoldering coal refuse materials, and structural fires.

6.2.5.1 Forest Fires

The Forest Service of the Department of Agriculture publishes information on the number of forest fires and the acreage burned (U.S. Forest Service, 1988). Estimates of the amount of material burned per acre are made to estimate the total amount of material burned. Similar estimates are made to account for managed burning of forest areas. Average emission factors were applied to the quantities of materials burned to calculate emissions.

6.2.5.2 Agricultural Burning

A study was conducted by EPA (Yamate, 1974) to obtain from local agricultural and pollution control agencies estimates of the number of acres and estimated quantity of material burned per acre in agricultural burning operations. These data have been updated and used to estimate agricultural burning emissions, based on average emission factors.

6.2.5.3 Coal Refuse Burning

Estimates of the number of burning coal-refuse piles existing in the United States are made in reports by the Bureau of Mines (U.S. Department of the Interior, 1971). This publication presents a detailed discussion of the nature, origin, and extent of this source of pollution. Rough estimates of the quantity of emissions were obtained using this information by applying average emission factors for coal combustion. It was assumed that the number of burning refuse piles decreased to a negligible amount by 1975.

6.2.5.4 Structural Fires

The United States Department of Commerce publishes, in their statistical abstracts, information on the number and types of structures damaged by fire (U.S. Department of Commerce, 1988). Emissions were estimated by applying average emission factors for wood combustion to these totals.

6.3 NATIONAL CO EMISSIONS ESTIMATES 1970-1988

Table 6-1 displays the total annual 1970-1988 CO emissions from the various source categories. The CO estimations cited herein are the result of current methodology and refined emission factors and should not be compared with data reported earlier. These data indicate that CO from all man-made sources in the U.S. declined from 101.4 teragrams in 1970 (one teragram equals 10^{12} grams, 10^{3} gigagrams, 10^{6} metric tons, or approximately 1.1 x 10^{6} short tons) to 61.2 teragrams in 1988. The majority, about 70 percent, of the CO emissions total comes from transportation sources, 12 percent comes from fuel combustion processes, 7 percent comes from industrial processes, and 11 percent comes from miscellaneous sources. Table 6-2 contains a more detailed listing of CO emissions from the dominant category, transportation sources.

The single largest contributing source of CO emissions is highway vehicles, which emit 60 percent of the total national CO estimate. Because of the implementation of the Federal Motor Vehicle Control Program (FMVCP), CO emissions from highway vehicles have declined 48 percent, from 65.3 teragrams in 1970 to 34.1 teragrams in 1988. Figure 6-1 displays how CO emissions from the major highway vehicle categories have changed from

TABLE 6-2. CARBON MONOXIDE EMISSIONS FROM TRANSPORTATION (GIGAGRAMS/YEAR)

Source Category	1970	1975	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988
Highway vehicles													
Gasoline-powered													
Passenger cars	49,090	41,430	37,840	34,450	31,850	30,160	30,150	29,510	27,790	25,410	23,650	22,530	21,220
Light trucks - 1	5,800	5,730	6,100	5,960	5,810	6,370	5,760	6,190	6,050	6,280	6,060	6,100	5,770
Light trucks - 2	2,070	2,450	4,120	4,340	4,210	4,700	4,220	4,610	4,450	4,330	4,040	3,740	3,540
Heavy duty vehicles	7,810	6,610	6,500	6,170	5,870	5,780	4,910	4,720	4,380	3,750	2,920	2,800	2,730
Motorcycles	260	540	550	490	370	280	200	190	170	130	120	130	120
Total - Gasoline	65,030	56,760	55,110	51,410	48,110	47,290	45,240	45,220	42,840	39,900	36,790	35,300	33,380
Diesel-powered													
Passenger cars	0	0	2	5	8	10	10	20	20	20	20	20	10
Light trucks	0	0	1	1	3	6	6	5	3	4	4	3	4
Heavy duty vehicles	300	390	500	530	610	700	680	650	650	770	670	680	720
Total - Diesel	300	390	503	536	621	716	696	675	673	794	694	703	734
Highway Vehicle Total	65,330	57,150	55,613	51,946	48,731	48,006	45,936	45,895	43,513	40,694	37,484	36,003	34,114
Aircraft	900	880	960	990	990	960	950	980	1,010	1,090	1,080	1,060	1,050
Railroads	250	240	260	270	270	250	240	190	200	190	180	190	190
Vessels	1,150	1,360	1,470	1,420	1,380	1,440	1,390	1,410	1,700	1,400	1,500	1,560	1,620
Farm Machinery	3,570	2,930	2,370	2,240	2,040	1,880	1,780	1,470	1,900	2,120	1,910	1,830	1,630
Construction Machinery	580	370	340	370	460	370	320	260	250	410	450	520	530
Industrial Machinery	1,780	1,060	1,070	820	1,110	1,330	1,190	1,040	900	850	840	880	880
Other Off-highway Vehicles	840	990	1,050	1,080	1,100	1,150	1,130	1,140	1,130	1,150	1,170	1,190	1,200
Transportation Total	74,400	64,980	63,133	59,136	56,081	55,386	52,936	52,385	50,603	47,904	44,614	43,233	41,214

Source: U.S. Environmental Protection Agency (1990b).

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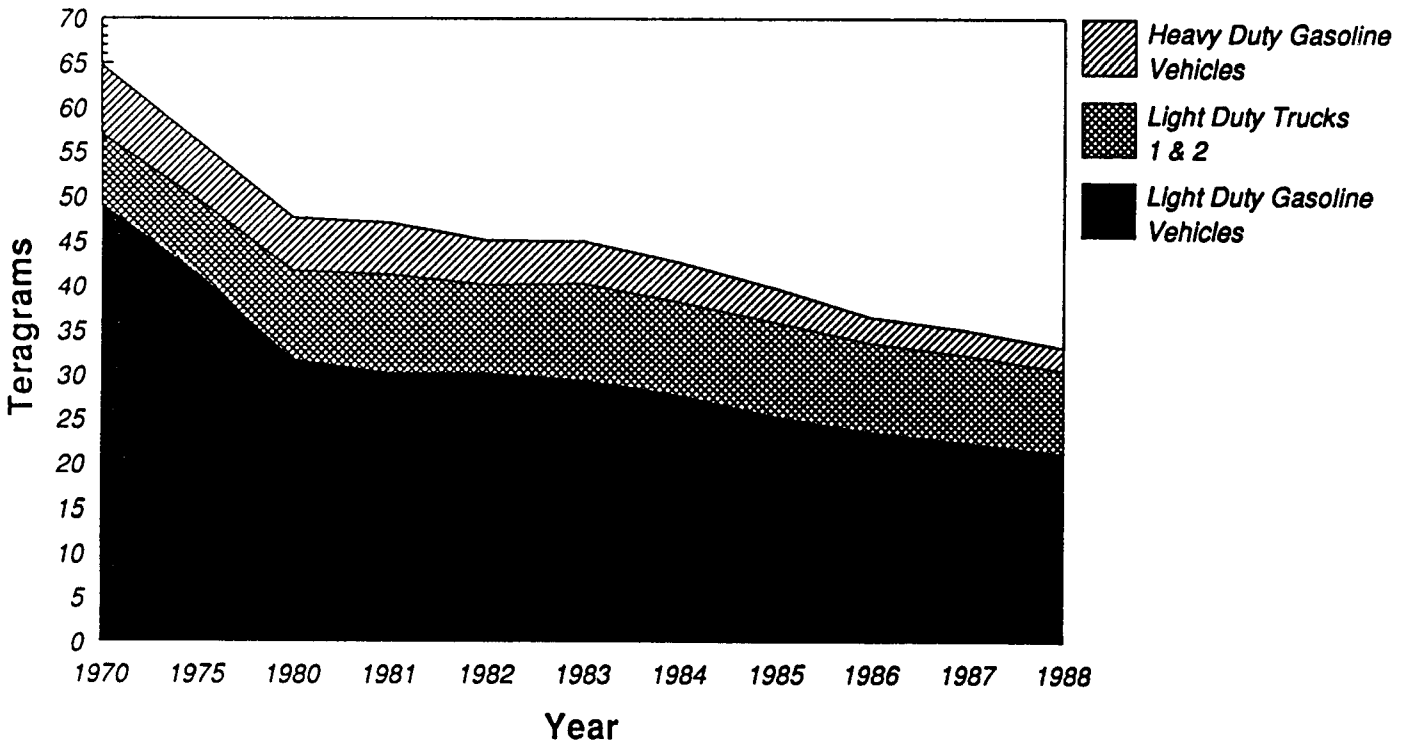

Figure 6-1. Estimated emissions of carbon monoxide from highway vehicles, 1970-1988.

Source: U.S. Environmental Protection Agency (1990b).

1970-1988 as a result of the FMVCP. Although VMT increased 38 percent from 1970 to 1978, total CO emissions from highway vehicles decreased 15 percent, because of the installation of FMVCP-mandated air pollution control devices on new vehicles. Petroleum crises contributed to a 1.7 percent decrease in VMT from 1978 to 1980. This lack of growth in vehicle travel together with an increased degree of pollution control because of stricter emission standards for new vehicles, coupled with the gradual disappearance of older uncontrolled vehicles from the vehicle fleet, produced an estimated 12 percent drop in highway vehicle CO emissions in this two year period from 1978 to 1980. Since 1980, VMT have grown each year. From 1980 to 1988, VMT increased by 33 percent. However, due to the FMVCP controls, CO emissions from highway vehicles actually decreased 30 percent during this period. Overall from 1970 to 1988, without the implementation of FMVCP, highway vehicle emissions would have increased 61 percent; with FMVCP implementation, emissions are estimated to have decreased 48 percent.

CO emissions from other sources have also generally decreased. In 1970, emissions from burning of agricultural crop residues were greater than in more recent years. Solid waste disposal emissions have also decreased as the result of implementation of regulations limiting or prohibiting burning of solid waste in many areas. Emissions of CO from stationary source fuel combustion occur mainly from the residential sector. These emissions were reduced somewhat through the mid-1970's as residential consumers converted to natural gas, oil, or electric heating equipment. Recent growth in the use of residential wood stoves has reversed this trend, but increased CO emissions from residential sources continue to be small compared to highway vehicle emissions. Nevertheless, in 1988 residential wood combustion accounted for about 10 percent of national CO emissions, more than any source category except highway vehicles. CO emissions from industrial processes have generally been declining since 1970 as the result of the obsolescence of a few high-polluting processes such as manufacture of carbon black by the channel process and installation of controls on other processes. However, industrial process emissions increased slightly (4 percent) from 1987 to 1988 due to increased industrial activity.

6.4 OUTDOOR AIR CONCENTRATIONS

6.4.1 Introduction

Ambient concentrations of carbon monoxide (CO) in urban communities vary widely with time and space. Actual human exposure to CO in various indoor and outdoor activities is affected by highly localized microenvironments which are influenced by nearness to sources, including vehicles, occupations, and by personal activities, such as smoking. Indoor sources and concentrations are summarized in Chapter 7. Exposure information is presented in Chapter 8. This section presents information about ambient concentrations. It will describe observed diurnal, seasonal, and annual patterns of ambient urban CO levels and will explain the importance of air monitoring site selection, of meteorological and geographic effects on CO exposures, techniques of CO trend analyses, and special CO exposure situations. An overview of meteorological diffusion models is also provided.

6.4.2 Site Selection

Site selection is one of the most complex and critical elements in the design of CO air monitoring programs. This is especially important for CO monitoring because the proximity of the monitor to traffic will influence the magnitude of CO concentrations. Naturally, the choice of monitoring sites depends greatly on the objective of the monitoring to be performed. The U.S. Environmental Protection Agency (1977a) recognizes the following as general objectives for monitoring:

1. To judge compliance with and/or progress made toward meeting ambient air quality standards.

2. To activate emergency control procedures to ameliorate air pollution episodes.

3. To observe pollution trends throughout the region, including the nonurban areas. (Information from nonurban areas is needed to evaluate whether air quality in the cleaner portions of a region is deteriorating significantly and to gain knowledge about background pollutant levels.)

4. To provide a data base for application in the evaluation of effects; in urban, land use, and transportation planning; in development and evaluation of abatement strategies; and in development and validation of diffusion models.

In addition to these general objectives, site selection is also based on the *scale of representativeness* that will meet the objectives. Data representativeness, like measures of concentration at a site, is dependent on the proximity of the monitor to the CO source but, further, is influenced by the intended use to which the data will be put. Ground level concentrations of CO within an urban area vary widely because the principal source of CO in cities is automobiles which, obviously, move and are more concentrated in some areas at some times than at other times. Monitoring sites at the edge of a highway will measure CO concentrations representative of a fairly small area. Sites well removed from highways can be representative of a fairly large-scale area. The EPA has defined six scales of spatial representativeness for CO monitoring sites: microscale, middle scale, neighborhood scale, urban scale, regional scale, and national and global scale (Federal Register, 1979).

Most CO monitoring conducted in the United States is for the purpose of determining attainment or nonattainment of air quality standards. Since monitoring resources have been and continue to be severely limited, monitoring sites are usually selected by a "worst case" principle; that is, they are set up where maximum CO concentrations are expected because the NAAQSs focus on peaks. As a result, many CO sites are located in close proximity to major highways, arterials, and downtown street canyons. This means that they are situated where maximum CO levels occur, but that their scale of representativeness is small. Monitoring results may thus relate primarily to pedestrian exposure near the monitor. Sites located away from the major roadways, but within highly populated neighborhoods with high traffic densities, may be more representative of the maximum CO concentrations to which a large portion of the population of a city may be exposed.

The EPA has published guidelines (Federal Register, 1979) for CO monitor siting (Table 6-3). EPA guidelines (U.S. Environmental Protection Agency, n.d.) give the highest priority to microscale sites within street canyons and to neighborhood sites where maximum concentrations are expected.

TABLE 6-3. SPECIFIC PROBE EXPOSURE CRITERIA

Site Type	Height Above Ground	Expected Concentration Gradient with Height (1-hr Average)	Separation of Monitor from Influencing Sources	General Remarks
Street Canyon				Central Business District. High density, slow-moving traffic.
Peak Concentration	3 ± 1/2 m	≈.5 ppm/m	Mid-sidewalk or 2 m from side of building. On leeward side of street.	Dense multiple-story buildings lining both sides of street.
Average Concentration	3 ± 1/2 m	≈3 ppm/m	Mid-sidewalk or 2 m from side of building.	
Neighborhood			Setback / VPD 3.5 km / 100,000 1.5 km / 50,000 200 m / 10,000 100 m / 5,000 35 m / 1,000 25 m / any	Commericial or residential neighborhood. This separation criteria limits the effect of these streets to ≈1 ppm.
Peak Concentration	3 ± 1/2 m	5%/m		
Average Concentration	3 ± 1/2 m	5%/m		
	<.3 ppm/m		Dependent on traffic volume, road configuration and setback distance of commercial or residential activity.	Stop and go or limited access traffic >50,000 VPD or greatest in area.
Background	3 to 10 m	.2%m	5 to 6 km; >3,000 VPH maximum. 400 m; >100 VPD.	35 km downwind in least frequent wind direction from city, limit effects to .2 ppm.
New Source Review				
Preconstruction	3 ± 1/2 m	5%/m	Usually the same as neighborhood.	Area of lowest concentration in proposed indirect source location for background.
Postconstruction	3 ± 1/2 m	>5%/m to <.5ppm	Usually the same as corridor or street canyon.	Area of maximum concentration in area of complete area source.

Source: Federal Register (1979).

The variability of CO concentration with height in the vicinity of a highway is sufficiently large that the representativeness of measurements will be strongly affected by variability of the inlet probe height. It is, therefore, necessary to standardize the height of the inlet probe so that data collected at one air monitoring station is comparable to data collected at others. In an effort to characterize typical human exposure, the sample inlet probe height should ideally be at breathing level. However, as a compromise between representation of breathing height and practical considerations, such as prevention of vandalism, it is recommended that inlets for most kinds of sampling be at a height of 3 $\pm$ 0.5 m (Altshuller et al., 1966; Bach et al., 1973). A one-meter minimum separation of the probe from adjacent structures is also recommended to avoid the frictional effects of surfaces on the movement of air (Anonymous, 1976).

Site selection for monitors used for purposes other than trend analysis and determination of compliance with air quality standards may not follow the specific criteria that apply to continuous monitoring sites. In fact, special purpose studies in which CO concentrations are measured at many locations provide information about the spatial variations of ambient CO that form the basis for setting site-selection criteria. Among the principal types of special purpose monitoring are research studies for diffusion model development and improvement and for source surveillance studies.

6.4.3 United States Data Base

Monitoring stations reporting data to EPA's Aerometric Information Retrieval System (AIRS) fall into two major categories: the National Air Monitoring Stations (NAMS) and the State and Local Air Monitoring Stations (SLAMS). The NAMS were established through monitoring regulations promulgated in May 1979 (Federal Register, 1979) to provide EPA with accurate and timely data on a national scale. The NAMS are located at sites expected to incur high pollutant concentrations and to typify areas with the potential for high population exposure. These stations meet uniform criteria for site location, quality assurance, and equivalent analytical methodology, sampling intervals, and instrument selection to assure consistent data reporting nationwide. The SLAMS, in general, meet the same rigid criteria but, in addition to the above siting criteria for highest concentrations and population exposure potential, they may be located to monitor a greater diversity of urban neighborhoods.

In accordance with requirements of the Clean Air Act and EPA regulations for State Implementation Plans (SIPs) (Code of Federal Regulations, 1977) ambient CO data from Federal networks must be reported each calendar quarter to AIRS. State and local agencies report most of the data from their SLAMS stations as well. As a result, continuous measurements of ambient CO concentrations from numerous cities throughout the United States are available from the U.S. Environmental Protection Agency.

Computer retrievals of raw data submitted to the EPA's AIRS data bank and published data summaries such as the *National Air Quality and Emission Trends Report* (U.S. Environmental Protection Agency, 1988) and *Air Quality Data - Annual Statistics* are available (U.S. Environmental Protection Agency, 1974b,c, 1976d,e,f,g,h, 1977b). However, state and local air pollution control agencies are not required to submit all CO data collected from their monitoring network. These agencies may also conduct special studies for certain "in-house" purposes. State departments of transportation and local metropolitan planning commissions are sources of CO data for the preparation of environmental impact statements for proposed transportation projects and/or in the preparation of SIP revisions. Air quality impact research sponsored by the EPA, the Federal Highway Administration, universities, and private industries also are sources of CO data.

6.4.4 Techniques of Data Analysis

Air quality surveys inherently involve taking a limited number of samples from a highly variable and uncontrolled population (i.e., the environment). For this reason, air quality data should be analyzed through statistical methods, which can be used to describe the behavior of the total population on the basis of a finite number of samples. In particular, statistical parameters can be calculated to describe the typical values observed, the maximum or peak values observed, and the range of values observed.

Although intermittent sampling is an important research tool for conducting special studies, the majority of CO monitoring instruments in use today are intended to operate continuously and to yield successive hourly averages. These data are applied for two principal uses: (1) characterizing environmental conditions by describing short-term (hourly, daily, seasonal) and long-term (year-to-year) urban CO concentration patterns, and

(2) evaluating, for statutory purposes, an area's status with respect to the 1-hour and 8-hour average NAAQS for CO.

At a minimum, an analysis of CO air quality data should include a comparison of the highest (or second highest) observed pollution concentration to established air quality standards. In addition, an analysis of CO data may include calculation of population statistics, frequency analyses, averaging time analyses, trend analyses, and case analysis.

6.4.4.1 Frequency Analysis

In most areas of air pollution monitoring modeling, we do not have enough knowledge about the generation, dispersion, and transport of air pollutants to formulate a convincing theoretical model for air quality data. Air pollutant concentrations are often generated by autocorrelated stochastic processes. In most situations we never know which of several hypothetical models are "correct." Fortunately, it is usually possible to identify time periods and pollutant averaging times when observations are approximately stationary and independent sequences of concentrations. Horowitz and Barakat (1979) showed that autocorrelation does not significantly affect the validity of the usual methods for estimating the parameters of the maximum pollutant concentration distribution. The most widely used model has been the two-parameter lognormal distribution which has played a major role in the formulation of air quality standards for many pollutants Georgopoulos and Seinfeld (1982). However, there are many data sets for which some other distribution fits better. These candidate models include the three-parameter lognormal, Weibull, exponential, and gamma distributions (Bencala and Seinfeld, 1976; Ott et al., 1979; Pollack, 1975; Simpson et al., 1984). This variety of distribution types probably reflects the phenomenon that an air pollution concentration is the superposition of a random number of point, line, and area sources of different emission strengths.

The NAAQSs for CO are currently based on a 1-hour and an 8-hour averaging time. Carbon monoxide data are most frequently collected in time averages of one hour. Evaluating compliance with the 1-hour standard simply requires rank-ordering 1-hour values for a year and comparing the second highest value with the 1-hour standard, which is currently 40 mg/m^3 (35 ppm), not to be exceeded more than once per year. If the second highest 1-hour value is less than 40 mg/m^3, the standard has been met.

Evaluating compliance with the 8-hour standard involves the calculation of *moving* 8-hour averages from the 1-hour data set. These 8-hour averages are also rank-ordered to obtain the second highest nonoverlapping value for comparison with the 8-hour standard, which is currently 10 mg/m^3 (9 ppm). For enforcement purposes, only nonoverlapping 8-hour intervals are counted as violations, as discussed in the Guidelines for the Interpretation of Air Quality Standards (U.S. Environmental Protection Agency, 1977c). It has been shown, however, that the full set of moving 8-hour averages should be examined for excessive values. Proposed simplifications, such as calculating only three consecutive nonoverlapping 8-hour averages per day, can easily result in missing peak 8-hour intervals and may not afford equitable comparisons among stations with differing diurnal patterns.

6.4.4.2 Trend Analyses

Carbon monoxide ambient concentrations vary considerably from hour to hour, day to day, season to season, and year to year. These variations are usually not random but follow fairly predictable temporal patterns according to season of the year, day of the week, and hour of the day. Long-term, statistical patterns in CO concentrations are referred to as trends. Carbon monoxide trends are best illustrated by graphs that can show diurnal, daily, seasonal, or yearly CO concentration comparisons. Examples of the different ways trends can be shown are provided later in this section. Carbon monoxide concentrations also follow fairly predictable spatial patterns. Spatial distributions of CO concentrations can be illustrated by the use of isopleth maps.

6.4.4.3 Special Analyses

A useful analysis technique is the "pollution rose," as illustrated in Figure 6-2. The pollution rose presents the joint frequency distribution of wind direction versus ambient CO concentration. The pollution rose is very helpful in determining the wind direction associated with the highest ambient CO concentrations and, intuitively, the location of high CO emissions sources.

Another analysis technique is case analysis, which can be used to characterize the meteorological and/or emission conditions associated with observed CO concentrations. For example, in order to characterize the meteorological conditions associated with the occurrence

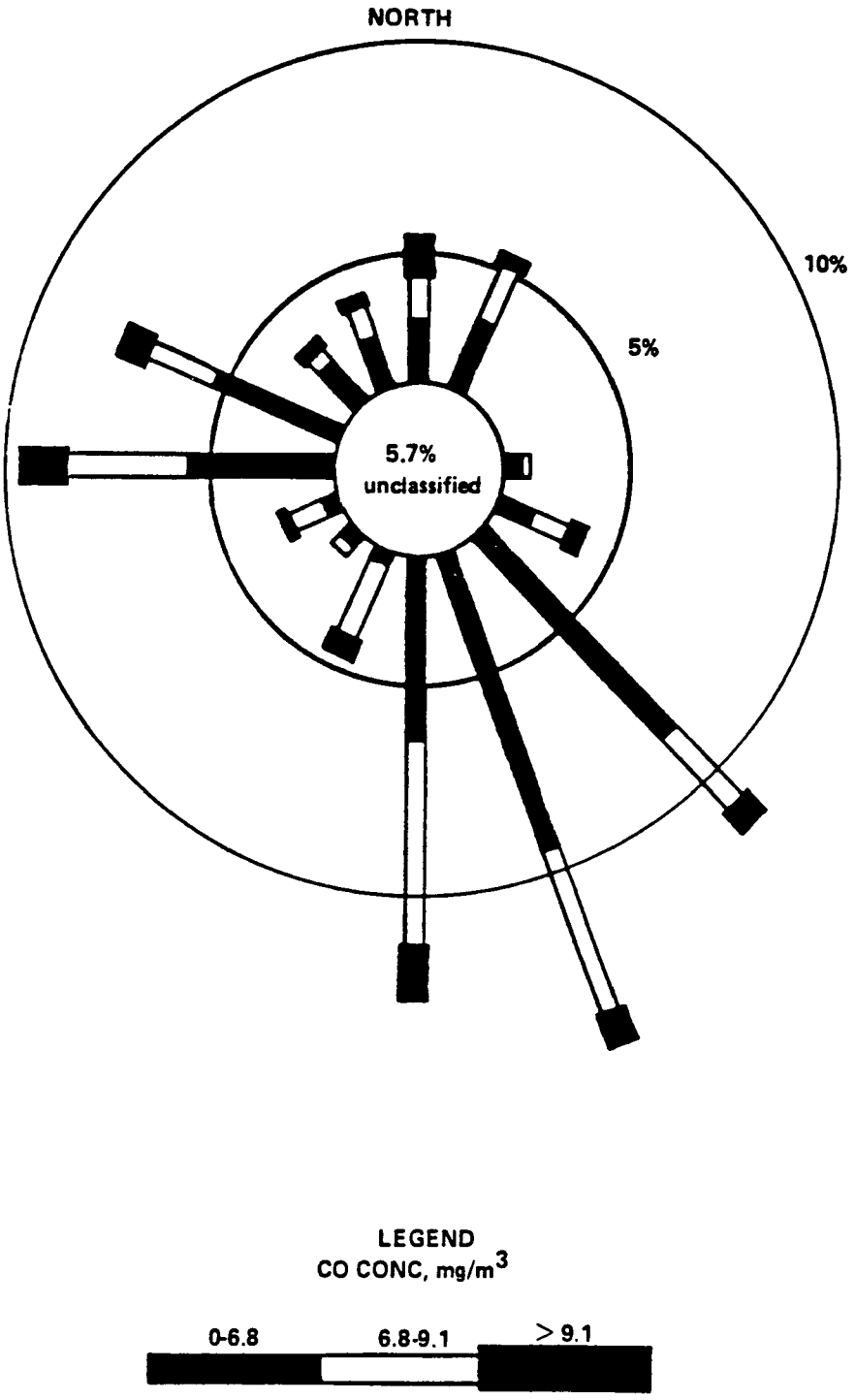

Figure 6-2. CO pollution rose for St. Louis, MO.

of high CO levels, meteorological records can be evaluated for the days when highest CO concentrations were observed concurrently at several monitoring sites throughout an urban area. The results of the analysis can then be used to develop a meteorological scenario for input to a mathematical model for the purpose of modeling "worst-case" CO concentrations.

6.4.5 Urban Levels of Carbon Monoxide

The ambient CO data cited in this document were obtained from EPA's Air Quality and Emissions Trend Report (1990) and directly from the Aerometric Information Retrieval System (AIRS, no date). To be included in the 10-year trend analyses, a given station had to report data for at least 8 of the 10 years in the period 1979-1988; 248 stations qualified. For the 5-year (1984-1988) trend and urbanized area trend analyses, a station had to report data for at least 4 of those five years; 359 stations qualified. The shorter time period was used in the urbanized area analyses to expand the number of stations available for analysis.

6.4.5.1 Ten-year CO Trends 1979-1988

Figure 6-3 illustrates the national 1979-1988 composite average trend for the second highest nonoverlapping 8-hour CO value for the 248 long-term sites and the subset of 72 NAMS sites (U.S. Environmental Protection Agency, 1990). The national average for all 248 stations and for the NAMS subset of 72 stations decreased both by 28 percent.

A Box plot of the data for all stations (Figure 6-4) provides a measure of the distribution changes (U.S. Environmental Protection Agency, 1990). Each horizontal line of a Box plot represents a percentile value. Starting at the top, each line represents the 95th, 90th, 75th, 50th (median), 25th, 10th, and 5th percentile values. The composite average is represented by an x near the median value. Although certain percentiles fluctuate from year to year, the general long-term improvement is clear.

The 10-year trend of the composite average of the estimated number of nonoverlapping 8-hr CO average concentrations that exceed the 8-hr NAAQS across all stations is shown in Figure 6-5 (U.S. Environmental Protection Agency, 1990). The trend is clearly decreasing with an 88 percent improvement for the 248 long-term stations. Note that these percentage improvements for exceedances are typically much larger than those found for the second

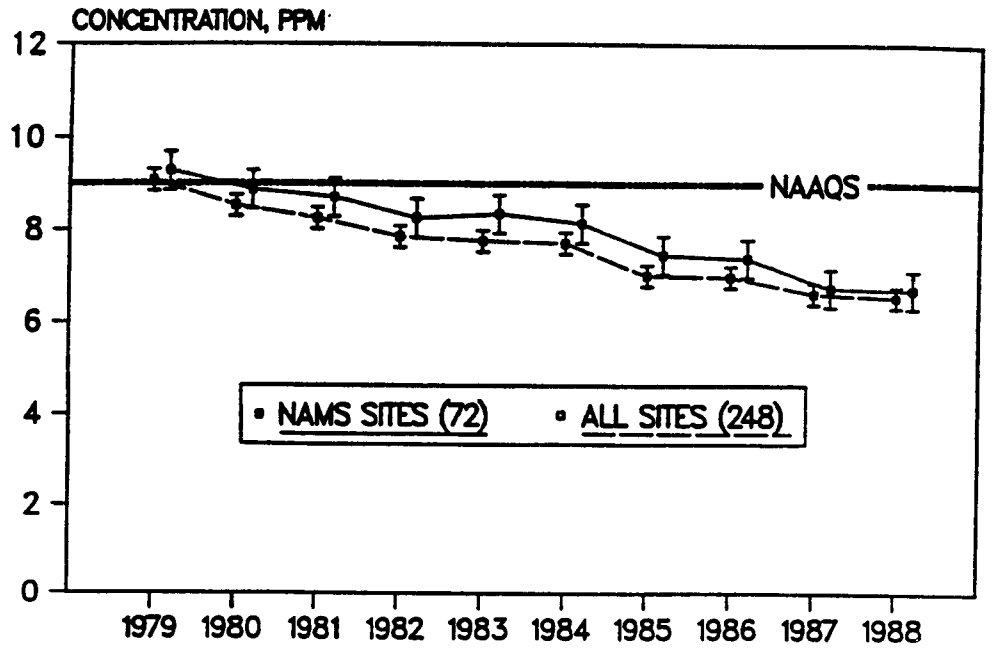

Figure 6-3. National trend in the composite average of the second highest nonoverlapping 8-hour average carbon monoxide concentration 1979-1988. Bars show 95 percent confidence intervals.

Source: (U.S. Environmental Protection Agency, 1990).

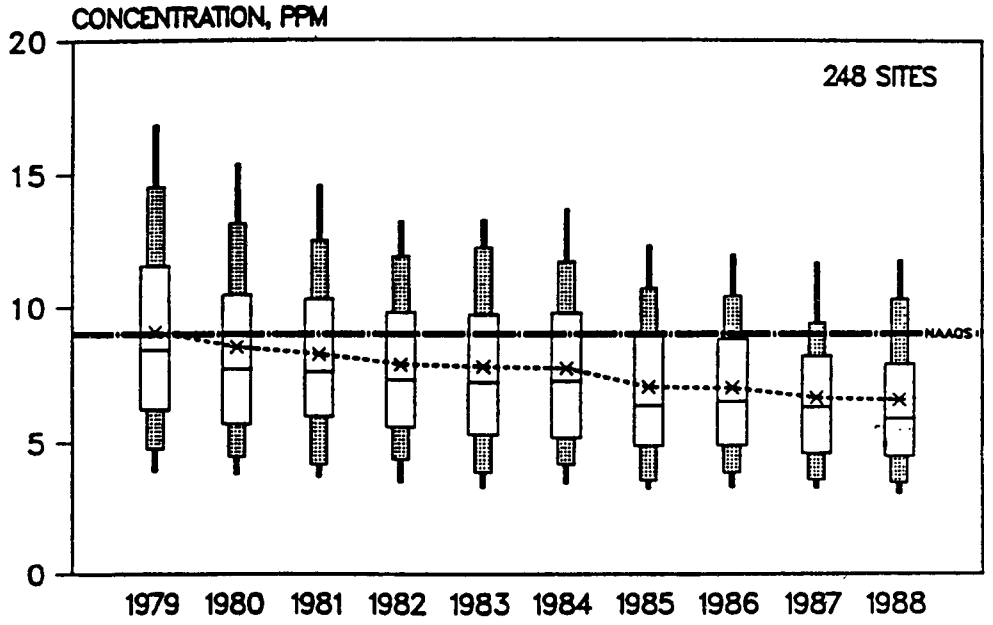

Figure 6-4. Boxplot comparisons of trends in second highest nonoverlapping 8-hour average carbon monoxide concentrations at 248 sites, 1979-1988.

Source: U.S. Environmental Protection Agency (1990).

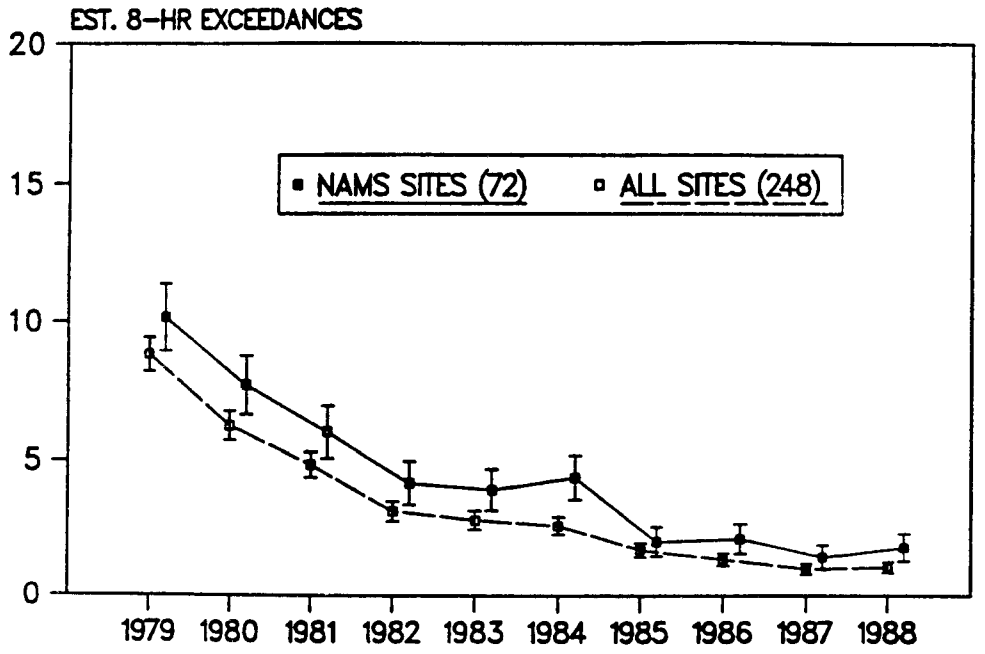

Figure 6-5. National trend in the composite average of the estimated number of exceedances of the 8-hour carbon monoxide NAAQS, 1979-1988. Bars show 95 percent confidence intervals.

Source: U.S. Environmental Protection Agency (1990).

maximum 8-hour concentrations depicted in Figure 6-4. The concentrations data are more likely to reflect percentage change in emission levels.

National CO emission estimates (Table 6-4) show a 25 percent decrease over the 10-year period (U.S. Environmental Protection Agency, 1990). The predominant CO emission source, transportation, accounted for about 72 percent of total CO emissions in

TABLE 6-4. NATIONAL CARBON MONOXIDE EMISSION ESTIMATES, 1979-1988 (million metric tons/year)

	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988
Source Category										
Transportation	59.1	56.1	55.4	52.9	52.4	50.6	47.9	44.3	43.2	41.2
Fuel Combustion	6.7	7.4	7.7	8.2	8.2	8.3	7.4	7.5	7.6	7.6
Industrial Processes	7.1	6.3	5.9	4.3	4.3	4.7	4.4	4.3	4.5	4.7
Solid Waste	2.3	2.2	2.1	2.0	1.9	1.9	2.0	1.7	1.7	1.7
Miscellaneous	6.5	7.6	6.4	4.9	7.7	6.3	5.3	5.0	7.1	6.0
Total	81.7	79.6	77.4	72.4	74.5	71.8	67.0	63.1	64.1	61.2

Note: The sums of sub-category may not equal total due to rounding.

Source: U.S. Environmental Protection Agency (1990).

1979, but had decreased to about 67 percent in 1988. This result provides further evidence that the Federal Motor Vehicle Control Program has been effective on a national scale with controls more than offsetting the growth during the period. It should be noted that CO monitors are typically located to identify potential problems and are placed in areas of high traffic densities that may not experience significant increases in traffic. Thus, CO levels at these locations may improve at a faster rate than the nationwide reduction in emissions.

6.4.5.2 Five-year CO Trends 1984-1988

Evaluation of five-year trends allows use of the expanded data base (359 stations). The composite averages (Figure 6-6) indicate 16 percent improvement between 1984 and 1988. Total estimated CO emissions (Table 6-4) decreased 15 percent across the five-year period; emissions from transportation sources decreased 19 percent.

Composite Regional averages for 1986 through 1988 of the second highest nonoverlapping 8-hour CO averages (Figure 6-7) show the largest declines occurring in Regions I, II, VI, VII, and VIII. Smaller, sometimes fluctuating declines occurred in Regions III, IV, V, and IX; Region X ended 1988 on a level with 1986.

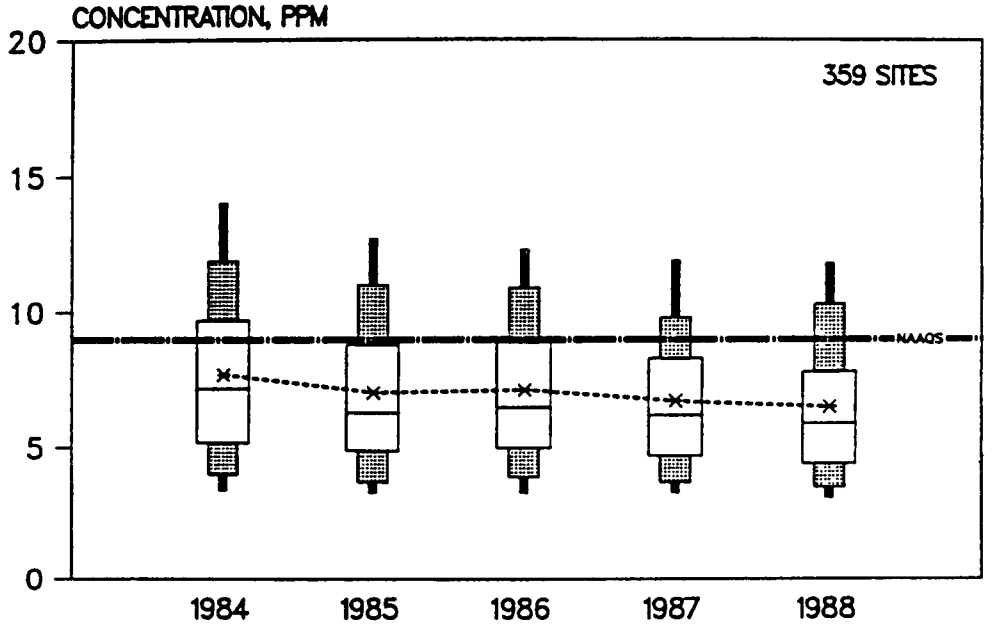

Figure 6-6. Boxplot comparisons of trends in second highest nonoverlapping 8-hour average carbon monoxide concentrations at 359 sites, 1984-1988.

Source: U.S. Environmental Protection Agency (1990).

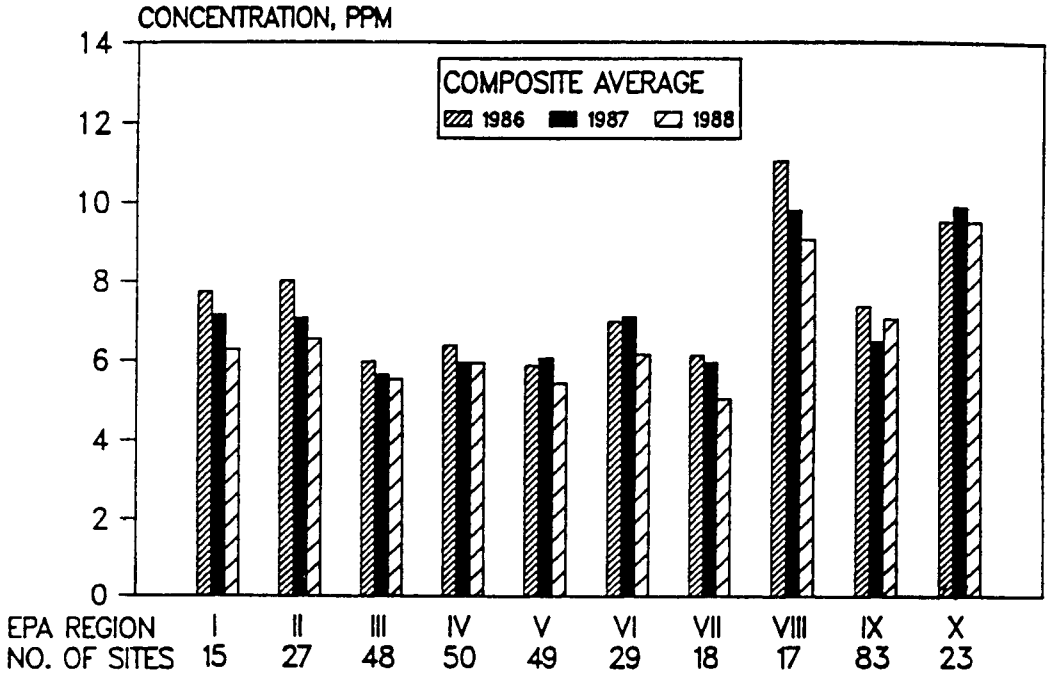

Figure 6-7. Regional comparisons of the 1986, 1987, 1988 composite averages of the second highest nonoverlapping 8-hour average carbon monoxide concentration.

Source: U.S. Environmental Protection Agency (1990).

6.4.5.3 Air Quality Levels in Metropolitan Statistical Areas

Metropolitan Statistical Areas (MSAs) consist of a central urban county or counties and any adjacent counties with at least 50% of their population within the urban perimeter. The nation's 339 MSAs, grouped by population range in Table 6-5, include 77% of the U.S. population. Figure 6-8 compares the highest second-high nonoverlapping 8-hour value recorded during 1988 for the 90 largest MSAs in the continental U.S. (not shown: Honolulu, HI, and San Juan, PR), containing approximately 55% of the U.S. population. Nineteen of these MSAs exceeded the current 8-hour standard of 9 ppm in 1988.

6.4.6 Effects of Meteorology and Topography

Meteorology governs the transport and dispersion of CO emissions in the atmosphere and thus has a strong influence on the ground level CO concentrations detected at receptor points downwind of emission sources. Meteorological parameters that determine CO

TABLE 6-5. DISTRIBUTION OF POPULATION IN METROPOLITAN STATISTICAL AREAS (Based on 1987 estimates)

Population Range	No. of MSAs	Total Population
≤100,000	27	2,274,000
100,000 ≤ 250,000	147	23,372,000
250,000 ≤ 500,000	73	25,218,000
500,000 ≤ 1,000,000	48	34,367,000
1,000,001 ≤ 2,000,000	26	38,685,000
> 2,000,000	18	65,747,000
Total	339	189,663,000

Source: U.S. Environmental Protection Agency (1990).

transport and dispersion patterns include wind speed, wind direction, atmospheric stability, and mixing depth. The relative importance of each parameter depends upon the scale of the analysis. For example, concentration patterns around an intersection would not be greatly influenced by mixing depth. However, concentration patterns over the whole urban area would be.

Wind direction determines the direction of horizontal transport of CO emissions and consequently the impact that CO emissions from one are will have on air quality in another area. If emissions are uniform across the urban area, as air flows across the whole urban area, the additive effect of the CO emissions being transported downwind will result in higher CO concentrations at the downwind edge of the urban area. However, concentrations at a particular location may be dominated by local emissions. Concentrations adjacent to a highway will be higher than urban levels away from large highways. Wind directions nearly parallel to a highway will allow for an accumulation of CO emissions in the downwind direction, resulting in CO concentrations higher than would be expected for winds perpendicular to the highway under the same conditions.

Low wind speeds provide little atmospheric dilution, allowing CO emissions to build up, resulting in higher CO concentrations. Conversely, high wind speeds aid in the dispersion of

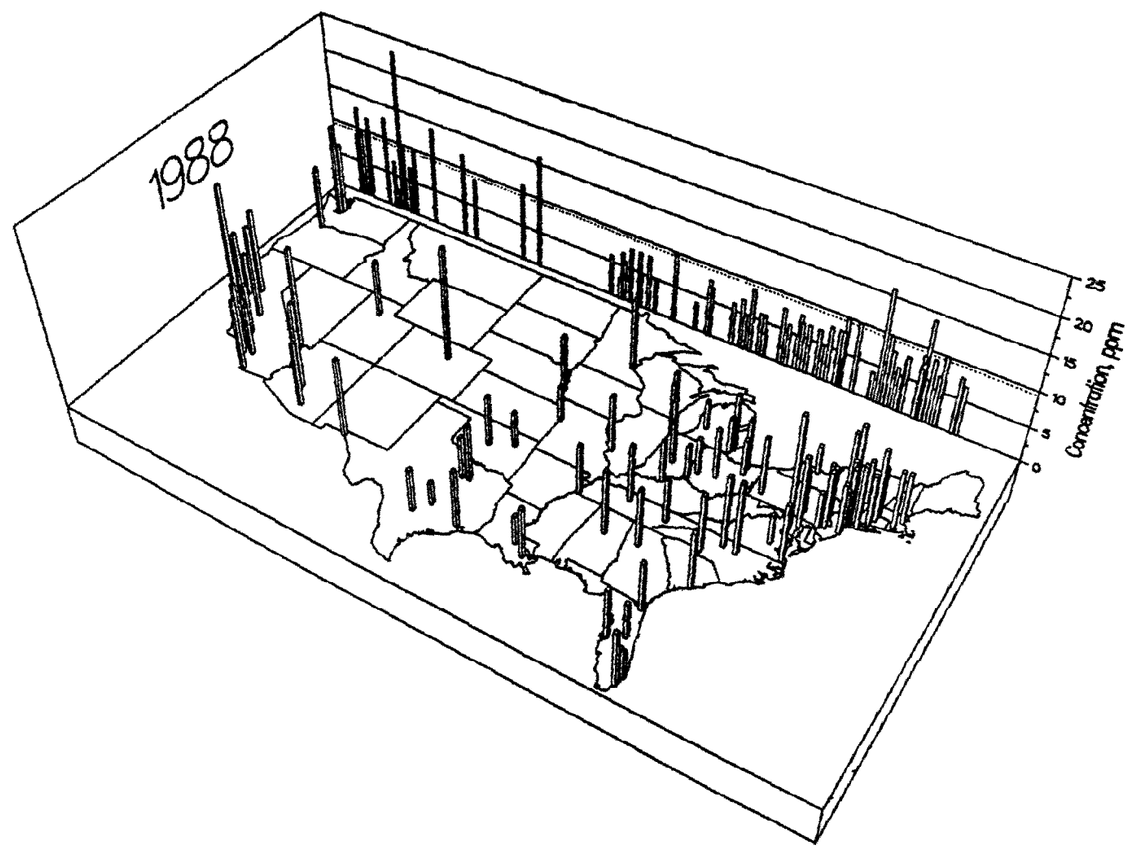

Figure 6-8. United States map of the highest second maximum nonoverlapping 8-hour average carbon monoxide concentration by Metropolitan Statistical Area for 1988.

Source: U.S. Environmental Protection Agency (1990).

CO emissions by increasing the amount of dilution that takes place, thus decreasing CO concentrations. The effect of surface roughness (i.e., mountains, buildings, etc.) on the wind speed profile over several types of topographic features is illustrated in Figure 6-9 (Benson, 1979). With increased surface roughness, either natural or man-made, the depth of the affected layer is increased. The winds affected by frictional drag are reduced, but the turbulence induced by mechanical effects in increased. The net effect of increased surface roughness over an urban area is to mix the CO emissions through a larger depth in the atmosphere, which aids in the dispersion of CO emissions. Thermal forces in the atmosphere either enhance or suppress the production of turbulent motion in the atmosphere. The dispersive properties of the atmosphere are correlated with atmospheric stability, which is generally easier to characterized.

Radiation and thermal properties of topographic features influence the heating and cooling of the atmosphere near the ground surface. The most notable of these effects is the urban "heat island" effect. Heat sources, including the asphalt and concrete associated with an urban area, tend to radiate heat, causing a "heat island" compared to the cooler surrounding terrain. The buoyant effect of warmer air over the city tends to induce thermal turbulence (i.e., more unstable atmospheric conditions), which tend to aid in the dispersion of CO emissions, thus lowering ambient CO concentrations.

Local wind circulations, such as sea-land breezes, lake-land breezes, or mountain-valley winds, are caused by the differential heating of topographic forms. These circulations generally flow in one direction during the day, and in the opposite direction at night. As a result, an urban area can experience "blow-back" of CO emissions emitted during the day; these will be experienced as higher CO concentrations at night. The boundary region between the local circulation winds and the prevailing synoptic flow sometimes remains nearly stationary, or slowly oscillates back and forth for periods up to several hours, and can be the site of nearly calmwind conditions. These characteristics result in slow net transport of CO emissions which then accumulate and result in higher ambient CO concentrations.

The depth through which pollutants are routinely mixed affects the total ventilation capacity of the atmosphere. When the potential temperature lapse rate is positive, the resulting increase in temperature with increase in height procedures an inversion or inversion lid that limits vertical mixing, and thereby limits the dilution capacity of the atmosphere.

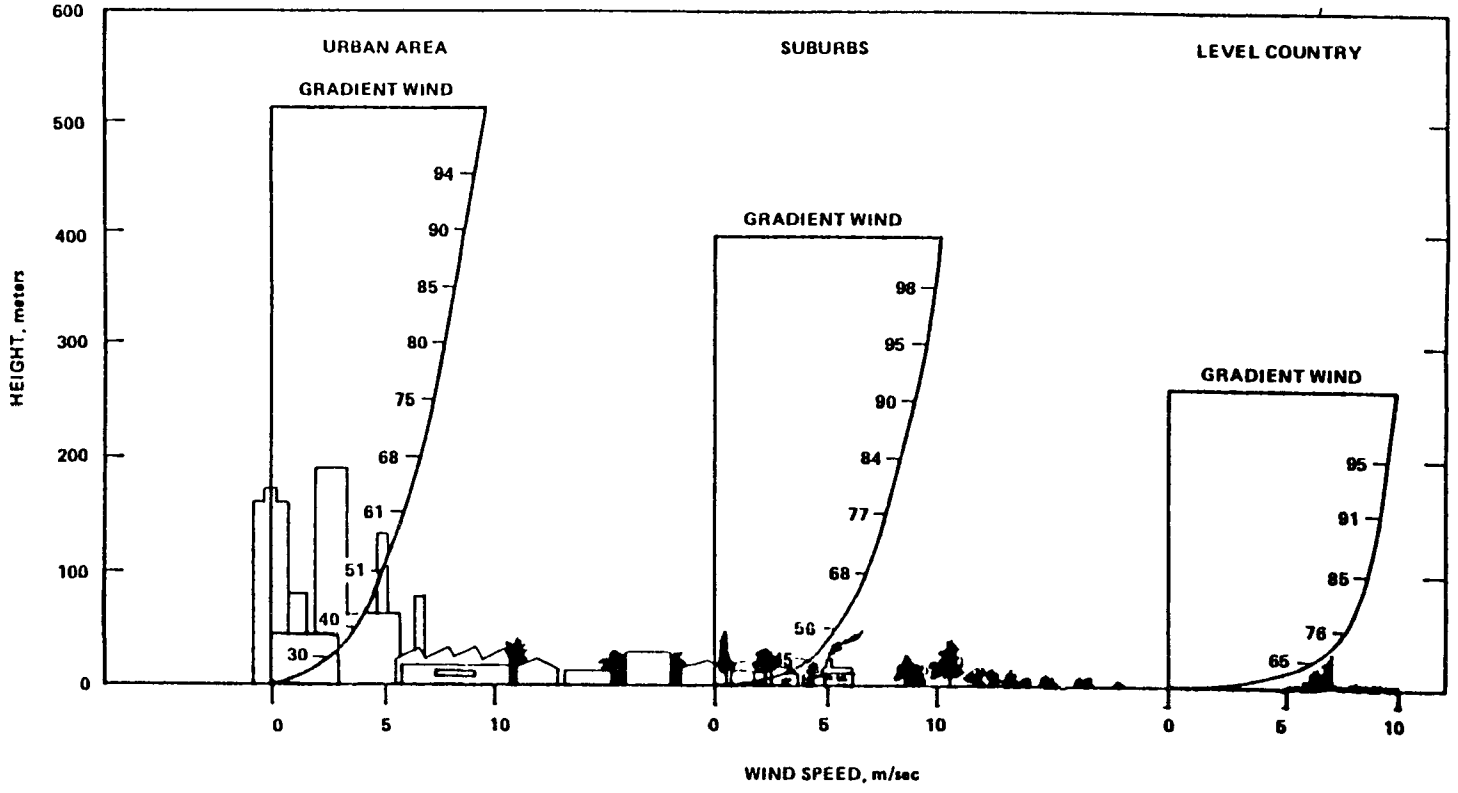

Figure 6-9. Effect of terrain roughness on the wind speed profile.

Source: Benson (1979).

An important form of inversion for CO dispersion is the surface or radiation inversion. This usually occurs at night with light winds and clear skies, when the loss of heat by longwave radiation from the ground surface cools the surface and subsequently the air adjacent to it. With the proper relative humidity, these same conditions will lead to the formation of radiation fog. The presence of early morning fog is often associated with a surface based temperature inversion. The surface inversion usually persists for hours, and because it typifies stable atmospheric conditions, it tends to result in high microscale and mesoscale CO concentrations.

Another type of inversion is the subsidence inversion. It is caused by a gradual descent of air aloft, that results in adiabatic warming of the descending layer. The resulting subsidence inversion is illustrated in Figure 6-10, which shows the temperature decreased with height and the capping by a subsidence inversion layer, above which there is a normal decrease of temperature with height. The subsidence inversion usually persists for days and tends to contribute to high urban background CO concentrations. The subsidence inversion is usually more persistent during summer and fall than in winter or spring.

The shape of typical plots of hourly CO concentrations can be attributed in large part to the effect of changing wind speeds, atmospheric stability, and inversion height during the course of a day. Figure 6-11 shows average hourly wind speeds and inversion heights occurring in Los Angeles during summer (Tiao et al., 1975). The higher wind speeds and inversion height during early afternoon are typical throughout the continental United States and play a significant role in lowering urban CO concentrations at midday. Traffic volumes, and subsequently CO emissions from cars, would still be expected to be high at this time of day. Around midnight, when traffic volumes are relatively low, the effects of low wind speeds and low inversion heights tend to cause increases in CO concentrations. Many monitoring stations in the United Sates observe these relatively high CO concentrations late at night.

Ambient surface temperature also has a unique effect on the production rate of CO emissions from automobiles. Using a variety of automobiles tested at artificially controlled ambient temperatures of 20°, 50°, 75°, and 110°F, the EPA (Bullin et al., 1986) found that lowest CO emissions were produced at 75°F and tend to increase with colder temperatures. Colder temperatures coupled with a strong surface based radiative inversion are generally

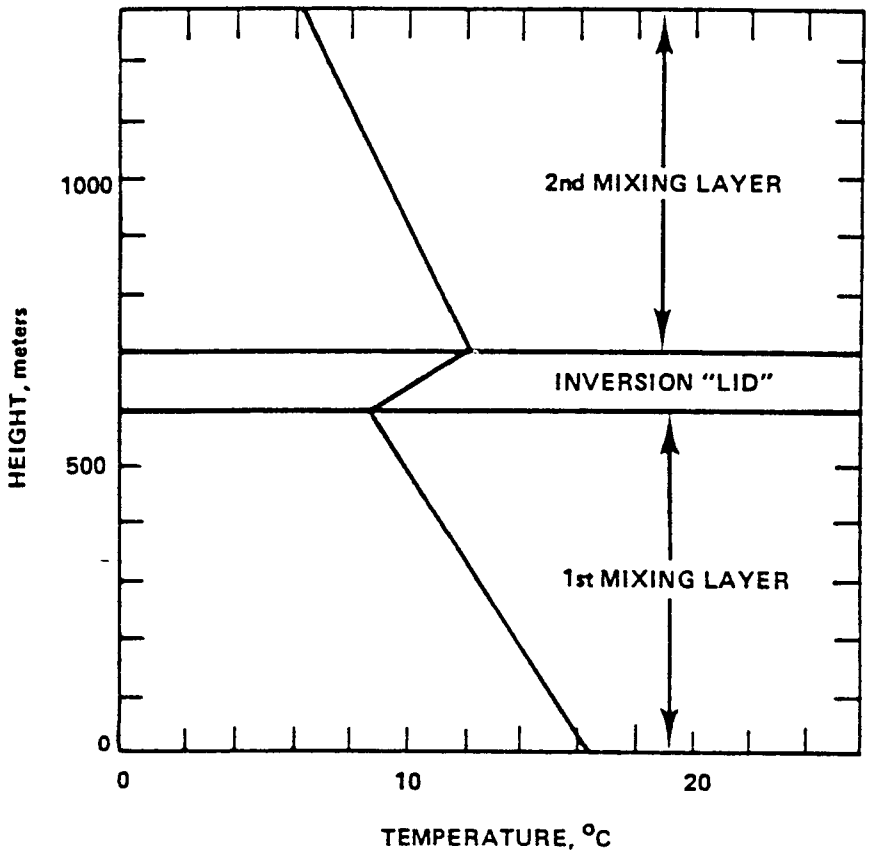

Figure 6-10. Schematic representation of an elevated inversion.

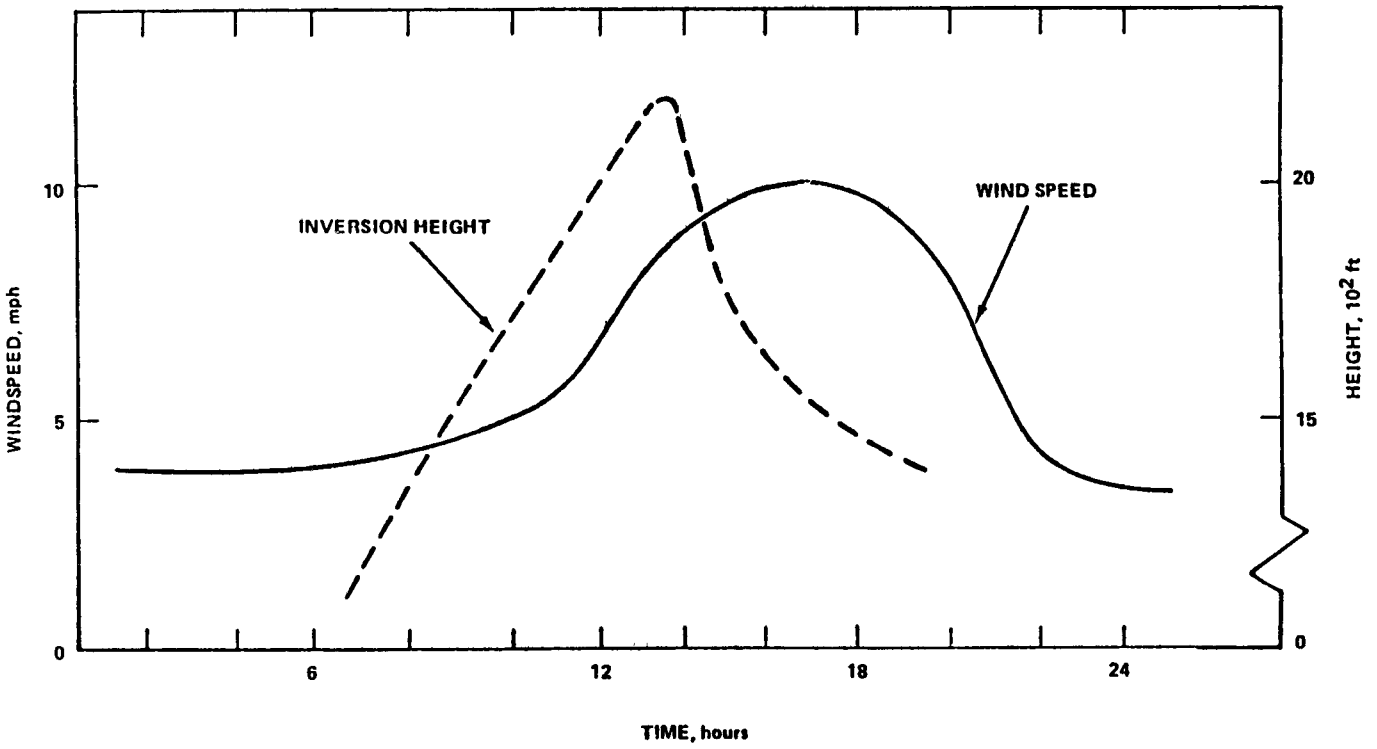

Figure 6-11. Hourly variations in inversion height and wind speed for Los Angeles in summer.

Source: Tiao et al. (1975).

associated with poor dispersion in the atmosphere. The combined effect of higher emission rates and poor dispersive conditions results in higher ambient CO concentrations than would be expected for warmer temperatures.

6.5 CARBON MONOXIDE DISPERSION MODELS

A dispersion model relates pollutant emissions to ambient air quality by providing a mathematical description of the transport, dispersion, and chemical transformations that occur in the atmosphere. This ability to relate source emissions to receptor air quality is very important to air quality maintenance planning and environmental impact assessment.

Dispersion models vary in complexity from simple empirical or statistical relationships to sophisticated multi-source models that describe the transport and dispersion of CO throughout an urban area. For estimates of ambient CO concentrations, a line source model is needed to estimate the CO levels near a highway, an intersection model is needed to estimate CO levels near an intersection, and an urban model is needed to estimate CO levels that result from the cumulative effects of urban sources such as roadways and wood stoves. The types of models used will depend mainly on the source configuration to be modeled (i.e., highway intersection, or urban area).

6.5.1 Line Source Modeling

Several models have been used to estimate CO concentrations from line sources. The guideline on Air Quality Models (Revised) (U.S. Environmental Protection Agency, 1986) makes specific recommendations on procedures to utilize for line source modeling. Refer to the latest version of this document for these recommendations. Available line source models are CALINE-3 (Benson, 1979), GMLINE (Chock, 1978), HIWAY-2 (Petersen, 1980), and PAL (Petersen, 1978). A brief description of each of the line source models excerpted from "Evaluation of Mobile Source Air Quality Simulation Models" (Wackter and Bodner, 1986) follows:

6.5.1.1 CALINE3

The CALINE3 model was developed by the California Department of Transportation. It simulates dispersion of highway emissions by dividing individual roadway links into a series of elements from which incremental concentrations are computed using a finite line source equation. The incremental concentrations are summed to obtain a total concentration estimate at a particular receptor location.

CALINE3 simulates the region directly over the roadway as a zone of uniform emissions and turbulence called the "mixing zone." This zone experiences increased dispersion due to mechanical turbulence created by moving vehicles as well as thermal turbulence created by hot vehicle exhaust. CALINE3 adjusts the level of turbulence as a function of wind speed. At low wind speeds residence time of an air parcel within the mixing zone is increased, resulting in turbulence enhancement through the use of a larger initial vertical sigma value.

The CALINE3 model includes options for simulating dispersion from four types of roadways: at grade, elevated filled sections, elevated bridges, and cut or depressed sections. Multiple lanes, links and orientations can be simulated.

6.5.1.2 GMLINE

GMLINE (Chock, 1978) was developed by General Motors Research Laboratories to describe dispersion near straight-line, at-grade highways. Multiple parallel or crossing roadway links can be simulated and the model allows for a variable emissions height. The model was not designed to treat cut-sections.

GMLINE simulates dispersion of vehicle emissions by dividing the roadway into separate, straight-line sources, each with a uniform emission rate. Downwind concentrations at a receptor are calculated for each infinite line source, then summed to obtain a total concentration. The model accounts for plume rise due to heated exhaust and includes a wind speed correction to account for increased turbulence created by traffic wakes.

6.5.1.3 HIWAY-2

HIWAY-2 (Petersen, 1980) was developed by EPA to replace the HIWAY model (Zimmerman and Thompson, 1975) for estimating roadway pollutant impacts. The model

was designed to determine concentrations at receptors downwind of at-grade roadways and cut sections (outside of the cut only).

HIWAY-2 simulates dispersion by treating highway emissions as a series of finite line sources, each with a uniform emission rate. Concentrations downwind are calculated by numerically integrating a Gaussian point-source plume along each line segment. The primary differences between HIWAY-2 and HIWAY are that HIWAY-2 includes a new set of dispersion curves and an aerodynamic drag factor to account for dispersion due to vehicle motion under low wind speed conditions.

6.5.1.4 PAL

The PAL model (Petersen, 1978) was developed by EPA to estimate pollutant dispersion from point, area and line sources. It was designed to simulate dispersion from several types of roadway geometries including straight or curved horizontal lines and straight or curved elevated lines with variable emissions along each line segment. Model documentation specifies that treatment of elevated line sources is appropriate for open bridge type road segments but not for elevated filled roadways. Cut or depressed roadway sections are not treated by PAL.

PAL determines concentrations at a receptor due to a line source by numerically integrating the Gaussian point source equation. Calculations are made for a number of points along the finite line, assuming a linear change in concentration between these points. Subsequent estimates of concentrations are made by including additional points along the line. When the difference between succeeding estimates becomes smaller than a prescribed value, the calculations are considered complete.

6.5.1.5 Model Evaluation

A comprehensive evaluation of CALINE3, GMLINE, HIWAY-2, and PAL was undertaken using 5 field measurement programs and is described in "Evaluation of Mobile Source Air Quality Simulation Models" (Wackter and Bodner, 1986). This report contains numerous tabulations of each model's performance in terms of statistical measures recommended by the American Meteorological Society. The results indicate that the GMLINE model performed the best most often, while the PAL model ranked lowest most

frequently. All the models tended to overpredict for light wind speeds and near parallel wind/road angles, while underpredictions occurred for high wind speeds.

6.5.2 Intersection Modeling

Several models have been used to estimate CO concentrations from intersections. The Guideline on Air Quality Models (Revised) (U.S. Environmental Protection Agency, 1986) makes specific recommendations on procedures to utilize for intersection modeling. Refer to the latest version of this document for these recommendations. Available intersection models are: "Volume 9" (U.S. Environmental Protection Agency, 1978), CAL3Q (Smith, 1985), CALINE4 (Benson, 1984), GIM (EMI Consultants, 1985), IMM (New York State Department of Transportation, 1980), and TEXIN2 (Bullin et al., 1986) a brief description of each of these models excerpted from the above references follows.

6.5.2.1 "Volume 9"

Carbon monoxide concentrations are calculated in a three-step process. In the first step, the network description and traffic demand volume are used to estimate the traffic flow characteristics. Emissions are then computed as the sum of two parts: cruise emissions produced by non-stopping vehicles and excess emissions emitted by stopping/starting vehicles. Lastly, the effect of atmospheric dispersion on actual concentrations at the specified receptor locations is estimated.

Excess emissions consist of deceleration, idle, and acceleration emissions due to vehicles stopping and starting at intersections. Idle emissions rates are determined using MOBILE3. Acceleration, deceleration, and cruise emission rates are determined using modal emission factors based on the updated (December 1977) version of the Modal Emissions Model (Kunselman et al., 1974). MOBILE3 correction factors (Wolcott, 1986) to the modal emission factors can then be utilized to adjust for calendar year, cold starts, hot starts, speed, temperature, and vehicle mix.

The traffic model contained in "Volume 9" calculates the length over which excess emissions apply. This calculation is based on the proportion of vehicles that stop and the number of vehicles subject to queueing delay. It should be noted that the traffic model

contained in "Volume 9" is not applicable for overcapacity intersections thus, "Volume 9" cannot be utilized for such intersections scenarios.

6.5.2.2 Intersection Midblock Model

The Intersection Midblock Model (IMM) is a combination of signalization and vehicle queueing estimation procedures using accepted traffic engineering principles. It also predicts emissions using the Modal Analysis Model and the MOBILE-2 program, and models dispersion with the HIWAY-2 model.

The IMM first calculates various traffic parameters. Once the traffic calculations have been performed, the estimation of emission rates is carried out. Using the input parameters of speed into the queue, speed out of the queue, deceleration into the queue and acceleration out of the queue, the IMM utilizes the Modal Analysis Model as a subroutine to calculate cruise and acceleration/deceleration emissions for all approaches. Idle emissions are calculated by use of the MOBILE-2 program. Based on the previously calculated queue lengths, a set of pseudolinks is constructed. These pseudolinks lie along the actual links with the same termination points and center lines as the actual links, but each has a length equal to the calculated queue length for that approach. The only emissions assigned to the actual links are the cruise emissions (calculated with the Modal Analysis Model). The emissions assigned to the pseudolinks are the excess emissions due to accelerating, decelerating and idling.

A correction factor is applied to the emissions calculated from the Modal Analysis Model since these apply only for 1977 emission rates from stabilized light-duty vehicles. The correction factor used is the ratio of the MOBILE-2 composite emission estimate for the specified scenario to the MOBILE-2 composite emission estimate for 1977 stabilized light-duty vehicles.

Once the traffic calculations have been performed and emission rates assigned to each lane, the HIWAY-2 model is employed as a subroutine to calculate carbon monoxide concentrations at selected receptors. For the special case of a "street canyon" intersection between tall buildings in a highly urban area, a special dispersion routine is used.

6.5.2.3 Georgia Intersection Model

The Georgia Intersection Model (GIM) uses a computer program to calculate the average vehicle delay, the average route speed, and the emission rate of carbon monoxide of vehicles traveling through the intersection over a distance called the "effective length" where speeds are lower due to the effect of vehicles slowing and stopping during red light cycles. It eliminates the need for using modal emission factors and allows for the analysis of overcapacity intersections.

GIM uses many of the same assumptions and equations as in the "Volume 9" approach, with few modifications. The procedure can be summarized briefly as follows. GIM calculates the effected length of roadway upstream of the intersection where vehicle speeds are reduced due to delays caused by vehicle slowing and stopping. It calculates the CO emissions for vehicles traversing the effected length, based on average speed over the length and MOBILE3 emission factors. Using this approach, modal emission factors (i.e., acceleration mode emissions, deceleration mode emissions, idle emissions, and cruise emissions) are not utilized. The output of GM defines finite line source segments with their associated CO emission rates which can be input to the CALINE3 line source dispersion model.

6.5.2.4 TEXIN2

The TEXIN2 Model follows a general three-step process:

(1) Estimation of traffic parameters.

(2) Estimation and distribution of vehicle emissions.

(3) Modeling downwind dispersion of pollutants.

Traffic parameters are calculated using either the modified Planning or Operations and Design procedures of the Critical Movement Analysis (CMA) (National Cooperative Highway Research Program, 1979) for signalized intersections. Basically, the difference between the two traffic algorithms concerns the different adjustment factors present in the CMA Operations and Design algorithm. These adjustment factors tend to decreased the capacity of a given intersection. Therefore, the Operations and Design technique will occasionally

calculate that an intersection is over capacity while the Planning procedure indicates that the intersection is below full capacity.

Research has provided adjustment factors for a number of elements that affect traffic flow and hence modify critical volumes. These elements are: (1) left turns; (2) bus and truck volume; (3) peaking characteristics; (4) lane width; (5) bus stop operations; (6) right turns with pedestrian activity; and (7) parking activity. In the TEXIN2 Model, the CMA Planning procedure utilizes only the left turn adjustment factor, while the CMA Operations and Design procedure uses the first four adjustment factors listed above with no additional user input. In both algorithms, left turns are treated in detail for the simple reason that left turns have a large impact on intersection capacity. This effect is created using passenger car equivalency (PCE) values. PCE values are multiplicative adjustment factors applied to the left turning traffic volumes.

The second function performed by TEXIN2 is the estimation of vehicle emissions. The emissions are modeled as the sum of two components: cruise and excess emissions. Cruise emissions and excess emissions are released by free-flowing and delayed vehicles, respectively. Initially, cruise emissions are assumed to be released along the entire length of each intersection leg. The emissions are subsequently redistributed to better reflect actual traffic movement. A modified version of the MOBILE3 program is used to estimate cruise emissions and an idle emission factor, while acceleration and deceleration emissions are calculated using modal emission factors as suggested by Ismart (1981). As an alternative, a shortcut method combining the MOBILE3 estimation of the idle emission factor with values for individual vehicle emission rates based on speed, temperature, percent hot/cold starts, and the vehicle scenario is available to the user (Federal Highway Administration, 19).

As used in TEXIN2, the MOBILE3 program provides inspection/maintenance (I/M) and antitampering program (ATP) options. To conserve computer time, several sizable portions of the extremely large MOBILE3 program were deleted, namely the nitrogen oxide and hydrocarbon emission factors modeling and user- supplied corrections to the emission rates. Since the MOBILE-2 program does not allow for California scenarios, the California data and options from the MOBILE-2 program were added to the emission routine.

6.5.2.5 CAL3Q

The CAL3Q model utilizes the Connecticut Department of Transportation queueing model to calculate traffic parameters including queue length. The average speed of vehicles through the intersection is estimated so a composite MOBILE3 emission factor can be applied over the length of the queue. In addition, the MOBILE3 idle emission rate is applied over the queue length. No modal emission factors are utilized in CAL3Q and the model cannot handle overcapacity intersections. The emissions, and queue length are input to the CALINE3 dispersion model to calculate carbon monoxide concentrations at selected receptors.

6.5.2.6 CALINE4

The CALINE4 intersection model focuses on a rather complex concept of spatially resolved modal emissions over links. A CALINE4 intersection link encompasses the acceleration and deceleration zones created by the presence of the intersection. Each link can treat only one direction of traffic flow, so that four links are required to model a full intersection.

Four cumulative modal emission profiles representing the deceleration, idle, acceleration and cruise modes of operation are constructed for each intersection link. These profiles are determined using the following input variables:

SP	=	Cruise speed (mph)
ACCT	=	Acceleration time (seconds)
DCLT	=	Deceleration time (seconds)
IDT1	=	Maximum idle time (seconds)
IDT2	=	Minimum idle time (seconds)
NCYC	=	Total number of vehicles per cycle per lane
NDLA	=	Number of vehicles delayed per cycle per lane.

NCYC and NDLA are chosen to represent the dominant movement for the link. The model assumes a uniform vehicle arrival rate, constant acceleration and deceleration rates, and full stops for all delayed vehicles. Acceleration and deceleration rates (ACCR, DCLR) and acceleration and deceleration lengths (LACC, LDCL) are determined using the input values for SPD, ACCT and DCLT. By assuming an "at rest" vehicle spacing (VSP) of 7 meters, the average queue length (LQU) is also determined. IDT1 represents the delay at full stop

experienced by the first vehicle in the queue. Similarly, IDT2 represents this same measure for the last vehicle. IDT2 is used to model a platooned arrival and should be assigned a value of zero for non-platooned applications.

The time rate modal emission factors over the link are computed by a rather complex method. To develop these factors, the model must be provided with composite emission rates for average route speeds of 0 (idle) and 16 mph. The resulting time rate factors are denoted as EFA (acceleration), EFD (deceleration), EFC (cruise) and EFI (idle).

The cumulative emission profile for a given mode is developed by determining the time in mode for each vehicle as a function of distance from link endpoint 1 (ZD), multiplying the time by the respective modal emission rate and summing the results over the number of vehicles per cycle per lane (NCYC). The elementary equations of motion are used to relate time to ZD for each mode. The assumed vehicle spacing (VSP) is used to specify the positional distribution of the vehicles. The total cumulative emissions per cycle per lane at distance ZD from XL1, YL1 are denoted as ECUMk(ZD) in the CALINE4 coding, where the subscript signifies the mode (1=accel., 2=decel., 3=cruise, 4=idle).

The CALINE4 model handles atmospheric dispersion, somewhat similarly to that in the CALINE3 model. The most significant difference is that CALINE4, unlike CALINE3, requires the input of site specific wind direction, fluctuation, and sigma-theta data.

6.5.2.7 Comparison of Intersection Models

A study was conducted by Braverman (1987) to compare the emission rates and distances over which acceleration, cruise, deceleration, and idle emissions occur as generated by different intersection models. The models included in the study were CAL3Q, GIM, IMM, TEXIN2, and "Volume 9". CALINE4 was not included in this study because it does not contain an explicit traffic model and does not print out emission rates.

In this study, scenarios for a simple undercapacity, near capacity, and overcapacity intersection were modeled. All of the parameters for each of the intersection scenarios modeled were held constant except for the approach volumes which were 408, 608, and 768 vehicles/hour for the under capacity, near capacity, and overcapacity scenarios, respectively. The parameters for the intersection scenarios modeled are given in Table 6-6.

The results of the emission rates and distances generated by the models are given in Tables 6-7, 6-8, and 6-9 for the undercapacity, near capacity, and overcapacity intersection scenarios, respectively. The traffic models contained in "Volume 9" and CAL3Q cannot handle overcapacity intersections, so no results are reported for these models for the overcapacity scenario. In addition, the traffic model contained in CAL3Q calculates the near capacity scenario as slightly overcapacity, so no results are reported for CAL3Q for the near capacity scenario.

TABLE 6-6. PARAMETERS FOR INTERSECTION SCENARIOS

Approach Volumes (Vehicles/Hour)	480*, 608*, and 768*
Approach Capacity (Vehicles/Hour)	640
Capacity Service Volume (Vehicles/Hour of Green Time)	1600
Cycle Length (Seconds)	90
Percent Green Time	40
Uninterrupted Speed (Miles/Hour)	30
Number of Lanes	1
Temperature (°F)	40
Year	1985
Percent Cold Non-Catalyst	20.6
Percent Hot Catalyst	27.3
Percent Cold Catalyst	20.6
Altitude	Low
Vehicle Mix Fractions	
Light Duty Gas Vehicle	0.652
Light Duty Gas Truck 1	0.128
Light Duty Gas Truck 2	0.087
Heavy Duty Gas Vehicle	0.040
Light Duty Diesel Vehicle	0.023
Light Duty Diesel Truck	0.008
Heavy Duty Diesel Vehicle	0.054
Motorcycle	0.007

*Undercapacity, near capacity, and overcapacity, respectively.

Source: Braverman (1987).

TABLE 6-7. RESULTS OF MODEL COMPARISONS FOR THE UNDERCAPACITY INTERSECTION SCENARIO

Model	Emission Rate (g/m-s) Unit Distance	Distance (m)	Emission Rate (g/s)
Volume 9	0.0327	106.3	3.476
IMM	0.0119*	220.1	2.615
TEXIN2	0.0236*	81.7	1.930
GIM	0.0102	162.1	1.653
CAL3Q	0.0218	54.0	1.177

*Emission Rate was obtained by multiplying each component (acceleration, United Distance deceleration, and idle) of emissions times the length over which they occur individually, summing the products, and dividing by the entire length of emissions.

Source: Braverman (1987).

TABLE 6-8. RESULTS OF MODEL COMPARISONS FOR THE NEAR CAPACITY INTERSECTION SCENARIO

Model	Emission Rate (g/m-s) Unit Distance	Distance (m)	Emission Rate (g/s)
Volume 9	0.0452	269.7	12.19
IMM	0.0229*	294	6.74
TEXIN2	0.0413*	141.5	5.85
GIM	0.0124	193.4	2.40

*Emission Rate was obtained by multiplying each component (acceleration, United Distance deceleration, and idle) of emissions times the length over which they occur individually, summing the products, and dividing by the entire length of emissions.

Source: Braverman (1987).

TABLE 6-9. RESULTS OF MODEL COMPARISONS FOR THE OVERCAPACITY INTERSECTION SCENARIO

Model	Emission Rate (g/m-s) Unit Distance	Distance (m)	Emission Rate (g/s)
IMM	0.0413*	611	25.24
GIM	0.0228	733.3	16.7
TEXIN2	0.0426*	176.6	7.53

*Emission Rate was obtained by multiplying each component (acceleration, United Distance deceleration, and idle) of emissions times the length over which they occur individually, summing the products, and dividing by the entire length of emissions.

Source: Braverman (1987).

The results indicate that under- to near-capacity situations the order of model predicted emission rates from highest to lowest is "Volume 9", IMM, TEXIN2, GIM, CAL3Q. For overcapacity situations, the order of model predicted emission rates from highest to lowest is IMM, GIM, TEXIN2. Note that "Volume 9", IMM, and TEXIN2 utilize modal emission factors. GIM and CAL3Q do not utilize modal emission factors; instead they utilize composite MOBILE3 emission factors. Since "Volume 9", IMM, and TEXIN2 give higher emission rates for the under to near capacity situations than GIM and CAL3Q, it can be inferred that models that utilize modal emission factors generate higher emission rates than models that utilize composite MOBILE3 emission factors. The reason that GIM gives higher emissions than TEXIN2 for the overcapacity scenario is that TEXIN2 simply extrapolates from the undercapacity situation to generate overcapacity emission rates, whereas GIM treats overcapacity as an entirely different situation.

6.5.3 Urban Area Modeling

Several models have been used to model the cumulative effects of urban CO sources such as roadways and wood stoves. The Guideline on Air Quality Models (Revised) (U.S. Environmental Protection Agency, 1986) does not recommend one specific model for

urbanwide CO analysis; instead, it recommends these analyses be considered on a case-by-case basis.

Urban exceedances of the 8-hour CO NAAQS result primarily from the cumulative effects of motor vehicle emissions throughout the urban area. The APRAC-3 model (Simmon et al., 1981), which is briefly described below, was developed to handle this situation.

6.5.3.1 APRAC-3

APRAC-3 is a Gaussian-plume diffusion model which computes hourly average carbon monoxide concentrations for any urban location. The model calculates contributions from dispersion on various scales: extraurban, mainly from sources upwind of the city of interest; intraurban, from freeway, arterial, and feeder street sources; and local, from dispersion within a street canyon. APRAC-3 requires an extensive traffic inventory for the city of interest.

Traffic links may have arbitrary length and orientation. Off-link traffic is allocated to two-mile square grids. Link traffic emissions are aggregated into a receptor oriented area source array. The boundaries of the area sources actually treated are (1) arcs at radial distances from the receptor which increase in geometric progression, (2) the sides of a 22.5° sector oriented upwind for distances greater than 1,000 m, and (3) the sides of a 45° sector oriented upwind for distances less than 1,000 m. A similar area source array is established for each receptor. Up to 625 receptors are accepted for a single-hour.

Meteorological data requirements are hourly wind direction (nearest 10 degrees), hourly wind speed, and hourly cloud cover for stability calculations. Constant, uniform (steady-state) wind is assumed within each hour. The model can interpolate winds at receptors if more than one wind is provided. Mixing height is ignored until the concentration equals that calculated using a box model. A box model the (uniform vertical distribution) is used beyond that distance.

A secondary contributor to some urban exceedances of the 8-hour CO NAAQS is the cumulative effect of wood stove emissions throughout the urban area. These emissions are trapped under the nighttime radiation inversion along with evening traffic emission on cold clear nights with light and variable winds. This situation can be handled best by either a Gaussian or a numerical model. A numerical model provides a better treatment than a

Gaussian model of the time dependent changes in meteorology under these conditions. However, use of numerical models is extremely data and resource intensive. Thus, numerical models have only been applied in very large cities. One numerical model that has been used in a few cases is the Urban Airshed Model (Ames et al., 1985). An acceptable Gaussian model for urban area applications is RAM (Catalano et al., 1987). A brief description of the Urban Airshed Model and RAM follows.

6.5.3.2 Urban Airshed Model

The Urban Airshed Model (Ames et al., 1985) simulates the major physical and chemical processes in the polluted troposphere. These include gas phase chemistry, advective transport, and turbulent diffusion. The modeling domain is divided into a large array of grid cells. Horizontally the cells are uniformly sized squares 3 to 5 kilometers on a side. Typically, four or five layers of cells represent the vertical domain. The depth of the layers is scaled by the height of the mixed layer and the height of the top of the modeling domain (region top). The latter typically ranges from 500 meters in the morning hours to 1,000 meters or more in the afternoon. Emissions are injected into individual cells depending on the location of the sources, their height of release, and the buoyant rise of individual stack gas plumes.

The theoretical basis for the Urban Airshed Model rests of the conservation of mass equation for atmosphere diffusion. Primary inputs to the Urban Airshed Model are point and area source emissions, initial and boundary concentrations both at the surface and aloft, and a variety of meteorological data. These include a three-dimensional wind field, mixing depths, surface temperature, and exposure class, the latter an indicator of thermal instability.

6.5.3.3 RAM

RAM (Catalano et al., 1987) provides a readily available computer program based on the assumptions of steady-state Gaussian dispersion for short-term (one-hour to one-day) determination of urban air quality resulting from pollutants released from point and/or area sources.

RAM is applicable for locations with level or gently rolling terrain where a single wind vector for each hour is a reasonable approximation of the flow over the source area

considered. Calculations are performed for each hour. Hourly meteorological data required are wind direction, wind speed, temperature, stability class, and mixing height.

Computations are performed hour by hour as if the atmosphere had achieved a steady-state condition. Therefore, errors will occur where there is a gradual buildup (or decrease) in concentrations from hour to hour, such as with light wind conditions. Also under light wind conditions the definition of wind direction is likely to be inaccurate, and variations in the wind flow from location to location in the area are quite probable.

Considerable time is saved in calculating concentrations from area sources by using a narrow plume simplification which considers sources at various distances on a line directly upwind from the receptor to be representative in the crosswind direction of the sources at those distances affecting the receptor. Area source sizes are used as given in the emission inventory in lieu of creating an internal inventory of uniform elements.

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7. INDOOR CARBON MONOXIDE SOURCES, EMISSIONS, AND CONCENTRATIONS

7.1 INTRODUCTION

The activities of individuals are the most important determinants of their exposure to air borne contaminants. In the course of a day individuals spend varying amounts of time in a variety of microenvironments (residences, industrial and nonindustrial workplaces, automobiles, public access buildings, outdoors, etc.). Exposures across all microenvironments need to be assessed in evaluating adverse health or comfort effects and in formulating cost-effective mitigation measures to reduce or minimize the risks associated with exposure. Exposure can be assessed by direct methods (personal monitoring or by measuring biomarkers of exposure) or by indirect methods (microenvironmental monitoring and questionnaires combined with an appropriate human exposure model).

In recent years there has been a growing recognition of the importance of nonindustrial indoor microenvironments in assessing exposures to a wide range of air contaminants (National Research Council, 1981; World Health Organization, 1985). This recognition reflects the fact that concentrations for many important air contaminants are higher in many indoor microenvironments than outdoors and that most individuals spend little time outdoors.

Carbon monoxide is introduced to indoor environments through emissions from a variety of combustion sources and in the infiltration or ventilation air from outdoors. The resulting indoor concentration, both average and peak, is dependent on a complex interaction of several interrelated factors affecting the introduction, dispersion, and removal of CO. These factors include, for example, such variables as: (1) the type, nature (factors affecting the generating rate of CO), and number of sources; (2) source-use characteristics; (3) building characteristics; (4) infiltration or ventilation rates; (5) air mixing between and within compartments in an indoor space; (6) removal rates and potential remission or generation by indoor surfaces and chemical transformations; (7) existence and effectiveness of air contaminant removal systems; and (8) outdoor concentrations; etc. The interaction of these factors to produce the resulting indoor concentrations usually is considered within the framework of the mass balance principle.

In its simplest form, where steady-state or equilibrium conditions are assumed for a single compartment with complete mixing and no air cleaner, the mass-balance model can be represented by the following equation.

$$C_i = C_1 + C_2 \tag{7-1}$$

where:

$$C_1 = PAC_o/A + K = \text{outdoor air contribution} \tag{7-2}$$

$$C_2 = S/V/A + K = \text{indoor source contribution} \tag{7-3}$$

and where:

C_i = steady-state indoor concentration of CO ($\mu g/m^3$)

C_1 = contribution to indoor CO from outdoor air ($\mu g/m^3$)

C_2 = contribution to indoor CO from indoor sources ($\mu g/m^3$)

C_o = outdoor CO ($\mu g/m^3$)

P = fraction of outdoor CO that penetrates the building shell

A = air-exchange rate in air changes per hour – ACH per hour

S = generation rate or source strength of CO ($\mu g/hr$)

V = volume of the indoor space (m^3)

K = removal rate of CO by indoor surfaces or chemical transformations – equivalent ACH

This simplified form of the model generally is used to evaluate CO levels indoors. In actuality, however, indoor spaces often are multicompartments with incomplete mixing where the source-generation and contaminant-removal rates and air-contaminant concentrations vary considerably in time. Equation 7-1 is useful particularly for determining the impact on indoor air-contaminant concentrations from sources that are used over relatively long periods of time

(e.g., unvented kerosene or gas space heaters) where steady-state or equilibrium conditions are reached. When applied to sources that are intermittent in their use (e.g., gas range or tobacco combustion), Equation 7-1 averages over the off/on periods of the sources to determine average input parameters for the model. Short-term indoor concentrations of air contaminants associated with sources whose use varies considerably with time can be modeled with the differential version of Equation 7-1, when detailed information on the time variability of the source use, mixing, and removal terms are available. Field data on short-term variability of contaminant concentrations and associated variables, however, are not available.

Carbon monoxide generally is assumed have low reactivity indoors (Yamanaka, 1984; Leaderer et al., 1986; Traynor et al., 1982; Borrazzo et al., 1987; Caceres et al., 1983), that is, CO removal by indoor surfaces or chemical transformations is approximately equal to zero for typical indoor CO residence times (K=0 in Equations 7-2 and 7-3). There are no chamber or field studies that have measured the penetration factor for CO. Given the low CO reactivity, P generally is assumed equal to one (P=1) for conditions where outdoor levels of CO do not vary rapidly. Under these typical assumptions (K=0 and P=1), indoor concentrations of CO can be represented by the following simplified form of Equations 7-1, 7-2, and 7-3.

$$C_i = C_o + S/V/A \qquad (7\text{-}4)$$

In the case where there are no indoor sources, then the average indoor concentration is equal to the average outdoor concentration. With short variations in outdoor concentrations, however, indoor CO concentrations will lag outdoor concentrations and will be dependent on the air-exchange rate in a space. When an indoor source exists, the indoor CO concentration will be equal to the outdoor concentration plus the contribution of the indoor source, which is a function of the source strength (CO emission rate), volume of the indoor environment and air-exchange rate.

This chapter will summarize the data currently available on emissions of CO from sources commonly found indoors and on levels of CO measured in a variety of indoor microenvironments.

7.2 EMISSIONS FROM INDOOR SOURCES

Carbon monoxide emitted directly into the indoor environment is one of several air contaminants resulting from combustion sources. Such emissions into occupied spaces can be unintentional or the result of accepted use of unvented or partially vented combustion sources. Faulty or leaky flue pipes, backdrafting and spillage from combustion appliances that draw their air from indoors, (i.e., Moffatt, 1986), improper use of combustion sources (i.e., use of a poorly maintained kerosene heater), and air intake into a building from attached parking garages are all examples of unintentional or accidental indoor sources of CO. The U.S. Departmental of Health and Human Services (1986) estimates between 700 and 1,000 deaths per year in the U.S. alone are due to accidental carbon monoxide poisoning. The number of individuals experiencing severe adverse health effects at sublethal carbon monoxide concentrations from accidental indoor sources is no doubt many times the estimated deaths. While the unintentional or accidental indoor sources of CO represent a serious health hazard, little is known about the extent of the problem. Such sources cannot be characterized for CO emissions in any standard way that would make the results extendable to the general population. Unintentional or accidental sources are not considered in this review of emissions of CO from indoor sources.

The major indoor sources of CO emissions that result from the accepted use of unvented or partially vented combustion sources include gas cooking ranges and ovens, gas appliances, unvented gas space heaters, unvented kerosene space heaters, cigarette combustion, and wood burning stoves. This section of the chapter will summarize the available CO-emission data for the major indoor-sources of CO. The experimental design, measurement methods, and results of studies of indoor-source CO emissions will be discussed.

The characterization of CO emissions from indoor sources is essential in providing source strength input data for indoor modeling, understanding fundamental processes influencing emissions, guiding field study designs aimed at assessing indoor CO exposures, identifying and ranking important sources, and in developing cost-effective mitigation measures that will minimize exposures.

7.2.1 Emissions from Gas Cooking Ranges, Gas Ovens, and Gas Appliances

Estimates indicate that gas (natural gas and liquid propane) is used for cooking, heating water, and drying clothes in approximately 45.1% of all homes in the United States (U.S. Bureau of the Census, 1982) and near 100% of the homes in other countries (e.g., The Netherlands). Unvented, partially vented, and improperly vented gas appliances, particularly the gas cooking range and oven, represent an important source category of CO emissions into the indoor residential environment. Emissions of CO from these gas appliances (the source term, S, in Equation 7-4) are a function of a number of variables relating the source type (range top or oven, water heater, dryer, number of pilot lights, burner design, etc.), source condition (age, maintenance, combustion efficiency, etc.), source use (number of burners used, frequency of use, fuel consumption rate, length of use, improper use, etc.) and venting of emissions (existence and use of outside vents over ranges, efficiency of vents, venting of gas dryers, etc.).

A number of chamber studies have investigated CO emissions from gas cooking ranges, ovens, and appliances. The studies have used two basic approaches. The first is called the direct or sampling-hood approach (Moschandreas et al., 1985; Himmel and DeWerth, 1974) and the second is the mass-balance or chamber approach (Moschandreas et al., 1985; Traynor et al., 1982; Leaderer, 1982). In the direct approach, emissions are sampled using a quartz hood through which the combustion emissions pass and are sampled. Because the effluent gases measured by this method contain substantial amounts of excess air that can vary considerably from run to run, the measured concentrations are converted to a hypothetical undiluted or "air-free" basis for calculating CO emission rates. This method is used in both chamber and field evaluations of emission rates (Moschandreas et al., 1985; Borrazzo et al., 1987). The mass-balance approach utilizes a well-mixed environmental chamber where the relationship between changes in concentration of CO over time in relation to outdoor concentration, source-emission rate, air-exchange rate, and removal rate are evaluated (mass-balance equation). Both approaches yield source emission rates for CO, usually expressed as micrograms per kilojoule (μg/kJ).

Emissions from gas range-top burners typically are evaluated using a standardized water load in a cooking pot (American National Standards Institute Z21.1-1974, 1982) or a

modification of it (Borrazzo et al., 1987). The cooking pot has a top that is sealed, except for a 3/4 in. pipe that extends from the center of the top to allow steam to escape.

Using both the direct-sampling hood and mass-balance approach and a standardized water load, Moschandreas et al. (1985) evaluated CO emissions from three new gas ranges (including pilot and non-pilot light and self-cleaning oven and conventional oven) with six hours of conditioning before use in actual testing. The data of Cole and Zawacki (1985) are incorporated into the Moschandreas et al. (1985) report. The range CO emissions were evaluated for appliance type, the conditions of blue-flame operation (burner air shutter set at the manufacturer's recommended level), and yellow-tipping (air shutters are closed – worst condition). Two natural gas mixes were evaluated: lean mix (983 Btu/scf) and rich mix (1022 Btu/scf).

A total of 116 direct-sampling experiments were conducted in which CO emissions were measured for all 12 burners (four burners per stove) using rich and lean fuels. Thirty direct-sampling experiments were conducted with the burners operating with yellow tipping. No significant differences (criterion: $p \leq 0.05$) were found by fuel type. The results of the tests using blue and yellow flame setting are shown in Table 7-1. The improper operation of the burners (yellow-tipping flame) resulted in an approximately two- to fivefold increase in CO emissions. Considerable variation in CO emissions from burner to burner within and between ranges were noted by the authors for blue-flame operation although overall CO emission averages for burners by each range were within a factor of two.

A total of 144 mass-balance experiments on the three ranges were conducted in a 33–m^3 chamber to evaluate the impact of fuel composition, range type, primary aeration level (blue or yellow flame), fuel-consumption rate (high–9149 Btu/h, medium–7673 Btu/h, low–1492 Btu/h, and warm–807 Btu/h), test chamber air-exchange rate, temperature and humidity (range of 15 to 50%), and temporal effects on CO-emission rates. CO emissions showed little variation by fuel composition (lean vs. rich), range type, test chamber air-exchange rate, and time. Yellow-tipping flame conditions resulted in a two- to tenfold increase in CO emissions over blue-flame operation conditions. No changes in emissions were noted as a function of changes in chamber temperature and relative humidity. Little change in CO emissions were noted for the high, medium, and low fuel-consumption rates while a sevenfold increase in emissions were observed for the warm setting. In a comparison

TABLE 7-1. CARBON MONOXIDE-EMISSION RATES[a] FOR 12 RANGE-TOP BURNERS OPERATING WITH BLUE AND YELLOW-TIPPING FLAMES BY THE DIRECT SAMPLING METHOD (calculated from Moschandreas et al., 1985)

Number of Tests	Gas Range	Flame Condition	Emission Rate (μg/kJ) Average	SD	Range
25	1	Blue[b]	50.7	9.46	17.2 - 107.5
33	2	Blue	34.3	4.93	15.1 - 71.4
58	3	Blue	70.9	12.9	15.1 - 215.0
11	1	Yellow[c]	190.0	5.8	53.8 - 344.0
9	2	Yellow	196.9	3.8	60.2 - 344.0
12	3	Yellow	108.4	5.6	94.6 - 227.9

[a]Lean and rich fuel mixtures combined.
[b]Blue-flame condition – well tuned.
[c]Yellow-tipping flame – improperly tuned.

of CO emission results obtained from both the direct-sampling and mass-balance experiments (Moschandreas et al., 1985), for blue-flame and yellow-tipping flame conditions, differences were observed. No clear trend emerged, however, because CO emissions varied among experimental runs by as much as an order of magnitude.

As part of the above study CO emissions from gas ovens, gas range pilot lights, and a gas dryer were evaluated for blue-flame operating conditions. The results of these experiments are shown in Table 7-2. Pilot light emissions are comparable to those of gas range burners (Table 7–1). Variability by oven use was observed but the limited data is not sufficient to draw any conclusions. Gas dryer CO emissions appear to be comparable to those from gas range burners.

Eighteen different gas ranges, representing greater than 90% of the gas stoves in use at the time, were tested for CO emissions by the American Gas Association Laboratories (Himmel and Dewerth, 1974). CO emissions were evaluated for top burners, ovens and broilers, burner pilot lights, and oven pilot lights. The protocol utilized the direct measurement method for both blue-flame (well-adjusted flame) and yellow-tipping flame (poorly adjusted flame) operating conditions. Range-top burner evaluations, a total of 72,

TABLE 7-2. CARBON MONOXIDE-EMISSION RATES[a] FOR GAS RANGE OVENS, GAS RANGE PILOT LIGHTS, AND GAS DRYERS (calculated from Moschandreas et al., 1985)

Gas Range	Burner	Number of Tests	Average Emission Rates (μg/kJ) Direct Method	(SD) Mass Balance
1	Bake	4	19.1 (6.7)	
1	Broil	4	13.8 (3.9)	
2	Broil	9	13.2 (2.1)	
3	Bake	2	68.5 (6.1)	
3	Broil	7	21.5 (1.0)	
3	Self-clean	3	16.0 (2.2)	
1	Oven door open[b]	3		54.6 (2.6)
1	Oven door closed[b]	3		127.3 (3.5)
2	Pilot light[c]	20		40.4 (5.2)
Gas dryer[d]		4/3	40.4 (3.0)	68.8 (14.2)

[a]Combined and rich and lean fuel and no oven load.
[b]Broiler operated.
[c]Results are on a per pilot light basis, experiments covered various pilot light combinations.
[d]Using Association of Home Appliance Manufacturers Standard HLD-2EC, four tests are by the direct method and three tests by the mass-balance method.

were made with a standard water pot load centered on the grate (American National Standards Institute, 1974). Oven tests, 27 in all, were conducted without a cooking load because the substantial thermal mass of the cavity itself makes a load unnecessary.

A summary of the CO-emission rates measured in the Himmel and Dewerth (1974) study are shown in Table 7-3. Yellow-tipping flame operating conditions resulted in higher CO emissions for burners and ovens than the blue-flame conditions. Considerable variability existed from burner to burner within and between gas ranges and among ovens, yet the average emission rates for blue-flame operation among top burners, ovens, and burner pilot lights were generally within a factor of four or five of each other. The authors noted that the CO emission-rate distributions were skewed, leading them to average the emission data using a log-normal transform and to present the average concentration and an interval representing 66% of the measurements. The infrared burner, pyrolytic self-cleaning oven, and oven pilot light emission rates were considerably higher than the typical range top burner.

TABLE 7-3. CARBON MONOXIDE-EMISSION RATES FROM 18 GAS RANGES, GAS OVENS, AND GAS PILOT LIGHTS FOR BLUE FLAME AND YELLOW-TIPPING FLAME BY THE DIRECT-SAMPLING METHOD

Burner Type	Average and Range of Emissions[a] (μg/kJ) Blue Flame	Yellow-Tipping Flame
Top burners	22.6 (8.0-64.2)[a]	156.6 (58.0-421.0)
Ovens and broilers	15.7 (6.3-38.8)	62.0 (11.1-349.2)
Top burners with thermostat	51.8 (11.9-228.8)	
Top burners (142 kJ/min)	15.3 (6.6-35.4)	
Top burners (190 kJ/min)	26.1 (9.4-72.0)	
Infrared burners	77.4	
Ovens and broilers with catalytic clean	11.9 (4.9-29.1)	53.5 (11.8-243.4)
Pyrolytic self-clean oven	87.7	
Pilot lights–burner	44.0 (30.4-63.8)	
a. Free standing	35.7	
b. Baffle around flame	28.3	
c. Baffle around flame and shield above flame	56.1 (39.6-69.7)[b]	
Pilot lights–oven	248.3 (146.5-420.0)	
a. Constant horizontal	322.2 (158.5-491.2)[b]	
b. Constant horizontal operates in two modes	208.8 (135.8-281.8)[b]	

[a]Values are the range of emission rates that contain two-thirds of the measured values.
[b]Values at the low and high measured level.

Source: Himmel and Dewerth (1974).

Himmel and Dewerth (1974) noted that significant differences ($p \geq 0.05$) for the range averages for all four burners existed for three of the eighteen ranges tested. Emissions from front burners were found to average 13% higher than back burners. Significant CO emission differences ($p \geq 0.05$) were noted between oven burners. Type of cooking pot (material), size of cooking pot, physical properties of the individual pots (density, thermal conductivity, etc.) did not have a pronounced impact on emissions. Burner cap design was found to influence CO emissions.

Using the indirect measurement method and the standard water pot load (American National Standards Institute, 1982), Tikalsky et al. (1987) reported the results of CO-emission measurements made on gas ranges in 10 homes with each home having a different range make, spanning a use age of from 7 to 30 years. The sample of homes was drawn from a sample of 50 homes from which house NO_2 measurements (Dames and Moore, 1986) were available. This is the only study reported where field measurements were made on gas cooking ranges actually in use. Five of the 10 homes were resampled after routine service adjustments. Emissions were measured for top burners and ovens (without a cooking load) by two different research groups using similar protocols but different air-sampling equipment. Emissions measurements were made for two top burners and for bake and broil oven use on each range. The top-burner emissions were measured for high, medium, and low settings.

Results of the Tikalsky et al. (1987) study showed CO-emission rates for the pre-serviced top burners (across all burners, burner settings, and both measurement groups) to range from 9.5 to 1746 μg/kJ. CO emissions for baking ranged from 6.9 to 413 μg/kJ, whereas emissions for broiling ranged from 4 to 310 μg/kJ. Low top-burner settings resulted in significantly higher CO emissions than the medium or high settings ($p \geq 0.05$). Comparison of the emission-rate measurements between the two measurement teams indicated that one team measured higher rates. CO emission rates showed a significant reduction after routine service adjustments ($p \geq 0.05$). The authors noted that the field measurements of CO emissions in their study sometimes exceeded those previously measured by other investigators by a factor of four, while oven emissions for both the bake and broil were within the range of those reported by others.

A number of studies of CO emission rates from gas cooking ranges have been conducted in which a limited number of samples (ranges, burners, and number of experiments) have

been collected. These studies have utilized the direct and mass-balance methods. The results of these studies for both top burners and ovens are shown in Table 7-4. As seen in the previous studies the CO-emission rates for both the top burners and ovens showed considerable variation with the yellow-tipping flame condition resulting in higher emissions than the blue-flame condition. Borrazzo et al. (1987) measured CO-emission rates for the pilot lights of the gas stove in their test house as well as for fugitive emissions from other vented combustion appliances (gas dryer, water heater, furnace, etc.). A CO-emission rate for a pilot light flow of 7.6 kJ/min was measured at 91 $\pm$ 16 μg/kJ, whereas emissions from other vented sources were negligible.

Natural gas is used for domestic water heating in approximately 55 million residences in the United States. Cole and Zawacki (1985) summarized the available data on CO emissions from domestic hot water heaters. They reported an average CO-emission rate for a total of 18 gas water heaters tested in three studies (Belles et al., 1979; Thrasher and DeWerth, 1977; A.G.A.L., 1983) of 12.0 μg/kJ. Thrasher and DeWerth (1977). In comparing emissions from 13 water heaters for blue-flame and yellow-tipping flame conditions, they found that yellow-tipping flame operation conditions of the heaters resulted in a fivefold increase in emissions.

The available literature for gas appliances indicates that CO emissions are (1) highly variable for range-top burners on a single range and between ranges and for ovens for blue-flame conditions (properly adjusted), varying by as much as an order of magnitude or more; (2) much higher for range top and oven burners operated under yellow-tipping flame conditions (improperly adjusted) than for blue-flame conditions; (3) not different for rich or lean fuels; (4) higher for top burners when they are operated under very low fuel consumption rates; (5) comparable for top burners, ovens, pilot lights, and unvented gas dryers; and (6) roughly comparable when obtained by either the direct or mass-balance method.

The data base on CO emissions from gas cooking ranges is largely based upon laboratory studies in which a relatively few ranges were tested. The one field study in which CO emissions were measured, for a small number of gas cooking ranges used in private residences, indicates that for top burners, the laboratory data may underestimate actual CO emission rates. More extensive field CO emission data for cooking ranges is needed to determine how representative the laboratory derived data is.

TABLE 7-4. CARBON MONOXIDE EMISSIONS FROM GAS RANGES FOR STUDIES OF SMALL SAMPLE SIZE

Study	Burner	Test[a] Method	Flame Condition	Number of Tests	Emission Rate (μg/kJ)
MIT/AGA (1976)	1 top burner	D[b]	Blue	1	11.6
Fortman et al. (1984)	4 top burners	D	Blue	11	110 ± 40
	2 ovens	D	Blue	4	25.8 ± 4
Borrazzo et al. (1987)	4 top burners	D	Blue	16	98 ± 18
	1 oven-300 kJ/min	D	Blue	2	150 ± 18
	-150 kJ/min	D	Blue	6	33 ± 1.3
	-160 kJ/min	D	Blue	2	33 ± 6.5
Cote et al. (1974)	2 ranges/top burner	C	Blue	2	56
	2 ranges/top burner	C	Yellow	2	92.5
	2 ovens	C	Blue	2	257
Traynor et al. (1982)	2 top burners	C	Blue	5	200 ± 34
	1 oven	C	Blue	2	226 ± 17
Goto & Tammura (1984)	1 top burner	C	Blue	1	86.9

[a]D = direct method, C = mass-balance chamber method.
[b]Did not use standard pot water load.

7.2.2 Emissions from Unvented Space Heaters

Unvented kerosene and gas space heaters are used in the colder climates to supplement central heating systems or in more moderate climates as the primary source of heat. During the heating season, space heaters generally will be used for a number of hours during the day resulting in emissions over relatively long periods of time.

Over the last several years there has been a dramatic increase in the use of unvented kerosene space heaters in residential and commercial establishments primarily as a supplemental heat source. The U.S. Consumer Product Safety Commission estimates that a total of 16.1 million such heaters have been sold through 1986 (Womble, 1988). A residential energy survey conducted by the U.S. Department of Housing and Urban Development (1980) estimated that three million residences use unvented gas space heaters (fueled by natural gas or propane), with their use more prevalent in the South Census region of the United States. The large number of unvented space heaters sold in the United States and the potential for their high use, particularly during periods when energy costs rise quickly, make them an important source of CO indoors.

CO emissions from unvented kerosene and gas space heaters can vary considerably and are a function of heater design (convective, radiant, combination, etc.), condition of heater, and manor of operation (e.g., flame setting).

Unvented gas space heaters (UVGSHs) range in size from 7000 to 40,000 Btu/h and vary in design and operation. Design characteristics of different heaters include the burners (cast iron, steel, ceramic tile, catalytic surfaces, screen, etc.), ignition, heat exchanger, and auxiliary equipment (i.e., oxygen depletion sensor). Operation characteristics include type of fuel (natural or LPG), input modulation, primary air-shutter, flame type (blue, yellow-tipping, infrared, etc.), and flame discharge temperature (blue flame or convective – 2800°F, infrared – 1800°F, and catalytic – 1200°F). UVGSHs often are distinguished by their flame discharge temperature and type of fuel used, when characterizing CO emissions. Both the direct (hood over the heater from which gases are sampled) and the mass balance or chamber methods have been used to evaluate emissions from invented gas space heaters. Many of the studies were parametric in nature, seeking to evaluate the impact of some of the design and operational features on emissions. Table 7-5 presents a general summary of the CO emission data from UVGSHs that were obtained by operating the heaters in a well-adjusted and typically full-input mode.

The summary data in Table 7-5 indicates that there is considerable variability of CO emissions from UVGSHs. Infrared heaters produce higher emissions than the convective or catalytic heaters. The mass-balance or chamber method seems to result in somewhat higher emissions than the direct method. The Traynor et al. (1984, 1985) data indicate, that for the

TABLE 7-5. CARBON MONOXIDE EMISSIONS FROM UNVENTED GAS SPACE HEATERS

Study	Type of Heater	Number of Heaters	Number of Tests/ Heaters	Fuel[a] Type	Test[b] Method	Fuel Consumption Rate (kJ/min)	Flame	Type(s)[c] of Burner	Suspended Radiating Tiles	Emission Rate (μg/kJ) Average	SD
Traynor et al. (1984, 1985)	Convective	9	1	NG	C	177 - 784	Blue	SP, DP, R	Yes	33	26
		3	1	P	C	353 - 660	Blue	SP, DP, R	Yes	16	1.9
		12	1	Both	C					29	2.5
	Infrared	4	1	NG	C	277 - 368	Infrared	CT	No	47	1.6
		1	1	P	C	258	Infrared	CT	No	45	
		5	1	Both	C					47	1.5
Moschandreas et al. (1985)	Convective	1	16	NG	D	186	Blue	R		9.7	0.4
			4		C	186	Blue	R		16.8	1.7
	Infrared	1	7	NG	D	260	Infrared	SP	No	69	0.9
			3		C	260	Infrared	SP	No	54.6	8.2
	Catalytic	1	6	NG	D	207	Blue	CT, R	No	9.0	0.9
			3		C	207	Blue	CT, R	No	14.2	2.6
Thrasher and DeWerth (1979)	Convective	2	2	NG	D	131	Blue	DP	No	3.1	
		3	3	NG	D	381	Blue	DP	Yes	5.2	
Zawacki et al. (1984)	Convective	1			D	263	Blue	R	Yes	16.3	
Private[d] Communication	Convective	1			U	211		RS	No	32.7	
	Infrared	1			U	ND		RS	Yes	O.22	

[a]NG = natural gas, P = propane.
[b]C = chamber mass balance method, D = direct method, U = unknown.
[c]SP = slotted port burner, DP = drilled port burner, R = pressed metal ribbon burner, CT = ceramic tile, RS = retention screen.
[d]Data obtained and reported by Moschandreas et al. (1985).

subsample of convective heaters tested for the impact of fuel (natural gas vs. propane), natural gas use results in higher emissions.

In a series of tests (mass-balance methods applied in a chamber and test house) on subsamples of heaters (Traynor et al., 1984, 1986) CO emissions were found to (1) be lower for partial input heater operation, (2) increase at lower chamber oxygen concentrations, (3) be comparable between chamber and test house studies and show some decrease in time in test house studies, and (4) be increased substantially for some maltuned heaters. Moschandreas et al. (1985) found no difference in emissions for lean versus rich fuel.

Unvented kerosene space heaters fall into four basic design categories: convective, radiant, two-stage, and wickless. The convective heaters operate at a relative high combustion temperature and, depending upon burner design, can be a blue or white flame. The radiant or infrared heaters utilize perforated ceramic or metal cylinders which become red hot. The two-stage heaters (newer design kerosene heaters) are very similar to the radiant heaters in design except they have a second combustion chamber above the first. The wickless heaters have a chamber where the fuel and air are mixed and combustion occurs with the resultant heat distributed via a fan. CO emissions from unvented kerosene heaters of the convective, radiant, and two-stage design have been evaluated by both the direct and mass-balance method for conditions of wick height (fuel consumption rate) for well-tuned heaters. Few emission data are available for the wickless heaters.

A summary of CO-emission data for unvented kerosene space heaters is shown in Table 7–6. There is considerable variability in emissions between and among heater types and heater wick settings. Radiant heaters, when operated under normal wick settings, produce considerably more CO than normal wick settings for the convective and two-stage heaters. Two-stage heater emissions, however, jump considerably at lower wick settings. Low-wick settings can increase CO emissions for convective heaters.

7.2.3 Emissions from Wood Stoves and Tobacco Combustion

Use of wood-burning stoves has been a popular cost savings alternative to conventional central heating systems using gas or oil. CO and other combustion by-products enter the indoor environment during fire start-up, fire-tending functions, or through leaks in the stove

TABLE 7-6. CARBON MONOXIDE EMISSIONS FROM UNVENTED KEROSENE SPACE HEATERS

Study	Type of[a] Heater	Number of Heaters	Test[b] Method	Fuel Consumption Rate (kJ/min)	Number of Tests	Emission Rate (μg/kJ) Average	SD
Leaderer (1982)	C	1	C	37.3	3	25.8	4.7
				97.9	3	22.3	1.5
				158.0	3	10.1	4.1
	R	1	C	84.4	3	72.9	2.6
				113	3	58.2	5.0
				144	3	42.6	2.5
Traynor et al. (1983)	C	2	C	130		60	1.1
				193		12	1.1
	R	3	C	113		173	1.4
				148		68	1.5
	2S	2	C	132		54	2.5
				182		9	1.2
Jones et al. (1983)[c]	C		D	202		4.7	
	R		D	168[d]		27.5	
Moschandreas et al. (1985)	C	1	C	100	4	35.3	8.2
	R	1	C	129	4	64.1	5.2

[a]C = convective, R = radiant, 2S = two-stage.
[b]C = chamber/mass balance method, D = direct/load method.
[c]As reported by Michandreas et al. (1985).
[d]Manufacturer's rating.

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or venting system. Hence it is difficult to evaluate indoor CO-emission rates for wood-burning stoves. Traynor et al. (1987) evaluated indoor CO levels from four wood-burning stoves (three airtight and one non-airtight stove) in a residence. The non-airtight stove emitted substantial amounts of CO to the residence, particularly when operated with a large fire. The airtight stoves contributed considerably less. The average CO source strengths during stove operation reported for the airtight stoves ranged from 10 to 140 cm^3/h, whereas levels for the non-airtight stove source strengths ranged from 220 to 1800 cm^3/h.

In 1980, 32% of the U.S. adult population was reported to be smokers (U.S. Department of Commerce, 1984). The combustion of tobacco represents an important source of indoor air contaminants. CO is emitted indoors from tobacco combustion through the exhaled mainstream smoke (MS) and from the smoldering end of the cigarette (sidestream smoke - SS). MS and SS CO-emission rates have been evaluated extensively in small chambers (less than a liter in volume) using a standardized smoking machine protocol. The results of these studies have been summarized and evaluated in the Surgeon General's reports (e.g., 1986) and the National Academy of Science Report on environmental tobacco smoke (1986). These results indicate considerable variability in total (MS+SS) CO emissions, with a typical range of from 40 to 67 mg/cig. A small chamber study of 15 brands of Canadian cigarettes (Rickert et al., 1984) found the average CO-emission rate (MS+SS) to be 65 mg/cig. A more limited number of studies have been done using large chambers with the occupants smoking or using smoking machines. Girman et al. (1982) reported a CO-emission rate of 94.6 mg/cig for a large chamber study in which one cigarette was evaluated. A CO-emission factor of 88.3 mg/cig was reported by Moschandreas et al. (1985) for a large chamber study of one reference cigarette.

7.2.4 Summary of Emission Data

Indoor sources of CO can be considered as unintentional or accidental (leaky flue pipes, backdrafting, etc.) and intentional (emissions from unvented combustion sources). Emissions from unintentional sources can result in indoor concentrations associated with serious acute health effects and result in several hundred deaths per year in the U.S. CO emissions from these unintentional sources, despite their importance, cannot be characterized in any standardized way. Unvented or partially vented gas cooking ranges and ovens, gas

appliances, unvented gas space heaters, unvented kerosene space heaters, cigarette combustion, and wood-burning stoves are all notable "intentional" indoor sources of CO emissions.

Unvented or partially vented sources of CO have been evaluated for CO emissions by either the direct method or the mass-balance approach. The direct method samples the emitted combustion gases as they pass through a sampling hood above the source. The mass-balance approach measures the changes in CO over time in an environmental chamber or test house in relation to changes in outdoor CO concentration, source emission rates, and CO removal rates. For gas range top burners, emissions typically are evaluated using a standardized water load in a cooking pot.

Emissions from unvented, partially vented, or improperly vented gas cooking ranges and ovens and gas appliances represent an important source of CO in the residential environment in the United States due to the high percentage of homes (approximately 45%) using gas to cook. CO emissions from these sources are a function of a number of variables relating to the source type (range top or oven, burner design, pilot light, etc.), source condition (age, maintenance, etc.), source use (number of burners used, fuel consumption rate, etc.) and use of outside vents. The source emission studies typically have been conducted in the laboratory setting and involved relatively few gas ranges and gas appliances. The reported studies indicate that CO emissions are highly variable among burners on a single gas cooking range and between gas cooking ranges and ovens, varying by as much as an order of magnitude. Operating a gas cooking range or oven under improperly adjusted flame conditions (yellow-tipping) can result in greater than a fivefold increase in emissions when compared to properly operating flame conditions (blue flame). Use of a rich or lean fuel appeared to have little effect on CO emissions. In general, CO emissions were roughly, on an average, comparable for top burners, ovens, pilot lights, and unvented gas dryers when corrected for fuel consumption rate. The emissions rates gathered by either the direct or mass-balance method were comparable. Only one study attempted to evaluate gas stove emissions in the field for a small number (10) of residences. This study found CO emissions to be as much as a factor of four higher than chamber studies. Given the prevalence of the source, limited field measurements and poor agreement between existing laboratory and field derived CO emission

data, there is a need to establish a better CO emission data base for gas cooking ranges in residential settings.

CO emissions from unvented gas space heaters were found to be variable from heater to heater but roughly comparable to those for gas cooking ranges. Infrared gas space heaters produced higher emissions than the convective or catalytic heaters. Emissions of CO for these heaters were higher for maltuned heaters and for the mass-balance versus direct method of testing. No differences for rich or lean fuel were found, but use of natural gas resulted in higher emissions than propane. Lower fuel consumption settings resulted in lower CO emissions. Emissions were observed to vary in time during a heater run and increase when room or chamber oxygen levels decreased.

Among the three principal unvented kerosene space heater designs (radiant, convective and two-stage burners), radiant heaters produced the highest CO emissions with the convective heaters producing the lowest emissions. Wick setting (low, normal, or high) had a major impact on emissions with the low-wick setting resulting in the highest CO emissions. Data from different laboratories are in good agreement for this source.

CO emissions into indoor spaces from wood-burning stoves occur during fire start-up, fire-tending, or through leaks in the stove or venting system. Few data are available characterizing CO emissions for normal wood stove or fireplace operation. The available data indicate that the non-airtight, wood-burning stoves can contribute substantial amounts of CO directly to the indoor environment while the airtight stoves contribute little or none.

Tobacco combustion represents an important indoor source of CO based upon the number of cigarettes smoked. In comparison to other unvented combustion sources, CO emissions into indoor spaces from tobacco combustion are relatively low and show little variation from brand to brand.

The available data on CO emissions from unvented combustion sources are based largely upon chamber or test house studies using the mass-balance or direct-measurement method for a small sample of sources (i.e., a small number of gas cooking ranges). Given the high variability of CO emissions observed from these sources in the available studies, additional data are needed to better understand the factors impacting those emissions. Little or nothing is known about CO emissions from unvented combustion sources actually in use in residences.

The few data available indicate that CO emissions from sources in the field are considerably more variable and typically higher than those observed in the chamber or test house studies.

7.3 CONCENTRATIONS IN INDOOR ENVIRONMENTS

CO concentrations in an enclosed environment are affected by a number of factors in addition to the source factors discussed in the previous sections. These factors include outdoor concentrations, proximity to outdoor sources (i.e., parking garages or traffic), volume of the space, and mixing within and between indoor spaces.

Outdoor CO concentrations have been measured in a number of locations across the United States utilizing continuous CO monitoring based upon NDIR spectroscopic detection. The NDIR instruments, however, are too bulky and complicated for either indoor or personal monitoring. Over the past decade small, lightweight, and portable CO monitors have been developed. These monitors are based primarily on electrochemical detection (see Chapter 5). These highly versatile CO monitors, when equipped with internal or external data loggers, have permitted the measurement of personal exposures to CO as well as CO concentrations in a number of indoor environments.

CO measurements in enclosed spaces have been made either in support of total personal exposure studies or in targeted indoor studies. In the personal exposure studies, individuals wear the monitors in the course of their daily activities, taking them through a number of different microenvironments. In targeted studies CO measurements are taken in indoor spaces independent of the activities of occupants of those spaces.

7.3.1 Indoor Concentrations Recorded in Personal Exposure Studies

Three studies have reported CO concentrations in various microenvironments as part of an effort to measure total human exposure to CO and to assess the accuracy of exposure estimates calculated from fixed-site monitoring data. In each study, subjects wore personal CO exposure monitors for one or more 24-h periods. CO concentrations were recorded on data loggers at varying time intervals as a function of time spent in various microenvironments. A activity diary was kept by participants where they were asked to provide information such as time, activity (i.e., cooking), location (microenvironment type),

presence and use of sources (smokers present, gas stove, etc.), etc. CO concentrations by microenvironment were extracted from the measured concentrations by use of the activity diaries. This section will discuss the results of those studies as they relate to the concentrations measured in different microenvironments. A discussion of the results as they relate to total exposure to CO are discussed in Chapter 8.

Two of the studies, conducted in Denver, CO, and Washington, DC, by EPA (Akland et al., 1985; Whitmore et al., 1984; Hartwell et al., 1984; Johnson, 1984), measured the frequency distribution of CO exposure in a representative sample of the urban population. The study populations were selected using a multistage sampling strategy. The third study, also conducted in Washington, DC, (Nagda and Koontz, 1985), utilized a convenience sample.

The first-mentioned Washington study obtained a total of 814 person-day samples for 1161 participants while the Denver study obtained 899 person-day samples for 485 participants. The Denver study obtained consecutive 24-h samples for each participant while the Washington study obtained one 24-h sample for each participant. Both studies were conducted during the winter of 1982-1983.

A comparison of CO concentrations measured in the Washington and Denver studies is shown in Table 7-7 (from Akland et al., 1985). Concentrations measured in all microenvironments for the Denver study were higher than those for the Washington study. This is consistent with the finding that daily maximum one- and eight-hour CO concentrations at outdoor fixed monitoring sites were about a factor of two higher in the Denver area than the Washington area during the course of the studies (Akland et al., 1985). The highest concentrations in both studies were associated with commuting while the lowest levels were measured in indoor environments. Concentrations associated with commuting are no doubt higher due to the proximity to and density of outside CO sources (cars, buses, and trucks) particularly during commuting hours when traffic is heaviest. Indoor levels, especially residential levels in the absence of indoor sources, are lower primarily due to the time of day of sampling (noncommuting hours with lower outdoor levels). A more detailed breakdown of CO concentrations by microenvironments for the Denver study is shown in Table 7-8 (Johnson, 1984). Microenvironments associated with motor vehicles result in the highest

TABLE 7-7. SUMMARY OF CO EXPOSURE LEVELS AND TIME SPENT PER DAY IN SELECTED MICROENVIRONMENTS

	Location							
	Denver, CO				Washington, DC			
	Concentration,[a] ppm			Median	Concentration,[a] ppm			Median
Microenvironment	n	$\bar{x}$	SE	time, min	n	$\bar{x}$	SE	time, min
Indoors, parking garage	31	18.8	4.96	14	59	10.4	4.43	11
In transit, car	643	8.0	0.32	71	592	5.0	0.14	79
In transit, other (bus, truck, etc.)	107	7.9	0.61	66	130	3.6	0.30	49
Outdoors, near roadway	188	3.9	0.36	33	164	2.6	0.20	20
In transit, walking	171	4.2	0.45	28	226	2.4	0.29	32
Indoors, restaurant	205	4.2	0.29	58	170	2.1	0.32	45
Indoors, office	283	3.0	0.20	478	349	1.9	0.27	428
Indoors, store/shopping mall	243	3.0	0.22	50	225	2.5	0.49	36
Indoors, residence	776	1.7	0.10	975	705	1.2	0.10	1,048
Indoor, total	776	2.1	0.09	1,243	705	1.4	0.08	1,332

[a]n = number of person-days with nonzero durations, $\bar{x}$ = mean, SE = standard error.

Source: Akland et al. (1985).

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TABLE 7-8. INDOOR MICROENVIRONMENTS LISTED IN DESCENDING ORDER OF WEIGHTED MEAN CO CONCENTRATION

Category	Number of Subjects	CO Concentration, ppm Mean	SD
Public garage	116	13.46	18.14
Service station or motor vehicle repair facility	125	9.17	9.33
Other location	427	7.40	17.97
Other repair shop	55	5.64	7.67
Shopping mall	58	4.90	6.50
Residential garage	66	4.35	7.06
Restaurant	524	3.71	4.35
Office	2,287	3.59	4.18
Auditorium, sports arena, concert hall, etc.	100	3.37	4.76
Store	734	3.23	5.56
Health care facility	351	2.22	4.25
Other public buildings	115	2.15	3.26
Manufacturing facility	42	2.04	2.55
Residence	21,543	2.04	4.06
School	426	1.64	2.76
Church	179	1.56	3.35

Source: Johnson et al. (1984).

concentrations, with concentrations reaching or exceeding the 9 ppm reference level (NAAQS).

No statistical difference ($p > 0.05$) in CO concentrations were found for residences with and without gas ranges in the Washington study. The results of a similar analysis on the Denver data, according to the presence or absence of selected indoor sources, is shown in Table 7–9 (Johnson, 1984).

Attached garages, use of gas ranges, and presence of smokers were all shown to result in higher indoor CO concentrations. Concentrations were well below the 9 ppm reference level (NAAQS), but substantially above concentrations in residences without the sources.

TABLE 7-9. WEIGHTED MEANS OF RESIDENTIAL EXPOSURE GROUPED ACCORDING TO THE PRESENCE OR ABSENCE OF SELECTED INDOOR CARBON MONOXIDE SOURCES

	Carbon Monoxide Concentration, ppm					
	Source Present		Source Absent			
CO Source	Mean	SD	Mean	SD	Difference in Means	Significance Level of t test[a]
Attached garage	2.29	5.34	1.88	3.00	0.41	$p<0.0005$
Operating gas stove	4.52	6.10	1.93	3.92	2.59	$p<0.0005$
Smokers	3.48	6.58	1.89	3.69	1.59	$p<0.0005$

[a]Student t test was performed on logarithms of PEM values.

Source: Johnson (1984).

In the second Washington study (Nagda and Koontz, 1985), a total of 197 person-days of samples were collected from 58 subjects, representing three population subgroups (housewives, office workers, and construction workers). A comparison of residential CO concentrations from that study as a function of combustion sources and whether smoking was reported is shown in Table 7-10. Use of gas ranges and kerosene space heaters were found to result in higher indoor CO concentrations. The statistical significance of the differences was not given. Concentrations were highest in microenvironments associated with commuting. The data collected in this study were consistent with the data collected in the EPA Washington study discussed above.

It is difficult for all three studies to assess the contribution to indoor CO concentrations from either outdoor or indoor sources because concentrations outside each indoor microenvironment were not measured.

TABLE 7-10. AVERAGE RESIDENTIAL CO EXPOSURES (ppm): IMPACT OF COMBUSTION APPLIANCE USE AND TOBACCO SMOKING[a]

Appliances	Reported Tobacco Smoking: No	Yes	All Cases
None	1.2 (66)	1.5 (12)	1.2 (78)
Gas stove	2.2 (15)	1.3 (1)	2.2 (16)
Kerosene space heater	5.1 (3)	ND[b]	5.1 (3)
Wood burning	0.7 (2)	ND[b]	0.7 (2)
Multiple appliances	1.0 (1)	ND[b]	1.0 (1)
All cases	1.5 (87)	1.5 (13)	1.5 (100)

[a]Percentage of subjects' time in their own residences indicated in parentheses for each category of appliance use and tobacco smoking.
[b]No data available.

Source: Nagda and Koontz (1985).

7.3.2 Targeted Microenvironmental Studies

As demonstrated from the personal exposure studies discussed above, individuals, in the course of their daily activities, can encounter a wide range of CO concentrations as a function of the microenvironments in which they spend time. A number of studies have been conducted over the last decade to investigate concentrations of CO in indoor microenvironments. These "targeted" studies have either focused on indoor CO concentrations as a function of the microenvironment or sources in specific microenvironments.

7.3.2.1 Indoor Microenvironmental Concentrations

A summary of the results of the larger studies that have investigated CO levels in various indoor environments, independent of the existence of specific indoor sources, is shown in Table 7-11. Major foci of these studies are microenvironments associated with commuting. A wide range of concentrations were recorded in these studies with the highest

TABLE 7-11. CARBON MONOXIDE CONCENTRATIONS[a] MEASURED IN VARIOUS INDOOR ENVIRONMENTS AS A FUNCTION OF MICROENVIRONMENTS

Study	Locations	Microenvironment	Average Time-Frame of Sampling (min)	Number of Observations	Inside Mean	Inside SD	CO - ppm Max	Outside Mean	Outside SD	Source Identified	Comments
Cortese and Spengler (1976)	Boston, MA	Autos	40-70	248	1.34	5.4				Traffic	66 volunteers used–some levels (4%) related to faulty exhaust
		Transit	40-70	28	7.4	3.7				Traffic	
		Split	40-70	70	8.3	2.8				Traffic	
		All	40-70	346	11.9	5.5	>35			Traffic	
		Outside[b]	40-70	1,076				6.0	4.0	Ambient	
Spengler et al. (1978)	Boston, MA	Seven skating rinks	40-160	17	53.6	18.0	192			Ice	Ventilation measures–cleaning from CO decay
Colwill and Hickman (1980)	London, England	Autos	65-90	11	25.2	7.0	40			Traffic	11 drivers over a 35 km route
		Outside[c]						47.0	13.1		
Ziskind et al. (1981)	Denver, CO and Boston, MA	Buses	~540	75	4-36[d]		84			Traffic	Only data gathered by electrochemical monitors presented. Passive dosimeter data not included; 58% of values for rides >8 h were >9 ppm
		Taxis	~540	38	10-17[d]		48			Traffic	
		Police cars	~540	19	0-46[d]		59			Traffic	
Wallace (1983)		One office	Hourly	80	19.0	5.9	50			Leakage from garage	65 employees affected; corrective action taken
Holland (1983)	Stamford, CT	Commercial	10-30	659	5.8	8.0	61	4.2[e]	3.0		
		Commuting	10-30	1,341	6.2	4.7	38	5.5[e]	4.1	Traffic	
		Residential	10-30	577	2.9	3.9	39	4.3[e]	3.1		
	Los Angeles, CA	Commercial	10-30	1,938	3.3	2.5	61	4.0	3.1		
		Commuting	10-30	96	16.1	5.8	42	5.8	4.2	Traffic	
		Residential	10-30	807	7.6	5.0	38	3.9	2.8		

TABLE 7-11 (cont'd). CARBON MONOXIDE CONCENTRATIONS[a] MEASURED IN VARIOUS INDOOR ENVIRONMENTS AS A FUNCTION OF MICROENVIRONMENTS

Study	Locations	Microenvironment	Average Time-Frame of Sampling (min)	Number of Observations	Inside Mean	Inside SD	CO - ppm Max	Outside Mean	Outside SD	Source Identified	Comments
	Phoenix, AZ	Commercial	10-30	380	2.2	2.2	17	2.8	2.5		
		Commuting	10-30	839	6.8	4.9	50	3.9	3.3	Traffic	
		Residential	10-30	48	5.8	3.6	17	2.4	2.1		
	Denver, CO	Commercial	10-30	1,949	5.9	4.3	30	5.0	3.3		
		Commuting	10-30	3,634	11.0	7.7	54	5.8	3.7	Traffic	
		Residential	10-30	528	5.6	4.4	45	3.1	2.2		
Flachsbart al. (1987)	Washington, DC	Autos	34-69	213	9.1-22.3	2-9	--	--	--	Traffic	Measurements made et during commuting hours
		Bus	82-115	35	3.7-10.2	1-7	--	--	--	Traffic	
		Rail	27-48	8	2.2-5.2	0.5-5	--	--	--	Traffic	
		2 Garages	3	47	21-94	10-56	--	--	--	Traffic	
Yocom et al. (1987)	Hartford CT	Public Building			1.8 -22.7	-	-	Very similar to indoor concentrations		Traffic	Two week averages day and night over a summer, fall, and winter period
		Office Building			2.1-22.9						
		Private Home			1.8-21.9						
Peterson and Sabersky (1975)	Los Angeles CA	Autos	3	-	<2.5	-	45	Similar to auto levels		Traffic	
Chaney (1978)	Several U.S. Cities	Autos			2-50	-	-	-		Traffic	Slower the traffic the higher the CO
Ziskind et. a. (1982)	Los Angeles CA	Home		564	4-4.6	-	-				
		Work		557	2.2-4.3	-	-				
		Commute		461	6.7-10.0	-	-				
Amendola and Hanes (1984)	New England	Service Station	480	81	2.2-110.8	-	110.8	-		Autos	Higher in Winter than Summer
		Car dealership									
Flachsbart and Ott (1984)	5 California cities	Enclosed parking	2-5	10	27.7	12.5	-	3.0 - 2.6		Autos	Indoor Values have outdoor concentrations subtracted
		Bldg. attached to enclosed parking	2-5	7	6.1	2.9	-			Autos	
		Commercial settings	2-5	202	2.1	1.6	-			Autos	

TABLE 7-11 (cont'd). CARBON MONOXIDE CONCENTRATIONS[a] MEASURED IN VARIOUS INDOOR ENVIRONMENTS AS A FUNCTION OF MICROENVIRONMENTS

Study	Locations	Microenvironment	Average Time-Frame of Sampling (min)	Number of Observations	CO - ppm Inside Mean	Inside SD	Inside Max	Outside Mean	Outside SD	Source Identified	Comments
Sisoric and Fugas (1985)	Zagreb Yugoslavia	8 institutions	Winter and summer periods	-	1.1-6.0	0.6-13.7	-	-		Traffic	

[a]All measurements made with electrochemical devices.
[b]Fixed central station sites.
[c]Measurement made outside auto.
[d]95% confidence limits.
[e]Average of two fixed sites.

CO concentrations found in the indoor commuting microenvironments. These concentrations frequently are higher than concentrations recorded at fixed-site monitors but lower than concentrations measured immediately outside the vehicles. Concentrations generally are higher in automobiles than in public transportation microenvironments. A number of the studies noted that CO concentrations in commuting vehicles can exceed both the eight-hour, 9-ppm level and the one-hour, 35-ppm level specified in the NAAQS (1970). Flachsbart et al. (1987) noted that the most important factors influencing CO concentrations inside automobiles were such factors as link-to-link variability (a proxy for traffic density, vehicle mix, and roadway setting), day-to-day variability (proxy for variations in meteorological factors and ambient CO concentrations), and time of day. This study noted that with increased automobile speed, interior CO concentrations decreased.

Service stations, car dealerships, parking garages and office space that have attached garages can exhibit high concentrations of CO due to automobile exhaust. In one case (Wallace, 1983), corrective measures reduced office space CO concentrations originating from an attached parking garage from 19 ppm to approximately 4 ppm. In an investigation of seven ice skating rinks in the Boston area, one study (Spengler et al., 1978) reported exceptionally high average CO concentrations (53.6 ppm) with a high reading of 192 ppm. Ice-cleaning machines and poor ventilation were found to be responsible.

Residential and commercial levels generally were found to have low concentrations, but no information was provided on the presence of indoor sources or outdoor levels.

7.3.2.2 Concentrations Associated with Indoor Sources

As noted earlier, the major indoor sources of CO in residences are gas ranges and unvented kerosene and gas space heaters, with properly operating wood-burning stoves and fireplaces (non-leaky venting system) and tobacco combustion of secondary importance. Properly used gas ranges (ranges used for cooking and not space heating) are used intermittently and thus would contribute to short-term peak CO levels indoors but likely would not result in substantial increases in longer-term average concentrations. Unvented kerosene and gas space heaters typically are used for several hours at a time and thus are likely to result in sustained higher levels of CO. The improper operation of gas ranges or unvented gas or kerosene space heaters (e.g., low-wick setting for kerosene heaters or yellow-

tipping operation of gas ranges) could result in substantial increases in indoor CO levels. CO levels indoors associated with tobacco combustion are, based upon source emission data, expected to be low unless there is a very high smoking density and low ventilation. In the absence of a leaky flue or leaky fire box, indoor CO levels from fire places or stoves should be low with short peaks associated with charging the fire when some back draft might occur.

The majority of studies investigating CO concentrations in residences, as a function of the presence or absence of a known CO source, typically have measured CO concentrations associated with the source's use over short time periods (on the order of a few minutes to a few hours). These studies typically have involved fewer than 10 residences and have reported peak CO levels (on the order of minutes). Only two studies (Hartwell et al., 1988; Koontz and Nagda, 1987) have reported long-term average CO concentrations (over several hours) as a function of the presence of a CO source for large residential sample sizes, while one study (McCarthy et al., 1987) reported longer term average indoor CO concentrations for a small sample.

Average Indoor Source Related Concentrations

As part of a study to determine the impact of combustion sources on indoor air quality, a sample of 382 homes in New York State (172 in Onondaga County and 174 in Suffolk County) were monitored for CO concentrations during the winter of 1986 (Hartwell et al., 1988). In this study four combustion sources were examined: gas cooking appliances, unvented kerosene space heaters, wood-burning stoves and fireplaces, and tobacco products. A factorial sample that included all sixteen combinations of combustion sources was utilized. CO concentrations were monitored in the main living area (e.g., family room) and source area (e.g., in the kitchen for homes with gas ranges) for each home over a three-day period using an electrochemical monitor with the data stored on a data logger. Outdoor CO levels were not recorded for these homes. CO concentrations were reported as averages for the full three-day period of measurement.

Average CO concentrations measured in the main living area as a function of county and the presence or absence of a combustion source are shown in Table 7-12. Gas ranges and kerosene heaters were found to result in small increases in average CO levels. Use of a wood-burning stove or fireplace resulted in lower average CO levels, presumably due to

TABLE 7-12. WEIGHTED SUMMARY STATISTICS FOR CO CONCENTRATIONS (ppm) IN THE MAIN LIVING AREA BY USE FOR SELECTED SOURCES BY COUNTY

Source and County	Source Present	Sample Size	Percent Detected	Arith. Mean	SE	Geo. Mean	Geo. SE
KEROSENE HEATER							
Onondaga	Yes	10	89.3*	3.33	1.34	2.20	1.33
	No	198	60.0	1.72	0.15	1.29	1.06
Suffolk	Yes	16	100.0*	3.86*	0.73	3.35*	1.22
	No	158	72.1	2.03	0.15	1.62	1.07
WOOD-BURNING STOVE/FIREPLACE							
Onondaga	Yes	39	44.5	1.04	0.09	0.93	1.09
	No	169	62.9	1.86*	0.16	1.37*	1.06
Suffolk	Yes	33	82.7	1.93	0.23	1.72	1.14
	No	141	72.7	2.24	0.17	1.72	1.07
GAS STOVE							
Onondaga	Yes	90	77.4*	2.29*	0.24	1.74*	1.08
	No	118	47.0	1.33	0.17	1.04	1.07
Suffolk	Yes	86	82.8	2.55*	0.21	2.04*	1.10
	No	88	68.2	1.91	0.19	1.51	1.09

*Significantly different at .05 level.

Source: Hartwell et al. (1988).

increased air-exchange rates associated with use. The study found no effect on average CO levels with tobacco combustion and no difference by location in the residence. The data base has not yet been analyzed for differences in short-term CO concentrations (eight-hour, one-hour, or less than one-hour concentrations) as a function of sources and source use. When

such an analysis is made available the impact of the combustion sources on residential CO levels will be much more pronounced.

Koontz and Nagda (1987 and 1988) utilizing Census data for sample selection, monitored 157 homes in 16 neighborhoods in North Central Texas over a nine-week period between January and March 1985. Unvented gas space heaters were used as the primary means of heating in 82 residences (13 had one UVGSH, 36 had two UVGSHs, and 33 had three or more UVGSHs) and as a secondary heat source in 29 (17 had one UVGSH and 12 had two or more UVGSHs). There was no gas space heater present or used in 41 of the homes and 5 of the homes were not included for various reasons (e.g., air sample lost). A majority of all the homes in each UVGSH use category had gas ranges and gas water heaters (typically greater than 80%). Air samples were collected for all residences on two separate occasions over integrating periods of approximately 15 h using Collectaire samplers. CO concentrations in each sampler then were measured using a electrochemical monitor. In 30% of the residences (46 residences) CO was monitored continuously, consisting of sequential 15-min averages over an average monitoring period of about five days with an electrochemical monitor. Measurements were made close to the geometric center of the house.

The cumulative frequency distributions for the first integrated CO measurements by source category are shown in Figure 7-1. Residences where UVGSHs are the primary heat source exhibited the highest CO concentrations. CO concentrations were greater than or equal to 9 ppm in 12% of the homes with the highest concentration measured at 36.6 ppm. No values were measured above 9 ppm for residences where a UVGSH was not used at all or was used as a secondary heat source. The second CO sample produced summary statistics virtually identical to the first. Table 7-13 presents a comparison of the CO concentrations measured in the continuously monitored residences (15-min average concentrations summed by one- and eight-hour time periods) with the one-hour, 35 ppm and eight-hour, 9 ppm CO standard by source category. The table also presents the mean concentrations measured in these home over the full five-day periods. Five of the residences exceeded the one-hour, 35 ppm level while seven of the residences exceeded the eight-hour, 9 ppm level. Higher CO levels were associated with maltuned unvented gas appliances and the use of multiple unvented gas appliances.

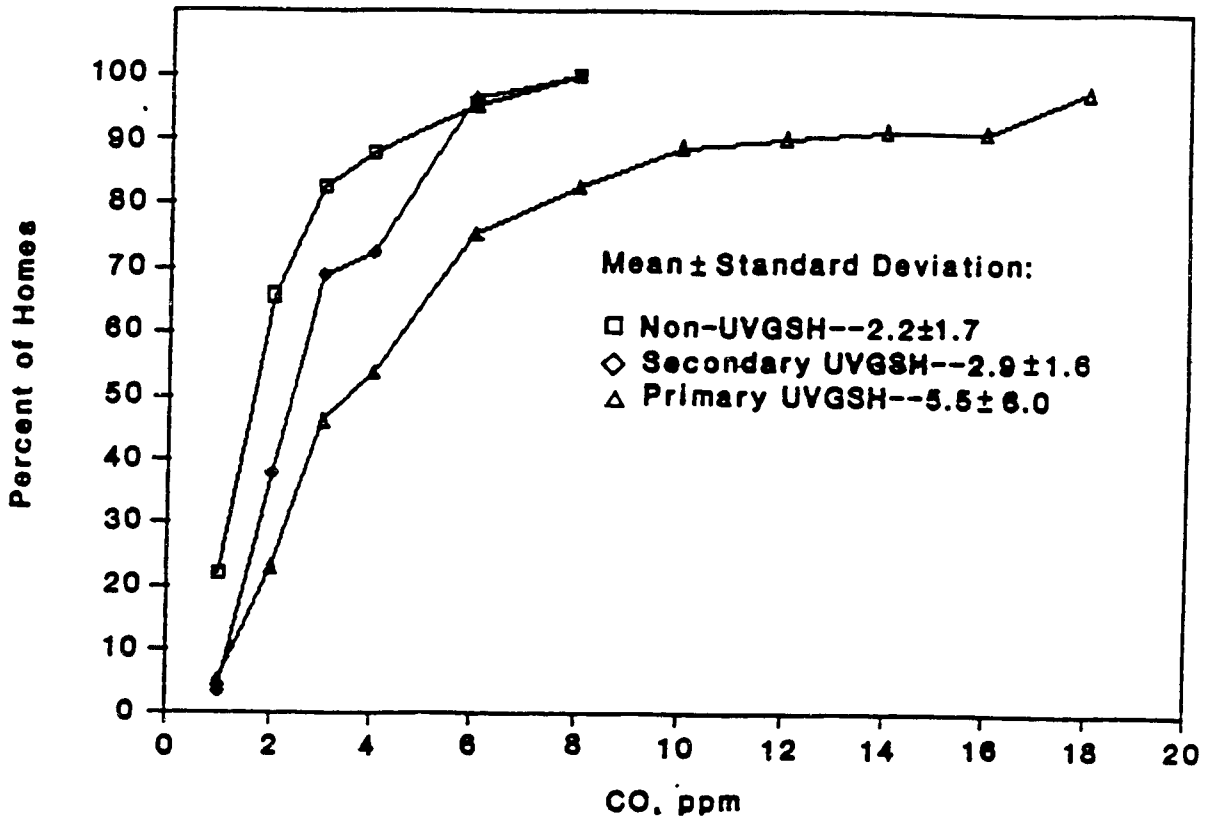

Figure 7-1. Cumulative frequency distributions and summary statistics for indoor CO concentrations in three groups of monitored homes.

Source: Koontz and Nagda (1988).

TABLE 7-13. SUMMARY OF CONTINUOUS CO MONITORING RESULTS BY HEATING EQUIPMENT

Heating Equipment	Number of Homes	Number Exceeding		CO Concentration, ppm	
		1-h, 34 ppm	8-h, 9 ppm	Mean	SD
Primary UVGSH	26	4	5	6.2	7.6
Secondary UVGSH	11	1	0	2.3	1.1
Non-UVGSH	9	0	2	2.2	1.2

Source: Koontz and Nagda (1988).

In a study of 14 homes with one or more unvented gas space heaters (primary source of heat) in the Atlanta, GA, area, McCarthy et al. (1987) measured CO levels by continuous NDIR monitors in two locations in the homes (room with the heater and a remote room in the house) and outdoors. Measurements were taken over five-minute periods in turn from each of the three sampling points for each house over 96-h sampling periods. The authors reported only the summary statistics for CO (average 96-h concentrations) based on the continuously collected data in the room with the heater and outdoors. One out of the 14 UVGSH homes exceeded 9 ppm during the sampling period. Mean indoor values ranged 0.26 ppm to 9.49 ppm and varied as a function of the use pattern of the heater. Only one of the homes used more than one heater during the air sampling. Outdoor concentrations varied from 0.3 ppm to 1.6 ppm.

Peak Indoor Source-Related Concentrations

Short-term or peak CO concentrations indoors associated with specific sources were obtained for a few field studies. The peak CO concentrations measured in these studies, by location in the house and presence of specific sources, are shown in Table 7-14. A wide range of peak CO concentrations were observed in these studies between and among residences with different indoor CO sources. The highest concentrations measured

TABLE 7-14. PEAK CO CONCENTRATIONS BY INDOOR SOURCE MEASURED IN FIELD STUDIES

Reference	Indoor Source[a]	Number of Residents	Location[b]	Averaging Time (min)	CO Concentration (ppm) Peaks	CO Concentration (ppm) Outside	Comments
Hartwell et al. (1988)	GR	12	K	30	1.8 - >100	0.7 - 10	Excluding one house with >100 range in kitchen is 1.8 - 15, wood stoves and smokers were present in same houses but no effect was seen
			LR, D, B	30	1.8 - 17		
	K	1	K	30	5.7	5.0	
			D	30	9.7	5.0	
Koontz et al. (1987)	UVGSHP, GR	26	C	15	?-69	--	Houses may contain more than one heater
	UVGSHS, GR	11	C	15	?-69	--	
	GR	9	C	15	?-26	--	
Leaderer et al. (1984)	GR	1	A	15	3.5		Outdoor levels subtracted
			B	15	3.0		
	CK	8	LR	5	0 - 3.2		Outdoor levels subtracted
			B	5	0 - 3.4		
	RK	5	LR	5	2.1 - 21.1		Outdoor levels subtracted
			B	5	4.8 - 8.2		

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TABLE 7-14 (cont'd). PEAK CO CONCENTRATIONS BY INDOOR SOURCE MEASURED IN FIELD STUDIES

Reference	Indoor Source[a]	Number of Residents	Location[b]	Averaging Time (min)	CO Concentration (ppm) Peaks	Outside	Comments
Lebret et al. (1987)	GA	12	K	1	4.0 - 90		Sample of Dutch homes
			LR	1	3.3 - 23		
			B	1	3.3 - 40		
Brunekreef et al. (1982)	GA	254	K	15	<10 - >600		Sample of Dutch homes, breathing zone samples, levels related to geisers
Moschandreas and Zabransky (1982)	GR	8	K	60	7.2 - 11.3	--	
			LR	60	1.0 - 12.6	--	
			B	60	1.0 - 13.0	--	
Sterling and Sterling (1979)	GR	9	K	2	29 - 120	3.0 - 8.5	Measurements were taken under a variety of gas range operating and ventilation conditions

[a]GR = gas range, K = unvented kerosene space heater, CK = unvented convective kerosene space heater, RK = radiant unvented kerosene space heater, UVGSHP = unvented gas space heater used as primary heat source, UVGSHS = UVGSH as a secondary heat source, GA = gas appliances includes geisers (water heaters).
[b]K = kitchen, LR = living room, D = den, B = bedroom.

(>600 ppm) were associated with emissions from geisers (water heaters), found in a large study conducted in The Netherlands (Brunekreef et al., 1982). Peak levels of CO associated with gas ranges were from 1.0 to over 100 ppm. This broad range is somewhat consistent with the range of CO emissions observed in studies evaluating CO emissions from gas ranges (i.e., Table 7-1). The variability is in part due to number of burners used, flame condition, condition of the burners, etc. As might be expected radiant kerosene heaters produced higher CO concentrations than convective heaters. UVGSHs generally were associated with higher CO peaks than gas ranges or kerosene heaters. As noted earlier the peaks associated with gas or kerosene heaters are likely to be sustained over longer periods of time because of the long source use times.

Test houses have been used by investigators to evaluate the impact of specific sources, modifications to sources, and variations in their use on residential peak CO concentrations.

In one of the earliest investigations of indoor air quality, Wade et al. (1975) measured indoor and outdoor CO levels in four houses that had gas stoves. Using an NDIR analyzer, indoor concentrations were found to range from 1.7 to 3.8 times higher than the outdoor levels. CO levels in one house exceeded 9 ppm, the NAAQS reference level. A time history of CO measured in one house is shown in Figure 7–2. For this house and for the time averaging period used, CO was well mixed through the house. As part of a modeling study of emissions from a gas range, Davidson et al. (1987) measured CO concentrations in three residences. Peak CO levels in excess of 5 ppm were measured in one town house.

Indoor CO levels associated with wood-burning stoves were measured in two test house studies. In one study (Humphreys et al. 1986) indoor CO levels associated with the use of both airtight (conventional and catalytic) and non-airtight wood heaters were evaluated in a 337 m^3 weatherized home. Indoor CO concentrations were higher than outdoor levels for all tests. Conventional airtight stoves produced indoor CO levels typically about 1 to 2 ppm above background level with a peak concentration of 9.1 ppm. Use of non-airtight stoves resulted in average indoor CO concentrations 2 to 3 ppm above outdoors with peak concentrations as high as 29.6 ppm. In a 236 m^3 house (Traynor et al., 1984), four wood-burning stoves (three airtight and one non-airtight) were tested. The airtight stoves generally resulted in small contributions to both average and peak indoor CO levels (0.1 to 1 ppm for

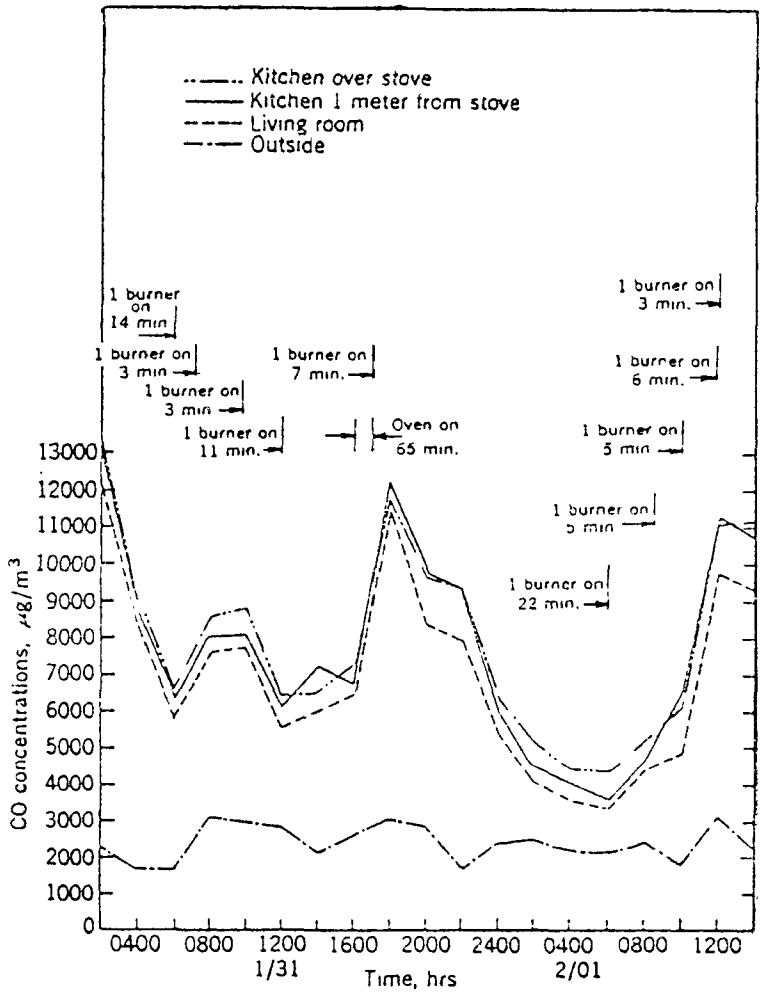

Figure 7-2. A time history of CO concentrations, 2-hour averages, winter of 1974.

Source: Wade et al. (1975).

the average and 0.2 to 2.7 ppm for the peak). The non-airtight stove contributed as much as 9.1 ppm to the average indoor level and 43 ppm to the peak.

Indoor Concentrations Related to Environmental Tobacco Smoke

Carbon monoxide has been measured extensively in chamber studies as a surrogate for environmental tobacco smoke (e.g., Bridge and Corn, 1972; Hoegg, 1972; Penkala and De Oliveira, 1975; Weber et al., 1976, 1979a,b; Weber, 1984; Leaderer et al., 1984; Clausen et al., 1985). Under steady-state conditions in chamber studies, where outdoor CO levels are monitored and the tobacco brands and smoking rates are controlled, CO can be a reasonably good indicator of environmental tobacco smoke (ETS) and is used as such. Under such chamber conditions CO concentrations typically range from less than 1 to over 10 ppm.

A number of field studies have monitored CO in different indoor environments with and without smoking occupants. A summary of the results of these studies is shown in Table 7–15 (National Research Council, 1986, Table 2-4). Although CO concentrations generally were higher in indoor spaces when smoking occurred, the concentrations were highly variable. The variability of CO production from tobacco combustion, number of cigarettes smoked, and differences in ventilation and variability of outdoor concentrations make it difficult to assess the contribution of tobacco combustion in indoor CO concentrations. The chamber studies and field studies conducted do indicate that under typical smoking conditions encountered in residences or offices, CO concentrations can be expected to be above background outdoor levels, but lower than the levels resulting from other unvented combustion sources. In indoor spaces where heavy smoking occurs and in small indoor spaces CO emissions from tobacco combustion will be an important contributor to CO concentrations.

7.3.3 Spatial Concentration Variations

Spatial variations of CO concentrations within a space are a function of mixing within and between spaces. Spatial variations of CO in a space are likely to be minimized if a continuous or nearly continuous source of CO exists (i.e., unvented kerosene or gas space heater) due to the strong convective currents which enhance rapid mixing. Intermittent sources (i.e., gas burner use or tobacco combustion) are likely to produce a more pronounced

TABLE 7-15. MEASURED CONCENTRATIONS OF CARBON MONOXIDE IN ENVIRONMENTAL TOBACCO SMOKE*

Location	Tobacco Burned	Ventilation	Indoor		Outdoor		References
			Mean	Range	Mean	Range	
Rooms	--	--	--	4.3 - 9	2.2 ± 0.98	0.4 - 4.5	Coburn et al. (1965)
Train	1 - 18 smokers	Natural	--	0 - 40	--	--	Harmsen and Effenberger (1957)
Submarines (66 m^3)	157 cigarettes/day	Yes	<40	--	--	--	Cano et al. (1970)
	94 - 103 cigarettes/day	Yes	<40	--	--	--	
18 military aircraft	--	Yes	<2 - 5	--	--	--	U.S. Department of Transportation (1971)
8 commercial aircraft	--	Yes	<2	--	--	--	U.S. Department of Transportation (1971)
Rooms	--	--	--	5 - 25	--	--	Porthein (1971)
14 public places	--	--	<10	--	--	--	Perry (1973)
Ferry boat	--	--	18.4 ± 8.7	--	3.0 ± 2.4	--	Godin et al. (1972)
Theater foyer	--	--	3.4 ± 0.8	--	1.4 ± 0.8	--	Godin et al. (1972)
Intercity bus	23 cigarettes	15 changes/h	32	--	--	--	Seiff (1973)
	3 cigarettes	15 changes/h	18	--	--	--	
2 conference rooms	--	8 changes/h	--	8 (peak)	1 - 2	--	Slavin and Hertz (1975)
Office	--	236 m^3/h	--	<2.5 - 4.6	--	--	Harke (1974)
	--	Natural	--	<2.9 - 9.0	--	--	--
Automobile	2 smokers	Natural	--	42 (peak)	--	13.5 (peak)	Harke and Peters (1974)
	(4 cigarettes)	Mechanical	--	32 (peak)	--	15.0 (peak)	
9 night clubs	--	Varied	13.4	6.5 - 41.9	--	--	Sebben et al. (1977)
14 restaurants	--	--	9.9 ± 5.5	--	9.2 (outdoor)	3.0 - 35	Sebben et al. (1977)
45 restaurants	--	--	8.2 ± 2.2	7.1 ± 1.7	--	--	Sebben et al. (1977)
33 stores	--	--	10.0 ± 4.2	11.5 ± 6.5	11.5 ± 6.5	--	Sebben et al. (1977)
3 hospital lobbies	--	--	--	4.8	--	--	Sebben et al. (1977)
6 coffee houses	Varied	--	2 - 23	--	--	--	Badre et al. (1978)
Room	18 smokers	--	50	--	--	--	Badre et al. (1978)
Hospital lobby	12 - 30 smokers	--	5	--	--	--	Badre et al. (1978)
2 train compartments	2 - 3 smokers	--	--	4 - 5	--	--	Badre et al. (1978)
Automobile	3 smokers	Natural, open	14	--	--	--	Badre et al. (1978)
	2 smokers	Natural, closed	20	--	--	--	Badre et al. (1978)
10 offices	--	--	2.5 ± 10	1.5 - 1.0	2.5 ± 1.0	1.5 ± 4.5	Chappell and Parker (1977)
15 restaurants	--	--	4.0 ± 2.5	1.0 - 9.5	2.5 ± 1.5	1.0 - 5.0	Chappell and Parker (1977)
14 night clubs and taverns	--	--	13.0 ± 7.0	3.0 - 29.0	3.0 ± 2.0	1.0 - 5.0	Chappell and Parker (1977)

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TABLE 7-15 (cont'd). MEASURED CONCENTRATIONS OF CARBON MONOXIDE IN ENVIRONMENTAL TOBACCO SMOKE*

Location	Tobacco Burned	Ventilation	Indoor		Outdoor		References
			Mean	Range	Mean	Range	
Tavern	–	Artifical	8.5	–	–	–	Chappell and Parker (1977)
	–	None	–	35 (peak)	–	–	Chappell and Parker (1977)
Office	–	Natural, open	1.0	10.0 (peak)	–	–	Chappell and Parker (1977)
Restaurant	–	Mechanical	5.1	2.1 - 9.9	4.8 (outdoors)	–	Fischer et al. (1978)
Restaurant	–	Natural	2.6	1.4 - 3.4	1.5 (outdoors)	–	Fischer et al. (1978)
Bar	–	Natural, open	4.8	2.4 - 9.6	1.7 (outdoors)	–	Weber et al. (1976)
Cafeteria	–	11 changes/h	1.2	0.7 - 1.7	0.4 (outdoors)	–	Weber et al. (1976)
44 offices	–	–	1.1	6.5 (max)	–	–	Weber (1984)
25 offices	–	–	2.78 ± 1.42	–	2.59 ± 2.33	–	Szadkowski and Harke (1976)
Tavern	–	6 changes/h	11.5	10 - 12	2 (outdoors)	–	Cuddeback et al. (1976)
Tavern	–	1 - 2 changes/h	12.0	3 - 22	–	–	Cuddeback et al. (1976)

*Time-weighted average (TWA) of carbon monoxide, 50 ppm (55 mg/m^3). TWA = average concentration to which worker may be exposed continuously for 8 hr without damage to health (National Institute for Occupational Safety and Health, 1971).

Source: NRC (1986) Table 2-4.

spatial gradient. The within-home spatial variations are related to such variables as air-exchange rates among rooms, air mixing within a room, volume of a house, and location and use of the source. The question of the spatial variability of CO indoors as a function of different indoor sources has not been evaluated in any detail in any field study.

7.3.4 Summary of Indoor Concentrations

Indoor concentrations of CO are a function of outdoor concentrations, indoor sources (source type, source condition, source use, etc.), infiltration/ventilation, and air mixing between and within rooms. In residences without sources, average CO concentrations are approximately equal to average outdoor levels. Proximity to outdoor sources (i.e., structures near heavily traveled roadways or with attached garages or parking garages) can have a major impact on indoor CO concentrations.

The development of small lightweight and portable electrochemical CO monitors over the past decade has permitted the measurement of personal CO exposures and CO concentrations in a number of indoor environments. The available data on indoor CO concentrations have been obtained from total personal exposure studies or studies where various indoor environments have been targeted for measurements.

The extensive total personal CO exposure studies conducted by EPA in Washington, DC, and Denver, CO, have shown that the highest CO concentrations occur in indoor microenvironments associated with transportation sources (parking garages, cars, buses, etc.). Concentrations in these environments were found to frequently exceed 9 ppm. Studies targeted toward specific indoor microenvironments also have identified the indoor commuting microenvironment as an environment in which CO concentrations frequently exceed 9 ppm and occasionally exceed 35 ppm. Special environments or occurrences (indoor ice skating rinks, offices where emissions from parking garages migrate indoors, etc.) have been reported where indoor CO levels can exceed the current ambient one- and eight-hour standards (9 and 35 ppm, respectively).

A majority of the targeted field studies monitored indoor CO levels as a function of the presence or absence of combustion sources (gas ranges, unvented gas and kerosene space heaters, wood burning stoves and fireplaces, and tobacco combustion). The results of these studies indicate that the presence and use of a unvented combustion source results in indoor

CO levels above those found outdoors. The associated increase in CO concentrations can vary considerably as a function of the source, source use, condition of the source, and averaging time of the measurement. Intermittent sources such as gas cooking ranges can result in high peak CO concentrations (in excess of 9 ppm), while long-term average concentrations (i.e., 24-h) associated with gas ranges are considerably lower (on the order of 1 ppm). The contribution of tobacco combustion to indoor CO levels is variable. Under conditions of high smoking and low ventilation the contribution can be on the order of a few parts per million. One study suggested that the contribution to residential CO concentrations of tobacco combustion is on the order of 1 ppm while another study showed no significant increase in residential CO levels.

Unvented combustion sources that are used for substantial periods of time (i.e., unvented gas and kerosene space heaters) appear to be the major contributors to residential CO concentrations. One extensive study of unvented gas space heaters indicated that 12% of the homes had 15–h average CO concentrations greater than 8 ppm with the highest concentration at 36.6 ppm. Only very limited data are available on the contribution of kerosene heaters to the average CO concentrations in residences and these data indicate a much lower contribution than gas heaters. Peak CO concentrations associated with both unvented gas and kerosene space heaters often exceed the current ambient one- and eight-hour, standards (9 and 35 ppm, respectively) in residences, and due to the nature of the source (continuous) those peaks tend to be sustained for several hours.

Very limited data on CO levels in residences with wood-burning stoves or fireplaces is available. Non-airtight stoves can contribute substantially to residential CO concentrations, while airtight stoves can result in small increases. The available data indicate that fireplaces do not contribute measurably to average indoor concentrations. No information is available for samples of residences with leaky flues. In addition, there is no information available on short-term indoor CO levels associated with these sources nor are there studies that examine the impact of attached garages on residential CO concentrations.

The available data on short-term (one-hour) and long-term (eight-hour) indoor CO concentrations as a function of microenvironments and sources in those microenvironments are not adequate to assess exposures in those environments. In addition, little is known about

the spatial variability of CO indoors. These indoor microenvironments represent the most important CO exposures for individuals and as such need to be characterized better.

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8. POPULATION EXPOSURE TO CARBON MONOXIDE

8.1 INTRODUCTION

A fundamental purpose of the Clean Air Act is to protect public health. The NAAQS are set at levels which attempt to provide a margin of safety to protect the health of the populace from adverse effects of air pollutants. In setting a pollutant standard, population exposure is an important consideration, because public health can be affected adversely by an air pollutant only if the following two conditions coincide.

(1) Persons actually are or potentially would be exposed in daily living to levels of the pollutant occurring in ambient air locations at or above undesirable concentrations.

(2) The air pollutant causes adverse effects on human health in sensitive population groups at these concentrations.

This chapter focuses on the degree to which the population actually is exposed to outdoor, in-transit, or indoor concentrations of CO that might produce adverse health effects. Chapter 10 deals with the second topic, the physiological and other health effects associated with a person's exposure to various concentrations of CO.

Carbon monoxide is emitted from sources of incomplete combustion of HC fuels.[1] Consequently, ambient concentrations of CO can reach high levels close to emission sources. The strong source-dependence of CO leads to highly variable spatial and temporal concentrations in urban environments (see Chapter 6). Because of the variable concentration patterns exhibited by CO, it is necessary to address the relationships between ambient concentrations and human exposures to evaluate the potential health risk associated with actual population exposures.

[1]Hydrocarbon fuels are burned incompletely by internal combustion engines (e.g., automobiles, trucks, and small utility engines), and by sources such as cigarettes, forest fires, and poorly adjusted gas burners.

Compliance with the NAAQS currently is judged by comparing the standards to data from fixed, ambient-air monitoring stations. The sites for such stations are chosen, however, to monitor ambient conditions in a number of neighborhood types (Ott, 1977) rather than actual human exposure. In fact, a number of studies have shown that ambient-air monitoring stations do not necessarily reflect the concentrations to which people are actually exposed. This difference between fixed stations and exposures occurs because of the spatial and temporal variability of carbon monoxide. In contrast to the stationary location of an ambient monitor, people are usually moving through a succession of microenvironments (e.g., homes, sidewalks, buses, automobiles, shopping malls, downtown street canyons, restaurants, offices, factories, and garages) where they may spend time in closer proximity to CO sources and in more enclosed spaces than the outdoors. The result is that existing ambient monitoring stations often do not reflect individual exposure patterns, nor do they necessarily reflect the highest concentrations to which those people are exposed. However, fixed monitors do give some general information on the overall level of exposure of a population to CO and are useful for a variety of other purposes (see Chapter 6).

Among all major air pollutants, CO has one of the clearest measures available of biological dose (see Section 8.5). The concentration of CO circulating in the blood, expressed as the percentage of Hb bound with CO, or COHb, is a useful measure of dose for relating this pollutant to deleterious health effects (see Chapter 10). Blood COHb is in turn a function of inhaled CO, breathing rate, blood volume, and other physiological factors (see Chapter 9: Pharmacokinetic modeling). Because the relationship between ambient CO and blood COHb is dynamic, it is necessary to know the timing and duration of an exposure series in order to predict resulting COHb.

Because of the spatial and temporal variability of CO as well as the known functional relationships between concentration and a measure of dose, CO is a model pollutant for development and evaluation of improved approaches for assessing human exposure. A number of field studies now have been undertaken that provide a quantitative assessment of the disparity between fixed monitoring stations and actual exposures. In addition, field measurements of body burden (for example, blood COHb, and breath CO) are available for comparison with fixed station monitoring data. Several personal-monitoring CO field studies have employed representative statistical sampling procedures, allowing inferences to be made

about the CO exposures (or COHb levels) of an entire population of a city or a region. Finally, models of population exposure and activity patterns have been developed to bridge the gap between ambient, fixed-station measurements, and actual personal exposures. Additional data need to be developed from personal monitoring field studies for use in validating these models. The models are important for improving our understanding of human exposure to CO and for evaluating different control strategies. The models can indicate locations and sources of most significant exposure and therefore may suggest control strategies to reduce human exposure and the resulting deleterious health effects.

8.2 EXPOSURE MONITORING IN THE POPULATION

In recent years, researchers have focused on the problem of determining actual population exposures to CO. There are two alternative approaches for estimating the exposures of a population to air pollution: the "direct approach" using field measurement of a representative population carrying PEMs; and the "indirect approach" involving computation from field data of activity patterns and measured concentration levels within microenvironments (Ott, 1982).

In the direct approach, as study participants engage in regular daily activities, they are responsible for recording their exposures to the pollutant of interest. Subjects can record their exposures in a diary, the method used in a study in Los Angeles (Ziskind et al., 1982), or they can automatically store exposure data in a data logger, the method used in studies in Denver (Johnson, 1984) and Washington, DC (Hartwell et al., 1984), which are summarized by Akland et al. (1985). In all of these studies, subjects recorded the time and nature of their activities while they monitored personal exposures to CO. The direct approach – sometimes called the Total Exposure Assessment Methodology (TEAM) – is useful to obtain an exposure inventory of a representative sample from either the general population, or from a specific subpopulation, which can be defined by many demographic, occupational, and health factors. The inventory can cover a range of microenvironments encountered over a period of interest (e.g., a day), or it can focus on one particular microenvironment. With this flexibility, policy analysts can assess the problem that emission sources pose to a particular subgroup (e.g., commuters) active in a specific microenvironment (e.g., automobiles).

The indirect approach to estimating personal exposure is to use PEMs or microenvironmental monitors (MEMs) to monitor microenvironments rather than individuals. Combined with additional data on human activities that occur in these microenvironments, data from the indirect approach can be used to estimate the percentage of a subpopulation that is at risk to pollutant concentrations that exceed national or state air quality standards. Flachsbart and Brown (1989) conducted this type of study to estimate merchant exposure to CO from motor vehicle exhaust at Honolulu's Ala Moana Shopping Center.

8.2.1 Personal Monitoring

The development of small PEM, as discussed in Chapter 5, made possible the large-scale CO human exposure field studies in Denver, CO, and Washington, DC, in the winter of 1982-1983 (Akland et al., 1985). These monitors proved effective in generating 24-h CO exposure profiles on 450 persons in Denver and 800 in Washington. Because personal monitoring techniques are new, and few field studies have been done, the science of measuring the exposures to chemicals in human populations is in an early stage of development. The use of PEMs and concurrent diaries in large-scale population studies requires rigorous quality control and introduces many new problems not present in ambient monitoring studies. The PEMs must be rugged, self-powered, lightweight, and free of drift while being carried and exposed to temperature variations; associated data loggers are required to store the continuous PEM readings. The diary format must be clear, easy for the subject to complete, and easy for the researcher to interpret. With good calibration practices, the CO PEMs can provide a precision of less than ± 1 ppm. The Denver-Washington, DC study is the only large-scale population exposure field study that yet has been undertaken. Despite the complexity of such a study, the large probability sample and high time resolution of the PEMs yielded a rich data base for characterizing the exposures of the population to CO in two major U.S. cities. The findings have greatly increased the understanding of the causes, severity, and variability of the exposures of human populations to CO.

Results from the Denver-Washington DC study (Akland et al., 1985) show that over 10% of the residents in Denver and 4% of the Washington DC residents were exposed to eight-hour average CO levels above 9 ppm during the winter study period. This degree of population exposure could not accurately be deduced from simultaneous data collected by the

fixed-site monitors without taking into account other factors such as contributions from indoor sources, elevated levels within vehicles, and individuals' activity patterns. In Denver, for example, the fixed-site monitors exceeded the 9 ppm level only 3.1% of the time. These results indicate that the effects of personal activity, indoor sources, and especially time spent commuting, greatly contribute to a person's CO exposure.

This study emphasizes that additional strategies are required to augment data from fixed site monitoring networks in order to evaluate actual human CO exposures and health risks within a community. The cumulative frequency distributions of CO data for both Denver and Washington DC in Figure 8-1 show that personal monitors often measure higher concentration than do fixed stations. As part of this study, comparisons were made of exposure to one-hour CO concentrations as determined by personal monitors and of measured ambient concentrations at fixed monitor sites. Correlations between personal monitor data and fixed-site data were consistently poor; the fixed-site data usually explained less than 10% of the observed variation in personal exposure. For example, one-hour CO measurements taken at the nearest fixed stations only were weakly correlated ($0.14 \leq r \leq 0.27$) with office or residential measurements taken with personal monitors (Akland et al., 1985).

The conclusion that exposure of persons to ambient CO and other pollutants does not directly correlate with concentrations determined at fixed-site monitors is supported by the work of others (Ott and Eliassen, 1973; Cortese and Spengler, 1976; Dockery and Spengler, 1981; Wallace and Ott, 1982).

In view of the high degree of variability of ambient CO concentrations over both space and time, (see Chapter 6) the reported results are not surprising. A given fixed monitor is unable to track the exposure of individuals to ambient CO as they go about their daily activities, moving from one location to another, and seldom in the immediate vicinity of the monitor. This does not necessarily mean, however, that fixed monitors do not give some general information on the overall level of exposure of a population to CO. The Akland data, although failing to show a correlation between individual personal monitor exposures and simultaneous nearest fixed-site monitor concentrations did suggest that, in Denver, aggregate personal exposures were lower on days of lower ambient CO levels as determined by fixed site monitors and higher on days of higher ambient levels. Also, both fixed-site and personal exposures were higher in Denver than in Washington.

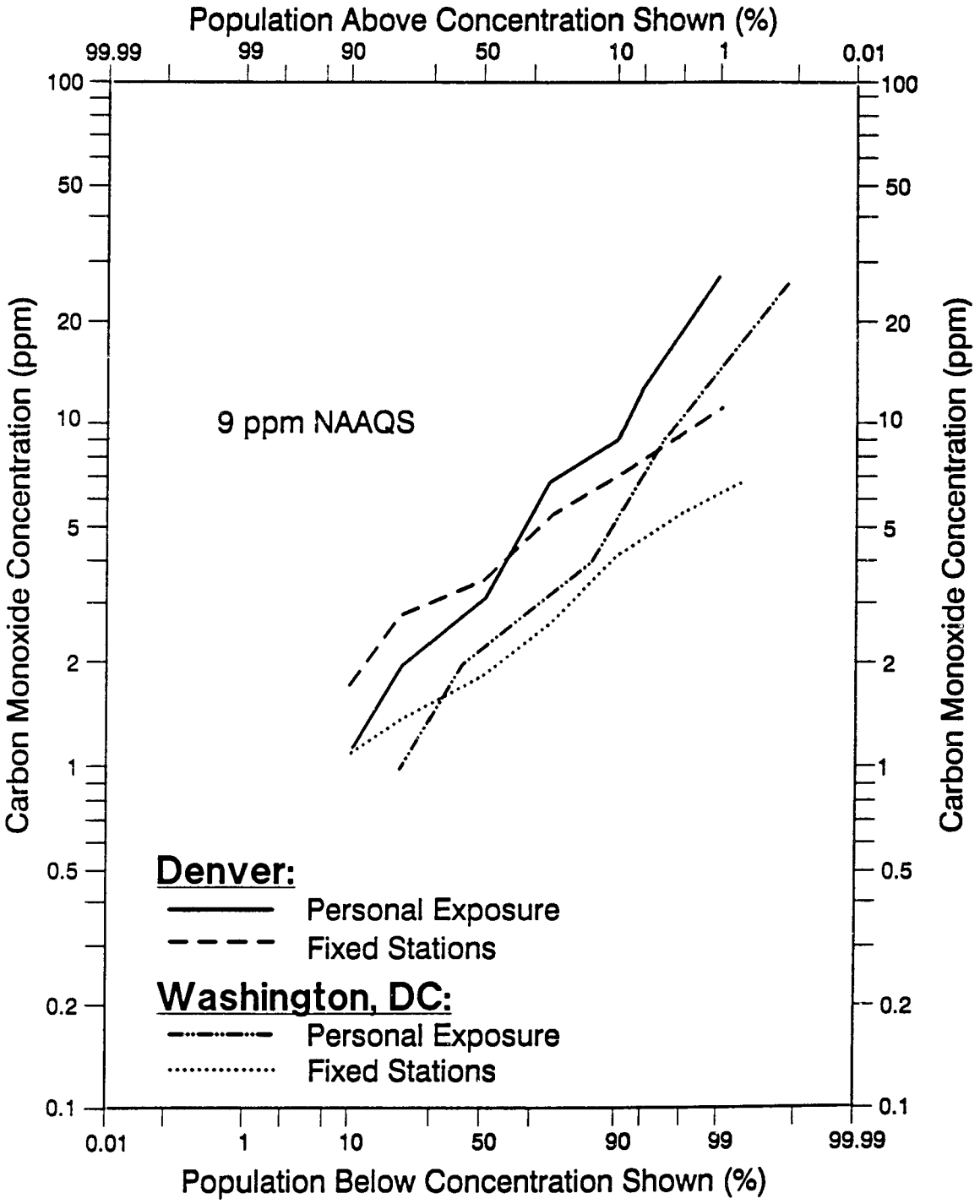

Figure 8-1. Frequency distributions of maximum eight-hour carbon monoxide population exposures and fixed-site monitor values in Denver, CO and Washington, DC; November 1982 - February 1983.

Source: Based on Akland, et al. (1984).

The PEMs have shown themselves to be powerful tools for quantifying air quality levels in in-transit, outdoor, and indoor microenvironments. A great number of microenvironments can be compared in one study. For example, Table 8-1 shows in-transit microenvironments in Denver, ranked from highest to lowest concentration by arithmetic mean. The in-transit microenvironment with the highest estimated CO concentration is the motor vehicle, whereas walking and bicycling have the lowest CO concentrations. Outdoor microenvironments also can be ranked (Table 8-2) for these data. Outdoor public garages and outdoor residential garages and carports had the highest CO concentrations; outdoor service stations, vehicle repair facilities, and parking lots had intermediate concentrations. In contrast, school grounds and residential grounds had relatively low concentrations, whereas extremely low CO concentrations were found in outdoor sports arenas, amphitheaters, parks, and golf courses. Finally, a wide range of concentrations was found in Denver within indoor micro-environments (Table 8-3). The highest indoor CO concentrations occurred in service stations, vehicle repair facilities and public parking garages; intermediate concentrations were found in shopping malls, residential garages, restaurants, offices, auditoriums, sports arenas, concert halls, and stores; the lowest concentrations were found in health care facilities, public buildings, manufacturing facilities, homes, schools, and churches.

One activity that influences personal exposure is commuting. An estimated 1% of the noncommuters in Washington were exposed to concentrations above 9 ppm for eight hours. By comparison, an estimated 8% of persons reporting that they commuted more than 16 h per week had CO exposures above the 9-ppm, eight-hour level. Finally, certain occupational groups whose work brings them in close proximity to the internal combustion engine had a potential for elevated CO exposures. These include automobile mechanics, parking garage or gas station attendants, crane deck operators, cooks, taxi, bus, and truck drivers, firemen, policemen, and warehouse and construction workers. Of the 712 CO exposure profiles obtained in Washington 29 persons fell into this "high- exposure" category. Of these, 25% had eight-hour CO exposures above the 9-ppm level.

Several field studies also have been conducted by the U.S. Environmental Protection Agency to determine the feasibility and effectiveness of monitoring selected micro-environments for use in estimating exposure profiles indirectly. One study (Flachsbart et al.,

TABLE 8-1. CARBON MONOXIDE CONCENTRATIONS IN IN-TRANSIT MICROENVIRONMENTS – DENVER, COLORADO

(Listed in descending order of mean CO concentration)

Microenvironment	n	Mean[a] (ppm)	Standard Error (ppm)
Motorcycle	22	9.79	1.74
Bus	76	8.52	0.81
Car	3,632	8.10	0.16
Truck	405	7.03	0.49
Walking	619	3.88	0.27
Bicycling	9	1.34	1.20

[a]An observation was recorded whenever a person changed a microenvironment, and on every clock hour; thus, each observation had an averaging time of 60 min or less.

Source: Johnson (1984).

1987) conducted in Washington in 1982-1983 concentrated on the commuting microenvironment, because earlier studies identified this microenvironment type as the single most important nonoccupational microenvironment relative to total CO population exposure. It was observed that for the typical automobile commuter the time-weighted average CO exposure while commuting ranged from 9 to 14 ppm. The corresponding rush-hour (7 to 9 am, 4 to 6 pm) averages at fixed-site monitors were 2.7 to 3.1 ppm.

8.2.2 Carbon Monoxide Exposures Indoors

The majority of people in the United States spend a majority of their time indoors; therefore, a comprehensive depiction of exposure to CO must include this setting. The indoor sources, emissions, and concentrations are sufficiently diverse, however, that only a few example studies can be cited here; a thorough discussion of CO in homes, offices, and similar environments, is presented in Chapter 7. Although a number of these studies report on

TABLE 8-2. CARBON MONOXIDE CONCENTRATIONS IN OUTDOOR MICROENVIRONMENTS – DENVER, COLORADO

(Listed in descending order of mean CO concentration)

Microenvironment	n	Mean[a] (ppm)	Standard Error (ppm)
Public garages	29	8.20	0.99
Residential garages or carports	22	7.53	1.90
Service stations or vehicle repair facilities	12	3.68	1.10
Parking lots	61	3.45	0.54
Other locations	126	3.17	0.49
School grounds	16	1.99	0.85
Residential grounds	74	1.36	0.26
Sports arenas, amphitheaters	29	0.97	0.52
Parks, golf courses	21	0.69	0.24

[a]An observation was recorded whenever a person changed a microenvironment, and on every clock hour; thus, each observation had an averaging time of 60 min or less.

Source: Johnson (1984).

microenvironmental concentrations, they do not specifically address human exposure while indoors.

Early studies date back to before 1970 when it was found that indoor and outdoor levels do not necessarily agree. For example, one study determined indoor-outdoor relationships for CO over two-week periods during summer, winter, and fall in 1969-1970 in buildings in Hartford, CT (Yocom et al., 1971). With the exceptions of the private homes, which were essentially equal, there was a day to night effect in the fall and winter seasons; days were

TABLE 8-3. CARBON MONOXIDE CONCENTRATIONS IN INDOOR MICROENVIRONMENTS - DENVER, COLORADO

(Listed in descending order of mean CO concentration)

Microenvironment	n	Mean[a] (ppm)	Standard Error (ppm)
Public garages	116	13.46	1.68
Service stations or vehicle repair facilities	125	9.17	0.83
Other locations	427	7.40	0.87
Other repair shops	55	5.64	1.03
Shopping malls	58	4.90	0.85
Residential garages	66	4.35	0.87
Restaurants	524	3.71	0.19
Offices	2,287	3.59	0.002
Auditoriums, sports arenas, concert halls	100	3.37	0.48
Stores	734	3.23	0.21
Health care facilities	351	2.22	0.23
Other public buildings	115	2.15	0.30
Manufacturing facilities	42	2.04	0.39
Homes	21,543	2.04	0.02
Schools	426	1.64	0.13
Churches	179	1.56	0.25

[a]An observation was recorded whenever a person changed a microenvironment, and on every clock hour; thus, each observation had an averaging time of 60 min or less.

Source: Johnson (1984).

higher by about a factor of 2. These differences are consistent with higher traffic-related CO levels outdoors in the daytime.

Indoor and outdoor CO concentrations were measured in four homes also in the Hartford, CT area in 1973-1974 (Wade et al., 1975). All used gas-fired cooking stoves. Concentrations were measured in the kitchen, living room, and bedroom. Stove use, as determined by activity diaries, correlated directly with CO concentrations. Peak CO concentrations in several of the kitchens exceeded 9 ppm, but average concentrations ranged from 2 to 3 ppm to about 8 ppm. These results are in general agreement with results obtained in Boston, MA (Moschandreas and Zabransky, 1982). In this study, they found significant differences between rooms in homes where there were gas appliances.

Effects of portable kerosene-fired space heaters on indoor air quality were measured in an environmental chamber and a house (Traynor et al., 1982). CO emissions from white flame (WF) and blue flame (BF) heaters were compared. The WF convective heater emitted less CO than the BF radiant heater. Concentrations in the residence were <2 ppm and 2 to 7 ppm, respectively. The authors conclude that high levels might occur when kerosene heaters are used in small spaces and/or when air exchange rates are low.

A rapid method using an electrochemical PEM to survey CO was applied in nine high-rise buildings in the San Francisco and Los Angeles areas during 1980 and 1984 (Flachsbart and Ott, 1986). One building had exceptionally high CO levels compared to the other buildings; average concentrations on various floors ranged from 5 to 36 ppm. The highest levels were in the underground parking garage, which was found to be the source of elevated CO within the building.

The effect of residential wood combustion and specific heater type on indoor CO has been investigated (Humphreys et al., 1986). Airtight and non-airtight heaters were compared in a research home in Tennessee. CO emissions from the non-airtight heaters was generally higher than from airtight heaters. Peak indoor CO concentration (ranging from 1.3 to 29.6 ppm, depending on heater type) was related to fuel reloadings.

CO levels in 254 Netherland homes with unvented gas-fired water heaters were investigated during the winter of 1980 (Brunekreef et al., 1982). Concentrations (ppm) at breathing height fell into the following categories: <10 (n=154), 11-50 (n=50), 51-100

(n=25), >100 (n=17). They found that a heater vent reduced indoor CO concentrations, and the type of burner affected CO levels.

Air pollution in Dutch homes was investigated by Lebret (1985). CO concentrations (ppm) in various locations were kitchen, 0 to 17.5; living room, 0 to 8.7; and bedroom, 0 to 3.5. CO levels were elevated in homes with gas cookers and unvented geysers (water heaters). Kitchen CO levels were higher than those in other locations due to peaks from the use of gas appliances. Living room CO values were slightly higher in houses with smokers. The overall mean CO level indoors was 0 to 2.7 ppm above outdoor levels.

In Zagreb, Yugoslavia, CO was measured in eight urban institutions housing sensitive populations, including kindergartens, a children's hospital, and homes for the elderly (Sisovic and Fugas, 1985). Winter CO concentrations ranged from 1.1 to 13.7 ppm, and summer concentrations ranged from 0.6 to 6.9 ppm. The authors attributed indoor CO concentrations to nearby traffic density, general urban pollution, seasonal differences, and day-to-day weather conditions. Indoor sources were not reported.

Toxic levels of CO also were found in measurements at six ice skating rinks (Johnson et al., 1975b). This study was prompted by the reporting of symptoms of headache and nausea among 15 children who patronized one of the rinks. CO concentrations were found to be as high as 304 ppm during operation of a propane-powered, ice-resurfacing machine. Depending on skating activity levels, the ice-resurfacing operation was performed for 10 min every one to two hours. As this machine was found to be the main source of CO, use of catalytic converters and properly tuning the engine greatly reduced emissions of CO. Similar findings have been reported by Spengler et al. (1978).

8.2.3 Carbon Monoxide Exposures Inside Vehicles

Studies of CO concentrations inside automobiles also have been reported over the past decade. Petersen and Sabersky (1975) measured pollutants inside an automobile under typical driving conditions. CO concentrations were generally less than 25 ppm, with one three-minute peak of 45 ppm. Average concentrations inside the vehicle were similar to those outside. No in-vehicle CO sources were noted.

Drowsiness, headache, and nausea were reported by eight children who had ridden in school buses for about two hours while traveling on a ski trip (Johnson et al., 1975a). The

students reporting symptoms were seated in the rear of the bus, which had a rear-mounted engine and a leaky exhaust. The exhaust system subsequently was repaired. During a later ski outing for students, CO concentrations also were monitored for a group of 66 school buses in the parking lot. The investigators found five buses with CO concentrations of 5 to 25 ppm (mean 15 ppm), 24 buses showing concentrations in excess of 9 ppm for short periods, and two buses showing up to 3 times the 9-ppm level for short periods. Drivers were advised to park so that exhausts from one bus would not be adjacent to the fresh air intake for another bus.

During a cross-country trip in the spring of 1977, Chaney (1978) measured in-vehicle CO concentrations. The CO levels varied depending on traffic speed. On expressways in Chicago, San Diego, and Los Angeles when traffic speed was less than 10 mph, CO exceeded 15 ppm. Levels increased to 45 ppm when traffic stopped. In addition, it was observed that heavily loaded vehicles (e.g., trucks) produced high CO concentrations inside nearby vehicles, especially when the trucks were ascending a grade.

Colwill and Hickman (1980) measured CO concentrations in 11 new cars as they were driven on a heavily trafficked route in and around London. The inside mean CO level for the 11 cars was 25.2 ppm vs. 47.0 ppm for the outside mean.

In a study mandated by Congress in the 1977 Clean Air Act Amendments, the EPA studied CO intrusion into vehicles (Ziskind et al., 1981). The objective was to determine whether CO was leaking into the passenger compartments of school buses, police cars, and taxis, and, if so, how prevalent the situation was. The study involved 1164 vehicles in Boston, and Denver. All vehicles were in use in a working fleet at the time of testing. The results indicated that all three types of vehicles often have multiple (an average of 4 to 5) points of CO intrusion – worn gaskets, accelerator pedals, rust spots in the trunk, and such. In 58% of the rides lasting longer than eight hours, CO levels exceeded 9 ppm. Thus the study provided evidence that maintenance and possibly design of vehicles may be an important factor in human exposure to CO.

Flachsbart (1989) investigated the effectiveness of priority lanes on a Honolulu arterial in reducing commuter travel time and exposure to CO. The CO concentrations and exposure of commuters in these lanes was substantially lower than in the nonpriority lanes. CO exposure was reduced approximately 61% for express buses, 28% for high-occupancy

vehicles, and 18% for carpools when compared to that for regular automobiles. The higher speed associated with priority lanes helped reduce CO exposure. These observations demonstrate that CO concentrations have a high degree of spatial variability on roadways.

Additional findings on CO levels inside vehicles are summarized in a literature review by Flachsbart and Ah Yo (1989). In general, a wide variation in CO exposures has been observed in in-transit microenvironments.

8.2.4 Carbon Monoxide Exposures Outdoors

Carbon monoxide concentrations in outdoor settings (besides those measured at fixed monitoring stations) also show considerable variability, as is evident from the eight Denver microenvironmental groupings listed in Table 8-2. Ott (1971) made 1128 CO measurements at outdoor locations in San Jose at breathing height over a six-month period and compared these results with the official fixed monitoring station data. This study included the measurements of the outdoor CO exposures of pedestrians in downtown San Jose by requiring them to carry personal monitoring pumps and bags while walking standardized routes on congested sidewalks. If an outdoor measurement was made more than 100 m away from any major street, its CO concentration was similar, suggesting the existence of a generalized urban background concentration in San Jose that was spatially uniform over the city (within a 33-km^2 grid) when one is sufficiently far away from mobile sources. Because the San Jose monitoring station then was located near a street with heavy traffic, it recorded concentrations approximately 100% higher than this background value. In contrast, outdoor CO levels from personal monitoring studies of downtown pedestrians were 60% above the corresponding monitoring station values and the correlation coefficient was low ($r = 0.20$). By collecting the pedestrian personal exposures over eight-hour periods, it was possible to compare the levels with the NAAQS concentration level. On two of seven days for which data were available, the pedestrian concentrations were particularly high (13 and 14.2 ppm) and were two to three times the corresponding levels recorded at the same time (4.4 and 6.2 ppm) at the air monitoring station (Ott and Eliassen, 1973; Ott and Mage, 1974). These results show that concentrations to which pedestrians are exposed on downtown streets can exceed a 9 ppm, 8-hour average while the official air monitoring station records values significantly less than that. It can be argued, however, that not many pedestrians spend eight hours

outdoors walking along downtown sidewalks, and that is one of the important reasons for including realistic human activity patterns in exposure assessments, as indicated in Section 8.3.

Godin et al. (1972) conducted similar studies in downtown Toronto using 100-mL glass syringes in conjunction with nondispersive spectrometry. They measured CO concentrations along streets, inside passenger vehicles, and at a variety of other locations. Like other investigators, they found that CO concentrations were determined by very localized phenomena. In general, CO concentrations in traffic and along streets were much higher than those observed at conventional fixed air monitoring stations. In a subsequent study in Toronto, Wright et al. (1975) used Ecolyzers to measure four to six minute average CO concentrations encountered by pedestrians and street workers and obtained similar results. Levels ranged from 10 to 50 ppm, varying with wind speed and direction, atmospheric stability, traffic density, and height of buildings. He also measured CO concentrations on the sidewalks of a street that subsequently was closed to traffic to become a pedestrian mall. Before the street was closed, the average concentrations at two intersections were 9.4 $\pm$ 4.0 ppm (st. dev.) and 7.9 $\pm$ 1.9 ppm; after the street was closed, the averages dropped to 3.7 $\pm$ 0.5 ppm and 4.0 $\pm$ 1.0 ppm, respectively, which were equivalent to the background level.

A large-scale field investigation was undertaken of CO concentrations in indoor and outdoor locations in five California cities using personal monitors (Ott and Flachsbart, 1982). For outdoor commercial settings, the average CO concentration was 4 ppm. This CO level was statistically, but not substantially, greater than the average CO concentration of 1.98 ppm recorded simultaneously at nearby fixed-monitoring stations. The final report of this field study (Flachsbart and Ott, 1984) contains an extensive literature review of CO exposures found in indoor, outdoor, and in-transit microenvironments.

8.3 ESTIMATING POPULATION EXPOSURE TO CARBON MONOXIDE

Accurate estimates of human exposure to CO are a prerequisite for a realistic appraisal of both the risks posed by the pollutant and the design and implementation of effective control

strategies. This section discusses the general concepts on which exposure assessment is based, the limitations of using ambient fixed-site monitoring data alone for estimating exposure, alternative approaches which have been proposed for estimating population exposure to air pollution, and specific applications of these approaches to estimating CO. Because of problems in estimating population exposure solely from fixed station data, several formal human exposure models have been developed. Some of these models include information on human activity patterns: the microenvironments people visit and the times they spend there. These models also contain submodels depicting the sources and concentrations likely to be found in each microenvironment, including indoor, outdoor, and in-transit settings.

8.3.1 Defining Concentration, Exposure, and Dose

In evaluating models for estimating CO, it is important to understand the basic concepts of concentration, exposure, and dose. Sexton and Ryan (1988) provide the following definitions.

The "concentration" of a specific air pollutant is the amount of that material per unit volume of air. Air pollution monitors measure pollutant concentrations, which may or may not provide accurate exposure estimates.

The term "exposure" is defined as any contact between air contaminant and the outer (e.g., skin) or inner (e.g., respiratory tract epithelium) surface of the human body. Exposure implies the simultaneous occurrence of two events (Ott, 1982):

(1) A pollutant concentration, C, is present at location x,y,z at time t.

(2) A person, i, is present at location x,y,z at time t.

A key distinction is apparent between a concentration and an exposure. The concentration of an airborne contaminant measured in an empty room is just that, a concentration. A concentration measured in a room with people present is a measurement of exposure. A measured concentration is a surrogate for exposure only to the degree to which it represents concentrations actually experienced by individuals.

A more important distinction exists between "exposure" and "dose." Whereas exposure is the pollutant concentration at the point of contact between the body and the external environment, dose is defined as the amount of pollutant that actually crosses one of the body's boundaries and reaches the target tissue. Among the factors that affect the magnitude of the dose received are respiration rate, respiration mode (e.g., mouth breathing versus nose breathing), uptake, metabolism, and clearance.

8.3.2 Components of Exposure

Two aspects of exposure bear directly on the related health consequences.

(1) Magnitude: What is the pollutant concentration?

(2) Duration: How long does the exposure last?

The magnitude is an important exposure parameter, since concentration typically is assumed to be directly proportional to dose, and ultimately, to the health outcome. But exposure implies a time component, and it is essential to specify the duration of an exposure. The health risks of exposure to a specific concentration for five minutes are likely to be different, all other factors being equal, than exposure to the same concentration for an hour.

The magnitude and duration of exposure can be determined by plotting an individual's air pollution exposure over time (Figure 8-2). The function $C_i(t)$ describes the air pollutant concentration to which an individual is exposed at any point in time t. The shaded area under the graph represents the accumulation of instantaneous exposures over some period of time (t_1-t_0). This area also is equal to the integral of the air pollutant concentration function, $C_i(t)$, between t_0 and t_1. Ott (1982) defines the quantity represented by this area as the integrated exposure.

By dividing the integrated exposure by the period of integration (t_1–t_0), the average exposure represents the average air pollutant concentration that an individual was exposed to over the defined period of exposure. To facilitate comparison with established air quality standards, an averaging period is chosen to equal the averaging period of the standard (t_s). In this case, the average exposure is referred to as a standardized exposure.

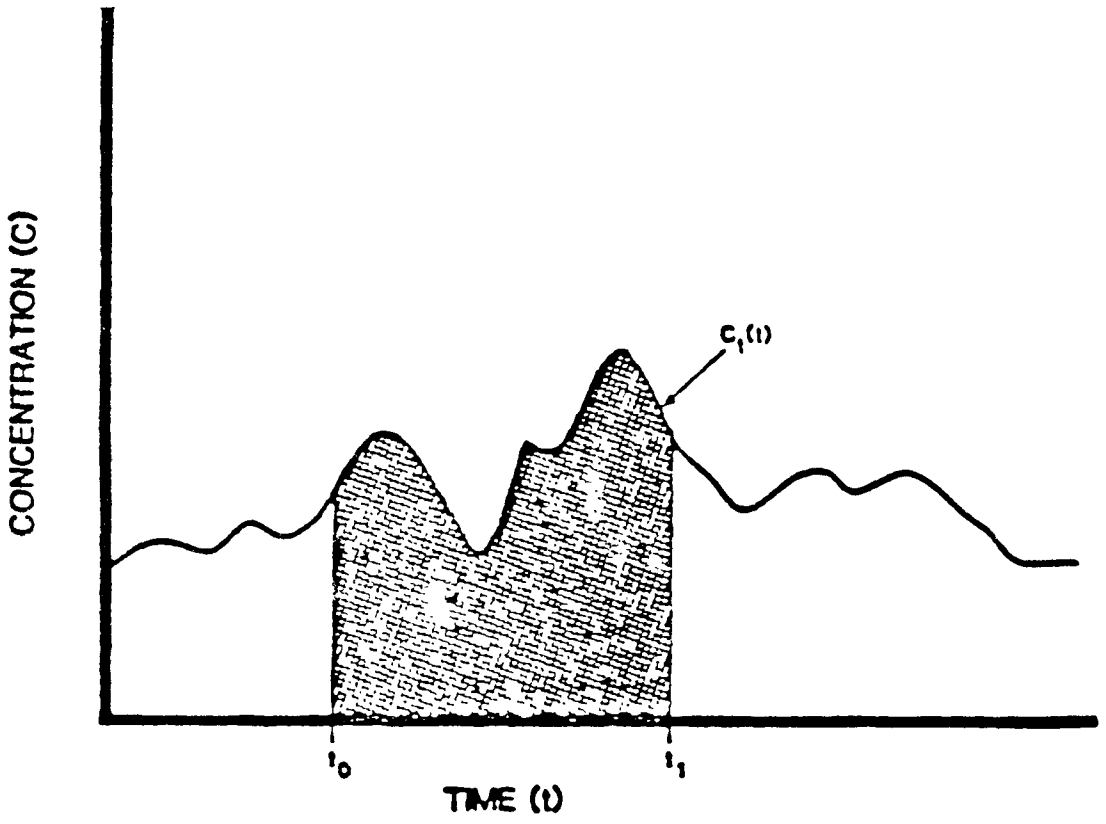

Figure 8-2. Typical individual exposure as a function of time.

Source: Ott (1982).

As previously discussed, exposure represents the joint occurrence of an individual being located at point (x,y,z) during time t, with the simultaneous presence of an air pollutant at concentration $C_{xyz}(t)$. Consequently, an individual's exposure to an air pollutant is a function of location as well as time. If a volume at a location can be defined such that air pollutant concentrations within it are homogeneous yet potentially different from other locations, the volume may be considered a "microenvironment" (Duan, 1982). Microenvironments may be aggregated by location (i.e., indoor or outdoor) or activity performed at a location (i.e., residential, commercial) to form microenvironment types.

It is important to distinguish between individual exposures and population exposures. Sexton and Ryan (1988) define the pollutant concentrations experienced by a specific individual during normal daily activities as "personal" or "individual" exposures. A personal exposure depends on the air pollutant concentrations that are present in the locations through which the person moves, as well as on the time spent at each location. Because time-activity patterns can vary substantially from person to person, individual exposures exhibit wide variability (Dockery and Spengler, 1981; Quackenboss et al., 1982; Sexton et al., 1984; Spengler et al., 1985; Stock et al., 1985; Wallace et al., 1985). Thus, although it is a relatively straightforward procedure to measure any one person's exposure, many such measurements may be needed to quantify exposures for a defined group. The daily activities of a person in time and space define his or her activity pattern. Accurate estimates of air pollution exposure generally require that an exposure model account for the activity patterns of the population of interest. The activity patterns may be determined through "time budget" studies of the population. Studies of this type have been performed by Szalai (1972), Chapin (1974), Robinson (1977), Michelson and Reed (1975), Johnson (1987) and Schwab et al. (1989). The earlier studies may now be dated and were not designed to investigate human exposure questions. Ongoing exposure studies have adopted the diary methods that were developed for sociological investigations and applied them to current exposure and time budget investigations. A few of these studies have been reported (e.g., Schwab et al., 1989; Johnson, 1987).

From a public health perspective, it is important to determine the "population exposure," which is the aggregate exposure for a specified group of people (e.g., a community, an identified occupational cohort). Because exposures are likely to vary

substantially between individuals, specification of the distribution of personal exposures within a population, including the average value and the associated variance, is often the focus of exposure assessment studies. The upper tail of the distribution, which represents those individuals exposed to the highest concentrations, is frequently of special interest because the determination of the number of individuals who experience elevated pollutant levels can be critical for health risk assessments. This is especially true for pollutants for which the relationship between dose and response is highly nonlinear.

8.3.3 Relationship to Fixed-Site Monitors

Many early attempts to estimate exposure of human population used ambient air quality from fixed stations. An example of such an analysis can be found in the 1980 Annual Report of the President's Council on Environmental Quality (CEQ, 1980). In this analysis, a county's exposure to an air pollutant was estimated as the product of the number of days that violations of the primary NAAQS were observed at county monitoring sites multiplied by the county's population. Exposure was expressed in units of person-days. National exposure to an air pollutant was estimated by the sum of all county exposures.

The methodology employed by CEQ provides a relatively crude estimate of exposure and is limited by four assumptions.

(1) The exposed populations do not travel outside areas represented by fixed-site monitors.

(2) The air pollutant concentrations measured with the network of fixed-site monitors are representative of the concentrations breathed by the population throughout the area.

(3) The air quality in any one area was only as good as that at the location that had the worst air quality.

(4) There were no violations in areas of the county not monitored.

Many studies cast doubt on the validity of this assumption for CO. Reviews of these studies are provided by Ott (1982) and by Spengler and Soczek (1984). Doubts over the

ability of fixed-site monitors alone to accurately depict air pollutant exposures are based on two major findings on fixed-site monitor representativeness.

(1) Indoor and in-transit concentrations of CO may be significantly different from ambient CO concentrations.

(2) Ambient outdoor concentrations of CO that people come in contact with may vary significantly from CO concentrations measured at fixed-site monitors.

In estimating exposure, CEQ also assumed that each person in the population spends 24 h at home. This assumption permitted the use of readily available demographic data from the U.S. Census Bureau. Data collected 20 years ago indicate that people spend a substantial portion of their time away from home. In a study of metropolitan Washington residents during 1968, Chapin (1974) found that people spent an average 6.3 h away from home on Sunday and 10.6 h away from home on Friday. This translates to between 26.4 and 44.3% of the day spent away from home. More recent personal exposure and time budget studies (e.g., Schwab et al., 1989; Johnson, 1987) also indicate that a substantial portion of time is spent away from home.

Fixed-site monitors measure concentrations of pollutants in ambient air. Ambient air has been defined by EPA in the Code of Federal Regulations (1977) as air that is "external to buildings, to which the general public has access." But the nature of modern urban life-styles in many countries, including the United States, indicates that people spend an average of over 20 h per day indoors (Meyer, 1983). Reviews of studies on this subject by Yocom (1982), Meyer (1983) and Spengler and Soczek (1984) show that indoor CO concentration measurements vary significantly from simultaneous measurements in ambient air. The difference between indoor and outdoor air quality and the amount of time people spend indoors reinforces the conclusion that using ambient air quality measurements alone will not provide accurate estimates of population exposure.

8.3.4 Alternative Approaches to Exposure Estimation

In recent years, the limitations of using fixed-site monitors alone to estimate public exposure to air pollutants have stimulated interest in using portable monitors to measure

personal exposure. These instruments, which were developed for CO in the late 1970s by Energetics Science Incorporated and by General Electric, are called PEMs. Wallace and Ott (1982) surveyed PEMs available then for CO and other air pollutants. (See Chapter 5, Section 5.4, for a more complete description of PEMs.)

The availability of these monitors has facilitated use of the direct and indirect approaches to assessing personal exposure (see Section 8.2). Whether the direct or indirect approach is followed, the estimation of population exposure requires a "model"; that is, a mathematical or computerized approach of some kind. Sexton and Ryan (1988) suggest that most exposure models can be classified as one of three types: statistical, physical, or physical-stochastic.

The statistical approach requires the collection of data on human exposures and the factors thought to be determinants of exposure. These data are combined in a statistical model, normally a regression equation or an analysis of variance (ANOVA), to investigate the relationship between air pollution exposure (dependent variable) and the factors contributing to the measured exposure (independent variables). An example of a statistical model is the regression model developed by Johnson et al. (1986) for estimating CO exposures in Denver based on data obtained from the Denver Personal Monitoring Study.

If the study group constitutes a representative sample, the derived statistical model may be extrapolated to the population defined by the sampling frame. It also should be noted that selection of factors thought to influence exposure has a substantial effect on the outcome of the analysis. Spurious conclusions can be drawn, for example, from statistical models that include parameters that are correlated with, but not causally related to, air pollution exposure.

In the physical modeling approach, the investigator makes an a priori assumption about the underlying physical processes that determine air pollution exposure and then attempts to approximate these processes through a mathematical formulation. Because the model is chosen by the investigator, it may produce biased results because of the inadvertent inclusion of inappropriate parameters or the improper exclusion of critical components. The NAAQS Exposure Model (NEM) as originally applied to CO by Johnson and Paul (1983) is an example of a physical model.

The physical-stochastic approach combines elements of both the physical and statistical modeling approaches. The investigator begins by constructing a mathematical model that

describes the physical basis for air pollution exposure. Then a random or stochastic component that takes into account the imperfect knowledge of the physical parameters that determine exposure is introduced into the model. The physical-stochastic approach limits the effect of investigator-induced bias by the inclusion of the random component, and allows for estimates of population distributions for air pollution exposure. Misleading results still may be produced, however, because of poor selection of model parameters. In addition, the required knowledge about distributional characteristics may be difficult to obtain. Examples of models based on this approach which have been applied to CO include the simulation of human activity and pollutant exposure (SHAPE) model (Ott, 1984; Ott et al., 1988) and two NEM-derived models developed by Johnson (1988) and by Johnson and Wijnberg (1988).

Table 8-4 provides a summary of the three model types. Table 8-5 lists exposure models which have been applied to CO by model type. These models are described in the following sections. General reviews of the exposure modeling literature have been provided by Repace et al. (1980), Ott (1985), Fugas (1986), Ott et al. (1986), Sexton and Ryan (1988), and Pandian (1987). EPA has developed a computerized bibliographic literature information system (BLIS) to facilitate access to literature concerned with total human exposure monitoring. Included in the BLIS data base is an extensive bibliography on human exposure modeling (Dellarco et al., 1988; Shackelford et al., 1988).

8.3.5 Statistical Models Based on Personal Monitoring Data

As discussed above, fixed-site monitoring data may not provide an accurate indication of personal exposure within an urban population, which is a function of both geographic location (e.g., downtown vs. suburbia) and immediate physical surroundings (e.g., indoors vs. outdoors). Better estimates of personal exposure can be developed by equipping a large number of subjects with portable monitors and activity diaries. If the subjects are properly selected, their exposures can be extrapolated to a larger "target" population.

Two such studies were conducted during the winter of 1982-1983 in Denver and Washington. In the Denver study, each of 454 subjects carried a PEM and completed an activity diary for two consecutive 24-h sampling periods and provided a breath sample at the end of each sampling period (Johnson, 1984). Each participant also was requested to complete a detailed background questionnaire. The questionnaire results and approximately

TABLE 8-4. COMPARISON OF DIFFERENT APPROACHES TO AIR POLLUTION EXPOSURE MODELING

Parameter	Statistical	Physical	Physical-stochastic
Method of formulation	Hypothesis testing	Physical laws	Physical Laws and Statistics
Required input	Collected data on human exposure	Knowledge of important parameters and their values in the system to be modeled	Knowledge of important parameters and their distributions in the systems to be modeled.
Advantages	Makes use of real data in the model building process	True model developed from a priori considerations	Model developed from a priori considerations. Stochastic part allows uncertainty to contribute, which reduces importance of research biases.
Disadvantages	Requires data on hand for model building; extrapolation beyond data base is difficult	Includes researcher's biases; must be validated	Requires much knowledge of system. Must be validated.

Source: Sexton and Ryan (1988).

900 subject-days of PEM and activity diary data collected between 1 November 1982, and 28 February 1983, were analyzed to determine if factors such as microenvironment and the presence of indoor CO sources significantly affect personal CO exposure. In addition, the exposure of a defined target population was extrapolated from exposures recorded by the study participants. Detailed descriptions of the Denver study design and data collection procedures, together with results of initial data analyses, are available in a report by Johnson (1984).

TABLE 8-5. MODELS WHICH HAVE BEEN USED TO ESTIMATE CO EXPOSURE BY MODEL TYPE

Model type	Model	References
Statistical	Regression models based on statistical analyses of data obtained from Denver and Washington Personal Monitoring Studies	Johnson et al. (1986)
	Results of ANOVA of data obtained from Washington Commuter Study	Flachsbart et al. (1987)
Physical	NAAQS Exposure Model (NEM)	Johnson and Paul (1983)
	Ott-Willits Commuter Model	Ott and Willits (1981)
	Simmon-Patterson Commuter Model	Simmon and Patterson (1983)
	Davidson Indoor Mass-Balance Models	Davidson et al. (1984)
	Pierce Integrated Exposure Model	Pierce et al. (1984)
	Duan Convolution Model	Duan (1985)
	Duan Hybrid Model	Duan (1985)
	Flachsbart Prototypical Commuter Models	Flachsbart (1985)
	Flachsbart-Ah Yo Commuter Model	Flachsbart and Ah Yo (1989)
Physical/ Stochastic	SHAPE	Ott (1984)
	Probabilistic NEM	Johnson and Wijnberg (1988)
	REHEX	Lurmann et al. (1989)

Source: Adapted from Sexton and Ryan (1988).

The Washington study has been described in detail by Hartwell et al. (1984). It differs from the Denver study in that (1) twice as many subjects were used in the Washington study, and (2) each subject carried a PEM and a diary for a single 24-h period. Results of analyses of the Washington data base are provided by Settergren et al. (1984), Clayton et al. (1985), and Johnson et al. (1986).

A primary goal of the Denver and Washington personal monitoring studies was to investigate whether personal exposures could be predicted by fixed-site ambient monitoring data. This investigation was conducted by performing linear regression analyses that used PEM values grouped by microenvironment as the dependent variable and simultaneously-recorded fixed-site values as the independent variable.

To perform these analyses, each PEM value had to be paired with a value reported by a single fixed-site monitor. Because the census tract of each nontransit PEM value was known, it was possible to use census tracts as a means of linking PEM and fixed-site values. Whenever a PEM value was reported for a given census tract, it was paired with the simultaneous value of the fixed-site monitor assigned to that census tract.

This analysis suggested that a linear regression analysis that pairs each PEM value reported for a nontransit microenvironment with the simultaneous value reported at the nearest fixed-site might be appropriate for the Denver study data. Weighted linear regression analyses were performed with the data grouped by selected codes related to microenvironment. Results for nontransit microenvironments are listed in Table 8-6. Values of R^2 range from 0.00 to 0.46. As might be expected, many of the microenvironments with small R^2 values are associated with local CO sources that tend to reduce the correlation between PEM value and nearest fixed-site value; however, other microenvironments not associated with local CO sources have relatively larger R^2 values (e.g., park or golf course, or "other locations").

Table 8-6 does not list any in-transit microenvironments because of the difficulty in pairing in-transit PEM values with a " nearest" fixed-site monitor value. In the Denver data base, each in-transit PEM value has two census tract listings, one associated with the start address and the other with the end address. Neither was considered a good indicator of the CO conditions encountered during the trip. An alternative procedure consisted of pairing in–transit PEM values with simultaneous values from a composite data set created by

TABLE 8-6. RESULTS OF WEIGHTED LINEAR REGRESSION ANALYSIS WITH NONTRANSIT PEM VALUE AS DEPENDENT VARIABLE AND SIMULTANEOUS VALUE AT NEAREST DENVER FIXED-SITE AS INDEPENDENT VARIABLE

Microenvironment		Linear regression[a]				
Category	Subcategory	n	Intercept	Slope	R^2	p[b]
Outdoors	Other location	115	0.35	1.11	0.46	0.000
Outdoors	Park or golf course	18	-0.09	0.39	0.44	0.003
Outdoors	School grounds	15	-0.37	1.15	0.27	0.049
Indoors	Service station or motor vehicle repair facility	112	4.18	1.68	0.27	0.000
Indoors	Restaurant	486	1.69	0.76	0.25	0.000
Outdoors	Service station or motor vehicle repair facility	11	1.61	1.21	0.23	0.134
Outdoors	Within 10 yards of road	468	1.58	0.89	0.21	0.000
Indoors	Church	178	0.09	0.70	0.21	0.000
Outdoors	Parking lot	51	2.26	0.60	0.21	0.000
Indoors	Other repair shop	46	3.69	0.88	0.18	0.003
Outdoors	Sports arena, amphitheater, etc.	16	3.05	-1.76	0.15	0.128
Indoors	Other public building	111	0.74	0.42	0.14	0.000
Indoors	Shopping mall	55	1.24	1.43	0.14	0.005
Indoors	Store	675	1.67	0.56	0.09	0.000
Indoors	Health care facility	333	0.97	0.45	0.09	0.000
Indoors	Residence	20,969	1.00	0.43	0.07	0.000
Indoors	School	342	0.97	0.32	0.07	0.000
Indoors	Office	2,090	2.53	0.34	0.05	0.000
Outdoors	Residential garage or carport	22	5.67	0.61	0.05	0.304
Not specified	Not specified	583	2.07	0.63	0.05	0.000
Outdoors	Residential grounds	70	0.84	0.30	0.04	0.099
	Public garage	139	8.44	0.72	0.04	0.019
Indoors	Auditorium, sports arena, concert hall, etc.	94	2.25	0.38	0.04	0.060
Indoors	Manufacturing facility	41	1.41	0.18	0.03	0.246
Indoors	Residential garage	66	4.98	0.14	0.00	0.662
Indoors	Other location	381	7.94	0.07	0.00	0.791

[a] Listed in order of R^2 value.

[b] Probability that slope = 0.

Source: Johnson et al. (1986).

averaging the data from the 15 fixed-site monitors. The composite data set was found to exhibit relatively high correlations with most of the fixed-site data sets. Consequently, the composite site was assumed to provide an indication of the average ambient CO level in the study area. Table 8-7 lists the results of linear regression analyses pairing in-transit PEM values with simultaneous values from the composite data set. Values of R^2 range from 0.04 (car) to 0.58 (motorcycle).

The linear regression analyses described above suggested that the correlation between PEM values and fixed-site CO values is weak for most microenvironments. A statistical analysis was subsequently performed to investigate whether the one-hour CO values reported by a particular fixed-site monitor or groups of fixed-site monitors were better correlated with PEM values. Again, the correlations were low with R^2 values ranging from approximately 0.01 to 0.05 (Johnson et al., 1986).

Similar regression analyses were performed on the Washington CO data, and are shown in Tables 8-8 and 8-9. Values of R^2 range from 0.00 to 0.66. Several of the microenvironments with small R^2 values are associated with local CO sources that tend to reduce the correlation between PEM value and nearest fixed-site value.

Only two nontransit microenvironments have R^2 values exceeding 0.20: hospital (R^2 = 0.66) and church (R^2 = 0.60). The R^2 value for office is 0.06; the R^2 value for residence is 0.02. The in-transit microenvironments also tend to have low R^2 values (e.g., the R^2 value for car is 0.08).

The analyses discussed above suggest that individual PEM readings are not highly correlated with simultaneous fixed-site readings. Also it was learned that composite fixed-site daily maximum values are poor predictors of daily maximum exposures. However, the magnitude of daily maximum eight-hour exposures among the Denver study participants on days when violations of the eight-hour NAAQS occurred (median exposure of 5.6 ppm) versus exposures on days when violations did not occur (median exposure of 3.2 ppm) was statistically significant at the $p < 0.001$.

8.3.6 Physical and Physical-Stochastic Models

In applying physical and physical-stochastic models, the analyst constructs a mathematical model that describes the physical basis for air pollution exposure. As discussed

TABLE 8-7. RESULTS OF WEIGHTED LINEAR REGRESSION ANALYSES WITH IN-TRANSIT PEM VALUE AS DEPENDENT VARIABLE AND SIMULTANEOUS VALUE FROM DENVER COMPOSITE DATA SET AS INDEPENDENT VARIABLE

In-Transit Subcategory	Linear Regression				
	n	Intercept	Slope	R^2	p[a]
Motorcycle	22	4.50	2.14	0.58	0.000
Bus	76	3.17	2.02	0.36	0.010
Walking	619	0.06	1.47	0.23	0.000
Truck	405	3.27	1.54	0.11	0.000
Car	3,632	6.01	0.78	0.04	0.000
All	4,763	5.15	0.92	0.05	0.000

[a]Probability that slope = 0.

Source: Johnson et al. (1986).

above, physical-stochastic models differ from physical models in that the former include a random component that reflects the analyst's imperfect knowledge concerning the physical parameters in the model.

The Convolution and Hybrid Models – Duan (1985) evaluated two methods for estimating CO exposures which combine activity pattern data obtained from one source with data on CO levels measured in microenvironments obtained from another source. Duan used the Washington Personal Monitoring Study (Hartwell et al., 1984) as the source of activity pattern data and the Washington Commuter Study (Flachsbart et al., 1987) as the source of the CO data. Each of 705 subjects in the former study completed a 24-h activity diary from which could be determined the sequence of microenvironments occupied by the subject. The latter study measured CO levels in a variety of microenvironments on each of 43 days. In the first method – referred to as the Convolution Method – each of the 43 sets of microenvironmental CO data was paired with each of the 705 person-days of activity diary data to yield (43) (705) = 30,315 "convoluted" person-days of CO exposure. The CO levels for all microenvironments occupied by a subject on a given convoluted person-day are obtained from a single day of microenvironmental monitoring data.

In the second method – referred to as the hybrid approach – the average CO level across all 43 days was determined for each microenvironment and was used as the estimate of CO

TABLE 8-8. RESULTS OF WEIGHTED LINEAR REGRESSION ANALYSES WITH NONTRANSIT PEM VALUE AS DEPENDENT VARIABLE AND SIMULTANEOUS VALUE AT NEAREST FIXED-SITE IN WASHINGTON, DC AS INDEPENDENT VARIABLE

Microenvironment		Linear regression				
Category	Subcategory[a]	n	Intercept	Slope	R^2	p[b]
Indoors	Hospital	46	-0.05	0.63	0.66	0.000
Indoors	Church	44	-0.04	0.58	0.60	0.000
Indoors	Garage	70	4.02	3.43	0.19	0.000
Outdoors	Park, sports arena	11	0.06	-0.01	0.15	0.239
Indoors	Laboratories	23	0.30	0.26	0.22	0.132
Outdoors	Residential area	82	0.53	0.52	0.10	0.003
Indoors	Office	1,741	0.94	0.45	0.10	0.003
Outdoors	Within 10 yards of road or street	224	1.33	0.50	0.04	0.002
Indoors	Store	178	1.25	0.33	0.02	0.047
Indoors	Residence	14,962	1.21	0.18	0.02	0.000
Outdoors	Garage, parking lot	38	5.05	-0.42	0.00	0.709
Indoors	Not specified	57	3.52	-0.16	0.00	0.751
Indoors	School, school gym	239	1.01	0.06	0.00	0.555
Indoors	Restaurant	120	2.88	-0.03	0.00	0.848
Indoors	Other indoor	129	5.07	0.09	0.00	0.900

[a]Listed in order of R^2 value.

[b]Probability that slope = 0.

Source: Johnson et al. (1986).

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TABLE 8-9. RESULTS OF WEIGHTED LINEAR REGRESSION ANALYSES WITH IN-TRANSIT PEM VALUE AS DEPENDENT VARIABLE AND SIMULTANEOUS VALUE FROM COMPOSITE WASHINGTON, DC DATA SET AS INDEPENDENT VARIABLE

In-Transit Subcategory[a]	Linear Regression				
	n	Intercept	Slope	R^2	p[a]
Train/subway	38	0.05	1.09	0.61	0.000
Jogging	11	0.43	0.67	0.25	0.118
Multiple response	20	-0.98	2.58	0.20	0.050
Missing	22	-0.21	1.83	0.13	0.100
Car	2,646	1.51	1.74	0.08	0.000
Truck	85	2.16	2.00	0.07	0.014
Bus	67	1.01	2.45	0.05	0.066
Walking	510	1.21	0.94	0.03	0.000
Van	21	1.91	0.33	0.03	0.478
Bicycle	16	3.62	-0.08	0.01	0.721

[a]Listed in order of R^2 value.

[b]Probability that slope = 0.

Source: Johnson et al. (1986).

exposure whenever a diary-derived activity pattern indicated a subject was in the microenvironment. This method yielded 705 person-days of CO exposure. The exposures estimated by each of the two methods were compared to exposures indicated by the PEMs carried by the Washington subjects. The convolution and hybrid methods produced exposure estimates that were, on average, approximately 40% higher than the PEM-derived exposure estimates. Despite this discrepancy, Duan (1985) found that the two methods were powerful predictors of PEM-derived exposure estimates, in that the correlations between model estimates and PEM-derived estimates were relatively high.

NAAQS Exposure Model (NEM) – In assessing the health risks associated with alternative forms of NAAQS, EPA routinely uses the NEM to estimate the pollutant exposures of

sensitive population groups. NEM itself is a general modeling framework that can be applied to estimate the exposures of the population to individual criteria air pollutants (Biller et al., 1981). The general NEM framework, which continues to evolve over time, can be tailored to reflect the characteristics of particular air pollutants. NEM is designed to estimate population exposures under alternative values of the NAAQS.

NEM divides time into finite intervals (e.g., 1 min, 10 min, 1 h) over which pollutant concentrations are assumed to be constant. Geographic locations can be as small as tiny microenvironments (e.g., homes, automobiles) or they can be aggregated into larger physical areas (e.g., neighborhoods). The population is divided into cohorts and their activity patterns (movement into successive microenvironments over time) are based on census data and information from transporation agencies (e.g., commuter travel times). Human activities can be represented either as deterministic or stochastic variables, as can pollutant concentrations.

In the initial application of NEM to CO (Johnson and Paul, 1983), four cities (Chicago, Los Angeles, Philadelphia, and St. Louis) were selected as representative study areas. In applications of NEM to CO, the assumption was made that the CO concentration reflects (1) ambient CO levels as reported by outdoor fixed-site monitors and (2) sources and sinks specific to a microenvironment. In the initial version of CO NEM, the CO exposure associated with an event occurring at time t in microenvironment m was estimated by a first order approximation which can be stated in general terms as:

$$CO(m,t) = MULT(m) * MON(t) + ADD(m) \qquad (8\text{-}1)$$

where MON(t) is the CO concentration expected to occur at a fixed-site monitor at time t, MULT(m) is a multiplicative constant specific to m, and ADD(m) is an additive constant specific to m (Johnson and Paul, 1983). This deterministic approximation does not capture the findings of PEM studies which point to relatively low correlations between microenvironment exposure concentrations and fixed-site monitor concentrations. Further, it captures neither the stochastic nature of any relationship that might exist between exposure concentrations and fixed-site monitor concentrations nor the stochastic nature of source/sink contributions within a microenvironment.

A modified version treated the term ADD(m) as an independent, identically-distributed stochastic variable which could be characterized by the Box-Cox distribution (Johnson et al., 1988). This change resulted in reduced levels of correlation between CO(m,t) and MON(t) that were in agreement with correlations observed in a personal monitoring study conducted in Denver, Colorado (Akland et al., 1985). A further refinement incorporates serial correlation (Johnson and Wijnberg, 1988).

Simulation of Human Activity and Pollutant Exposure (SHAPE) – SHAPE simulates the activity patterns and CO exposures of a sample of urban commuters during their daily routines (Ott, 1984). The simulation is over a fixed period for all individuals in the sample, usually a 24-h period. The model uses the following equation (Duan, 1981, 1982):

$$E_i = \sum_{j=1}^{J} c_j t_{ij}, \tag{8-2}$$

where E_i is integrated CO exposure of person i, c_j is concentration encountered in microenvironment j, t_{ij} is time spent by person i in microenvironment j, J is number of microenvironments visited, and

$$\sum_{j=1}^{J} t_{ij} = T, \tag{8-3}$$

the time period under consideration.

E_i is expressed in parts per million-minutes (ppm-min) or ppm-h, as it is a product of concentration and time. If T is an averaging time, such as eight-hour, dividing E_i by T gives the average eight-hour exposure. The SHAPE model computes hourly exposure (and eight-hour running average exposure) dynamically over 24-h for each individual in the sample. The modeling of exposures and the various equations and definitions to be used are discussed by Duan (1982) and Ott (1982, 1984). Applying Equation 8-2 in an exposure model requires both the microenvironmental concentrations (the c_j's) and the activity pattern times (the t_{ij}'s) for each person.

A fundamental assumption about microenvironmental pollutant concentrations for inert pollutants such as CO in the SHAPE model is the "superposition hypothesis." According to this hypothesis, the total concentration $c_j(t)$ as a function of time encountered in microenvironment j is treated as the sum of two concentration components: (1) a microenvironmental component concentration $c_m(t)$ resulting from the sources of CO within the microenvironment, and, (2) an ambient (background) component concentration $c_u(t)$ assumed to be free of any microenvironmental source influences; that is,

$$c_j(t) = [c_m(t) + c_u(t)]_j, \tag{8-4}$$

The basis for this hypothesis is the interpretation of the spatial variability of CO concentrations from field studies (Ott, 1971; Ott and Eliassen, 1973).

In the SHAPE model, the microenvironmental component depends only on the sources of CO within the microenvironment and is independent of location in the urban area or of conditions in the metropolitan area. An example is the CO concentrations contributed by motor vehicles inside an indoor parking garage. In contrast, the background concentration component is the CO concentration that would be present if there were no specific sources of CO. For example, in a house or building, the background component would be the CO in the outdoor air entering through the ventilation system or the windows, which depends primarily on seasonal and daily changes in meteorological conditions.

Because data on true ambient background concentrations of CO are generally unavailable for the many microenvironments that an urban population regularly visits on a daily basis, Ott et al. (1988) investigated the use an "overall surrogate" ambient CO concentration thought to be associated with all the microenvironments of an urban area. Usually, the only data available to serve as an overall surrogate measurement are CO concentrations measured by fixed monitoring stations located in metropolitan areas. These data may yield unrealistically high estimates of ambient CO levels as most air monitoring stations are placed near streets with heavy traffic. Ott recommended using the ambient component given by the hourly CO readings from fixed-site monitors located away from streets, but the hourly average of all fixed stations in Denver performed satisfactorily.

The original version of SHAPE (Ott, 1981, 1984) assumed that pollutant concentrations in microenvironments behave stochastically. This assumption was based partly on a study by Ott and Willits (1981) in which CO concentrations inside an automobile passenger compartment were found to show considerable random fluctuation from minute to minute. The CO data were collected on drives during a one-year study of an urban arterial highway, El Camino Real in California. Statistical analysis indicated that the one-minute average CO concentration [$c_j(t)$] could be treated as independent, lognormally distributed random variables during the length of a car trip (one hour or less). Ott and Willits (1981) developed these conclusions for the exposures incurred by the occupants of vehicles free of CO intrusion from the vehicle's own exhaust system.

The SHAPE model (Ott, 1981, 1984) was designed with these findings in mind. All microenvironmental CO component concentrations were represented by stationary two-parameter lognormal distributions with $c_u(t)$ held constant. Thus, the computer treated the microenvironmental component as the random variable $[c_m]_j$ whose mean and variance for each microenvironment j where specified by the user and were held constant. The values of the mean and variance usually were based on CO field studies in various microenvironments reported in the literature (inside moving automobiles, buses, trucks; on bicycles in traffic; in indoor parking garages, houses, and similar environments) and on the judgment of the user.

The SHAPE model (Ott, 1981, 1984) originally sampled microenvironmental CO concentrations on a minute-by-minute basis. Fourteen microenvironments were defined for this purpose. Associated with each was a lognormal distribution of one-minute CO values from which one-minute CO exposures were drawn.

The original SHAPE model simulated activity patterns for each individual by sampling from probability distributions representing the chance of entry, the time of entry, and time spent in specific activities or microenvironments (Ott, 1981). For example, the probability distributions for the starting times of home-to-work trips, trip times, and travel modes (the proportion of commuters traveling to work by car, bus, truck, and such) were based on data provided by Svercl and Asin (1973). Reliable data were not available for some activities; in these cases the probability distributions were assumed by the user.

In an attempt to validate SHAPE, Ott et al. (1988) compared measured personal CO exposures obtained from the Denver personal monitoring study to CO exposures estimated by

SHAPE. Microenvironmental CO concentrations for the model were generated by Monte Carlo simulation based on Denver PEM data reported for 22 microenvironments. The activity simulation portions of the model were modified to accommodate actual activity data obtained from the diaries carried by Denver subjects.

A total of 899 24-h responses from the Denver study yielded 772 usable profiles after invalid responses were eliminated, giving 33 paired days of observations (CO exposure profiles from two successive days for the same respondent). From these data, 22 microenvironments were identified with at least 10 measurements on each of the two days. Microenvironmental CO concentrations were calculated by subtracting hourly ambient background CO concentrations. Ambient background CO concentrations were estimated by three different approaches. All three yielded similar results, with the average value from all fixed monitoring sites performing slightly better than the nearest fixed monitoring site. For nearly every microenvironment, the study found negligible differences between the microenvironmental CO frequency distributions on the two days, showing the statistical stability of the microenvironmental concentrations.

In the SHAPE validation project (Ott et al., 1988), the microenvironmental CO frequency distributions for Day 1 provided the basis for SHAPE model estimates of Day 2 exposure profiles, and the activity patterns were based on the Denver diaries for Day 2 (the observed times at which people entered and left each microenvironment). The CO exposure profiles were calculated using Monte Carlo sampling from the Day 1 microenvironmental CO concentration distributions and adding the estimated ambient background components.

The arithmetic means of the predicted one- and eight-hour maximum average CO exposures agreed well with the corresponding observed arithmetic means. The variability of the observed values, however, exceeded the variability of the predicted values by a significant amount (Figures 8-3 and 8-4). Ott et al. (1988) suggested that the lack of agreement may be caused by use of a histogram rather than a continuous distribution in implementing the Monte Carlo simulation or the model's implicit assumption that the successive exposures of a subject are uncorrelated. Ott et al. (1988) suggested that better estimates would result if an autoregressive process was used to model successive exposures.

Commuter Exposure Models – Ott and Willits (1981) conducted a study in which the CO exposures of occupants of a motor vehicle were measured by weekly drives on an urban

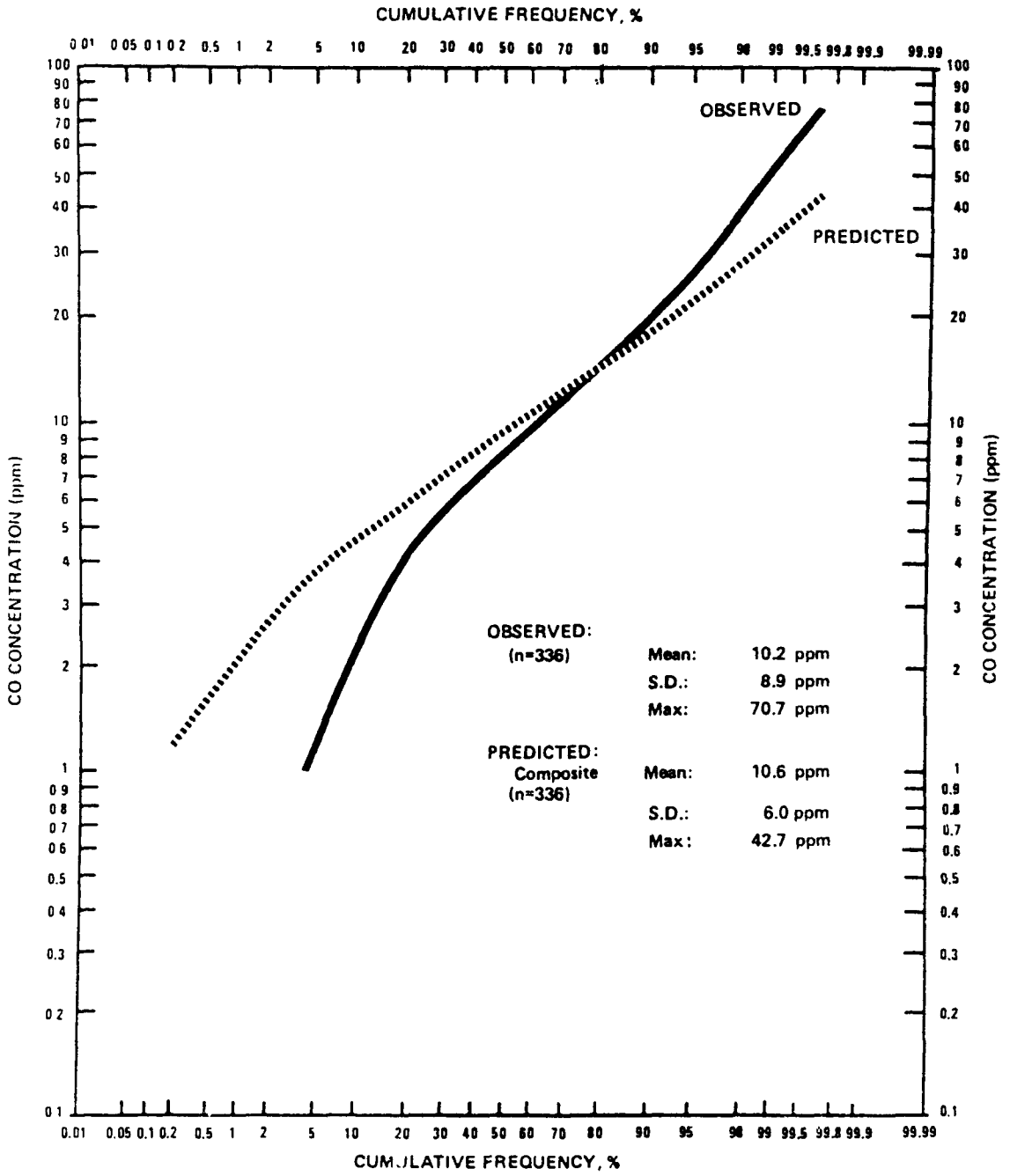

Figure 8-3. Logarithmic-probability plot of cumulative frequency distribution of maximum one-hour average exposure of CO predicted by SHAPE, plus an observed frequency distribution for Day 2 in Denver.

Source: Ott et al. (1988).

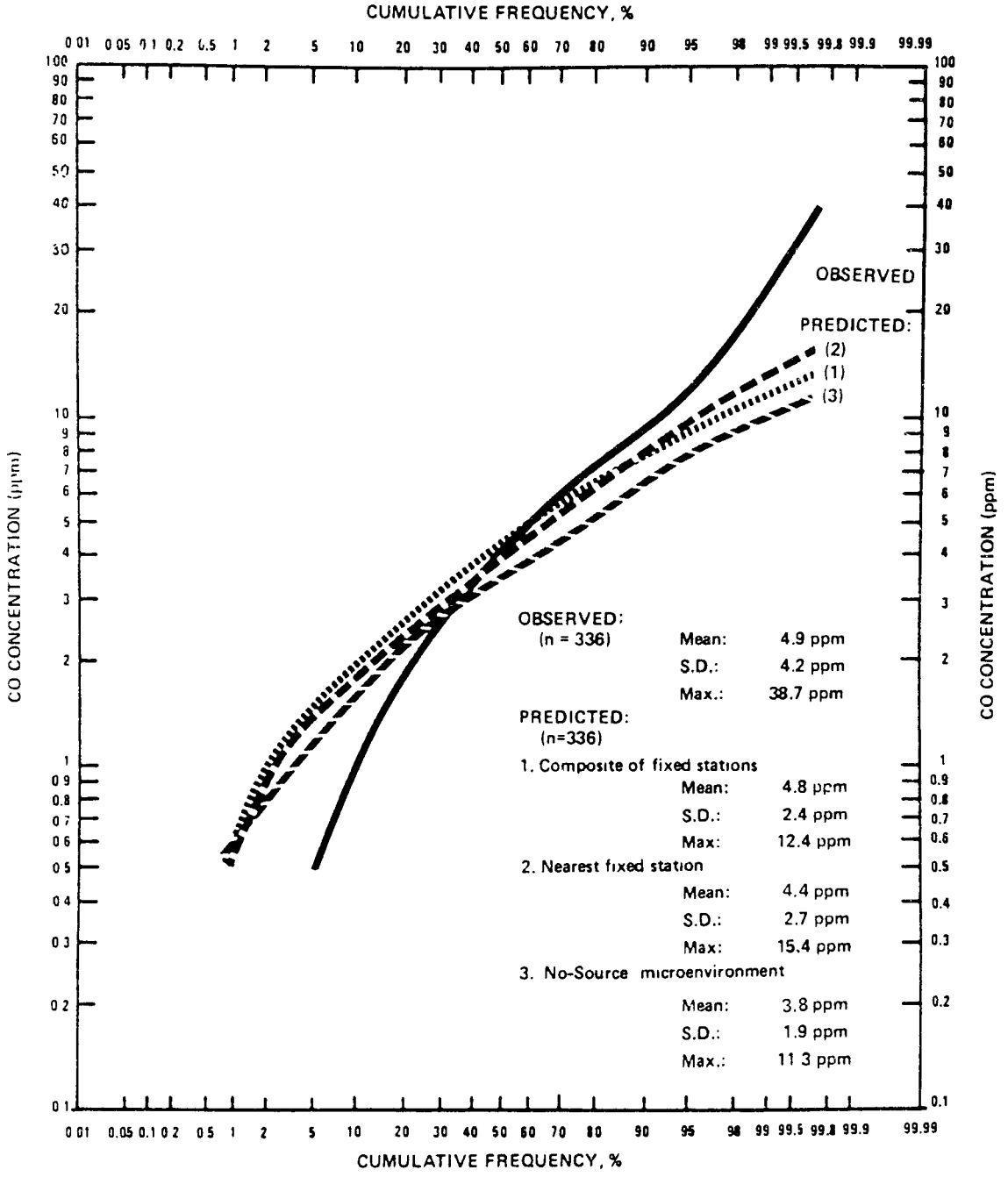

Figure 8-4. Logarithmic-probability plot of cumulative frequency distribution of maximum moving average eight-hour exposure of CO predicted by SHAPE, plus an observed frequency distribution for Day 2 in Denver.

Source: Ott et al. (1988).

artery in California. The study consisted of 93 repeated drives over exactly the same route – 5.9 miles in each direction for an 11.8 mile total distance – on El Camino Real with a 1974 VW test vehicle. Data were collected on CO levels inside the passenger compartment of the motor vehicle, traffic counts and time spent waiting at each traffic light, meteorological factors, as well as other variables. Measurements in the vehicle showed that the passenger compartment was free of self-generated CO intrusion. Ott and Willits developed a theoretical model for estimating diffusion of CO into a motor vehicle and then applied the model to data collected during the study. The model incorporates a time constant that was found to vary according to the position of the windows (closed, partially open, completely open).

Simmon and Patterson (1983) developed a model for simulating commuter exposures individually and collectively based on traffic flow, emissions, and atmospheric dispersion. This model consists of two programs that are run separately on the computer. The first program is an emissions preprocessor, which has been separated from the main model to facilitate updating of the model package when emission factors are revised by EPA. The second program is the main portion of the commuter exposure model, which simulates traffic flow, computes the emission rates resulting from the traffic (using the emission factors calculated by the preprocessor), simulates the dispersive effects of the atmosphere, and computes statistics describing commuter exposure. Because the model treats the spatial variation of exposure, regions of the city in which commuters experience high exposures can be identified from model output. If a single commute pathway is of interest, that pathway can be examined in detail. Dispersion modeling is performed by the CALINE 3 model. In-vehicle CO concentrations are assumed to equal roadway CO concentrations. To date, the Simmon-Patterson model has not been used in a modeling analysis.

Petersen and Sabersky (1975) conducted experiments to measure the CO concentrations inside a vehicle under typical driving conditions during the summer in Los Angeles, CA. They observed that the average CO concentrations inside the vehicle were about equal to the outside air concentrations.

Petersen and Allen (1982) conducted a similar experiment in Los Angeles over 5 days in October 1979. They found that the average ratio of interior to exterior CO concentrations was 0.92. However, the hourly average interior CO concentrations were 3.9 times higher than the fixed-site measurements. In their analysis of the factors that influence interior CO

levels, they observed that traffic flow, and traffic congestion (stop-and-go) are important, but "comfort state" (i.e., car windows open/closed, fan on/off, etc.) and meteorological parameters (i.e., wind speed, wind direction) have little influence on incremental exposures.

Flachsbart (1985) developed three empirical models for predicting commuter exposure inside a well-ventilated vehicle on a congested Honolulu artery during morning rush hour under neutral atmospheric stability. PEMs were used to collect exposure data for commuting trips on 12 days between November 1981 and April 1982. Model A assumed that commuter CO exposure was a function of the roadway's source strength and the ambient CO level, as expressed in the following equation.

$$\text{Commuter CO} = (0.00012728)(\text{CO emissions/mi})^{1.06} + \text{ambient CO} \qquad (8\text{-}5)$$

Model B assumed that the roadway's source strength was diluted by windspeed, as expressed in the following equation.

$$\text{Commuter CO} = (0.0001972)\,\frac{(\text{CO emissions/mi})^{1.039}}{(\text{windspeed})^{0.083}} + \text{ambient CO} \qquad (8\text{-}6)$$

Model C assumed that commuter CO exposure was simply a function of the emission factor and ambient CO level. This model was developed for situations for which the analyst does not have access to traffic counts.

$$\text{Commuter CO} = (0.0713358)(\text{CO emission factor})^{1.289} + \text{ambient CO} \qquad (8\text{-}7)$$

Flachsbart considered these models to be prototypes because they were the first such models to link commuter exposure, inside a vehicle, directly to automotive emission factors. Each model assumed that exposure is an additive function of a background CO level and a roadway CO contribution, as affected by meteorological and traffic characteristics.

Flachsbart compared the observed exposure values with exposures predicted by each of the three models. Correlations between observed and predicted values, expressed as R^2, were 0.78 for Models A and B, and 0.64 for Model C.

Flachsbart's prototypical models (1985) served as model templates in subsequent efforts by Flachsbart and Ah Yo (1989) to develop a general model of commuter exposure based on data obtained from a study of commuter exposures in Washington. Their approach described commuter exposure on a specified commuting link with an expression that superimposes a microenvironment component upon a background concentration:

$$E_i = B_i + M_i \tag{8-8}$$

where:

E_i = commuter exposure on link i,
B_i = background concentration on link i,
M_i = microenvironment concentration on link i.

Ideally, the background concentration should be measured near the link and should reflect concentrations that would exist on the roadway if there were no traffic. Flachsbart (1985) approximated this value with CO ambient air quality readings from the nearest fixed-site station away from heavy traffic. The microenvironment component mathematically describes the air pollutant emission and dispersion processes over the roadway. This component also considers how the air pollutant infiltrates the vehicle's interior. An air pollutant infiltration factor, however, was not included in Flachsbart's prototypal models, since there was a free exchange of air between the vehicle and the ambient environment.

Using the format of the Honolulu prototypal models, Flachsbart and Ah Yo (1989) developed 33 commuter exposure models from the Washington survey data base. Of these models, only five were considered unsatisfactory based on the statistical significance of the model or an illogical sign for the emission coefficient. However, the explanatory power of the best of these models (R^2 = 0.12) did not approach that of the worst Honolulu model (R^2 = 0.63).

Flachsbart and Ah Yo (1989) found use of the Honolulu prototypal models for characterizing the Washington data to be overly simplistic. For morning trips originating in low density suburbs, the Washington data showed that a commuter's average exposure to CO was less than the ambient concentration measured at the fixed-site station providing the background concentration. In addition, commuters, who began their homeward evening trips from highly polluted parking garages, had unusually high concentrations in their cars as they traveled along downtown streets. Tests of each vehicle at the beginning, middle, and end of the study indicated that the high CO levels were not caused by leaks from the exhaust system into the passenger compartment.

These observations suggested that vehicle occupants were, to some degree, "encapsulated" from the ambient environment such that their exposure on the early links of a trip had more to do with the concentration inside the vehicle (prior to the trip) than with any traffic or meteorological factors on these links. Statistical analysis supported this hypothesis. For the evening commute from downtown Washington on Route 1, the average CO exposure on the link was significantly correlated with pretrip interior CO concentrations. For the morning commute into downtown Washington on Route 2, the average link exposure was well correlated with pretrip interior CO concentrations.

Given winter temperatures and closed windows and vents on the test vehicles, Flachsbart and Ah Yo (1989) decided to treat the roadway setting and the vehicular passenger compartment as separate microenvironments. Each microenvironment was modeled separately and then combined into a two-stage model.

The data base available for development of a roadway CO empirical model was limited to 150 measurements of roadway CO. Of 43 different models applied to this data set, the best model was a loglinear relationship between predicted roadway CO concentrations and the density of CO emissions. This density was the product of the CO emission factor and the average 15-min traffic count divided by the test vehicle's average link speed. This model had an R^2 value equal to 0.26; the F statistic was significant at $p<0.0001$. The final step of the regression left two independent variables in the equation: the CO emission factor and the average 15-min traffic count.

The equation for this model was:

$$CO_{RP} = (0.7906252[(F_e)(Q_T)/U_V]^{0.366992} \quad (8\text{-}9)$$

where:

CO_{RP} = predicted CO concentration within the roadway microenvironment (ppm),

F_e = MOBILE3 emission factor estimated using observed traffic speeds, ambient temperatures, the percentages of five vehicle types, and default values for other required inputs (g/veh-mi),

Q_T = observed average 15-min traffic count (veh/15 min),

U_V = test vehicle's average link speed.

Flachsbart and Ah Yo (1989) assumed that commuters are exposed to CO from three major sources within the passenger compartment: passenger smoking, vehicle exhaust system leaks, and emissions from traffic. Flachsbart and Ah Yo (1989) further assumed that the in-vehicle CO concentrations created by these three sources can be described by box or cell models. Such models are based on the principle of conservation of mass: The total mass of an air pollutant within a volume is equal to the balance of the mass entered, exited, emitted, and reacted within that volume. Using this principle, Flachsbart and Yo (1989) derived a theoretical commuter exposure model for the passenger compartment:

$$E = CO_R + (T/t_R)[CO_v - CO_R][1 - e^{(t_R)}/T] \quad (8\text{-}10)$$

where:

E = average CO exposure of the commuter (ppm),
CO_R = observed CO concentration within the roadway microenvironment (ppm),
T = time constant for the vehicle (s),
t_R = time vehicle spends within the roadway microenvironment (s),
CO_v = CO concentration within the vehicle when it enters the microenvironment (ppm),
e = base of a natural logarithm (2.72).

This model predicts commuter exposure to CO inside a vehicle by exponentially diffusing observed roadway concentrations and by exponentially decaying initial compartmental concentrations that exist when the vehicle enters a new link on the roadway. The plot of the observed average CO exposure with average CO exposures estimated with Equation 8-10 suggested a linear relationship. These data had an $R^2 = 0.75$ and the significance of the F statistic was $p<0.001$.

Predicted values CO_{RP} generated by the roadway microenvironmental model (Equation 8-9) were substituted for the observed roadway concentrations CO_R in the passenger compartment model (Equation 8-10). The values estimated by the resulting two-stage model correlated well with the observed values ($R = 0.737$); the coefficient of determination (R^2) indicated that the estimates explained approximately 54% of the variation in observed average exposures. Although the two-stage model did not have the predictive power of the passenger compartment model which used observed roadway CO concentrations, Flachsbart and Ah Yo (1989) considered the performance of the two-stage model to be respectable and far better than any of the 33 models initially developed.

Other Exposure Models – Davidson et al. (1984) developed one- and two-compartment mass-balance models for estimating indoor pollutant concentrations. They compared measured levels of NO, NO_2, and CO in a new townhouse residence with estimates provided by the one-compartment model. The townhouse was constructed according to rigid energy-conservation guidelines. Reasonable agreement between estimated and measured concentrations was observed, although the measured CO levels decayed somewhat faster than predicted.

Pierce et al. (1984) presented a model for estimating integrated (i.e., cumulative) and average exposures based on an activity pattern listing a sequence of indoor and outdoor locations and estimates of the pollutant concentration at each location. The model was used to estimate CO exposures for a hypothetical 24-h activity pattern. The CO level assigned to each location was derived from microenvironmental monitoring data obtained from other researchers.

8.4 OCCUPATIONAL EXPOSURE TO CARBON MONOXIDE

Carbon monoxide is a ubiquitous contaminant occurring in a variety of settings. Exposures, both acute and chronic, that occur in the occupational environment represent only one of several sources that may contribute to a potential body burden for carbon monoxide. Two main sources for background exposures in both occupational and nonoccupational settings appear to be smoking and the internal combustion engine (National Academy of Sciences, 1969). Smoking is a personal habit that must be considered in evaluating exposures in general, as well as those occurring in work places.

In addition, work environments are often located in densely populated areas, and such areas frequently have a higher background concentration of CO compared to less densely populated residential areas. Thus, background exposures during work hours may be greater than during nonwork hours. There are several sources other than smoking and the internal combustion engine that contribute to exposure during work hours. These include contributions to background by combustion of organic materials in the geographic area of the work place, work in specific industrial processes that produce CO, and work in environments that result in accumulations of CO, such as garages, toll booths, and confined spaces.

8.4.1 Historical Perspective

Production of CO results from incomplete combustion of organic substances such as natural gas, coal, wood, petroleum, coal, coke, vegetation, explosives, and manufactured gas. A rich fuel mixture favors generation of CO. Carbon monoxide also can be produced when rapid cooling or submersion of the flame is used to quench the combustion process.

Dangerous concentrations of carbon monoxide can occur in numerous settings, including environmental background, the home, and the street – at work or play. Sources include exhaust gases from internal combustion engines, gas manufacturing plants, blast furnaces in iron and steel manufacturing, coke ovens, coal mines, incinerators, and numerous other processes that involve combustion of organics. CO is used in the manufacture of metal carbonyls, and CO is produced in industrial quantities by the partial oxidation of hydrocarbons or natural gas, and by gasification of coal or coke (Lundgren, 1971). (See Chapter 6 for a more complete discussion of sources and emissions of CO.)

Both chronic and acute CO intoxication in a variety of occupations and processes is discussed by Grut (1949). Acute effects related to production of anoxia from exposures to CO historically have been a basis for concern. In recent years, however, this concern has grown to include concerns for potential effects from chronic exposures as well (Rosenstock and Cullen, 1986a, 1986b; Sammons and Coleman, 1974).

With regard to the occupational environment, the National Institute for Occupational Safety and Health (1972) published "Criteria for a Recommended Standard...Occupational Exposure to Carbon Monoxide." NIOSH observed that "... the potential for exposure to carbon monoxide for employees in the work place is greater than for any other chemical or physical agent." NIOSH recommended that exposure to CO be limited to a concentration no greater than 35 ppm, expressed as TWA for a normal eight-hour workday, 40 hours per week. A ceiling concentration was also recommended at a limit of 200 ppm, not to exceed an exposure time greater than 30 min. Occupational exposures at the proposed concentrations and conditions underlying the basis of the standard were considered to maintain COHb in blood below 5%. The Occupational Safety and Health Administration has recently adopted these exposure limits in order to substantially reduce the risk of deleterious health effects among American workers (Federal Register, 1989).

Although it was not stated, the basis of the recommended NIOSH standard (i.e., maintaining COHb below 5% in blood), assumes that contributions from other nonoccupational sources would also be less than a TWA concentration of 35 ppm. It was recognized that such a standard may not provide the same degree of protection to smokers, for example. Although recognizing that biologic changes might occur at the low level of exposure recommended in the proposed standard, NIOSH concluded that subtle aberrations in the nervous system with exposures producing COHb concentrations in blood at or below 5% did not demonstrate significant impairments which would cause concern for the health and safety of workers. In addition, NIOSH observed that individuals with impairments that interfere with normal O_2 delivery to tissues (e.g., emphysema, anemia, coronary heart disease) may not have the same degree of protection as for less impaired individuals. It also was recognized that work at higher altitudes (e.g., 5000 to 8000 feet above sea level) would necessitate decreasing the exposure limit below 35 ppm, to compensate for a decrease in the oxygen partial pressure as a result of high altitude environments and a corresponding decrease

in oxygenation of the blood. High altitude environments of concern include airline cabins at a pressure altitude of 5000 feet or greater (National Research Council, 1986) or work in high mountain tunnels (Miranda et al., 1967).

8.4.2 Exposure Monitoring Techniques

Exposures to CO in air can be manifested in a variety of ways. At low levels, manifestations include development and reporting of symptoms. In the work place, environmental monitoring and inventory of sources for the presence of CO may occur. Additionally, biologic tests, medical surveillance, diagnosis and treatment may be conducted on individuals who show signs and symptoms of exposure. Finally, mathematical models may be used to predict exposures, doses, and responses to CO inhalation.

Acute and chronic CO intoxication (Grut, 1949) may be indicated by a range of signs and symptoms from headache, dizziness, weakness, and nausea at low levels and short durations of exposure to unconsciousness, coma, and death at high levels and durations of exposure. Headache and nausea resulting from CO intoxication has been described in a study of tollbooth collectors (Johnson et al., 1974) exposed at low concentrations of CO from exhaust gases.

A medical study of the occupational hazards of fire fighting demonstrates the signs and symptoms of CO, as well as other associated exposures (Gordon and Rogers, 1969). A group of 35 fire fighters were evaluated in a medical study for heart, lung, liver, and kidney diseases, and were also provided neurologic examinations. Half of the study group were smokers. Baseline tests including enzyme tests, EKG, COHb, and other measurements were conducted at the start of the study. The fire fighters were in normal ranges for COHb and the enzyme tests performed. They were followed through 31 fires of less than five minutes, 4 fires of more than five minutes, and 6 staged fires; they were also subjected to exercise tests. Occasionally, there were substantial exposures to CO, and changes in blood enzyme levels were greater when fighting longer fires. These changes were not associated with exercise, and they were reversible when not fighting fires. EKG tests did not reflect changes related to enzyme levels. Masks were found to provide substantial protection.

Occupational exposure and associated signs and symptoms for fire fighters also have been described in a study using age-matched controls (Sammons and Coleman, 1974). Blood

samples were collected from a group of 27 fire fighters and a group of 27 control subjects every 28 days for five months. Differences between the cardiac enzyme levels found in fire fighters versus those of the matched control suggested that chronic low level exposures to CO have a deleterious effect on the body and myocardium.

Environmental monitoring for CO is often carried out in studies that are primarily concerned with potential exposures to other substances, such as exhaust gases, environmental tobacco smoke and combustion processes. CO analyses also are used to screen for the presence of other gaseous pollutants. Exposures to CO therefore are often associated with exposures to other substances as well, including lead, particulate matter containing polyaromatic hydrocarbons (PAHs), NOs, and SO_2.

Monitoring for exposures to CO has included peak and TWA sampling of ambient or breathing zone air, collection and analysis of expired air, analysis of blood gases by gas chromatographic methods, and use of empirical relationships to estimate CO in air from determinations of percent COHb in blood. Measurements techniques for CO include infrared, volumetric, colorimetric tubes, electrolytic detection, and gas chromatographic methods. Samples are collected to represent the breathing zone or environmental air; these may be grab samples or periodic or continuous samples.

Several investigators have proposed approaches to medical surveillance of workers who are potentially exposed to carbon monoxide. Medical surveillance activity is usually precipitated by complaints that are associated with a source of potential exposure to CO. A recent study of stevedores who loaded and unloaded cars and diesel trucks in a ferrying operation (Purdham et al., 1987), assessed medical conditions by administering a questionnaire and conducting pulmonary function tests. The questionnaire included questions on work history; smoking history; respiratory symptoms; and nose, eye, and skin complaints. Questions on respiratory symptoms included details on cough, sputum, wheeze, chest tightness, and shortness of breath. Pulmonary function tests were conducted for forced vital capacity (FVC) and forced expiratory volume at one minute (FEV_1). The subjects were seated and their noses were clipped closed for the tests. A minimum of three and as many as six efforts were required for each subject.

The focus of the study was on characterizing adverse responses to exhaust fumes, primarily from diesel trucks, and secondarily from gasoline-powered vehicles transported in

garages on the ferry. The medical findings were that the stevedores had significantly lower values for all lung function tests except for FVC, as compared to unexposed controls, and to normal values for a general population. Environmental sampling for CO and other substances in exhaust fumes then were conducted. There was no direct correlation offered by the authors between exposure to CO and the differences found in the medical assessments of the stevedores versus the controls. The authors suggested use of percent COHb to assess CO exposure, and they recommended that a larger group of longshoreman should be assessed for chronic obstructive pulmonary disease.

Rosenstock and Cullen (1986a) have linked cardiovascular diseases occasioned by angina at the end of a workday with high percent COHb when this phenomenon is associated with exposure to CO in the work place. Consequences of chronic low level exposure are not well established; however, in workers with underlying coronary artery heart disease, a level of 3 to 5% COHb has been associated with increasing frequency of angina and decrease in exercise tolerance (See Chapter 10). When levels approaching 25% COHb are reached, there are manifestations of ischemia, dysrhythmias and EKG abnormalities in otherwise healthy workers.

Miranda et al. (1967) feel that medical surveillance for high altitude work should include screening for cardiopulmonary abnormalities and blood dyscrasias (sickle-cell anemia). They also recommend acclimatization before the start of work.

This study classified the onset of CO intoxication into three groups: fulminating (a decrease in O_2 to tissues within seconds), acute (a decrease in O_2 occurring in minutes), and chronic (a decrease in O_2 oxygen to tissues over days, months, or years).

Miranda et al. (1967) listed the concerns for evaluation of CO exposures at high altitudes as: decreased oxygen in the air, percent COHb due to smoking, and accumulation of fumes, particularly in vehicular tunnels. Altitude tolerance is lowered by about 335 ft for each percentage point increase in COHb. The average percent COHb for smokers who smoke 20 to 30 cigarettes per day is 5%, with a range of 3 to 10%. To decrease from 20 to 5% COHb requires breathing fresh air at sea level for three to five hours. Inhalation of CO at a concentration of 100 ppm for two hours at 11,000 feet results in 18 $\pm$ 5% COHb. This level does not threaten survival, but it may impair visual threshold (see Chapter 10).

Empirical relationships have been proposed for use as diagnostic criteria for CO intoxication (Castellino, 1984). The criteria proposed are shown in Table 8-10.

Blankart et al. (1986) found hyperbaric O_2 to be the best form of treatment for decreasing the percent COHb in blood when it was administered to traffic policemen in a clinical study. The study compared cycling ergometry, administration of pure O_2 at atmospheric pressure, and administration of pure O_2 under hyperbaric conditions (2.8 atm). The authors recommended the hyperbaric treatment approach for both acute and chronic CO poisoning.

A study of toll bridge authority workers investigated normal red cell adaptation to anemia as a measure of CO effects on tollbooth collectors and maintenance personnel (Goldstein et al., 1975). Diphosphoglycerides (DPG) increase the release of oxygen to tissues as an adaptive mechanism in anemia. Results of the studies were inconclusive, in that they considered increased DPG to be a response to hypoxia from increased percent COHb. However, formation of methoxyhemoglobin from exposures to NO was independent of the COHb reaction, and the hypoxic effects of CO and NO exposures were considered to be additive.

Use of percent COHb in blood has been proposed for use as a biological exposure index (BEI), as a supplement to the threshold limit value (TLV) value for CO exposure recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) (Lowry, 1986). The proposed BEI is intended to be an index of exposure. It is not necessarily an indication of an adverse response.

Finally, Hickey et al. (1975) expressed the need to consider genetic and other factors resulting in differences in hemoglobin and other individual characteristics that could influence the extent of COHb formation on exposures to CO in air or cigarette smoke.

8.4.3 Occupational Exposures

The number of persons potentially exposed to CO in the work environment is greater than that for any other physical or chemical agent (Hosey, 1970), with estimates as high as 975,000 occupationally exposed at high levels (National Institute for Occupational Safety and Health, 1972).

TABLE 8-10. DIAGNOSTIC CRITERIA FOR CO INTOXICATION

Normal		Abnormal
Nonsmokers	Smokers	Increased Surveillance
COHb <3%	COHb <8%	COHb 8 to 12%
SCN/blood <40 mg/L	SCN/blood <200 mg/L	
		Increased Risk
		COHb 12 to 15%
		Medical Treatment COHb > 15%

Source: Castellino (1984).

The contribution of occupational exposures can be separated from other sources of exposure, but there are at least two conditions to consider.

(1) When CO concentrations at work are higher than the CO equilibrium concentration associated with the percent COHb at the start of the work shift, there will be a net absorption of CO and an increase in percent COHb. Nonsmokers will show an increase that is greater than that for smokers because they start from a lower baseline COHb level. In some cases, nonsmokers may show an increase, and smokers a decrease in percent COHb.

(2) When CO concentrations at work are lower than the equilibrium concentration necessary to produce the worker's current level of COHb, then the percent COHb will show a decrease. There will be a net loss of CO at work.

Occupational exposures can stem from two sources: (1) through background concentrations of CO obtained by working in a densely populated area (as compared to the residential environment), or (2) through work in industrial processes that produce CO as a product or by-product. In addition, work in environments that tend to accumulate CO concentrations may result in occupational exposures. Rosenman (1984) lists a number of occupations where the workers may be exposed to high CO concentrations. This list includes acetylene workers, blast furnace workers, coke oven workers, diesel engine operators, garage

mechanics, steel workers, metal oxide reducers, miners, mond process (nickel refining) workers, organic chemical synthesizers, petroleum refinery workers, pulp and paper workers, and water gas workers. In addition, because methylene chloride is metabolized to CO in the body, aerosol packagers, anesthetic makers, bitumen makers, degreasers, fat extractors, flavoring makers, leather finish workers, oil processors, paint remover makers, resin makers, solvent workers, and stain removers also can have high COHb levels.

Background sources are generally a result of combustion of organic materials. With rich fuel mixtures, decreased amounts of O_2 are available, and therefore production of CO as a product of incomplete combustion is favored. There are numerous sources for CO background exposures, and there is considerable variation and uncertainty in identifying the CO exposure resulting from specific sources. Traffic patterns and emissions from mobile sources, as well as an overlay of emissions from stationary sources along with wind and weather conditions, make predictions difficult. (See Chapters 6 and 7 for a complete discussion of the mobile, stationary, and indoor sources and emissions of CO.)

Investigations and analyses of exhaust gas in Paris (Chovin, 1967) showed that CO air concentrations were correlated with the activity of and distribution pattern for traffic in Paris. The average CO concentrations for the years 1965 and 1966 were 16.0 and 16.6 ppm, based on 15,187 samples for 1965 and 15,203 samples for 1966, respectively. The maps of pollutant distribution indicate that the areas of high and low concentrations were similar for each year and were closely associated with the volumes and patterns of vehicular traffic. When the measured concentration of CO in the air exceeded 100 ppm, the sample was automatically diluted 10-fold for analysis, thereby introducing dilution and scale factors as possible sources of error at high concentrations of CO. The variations in the measurements of CO were closely linked to variations in the volume of traffic at each sampling location. Carbon Monoxide concentrations in the blood were determined for 331 traffic policemen during 5 hours of duty. Blood samples were collected at the beginning and end of the five-hour shifts. Carbon monoxide in blood was determined by heating samples and measuring the evolved gas by an infrared method. The values obtained were compared with the average concentrations of CO found for the air breathed. The correlation was good between CO in blood and CO in the air breathed for nonsmokers, but with smokers, initial concentrations of CO in blood were high, and there was often a decrease in the CO in blood over an exposure

period. This was observed with sampling of smokers and nonsmokers at the same locations with similar concentrations and durations of exposure. Car drivers showed increases in CO concentrations in blood, as did traffic policemen who were nonsmokers. Carbon Monoxide concentrations in blood for smoking and nonsmoking drivers involved in traffic accidents were greater than those for traffic policemen and others in the population considered to be accidentally exposed to CO.

Aircraft accidents involving 113 aircraft, 184 crew members, and 207 passengers were investigated to characterize accident toxicology and to aid in search for causation of a crash (Blackmore, 1974). Determinations of percent COHb in blood samples obtained from victims enabled differentiation of a variety of accident sequences involving fires. For example, percent COHb determinations combined with passenger seating information and crew assignments can allow differentiating between fire in flight or after the crash, survivability of crash with death due to smoke inhalation, specific equipment malfunctions in equipment operated by a particular crew member, or defects in space heating in the crew cabin or passenger compartment. One accident in the series was associated with a defective space heater in the crew compartment. Another accident also was suspicious with regard to a space heater.

Contributions to background CO concentrations from industrial processes may be determined by an inventory of sources and locations for the processes, as well as by emission rates for CO as a function of production, and the air pollution distribution pattern for the region (see Chapter 6). The types and distributions of industrial and community activities contributing to CO concentrations in air depend on identification of the various sources and volumes of production involved. Production schedules are dynamic; it is therefore difficult to model sources and predict levels.

Carbon monoxide concentrations measured in the air were used to classify workers from 20 foundries into three groups: those with definite occupational exposure, those with slight exposure, and controls (Hernberg et al., 1976). Angina pectoris, EKG findings, and blood pressures of foundry workers were evaluated in terms of CO exposure for the 1000 workers who had the longest occupational exposures for the 20 foundries. Angina showed a clear dose response with exposure to CO either from occupational sources or from smoking, but there was no such trend in EKG findings. The systolic and diastolic pressures of CO-exposed

workers were higher than those for other workers, when age and smoking habits were considered.

Carboxyhemoglobin and smoking habits were studied for a population of steel workers and compared to blast furnace workers, as well as to employees not exposed at work (Jones and Walters, 1962). Carbon monoxide is produced in coke ovens, blast furnaces, and in sintering operations. Exhaust gases from these operations are often used for heating and as fuels for other processes. Fifty-seven volunteers working in the blast furnace area were studied for smoking habits, symptoms of CO exposure, and estimations of COHb levels by an expired air technique. The main increase in COHb for blast furnace personnel was 2.0% for both smokers and nonsmokers in the group. For smokers in the unexposed control group, there was a decrease in percent COHb. A follow-up study found similar results (Butt et al., 1974). Virtamo and Tossavainen (1976) report a study of CO measurements in air of 67 iron, steel, or copper alloy foundries. Blood COHb of ironworkers exceeded 6% in 26% of the nonsmokers and 71% of the smokers studied.

Poulton (1987) found that a medical helicopter with engine running in a narrowed or enclosed helipad was found to be a source of potential exposure to CO, JP-4 fuel and possibly other combustion products for flight crews, medical personnel, bystanders and patients being evacuated. Measurements were made by means of a portable infrared analyzer. Carbon monoxide concentrations were found to be greatest near the heated exhaust. Concentrations ranged from 8 ppm to 43 ppm.

Exhaust from seven most commonly used chain saws (Nilsson et al., 1987) were analyzed under laboratory conditions to characterize emissions. The investigators conducted field studies on exposures of loggers using chain saws in felling operations, and also in limbing and bucking into lengths. In response to an inquiry, 34% of the loggers responded that they often experienced discomfort from the exhaust fumes of chainsaws, and another 50% complained of occasional problems. Sampling for CO exposures was carried out for five days during a two-week work period in a sparse pine stand at an average wind speed of 0 to 3 m/s, a temperature range of 16 to 1°C, and a snow depth of 50 to 90 cm. Carbon monoxide concentrations ranged from 10 to 23 mg/m^3 (9 to 20 ppm) with a mean value of 20.0 mg/m^3. Carbon monoxide concentrations measured under similar but snow free conditions ranged from 24 to 44 mg/m^3 with a mean value of 34.0. In another study, CO

exposures were monitored for nonsmoking chain saw operators with average exposures recorded from 20 to 55 ppm with COHb levels ranging from 1.5 to 3.0% (Van Netten et al., 1987).

Fork lift operators, stevedores and winch operators were monitored for CO in expired air to calculate percent COHb, using an MSA analyzer (Breysse and Bovee, 1969). Periodic blood samples were collected to validate the calculations. Bull operators and stevedores work in the holds of ships; winch operators do not work in the holds. The ships to be evaluated were selected on the basis of their use of gasoline-powered fork lifts for operations. To evaluate seasonal variations in percent COHb, analyses were performed for one five-day period per month for a full year. Efforts were made to select a variety of ships for evaluation. A total of 689 determinations of percent COHb were made from blood samples to compare with values from expired air samples. The samples were collected on 51 separate days involving 26 different ships. Two hundred men were available before work, while only 147 were available at the end of the work day. Men lost to follow-up either left before the end of shift or were transferred to other work. Smoking was found to be a major contributing factor to percent COHb levels found. Carboxyhemoglobin values for nonsmokers indicated that the use of gasoline powered lifts in the holds of the ships did not produce a CO concentration in excess of 50 ppm for up to eight hours as a TWA under the work rules and operating conditions in practice during the study. Smoking behavior confounded exposure evaluations. The exposure conditions may not provide the same degree of protection for smokers as they do for nonsmokers.

Carbon monoxide concentrations have been measured in a variety of work places where potential exists for accumulation from outside sources. Exposure conditions in work places, however, are substantially different. There is no standard approach that applies in all situations requiring evaluation and study. The methods to be applied, group characteristics, jobs being performed, smoking habits, and physical characteristics of the facilities themselves introduce considerable variety in the approaches used. Typical studies are discussed below.

Wallace (1983) investigated CO in air and breath of employees working in an office constructed in an underground parking garage at various times over a one-month period. Carbon monoxide levels were determined by use of a device containing a proprietary solid polymer electrolyte to detect electrons emitted in the oxidation of CO to CO_2. The device

was certified by the Mine Safety and Health Administration (MSHA) to be accurate within 15%. A data logger was attached to provide readings each second, and to provide one-hour averages from the CO monitors placed on desks. Variation in CO measurements in ambient air showed a strong correlation with traffic activity in the parking garage. Initially, the office CO levels were found to be at an average of 18 ppm per day with the average from 12:00 to 4:00 p.m. at 22 ppm and from 4:00 to 5:00 p.m. at 36 ppm. Analyses of expired air collected from a group of 20 nonsmokers working in the office showed a strong correlation with ambient air concentrations for CO and traffic activity. For example, the average CO in expired air for one series of measurements was 23.4 ppm, as compared to simultaneous measurements of air concentrations of CO at 22 to 26 ppm. After a weekend, CO concentrations in breath on Monday morning were substantially decreased (around 7 ppm) but rose again on Monday afternoon to equal the air levels of 12 ppm. Closing fire doors, and the use of existing garage fans decreased CO concentrations in the garage offices to 2 ppm or less, concentrations similar to those for other offices in the complex that were located away from the garage area.

Carboxyhemoglobin levels (Ramsey, 1967) were determined over a three-month period during winter months for 38 parking garage attendants, and the values for COHb were compared with values from a group of 27 control subjects. Blood samples were collected by finger stick on Monday mornings at the start of the work week, at the end of the work shift on Mondays and at the end of the work week on Friday afternoons. Hourly analyses were carried out on three different weekdays using potassium palado sulfite indicator tubes for the concentrations of CO at three of the six garages in the study. Hourly values ranged from 7 to 240 ppm, and the composite mean of the 18 daily averages was 58.9 $\pm$ 24.9 ppm. While the Monday versus Friday afternoon values for COHb were not significantly different, there were significant differences between Monday morning and Monday afternoon values. Smokers showed higher starting baseline values, but there was no apparent difference in net increase in COHb body burden between smokers and nonsmokers. COHb values for nonsmokers ranged from a mean of 1.5 $\pm$ 0.83% for the a.m. samples to 7.3 $\pm$ 3.46% for the p.m. samples. For smokers these values were 2.9 $\pm$ 1.88% for the a.m. and 9.3 $\pm$ 3.16% for the p.m. The authors observed a crude correlation between daily average for CO in air and COHb values observed for a two-day sampling period.

In a study of motor vehicle examiners conducted by NIOSH (Stern et al., 1981) CO levels were recorded in six outdoor motor vehicle inspection stations with TWA levels of 4 to 21 ppm. In contrast, the semi-open and enclosed stations had levels of 10 to 40 ppm TWA. The levels exceeded the recommended NIOSH standard of 35 ppm TWA on 10% of the days sampled. In addition, all stations experienced peak short-term levels above 200 ppm.

Carboxyhemoglobin levels were measured for 22 employees of an automobile dealership during the winter months when garage doors were closed and ceiling exhaust fans were turned off (Andrecs et al., 1979). Employees subjected to testing included garage mechanics, secretaries, and sales personnel. This included 17 males aged 21 to 37 and five females aged 19 to 36. Blood samples were collected on a Monday morning before start of work, and on Friday at the end of the work week. Analysis for COHb was by addition of sodium dithionite and tris aminomethane, and COHb was measured in duplicate samples using a spectrophotometer. Smokers working in the garage area showed a Monday mean value for COHb of 4.87 $\pm$ 3.64% and a Friday mean value of 12.9 $\pm$ 0.83%. Nonsmokers in the garage showed a corresponding increase in COHb, with a Monday mean value of 1.50 $\pm$ 1.37% and a Friday afternoon mean value of 8.71 $\pm$ 2.95%. Nonsmokers working in areas other than the garage had a Friday mean value of 2.38 $\pm$ 2.32%, which was significantly lower than the mean values for smokers and nonsmokers in the garage area. Environmental concentrations or breathing zone samples for CO were not collected. The authors concluded that smokers have a higher baseline level of COHb than do nonsmokers, but both groups show similar increases in COHb during the work week while working in the garage area. The authors observed that the concentrations of COHb found in garage workers were at levels reported to produce neurologic impairment. These results are consistent with those reported by Amendola and Hanes (1984). They reported some of the highest indoor levels collected at automobile service stations and dealerships. Concentrations ranged from 16.2 to 110.8 ppm on cold weather to 2.2 to 21.6 ppm in warm weather.

A group of 34 employees, 30 men and 4 women, working multi-story garages, were evaluated for exposures to exhaust fumes (Fristedt and Akesson, 1971). Thirteen were service employees working at street level, and 21 were shop employees working either one story above or one story below street level. Six facilities were included in the study. Blood samples were collected on a Friday at four facilities, on Thursday and Friday at another, and

on a Thursday only at a sixth facility. The blood samples were evaluated for red blood cell (RBC), and white blood cell (WBC) counts, COHb, lead and delta-ALA. Work histories, medical case histories, and smoking habits were recorded. Among the employees evaluated, 11 of 24 smokers and 3 of 10 nonsmokers complained of discomfort from exhaust fumes. Smokers complaining of discomfort averaged 6.6% COHb and nonsmokers complaining averaged 2.2% COHb. The corresponding values for non-complaining workers averaged 4.2% and 1.1%, respectively.

Air pollution by CO in underground garages was investigated as part of a larger study of traffic pollutants in Paris (Chovin, 1967). Work conducted between the hours of 8:00 a.m. and 10:00 p.m. resulted in exposures in excess of 50 ppm and up to 75 ppm, on a TWA basis.

As part of a larger study of CO concentrations and traffic patterns in Paris (Chovin, 1967), samples were taken in road tunnels. There was good correlation between traffic volumes combined with the lengths of the tunnels and CO concentrations found. None of the tunnels studied had mechanical ventilation. The average CO concentrations in the tunnels were 27 and 30 ppm for 1965 and 1966, respectively, as compared to an average of 24 ppm CO in the streets for both years. The "real average risk" for a man working or walking in a street or tunnel was considered by the authors to be 3 to 4 times less than the maximal risk indicated by values for CO from instantaneous air sample measurements. In the United States, Evans et al. (1988) studied bridge and tunnel workers in metropolitan New York City. The average COHb concentration over the 11 years of study averaged 1.73% for nonsmoking bridge workers and 1.96% for tunnel workers.

In a discussion of factors to consider in CO control of high altitude highway tunnels, Miranda et al. (1967) reviewed the histories of several tunnels. Motor vehicles were estimated to emit about 0.1 lb of CO/mi at sea level. At 11,000 feet and a grade of 1.64%, emissions were estimated at 0.4 lb/mi (for vehicles moving upgrade). Tunnels with ventilation are generally designed to control CO concentrations at or below 100 ppm. The Holland Tunnel in New York was reported to average 65 ppm, with a recorded maximum of 365 ppm due to a fire. For the Sumner Tunnel in Boston, ventilation is started at CO concentrations of 100 ppm and additional fans are turned on with the sounding of an alarm at 250 ppm. The average value for CO concentration is 50 ppm. The Mont Blanc Tunnel is

7.2 mi long at an average elevation of 4179 ft. This tunnel is designed to maintain CO concentrations at or below 100 ppm. The Grand Saint Bernard tunnel is 3.5 mi long at an average elevation of 6000 feet. The tunnel is designed to maintain CO concentrations at or below 200 ppm. For the tunnel at 11,000 feet, the authors recommended maintaining CO concentrations at or below 25 ppm for long-term exposures, and no greater than 50 ppm for peaks of one-hour exposure. The recommendations are based on considerations of a combination of hypoxia from lack of O_2 due to the altitude and stress of CO exposures of workers and motorists. The authors recommend that warning signs and notices be posted to warn susceptible individuals to take another route.

Carbon monoxide exposures of tollbooth operators were studied along the New Jersey Turnpike. The results reported by Heinold et al. (1987), indicated peak exposures for one-hour ranged from 12 to 24 ppm with peak eight-hour exposures of 6 to 15 ppm.

Carboxyhemoglobin levels were determined for 15 nonsmokers at the start, middle, and end of a 40-day submarine patrol (Bondi et al., 1978). Values found were 2.1%, 1.7%, and 1.7%, respectively. The average ambient air concentration for CO was 7 ppm. The authors observed that the levels of percent COHb found would not cause significant impairment of the submariners.

In contrast, Iglewicz et. al. (1984) found in a 1981 study that CO concentrations inside ambulances in New Jersey were often above the EPA eight-hour standard of 9 ppm. For example, measurements made at the head of the stretcher exceeded 9 ppm on nearly 27% of the 690 vehicles tested, with 4.2% (29 vehicles) exceeding 35 ppm.

Environmental tobacco smoke (ETS) has been reviewed (National Research Council, 1986) for contributions to air contaminants in airliner cabins, and to potential exposures for passengers and flight crew members. ETS is described as a complex mixture containing many components. Analyses of CO content and particulate matter in cabin air were used as surrogates for the vapor phases and solid components of ETS, respectively. A mathematical model was developed and used to calculate the dilution of contaminants by outside make-up air. Total emissions for CO in mainstream smoke range from 10,000 to 23,000 mg per cigarette. More CO is emitted in sidestream smoke; the ratio of sidestream smoke to mainstream smoke ranges from 2.5:1 to 4.7:1. This ratio depends on the length of time a cigarette is held without active smoking compared to the total inhalation and smoking time.

The amount of CO in the cabin environment depends on the rate and number of cigarettes smoked, and on the rate of dilution by outside make-up air. An additional factor to consider is the influence of pressure altitude on the absorption of CO and other gases. The legal limit for pressure altitude is 8000 feet. The partial pressure of O_2 is 120 mm Hg assuming 20% O_2 in the cabin air, compared to 152 mmHg at sea level. It is possible that the absorption rate for CO would be increased under hypobaric conditions.

An examination of CO hazard in city traffic for policemen in three Swedish towns (Gothe et al., 1969) showed that the increases observed in the percent COHb in blood for a group of 28 policemen were associated with exposures to exhaust fumes from heavy traffic. Conversely, results from studies of 28 traffic policemen who were smokers and had relatively high percent COHb in blood at the beginning of a work period either showed no change, or showed a decrease in percent COHb while exposed to exhaust fumes in directing traffic. Exposures were higher in a larger, more congested city, as compared to two smaller cities in the study.

Carbon monoxide levels in city driving in Los Angeles were measured using a prototype CO measuring device mounted in the passenger seat (Haagen-Smit, 1966). Carbon monoxide concentrations were continuously monitored and were sampled by means of a glass tube projecting through the window. Typical commuting trips were made throughout the downtown Los Angeles area during commuting hours. The distance traveled was about 30 mi. The shortest time was 40 min and the longest time was one-hour and 55 min. Concentrations of CO averaged 37 ppm for the best trips, with an average of 54 ppm in heavy traffic moving at 20 mph; peak CO concentrations reached as high as 120 ppm.

A study of municipal bus drivers in the San Francisco Bay area by Quinlan et al. (1985) showed a TWA of 1 to 23 ppm, with mean TWA = 5.5 ppm and standard deviation of 4.9 ppm. The peak exposures ranged from 7 to 47 ppm with mean 25.3 ppm and standard deviation of 12.5 ppm.

Cooke (1986) reports finding no significant increases outside normal ranges, as compared to the general population, for levels of blood lead and COHb in a group of 13 roadside workers. Samples were collected in the afternoon of a workday. Among the subjects, 7 to 13 were smokers and showed percent COHb in blood ranging from 3.0 to 8.8 (mean of 5.5%). Each nonsmoker percent COHb ranged from 0.5 to 1.4 (mean of 1.2%).

Each smoker had smoked at least one cigarette in the four hours preceding collection of blood samples. No samples were collected before start of work, and no measurements of CO in air at the work sites were presented.

8.5 BIOLOGICAL MONITORING

A unique feature of carbon monoxide exposure is that there is a biological marker of the dose that the individual has received: the blood level of CO. This level may be calculated by measuring blood COHb or by measuring CO in exhaled breath.

8.5.1 Blood Carboxyhemoglobin Measurement

Carbon monoxide in the inspired air is rapidly transferred to the blood in the alveoli at a rate that is dependent upon several physiological variables. The blood level of CO is conventionally represented as a percentage of the total Hb available (i.e., the percentage of Hb that is in the form of percent COHb or simply COHb). The high affinity of CO for Hb has the effect of retaining the bulk (90 to 95%) of the absorbed gas in the vascular space and at the same time amplifying the exposure. This latter phenomenon occurs because the affinity of Hb for CO is 200 to 250 times that for O_2 (Douglas et al., 1912) resulting in a relatively high COHb level at very low partial pressures of CO in the alveolar gas phase. The primary physical and physiological variables that determine the relationship between ambient exposure and blood levels of CO are presented in detail in Chapter 9.

8.5.1.1 Measurement Methods

Any technique for the measurement of CO in blood must be specific for CO and have sufficient sensitivity and accuracy for the purpose of the values obtained. The majority of technical methods that have been published on measurement of CO in blood have been for forensic purposes. These methods are less accurate than generally required for the measurement of low levels of COHb (<5% COHb). Blood levels of CO resulting from exposure to existing NAAQS levels of CO would not be expected to exceed 5% COHb in nonsmoking subjects. The focus of the forensic methods has been the reliability of measurements over the entire range of possible values: from less than 1% to 100% COHb.

These forensically oriented methods are adequate for the intended use of the values and the nonideal storage conditions of the samples being analyzed.

In the areas of exposure assessment and low level health effects of CO, it is more important to know the accuracy of any method in the low level range of 0 to 5% COHb. There is little agreement upon acceptable reference methods in this range nor are there accurate reference standards available in this range. The use of techniques that have unsubstantiated accuracy in the low range of COHb levels can lead to considerable differences in estimations of exposure conditions. Measurement of low levels of CO in blood demands careful evaluation because of the implications based upon this data for the setting of air quality standards. Therefore this section will focus on the methods that have been evaluated at levels below 10% COHb and methods that have been extensively used in assessing exposure to CO.

The measurement of CO in blood can be accomplished by a variety of techniques that have been divided into destructive and nondestructive methods (U.S. Environmental Protection Agency, 1979). Carboxyhemoglobin can be determined nondestructively by observing the change in the absorption spectrum in either the Soret or visible region brought about the combination of CO with Hb. With present optical sensing techniques, however, all optical methods are limited in sensitivity to approximately 1% of the range of expected values. If attempts are made to expand the lower range of absorbances, sensitivity is lost on the upper end where, in the case of COHb, total Hb is measured. For example, in the spectrophotometric method described by Small et al. (1971), a change in absorbance equal to the limits of resolution of 0.01 units can result in a difference in 0.6% COHb. Therefore, optical techniques can not be expected to obtain the resolution that is possible with other means of detection of CO (Table 8-11). The more sensitive (higher resolution) techniques require the release of the CO from the Hb into a gas phase that can be detected directly by: (1) infrared absorption (Coburn et al., 1964; Maas et al., 1970) following separation using gas chromatography; (2) the difference in thermal conductivity between CO and the carrier gas (Allred et al., 1989; Ayres et al., 1966; Dahms and Horvath, 1974; Goldbaum et al., 1986; Horvath et al., 1988; McCredie and Jose, 1967); (3) the amount of ionization following quantitative conversion of CO to CH_4 and ionization of the CH_4 (Clerbaux et al., 1984; Collison et al., 1968; Constantino et al., 1986; Dennis and Valeri, 1980; Guillot et al.,

TABLE 8-11. COMPARISON OF REPRESENTATIVE METHODS FOR ANALYSIS OF CARBON MONOXIDE IN BLOOD

Source	Method	Resolution[a] ml/dl	CV%[b]	Reference Method	r[c]
Gasometric Detection					
Scholander and Roughton (1943)	Syringe-capillary	0.02	2 to 4%	Van Slyke	ND[d]
Horvath and Roughton (1942)	Van Slyke	0.03	6%	Van Slyke-Neill	ND
Spectrophotometric Detection					
Coburn et al. (1964)	Infared	0.006	1.8%	Van Slyke-Syringe	ND
Small et al. (1971)	Spectro-photometry	0.12	ND	Flame Ionization	ND
Maas et al. (1970)	CO-Oximeter (IL 182)	0.21	5%	Spectrophotometric	ND
Brown (1980)	CO-Oximeter (IL-282)	0.2	5%	Flame Ionization	0.999
Gas Chromatography					
Ayres et al. (1966)	Thermal conductivity	0.001	2.0%	ND	ND
Goldbaum et al. (1986)	Thermal conductivity	ND	1.35%	Flame Ionization	0.996
McCredie and Jose (1967)	Thermal conductivity	0.005	1.8%	ND	ND
Dahms and Horvath (1974)	Thermal conductivity	0.006	1.7%	Van Slyke	0.983
Collison et al. (1968)	Flame ionization	0.002	1.8%	Van Slyke	ND
Kane (1985)	Flame ionization	ND	6.2%	CO-Oximeter	1.00
Vreman et al. (1984)	Mercury vapor	0.002	2.2%	ND	ND

[a]The resolution is the smallest detectable amount of CO or the smallest detectable difference between samples.

[b]Coefficient of variation was computed on samples containing less than 15% COHb, where possible.

[c]The r value is the correlation coefficient between the technique reported and the reference method used to verify its accuracy.

[d]Indicates no data were available.

1981; Kane, 1985; Katsumata et al., 1985); or (4) the release of Hg vapor due to the combination of CO with mercuric oxide (Vreman et al., 1984).

Sample Handling

Carbon monoxide bound to Hb is a relatively stable compound which can be dissociated by exposure to O_2 or ultraviolet (UV) radiation (Chace et al., 1986; Horvath and Roughton, 1942). Ultraviolet light has not been shown by Goldstein et al. (1986) to affect COHb levels in glass vials exposed to room lighting conditions, however the ability of UV light to penetrate these tubes was not demonstrated. If the blood sample is maintained in the dark under cool, sterile conditions, the CO content will remain stable for a long period of time. Various investigators have reported no loss of percent COHb over 10 days (Collison et al., 1968), three weeks (Dahms and Horvath, 1974), four months (Ocak et al., 1985) and six months (Vreman et al., 1984). The anticoagulant system used appears to influence the CO level since some EDTA vacutainer tube stoppers contain CO (Vreman et al., 1984). The increased levels of COHb due to this amount of CO have been demonstrated (Goldstein et al., 1986; Vreman et al., 1984). The stability of the CO content in properly stored samples does not indicate that constant values will be obtained by all techniques of analysis. The spectrophotometric methods are particularly susceptible to changes in optical qualities of the sample which results in small changes in COHb with storage (Allred et al., 1989).

Carboxyhemoglobin values obtained with the IL 282 CO-Oximeter have been shown to decrease over the first three days following collection (Allred et al., 1989; Goldstein et al., 1986). This decrease occurs within the first 24 h (Allred et al., 1989) and does not fall further over the next 14 days (Goldstein et al., 1986). Storage of blood samples can result in the formation of methemoglobin (Goldstein et al., 1986) and under some conditions sulfhemoglobin (Rai and Minty, 1987). Both species of Hb can result in the optical methods of COHb detection being incorrect depending upon the specific wavelengths utilized.

Therefore the care needed to make a COHb determination depends upon the technique that is being utilized. It appears as though measurement of low levels of COHb with optical techniques should be conducted out as soon as possible following collection of the samples.

Potential Reference Methods

Exposure to CO at equilibrium conditions results in COHb levels of between 0.1 and 0.2% COHb for each part per million of CO in the atmosphere. A reference technique for the measurement of COHb should be able to discriminate between two blood samples with a difference of 0.1% COHb (approximately 0.02 mL/dL). To accomplish this task the coefficient of variation (standard deviation of repeated measures on any given sample divided by the mean of the values times 100) of the method should be less than 5% so that the two values that are 0.1% COHb different can be statistically proven to be distinct. In practical terms a reference method should have the sensitivity to detect approximately 0.025% COHb to provide this level of confidence in the values obtained.

The accurate measurement of CO in a blood sample requires the quantitation of the content of CO in blood. Optically based techniques have limitations of resolution and specificity due to the potential interference from many sources. The techniques that can be used as reference methods involve the quantitative release of CO from the Hb followed by the measurement of the amount of CO released. Classically this quantitation was measured manometrically with a Van Slyke apparatus (Horvath and Roughton, 1942) or a Roughton-Scholander syringe (Roughton and Root, 1945). These techniques have served as the "Gold Standard" in this field for almost 50 years. However, there are limitations of resolution with these techniques at the lower ranges of COHb. The gasometric standard methodology has been replaced with head-space extraction followed by the use of solid phase gas chromatographic separation with several different types of detection: thermal conductivity, flame ionization, and mercury vapor reduction. With the use of National Institute of Standards and Technology (NIST) standard gas mixtures of CO, the gas chromatographic techniques can be standardized when proper consideration is given to potential sources of loss of standard. The CO in the headspace can also be quantitated by infrared detection which can be calibrated with gas standards.

Flame Ionization Detection. This technique requires the separation of CO from the other headspace gases and the reduction of the CO to CH_4 by catalytic reduction. Collison et al. (1968) reported that the results from their method correlated with the Van Slyke gasometric method at high levels of CO (8 to 13 mL/dL) where the error in the gasometric

method was minimal. The values obtained from the two independent techniques were highly significantly correlated ($p<0.0001$) with a linear regression $r = 0.992$. The limit of detection was reported to be 0.01% COHb using 100 μL of blood. The coefficient of variation was 1.08% on a sample containing approximately 50% COHb and 1.80% on a sample containing approximately 0.8% COHb. The basic technique of Collison et al. (1968) using headspace analysis and flame ionization detection is the most sensitive method that has been compared with the gasometric methods. Modifications of this method have been widely used by other investigators for evaluating technically simpler methods of CO analysis (Clerbaux et al., 1984; Collison et al., 1968; Dennis and Valeri, 1980; Guillot et al., 1981; Kane, 1985; Katsumata et al., 1985). This method conforms to all the requirements of a reference method.

Thermal Conductivity Detection. Ayres et al. (1966) reported a method for using vacuum extraction of CO from blood in a Van Slyke apparatus for gas chromatographic separation with thermal conductivity analysis of the CO. The gas phase of the reaction chamber was eluted onto a 5A molecular-sieve column for separation of the components. This technique was reported to have a lower limit of detectability of 0.001 mL/dL or approximately 0.005% COHb. The coefficient of variation was reported to be 1.95% on a sample of unspecified percent COHb. The analysis system was calibrated using a gas sample of known CO content injected directly onto the column. No comparisons were performed with other standard techniques. McCredie and Jose (1967) also reported results from chromatographic separation of vacuum extracted gas. Thermal conductivity detection enabled the limit of detection to be 0.005 mL/dL or approximately 0.025% COHb. This system was also calibrated with standard gas mixtures injected directly onto the column. A coefficient of variation was not presented but a standard deviation of 0.004 mL/dL on a series of repeat analyses on an average blood sample indicates that this method is sufficiently reproducible. This would represent a coefficient of variation on the blood CO content measured from the average nonsmoker of 2.5%. Dahms and Horvath (1974) described a technique of headspace analysis of CO using thermal conductivity detection. The CO was released from the blood while the mixture was stirred to produce a vortex, using Van Slyke reagents in a sealed reaction vial. The extraction occurred into the headspace of a sealed vial pressurized to the

head pressure on the column. The limit of detection with this technique was 0.006 mL/dL or 0.03% COHb with a coefficient of variation of 1.7% on a sample containing 6.5% COHb. This method used standard gases injected into the reaction vial to calibrate the system. The results of this technique were compared to the standard Van Slyke method (Horvath and Roughton, 1942) over the whole range of values and more specifically on 90 blood samples containing less than 10% COHb. The correlation coefficient between the gas chromatography and the Van Slyke method was 0.984. Linear regression analysis demonstrated essentially a zero intercept (0.009 mL/dL) between the two techniques. This close agreement between values obtained with these independent methods provides a basis for the use of standard gases to calibrate gas chromatographic techniques. All of the above mentioned gas chromatographic methods for determination of CO in blood are acceptable as reference methods.

Infrared Detection. Coburn et al. (1964) described a method for extracting CO from blood under normal atmospheric conditions and then injecting the headspace gas into an infrared analyzer. This technique has a reported limit of detectability of 0.007 mL/dL or 0.035% COHb. The coefficient of variation was 1.8% on an average COHb of 1.67%. The results of this technique were compared with the gasometric technique of Roughton and Root (1945) on five samples; there was no difference between the two techniques. This method is acceptable as a reference method for the measurement of CO in blood.

Hemoglobin Measurement. The conventional means of representing the quantity of CO in a blood sample is the percent COHb: the percentage of the total CO combining capacity that is in the form of COHb. This is conventionally determined by the use of the following formula:

$$\%\text{COHb} = [\text{CO content}/(\text{hemoglobin} \times 1.389)] \times 100 \qquad (8\text{-}11)$$

where:

CO content = cc/dL blood STPD,
hemoglobin = g/dL blood, and
1.389 = the stoichiometric combining capacity of hemoglobin for CO in units of mL/g STPD.

The analytical methods that quantify the CO content in blood require the conversion of these quantities to percent COHb. The product of the Hb and the theoretical combining capacity (1.389 according to International Committee for Standardization in Haemotology, 1978) yields the CO capacity. With the use of capacity and the measured content, the percent of CO capacity (percent COHb) is calculated. To be absolutely certain of the accuracy of the Hb measurement, the theoretical value should be routinely substantiated by direct measurement (internal validation) of the Hb CO combining capacity. The total CO combining capacity should be determined as accurately as the content of CO. The error of the techniques that measure CO content are dependent on the error in Hb analysis for the final form of the data, percent COHb. Therefore the actual CO combining capacity should be measured and compared with the calculated value based upon the reference method for Hb measurement. The measurement of CO combining capacity can be routinely carried out by equilibration of a blood sample with CO (Allred et al., 1989).

The standard methods for Hb determination involve the conversion of all species of Hb to cyanmethemoglobin with the use of a mixture of potassium ferricyanide, potassium cyanide, and sodium bicarbonate. Three combinations of similar reagents have been routinely used for the quantification of Hb. Drabkin's solution contains 0.6 mM $K_4Fe(CN)_6$, 0.8 mM KCN, and 12 mM $NaHCO_3$ (Drabkin and Austin, 1932). Van Kampen and Zijlstra (1961) substituted 0.7 mM K_2HPO_4 for the bicarbonate in the reagent mixture. A third reagent for producing cyanmethemoglobin is that of Taylor and Miller (1965) who increased the concentration of potassium ferricyanide to 3 mM in Van Kampen and Zijlstra's mixture to decrease the reaction time with COHb. The presence of high levels of COHb slows the rate of conversion to cyanmethemoglobin so that the use of the conventional Drabkin's reagent requires a reaction time of at least 180 min (Allred et al., 1989; Kane, 1985) as opposed to the recommended time of 20 to 30 min. This increased reaction time is essential for the

accurate comparison of cyanmethemoglobin values with CO combining capacity measurements. If the reaction is not permitted to go to completion the spectrophotometric method will underestimate the amount of Hb present in the sample.

Other Methods of Measurement

There are a wide variety of techniques that have been described for the analysis of CO in blood. These methods have been reviewed previously (U.S. Environmental Protection Agency, 1979) and include UV-visible spectrophotometry (Brown, 1980; Small et al., 1971; Zwart et al., 1984; 1986), magnetic circular dichroism spectroscopy (Wigfield et al., 1981), photochemistry (Sawicki and Gibson, 1979), gasometric methods (Horvath and Roughton, 1942; Roughton and Root, 1945), and a calorimetric method (Sjostrand, 1948). Not all of these methods have been as well characterized for the measurement of low levels of COHb as those listed above as potential reference methods.

Spectrophotometric Methods. The majority of the techniques are based upon optical detection of COHb which is more rapid than the reference techniques because these methods do not involve extraction of the CO from the blood sample. These direct measurements also enable the simultaneous measurement of several species of hemoglobin including reduced Hb, O_2Hb, and COHb. The limitations of the spectrophotometric techniques have been reviewed by Kane (1985). The optical methods utilizing ultraviolet wave lengths require dilution of the blood sample which can lead to the loss of CO due to the competition with the dissolved O_2 in solution. Removing the dissolved O_2 with dithionite can lead to the formation of sulfhemoglobin which interferes with the measurement of COHb (Rai and Minty, 1987). Another limitation is that the absorption maxima (and spectral curves) are not precisely consistent between individuals. This may be due to slight variations in types of hemoglobin in subjects. For these reasons the techniques using fixed wave length measurement points would not be expected to be as precise, accurate, or specific as the proposed reference methods mentioned above.

Rodkey et al. (1979) reported a modification of the spectrophotometric technique for measuring COHb. This method converts all the hemoglobin species in a blood sample to either COHb or Hb by the quantitative addition of the reducing agent sodium hydrosulfite.

The absorbance at 420 nm was used for the determination of COHb and 432 nm for Hb. The optically based values were compared with those obtained by gas chromatography on the same 28 samples. Twenty-five of these values were below 6% COHb and linear regression analysis demonstrated a slope of 1.038 with an intercept of -0.154 and an r = 0.994. The number of samples studied was relatively small and no error term was presented for the relationship. Visual inspection of the data, however, indicates a wide scatter of optical values for any given gas chromatograph value when the levels were at or below 1% COHb (normal range of values for unexposed, nonsmoking individuals).

A multicomponent spectrophotometric technique for the measurement of hemoglobin derivatives was reported by Zwart et al. (1984). This technique employs a multiwavelength spectrophotometer that uses reversed optics to enable the rapid collection of the absorbance spectrum from an array of photomultiplier tubes that detect transmission of light at intervals of 2 nm. This method offers the possibility of instantaneous absorption data over the entire spectrum rather than the collection of data at a few selected wavelengths. This optical system offers the potential for correcting for individual variability in absorption characteristics of hemoglobin. The COHb data produced with this technique has not been compared with any of the proposed reference methods but has been compared with that obtained from the mercury vapor detector. The correlation coefficient of the optical data with the gas chromatographic-mercury vapor technique was only 0.87; linear regression analysis resulted in the following relationship: GC = 0.65 (MCA) + 0.24 (Vreman et al., 1987).

Mercury Vapor Detection. The most sensitive detector for the measurement of CO is the UV-photometer that senses mercury vapor produced by the reaction of CO with HgO (Trace Analytical). This unit has the reported ability to resolve 1 ppb. The use of such a sensitive detector for blood determinations requires that measurements be carried out on only 1 to 10 μl quantities of blood. Vreman et al. (1984) reported the use of this detector following gas chromatographic separation of the CO from other gases in blood. Mercuric oxide will react with other gases so the chromatographic separation is an essential step in the use of this detector. Values for COHb obtained with this technique have not been compared those obtained with any of the proposed reference methods. The COHb analysis method of Vreman et al. (1984) was used in a parallel with a gas chromatography method using thermal

conductivity detection for the routine measurement of COHb in a series of samples from subjects exposed to CO to produce levels of COHb up to 6% (Allred et al., 1989). Paired data from samples analyzed by both techniques were obtained on 108 samples. The values were significantly correlated r = 0.987; however, the reduction gas analyzer results were not corrected to STPD conditions, so an absolute comparison was not possible. This technique needs further validation by comparison with other methods to assure that the levels measured are accurate.

CO-Oximeter Measurements of Carboxyhemoglobin

The speed of measurement and relative accuracy of spectrophotometric measurements over the entire range of expected values led to the development of CO-Oximeters. These instruments utilize from two to seven wavelengths in the visible region for the determination of proportions of oxyhemoglobin, carboxyhemoglobin, reduced hemoglobin and methemoglobin. The proportion of each species of Hb is determined from the absorbance and molar extinction coefficients at present wavelengths. All of the commercially available instruments provide rapid results for all the species of Hb being measured. In general, the manufacturers' listed limit of accuracy for COHb for all of the instruments is 1% COHb. However, this level of accuracy is not suitable for measurements associated with background CO levels (<2% COHb) because it corresponds to errors exceeding 50%. The precision of measurement for these instruments is excellent and has misled users regarding the accuracy of the instrument. The relatively modest level of accuracy is adequate for the design purposes of the instrument; however, at low levels of COHb the ability of the instrument to measure the percent COHb accurately is limited.

The commercially available instruments for the measurement of COHb all utilize the same basic principles: hemolysis, constant temperature, and the measurement of absorbance at several wave lengths. These instruments have been designed to provide information regarding COHb measurement that is ±1% COHb. However, these instruments are all very precise so that the coefficient of error between repeat measurements (standard deviation of repetitions/mean of the repetitions) is very low. Unfortunately, very few studies have evaluated the accuracy of the measurements made with these instruments as a routine aspect of quality control. The concern regarding the accuracy of any optical measurement on a

diluted blood sample should be of greatest concern due to the wide variety of substances that can subtly alter the absorption spectrum of Hb and the optical quality of the blood sample itself. Because of the widespread use of these instruments, the evaluations of this instrument will be carefully reviewed. These instruments consist of the Instrumentation Laboratories CO-Oximeters known as the IL 182 and the IL 282, the Radiometer Oximeter OSM-3, and the Corning Oximeter 2500. There is very little information regarding the accuracy of the OSM-3 in the low range of COHb values compared to the data obtained from paired analysis with a reference method.

The instruments that have been used to the greatest extent in the health effects of CO have been the IL 182 and IL 282 (Instrumentation Laboratory, Inc., Lexington, MA). The IL 282 instrument uses absorbances at four wavelengths in the visible region and a matrix of molar extinction coefficients to calculate each species of hemoglobin. This method is susceptible to interference from high concentrations of methemoglobin and sulfhemoglobin. The IL 282 CO-Oximeter has been shown to provide accurate data when the range of 0 to 100% COHb is considered (Brown, 1980). However, comparison of the results from this method with the proposed reference methods indicates that at low levels of COHb the results from this instrument are not sufficiently accurate to warrant their use alone for low level COHb investigation. Resting levels of percent COHb have been shown to be below 0.9% for non-smokers by all the proposed reference methods (Ayres et al., 1966; Coburn et al., 1964; Collison et al., 1968; Dahms and Horvath, 1974; McCredie and Jose, 1967). The limit of accuracy for the IL 282 CO-oximeter for percent COHb is 1%, which has raised concern over the capability of all CO-Oximeters in the low range of COHb levels. Therefore the accuracy of these instruments has been determined by paired observations on blood samples with the CO-Oximeter and a reference method. The results are shown in Table 8-12 below.

The results from the linear regression analyses of all these comparisons indicate that there is considerable difference between instruments of the same model type. The slope of the relationship between the optical methods are sufficiently close to unity that there is no difference between instruments in the linearity of the measurements. Confidence intervals for the regressions are not given so this comparison can not be made. The intercept values vary widely relative to the purpose of accurately measuring low levels of COHb. These differences probably reflect the difference between instruments. In order to use these

TABLE 8-12. EVALUATION OF THE ABILITY OF CO-OXIMETERS TO MEASURE LOW LEVELS OF COHb AS COMPARED TO PROPOSED REFERENCE METHODS

Instrument	Reference Method[a]	Slope	Intercept	R	n	COHb Range	Reference
IL 182	GC-FID	0.690*GC	+3.59	0.59	16	<15%	Constantino et al. (1986)
IL 182	GC-FID	1.049*GC	-0.54	ND[b]	275	<15%	Guillot et al. (1981)
IL 182	Infrared	0.977*IR	+3.33	ND	12	<100%	Maas et al. (1970)
IL 282	GC-FID	0.990*GC	+0.45	0.997	39	<100%	Dennis and Valeri (1980)
IL 282	GC-FID	1.122*GC	-0.907	0.993	13	<17%	Dennis and Valeri (1980)
IL 282	GC-TCD	0.919*GC	-0.068	0.961	20	<8%	Goldbaum et al. (1986)
IL 282	GC-FID	0.895*GC	+0.66	0.856	16	<15%	Constantino et al. (1986)
IL 282	CG-TCD	1.0069*GC	-0.01	0.99	ND	<9%	Horvath et al. (1988)
		1.05*GC	+0.79	0.99	203	<6%	Allred et al. (1989)
		1.05*GC	+0.55		192	<6%	Allred et al. (1989)
		1.05*GC	+0.47		162	<6%	Allred et al. (1989)
Corning 2500	GC-FID	0.92*GC	+1.17	0.979	50	<20%	Kane (1985)
Corning 2500	GC-FID	1.013*GC	-1.279	0989	286	<15%	Tikuisis et al. (1987)

[a]Abbreviations: GC-TCD is gas chromatography thermal conductivity detection; GC-FID is gas chromatography with flame ionization detection.

[b]Indicates no data were available.

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instruments for the measurement of low levels of COHb they must be individually and routinely calibrated with a reference method. The linearity of the response of the instruments implies that a standard correction can be applied to the value for COHb with the result that the average value of COHb obtained with these instruments will be correct.

The interaction of Hb species with the measurement of COHb below 10% has been evaluated by Allred et al. (1989). In freshly drawn blood samples, levels of COHb were maintained constant, as measured by GC, while levels of metHb, total Hb and O_2Hb were varied. Only the level of O_2Hb interacted significantly with the COHb value. In a series of 46 subjects the effect of O_2Hb was measured to determine its role in routine measurements of COHb. The effect of O_2Hb varied considerably between individuals, with the average change being approximately 0.1% COHb for every 10% change in O_2Hb. Almost all COHb measurements were made on venous blood which can vary considerably in O_2Hb concentration and consequently affect the measurement of low levels of COHb.

Hydrogen ion concentration was shown to have an effect on the measured percent COHb in blood stored in acid citrate dextrose (ACD) solution for two days. However the effect of pH on percent COHb in freshly drawn samples has not been clearly demonstrated (Allred et al., 1989). Hydrogen ion concentration has been demonstrated to change the absorbance spectrum of oxyhemoglobin and therefore may be expected to have an effect on the ability of CO-Oximeters to measure COHb. Plasma lipid, triglyceride and cholesterol levels were found to not have any effect on the ability of the IL282 CO-Oximeter to measure COHb as determined by the difference between in instrument value and the reference value obtained by gas chromatography.

The content of CO in blood stored in a tightly capped syringe at 4°C in the dark has been shown to remain stable for up to four months. Measurement of COHb by IL 282 CO-Oximeter on blood samples (COHb range of 4.3 to 1.3%) within 15 min of collection, followed by storage for 24 and 48 h as described above, resulted in a decrease in the detected percent COHb. The apparent loss of COHb occurred in the first 24 h and averaged 16% (Allred et al., 1989). There was no change in percent COHb as determined by GS. It is not clear when in the first 24-h period this change occurred.

The use of CO-Oximeters to measure low levels of COHb can provide useful information regarding mean values, provided a reference technique is used to properly

calibrate the instrument. It has been shown, however, that the range of values obtained with the optical method will be greater than that obtained with a reference method. In a group of subjects with cardiovascular disease the standard deviation of the percent COHb values for non-smoking, resting subjects was 2 to 2.5 times greater for the CO-Oximeter values than for the GC values on paired samples (Allred et al., 1989). Therefore, the potential exists with the CO-Oximeter for having an incorrect absolute value for COHb as well as an incorrectly broadened range of values.

In addition, it is not clear exactly how sensitive the CO-Oximeter techniques are to small changes in COHb at the low end of the CO dissociation curve. Allred et al. (1989) have noted that the interference from changing O_2 saturation can have a very significant influence on the apparent COHb reading in a sample. The interaction between Hb species was also reported by Dennis and Valeri (1980). This suggests nonlinearity or a disproportionality in the absorption spectrum of these two species of Hb. It is also a potential source of considerable error in the estimation of COHb by optical methods.

8.5.1.2 Carboxyhemoglobin Measurements in Populations

Numerous studies have used the above described methodologies to characterize the levels of COHb for the general population. These studies have been designed to determine frequency distributions of COHb levels in the populations being studied. In general the higher the frequency of COHb levels above baseline in nonsmoking subjects the greater the incidence of significant CO exposure.

Carboxyhemoglobin levels in blood donors have been studied for various urban populations in the United States. Included have been studies of blood donors and sources of CO in the metropolitan St. Louis population (Kahn et al., 1974), evaluation of smoking and COHb in the St. Louis metropolitan population (Wallace et al., 1974), analyses of 16,649 blood samples for COHb provided by the Red Cross Missouri-Illinois blood donor program (Davis and Gantner, 1974), a survey of blood donors for percent COHb in Chicago, Milwaukee, New York and Los Angeles (Stewart et al., 1976), a national survey for COHb in American blood donors from urban, suburban, and rural communities across the United States (Stewart et al., 1974), and the trend for percent COHb associated with vehicular traffic in Chicago blood donors (Stewart et al., 1976). These extensive studies of volunteer blood

donor populations show three main sources of exposure to CO in urban environments. These are smoking, general activities (usually associated with internal combustion engines), and occupational exposures. For comparisons of sources, the populations are divided into two main groups – smokers and nonsmokers. The main groups often are divided further into subgroups consisting of industrial workers, drivers, pedestrians, and others, for example. Among the two main groups, smokers show an average of 4% COHb with a usual range of 3 to 8%; nonsmokers average about 1% COHb (Radford and Drizd, 1982). Smoking behavior generally occurs as an intermittent diurnal pattern, but in some individuals who chain smoke, COHb levels can rise to a maximum of about 15%.

In addition to tobacco smoke, the most significant sources of other potential exposure to CO in the population are community air pollution, occupational exposures, and household exposures (Goldsmith, 1970). Community air pollution comes mainly from auto exhaust and has a typical intermittent diurnal pattern (see Chapter 6). Occupational exposures occur for up to eight hours for 5 days a week, producing COHb levels generally less than 10%. However, exposures to high concentrations of CO in occupational settings have caused death from CO intoxication. Household exposures usually result in less than 2% COHb, but high concentrations, occurring particularly during nighttime hours, have been known to cause death. For example, during the winter, a number of people die as a result of using a variety of space heating devices in poorly ventilated spaces (Goldsmith, 1970). Poorly vented floor heaters are also a source of CO intoxications, with many such exposures occurring at night.

More recent studies characterizing COHb levels in the population have appeared in the literature. Turner et al. (1986) used an IL 182 CO-Oximeter to determine percent COHb in venous blood of a study group consisting of both smoking and nonsmoking hospital staff, inpatients and outpatients. Blood samples were collected for 3487 subjects (1255 nonsmokers) during morning hours over a five-year period. A detailed smoking history was obtained at the time of blood collection. Secondary pipe or secondary cigar smokers were considered to be those who were initially cigarette smokers but subsequently switched to cigars or pipes. Primary cigar or pipe smokers were those who had never smoked cigarettes and were not in the habit of inhaling large amounts of tobacco smoke as is the observed custom with cigarette smoking. Using 1.7% COHb as a normal cutoff value, the distribution for the population studied showed above normal results for 94.7% of cigarette smokers,

10.3% of primary cigar smokers, 97.4% of secondary cigar smokers, and 94.7% of secondary pipe smokers.

Zwart and Van Kampen (1985) tested a blood supply using a routine spectrophotometric method for total Hb and for COHb in 3022 samples of blood for transfusion in hospital patients in the Netherlands. For surgery patients over a one-year period, the distribution of percent COHb in samples collected as a part of the surgical protocol showed 65% below 1.5% COHb, 26.5% between 1.5 and 5% COHb, 6.7% between 5 and 10% COHb, and 0.3% in excess of 10% COHb. This distribution of percent COHb was homogeneous across the entire blood supply, resulting in 1 in 12 patients having blood transfusions at 75% available Hb capacity.

Radford and Drizd (1982) have analyzed blood COHb in approximately 8400 samples obtained from respondents in the 65 geographic areas of the nationwide Health and Nutrition Examination Survey (HANES) during the period 1976-1980. When the frequency distributions of blood COHb levels are plotted on logarithmic-probability paper (Figure 8-5) to facilitate comparison of the results for different age groups and smoking habits, it is evident that adult smokers in the U.S. have COHb levels considerably higher than those of nonsmokers, with 79% of the smokers' blood samples above 2% COHb and 27% of the observations above 5% COHb. The nationwide distributions of persons aged 12 to 74 who have never smoked and ex-smokers were similar, with 5.8% of the ex-smokers and 6.4% of the never-smokers above 2% COHb. It is evident that a significant proportion of the nonsmoking United States population had blood levels above 2% COHb. For these two nonsmoking groups, blood levels above 5% were found in 0.7% of the never-smokers and 1.5% of the ex-smokers. It is possible that these high blood levels could be due, in part, to misclassification of some smokers as either ex- or nonsmokers. Children aged 2 to 11 had lower COHb levels than the other groups, with only 2.3% of the children's samples above 2% COHb and 0.2% above 5% COHb.

Wallace and Ziegenfus (1985) utilized the Radford HANES data to analyze the relationship between the measured COHb levels and the associated eight-hour CO concentration at nearby fixed monitors. COHb data were available for a total of 1658 nonsmokers in 20 cities. The day and hour the blood samples were drawn for each individual were obtained from the NHANES II data, and the preceding one-hour and eight-hour running

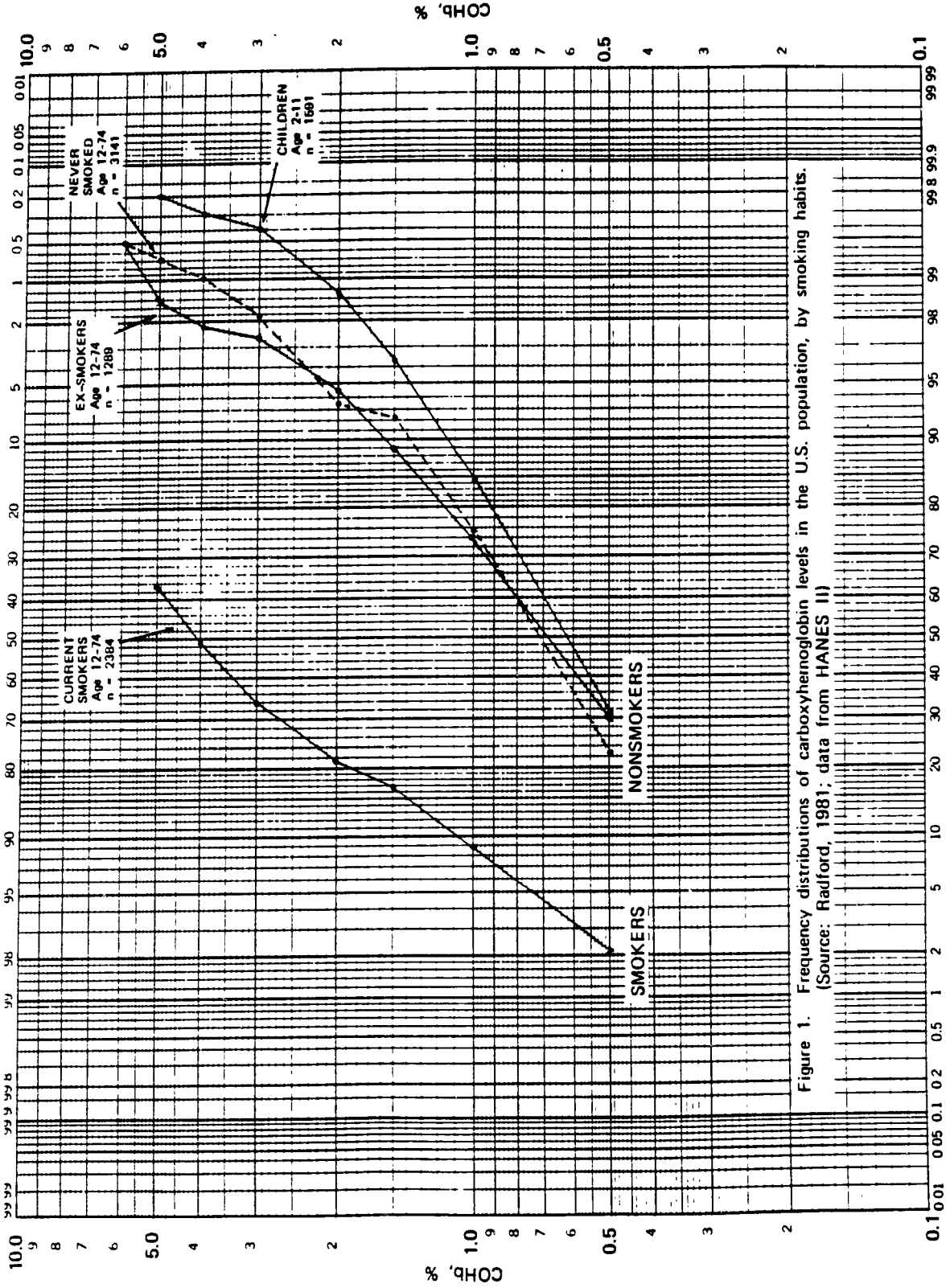

Figure 8-5. Frequency distributions of carboxyhemoglobin levels in the U.S. population, by smoking habits.

Source: Adapted from Radford and Drizd (1982); data for NHANES II.

average ambient CO levels at each fixed station in the city were calculated using the U.S. EPA centralized data base (SAROAD). For each of the 20 cities the station with the highest Spearman correlation between COHb concentrations and the preceding eight-hour CO averages was selected for a linear regression. The results (Table 8-13) show that 17 of the 20 stations had R^2 values ranging from 0.00 (6 cities) to 0.10.

Finally, because the participants were part of a nationwide probability sample, all COHb data were merged with the CO data from the station within each city that showed the strongest correlation with the COHb values and a linear regression was run. The R^2 value for the 1528 paired measurements was 0.031 (i.e., only 3% of the variance in the COHb concentrations was explained by the ambient CO data). The authors concluded that fixed outdoor CO monitors alone are, in general, not providing useful estimates of carbon monoxide exposure of urban residents.

8.5.2 Carbon Monoxide in Expired Breath

Carbon monoxide levels in expired breath can be used to estimate the levels of carbon monoxide in the subject's blood. The basic determinants of CO levels in the alveolar air have been described by Douglas et al. (1912), indicating that there are predictable equilibrium conditions that exist between CO bound to the Hb and the partial pressure of the CO in the blood. The equilibrium relationship for CO between blood and the gas phase to which the blood is exposed can be described as follows:

$$P_{CO}/P_{O2} = M\ (\%COHb/\%O_2Hb) \qquad (8\text{-}12)$$

where:

P_{CO} = partial pressure of CO in the blood,
P_{O2} = partial pressure of O_2 in the blood,
M = Haldane constant (reflecting the relative affinity of the hemoglobin for O_2 and CO),
%COHb = percent of total Hb combining capacity bound with CO, and
$\%O_2Hb$ = percent of total Hb combining capacity bound with O_2.

TABLE 8-13. REGRESSION PARAMETERS FOR THE RELATIONSHIP BETWEEN COHb AND EIGHT-HOUR CO AVERAGES FOR 20 CITIES[a]

City	*n*	Slope[b]	Intercept[c]	R^2
Atlanta	63	0.12(±0.03)	0.41(±0.09)	0.27
Bronx	65	0.18(±0.10)	0.60(±0.29)	0.05
Cincinnati	93	-0.02(±0.21)	0.94(±0.22)	0.00
Chicago	78	-0.02(±0.06)	1.21(±0.18)	0.00
Dayton	91	-0.03(±0.08)	0.93(±0.15)	0.00
Des Moines	90	0.003(±0.03)	0.52(±0.12)	0.00
Washington	73	0.06(±0.04)	1.38(±0.18)	0.03
Hampton	89	0.16(±0.10)	0.50(±0.09)	0.03
Honolulu	65	0.39(±0.14)	0.44(±0.18)	0.11
Houston	71	0.24(±0.12)	0.68(±0.15)	0.06
Indianapolis	93	0.0005(±0.019)	0.79(±0.07)	0.00
Los Angeles	66	0.12(±0.03)	0.99(±0.18)	0.16
Manhattan	71	0.09(±0.03)	0.84(±0.08)	0.10
Pittsburgh	55	0.03(±0.02)	0.77(±0.13)	0.05
Racine	91	-0.12(±0.13)	0.75(±0.14)	0.01
Rock Hill	85	0.23(±0.11)	0.61(±0.24)	0.05
San Diego	67	0.01(±0.08)	0.84(±0.13)	0.00
San Jose	59	0.08(±0.04)	0.87(±0.11)	0.06
Tacoma	82	0.04(±0.06)	0.76(±0.14)	0.01
Washington	73	0.06(±0.04)	1.38(±0.18)	0.03
Wichita	81	-0.11(±0.28)	0.84(±0.35)	0.00
All cities	1528	0.066(±0.009)	0.77(±0.03)	0.03

[a]For cities with multiple CO stations, the station with the strongest Spearman correlation was chosen for the regression.
[b]Percent COHb per mg/m^3.
[c]Percent COHb.

Source: Wallace and Ziegenfus (1985).

The partial pressure of CO in the arterial blood will reach a steady state value relative to the partial pressure of CO in the alveolar gas. Therefore, by measuring the end-expired breath from a subject's lungs, one can measure the end-expired CO partial pressure and, with the use of the Haldane relationship, estimate the blood level of COHb. This measurement will always be an estimate because the Haldane relationship is based upon attainment of an equilibrium which does not occur under physiological conditions.

The measurement of CO levels in expired breath to estimate blood levels is based upon application of the Haldane relationship to gas transfer in the lung (Equation 8-12). For example, when the O_2 partial pressure is increased in the alveolar gas, it is possible to predict the extent to which the partial pressure of CO will increase in the alveolar gas. This approach is limited, however, because of the uncertainty associated with variables that are known to influence gas transfer in the lung and that mediate the direct relationship between liquid phase gas partial pressures and air phase partial pressures.

The basic mechanisms that are known to influence CO transfer in the lung have been identified through the establishment of the techniques to measure pulmonary diffusion capacity for CO (Forster, 1964). Some of the factors that can result in decreased diffusion capacity for CO (altering the relationship between expired CO pressures and COHb levels) are increased membrane resistance, intravascular resistance, age, alveolar volume, pulmonary vascular blood volume, pulmonary blood flow, and ventilation/perfusion inequality (Forster, 1964). The extent to which each of these variables actually contributes to the variability in the relationship has not been experimentally demonstrated. There are very few experiments that focus on the factors leading to variability in the relationship between alveolar CO and percent COHb at the levels of COHb currently deemed to be of regulatory importance. This may be due in part to the difficulties in working with analytical techniques, particularly the blood techniques, that are very close to their limits of reproducibility. For example, a change of approximately 6 ppm of CO in the alveolar gas occurs for every change of 1% COHb (Jones et al., 1958). Therefore, in order to reliably measure COHb levels to better than 0.1% COHb the analytical method must be able to resolve at least 0.5 ppm CO. This is well within the range of precision of the electrochemical methods (Lambert et al., 1988; Wallace et al., 1988). Without the use of a well-established method for the measurement of CO levels in

blood, the influence of all the physiological variables on the accuracy of this method remain undetermined.

The expired breath method for obtaining estimates of blood levels of CO has a distinct advantage for monitoring large numbers of subjects because of the non-invasive nature of the method. Other advantages include the ability to obtain an instantaneous reading and the ability to take an immediate replicate sample for internal standardization. The breathholding technique for enhancing the normal CO concentration in exhaled breath has been widely used; however, it should be noted that the absolute relationship between breathhold CO pressures and blood CO pressures has not been thoroughly established for percent COHb levels below 5%. The breathholding method allows time (20 seconds) for diffusion of CO into the alveolar air so that CO levels are higher than following normal tidal breathing.

Partial pressures of CO in expired breath are highly correlated with percent COHb levels over a wide range of COHb levels (Table 8-14). The accuracy of the breathhold method is unknown due to the lack of paired sample analyses of CO partial pressures in exhaled breath and concurrent COHb levels in blood utilizing a sensitive reference method (see Section 8.5.1). No one has attempted to determine the error of estimate involved in applying group average regression relationships to the accurate determination of COHb. Therefore, the extrapolation of breathhold CO partial pressures to actual COHb levels must be made with reservation until the accuracy of this method is better understood.

8.5.2.1 Measurement Methods

Ventilation in healthy individuals involves air movement through areas in the pulmonary system that are either primarily involved in conduction of gas or in gas exchange in the alveoli. In a normal breath (tidal volume) the proportion of the volume in the non-gas exchanging area is termed the dead space. In the measurement of CO in the exhaled air, the dead space gas volume serves to dilute the alveolar CO concentration. Several methods have been developed to account for the dead space dilution.

TABLE 8-14. SUMMARY OF STUDIES COMPARING END-EXPIRED BREATH CO WITH COHb LEVELS

Thesis	Methods	Sample population (n)	% COHb range	Expired CO range (ppm)	Blood-breath relationship	Reference
Developed rebreathing method to estimate COHb from alveolar air CO concentration	Rebreathing into Douglas bag	23 (sex not reported)	5-35	—	$M \frac{P_{CO}}{P_{O_2}} = \frac{COHb}{O_2Hb}$	Sjöstrand (1948)
Relationship between alveolar breath CO and blood COHb levels	Rebreathing method of Sjöstrand (1948) Blood: venous; van Slyke	55 (men and women; smokers and nonsmokers)	0-6	—	No regression equation reported; line of fit as predicted by Haldane equation	Carlsten et al. (1954)
Using lungs as aero-tonometers, sampling of alveolar air allows estimation of COHb	20-s breath-hold; save end-expired sample Breath: NDIR corrected for CO_2 Blood: Venous; NDIR	13 (men and women)	0.7-26.0	2-185	Line of fit as predicted by Haldane equation: $\%COHb = \frac{0.206[CO_{ppm}]}{1+0.00206[CO_{ppm}]}$	Jones et al. (1958)
Verify method of Jones et al. (1958); apply to community exposure survey	20-s breath-hold; first few hundred ml volume discarded; save end-expired sample Breath: IR (CO_2 scrubbed by Ascarite) Blood: Venous; NDIR	4 (men; 2 smokers, 2 nonsmokers)	1.2-20.0	3-100	$\%COHb = 0.2[CO_{ppm}]+0.5$	Ringold et al. (1962)
End-expired breath measurements can be used as an indicator of exposure to cigarette smoking and community air pollution	Not described	209 (men, long shoremen, smokers and nonsmokers)	0.2-19.0	0-82	For respondents(N=130) with cardiorespiratory conditions: $\%COHb = 1.09+0.14[CO_{ppm}]$ $r^2 = 0.56$	Goldsmith (1965)
Experimental exposure study correlating alveolar breath CO with venous blood COHb	20-s breath-hold; discard first half expired; save end-expired Breath: GC and long path IR Blood: Venous; GC	14 (men, white, ages 24 to 42 year)	0-32	4-250	$\%COHb = 109.08 +7.60[CO_{ppm}]-11.89$ SE = 1.06% COHb r = 0.976	Peterson (1970)

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TABLE 8-14 (cont'd). SUMMARY OF STUDIES COMPARING END-EXPIRED BREATH CO WITH COHb LEVELS

Thesis	Methods	Sample population (n)	% COHb range	Expired CO range (ppm)	Blood-breath relationship	Reference
Epidemiologic research investigating tobacco smoking behavior and blood COHb levels	20-s breath-hold; discard first 300 ml; save next 500 ml expired air Breath: IR (CO_2 scrubbed by soda lime) Blood: Venous; Spectrophotometric	59 (men and women, smokers and nonsmokers)	0.3-8.1	2-41	No regression equation reported; estimated regression from bivariate plot: $\%COHb = 0.21[CO]$	Rea et al. (1973)
Developed practical method to rapidly estimate COHb from breath samples in field firefighting situation	20-s breath-hold; discard first portion; save remainder expired breath Breath: Electrochemical (Ecolyzer 2100) and GC Blood: not described	56 (men, fire-fighters)	0.8-33	1-239	Line of fit as predicted by Haldane equation (without correction for water vapor pressure): $\%COHb = \frac{0.197[CO_{ppm}]}{1+0.00197[CO_{ppm}]}$	Stewart et al. (1976)
End-expired air analysis may be used to distinguish between populations of smokers and non-smokers	Breath: IR (CO_2 scrubbed by soda lime) Blood: Venous; spectrophotometric (Tietz and Fiereck, (1973)	14 (sex not reported)	0.3-8.0	4-46	$\%COHb = 0.18[CO_{ppm}]-0.26$ $r^2 = 0.92$; 95% confidence limits = ±1% COHb	Rawbone et al. (1976)
Ambient CO levels during time of breath-holding maneuver bias % COHb estimate	20-s breath-hold; discard first portion; save end-expired Breath: Electrochemical (Ecolyzer 2000) Blood: Venous; IL 192 (verified by unspecified spectrophotometric technique)	46 (sex not reported)	0.4-11.5	2-64	For constant, low ambient CO environment: $\%COHb = 0.18[CO_{ppm}]$ $r^2 = 0.94$ For fluctuating, high ambient CO environment: $\%COHb = 0.14[CO_{ppm}]$ $r^2 = 0.48$	Smith (1977)

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TABLE 8-14 (cont'd). SUMMARY OF STUDIES COMPARING END-EXPIRED BREATH CO WITH COHb LEVELS

Thesis	Methods	Sample population (n)	% COHb range	Expired CO range (ppm)	Blood-breath relationship	Reference
Mixed-expired air samples are equivalent to 30-s end-expired air sample collection method	30-s breath-hold and rebreathing methods Breath: IR (CO_2 scrubbed by soda lime) Blood: Venous, IL282; verified by spectrophotometric method of Tietz and Fiereck (1973)	29 (sex not reported) (4 non smokers, 25 smokers)	0.8-10.4	8-62	%COHb = 0.395[CO_{ppm}] -0.0032([CO_{ppm}])^2-2.4	Rees et al. (1980)
End-expired breath analysis is useful for estimating %COHb in traffic control personnel	Breath: Electrochemical, Ecolyzer 2000 Blood: Venous; IL282	ND	1.1-12.5	5-60	Cites Stewart and (1980) Stewart (1978): %COHb = 0.202[CO_{ppm}] +0.0365	Jabara et al. (1980)
In subjects with emphysema, decreased end-expired [CO] is attributed to impaired diffusion	20-s breath-hold; expire to bag Breath: Electrochemical, Ecolyzer 2000 Blood: Venous; IL282	182 smokers 35 emphysema patients (sex not reported)	0.3-14.5	4-90	For normal smokers: %COHb = -0.28+0.175[CO_{ppm}] r^2 = 0.98;SE = 0.76%COHb For emphysema patients: %COHb= -0.12+0.211[CO_{ppm}] r^2 = 0.92 Slopes of two regression lines were significantly different	Jarvis et al. (1980)
End-expired breath analysis may be used to distinguish between smokers and non-smokers	20-s breath-hold; expire to collection tube Breath: Electrochemical, Ecolyzer 2000 Blood: Venous, IL182	187 (men; 162 smokers, 25 non smokers)	0.4-13	3-65	%COHb = 0.18[CO_{ppm}] -0.14 r = 0.97	Wald et al. (1981)

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TABLE 8-14 (cont'd). SUMMARY OF STUDIES COMPARING END-EXPIRED BREATH CO WITH COHb LEVELS

Thesis	Methods	Sample population (*n*)	% COHb range	Expired CO range (*ppm*)	Blood-breath relationship	Reference
To most accurately estimate % COHb, end-expired breath samples require a correction for inspired ambient CO at time of sampling	20-s breath-hold; discard first portion; save end-expired Breath: Electrochemical, COED-1 (GE) Blood: Not sampled	1 (male, non smoker)	—	—	$[CO_{ppm}]_{measured}$ = $0.83[CO_{ppm}]_{alv}$ $+0.17[CO_{ppm}]_{inspired}$	Wallace (1983)
The correction for inspired air may vary between persons	20-s breath-hold at room air CO level, and at 10, 30, and 50 ppm CO	7 (sex not reported)	—	10-50	$[CO_{ppm}]_{measured}$ = $0.83[CO_{ppm}]_{alv}$ $+0.17(\pm 0.11)$ $[CO_{ppm}]_{inspired}$	Wallace et al. (1988)
Cigarette smoking interferes with alveolar sampling	20-s breath-hold Breath: IR (CO_2 scrubbed before analysis) Blood: Venous; OSM2 spectrophotometer	101 smokers (42 men; 59 women)	0-12	4-71	%COHb = 0.034 + 0.179 $[CO_{ppm}]$ r = 0.938	Guyatt et al. (1988)

Notes: ND = No data are available. See glossary of terms and symbols for abbreviations and acronyms.

Source: Adapted from Lambert and Colome (1988).

Mixed Expired Gas Using the Bohr Equation

This technique involves the measurement of the mixed expired CO concentration from which the alveolar CO concentration is calculated. The Bohr equation used to determine the physiological dead space is:

$$F_{Ex} * V_E = F_{Ax} * V_A + F_{Ix} * V_D \qquad (8\text{-}13)$$

where:

F_{Ex} = the fractional concentration of a gas in the mixed expired air,
V_E = the minute volume of ventilation or a tidal volume,
F_{Ax} = the fractional concentration of the gas in the alveolar space,
V_A = the volume of alveolar gas,
F_{Ix} = the fractional concentration of gas in the inspired air,
V_D = the volume of dead space gas.

Solving this equation for CO concentration in the alveolar gas results in:

$$F_{A_{CO}} = (V_E * F_{E_{CO}} - V_D * F_{I_{CO}})/(V_E - V_D) \qquad (8\text{-}14)$$

This equation has been used by Rawbone et al. (1976) to describe the relationship between alveolar CO concentrations and COHb levels. These investigators measured inspired ventilatory volume, inspired CO concentration and estimated dead space from anatomical correlations. Carbon monoxide concentration must be converted to partial pressure in order to relate alveolar gas tension to percent COHb. However, the transfer of CO from blood to the alveolar gas phase is not in equilibrium so the alveolar gas is a reflection of the P_{CO} in the capillary blood. This is demonstrated by the increase in alveolar CO with breathholding. The relationship between alveolar levels determined from mixed expired CO concentrations and percent COHb is comparable to that of other methods (Table 8-14).

Breathhold

Early methods of measurement of CO concentration in air samples by non-chromatographic techniques required a relatively large sample of gas, usually larger than 1 L. Therefore, end-tidal (alveolar) gas samples from normal respiration would not provide a sample of sufficient volume for analysis. Jones et al. (1958) developed a method of inspiration to total lung capacity followed by a breathhold period of various durations. A breathhold times of 20 s was found to provide near maximal values for CO pressures. The breathhold period allows more time for diffusion of CO from the blood into the alveolar space.

The precision of the method has been found to be of the order of 0.1 to 0.2 ppm by several investigators (Hartwell et al., 1984; Wallace et al., 1988; Lambert et al., 1988). This is the theoretical equivalent of 0.02 to 0.04% COHb. Physiologically, however, the breath-hold gas is not normal alveolar gas, since this breathhold maneuver results in the CO_2 concentration being below normal, with presumably an elevated O_2 tension (Jones et al., 1958; Guyatt et al., 1988).

The blood-breathhold alveolar air CO relationship is influenced by the inspired pressure level of CO. Several investigators (Smith, 1977; Wallace, 1983; Wallace et al., 1988) have found that a correction is required in the CO pressure found in the breathhold sample. This is an important consideration when this method is used to assess the exposure of subjects in their normal environment (see Section 8.5.2.2).

Rebreathing

The earliest approach to obtaining a sufficient volume of exhaled air was rebreathing 5 L of O_2 for two to three minutes while removing the CO_2 (Hackney et al., 1962; Carlsten et al., 1954). Hackney et al. (1962) reported that the O_2 content in the rebreathing system fell due to dilution over the first minute after which time the decline in O_2 was related to the O_2 consumption of the subject. The CO concentration in the system reached its peak value at one minute of rebreathing in healthy subjects. Hackney et al. also reported that the CO concentration in the system was related to the O_2 tension in the system. The advantage to using a rebreathing system is that the ratio of change in percent COHb to change in expired CO is between 27 (Hackney et al., 1962) and 30 ppm/percent COHb (Carlsten et al., 1954).

This a gain of fivefold over the breathhold method of Jones et al. (1958). The disadvantage is the time required for the measurement and the need to measure O_2 in the system.

Summary of the Methods

Kirkham et al. (1988) compared all three techniques for measuring expired CO to predict percent COHb. The rebreathing and breathhold methods both yield approximately 20% high levels of "alveolar" CO than does the Bohr computation from mixed expired gas. Subjects rebreathed from a system that contained 20% O_2 for the three minutes of the rebreathing. Kirkham et al. (1988) also carried out an experiment to determine if these techniques had reached a steady state between alveolar gas and blood levels. If a steady state existed, then changes in ventilation/perfusion and capillary blood volume would not effect the relationship. Ventilation/perfusion was altered by changing body position from lying to standing. Both the mixed expired and breathholding techniques showed a significant decline in the alveolar CO tension when standing. Therefore, measurements of expired CO must be made in the same body position relative to control measurements or reference measurements.

The conventional relationship between blood and expired CO is assumed to be linear (Table 8-14). Data collected by Rees et al. (1980), however, indicates that the relationship is not linear. A second order polynomial equation proved to be the best fit of the data where: percent COHb = $3.95\ (CO) - 0.32\ (CO)^2 - 2.4$. Guyatt et al. (1988) also reported a nonlinear relationship where: $\%COHb = -0.47 + 0.217\ (CO) - 0.0006\ (CO)^2$. Peterson (1970) also found that a quadratic equation described the relationship between $F_{A(CO)}$ and percent COHb over the range of 0 to 30% COHb. Without more precise data, the relationship between $F_{A(CO)}$ and COHb for under 5% COHb appears to be sufficiently linear to justify the use of a linear expression to predict percent COHb from $F_{A(CO)}$ measurements.

8.5.2.2 Breath Measurements in Populations

There are numerous approaches described in the literature utilizing the above methods for the collection and analysis of CO in expired air. In addition, many of the investigators have also provided data demonstrating a relationship between the concentration of CO in ambient or expired air samples and the percent COHb in blood. All of these approaches show internally consistent results and are based on the assumption that the air collection

methodology represents expired alveolar air. In making comparisons, differences in collection methods, analytical techniques, smoking history, and types of subjects being studied must be considered. For example, possible subjects include hospital patients with certain types of medical histories, joggers, and the general population. Sampling locations vary as well, ranging from outdoors to indoors, and from clinics to living rooms.

A study in which breath measurements of CO were used to detect an indoor air problem has been reported (Wallace, 1983). Sixty-five workers in an office had been complaining for some months of late-afternoon sleepiness and other symptoms, which they attributed to the new carpet. About 40 of the workers had their breath tested for CO on a Friday afternoon and again on a Monday morning. The average breath CO levels decreased from 23 ppm on Friday to 7 ppm on Monday morning (Figure 8-6), indicating a work-related condition. Non-working fans in the parking garage and broken fire doors were identified as the cause of the problem. In this case, the ease with which the breath measurements were taken contributed to the swiftness with which the problem was identified and rectified (Figure 8-7). All measurements were taken in a period of less than two hours, without the necessity for drawing blood, sterilizing needles, or using a trained phlebotomist.

Wald et al. (1981) obtained measurements of percent COHb for 11,749 men, ages 35 to 64, who attended a medical center in London for comprehensive health screening examinations between 11am and 5pm. The time of smoking for each cigarette, cigar, or pipe since waking was recorded at the time of collection of a venous blood sample. COHb was determined using an IL 181 CO–Oximeter. Using 2% COHb as a normal cutoff value, 81% of cigarette smokers, 35% of cigar and pipe smokers, and 1% of nonsmokers were found to be above normal. An investigation of COHb and alveolar CO was conducted on a subgroup of 187 men (162 smokers and 25 nonsmokers). Three samples of alveolar air were collected at two-minute intervals within five minutes of collecting venous blood for COHb estimation. Alveolar air was collected by having the subject hold his breath for 20 s and then exhale through a one-meter glass tube with an internal diameter of 17 mm and fitted with a three-liter anesthetic bag at the distal end. Air at the proximal end of the tube was considered to be alveolar air, and a sample was removed by a small side tube located at 5 mm from the mouthpiece. CO content was measured using an Ecolyzer. The instrumental measurement is based on detection of the oxidation of CO to CO_2 by a catalytically active electrode in an

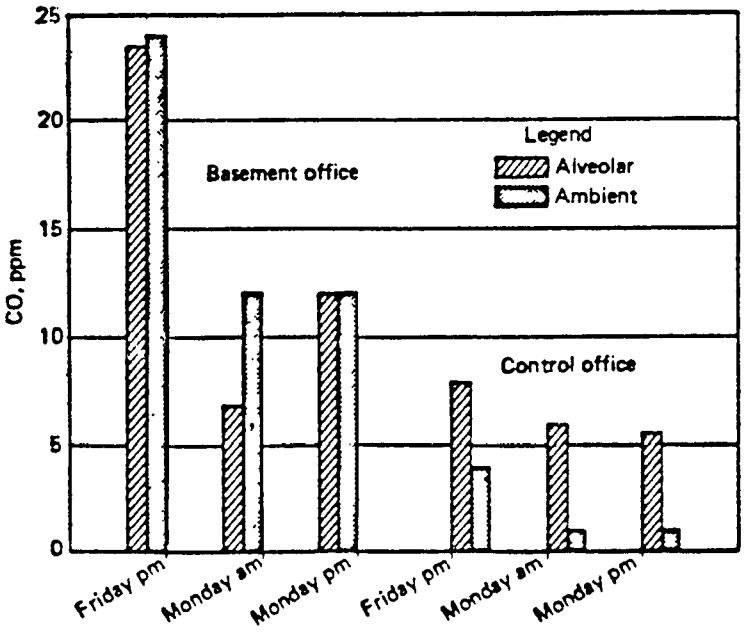

Figure 8-6. Changes in alveolar CO of nonsmoking basement office workers compared to nonsmoking workers in other offices between Friday afternoon, Monday morning, and Monday afternoon.

Source: Wallace (1983).

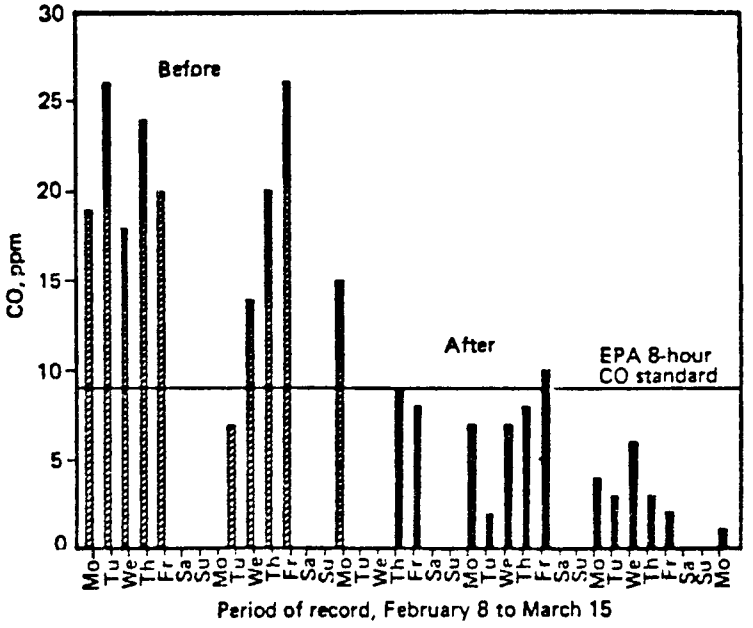

Figure 8-7. Eight-hour average CO concentrations in basement office before and after corrective action.

Source: Wallace (1983).

aqueous electrolyte. The mean of the last two readings to the nearest 0.25 ppm was recorded as the alveolar CO. Subjects reporting recent alcohol consumption were excluded because ethanol in the breath affects the response of the Ecolyzer. A linear regression equation of percent COHb on alveolar CO (see Table 8-14) had a correlation coefficient of 0.97, indicating that a COHb level could be estimated reliably from an alveolar CO level.

Honigman et al. (1982) determined alveolar CO concentrations by end-expired breath analysis for athletes (joggers). The group included 36 nonsmoking males and 7 nonsmoking females, all conditioned joggers, covering at least 21 mi per week for the previous six months in the Denver area. The participants exercised for a 40-min period each day over one of three defined courses in the Denver urban environment (elevation 1610 meters). Expired air samples were collected and analyzed before start of exercise, after 20 min and again at the end of the 40-min exercise period. Heart rate measurements at 20 min and 40 min were 84 and 82% of mean age predicted maxima, respectively, indicating exercise in the aerobic range. Relative changes in expired air CO concentrations were plotted and compared to ambient air concentrations for CO measured at the time of collecting breath samples. Air and breath samples were analyzed using an MSA model 70. Relative changes in expired end air CO based on the concentration of CO in breath before the start of exercise were plotted in terms of the ambient air concentrations measured during the exercise period, at both 20 and 40 min of exercise. For ambient concentrations of CO below 6 ppm, the aerobic exercise served to decrease the relative amount of end air expired CO as compared to the concentration measured before the start of exercise. For ambient concentrations in the range of 6 to 7 ppm, there was no net change in the CO concentrations in the expired air. For ambient air concentrations in excess of 7 ppm, the aerobic exercise resulted in relative increases of expired CO, with the increases after 40 min being greater than similar increases observed at the 20 min measurements. Sedentary controls at the measurement stations showed no relative changes. Thus, aerobic exercise, as predicted by the physiologic models of uptake and elimination, is shown to enhance transport of CO, thereby decreasing the time to reach equilibrium conditions.

Verhoeff et al. (1983) surveyed fifteen identical residences which used natural gas for cooking and geyser units for water heating. CO concentrations in the flue gases were measured using an Ecolyzer (2000 series). The flue gases were diluted to the dynamic range

of the instrument for CO (determined by Draeger tube analyses for CO_2 dilution to 2-2.5%). Theoretical concentrations for CO_2 in the flue gasses is 11.70% CO_2 under conditions of zero excess air for the natural gas to air mixture used. Breath samples were collected from 29 inhabitants by having each participant hold a deep breath for 20 seconds and exhale completely through a glass sampling tube (225 mL volume). The sampling tube was stoppered and taken to a laboratory for analysis of CO content using a gas-liquid chromatograph (Hewlett Packard, 5880A). The overall coefficient of variation for sampling and analysis was 7%, based on results of previous measurements. No significant differences were observed for nonsmokers as a result of their cooking or dishwashing activities using the natural gas fixtures. There was a slight increase in expired air CO for smokers, but this may be due to the possibility of increased smoking during the dinner hour.

Wallace et al. (1984) report data on measurements of end expired air CO and comparisons with predicted values based on personal CO measurements for populations in Denver and Washington, D.C. Correlations between breath CO and preceding eight-hour average CO exposures were high (0.6 to 0.7) in both cities. However, breath CO levels showed no relationship with ambient CO measurements at the nearest fixed-station monitor. Correlation coefficients were calculated for one-hour, two-hour, . . . up to 10-h average personal CO exposures; the highest correlations occurred at seven- to nine-hours, providing support for the EPA choice of 8 h as an averaging time for the NAAQS.

The major large-scale study employing breath measurements of CO was carried out by EPA in Washington and Denver in the winter of 1982-1983 (Johnson 1984; Hartwell et al., 1984; Akland et al., 1985; Wallace et al., 1984, 1988). In Washington, 870 breath samples were collected from 812 participants; 895 breath samples were collected from 454 Denver participants (two breath samples on two consecutive days in Denver). All participants also carried personal monitors to measure their exposures over a 24-h period in Washington or a 48-h period in Denver. The subjects in each city formed a probability sample representing 1.2 million adult nonsmokers in Washington and 500,000 adult nonsmokers in Denver. The distribution of breath levels in the two cities is shown for the subjects themselves ("unweighted" curves) and the larger populations they represented ("weighted" curves) in Figure 8-8.

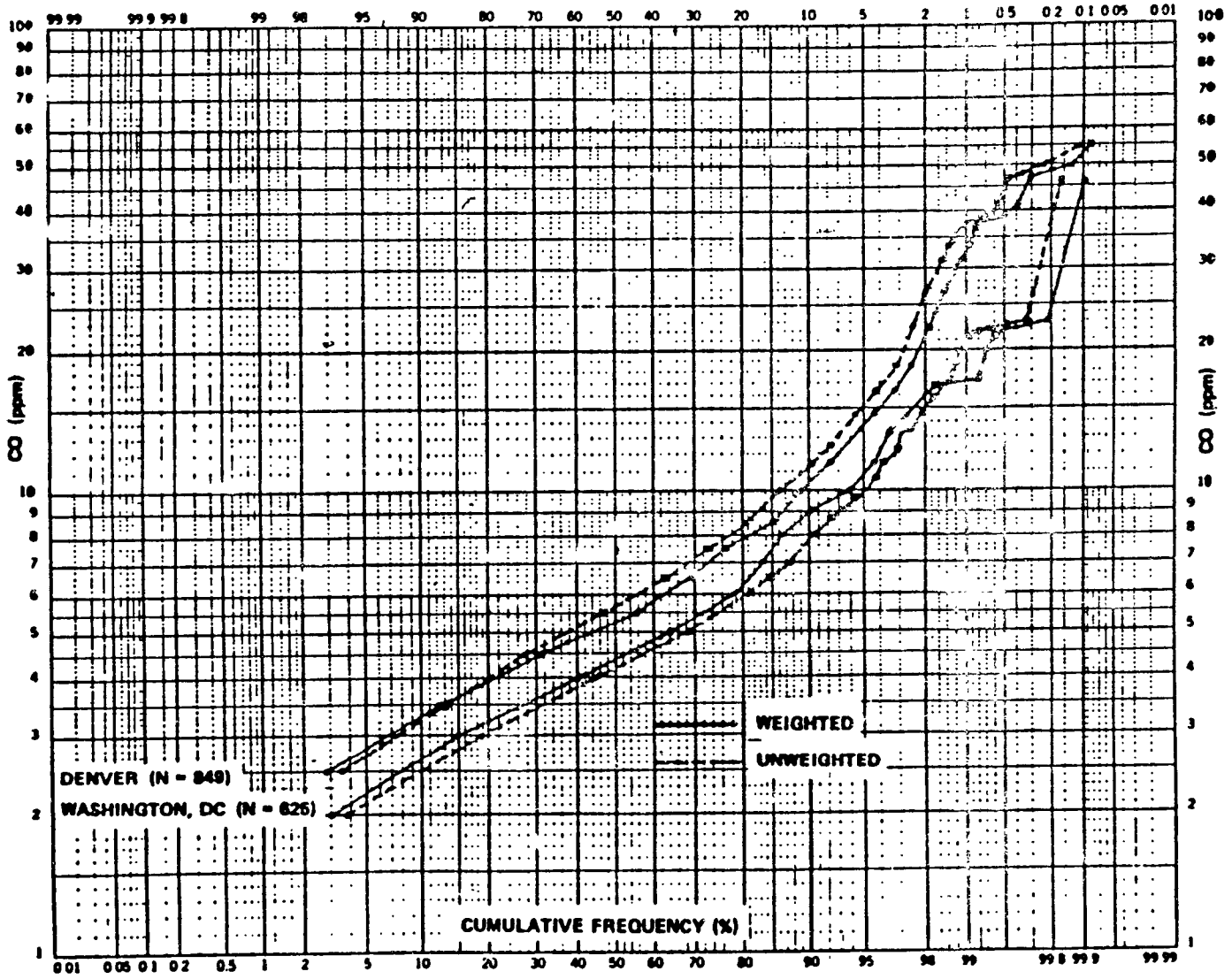

Figure 8-8. Distributions of CO in breath of adult nonsmokers in Denver and Washington.

Source: Wallace et al. (1988).

These distributions appear to be roughly lognormal, with geometric means of 5.2 ppm CO for Denver and 4.4 ppm for Washington. Geometric standard deviations were about 1.6 for each city. Arithmetic means were 7.1 ppm for Denver and 5.2 ppm for Washington.

Of greater regulatory significance is the number of people whose COHb levels exceeded the value of 2.1%, because EPA has determined that the current 9 ppm, eight-hour average standard would keep more than 99.9% of the most sensitive nonsmoking adult population below this level of protection (Federal Register, 1985). An alveolar CO value of about 10 ppm would correspond to a COHb level of 2%. The percent of people with measured breath values exceeding this level was about 6% in Washington. This percentage was increased to 10% when the correction for the effect of room air was applied (Figure 8-9). Of course, since the breath samples were taken on days and at times when they were not necessarily at their highest level during the year, these percentages are *lower limits* of the estimated number of people who may have incurred COHb levels above 2%. Yet the two central stations in Washington recorded a total of one exceedance of the 9 ppm standard during the winter of 1982-1983. Models based on fixed-station readings would have predicted that an exceedingly tiny proportion of the Washington population received exposures exceeding the standard. Therefore, the results from the breath measurements indicated that a much larger portion of both Denver and Washington residents were exceeding 2% COHb than was predicted by models based on fixed-station measurements.

It also should be noted that the number of people with measured maximum eight-hour exposures exceeding the EPA outdoor standard of 9 ppm was only about 3.5% of the Washington subjects. This value appears to disagree with the value of 10% obtained from the corrected breath samples. However, the personal monitors used in the study were shown to experience several different problems, including a loss of response associated with battery discharge toward the end of the 24-h monitoring period, which caused them to read low. Therefore, Wallace et al. (1988) concluded that the breath measurements were correct and the personal air measurements were biased low. The importance of including breath measurements in future exposure and epidemiology studies is indicated by this study.

Hwang et al. (1984) describe the use of expired air analysis for CO in an emergency clinical setting to diagnose the presence and extent of CO intoxication. The subjects were 47 Korean patients brought for emergency treatment showing various levels of

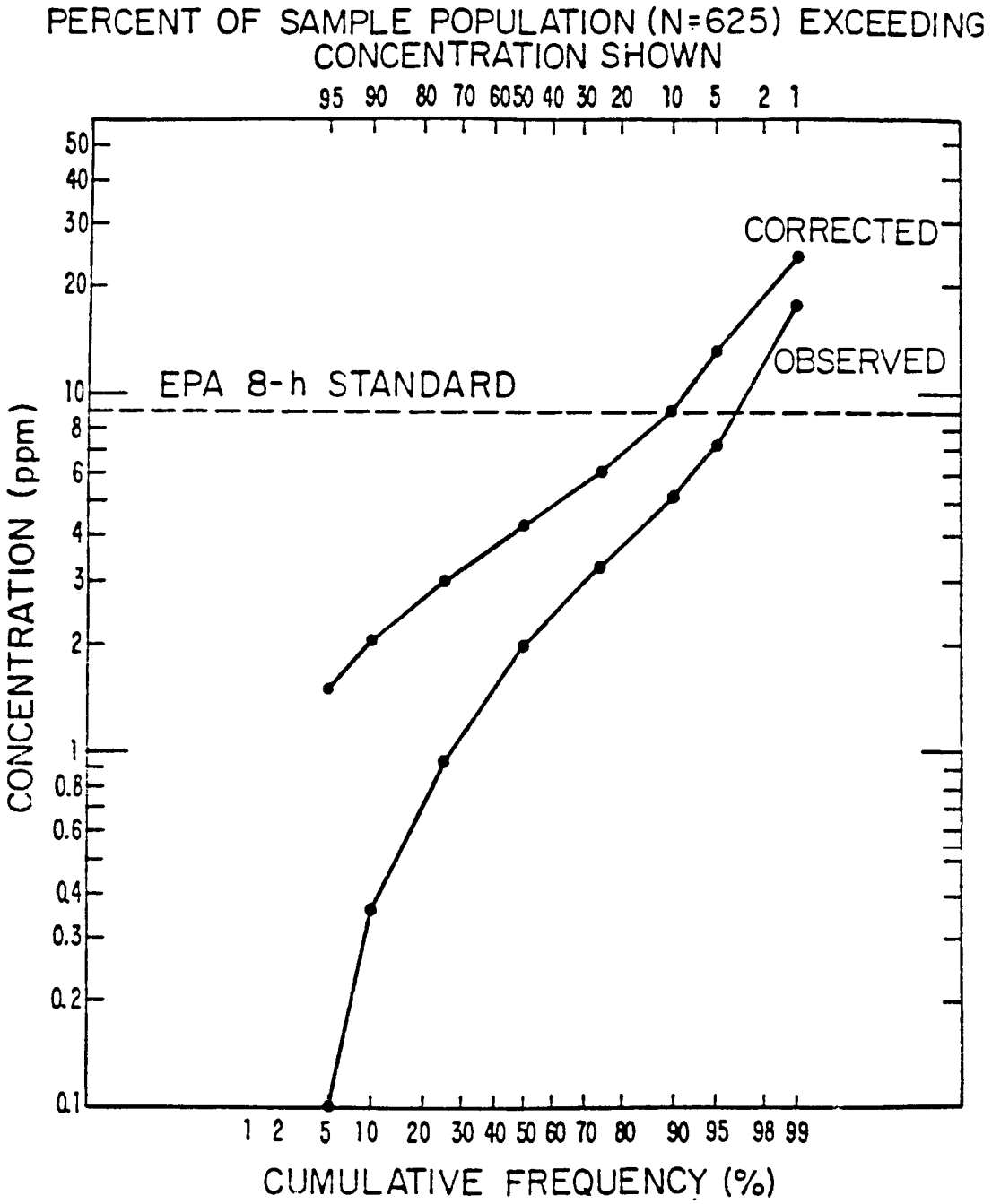

Figure 8-9. Percent of Washington sample population with eight-hour average CO exposures exceeding the concentrations shown. The eight-hour period ended at the time the breath sample was taken. The curve marked "OBSERVED" contains the actual readings of the personal monitors; these readings were corrected using the measured breath values.

Source: Wallace et al. (1988).

consciousness ranging from alertness (11), drowsiness (21), stupor (7), semicoma (5), coma (1), and unknown (2). The study group included 16 males, ages 16 to 57, and 31 females, ages 11 to 62. Exposure durations ranged from two to ten hours, with all exposures occurring in the evening and nighttime hours. The source of CO was mainly from use of charcoal fires for cooking and heating. In order to estimate expired air CO concentrations, a detector tube (Gastec 1La containing potassium palado sulfite as both a reactant and color change indicator for the presence of CO on silica gel) was fitted to a Gastec manual sampling pump. One stroke of the sampling plunger represents 100 cc of air. A 100-cc expired air sample was collected by inserting a detector tube at a nostril and slowly pulling back the plunger for one full stroke for expired air. A 10-cc sample of venous blood also was collected at this time for determination of percent COHb using a CO-Oximeter. The subjects showed signs of acute intoxication, and two relationships were found: a low CO (less the 100 ppm) and a high CO, (greater than 100 ppm) between expired air CO (CO_{exp}) and percent COHb.

Cox and Whichelow (1985) analyzed end-exhaled air (collected over approximately the last half of the exhalation cycle) for CO concentrations for a random population of 168 adults - 69 smokers and 99 nonsmokers. The results were used to evaluate the influence of home heating systems on exposures to and adsorption of CO. Ambient indoor concentrations of CO were measured in the homes of study subjects. The subjects included 86 men and 82 women, ranging in age from 18 to 74. Interviews were conducted usually in the living room of the subject's home. The type of heating system in use was noted and indoor air concentration of CO was measured using an Ecolyzer. After the ambient indoor CO was determined, a breath sample was collected from the subject. The subject was asked to hold a deep breath for 20 s, and then to exhale completely into a trilaminate plastic bag. The bag was fitted to the port of the Ecolyzer and the CO content of the exhaled air was measured. For smokers, the time since smoking their last cigarette and the number of cigarettes per day were noted. For nonsmokers there was a strong correlation between ambient CO and expired air CO. With smokers, the correlation was strongest with the number of cigarettes per day. The data also supported the supposition that smokers are a further source of ambient CO in the indoor environment.

Lambert et al. (1988) compared breath CO levels to blood COHb levels in 28 subjects (including two smokers). Breath CO was collected using the standard technique developed by Jones et al. (1958): maximal inspiration followed by a 20-s breath hold and discarding the first portion of the expired breath. One-liter bags were used to collect the breath samples, which were measured on an Ecolyzer 2000 monitor equipped with Purafil® and activated charcoal filters to scrub interferences such as alcohol. Excellent precision ($\pm$0.2 ppm) was obtained in 35 duplicate samples. Blood samples were collected within 15 min of the breath samples using a gas-tight plastic syringe rinsed with sodium heparin. Carboxyhemoglobin was measured using an IL 282 CO-Oximeter. Some samples also were measured using a GC. The CO-Oximeter appeared to be reading high, particularly in the <2% COHb range of interest. A reading of 0.5 %COHb on the particular CO-Oximeter used in this study would be only 0.3% using the GC and a reading of 1% COHb on the CO-Oximeter would be only 0.7% on the GC.

The results showed poor correlation between the pooled nonsmokers' breath CO and blood COHb levels (n = 104 measurements, $r^2 = 0.19$). However, better correlation was observed for three individual nonsmoking subjects, who appeared to have roughly parallel slopes (0.13 to 0.27) but widely differing blood COHb intercepts (0.1, 0.4, and 1.0 %COHb). The authors interpreted these findings as suggesting that the CO-Oximeter may be sensitive to an unidentified factor in the blood of individuals. Possible factors suggested by the authors include triglycerides and hemochromagens (a group of compounds formed when heme combines with organic nitrogen species), which are known to absorb light in the 550 to 555 nm wavelength used by the CO-Oximeter. Another concern regarding the CO-Oximeter is the calibration method, which uses saturated (98%COHb) bovine serum as the only span calibration point. This is far above the 0.5 to 3 %COHb range of interest for nonsmoking subjects.

In view of the great dependence in laboratory studies on the CO-Oximeter, the authors concluded that there was "an important and immediate need to further investigate the instrument's performance at COHb levels resulting from typical ambient exposures." Such studies should include a comprehensive side-by-side study with other reference methods, including gas chromatography, manometry, and other spectrophotometric methods. Full spectral scans should be performed to quantify light absorbance and scattering effects on

COHb measurement. Also, an improved calibration method should be developed, including whole blood and dye standards and the use of multiple calibration points in the 0 to 3% COHb range of interest.

8.5.3 Potential Limitations

8.5.3.1 Pulmonary Disease

A major potential influence on the relationship between blood and alveolar partial pressures of CO is the presence of significant lung disease. Hackney et al. (1962) demonstrated the slow increase in exhaled CO concentration in a rebreathing system peaked after 1.5 minutes in healthy subjects but required 4 minutes in a subject with lung disease. These findings have been substantiated by Guyatt et al. (1988) who reported that patients with pulmonary disease did not have the same relationship between percent COHb and breathhold CO concentrations. The group with pulmonary disease had a FEV_1/FVC percentage of $<71.5\%$ compared to the healthy subjects with a FEV_1/FVC percentage of $>86\%$. The linear regression for the healthy group was COHb = 0.629 + 0.158(ppm CO); and for the pulmonary disease group was COHb = 0.369 + 0.185(ppm CO). This means that at low CO levels, individuals with obstructive pulmonary disease would have a lower "alveolar" CO level for any given percent COHb level than would the healthy subjects.

8.5.3.2 Subject Age

The relationship between age and COHb level is not well established. Kahn et al. (1974) reported that nonsmoking subjects under the age of 19 years had a significantly lower percent COHb than older subjects but there was no difference in COHb between the ages of 20 and 59 years. Kahn et al. also reported that there was a slight decrease in the COHb levels in nonsmoking subjects over the age of 60 years. Radford and Drizd (1982) also reported that younger subjects, 3 to 11 years' old, had lower levels of COHb than did the older age group of 12 to 74 years. Goldsmith (1970) reported that expired CO levels were unchanged with age in nonsmokers; however, there was a steady decline in the expired CO levels with age in smokers. The decrease in expired CO is disproportionately large for the decrease in COHb levels measured by Kahn et al. (1974) in older subjects. Therefore, by comparison of the data from these two studies, it would appear that older subjects have higher

levels of COHb than predicted from the expired CO levels. It is not known how much of this effect is due to aging of the pulmonary system, resulting in a condition similar to the subjects with obstructive pulmonary disease.

8.5.3.3 Effects of Smoking

Studies evaluating the effect of cigarette smoking on end-expired CO have found a phasic response that depends on smoking behavior (Woodman et al., 1987; Henningfield et al., 1980). There is an initial rapid increase in the CO concentration of expired air as a result of smoking. This is followed by a rapid (five-minute) decrease after cessation of smoking and a slow decrease over the 5- to 60-min period after smoking. A comparison of the results from one study (Tsukamoto and Matsuda, 1985) showed that the CO concentration in expired air increases by approximately 5 ppm by smoking one cigarette. This corresponds to an increase of 0.67% COHb based on blood-breath relationships developed by the authors. Use of cigarettes with different tar and nicotine yields or the use of filter tip cigarettes showed no apparent effect on end-expired CO concentrations (Castelli et al., 1982). However, knowledge of the breath sample results does. King et al. (1983) were able to show that immediate feedback on CO concentrations promoted behavioral changes in cigarette smokers which subsequently resulted in lower CO concentrations in expired air for return visits. Furthermore, reported rates of smoking were lower for the second visit than those reported for the first visit.

The relationship between breathhold CO and blood CO is apparently altered due to smoking making the detection of small changes difficult. Guyatt et al. (1988) have shown that smoking one cigarette results in a variable response in the relationship between breath-hold CO and COHb levels. The range of $F_{A(CO)}$ values for a 1% increase in COHb was from -5 ppm to +5 ppm. The correlation between the change in $F_{A(CO)}$ and the change in COHb in 500 subjects was only 0.705. This r value indicates that only 50% of the change in $F_{A(CO)}$ was due to changes in COHb. It is not known how much of this residual error is due to subject compliance or to error in the method. Therefore, the results obtained with breathholding in smoking subjects should be viewed with caution unless large differences in $F_{A(CO)}$ are reported (i.e., considerable cigarette consumption is being evaluated).

In summary, the measurement of exhaled breath has the advantages of ease, speed, precision, and greater subject acceptance than measurement of blood COHb. However, the accuracy of the breath measurement procedure and the validity of the Haldane relationship between breath and blood at low environmental CO concentrations remains in question. There appears to be a clear research need to validate the breath method at low CO exposures. In view of the possible problems with the CO-Oximeter, such validation should be done using gas chromatography for the blood COHb measurements.

8.6 SUMMARY AND CONCLUSIONS

The current NAAQS for CO (9 ppm for eight hours, 35 ppm for one hour) are designed to protect against actual and potential human exposures in outdoor air that would cause adverse health effects. Compliance with the NAAQS is determined by measurements taken at fixed-site ambient monitors, the use of which is intended to provide some measure of the general level of exposure of the population represented by the CO monitors. Results of both exposure monitoring in the field, and modeling studies, summarized in this Chapter indicate that individual personal exposure does not directly correlate with CO concentrations determined by using fixed-site monitors alone. This observation is due to the mobility of people and to the spatial and temporal variability of CO concentrations. While failing to show a correlation between individual personal monitor exposures and simultaneous nearest fixed-site monitor concentrations, studies do suggest that aggregate personal exposures are lower on days of lower ambient CO levels as determined by the fixed-site monitors and higher on days of higher ambient levels.

Cigarette consumption represents a special case of CO exposure; for the smoker it almost always dominates over personal exposure from other sources. Studies by Radford and Dridz (1982) show that COHb levels of cigarette smokers average 4% while those of nonsmokers average 1%. Therefore, this summary focuses on environmental exposure of nonsmokers to CO.

People encounter CO in a variety of environments that include travelling in motor vehicles, working at their jobs, visiting urban locations associated with combustion sources, or cooking over a gas range. Studies of human exposure have shown that among these

settings the motor vehicle is the most important for regularly encountered elevations of CO. Studies by Flachsbart et al. (1987) indicated that CO exposures while commuting in Washington, D.C. average 9 to 14 ppm at the same time that fixed station monitors record concentrations of 2.7 to 3.1 ppm. Similar studies conducted by EPA in Denver and Washington have demonstrated that the motor vehicle interior has the highest average CO concentrations (averaging 7 to 10 ppm) of all microenvironments (Johnson, 1984). In these studies, 8% of all commuters experienced eight-hour exposures greater than 9 ppm while only 1% of noncommuters received exposures over that level. Furthermore, commuting exposures have been shown to be highly variable with some commuters breathing CO in excess of 25 ppm.

Another important setting for CO exposure is the workplace. In general, exposures at work exceed CO exposures during nonwork periods, apart from commuting to and from work. Average concentrations may be elevated during this period since workplaces are often located in congested areas that have higher background CO concentrations than do many residential neighborhoods. Occupational and nonoccupational exposures may overlay one another and result in a higher concentration of CO in the blood. Certain occupations also increase the risk of high CO exposure (e.g., those occupations involved directly with vehicle driving, maintenance, and parking). Occupational groups exposed to CO by vehicle exhaust include auto mechanics; parking garage and gas station attendants; bus, truck or taxi drivers; police and warehouse workers. Other industrial processes produce CO directly or as a by-product, including steel production, coke ovens, carbon black production, and petroleum refining. Firefighters, cooks, and construction workers also may be exposed at work to higher CO levels. Occupational exposure in industries or setting with CO production also represent some of the highest individual exposures observed in field monitoring studies. For example, in EPA's CO exposure study in Washington, of the approximately 4% (29 of 712) of subjects working in jobs classified as having a high potential for CO exposure, seven subjects (or approximately 25%) experienced eight-hour CO exposures in excess of 9 ppm.

The highest indoor nonoccupational CO exposures are associated with combustion sources and include enclosed parking garages, service stations, restaurants and stores. The lowest indoor CO concentrations are found in homes, churches, and health care facilities. EPA's Denver Study showed that passive cigarette smoke is associated with increasing a

nonsmoker's exposure by an average of about 1.5 ppm and that use of a gas range is associated with about 2.5 ppm increase at home. Other sources which may contribute to CO in the home include combustion space heaters and wood burning stoves.

As noted above, people encounter different and often higher exposures than predicted from fixed-site monitoring data, because of the highly localized nature of CO sources. For example, during the winter sampling period, 10% of Denver volunteers and 4% of Washington volunteers recorded personal exposures in excess of 9 ppm for eight hours. Breath measurements from the Washington volunteers indicated that as much as 9% of the population could have experienced a 9 ppm, eight-hour average. In contrast, during the entire winter period of 1982-1983, the two ambient CO monitors in Washington reported only one exceedance of the 9-ppm level. In another study, using data from analyses of COHb in blood, Wallace and Ziegenfus (1985) report that CO in blood is uncorrelated with CO measured by ambient monitors. These findings point out the necessity of having personal CO measurements augment fixed-site ambient monitoring data when total human exposure is to be evaluated. Data from these field studies can be used to construct and test models of human exposure that account for time and activity patterns known to affect exposure to CO. Models developed to date tend to underpredict the variability of CO exposures observed in field studies and have not been able to successfully predict individual exposures. The models may be modified and adjusted using information from field monitoring studies in order to capture the observed distribution of CO exposures, including the higher exposures found in the tail of the exposure distribution. The models also are useful for evaluating alternative pollutant control strategies.

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9. PHARMACOKINETICS AND MECHANISMS OF ACTION OF CARBON MONOXIDE

Pharmacokinetics in the classical sense has been concerned primarily with the determination of blood levels for various dosage regimens of pharmacological agents. More modern approaches tend to extend the definition to include other aspects of substance kinetics. For example, it may include membrane diffusion, substance binding and release characteristics, modeling, metabolic pathways, and other processes. The general tendency is to depart from anatomically or physiologically defined region(s) to a more encompassing and unifying concept of compartment(s) comprised of real as well as abstract constructs (Bischoff, 1986). It will be in this sense that the CO pharmacokinetics will be approached and presented in this chapter.

9.1 ABSORPTION, DISTRIBUTION, AND PULMONARY ELIMINATION

9.1.1 Introduction

The scope of this chapter and generally of this criteria document does not allow for an extensive review of the mechanisms and factors involved in CO uptake and elimination. The review will concentrate on fundamental processes and the key factors affecting CO metabolism and resultant effects. For a more in-depth explanation of certain facets of CO toxicity the reader is referred to other chapters of this document and to other review material (Fishman et al., 1987).

9.1.2 Pulmonary Uptake

9.1.2.1 Mass Transfer of Carbon Monoxide

Although CO is not one of the respiratory gases, the similarity of the physicochemical properties of CO and O_2 permit an extension of the findings of studies on the kinetics of transport of O_2 to that of CO.

The rate of formation and elimination of COHb, its concentration in blood, as well as its catabolism is controlled by numerous physical and physiological mechanisms. The relative contribution of these mechanisms to the overall COHb kinetics will depend on the environmental conditions (ambient CO concentration, altitude, etc.), physical activity of an individual, and many other physiological processes, some of which are complex and still poorly understood.

The mass transport of CO between the airway opening (mouth and nose) and red blood cell (hemoglobin) is predominantly controlled by physical processes. The CO transfer to the Hb-binding sites is accomplished in two sequential steps: (1) transfer of CO in a gas phase, between the airway opening and the alveoli, and (2) transfer in a "liquid" phase, across air-blood interface including the red blood cell (RBC). While the mechanical action of the respiratory system and the molecular diffusion within the alveoli are the key mechanisms of transport in the gas phase, the diffusion of CO across the alveolo-capillary barrier, plasma, and RBC is the virtual mechanism of the liquid phase.

9.1.2.2 Effects of Dead Space and Uneven Distribution of Ventilation and Perfusion

Ideally, the optimal transfer of gases across alveolo-capillary membrane can be achieved only if regional distribution of ventilation is uniform and matches regional blood flow. Numerous studies have shown that in the upright subject ventilation is preferentially distributed to the lower lung zones (Milic-Emili et al., 1966). Besides posture (Clarke et al., 1969), changes in resting lung volume (Sutherland et al., 1968), airway resistance (Hughes et al., 1972), and lung compliance (Glaister et al., 1973) by either exogenous factors or pathophysiological conditions will aggravate maldistribution of ventilation. The unevenness is further affected by inspiratory (Anthonisen et al., 1970) and expiratory flow rates (Millette et al., 1969), which influence sequential filling and emptying of the lung regions.

Even in perfectly healthy subjects the homogeneity of ventilation, perfusion, and consequent $\dot{V}_A/\dot{Q}$ ratio of unity is unattainable because of a right-to-left shunt. Normally, only a small amount of mixed venous blood (2 to 4%) bypasses the alveoli and reaches systemic circulation without oxygenation. Any increase in the alveolo-arterial O_2 gradient (A-a DO_2) will contribute to hypoxemia, thus enhancing CO loading (Riley and Permutt, 1973). It follows that any imbalance in the distribution patterns of these two compartments must result

in a decrease in the efficiency of gas exchange (Scrimshire, 1977) including CO. The average ventilation to perfusion ratio of about 0.9 reported in the upright subjects indicates that overall perfusion ($\dot{Q}$) exceeds ventilation ($\dot{V}$) ; regional nonuniformity, however, is considerably greater (the $\dot{V}_A/\dot{Q}$ ratios range from 0.6 to 3.0; Inkley and MacIntyre, 1973). Consequently, in the underventilated but overperfused regions of the lung the amount of CO available for diffusion will be less than if the ventilation and perfusion were matched, while in the overventilated but underperfused regions the amount of CO that could diffuse would be the same as if the distributions were matched. On exercise, when the distribution of both ventilation and perfusion becomes more uniform, the ratios approach unity and the rate of COHb formation will accelerate (Harf et al., 1978).

Besides regional inhomogeneity of distribution, the bulk movement of inhaled air will be influenced by factors related to inspiratory flow and subsequent mixing with residual air. At rest, mixing of gases is almost complete and no discernible stratification of concentration between the large airways and the alveoli occurs. However, any changes in ventilation or pattern of breathing (e.g., during exercise) will aggravate stratified inhomogeneity and increase a concentration gradient between central and peripheral airways. The relative effects of ventilation and perfusion inhomogeneities on convectional and diffusional transport of CO will very much depend on the rate of change and concentration of CO in inspired air. The higher the concentration and the shorter the rise time of CO in the inspired air, the greater the effects these factors will have on the CO uptake and ultimately COHb concentration in blood.

The ventilation-perfusion unevenness will not only contribute to hypoxemia, but the mismatch will influence the size of the physiological dead space (V_D) (Standfuss, 1970) and ultimately alveolar ventilation, which is one of the principal, but seldom-measured determinants of the rate of uptake of CO (see Section 9.3 on Coburn-Forster-Kane [CFK] modeling). Any increase in a dead space to tidal volume ratio (V_D /V_T) will decrease $\dot{V}_A$ and vice versa. In normal healthy subjects at rest V_D comprises about 25 to 45% of tidal volume; in older subjects or in patients with pulmonary disease the percentage might be as high as 70% (Martin et al., 1979).

9.1.2.3 Alveolo-Capillary Membrane and Blood-Phase Diffusion

While the above mechanisms controlling the rate of formation of blood COHb are predominantly active processes, the second key mechanism, a diffusion of gases across the alveolar air-hemoglobin barrier, is an entirely passive process. In order to reach the Hb–binding sites, the CO and other gas molecules have to pass across the alveolo-capillary membrane, diffuse through the plasma, pass across the RBC membrane, and finally the RBC stroma before reaction between CO and Hb can take place. The molecular transfer across the membrane and the blood phase is governed by general physicochemical laws, particularly by the Fick's first law of diffusion. The exchange and equilibration of gases between the two compartments (air and blood) is very rapid. The dominant driving force is a partial pressure differential of CO across this membrane. For example, inhalation of a bolus of air containing high levels of CO will rapidly increase blood COHb; by immediate and tight binding of CO to Hb the partial pressure of CO within the RBC is kept low, thus maintaining a high pressure differential between air and blood, and consequent diffusion of CO into blood. Subsequent inhalation of CO-free air progressively decreases the gradient to the point of its reversal (higher CO pressure on the blood side than alveolar air) and CO will be released into alveolar air. Because binding of CO to Hb is a much stronger and considerably faster reaction (half-time <0.07) than clearance of CO by ventilation, the air-blood pressure gradient is usually higher than the blood-air gradient, and the CO uptake will be a proportionally faster process than CO elimination. The rate of CO release will be further affected by the products of tissue metabolism. Under pathologic conditions, where one or several components of the air-blood interface might be severely affected, as in emphysema, fibrosis, or edema, both the uptake and elimination of CO will be affected.

The rate of diffusion of gases might be altered considerably by many physiological factors acting concomitantly. Diurnal variations in CO diffusion related to variations in Hb have been reported in normal healthy subjects (Frey et al., 1987). Others found the changes to be related also to physiological factors such as O_2Hb, COHb, partial pressure of alveolar CO_2, ventilatory pattern, oxygen consumption ($\dot{V}O_2$), blood flow, functional residual capacity, etc. (Forster, 1987). It has been confirmed repeatedly that diffusion is body-position and ventilation dependent. In a supine position at rest, CO diffusion has been significantly higher than that at rest in a sitting position. In both positions CO diffusion during exercise has been

greater than at rest (McClean et al., 1981). CO diffusion will increase with exercise, and at maximum work rates the diffusion will be maximal regardless of position. This increase is attained by increases in both the membrane-diffusing component and the pulmonary capillary blood flow (Stokes et al., 1981). Diffusion seems to be relatively independent of lung volume within the midrange of vital capacity. However, at extreme volumes the differences in diffusion rates could be significant; at total lung capacity the diffusion is higher, while at residual volume it is lower than the average (McClean et al., 1981). Smokers showed on the average lower diffusion rates than nonsmokers (Knudson et al., 1989).

The above physiological processes will affect minimally COHb formation in healthy individuals exposed to low and relatively uniform levels of CO. Under such ambient conditions these factors will be the most influential during the initial period of CO distribution and exchange. If sufficient time is allowed for equilibration, the sole determinant of COHb concentration in blood will be the ratio of CO to O_2. However, the shorter the half-time for equilibration (e.g., due to hyperventilation, high concentration of CO, increased cardiac output, etc.) the more involved these mechanisms will become in modulating the rate of CO uptake (Pace et al., 1950; Coburn et al., 1965). At high transient CO exposures of resting individuals both the cardiac and the lung function mechanisms will control the rate of CO uptake. Incomplete mixing of blood might result in a substantial difference between the arterial and venous COHb concentrations (Godin and Shephard, 1972). In chronic bronchitics, asthmatics, and other subpopulations at risk (pregnant women, the elderly, etc.) the kinetics of COHb formation will be even more complex, because any abnormalities of ventilation and perfusion and gas diffusion will aggravate CO exchange (see Chapter 12 for details on subpopulations at risk).

9.1.3 Tissue Uptake

Distribution of CO within the tissue(s) will be determined primarily by exchange and chemical reaction kinetics. In order to facilitate understanding of these well integrated processes it would be helpful to consider CO uptake by the most involved physiological compartments/organs.

9.1.3.1 The Blood

Although the rate of CO binding with Hb is about 1/5 slower and the rate of dissociation from Hb is an order of magnitude slower than the respective rates for O_2, the CO chemical affinity (M) for Hb is about 245 (240 to 250) times greater than that of O_2 (Roughton, 1970). One part of CO and 245 parts of O_2 would form equal parts of O_2Hb and COHb (50% of each) which would be achieved by breathing air containing 21% oxygen and 570 ppm CO. Moreover, under steady-state conditions (gas exchange between blood and atmosphere remains constant), the ratio of COHb to O_2Hb is proportional to the ratio of their respective partial pressures. The relationship between the affinity constant M and PO_2 and PCO first expressed by Haldane (1898), has the following form.

$$COHb/O_2Hb = M * (PCO/PO_2) \qquad (9\text{-}1)$$

At equilibrium, when Hb is maximally saturated by O_2 and CO at their respective gas tensions, the M value for all practical purposes is independent of pH and 2,3-DPG over a wide range of PCO/PO_2 ratios. The M, however, is temperature dependent (Wyman et al., 1982).

Under dynamic conditions competitive binding of O_2 and CO to Hb is complex; simply said, the greater the number of hemes bound to CO, the greater is the affinity of free hemes for O_2. Any decrease in the amount of available Hb for O_2 transport (CO poisoning, bleeding, anemia, blood diseases, etc.) will reduce the quantity of O_2 carried by blood to the tissue. However, CO not only occupies O_2-binding sites, molecule for molecule, thus reducing the amount of available O_2, but also alters characteristic relationships between O_2Hb and PO_2 which in normal blood is S-shaped. With increasing concentration of COHb in blood, the dissociation curve is shifted gradually to the left and its shape is transformed into that of a rectangular hyperbola (Figure 9-1). Because the shift occurs over a critical saturation range for release of O_2 to tissues, a reduction in O_2Hb by CO poisoning will have more severe effects on the release of O_2 than the equivalent reduction in Hb due to anemia. Thus, in an anemic patient (50%) at the tissue PO_2 of 26 torr (v'_1), 5 vol % of O_2 (50% desaturation) might be extracted from blood, the amount sufficient to sustain tissue metabolism. In contrast, in a person poisoned with CO (50% COHb), the tissue PO_2 will

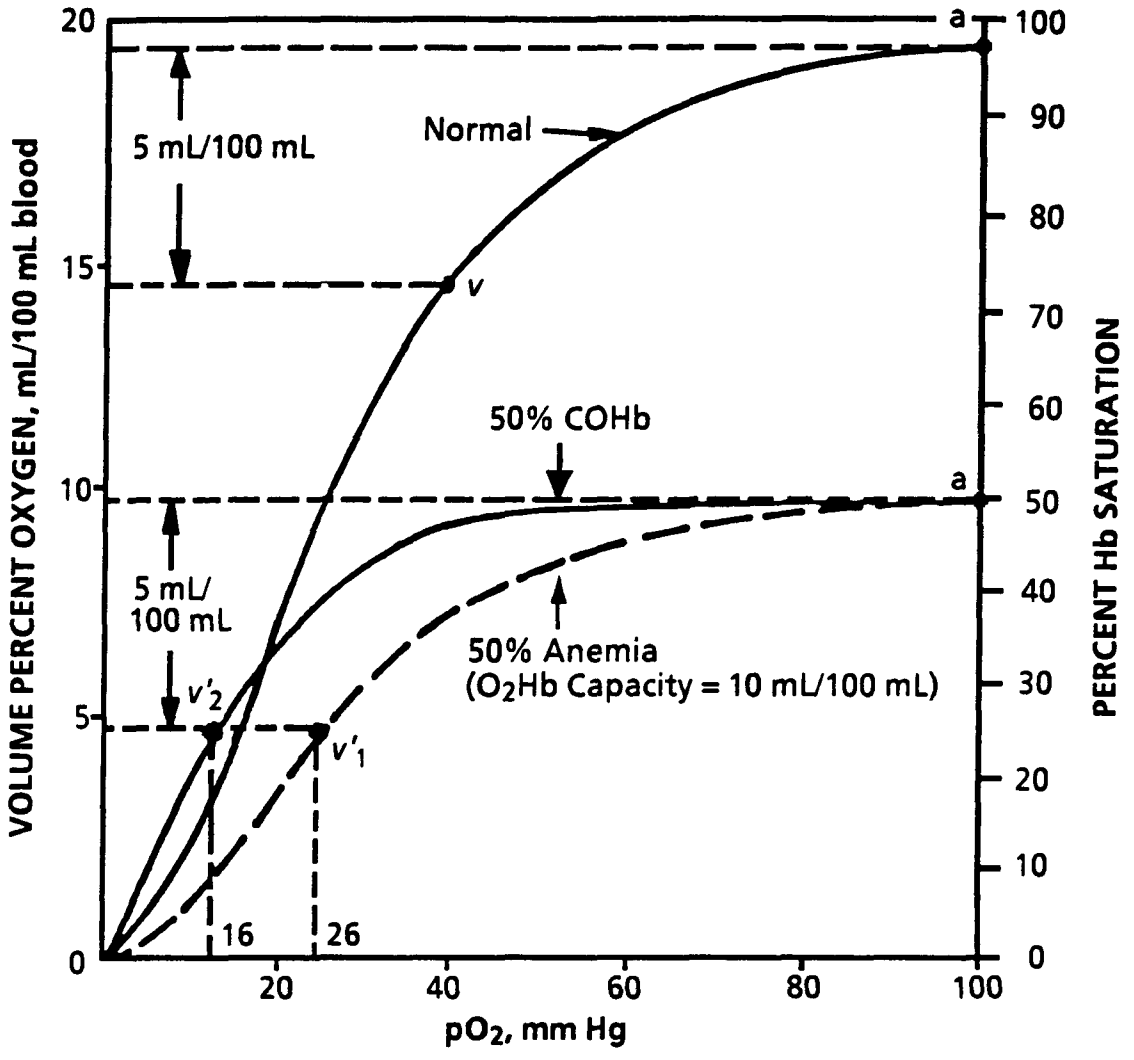

Figure 9-1. Oxyhemoglobin dissociation curves of normal human blood, of blood containing 50% carboxyhemoglobin, and of blood with a 50% normal hemoglobin concentration due to anemia.

Source: Adapted from Coburn et al. (1977); Rahn and Fenn (1955); Roughton and Darling (1944).

have to drop to 16 torr (v'_2 ; severe hypoxia) to release the same, 5 vol % O_2 (Figure 9-1). Any higher demand on oxygen under these conditions (e.g., by exercise) might result in coma of the CO-poisoned individual.

9.1.3.2 The Lung

Although the lung in its function as a transport system for gases is exposed continuously to CO, very little CO actually diffuses and is stored in the lung tissue itself, except for the alveolar region. The epithelium of the conductive zone (nasopharynx and large airways) presents a significant barrier to diffusion of CO (Guyatt et al., 1981). Therefore, diffusion and gas uptake by the tissue, even at very high CO concentrations, will be very slow; most of this small amount of CO will be dissolved in the mucosa of the airways. Diffusion into the submucosal layers and interstitium will depend very much on the concentration of CO and duration of exposure. Experimental exposures of the oronasal cavity of monkeys to very high concentrations of CO for a very short period of time increased their blood COHb level to only 1.5%. Comparative exposures of the whole lung, however, elevated COHb to almost 60% (Schoenfisch et al., 1980). Thus diffusion of CO across the airway mucosa will contribute very little if at all to overall COHb concentration. In the transitional zone (≤20th generation) where both conductive and diffusive transport take place, diffusion of CO into lung interstitium will be much easier, and at times more complete. In the respiratory zone (alveoli), which is the most effective interface for CO transfer, diffusion into lung interstitium will be complete. Because the total lung tissue mass is rather small compared to other CO compartments, relatively small amount of CO (primarily as dissolved CO) will be distributed within the lung structures.

9.1.3.3 Heart and Skeletal Muscles

The role of myoglobin in O_2 transport is not yet fully understood. Myoglobin (Mb) as a respiratory hemoprotein of muscular tissue will undergo a reversible reaction with CO in a manner similar to O_2. The greater affinity of O_2 for myoglobin than hemoglobin (hyperbolic versus S-shaped dissociation curve) is in this instance physiologically beneficial because a small drop in tissue PO_2 will release a large amount of O_2 from oxymyoglobin (O_2Mb). The

main function of Mb is thought to serve as a temporary store of O_2 and act as a diffusion facilitator between hemoglobin and the tissues (for details see Section 9.4.2).

Myoglobin has an affinity constant approximately eight times lower than hemoglobin (M=20 to 40 vs. 245, respectively). As with Hb, the combination velocity constant between CO and Mb is only slightly lower than for O_2, but the dissociation velocity constant is much lower than for O_2. The combination of greater affinity (Mb is 90% saturated at PO_2 of 20 mmHg) and lower dissociation velocity constant for CO favors retention of CO in the muscular tissue. Thus, a considerable amount of CO potentially can be stored in the skeletal muscle. The ratio of carboxymyoglobin (COMb) to COHb saturation for skeletal muscle of a resting dog and cat has been determined to be 0.4 to 0.9; for cardiac muscle the ratio is slightly higher (0.8 to 1.2) (Coburn et al., 1973; Sokal et al., 1986). Prolonged exposures did not change this ratio in either muscle indicating that certain, not yet identified, mechanisms prevented equilibrium between the vascular and extravascular compartments (Sokal et al., 1984). During exercise the relative rate of CO binding increases more for Mb than for Hb and CO will diffuse from blood to skeletal muscle (Werner and Lindahl, 1980); consequently, the COMb/COHb will increase for both skeletal and cardiac muscles (Sokal et al., 1986). A similar shift in CO has been observed under hypoxic conditions because a fall in intracellular PO_2 below a critical level will increase the relative affinity of Mb to CO (Coburn et al., 1971). Consequent reduction in Mb-carrying capacity of O_2 might have a profound effect on the supply of O_2 to the tissue (see Section 11.1).

9.1.3.4 Brain and Other Tissues

Apart from Hb and Mb, which are the largest stores of CO, other hemoproteins will react with CO. However, the exact role of such compounds on O_2-CO kinetics still needs to be ascertained (see Section 9.4). Concentration of CO in brain tissue has been found to be about 30 to 50 times lower than that in blood. During the elimination of CO from brain the above ratio of concentrations was still maintained (Sokal et al., 1984). (For a more in-depth discussion see Chapter 10, Section 10.4.)

9.1.4 Pulmonary and Tissue Elimination

An extensive amount of data available on the rate of CO uptake and the formation of COHb contrast sharply with the limited information available on the dynamics of CO washout from body stores and blood. Although the same factors that govern CO uptake will affect CO elimination, the relative importance of these factors might not be the same (Landaw, 1973; Petersen and Stewart, 1970). Both the formation as well as the decline of COHb fit a second-order function best, increasing during the uptake period and decreasing during the elimination period. Hence, an initial rapid decay will gradually slow down (Landaw, 1973; Wagner et al., 1975; Stewart et al., 1970). The elimination rate of CO from an equilibrium state will follow a monotonically decreasing second-order (logarithmic or exponential) function (Pace et al., 1950). The rate, however, might not be constant following transient exposures to CO, whereas at the end of exposure the steady-state conditions were not reached yet. In this situation, particularly after very short and high CO exposures, it is possible that COHb decline could be biphasic and it can be approximated best by a double-exponential function: The initial rate of decline or "distribution" might be considerably faster than the later "elimination" phase (Wagner et al., 1975). Reported divergence of COHb decline rate in blood and in exhaled air suggests that CO elimination rate(s) from extravascular pool(s) is (are) slower than that reported for blood (Landaw, 1973). Although the absolute elimination rates are associated positively with the initial concentration of COHb, the relative elimination rates appear to be independent of the initial concentration of COHb (Wagner et al., 1975).

The half-time of CO disappearance from blood under normal recovery conditions while breathing air showed considerable between-individual variance. For COHb concentration of 2 to 10%, the half-time ranged from 3 to 5 h (Landaw, 1973); others reported the range to be 2 to 6.5 h for slightly higher initial concentrations of COHb (Petersen and Stewart, 1970). Increased inhaled concentration of oxygen accelerated elimination of CO; by breathing 100% oxygen the half-time was shortened by almost 75% (Petersen and Stewart, 1970). The elevation of partial pressure of oxygen to three atmospheres reduced the half-time to about 20 min, which is approximately a 14-fold decrease over that seen when breathing room air (Britten and Myers, 1985; Landaw, 1973). Although the washout of CO can be somewhat accelerated by an admixture of 5% CO_2 in O_2, hyperbaric O_2 treatment is more effective in facilitating displacement of CO.

9.2 TISSUE PRODUCTION AND METABOLISM OF CARBON MONOXIDE

In the process of natural degradation of hemoglobin to bile pigments, a carbon atom (a-bridge C) is separated from the porphyrin nucleus and subsequently is catabolized by microsomal heme oxygenase into CO. The major site of heme breakdown and therefore the major production organ of endogenous CO is the liver (Berk et al., 1976). The spleen and the erythropoietic system are other important catabolic generators of CO. Because the amount of porphyrin breakdown is stoichiometrically related to the amount of endogenously formed CO, the blood level of COHb or the concentration of CO in the alveolar air has been used with mixed success as quantitative indices of the rate of heme catabolism (Landaw and Callahan, 1970; Solanki et al., 1988). Not all of endogenous CO comes from RBC degradation. Other hemoproteins, such as myoglobin, cytochromes, peroxidases, and catalase contribute approximately 20 to 25% to the total amount of generated CO (Berk et al., 1976). Approximately 0.4 mL/h of CO is formed by hemoglobin catabolism and about 0.1 mL/h originates from nonhemoglobin sources (Coburn et al., 1964). Metabolic processes other than heme catabolism contribute only a very small amount of CO (Miyahara and Takahashi, 1971). In both males and females, week-to-week variations of CO production are greater than day-to-day or within-day variations. Moreover, in females COHb levels fluctuated with the menstrual cycle; the mean rate of CO production in the premenstrual, progesterone phase almost doubled (Lynch and Moede, 1972; Delivoria-Papadopoulos et al., 1970). Neonates and pregnant women also showed a significant increase in endogenous CO production related to increased breakdown of RBC.

Any disturbance leading to increased destruction of RBC and accelerated breakdown of other hemoproteins would lead to increased production of CO. Hematomas, intravascular hemolysis of RBC, blood transfusion, and ineffective erythropoiesis all will elevate CO concentration in blood. Degradation of RBC under pathologic conditions such as anemias (hemolytic, sideroblastic, sickle cell), thalassemia, Gilbert's syndrome with hemolysis, and other hematological diseases also will accelerate CO production (Berk et al., 1974; Solanki et al., 1988). In patients with hemolytic anemia the CO production rate was 2 to 8 times higher, and blood COHb concentration 2 to 3 times higher than in normals (Coburn et al., 1966). Increased CO-production rates have been reported after administration of

phenobarbital, diphenylhydantoin (Coburn, 1970), and progesterone (Delivoria-Papadopoulos et al., 1970).

9.3 MODELING CARBOXYHEMOGLOBIN FORMATION

9.3.1 Introduction

The NAAQS for CO were designed to establish ambient levels of CO which would protect sensitive individuals from experiencing adverse health effects. In retaining the current CO primary standards, both EPA and the Clean Air Scientific Advisory Committee concluded that the critical effects level for NAAQS-setting purposes was approximately 3% COHb without including a margin of safety (Federal Register, 1985). Using exposure modeling and available monitoring data, EPA estimated that the current 9 ppm, eight-hour average standard would keep more than 99.9% of the adult population with cardiovascular disease below 2.1% COHb. Considering uncertainties regarding the lowest level at which adverse health effects may occur, as well as uncertainties about the exposure estimates, EPA concluded that this level of protection would provide an adequate margin of safety for this sensitive group. Because of the variability of ambient CO concentration profiles, and other exogenous and endogenous factors affecting formation of COHb in an individual, it is obvious that the only practical approach to evaluate the protection provided by these standards is to continue to use mathematical models. The COHb formation modeling, however, has much wider application because the quantification of the relationship between exogenous CO and blood COHb is also of clinical and occupational interest.

9.3.2 Regression Models

The most direct approach to establishing a prediction equation for COHb is to regress observed COHb values against the level and duration of exogenous CO exposure. Inclusion of other predictor variables such as initial COHb level and alveolar ventilation generally will improve the precision of the predictions. All regression models are purely empirical and have no physiological basis. Their applicability therefore is limited to the exact conditions that were used to collect the data on which they are based. So far, the most viable models have been tested and used to estimate COHb levels for healthy subjects only. No validation studies

have been reported on potentially at-risk subpopulations (see Chapter 12), such as patients with cardiovascular or hematologic dysfunction.

Peterson and Stewart (1970) developed regression Equation 9-2 for percent COHb after exposure to moderate CO levels, where CO refers to the concentration of CO in ambient air inhaled parts per million, t is the exposure duration in minutes, and t′ is the postexposure time in minutes. The final term (-.00094t′) reflects CO elimination and was computed using

$$\text{Log}_{10}\ \%\text{COHb} = .85753\ \text{Log}_{10}\ \text{CO} + .62995\ \text{Log}_{10}\ t - 2.29519 - .00094t' \qquad (9\text{-}2)$$

the average COHb half-life found in the study. The percent COHb in the blood samples was determined twice, using an IL CO-Oximeter and a gas chromatograph. The percent COHb values that were used to estimate the equation were themselves averages over observations on 2 to 10 subjects (r = 0.985). The range of CO concentrations used was 25 to 523 ppm CO, and the exposures lasted from 15 min to eight hours. The subjects were 18 healthy males that did not smoke during the duration of the study. More recently Equation 9-2, without its final term, was modified by Zankl (1981) to correct the time, t, in the equation for altitude and subject activity level. No justification, however, nor reference was cited for these changes.

Another regression equation (9-3) developed by Stewart et al. (1973) applies to briefer exposures of considerably higher levels of CO. In this study the exposures ranged from 1000 ppm (for 10 min) to 35,600 ppm (for 45 sec). The regression equation was based on

$$\begin{aligned}\text{Log}_{10}[\%\text{COHb}(t)] = {} & \text{Log}_{10}[\%\text{COHb}(t)] + \text{Log}_{10}[\%\text{COHb}(t_0)] \\ & + 1.036\ \text{Log}_{10}\ \text{CO} - 4.4793 \\ & + \text{Log}_{10}\ (\text{liters inhaled})\end{aligned} \qquad (9\text{-}3)$$

13 experimental exposures but only on six different subjects (r = 0.995). The subjects remained sedentary throughout the study. Possible correlations between readings on the same subject were not taken into account. The predicted quantity is the logarithm of the "increase in percent COHb saturation in venous blood per liter of CO mixture inhaled." The percent COHb in the blood samples was determined twice, using automated blood analyzing system and a gas chromatograph. The increase in COHb saturation was computed using the peak

COHb concentration occurring approximately two minutes after CO exposure stopped. However, the immediate postexposure inhalation of pure O_2 almost certainly lowered the peak COHb values and influenced subsequent estimates.

9.3.3 The Coburn-Forster-Kane Differential Equations

In 1965, Coburn, Forster, and Kane developed a differential equation to describe the major physiological variables that determine blood [COHb] for the examination of the endogenous production of CO. The equation, referred to as the CFK model, is still much in use today for the prediction of [COHb] consequent to inhalation of CO for two reasons. First, the model is quite robust to challenges to the original assumptions. Second, the model can be relatively easily adapted to more specialized applications.

9.3.3.1 Linear and Nonlinear CFK Differential Equations

Equation 9-4 represents the linear CFK model, with constant O_2Hb level:

$$V_B\, d[COHb]/dt = \dot{V}_{CO} - [COHb]P_cO_2 / MB[0_2Hb] + P_iCO/B \qquad (9\text{-}4)$$

where:

[COHb] = milliliters of CO per milliliter of blood, maximum O_2 capacity of blood

$[O_2Hb]$ = milliliters of O_2 per milliliter of blood (=0.2)

Hb = grams hemoglobin per milliliter of blood, hemoglobin concentration in blood (=1.38)

$B = 1/D_LCO + P_L/\dot{V}_A$

D_LCO = milliliters per minute per millimeter of Hg, pulmonary diffusing capacity for CO (=30)

P_L = millilmeters of Hg, pressure dry gases in the lungs (=713)

$\dot{V}_A$ = milliliters per minute alveolar ventilation rate (=6000)

M = Haldane affinity ratio (=218)

V_B = millimeters of blood volume (=5500)

V_{co} = milliliters per minute, endogenous CO production (=0.007)

PI_cO = millimeters of Hg, partial pressure CO in air inhaled

P_cO_2 = millimeters of Hg, average partial pressure of O_2 in lung capillaries (=100)

The values in parentheses are the values given in Peterson and Stewart (1970), although it is not clear whether a consistent set of conditions (i.e., BTPS or STPD) was used. Restricting the conditions to low CO exposures allows the mathematical assumption of instant equilibration of (1) the gases in the lungs, (2) COHb concentrations between venous and arterial blood, and (3) COHb concentrations between the blood and CO stores in nonvascular tissues. In addition, the washout time becomes unimportant, and the inhaled and exhaled volumes could be presumed equal. In solving Equation 9-4, Coburn, Forster, and Kane (1965) further assumed that $[O_2Hb]$ is constant and not dependent on [COHb]. The resulting linear differential equation is restricted to relatively low COHb levels. For high ambient CO levels, it may erroneously predict equilibrium values greater than 100% COHb.

The advantage to using the linear differential equation (where applicable) is that the solution can be written explicitly as.

$$[COHb]\,(t) = [COHb]_o e^{-At} + C/A\,(1 - e^{-At}) \qquad (9\text{-}5)$$

where

$$A = P_cO_2 / V_B\, MB\, [O_2\, Hb]$$
$$C = \dot{V}_{CO}/V_B + P_I\, CO / V_B\, B$$

From this solution, we see that for small t, the formation of COHb proceeds linearly, as

$$\Delta\,[COHb] \approx P_I\, CO\,(t) / V_B\, B \qquad (9\text{-}6)$$

Since O_2 and CO combine with Hb from the same pool, higher COHb values do affect the amount of Hb available for bonding with O_2. Such interdependence can be modeled by substituting (1.38 Hb - [COHb]) for [O_2Hb]) (see e.g., Tikuisis et al., 1987b). The CFK differential equation then becomes nonlinear and iterative methods or numerical integration must be used to solve the equation (Muller and Barton, 1987). Solutions of either CFK equation require that the volumes of all gases be adjusted to the same conditions. Coburn, Forster, and Kane (1965) use STPD conditions, but the equation can be solved under any conditions if consistently used (Tikuisis et al., 1987a,b).

The equilibrium value predicted by the nonlinear differential equation will always be less than 100% COHb, and is given by the following expression.

$$[COHb] = 1.38\ Hb\ M(P_iCO + B\dot{V}_{co}) / P_cO_2 + M\ (P_iCO + B\dot{V}_{co} \qquad (9\text{-}7)$$

A sensitivity analysis has been done on the parameters of both the linear and nonlinear CFK equation at five different work levels (McCartney, 1990). The author shows that a 1% error in any one of the parameters produces no more than a 1% error in COHb prediction by the nonlinear model.

The nonlinear CFK model is more accurate physiologically, but has no explicit solution. It is reasonable, therefore, to ask under what conditions the solutions to the linear and nonlinear equations are "close" together. Because both solutions are generated by known differential equations, the question is a purely mathematical one. The precise answer is complex and depends on the ambient CO level. In general, the linear CFK differential equation is a better approximation to the nonlinear equation during the uptake of CO than during the elimination of CO. The approximation also is better for COHb levels further from the equilibrium predicted by the nonlinear model. In particular, it can be shown that as long as the linear CFK equation predicts COHb levels at or below 6% COHb, the solution to the nonlinear CFK model will be no more than 0.5% COHb away (Smith et al., 1990).

9.3.3.2 Confirmation Studies of the CFK Model

Since the publication of the original paper (Coburn et al., 1965), other investigators have tested the fit of the CFK model to experimental data by using different exposure profiles

and different approaches to evaluating the parameters of the model. Stewart et al. (1970) and Peterson and Stewart (1970) tested the CFK linear differential equation on 18 resting subjects exposed to 25 CO exposure profiles for periods of one-half to 24 hours and to CO concentrations ranging from 1 to 1000 ppm. All physiological coefficients were assumed (see p. 9-14). The percent COHb in the blood samples was determined twice, using an IL CO-Oximeter and a gas chromatograph. It is important to note that in this experiment the predictions were compared to individual observations instead of averages. The predicted values yielded COHb values quite close to the measured values. The greatest discrepancy (4.9%) was observed in the experiment with steadily rising inhaled CO concentration over a two-hour period, which is not surprising because the authors assumed a constant inhaled concentration of CO in solving the CFK equation.

In 1975, Peterson and Stewart presented a second series of experiments testing the nonlinear CFK model. Three women were included among the 22 subjects, and three different levels of exercise were used. The parameter values of PCO_2, D_LCO, V_B, and $\dot{V}_A$ were estimated for each subject. The percent COHb in the blood samples was determined by a CO-Oximeter that was continually compared to a gas chromatograph. Based on summary data, they concluded that the predicted and measured values were very close for both males and females under conditions at rest and exercise as well.

In 1981 Joumard et al. tested both the linear and nonlinear CFK models for CO uptake and elimination in pedestrians and car passengers exposed to ambient CO levels in the city of Lyon, France. The cohort, consisting of 37 male and 36 female nonsmoking subjects who were 18 to 60 years old, was divided into two groups. One group was driven around the city in cars while the second group walked on the street at a nearly uniform pace. Each journey lasted about two hours. Blood COHb readings were taken at the beginning and end of each journey. The percent COHb in the blood samples was determined by infrared spectroscopy. All other physiological parameters were estimated. As might be expected at these COHb levels ($\sim$2.3%), the authors found no significant difference between the linear and nonlinear CFK equations. No significant difference ($\alpha = 0.05$) was found between the final predicted and observed COHb values except for male pedestrians. The unspecified difference for that group was attributed to an underestimate of the alveolar ventilation.

In 1984, Hauck and Neuberger ran a series of experiments testing the predictive ability of the CFK model on four subjects exposed to a total of 10 different CO exposure profiles combined with a variety of exercise (bicycle ergometer) patterns so that each exposure was a unique combination of CO concentration and exercise pattern. The group, all nonsmokers, included three adult males and one ten-year-old female. The COHb values were calculated at 1-min intervals using a numerical solution of the CFK model; all but ventilation-derived parameters, which were updated every minute, were kept constant. The percent COHb in the blood was determined by an improved van Slyke method. The maximal differences within each experimental run (expressed as percent of a maximal predicted value) ranged from 4.2 to 11.1%.

The most recent validation of the nonlinear CFK model was reported by Tikuisis et al. (1987a,b). Experiments were completed on 6 to 11 nonsmoking middle-aged males. All of the CFK parameters but D_LCO and $\dot{V}_A$ were estimated; D_LCO and $\dot{V}_A$ were measured for each subject. The percent COHb in the blood samples was determined by gas chromatography. Several transient intermittent CO exposure profiles were tested: 1500 ppm for 5 min, and 7500 ppm for 1 min at rest along with stepwise symmetric profiles of 500 to 4000 ppm for 4.5 min and 4000 ppm for 75 during rest and intermittent exercise ($\dot{V}_A \approx 30$L/min; Figure 9-2). On an average, the predicted and measured values at rest were very close, with the CFK model slightly overpredictive (<0.5% COHb). This overprediction was greater during exercise, reaching almost 3% COHb in one of the subjects (Figure 9-2). It is of interest to note that predicted values based on a current National Institute for Occupational Safety and Health (NIOSH) solution of the CFK model are even higher, overpredicting by as much as 6% COHb. The model appeared to be most sensitive to $\dot{V}_A$; thus errors in conversion of gas volumes (e.g., from ATPS to BTPS) will affect the predicted values.

9.3.3.3 Modified CFK Models

Bernard and Duker (1981) simplified the linear form of the CFK model in a unique way. Using regression equations from the literature, they were able to relate physiological parameters to the O_2 uptake by the body ($\dot{V}O_2$), which in turn related to an activity level. A linear relationship was assumed between the rate of O_2 uptake and the maximum COHb level

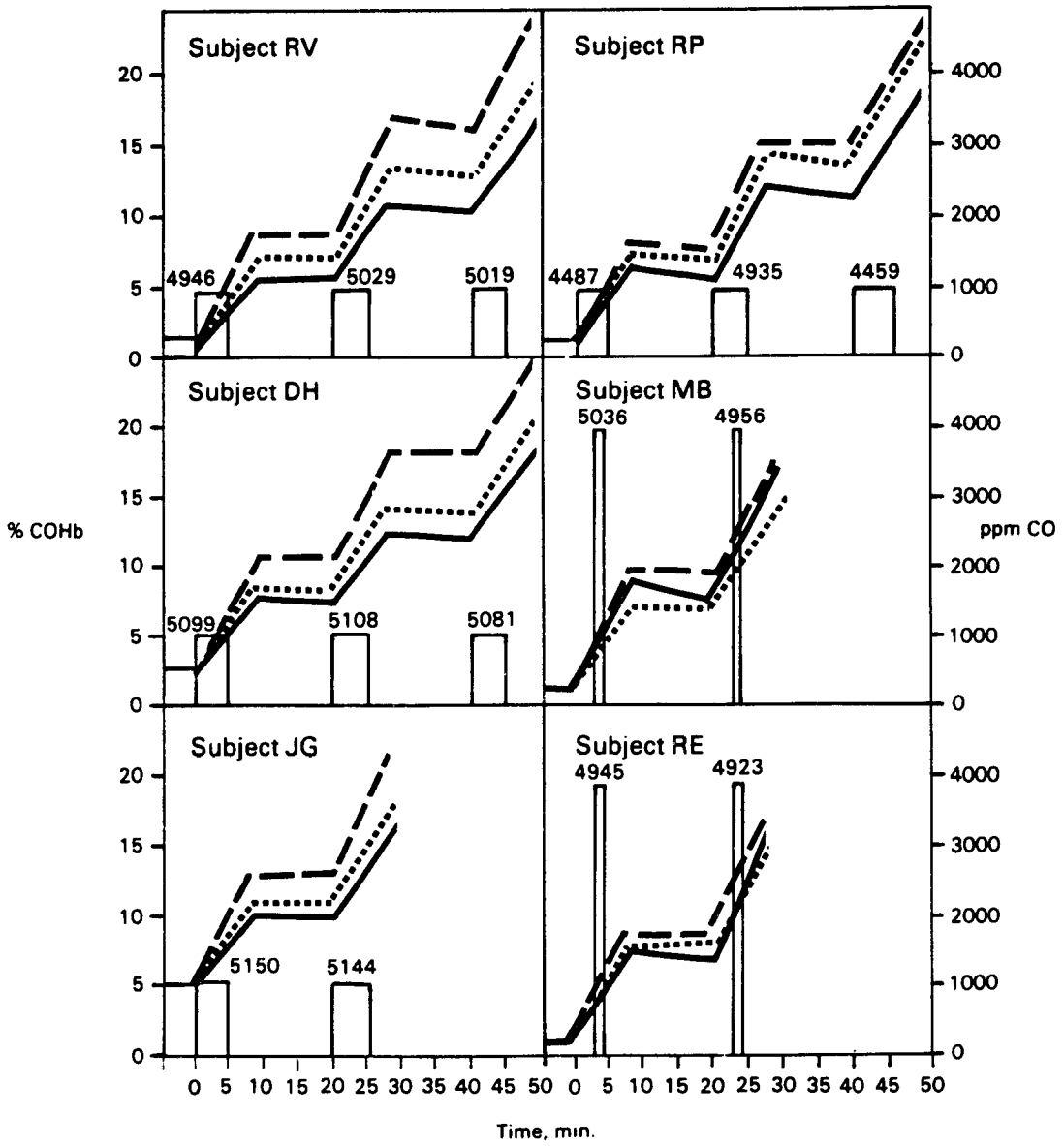

Figure 9-2. Measured and predicted COHb concentrations from six intermittently exercising subjects. The solid lines represent the measured percent COHb; the short-dashed lines are the solutions to the nonlinear CFK equation; and the long-dashed lines are predicted values based on the CFK model adapted by NIOSH.

Source: Tikuisis et al. (1987b).

under which that rate could be sustained. A summary of predictive relationships between pairs of variables were developed, but none were experimentally tested.

A more fundamental modification of the CFK model was made by Hill et al. (1977) to study the effect of CO inspired by the mother on the level of fetal COHb. The Hill equation (9-8) combines the CFK equation (for maternal COHb), with a term denoting COHb transfer from the placenta into the fetus (the subscripts m and f denote maternal and fetal quantities, respectively).

$$V_{Bm}\, d[COHb_m]/dt = \dot{V}_{COm} - [COHb_m]\, P_cO_2/(M_m[O_2Hb]B) + P_fCO/B - D_pCO\,(P_mCO - P_fCO) \qquad (9\text{-}8)$$

Thus, Equation 9-8 is the same as Equation 9-4, except for the final term on the right. D_pCO is the CO diffusion coefficient across the placenta. P_mCO and P_fCO are the partial pressures of CO in the maternal and fetal placental capillaries, respectively. The latter two quantities are estimated using the Haldane relationship and separate models for the lungs and placenta. The level of fetal COHb is predicted from a similar equation. Comparative evaluation of predicted and measured fetal COHb concentrations under time-varying and steady-state conditions in both men and animals showed acceptable agreement only under steady-state conditions (Hill et al., 1977; Longo and Hill, 1977).

9.3.3.4 Application of the CFK Model

Ott and Mage (1978), using a linear differential equation model that was patterned after the linear CFK differential equation, examined the dynamics of blood COHb concentration fluctuation as a function of ambient CO concentration for a one-year period. Other parameters of the model were estimated and kept constant. The calculated COHb levels exceeded 2% on 25 occasions without violating the one-hour standard, whereas the eight-hour standard was violated 23 times. During the same year 29 violations of the CO standard occurred but the 2% COHb level was exceeded in only 23 instances. Besides evaluation of the averaged CO concentrations, the authors examined the effects of peak, transient CO concentrations on the target COHb. They showed that the presence of such spikes in CO data averaged over hourly intervals may lead to underestimating the COHb level (due to exogenous

CO) by as much as 21%. Consequently, they recommended that monitored CO be averaged over shorter periods, such as 10 to 15 min. (See Chapter 8 for a more complete description of population exposure to CO.)

Venkatram and Louch (1979) extended the above application to more dynamic conditions by fitting interpolated values of the ambient one-hour CO averages from Toronto, Canada into the CFK model. In addition, they reexpressed the solution of the model from units of percent COHb to parts per million of CO. Such a transformation allows the examination of a variety of CO concentration profiles, while keeping a simple preselected target COHb as a constant. They calculated that a 2% COHb level in blood very likely would be exceeded on numerous occasions without ever violating the standard. By including transients their approach appears to predict COHb more accurately, particularly in response to eight-hour running averages.

Biller and Richmond (1982) investigated the effects of inhaling various patterns of hourly-averaged CO concentrations that just attained alternative 1-hour and 8-hour CO NAAQS using the CFK equation. Their analysis also estimated the distributions of various physiological parameters that are inputs to the CFK equation for individuals with cardiovascular disease. The authors found that depending on which air quality pattern was used, the percentage of the population exceeding 2.1% COHb ranged from less than 0.01% to 10%.

More recently, Saltzman and Fox (1986) investigated the effect of inhaling oscillating levels of CO on the COHb level of rabbits using the linear CFK equation simplified by combining the original parameters. They concluded that ambient CO values could be averaged safely over any time period less than or equal to the half-life of blood COHb.

9.3.4 Summary

The best all around model for COHb prediction is still the equation developed by Coburn, Forster, and Kane (1965). The linear solution is useful for examining air pollution data leading to relatively low COHb levels, whereas the nonlinear solution shows good predictive power even for high CO exposures. The two regression models might be useful only when the conditions of application closely approximate those under which the parameters were estimated.

It is important to remember that almost all of the above studies assumed a constant rate of CO uptake and elimination, which is rarely true. A number of physiological factors, particularly changes in ventilation, will affect both rates. The predicted COHb values also will differ from individual to individual due to smoking, age, or lung disease. There does not appear to be a single optimal averaging time period for ambient CO; however, the shorter the period the greater the precision. In general, the averaging time period should be well within the [COHb] half-life, which decreases with increased activity.

9.4 INTRACELLULAR EFFECTS OF CARBON MONOXIDE

9.4.1 Introduction

The principal cause of CO toxicity is tissue hypoxia due to CO binding to Hb, yet certain physiological aspects of CO exposure are not explained well by decreases in intracellular PO_2 related to the presence of COHb. For many years, it has been known that CO is distributed to extravascular sites such as skeletal muscle (Coburn et al., 1971; Coburn et al., 1973) and that 10 to 50% of the total body store of CO may be extravascular (Luomanmaki and Coburn, 1969). Furthermore, extravascular CO is metabolized slowly to CO_2 *in vivo* (Fenn, 1970). Consequently, secondary mechanisms of CO toxicity related to intracellular uptake of CO have been the focus of a great deal of research interest. CO binding to many intracellular compounds has been well documented both *in vitro* and *in vivo*, however, it is still uncertain whether or not intracellular uptake of CO in the presence of Hb is sufficient to cause either acute organ system dysfunction or long-term health effects. The virtual absence of sensitive techniques capable of assessing intracellular CO binding under physiological conditions has resulted in a variety of indirect approaches to the problem as well as many negative studies. The purposes of this section of the document are to summarize current knowledge pertaining to intracellular CO-binding proteins and to evaluate the potential contribution of intracellular CO uptake to the overall physiological effects of CO exposure. Selected aspects of this topic have been reviewed previously (Forster, 1970; Coburn et al., 1977; Coburn, 1979; Piantadosi, 1987; Coburn and Forman, 1987).

CO is known to react with a variety of metal-containing proteins found in nature. CO-binding metalloproteins present in mammalian tissues include O_2-carrier proteins such as

hemoglobin (Douglas et al., 1912) and myoglobin (Antonini and Brunori, 1971) and metalloenzymes (oxidoreductases) such as cytochrome *c* oxidase (Keilin and Hartree, 1939), cytochromes of the P-450 type (Omura and Sato, 1964), tryptophan oxygenase (Tanaka and Knox, 1959), and dopamine hydroxylase (Kaufman, 1966). These metalloproteins contain iron and/or copper centers at their active sites that form metal-ligand complexes with CO in competition with molecular oxygen. CO and O_2 form complexes with metalloenzymes only when the iron and copper are in their reduced forms (Fe II, Cu I). Caughey (1970) has reviewed the similarities and differences in the physicochemical characteristics of CO and O_2 binding to these transition metal ions. The competitive relationship between CO and O_2 for the active site of intracellular hemoproteins usually is described by the Warburg partition coefficient (K), which is the CO/O_2 ratio that produces 50% inhibition of the O_2 uptake of the enzyme or, in the case of myoglobin, a 50% decrease in the number of available O_2-binding sites.

The measured Warburg coefficients of various mammalian CO-binding proteins have been tabulated recently by Coburn and Forman (1987) (see Table 9-1). These K values range from approximately 0.025 for myoglobin to 0.1 to 12 for cytochromes P-450. K values of 2 to 28 have been reported for cytochrome *c* oxidase (Keilin and Hartree, 1939; Wohlrab and Ogunmola, 1971; Wharton and Gibson 1976). By comparison, the K value for human hemoglobin of 0.005 is some three orders of magnitude less than that of cytochrome *c* oxidase. This means, for example, that CO would bind to cytochrome oxidase *in vivo* only if O_2 gradients from RBCs in the capillary to the mitochondria were quite steep. Application of K values for intracellular hemoproteins in this way, however, needs to be used with caution because most measurements of CO binding have not been made at physiological temperatures or at relevant rates of electron transport.

Apart from questions about the relevance of extrapolating *in vitro* partition coefficients to physiological conditions, experimental problems arise that are related to determining actual CO/O_2 ratios in intact tissues. Reasonably good estimates of tissue P_{co} may be obtained by calculating the value in mean capillary blood from the Haldane relationship (Coburn et al., 1977), neglecting the low rate of CO metabolism by the tissue. Experimental estimates of the P_{co} in animal tissues have been found to be in close agreement with these calculations and average slightly less than alveolar P_{co} (Goethert et al., 1970; Goethert, 1972). In general,

TABLE 9-1. *IN VITRO* INHIBITION RATIOS FOR HEMOPROTEINS THAT BIND CARBON MONOXIDE

Hemoprotein	Source	R[a]	M[b]	Temperature (°C)
Hemoglobin	Human RBC	0.0045	218	37
Myoglobin	Sperm whale	0.025 – 0.040	25 – 40	25
Cytochrome *c* oxidase	Bovine heart	5 – 15	0.1 – 0.2	25
Cytochrome P-450	Rat liver	0.1 – 12	10 – 0.1	30 – 37
Dopamine β hydroxylase	Bovine adrenal	2	0.5	—
Tryptophan oxygenase	*Pseudomonas*	0.55	1.8	25

[a]R = CO/O_2 at 50% inhibition
[b]M = 1/R

Source: Adapted from Coburn and Forman (1987).

steady state estimates for tissue P_{CO} range from 0.02 to 0.5 torr at COHb concentrations of 5 to 50%. Therefore, at 50% COHb, a CO/O_2 ratio of 5 may be achieved at sites of intracellular O_2 uptake only if tissue PO_2 in the vicinity of the CO-binding proteins is approximately 0.1 torr.

Whether such low intracellular PO_2 values exist in target tissues such as brain and heart during CO exposure is difficult to determine from the existing scientific literature. Experimental measurements of tissue PO_2 using polarographic microelectrodes indicate significant differences in PO_2 in different tissues and regional differences in PO_2 within a given tissue. This normal variability in tissue PO_2 is related to differences in capillary perfusion, red blood cell spacing, velocity and path length, and local requirements for O_2. Normal PO_2 values obtained from such recordings are generally in the range of 0 to 30 torr (Leniger-Follert et al., 1975). These PO_2 values usually represent average interstitial values, although it is often difficult to determine the exact location of the electrode and the effect of O_2 consumption by the electrode on the PO_2 measurement. Furthermore, the gradient between the capillary and the intracellular sites of O_2 utilization are thought to be quite steep (Sies, 1977). A major component of the gradient arises between the red blood cell and interstitium (Hellums, 1977) but the PO_2 gradient between the cell membrane and respiring mitochondria and other O_2-requiring organelles remains undetermined in intact normal tissues. Even less is known about intracellular PO_2 in the presence of COHb. It has been determined, however, that both PO_2 in brain tissue (Zorn, 1972) and cerebrovenous PO_2 (Koehler et al., 1984) decrease linearly as a function of COHb concentration. Presumably then, intracellular PO_2 declines with increasing COHb concentration, and at certain locations, CO forms ligands with the O_2-dependent, intracellular hemoproteins. As the intracellular PO_2 decreases, the CO/O_2 ratio in the tissue increases at constant P_{CO} and an increasing fraction of the available intracellular O_2-binding sites become occupied by CO.

The intracellular uptake of CO behaves according to the preceding general principles; most of the experimental evidence for this line of reasoning was derived from *in vivo* studies of COHb formation by Coburn and colleagues (1965) at the University of Pennsylvania. For all intracellular hemoproteins, however, two crucial quantitative unknowns remain. These are (1) the fraction of intracellular-binding sites in discrete tissues inhibited by CO at any level of COHb saturation, and (2) the critical fraction of inhibited sites necessary to amplify or initiate

a deleterious physiological effect, or trigger biochemical responses with long-term health effects. In general then, the activities of certain intracellular hemoproteins may be altered at physiologically tolerable levels of carboxyhemoglobin. The problem is in determining what level of intracellular reserve is available during CO hypoxia. In view of this general conclusion, recent literature for the candidate hemoproteins has been evaluated to obtain positive evidence for intracellular CO binding and corroboration of functional consequences of the intracellular CO effects at specific COHb levels.

9.4.2 Carbon Monoxide Binding to Myoglobin

The red protein myoglobin is involved in the transport of O_2 from capillaries to mitochondria in red muscles. The binding of CO to Mb in heart and skeletal muscle *in vivo* has been demonstrated at levels of COHb below 2% in heart and 1% in skeletal muscle (Coburn and Mayers, 1971; Coburn et al., 1973). The ratio of COMb/COHb saturation has been found to be approximately one in cardiac muscle and less than one in skeletal muscle. These ratios did not increase with increases in COHb up to 50% saturation. In the presence of hypoxemia and hypoperfusion, the amount of CO uptake by Mb has been measured and was shown to increase (Coburn et al., 1973; Coburn et al., 1971). A similar conclusion has been reached during maximal exercise in humans, where CO shifts from Hb to the intracellular compartment (i.e., Mb, at COHb levels of 2 to 2.5%) (Clark and Coburn, 1975). The significance of CO uptake by Mb is uncertain because our understanding of the functional role of Mb in working muscle is incomplete. Myoglobin undoubtedly enhances the uptake of O_2 by muscle cells so that the continuous O_2 demand of working muscle is satisfied (Wittenberg et al., 1975). Myoglobin may contribute to muscle function by serving as an O_2 store, by enhancing intracellular diffusion of O_2, or by acting as an O_2 buffer to maintain a constant mitochondrial PO_2 during changes in O_2 supply. Functional Mb has been found to be necessary for maintenance of maximum O_2 uptake and mechanical tension in exercising skeletal muscle (Cole, 1982). The binding of CO to Mb would therefore be expected to limit O_2 availability to mitochondria in working muscle. This possibility has been verified theoretically by computer simulations of Hoofd and Kreuzer (1978) and Agostoni et al. (1980). The three-compartment (arterial and venous capillary blood, and Mb) computer model of Agostoni et al. (1980) predicted that COMb formation in low PO_2 regions of the heart (e.g.,

subendocardium) could be sufficient to impair intracellular O_2 transport to mitochondria at COHb saturations of 5 to 10%. The [COMb] also was predicted to increase during conditions of hypoxia, ischemia, and increased O_2 demand.

The direct effects of CO on cardiac function also have been evaluated in the absence of Hb in fluorocarbon-perfused rabbits (Takano et al., 1981). Exposure of these animals to high concentrations of CO (CO/O_2 = 0.05-0.25) significantly decreased the heart rate-systolic pressure product in the absence of COHb formation. Cardiac output and [COMb], however, were not determined. Increases in cardiac [COMb] have been measured after heavy work loads in CO-exposed rats, independent, of changes in [COHb] (Sokal et al., 1986). These investigators reported that exercise significantly increased cardiac [COMb] at COHb saturations of approximately 10, 20, and 50%, although metabolic acidosis worsened only at 50% COHb. It remains unknown, however, whether or not low [MbCO] could be responsible for decreases in maximal O_2 uptake during exercise reported at COHb levels of 4 to 5% (see Chapter 10, Section 10.3).

9.4.3 Carbon Monoxide Uptake by Cytochrome P-450

Mixed-function oxidases (cytochrome P-450) are involved in the detoxification of a number of drugs and steroids by "oxidation." These enzymes are distributed widely throughout mammalian tissues; the highest concentrations are found in the microsomes of liver, adrenal gland, and the lungs of some species (Estabrook et al., 1970). These oxidases also are present in low concentrations in kidney and brain tissues. Mixed-function oxidases catalyze a variety of hydroxylation reactions involving the uptake of a pair of electrons from NADPH with reduction of one atom of O_2 to H_2O and incorporation of the other into substrates (White and Coon, 1980). These enzymes bind CO, and their Warburg binding coefficients range from 0.1 to 12 *in vitro* (see Coburn and Forman, 1987). The sensitivity of cytochrome P-450 to CO is increased under conditions of rapid electron transport (Estabrook et al., 1970), however, previous calculations have indicated that tissue P_{CO} is too low to inhibit the function of these hemoproteins *in vivo* at less than 15 to 20% COHb (Coburn and Forman, 1987). There have been few attempts to measure CO-binding coefficients in intact tissues. In isolated rabbit lung, the effects of CO on mixed-function oxidase are consistent with a Warburg coefficient of approximately 0.5 (Fisher et al., 1979). CO exposure

decreases the rate of hepatic metabolism of hexobarbital and other drugs in experimental animals (Montgomery and Rubin, 1973; Roth and Rubin, 1976a,b). Most authors have concluded that these effects of CO on xenobiotic metabolism are attributable entirely to COHb-related tissue hypoxia because they are no greater than the effects of "equivalent" levels of hypoxic hypoxia. Three optical studies of rat liver perfused *in situ* with Hb-free buffers have demonstrated uptake of CO by cytochrome P-450 at CO/O_2 ratios of 0.03 to 0.10 (Sies and Brauser, 1970; Iyanagi et al., 1981; Takano et al., 1985). In the study by Takano et al. (1985) significant inhibition of hexobarbital metabolism was found at a CO/O_2 of about 0.1. This CO/O_2 ratio, if translated directly to [COHb], would produce [COHb] that are incompatible with survival (~95%). At present, there is no scientific evidence that CO significantly inhibits the activity of mixed-function oxidases at COHb saturations below 15 to 20%. Although most studies do not indicate effects of CO on cytochrome P-450 activity at physiologically relevant CO concentrations, specific P-450 isoenzymes may have higher affinities for CO. Also, the rate of substrate metabolism and substrate type may increase CO binding by P-450 enzymes. More basic research is needed in this area because of the important role of these enzymes in living organisms.

9.4.4 Carbon Monoxide and Cytochrome c Oxidase

Cytochrome *c* oxidase, a.k.a. cytochrome *a* a_3, is the terminal enzyme in the mitochondrial electron transport chain that catalyzes the reduction of molecular O_2 to water. Although the enzyme complex binds CO, three reasons are often cited for why this should occur only under conditions of severe hypoxia. First, the Warburg binding constant for cytochrome oxidase is unfavorable for CO uptake relative to the other candidate hemoproteins. Second, the enzyme has an *in vitro* Michaelis-Menten constant (K_m) for O_2 of less than 1 torr (Chance and Williams, 1955). Because intracellular PO_2 is probably higher than this, the oxidase should remain oxidized until severe tissue hypoxia is present. The above arguments, however rational, are not supported well by *in vivo* observations and may not be valid for the conditions encountered in living systems. The reasons for this difficulty center around differences in the redox behavior of cytochrome oxidase *in vivo* relative to its *in vitro* behavior. The enzyme has a high resting reduction level at normal PO_2 in brain (Jobsis et al., 1977) and other tissues, and its oxidation state varies directly with PO_2 *in vitro*

(Kreisman et al., 1981). These findings may indicate that the oxidase operates near its effective $K_m$ratios *in vivo* or that the availability of O_2 to each mitochondrion or respiratory chain is not continuous under most physiological circumstances. There also may be differences in or regulation of the K_m for O_2 of the enzyme according to regional metabolic conditions. For example, the apparent K_m for O_2 of cytochrome oxidase increases several times during rapid respiration (Oshino et al., 1974), and in isolated cells it varies as a function of the cytosolic phosphorylation potential (Erecinska and Wilson, 1982). Conditions of high respiration and/or high cytosolic phosphorylation potential *in vitro* increase the concentration of CO-cytochrome oxidase at any CO/O_2 ratio. This concept is particularly relevant for tissues like the heart and brain.

Enhanced sensitivity of cytochrome oxidase to CO has been demonstrated in uncoupled mitochondria, where CO/O_2 ratios as low as 0.2 delay the oxidation of reduced cytochrome oxidase in transit from anoxia to normoxia (Chance et al., 1970). Several studies of respiring tissues, however, have found CO/O_2 ratios of 12 to 20 to be necessary for 50% inhibition of O_2 uptake (Coburn et al., 1979; Fisher and Dodia, 1981; Kidder, 1980). In this context, it is important to note that in a given tissue, the CO/O_2 ratio necessary to inhibit one half of the O_2 uptake does not necessarily correspond to CO binding to one half of the oxidase molecules. This is because unblocked cytochrome oxidase molecules may oxidize respiratory complexes of blocked chains, thus causing the O_2 consumption to fall more slowly than predicted for strictly linear systems. The capacity of tissues to compensate for electron transport inhibition by branching has not been investigated systematically as a function of PO_2, CO/O_2 ratio, cytosolic phosphorylation potential, or rate of electron transport *in vivo*.

The contention that intracellular CO uptake by cytochrome oxidase occurs is supported by a few experiments. It has been known for many years, primarily through the work of Fenn (Fenn and Cobb, 1932; Fenn, 1970), that CO is slowly oxidized in the body to CO_2. This oxidation occurs normally at a much lower rate than the endogenous rate of CO production, however, the rate of oxidation of CO increases in proportion to the CO body store (Luomanmaki and Coburn, 1969). The oxidation of CO to CO_2 was shown in 1965 by Tzagoloff and Wharton to be catalyzed by reduced cytochrome oxidase. More recently, Young et al. (1979) demonstrated that oxidized cytochrome oxidase promotes CO oxidation, and subsequently, that cytochrome oxidase in intact heart and brain mitochondria was capable

of catalyzing the reaction at a CO/O_2 ratio of approximately 4 (Young and Caughey, 1986). The physiological significance of this reaction is unknown.

Other studies indicating possible direct effects of CO on cytochrome oxidase include a photoreversible effect of 500 to 1000 ppm CO on spontaneous electrical activity of cerebellar Purkinje cells in tissue culture (Raybourn et al., 1978). These CO concentrations would be expected to produce [COHb] in the range of 33 to 50%. At 7.5% COHb, inhibition of the b-wave of the electroretinogram has been reported in the cat (Ingenito and Durlacher, 1979). Persistent changes in the retinogram were reminiscent of the "remnant effect" of CO on visual thresholds in humans reported by Halperin et al. (1959). Other optical evidence suggesting that cytochrome oxidase is sensitive to CO *in vivo* comes from studies of the effects of CO on cerebrocortical cytochromes in fluorocarbon-perfused rats (Piantadosi et al., 1985, 1987). In these studies, CO/O_2 ratios of 0.006 to 0.06 were associated with spectral evidence of CO binding to reduced cytochrome oxidase. The spectral data also indicated that the intracellular uptake of CO produced increases in the reduction level of *b*-type cytochromes in the brain cortex. At CO/O_2 ratios of 0.06, most (>80%) of the cytochrome *b* became reduced in the cerebral cortex. The cytochrome *b* response is not understood well; it is thought to represent an indirect (e.g., energy-dependent) response of mitochondrial *b*-cytochromes to CO because these cytochromes are not known to bind CO *in situ*. The CO/O_2 ratios used in the studies of Piantadosi et al. (1985, 1987) would produce [COHb] in the range of 50 to 90%. The venous PO_2 in those experiments, however, was about 100 torr; thus at tissue PO_2s that are significantly lower, this effect should occur at lower COHb saturations. It is unlikely, however, that cerebral uptake of CO is significant at COHb below 5% because tissue P_{CO} is so low in the presence of Hb. The physiological significance of these effects of CO have not yet been determined.

Direct effects of CO on mitochondrial function have been suggested by several recent studies which indicate decreases in cytochrome oxidase activity by histochemistry in brain and heart after severe CO intoxication in experimental animals (Pankow and Ponsold, 1984; Savolainen et al., 1980; Somogyi et al., 1981). The magnitude of the decrease in cytochrome oxidase activity may exceed that associated with severe hypoxia, although problems of determining "equivalent" levels of CO hypoxia and hypoxic hypoxia have not been addressed adequately by these studies. The effects of passive cigarette smoking on oxidative

phosphorylation in myocardial mitochondria have been studied in rabbits (Gvozdjakova et al., 1984). Mitochondrial respiratory rate (State 3 and State 4) and rates of oxidative phosphorylation were found to be decreased significantly by [COHb] of 6 to 7%. These data, however, are not definitive with respect to CO because they include effects of nicotine, which reached concentrations of 5.7 μg/L in blood. A recent study by Snow et al. (1988) in dogs with prior experimental myocardial infarction indicated that a COHb of 9.4% increased the resting reduction level of cytochrome oxidase in the heart. The CO exposures also were accompanied by more rapid cytochrome oxidase reductions after coronary artery occlusion and less rapid reoxidation of the enzyme after release of the occlusion. The authors concluded that CO trapped the oxidase in the reduced state during transient cardiac ischemia. There is also evidence that formation of the CO-cytochrome oxidase ligand occurs in the brain of the rat at COHb saturations of 40 to 50% (Brown and Piantadosi, 1990). This binding appears to be related to hypotension and probable cerebral hypoperfusion during CO exposure. This effect is in concert with experimental evidence that CO produces direct vasorelaxation of smooth muscle. This vasodilation occurs in rabbit aorta (Coburn et al., 1979), in the coronary circulation of isolated perfused rat heart (McFaul and McGrath, 1987), and in the cerebral circulation of the fluorocarbon-perfused rat (Piantadosi et al., 1987). The mechanism of this vasodilator effect is unclear, although it appears to be related to decreased calcium concentrations in vascular smooth muscle (Lin and McGrath, 1988) and elevation of cellular cyclic guanosine monophosphate (GMP) levels (Ramos et al., 1989). The stimulus does not require hypoxia, adenosine or prostaglandins and it is possible that it represents a direct toxic effect of CO on the cytochrome system in vascular smooth muscle. The physiological significance of this phenomenon is undetermined.

In summary, there is evidence to suggest that CO binds to cytochrome oxidase in mammalian heart and brain tissues at a range of systemic PO_2 values. The only experimental evidence at present that this effect occurs at COHb levels less than 10% is the slow oxidation of CO to CO_2, which has been shown to occur *in vivo* and in isolated mitochondria *in vitro*. Experimental evidence indicates that CO binding to cytochrome oxidase does occur during tissue hypoxia produced by overtly toxic COHb concentrations. The physiological significance of these effects beyond those of tissue hypoxia remains unknown. Once CO binding to cytochrome oxidase occurs, however, the small rate constant for CO dissociation

from the enzyme yields an apparent rate-dependent inhibition constant for CO under nonequilibrium conditions. This means that at high rates of respiration and low O_2 concentrations, recovery of enzymatic function by the oxidase is relatively slow in comparison to simple O_2 deprivation.

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10. HEALTH EFFECTS OF CARBON MONOXIDE

10.1 INTRODUCTION

Concerns about the potential health effects of exposure to CO have been addressed in extensive studies with various animal species as subjects. Under varied experimental protocols, considerable information has been obtained on the toxicity of CO, its direct effects on the blood and other tissues, and the manifestations of these effects in the form of changes in organ function. Many of these studies, however, have been conducted at extremely high levels of CO (i.e., levels not found in ambient air). Although severe effects from exposure to these high levels of CO are not directly germane to the problems from exposure to current ambient levels of CO, they can provide valuable information about potential effects of accidental exposure to CO, particularly those exposures occurring indoors. These higher level studies, therefore, are being considered in this chapter only if they extend dose-response information or if they provide clues to other potential health effects of CO that have not been identified already. Emphasis has been placed on studies conducted at ambient or near-ambient concentrations of CO that have been published in the more recent peer-reviewed literature since completion of the previous criteria document (U.S. Environmental Protection Agency, 1979) and an addendum to that document (U.S. Environmental Protection Agency, 1984). Where appropriate, information available from older studies either has been summarized in the text or placed in tables.

The effects observed from nonhuman experimental studies have provided some insight into the role CO plays in cellular metabolism. Caution must be exercised, however, in extrapolating the results obtained from these data to man. Not only are there questions related to species differences, but exposure conditions differ markedly in the studies conducted by different investigators. Although these studies must be interpreted with caution, they do serve the valuable ends of (1) suggesting studies to be verified in man, (2) exploring the properties and principles of an effect much more thoroughly and extensively than is possible in man, (3) protecting human subjects from unwarranted exposure, (4) permitting a compression of exposure duration in relation to aging as a result of the shorter life

expectancies of laboratory animals, and (5) providing tissues, organs, and cellular material more readily, allowing more precise observation of specific functions.

Fortunately, our knowledge of the influence of CO on biological systems is not limited to studies on nonhuman animals. Many direct experiments on humans have been conducted during the last century. Although many reports describe inadvertent exposures to various levels of CO, there are a considerable number of precise and delineated studies utilizing human subjects. Most of these have been conducted by exposing young adult males to concentrations of CO equivalent to those frequently or occasionally detected during ambient monitoring. Research on human subjects, however, also can be limited by methodological problems. As with the literature on experimental laboratory animals, many methodological and reporting problems make the data difficult to interpret. These problems include (1) failure to measure blood COHb levels; (2) failure to distinguish between the physiological effects from a CO dose of high concentration (i.e., bolus effect) and the slow, insidious increment in COHb over time from lower inhaled CO concentrations; (3) failure to distinguish between normal blood flow and blood flow increased in response to hypoxia (compensatory responses); and (4) the use of small numbers of experimental subjects. Other factors involve failure to provide control measures (e.g., double-blind conditions) for experimenter bias and experimenter effects; control periods so that task-learning effects do not mask negative results; homogeneity in the subject pool, particularly in groups labeled "smokers"; control of possible boredom and fatigue effects; and poor or inadequate statistical treatment of the data. In this chapter, an effort will be made to account for such methodological and reporting problems whenever possible by making appropriate comments in the text. Contributors to this chapter are limited, however, by the data provided in the reports published in the peer-reviewed literature. For example, information on the COHb levels achieved and the duration of exposure utilized in the studies will be provided in the text or tables if they were available in the original manuscript. Where this information is lacking, only the CO levels (parts per million) will be reported.

An almost universal problem in research on both humans and laboratory animals is the use of inappropriate statistical techniques for data analysis. Experimenters commonly use tests designed for simple two-group designs when analysis of variance is required, or use of several univariate tests when more than one dependent variable is measured and multivariate

tests are inappropriate. Such statistical problems usually yield results in which the p- value is too small, so that possibility exists that too many results were falsely declared to be statistically significant. Possible consequences of such errors will be discussed in the text or appropriate corrections will be made. Unless actual p values are given, all statements of effects reported in the text or tables are statistically significant at $p \leq 0.05$.

One problem that is particularly unique to human research is that only low levels of CO exposure are commonly used. In such instances of low-level exposure, research findings necessarily deal with near-threshold effects. When research, by necessity, is restricted to such barely noticeable effects it may be expected that (1) results will be more variable because of statistical sampling fluctuations, and (2) other uncontrolled variables that also affect the dependent variable in question will be of major importance and will increase the variability of results. For these reasons, data on human subjects, although being of prime interest, also will be of highest variability. Such high variability must be resolved with (1) large groups of subjects, (2) theoretical interpretation of results relying on knowledge gained from experimental laboratory animal data, and (3) consideration of consistency of the data within and across experiments.

This chapter is intended to review available data from published studies in which both humans and laboratory animals have been exposed to low levels of CO. The chapter is divided according to specific health effects starting with pulmonary and cardiovascular effects. The neurobehavioral effects of CO are described next, followed by developmental toxicity and other systemic effects of CO. Finally, adaptation to CO exposure is discussed. An introduction and summary is provided for each major section of the chapter in order to set the tone for a clearer understanding of the health effects of CO. Although human and laboratory animal data may be presented separately under each effect category, the summary and conclusion of these sections makes an attempt to integrate the relevant material from each of these types of studies.

10.2 ACUTE PULMONARY EFFECTS OF CARBON MONOXIDE

10.2.1 Introduction

The binding of carbon monoxide to hemoglobin, producing COHb, decreases the O_2–carrying capacity of blood and interferes with O_2 release at the tissue level; these two main mechanisms of action underly the potentially toxic effects of low-level CO exposure (see Chapter 9). Impaired delivery of O_2 can interfere with cellular respiration and result in tissue hypoxia. Hypoxia of sensitive tissues, in turn, can affect the function of many organs including the lungs. The effects would be expected to be more pronounced under conditions of stress, as with exercise, for example. Although the physiological mechanism by which adverse effects of COHb formation are well known, CO-induced toxicity at the cellular level and its related biochemical effects still are not fully understood. Other mechanisms of CO-induced toxicity have been hypothesized, but none have been demonstrated to operate at relatively low (near-ambient) CO exposure levels. The effect of CO on cytochromes involved in cellular oxidative pathways is just one of the possible mechanisms of action of CO. Mitochrondia, the principal site of oxygen utilization, are present in parenchymal lung cells and the highest concentrations are found in the type 2 epithelial cell. Prolonged exposure to low levels of CO, therefore, may potentially interfere with cell function and cause loss of alveolar epithelial integrity.

This section will review the available literature on morphological effects of CO and determine if it is likely that CO can cause direct toxicity to cells lining the respiratory tract through an effect on O_2 transport or cellular metabolism. In addition, this section will review a predominately newer data base on the effects of CO on pulmonary function.

10.2.2 Effects on Lung Morphology

Reports appearing in the published literature have investigated the histotoxic effects of CO on lung parenchyma and vasculature, an area not reviewed in the previous criteria document (U.S. Environmental Protection Agency, 1979). Results from human autopsies have indicated that severe pulmonary congestion and edema was produced in the lungs of individuals who died from acute smoke inhalation resulting from fires (Burns et al., 1986; Fein et al., 1980). These individuals, however, were exposed to relatively high concentrations of CO as well as other combustion components of smoke, such as carbon

dioxide, hydrogen cyanide, various aldehydes (e.g., acrolein), hydrochloric acid, phosgene, and ammonia (see Section 11.3.2). If CO, contained in relatively high concentrations in the inhaled smoke, was responsible for the pathological sequelae described in fire victims, then to what extent can edema be attributed to the primary injury of capillary endothelial or alveolar epithelial cells?

10.2.2.1 Studies in Laboratory Animals

Laboratory animal studies by Niden and Schulz (1965) and Fein et al. (1980) found that very high levels of CO (5000 to 10,000 ppm) for 15 to 45 min were capable of producing capillary endothelial and alveolar epithelial edema in rats and rabbits, respectively. Evidence of increased capillary permeability to protein also was reported in early studies on human subjects by Siggaard-Andersen et al. (1968) and Parving (1972) following acute, high-level CO exposure. These effects of CO have not been reported, however, at lower levels of CO exposure.

In a small number (n = 5) of New Zealand white rabbits, Fein et al. (1980) reported a significant increase in the permeability of ^{51}Cr-EDTA from alveoli to arterial blood within 15 min after the start of exposure to 0.8% (8000 ppm) CO. Passage of this labeled marker persisted and increased throughout the remaining 30 min of the study. The mean COHb level after exposure was 63 $\pm$ 4 (SEM) percent. Although morphometric examination was not performed, transmission electron microscopy (TEM) showed evidence of capillary endothelial and alveolar epithelial swelling and edema along with detachment of the endothelium from the basement membrane. Mitochondria were disintegrated and alveolar type 2 cells were depleted of lamellar bodies. None of these effects were found in four control animals exposed to air.

Despite an increase in gross lung weight, Penney et al. (1988a) were unable to demonstrate any evidence of edema in the lungs of male albino rats after 7.5 weeks of exposure to incrementally increasing concentrations of CO ranging from 250 to 1300 ppm. The authors also reported that this effect was not due to increased blood volume in the lung nor due to fibrosis, as measured by lung hydroxyproline content. There was, therefore, no obvious explanation for the lung hypertrophy reported in this study after chronic exposure to high concentrations of CO.

Fisher et al. (1969) failed to find any histologic changes in the lungs of mongrel dogs exposed to CO concentrations of 8000 to 14,000 ppm for 14 to 20 min (up to 18% COHb). Similarly, no morphological changes were found by Hugod (1980) in the lungs of adult rabbits continuously exposed to 200 ppm CO for up to six weeks (range of 11.9 to 19% COHb) or to 1900 ppm CO for five hours (range of 31 to 39% COHb).

Niden (1971) speculated about possible effects of low levels of CO on cellular oxidative pathways when he reported that exposure of mice to concentrations of CO from 50 to 90 ppm for one to five days, resulting in COHb levels of $<10\%$, produced increased cristae in the mitochondria and dilation of the smooth endoplasmic reticulum in the nonciliated bronchiolar (Clara) cell. Minimal changes, consisting of fragmentation of lamellar bodies, were found in the type 2 epithelial cell. Morphological appearance of the remaining cells of the terminal airways was normal. The results of this study were not presented in detail, however, and have not been confirmed at low concentrations of CO. Thus, the significance, if any, of changes in the structure of cells lining the terminal airways is unknown.

Weissbecker et al. (1969) found no significant changes in the viability of alveolar macrophages exposed *in vitro* to high concentrations of CO (up to 190,000 ppm). These results were later confirmed in more extensive *in vivo* exposure studies by Chen et al. (1982). They obtained alveolar macrophages by bronchoalveolar lavage from rats exposed to 500 ppm (41 to 42% COHb) from birth through 33 days of age. Morphological and functional changes in the exposed cells were minimal. There were no statistically significant differences in cell number, viability, maximal diameter, surface area, or acid phosphatase activity. The phagocytic ability of alveolar macrophages was enhanced by CO exposure, as determined by a statistically significant ($p<0.05$) increase in the percentage of spread forms and cells containing increased numbers of retained latex particles. The biological significance of this finding is questionable, however, because very few ($n = 5$) animals were evaluated and no follow-up studies have been performed.

10.2.2.2 Studies in Humans

In a study by Parving (1972) on 16 human subjects, transcapillary permeability to ^{131}I–labeled human serum albumin increased from an average 5.6% per hour in controls to 7.5% per hour following exposure to CO. The subjects were exposed for three to five hours to 0.43% (4300 ppm) CO, producing approximately 23% COHb. There were no associated changes in plasma volume, hematocrit, or total protein concentration.

The only other relevant permeability studies were conducted on cigarette smoke. Mason et al. (1983) showed rapidly reversible alterations in pulmonary epithelial permeability induced by smoking using ^{99m}TcDTPA as a marker. This increased permeability reverted to normal fairly rapidly when subjects stopped smoking (Minty et al., 1981). Using a rat model, the permeability changes associated with cigarette smoke were demonstrated later by Minty and Royston (1985) to be due to the particulate matter contained in the smoke. The increase in ^{99m}TcDTPA clearance observed after exposure to dilute whole smoke did not occur when the particles were removed, suggesting that the CO contained in the gaseous phase does not alter permeability of the alveolar-capillary membrane.

10.2.3 Effects on Lung Function

10.2.3.1 Lung Function in Laboratory Animals

Laboratory animal studies of lung function changes associated with CO exposure parallel the morphology studies previously described (see Section 10.2.2) because high concentrations (1500-10,000 ppm) of CO were utilized.

Fisher et al. (1969) ventilated the left lung of seven dogs with 8 to 14% CO for 14 to 20 min. Femoral artery blood COHb levels ranged from 8 to 18% at the end of CO breathing. No changes in the diffusing capacity or pressure-volume characteristics of the lung were found.

Fein et al. (1980) measured lung function in the same study discussed in Section 10.2.2. Nine New Zealand white rabbits were exposed for 45 min to either 0.8% CO or air. After CO exposure, COHb levels reached 63%. Dynamic lung compliance significantly decreased and airway resistance significantly increased at 15 and 30 min after the start of CO exposure, respectively. Mean blood pressure fell to 62% of the baseline value by

the end of exposure; heart rate was not changed. Arterial pH decreased progressively throughout exposure although there were no changes in the alveolar-arterial PO_2 difference.

Robinson et al. (1985), also interested in the effects of acute CO poisoning in humans, used mongrel dogs to examine ventilation ($\dot{V}_A$) and perfusion ($\dot{Q}$) distribution during and following CO exposure. A small number (n = 5) of mongrel dogs were exposed to 1% CO (10,000 ppm) for 10 min, resulting in peak COHb levels of 59 ± 5.4%. Inert gas distributions were measured at peak exposure and 2, 4, and 24 h after exposure. No changes in $\dot{V}_A/\dot{Q}$ were found. Previous studies were unable to show accumulation of lung water in the same model (Halebian et al., 1984a,b). The authors concluded that other constituents of smoke, besides CO, were responsible for the pulmonary edema and $\dot{V}_A/\dot{Q}$ mismatching found in victims exposed to smoke in closed-space fires.

Very little is known about the effects of CO on ventilation in laboratory animals and the few studies available are contradictory. No effects of CO on ventilation were found in unanesthetized rabbits (Korner, 1965) or cats (Neubauer et al., 1981), while large increases were reported in conscious goats (Chapman et al., 1980; Doblar et al., 1977; Santiago and Edelman, 1976). In anesthetized cats, high concentrations of CO (10,000 ppm) increased ventilation (Lahiri and Delaney, 1976). Gautier and Bonora (1983) used cats to compare the central effects of hypoxia on control of ventilation under conscious and anesthetized conditions. The cats were exposed for 60 min to either low inspired O_2 fraction ($^FIO_2$ = O.115) or CO diluted in air. In conscious cats, 1500 ppm CO caused a decreased ventilation, while higher concentrations (2000 ppm) induced first a small decrease followed by tachypnea that is typical of hypoxic hypoxia in carotid-denervated conscious animals. In anesthetized cats, however, CO caused only mild changes in ventilation.

Other respiratory effects of CO hypoxia, such as the increased total pulmonary resistance estimated by tracheal pressure, have been reported in anesthetized laboratory rats and guinea pigs (Mordelet-Dambrine et al., 1978; Mordelet-Dambrine and Stupfel, 1979). The significance of this effect is unknown, however, particularly under the extremely high CO exposure conditions utilized in these studies (4 min inhalation of 2.84% CO) that produced COHb concentrations >60% (Stupfel et al., 1981). Similar increases in tracheal pressure also were seen with hypoxic hypoxia ($^FIO_2$ = 0.89), suggesting a possible general mechanism associated with severe tissue hypoxia.

10.2.3.2 Lung Function in Humans

Human studies of pulmonary function mostly are devoted to the identification of effects occurring in the lungs of individuals exposed to relatively high concentrations of CO. Older studies in the literature describe the effects of brief, controlled experiments with high CO-air mixtures. Chevalier et al. (1966) exposed 10 subjects to 5000 ppm CO for 2 to 3 min until COHb levels reached 4%. Measurements of pulmonary function and exercise studies were performed before and after exposure. Inspiratory capacity and total lung capacity decreased 7.5 ($p<0.05$) and 2.1% ($p<0.02$), respectively, while maximum breathing capacity increased 5.7% ($p<0.05$) following exposure. Mean resting diffusing capacity of the lungs decreased 7.6% ($p<0.05$) compared to air-exposed controls. Fisher et al. (1969) exposed a small number ($n = 4$) of male subjects, aged 23 to 36 years, to 6000 ppm CO for 6 s, resulting in estimated COHb concentrations of 17 to 19%. There were no significant changes in lung volume, mechanics, or diffusing capacity. Neither of these studies was definitive, however, and no follow-up studies were reported.

More recent studies in the literature describing effects of CO on pulmonary function have been concerned with exposure to the products of combustion and pyrolysis from such sources as tobacco, fires, or gas- and kerosene-fueled appliances and engines. One group of individuals, representing the largest proportion of the population exposed to CO, is tobacco smokers. The reader is referred to Section 11.4 for a discussion on environmental tobacco smoke and to other reviews on the direct effects of smoking.

A second group evaluated for potential changes in acute ventilatory function includes occupations where individuals are exposed to variable, and often unknown, concentrations of CO in both indoor and outdoor environments (see Section 8.4 for a more complete discussion of occupational exposure to CO). Firefighters, tunnel workers, and loggers are typical examples of individuals at possible risk. Unfortunately, as described above in Section 10.2.2, these individuals also are exposed to high concentrations of other combustion components of smoke and exhaust. It is very difficult to separate the potential effects of CO from those due to other respiratory irritants (see Section 11.3.2 for more complete discussion of exposure to combustion products).

Firefighters previously have been shown to have a greater loss of lung function associated with acute and chronic exposure to smoke inhalation (as reviewed by Sparrow

et al., 1982). None of these earlier studies, however, characterized the exposure variables, particularly the concentrations of CO found in smoke, nor did they report the COHb levels found in firefighters after exposure. Most reports of lung function loss associated with other occupational exposures also fail to characterize exposure to CO. The following studies have attempted to monitor, or at least estimate, the CO and COHb levels found in occupational settings where lung function also was measured.

Sheppard et al. (1986) reported that acute decrements in lung function were associated with routine firefighting. Baseline airway responsiveness to methacholine was measured in 29 firefighters from one fire station in San Francisco, CA, who were monitored over an eight-week period. Spirometry was measured before and after each 24-h workshift and after each fire. Exhaled gas was sampled 55 times from 21 firefighters immediately after each fire and analyzed for CO. Despite the use of personal respiratory protection, exhaled CO levels exceeded 100 ppm on four occasions, with a maximum of 132 ppm, corresponding to calculated COHb values of 17 to 22%. Of the 76 spirometry measurements obtained within two hours after a fire, 18 showed a greater fall in forced expiratory volume (FEV_1) and/or forced vital capacity (FVC) compared to routine workshifts without fires. Decrements in lung function persisted for as long as 18 h in some of the individuals, but they did not appear to occur selectively in those individuals with preexisting airway hyperresponsiveness.

Evans et al. (1988) reported on changes in lung function and respiratory symptoms associated with exposure to automobile exhaust among bridge and tunnel officers. Spirometry and symptom questionnaires were administered on a voluntary basis to 944 officers of the Triborough Bridge and Tunnel Authority in New York City over an 11-year period between 1970 and 1981. Regression analyses were performed on 466 individuals (49%) who had been tested at least three times during that period. Carboxyhemoglobin levels were calculated from expired-air breath samples. Small, but significant differences were found between the bridge and tunnel officers. Estimated levels of COHb were consistently higher in tunnel workers compared to bridge workers for both nonsmoking individuals (1.96 and 1.73%, respectively) and smoking individuals (4.47 and 4.25%, respectively). Lung function measures of FEV_1 and FVC were reduced, on an average, in tunnel versus bridge workers. There were no reported differences in respiratory symptoms except for a slightly higher symptom prevalence in tunnel workers who smoked. Because differences in lung function between the two groups

were small, it is questionable if the results are clinically significant or if they were even related to CO exposure.

Hagberg et al. (1985) evaluated the complaints of 211 loggers reporting dyspnea and irritative symptoms in their eyes, nose, and throat after chain-saw use. Measurements of lung spirometry, COHb, and exposure to CO, HCs, and aldehydes were conducted on 23 loggers over 36 work periods lasting two hour each. Ventilation levels during tree felling averaged 41 L/min. Carboxyhemoglobin levels increased after chain-saw use ($p<0.05$) but were weakly correlated ($r = 0.63$) with mean CO concentrations of 17 ppm (4 to 73 ppm range) in nonsmokers. Corresponding COHb levels were apparently $<2\%$; unfortunately, the absolute values before and after exposure were not reported. Peripheral bronchoconstriction, measured by a decreased FEV_1/FVC ($p<0.03$) and forced expiratory flow $(FEF)_{25-75\%}$ ($p<0.005$), was found after the work periods but no correlations were obtained between lung function, COHb levels, and exposure variables. There were no reported changes in FEV_1 or FVC.

High CO concentrations also can be found indoors near unvented space heaters (see Section 7.2). The potential effects on lung function by indoor combustion products of kerosene space heaters was evaluated by Cooper and Alberti (1984). Carbon monoxide and SO_2 concentrations were monitored in 14 suburban homes in Richmond, VA, during January and February of 1983 while modern kerosene heaters were in operation. Spirometry was measured in 29 subjects over a two-day period, randomizing exposures between days with and without the heater on. During heater operation, CO concentration was 6.8 ± 5.9 ppm (0 to 14 ppm range), and SO_2 concentration was 0.4 ± 0.4 ppm (0 to 1 ppm range). On control days, indoor CO concentration was 0.14 ± 0.53 ppm, whereas SO_2 was undetectable. Six of the homes had CO concentrations exceeding the NAAQS primary eight-hour standard of 9 ppm. Corresponding outdoor CO concentrations were 0 to 3 ppm. Carboxyhemoglobin levels significantly increased from $0.82 \pm 0.43\%$ on control days to $1.11 \pm 0.52\%$ on days when kerosene heaters were used. Exposure to heater emissions, however, had no effect on FVC, FEV_1, or maximum mid-expiratory flow rate (MMFR).

Most of the published community population studies on CO have investigated the relationship between ambient CO levels and hospital admissions, deaths, or symptoms attributed to cardiovascular diseases (see Section 10.3). Little epidemiological information is

available on the relationship between CO and pulmonary function, symptomatology, and disease.

One study by Lutz (1983) attempted to relate levels of ambient pollution to pulmonary diseases seen in a family practice clinic in Salt Lake City, UT, during the winter of 1980-1981, when heavy smog conditions prevailed. Data on patient diagnoses; local climatological conditions; and levels of CO, O_3, and particulate matter were obtained over a 13-week period. Pollutant levels were measured daily and then averaged for each week of the study; absolute values were not reported. For each week, weighted simple linear regression and correlation analyses were performed. Significant correlations ($p = 0.01$) between pollution-related diseases and the environmental variables were found for particulate ($r = 0.79$), O_3 ($r = -0.67$), percent of smoke and fog ($r = 0.79$), but not for CO ($r = 0.43$) or percent of cloud cover ($r = 0.33$). The lack of a significant correlation with CO was explained by a small fraction (2%) of diagnoses for ischemic heart disease compared to a predominance of respiratory tract diseases such as asthma, bronchitis, bronchiolitis, and emphysema.

Daily lung function in a large community population exposed to indoor and outdoor air pollution was measured in Tucson, AZ, by Lebowitz et al. (1983a,b, 1984, 1985, 1987), Lebowitz (1984), and Robertson and Lebowitz (1984). Subsets of both healthy subjects and subjects with asthma, allergies, and airway obstructive disease were drawn from a symptom-stratified, geographic sample of 117 middle-class households. Symptoms, medication use, and peak flow measurements were recorded daily over a two-year period. Indoor and outdoor monitoring was conducted in a random sample of 41 representative houses. Maximum one-hour concentrations of O_3, CO, and NO_2 and daily levels of TSP, allergens, and meteorological variables were monitored at central stations within one-half mile of each population subset. Indoor pollutant measurements were made for particles and CO, indicating that gas stoves and tobacco smoking were the predominant indoor sources. Levels of CO were low, averaging less than 2.4 ppm indoors and 3.8 to 4.9 ppm outdoors. Spectral time series analysis was used to evaluate relationships between environmental exposure and pulmonary effects over time (Lebowitz et al., 1987; Robertson and Lebowitz, 1984). Asthmatics were the most responsive while healthy subjects showed no significant responses. Outdoor O_3, NO_2, allergens, meteorology, and indoor gas stoves were significantly related to symptoms and peak flow.

10.2.4 Summary

Currently available studies on the effects of CO exposures producing COHb concentrations of up to 39% fail to find any consistent effects on lung parenchyma and vasculature (Hugod, 1980; Fisher et al., 1969) or on alveolar macrophages (Chen et al., 1982; Weissbecker et al., 1969). The lack of significant changes in lung tissue is consistent with the lack of histologic changes in the pulmonary and coronary arteries (see Section 10.3.4). Alveolar epithelial permeability to ^{51}Cr-EDTA increased in rabbits (Fein et al., 1980) exposed to high concentrations of CO (63% COHb), and increased capillary endothelial permeability to ^{131}I-labeled human serum albumin was reported in early human studies (Parving, 1972) following acute, high-level CO exposure (23% COHb); however, no accumulation of lung water was found in dogs (Halebian et al., 1984a,b) with COHb levels of 59% and no edema was found in the lungs of rats chronically exposed to CO concentrations as high as 1300 ppm (Penney et al., 1988a). In addition, no changes in diffusing capacity of the lung were found in dogs with COHb levels up to 18% (Fisher et al., 1969). It is unlikely, therefore, that CO has any direct effect on lung tissue except at extremely high concentrations. The capillary endothelial and alveolar epithelial edema found with high levels of CO exposure in victims of CO poisoning may be secondary to cardiac failure produced by myocardial hypoxia (Fisher et al., 1969) or may be due to acute cerebral anoxia (Naeije et al., 1980).

Ventilatory responses to CO are related to the CO concentration as well as to the experimental conditions and the animal species being studied. In conscious goats (Chapman et al., 1980; Doblar et al., 1977; Santiago and Edelman, 1976) and cats (Gautier and Bonora, 1983), after an initial depression, ventilation suddenly increases, particularly at high CO concentrations (>2000 ppm). This response may result from the direct effects of hypoxia (and possibly central acidosis) and/or a specific CNS effect of CO (see Section 10.3). No effects on ventilation and perfusion distribution were found, however, in dogs exposed to 1% CO for 10 min, resulting in COHb levels of 59% (Robinson et al., 1985). At very high concentrations of CO (COHb >60%) total pulmonary resistance, measured indirectly by tracheal pressure, was reported to increase (Mordelet-Dambrine et al., 1978; Mordelet-Dambrine and Stupfel, 1979).

Human studies on the pulmonary function effects of CO are complicated by the lack of adequate exposure information, the small number of subjects studied, and the short exposures explored. Occupational or accidental exposure to the products of combustion and pyrolysis, particularly indoors, may lead to acute decrements in lung function if the COHb levels are >17% (Sheppard et al., 1986) but not at concentrations <2% (Evans et al., 1988; Hagberg et al., 1985; Cooper and Alberti, 1984). It is difficult, however, to separate the potential effects of CO from those due to other respiratory irritants in the smoke and exhaust. Community population studies on CO in ambient air have not found any relationships with pulmonary function, symptomatology, and disease (Lebowitz et al., 1987; Robertson and Lebowitz, 1984; Lutz, 1983).

10.3 CARDIOVASCULAR EFFECTS OF CARBON MONOXIDE

10.3.1 Introduction

Carbon monoxide exposure exerts deleterious effects in humans by several known mechanisms. Carbon monoxide combines with Hb to form COHb, which directly decreases the O_2 content of blood. In addition, CO shifts the oxyhemoglobin dissociation curve to the left, providing less O_2 to the tissues at a given tissue PO_2. Although no clinical studies have been done, *in vitro* studies suggest that CO also may exert a deleterious effect in man with coronary artery disease (injured vascular endothelium) by inhibiting the effects of oxyhemoglobin on the action of acetylcholine (Ignarro et al., 1987). Acetylcholine causes a release of endothelium-derived relaxing factor (EDRF). Carbon monoxide exposure in patients with diseased endothelium could accentuate acetylcholine-induced vasospasm and aggravate silent ischemia.

This section will discuss studies in man dealing with the effects in healthy individuals, in patients with heart disease, and in other susceptible populations.

10.3.2 Experimental Studies in Humans

10.3.2.1 Cardiorespiratory Response to Exercise

Effects in Healthy Individuals

The most extensive human studies on the cardiorespiratory effects of CO are those involving the measurement of O_2 uptake during exercise. These studies were discussed in the previous CO criteria document (U.S. Environmental Protection Agency, 1979), an addendum to that document (U.S. Environmental Protection Agency, 1984), and in other published reviews (Horvath 1981; Shephard, 1983,1984).

Healthy young individuals were used in most of the studies evaluating the effects of CO on exercise performance (see Table 10-1); healthy older individuals were studied in only two (Raven et al., 1974a; Aronow and Cassidy, 1975). In these studies, O_2 uptake during submaximal exercise for short durations (5 to 60 min) was not affected by COHb levels as high as 15 to 20% (Table 10-1). Under conditions of short-term maximal exercise, however, statistically significant decreases (3 to 23%) in maximal O_2 uptake ($\dot{V}O_2$ max) were found at COHb levels ranging from 5 to 20% (Klein et al., 1980; Stewart et al., 1978; Weiser et al., 1978; Ekblom and Huot, 1972; Vogel and Gleser, 1972; Pirnay et al., 1971). In another study by Horvath et al. (1975), the critical level at which COHb marginally influenced $\dot{V}O_2$ max ($p<0.10$) was approximately 4.3%. The data obtained by Horvath's group and others are summarized in Figure 10-1. There is a linear relationship between decline in $\dot{V}O_2$ max and increase in COHb that can be expressed as percent decrease in $\dot{V}O_2$ max = 0.91 (% COHb) + 2.2 (U.S. Environmental Protection Agency, 1979; Horvath (1981). Short-term maximal exercise duration also has been shown to be reduced (3 to 38%) at COHb levels ranging from 2.3 to 7% (Horvath et al., 1975; Drinkwater et al., 1974; Raven et al., 1974 a,b; Weiser et al., 1978; Ekblom and Huot, 1972). (See Table 10-1.)

Acute effects of cigarette smoke on maximal exercise performance are apparently similar to those described above in subjects exposed to CO. Hirsch et al. (1985) studied the acute effect of smoking on the cardiorespiratory function during exercise in nine healthy male subjects who were current smokers. They were tested twice–once after smoking three cigarettes per hour for five hours and once after not having smoked. The exercise tests were done on a bicycle ergometer with analysis of gas exchange and intra-arterial blood gases and

TABLE 10-1. SUMMARY OF EFFECTS OF CARBON MONOXIDE ON MAXIMAL AND SUBMAXIMAL EXERCISE PERFORMANCE

Exposure[a,b]	COHb[c]	Subjects(s)	Observed Effects[d]	Conclusions	Reference[e]
50 and 100 ppm CO 4-h treadmill exercise at 85% maximal heart rate (HR)	2.17% (50 ppm) 4.15% (100 ppm)	23 males 20-38 years (8 smokers)	Mean exercise duration was 19 s shorter on CO days; coagulation variables, cholesterol, and triglycerides were not significantly changed	Submaximal exercise duration decreased significantly at 4% COHb	Brinkhouse (1977)
50 ppm CO, 25 and 35°C 5-min treadmill exercise to exhaustion	2.3% (nonsmokers) 5.1% (smokers)	16 males 40-57 years (7 smokers)	No change in $\dot{V}O_2$ max; total work time decreased at 25°C in older nonsmokers	No significant decrease in $\dot{V}O_2$ max in older men exposed to CO but work time to exhaustion decreased in nonsmokers at 2.3% COHb	Raven et al. (1974a)
50 ppm CO, 35°C 20-min treadmill exercise to exhaustion	2.5% (nonsmokers) 4.1% (smokers)	20 young males equally divided by smoking history	No change in $\dot{V}O_2$ max; exercise duration decreased in non smokers; change in respiratory pattern in both smokers and nonsmokers	Work time decreased in nonsmokers at 2.5% COHb	Drinkwater et al. (1974)
50 ppm CO, 25°C 5-min treadmill exercise to exhaustion	2.7 (nonsmokers) 4.5% (smokers)	20 males 21-30 years equally divided by smoking history	No change in $\dot{V}O_2$ max or work time; no smoking effect	No significant decrease in maximal exercise performance	Raven et al. (1974b)
75 and 100 ppm CO 15-min treadmill exercise to exhaustion	3.3-4.3%	4 males 24-33 years (1 smoker)	$\dot{V}O_2$ max decreased ($p<0.10$) at 4.3% COHb; lower work times and ventilatory volumes at all COHb levels ($p<0.05$)	Maximal exercise performance decreased at COHb >4%	Horvath et al. (1975)
100 ppm CO 1 h treadmill exercise to exhaustion	3.95%	9 male 1 female nonsmokers 44-55 years	Mean exercise time until exhaustion decreased 5% ($p<0.001$)	Exercise time decreased in older nonsmokers at 3.95% COHb	Aronow and Cassidy (1975)
0.5% CO 2.5-3.5 min 5-min submaximal exercise at 1.84 L/ min $\dot{V}O_2$	3.95%	10 nonsmokers $\bar{x}$ = 30 years	No change in mean $\dot{V}O_2$; O_2 debt per $\dot{V}O_2$ increased 14%	Work at 4% COHb was performed with greater metabolic cost	Chevalier et al. (1966)

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TABLE 10-1 (cont'd). SUMMARY OF EFFECTS OF CARBON MONOXIDE ON MAXIMAL AND SUBMAXIMAL EXERCISE PERFORMANCE

Exposure[a,b]	COHb[c]	Subjects(s)	Observed Effects[d]	Conclusions	Reference[e]
50 ppm CO, 25 and 35°C 4-h exercise at 35% $\dot{V}O_2$ max	4.6-6.8%	19 males 18-55 years	Stroke volume decreased with higher ambient temperature; HR increased with CO exposure but no change in cardiac output or stroke volume	No major change in cardio-respiratory response to submaximal work with COHb levels <7%	Gliner et al. (1975)
15-min rebreathing to achieve target COHb; exercise at 30, 70, 100% $\dot{V}O_2$ max	4.8-21.2%	10 subjects 22-34 years	During maximal exercise, work time and $\dot{V}O_2$ max significantly decreased at 7-20% COHb; no change in $\dot{V}O_2$ with submaximal exercise	Maximal exercise performance and $\dot{V}O_2$ max decreased with increasing COHb	Ekblom and Huot (1972)
30 ppm CO 5-h treadmill exercise until exhaustion	5.0%	6 male non nonsmokers 25-39 years	$\dot{V}O_2$ max decreased while $\dot{V}_E$ and HR both increased	Maximal O_2 uptake decreased at 5% COHb	Klein et al. (1980)
20-min rebreathing to achieve target COHb; treadmill exercise until exhaustion	5.1%	9 male nonsmokers 24.7 ± 1.4 years residents of Denver, CO	Total exercise time decreased 3.8%; total work performed decreased 10%, and $\dot{V}O_2$ max decreased 2.8%	Maximal exercise performance in Denver, CO, (1610 m) decreased at 5% COHb	Weiser et al. (1978)
20,000 ppm CO for 45 s followed by 30 ppm for 4 h; treadmill exercise until exhaustion	5.5%	6 male nonsmokers 25-39 years	Maximal exercise time and $\dot{V}O_2$ decreased while HR and $\dot{V}_E$ increased	Maximal exercise performance decreased at 5.5% COHb	Stewart et al. (1978)
100 ppm CO 1-h bicycle exercise at 50% $\dot{V}O_2$ max	7.3% (non smokers) 9.5% (smokers)	12 males 12 females equally divided by smoking history	No change in FEV_1, $FEF_{25-75\%}$, VC, $\dot{V}O_2$, $\dot{V}_E$), TV, or f_B.	CO did not affect pulmonary function, subjective symptoms, or exercise metabolism	DeLucia et al. (1983)
10,000 ppm CO bolus followed by 60-70 ppm for 5 min	7.8%	9 male nonsmokers	$\dot{V}_E$ and breathing frequency (f_B) increased while $\dot{V}O_2$ max and (A-a) O_2 difference decreased with exercise	Maximal O_2 uptake decreased at 8% COHb	Collier et al. (1972)

TABLE 10-1 (cont'd). SUMMARY OF EFFECTS OF CARBON MONOXIDE ON MAXIMAL AND SUBMAXIMAL EXERCISE PERFORMANCE

Exposure[a,b]	COHb[c]	Subjects(s)	Observed Effects[d]	Conclusions	Reference[e]
15-min rebreathing to achieve target COHb; exercise at 30, 70, and 100% $\dot{V}O_2$ max	12.8-15.8%	9 males 23-34 years	$\dot{V}O_2$ max decreased 14.2% with maximal exercise; no change in ventilation or $\dot{V}O_2$ with submaximal exercise	Maximal exercise performance decreased after CO exposure	Ekblom et al. (1975)
0.05% CO 5-min moderate exercise for 15 min at 4 km/hr	15.4%	5 males 24-35 years	Increased HR but no change in $\dot{V}O_2$ or ventilation with submaximal exercise; $\dot{V}O_2$ max decreased 15.1%	Maximal O_2 uptake decreased at 15% COHb	Pirnay et al. (1971)
0.15-0.35% CO >70 min	16-52%	4 males 21-33 years	No hyperpnea at rest; arterial PCO_2 increased and pH decreased; cardiac output increased with increasing COHb	CO has a depressive action on the respiratory center	Chiodi et al. (1941)
225 ppm CO 1-h bicycle exercise at 50, 75, and 100% $\dot{V}O_2$ max	18-20%	8 males 20-23 years (3 smokers)	$\dot{V}O_2$ max decreased 23% ($p<0.001$); with submaximal exercise HR increased ($p<0.05$) while $\dot{V}O_2$ was unchanged	Maximal O_2 uptake decreased at >18% COHb	Vogel and Gleser (1972)
225 ppm CO 1-h bicycle exercise at 45, 75, and 100% $\dot{V}O_2$ max	20.3%	16 males (6 smokers)	$\dot{V}O_2$ max decreased 24% ($p<0.001$); no change in work efficiency or $\dot{V}O_2$ with submaximal exercise	Maximal O_2 uptake decreased at >20% COHb	Vogel et al. (1972)

[a]Exposure concentration, duration, and activity level.
[b]1 ppm = 1.145 mg/m^3; 1 mg/m^3 = 0.873 ppm at 25°C, 760 mm Hg; 1% = 10,000 ppm.
[c]Estimated or measured blood carboxyhemoglobin (COHb) levels.
[d]See glossary of terms and symbols for abbreviations and acronyms.
[e]Cited in U.S. Environmental Protection Agency (1979; 1984).

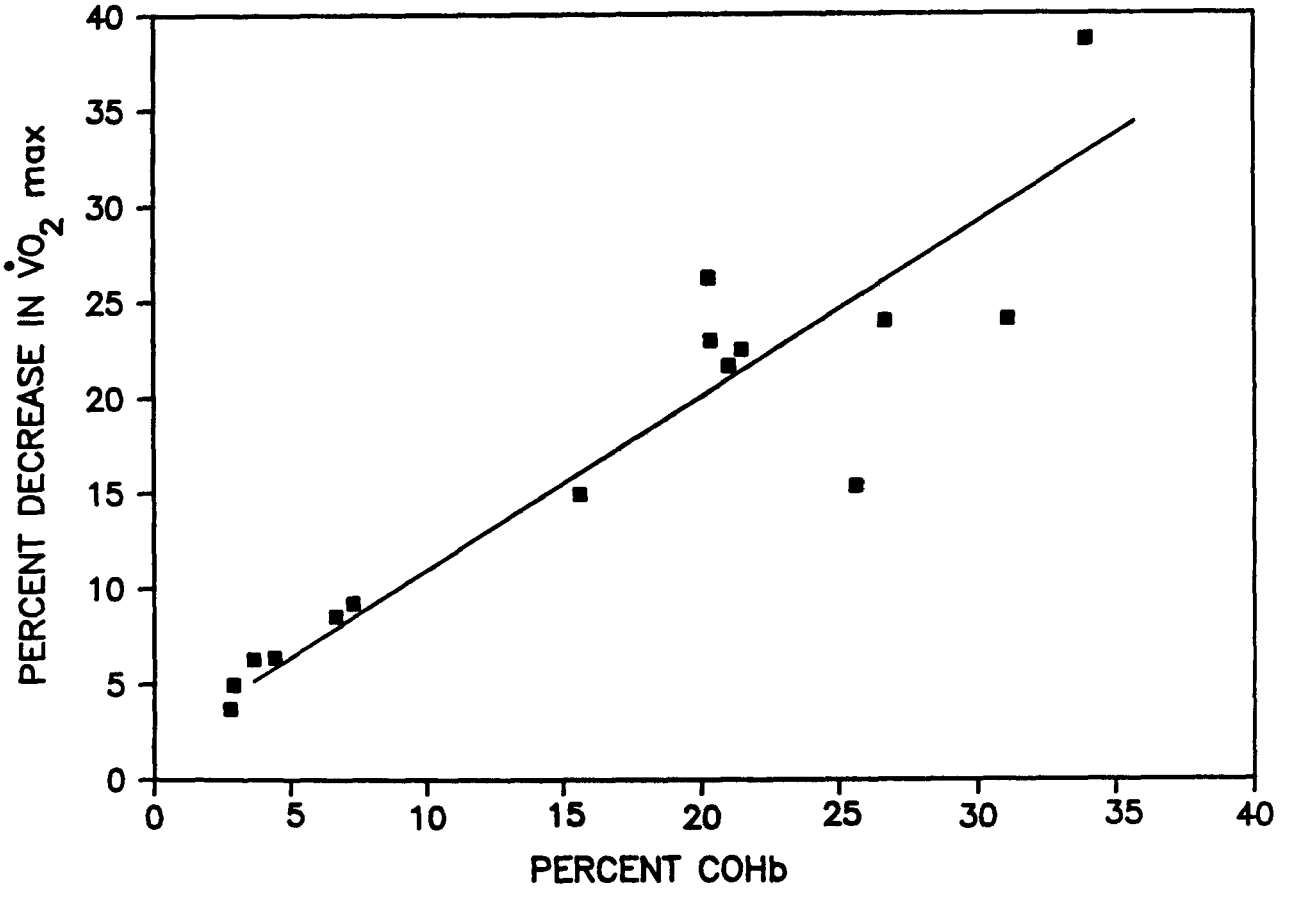

Figure 10-1. Relationship between carboxyhemoglobin level (COHb) and decrement in maximal oxygen uptake ($\dot{V}O_2$ max) for healthy nonsmokers.

Source: Adapted from U.S. Environmental Protection Agency (1979) and Horvath (1981).

pressures. On the smoking day, the maximal O_2 uptake was significantly decreased by 4% and the anaerobic threshold was decreased by 14%. The rate-pressure product was a significant 12% higher at comparable work loads of 100 watts on the smoking day compared to the nonsmoking day. There were no changes due to smoking, however, on the duration of exercise or on the mean work rate during maximal exercise testing. The blood COHb level before exercise was 1.8% on the nonsmoking and 6.6% on the smoking day. At peak exercise the COHb was 0.9% and 4.8%, respectively, on the nonsmoking and smoking day. The authors concluded that the main adverse effect of smoking was due to CO, although the increase in rate-pressure product also might be the result of the simultaneous inhalation of nicotine. They felt that the magnitude of change in performance indicators corresponded well with earlier reports.

It would be interesting, therefore, to determine if smokers and nonsmokers had different responses to CO exposure. Unfortunately, smokers and nonsmokers were not always identified in many of the studies on exercise performance, making it difficult to interpret the available data. Information derived from studies on cigarette smoke is also sparse. As a result, attempts to sort out the acute effects of CO from those due to other components of cigarette smoke have been equivocal. Seppanen (1977) reported that the physical work capacities of cigarette smokers decreased at 9.1% COHb levels after breathing either boluses of 1100 ppm CO or after smoking cigarettes. The greatest decrease in maximal work, however, was observed after CO inhalation.

Klausen et al. (1983) compared the acute effects of cigarette smoking and inhalation of CO on maximal exercise performance. They studied 16 male smokers under three different conditions: after eight hours without smoking (control), after inhalation of the smoke of three cigarettes, and after CO inhalation. Just before maximal exercise testing the arterial CO saturation reached 4.51 and 5.26% after cigarette smoke and CO inhalation, respectively, compared to 1.51% for controls. Average maximal O_2 uptake decreased by about 7% with both smoke and CO. Exercise time, however, decreased 20% with smoke but only 10% with CO, suggesting that nicotine, smoke particles, or other components of tobacco smoke may contribute to the observed effects. The authors, therefore, concluded that a specified COHb level induced by either smoke or CO decreased maximal work performance to the same

degree. Of note is the more marked decrease in work time compared to maximal O_2 uptake induced by CO, a finding that agrees with the Ekblom and Huot (1972) results (see Table 10-1).

If the magnitude of the effect of CO exposure is due only to a decrease in O_2-carrying capacity proportional to the COHb concentration, the magnitude should be roughly the same as if the O_2 capacity is decreased by anemia. Celsing et al. (1987) found in a series of very carefully performed studies in normal subjects that maximal O_2 uptake decreased by 19 mL/min/kg per gram per liter change in Hb over a wide range of Hb concentrations from 137 to 170 g/L. This decrease corresponds to a 2% decrease in maximal O_2 uptake for every 3% decrease in Hb concentration in a well-trained subject. The decrease also corresponds to the decrease in $\dot{V}O_2$ max reported by Ekblom and Huot (1972) and Horvath et al. (1975). However, Ekblom and Huot found a much more marked effect on maximal work time (i.e., work on a constant load until exhaustion with a duration of about 6 min). An explanation for the marked decrease in maximal work time could be that CO has a negative effect on the oxidative enzymatic system wheareas the decrease in work time is due to a combination of a decrease in O_2 capacity and a less efficient oxidative enzymatic system. If the data are extrapolated to lower COHb values, a 3% level of COHb should decrease the maximal work time by about 20%. However, this decrease is more than the 10% average decrease reported by Klausen et al. (1983) where they also found more marked effects in less well-trained subjects compared to well-trained subjects.

Effects in Individuals with Heart Disease

The previous criteria document (U.S. Environmental Protection Agency, 1979) concluded that patients with heart disease are especially at risk to CO exposure sufficient to produce 2.5 to 3% COHb. This statement was based primarily on studies initiated by Aronow et al. (1972) and Aronow and Isbell (1973) demonstrating that patients with angina pectoris, when exposed to low levels of CO, experienced reduced time to onset of exercise-induced chest pain as a result of insufficient O_2 supply to the heart muscle. A study by Anderson et al. (1973) reported similar results at mean COHb levels of 2.9 and 4.5% (see Table 10-2).

TABLE 10-2. SUMMARY OF EFFECTS OF CARBON MONOXIDE EXPOSURE IN PATIENTS WITH ANGINA

Exposure[a,b]	COHb[c]	COHb[d]	ΔCOHb[e]	Subject(s)	Observed Effects	Reference
50 or 100 ppm CO for 50 min of each hour x 4 h; postexposure exercise on a treadmill	2.9% (SP) 4.5% (SP)	ND	1.6% 3.2%	10 males, 5 smokers and 5 nonsmokers, with reproducible exercise-induced angina; 49.9 years	Duration of exercise before onset of angina was significantly shortened at 2.9 and 4.5% COHb ($p<0.005$); duration of angina was significantly prolonged at 4.5% ($p<0.01$) but not at 2.9% COHb. The response of smokers was not significantly different from that of nonsmokers.	Anderson et al. (1973)[f]
100 ppm CO for 60 min; postexposure incremental exercise at 48.6 L/min on a cycle ergometer	3.0% (CO-Ox)	2.8% (CO-Ox)	1.5%	24 male nonsmokers with reproducible exercise-induced angina; 59 ± 1 years (49-66 years)	Time to onset of angina decreased 5.9% ($p = 0.046$); no significant effect on the duration of angina. O_2 uptake at angina was reduced about 3% ($p = 0.04$). There were no significant changes in heart rate or systolic blood pressure at angina.	Kleinman et al. (1989)
117 or 253 ppm CO for 50-70 min; pre- and post-exposure incremental exercise at ~6 METS on a treadmill (modified Naughton protocol)	3.2% (CO-Ox) 5.6% (CO-Ox) 2.4% (GC) 4.7% (GC)	2.7% (CO-Ox) 4.7% (CO-Ox) 2.0% (GC) 3.9% (GC)	2.0% 4.4% 1.8% 4.0%	63 male nonsmokers with reproducible exercise-induced angina; 62 ± 8 years (41-75 years)	Earlier onset of myocardial ischemia was found with CO exposure: time to ST endpoint decreased 5.1 and 12.1% ($p<0.05$) and time to angina onset decreased 4.2 and 7.1% ($p<0.05$) at 2.0 and 3.9% COHb (GC), respectively; mean duration of exercise was significantly shorter at 3.9% COHb. A significant linear dose-response relationship was found for time to ST change for the range of COHb levels from 0.2 to 5.1% (GC). Changes in performance are clinically significant.	Allred et al. (1989a,b)

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TABLE 10-2 (cont'd). SUMMARY OF EFFECTS OF CARBON MONOXIDE EXPOSURE IN PATIENTS WITH ANGINA

Exposure[a,b]	COHb[c]	COHb[d]	ΔCOHb[e]	Subject(s)	Observed Effects	Reference
100-200 ppm CO for 60 min; postexposure incremental exercise at 317 KPM on a cycle ergometer	3.8% (CO-Ox)	3.6% (CO-Ox)	2.2%	25 male and 5 female nonsmokers with evidence of exercise-induced angina on at least one day; 58 ± 11 years (36-75 years)	No significant difference in time to onset or duration of angina. No significant difference in maximal exercise time, maximal ST segment depression, or time to significant ST segment depression during exercise. No significant difference in maximal ejection fraction; small decreases in blood pressure ($p = 0.031$) and change in ejection fraction ($p = 0.049$) during CO exposure requires further evaluation. Actuarial analysis (Bissette et al., 1986) including 3/30 subjects experiencing angina only on the CO exposure day showed a significant decrease in time to onset of angina after CO exposure.	Sheps et al. (1987)
100-200 ppm CO for 60 min; postexposure incremental exercise @300 KPM on a cycle ergometer	5.9% (CO-Ox)	5.2% (CO-Ox)	4.2%	22 male and 8 female nonsmokers with evidence of exercise-induced angina on at least one day; 58 ± 11 years (36-75 years)	Earlier onset of ventricular dysfunction, angina, and poorer exercise performance was found with CO exposure; mean duration of exercise was shorter ($p<0.05$); subjects were likely to experience angina earlier during exercise with CO ($p<0.05$) using actuarial analysis. Both the level ($p = 0.05$) and change in left ventricular ejection fraction at submaximal exercise ($p = 0.05$) were less on CO-exposure compared to air-exposure day. There was no significant difference in the peak exercise left ventricular ejection fraction.	Adams et al. (1988)

[a]Exposure concentration, duration, and peak activity level. NOTE: Because oxygen consumption was not measured, it is not possible to determine the actual level of exercise at which angina occurred.
[b]$1_{ppm} = 1.145\ mg/m^3$; $1\ mg/m^3 = 0.873$ ppm at 25° C, 760 mm Hg; 1% = 10,000 ppm.
[c]Measured blood carboxyhemoglobin (COHb) level after CO exposure; GC = gas chromatograph; CO-Ox = CO-Oximeter; SP = spectrophotometric method of Buchwald (1969).
[d]Measured blood carboxyhemoglobin (COHb) level after exercise stress test; GC = gas chromatograph; CO-Ox = CO-Oximeter; ND = not determined.
[e]Postexposure increase in COHb over baseline.
[f]Cited in U.S. Environmental Protection Agency (1979; 1984).

In 1981, Aronow reported an effect of 2% COHb on time to onset of angina levels in 15 patients. The protocol was similar to previously reported studies, with patients exercising until onset of angina. Only 8 of the 15 subjects developed more than 1 mm ischemic ST segment depression at the onset of angina during the control periods. This was not significantly affected by CO. It is questionable, therefore, as to whether the remaining patients truly met adequate criteria for ischemia despite angiographically documented cardiac disease. After breathing 50 ppm of CO for one hour, the patients' times to onset of angina significantly decreased from a mean of 321.7 $\pm$ 96 s to 289.2 $\pm$ 88 s.

In 1983, the studies by Aronow and his colleagues were reevaluated by an ad hoc committee to the EPA (especially the 1981 study). The committee concluded that the results of Aronow's studies did not meet a reasonable standard of scientific quality and, therefore, should not be used by the Agency in defining the critical COHb level at which adverse health effects of CO are occurring. A summary of the committee findings and a reevaluation of the key health effects information reported to be associated with relatively low level CO exposure can be found in an addendum to the 1979 criteria document for CO (U.S. Environmental Protection Agency, 1984).

The experimental design used in the Aronow studies on CO exposure effects in patients with angina set the stage for subsequent, more precisely designed studies. Aronow and his colleagues used the subjective measure of time to onset of angina as their only significant variable of CO effect. In an attempt to improve upon these earlier preliminary studies, the more recent studies employed electrocardiogram (EKG) changes as objective measures of ischemia. Another consideration in the conduct of the newer studies on angina was to establish better the dose response relationships for low levels of CO exposure. While the COHb level is accepted as the best measure of the effective dose of CO, the reporting of low level effects is problematic because of inconsistencies in the rigor with which the devices for measuring COHb have been validated. The most frequently used technique for measuring COHb has been the optical method found in the IL series of CO-Oximeters (CO-Ox). Not only is there a lot of individual variability in these machines, but recent comparisons with the gas chromatographic (GC) technique of measuring COHb have suggested that the optical method may not be a suitable reference technique for measuring low levels of COHb. (See Chapter 8, Section 8.5 for more details.) Several additional studies have appeared in the

literature to help define better the precise COHb levels at which cardiovascular effects occur in angina patients (see Table 10-2).

Sheps et al. (1987) studied 30 patients with ischemic heart disease age 38 to 75 years and assessed not only symptoms during exercise, but radionuclide evidence of ischemia (left ventricular ejection fraction changes). This study was designed to be representative of a broad group of patients with myocardial ischemia. Patients were nonsmokers with ischemia, defined either by exercise-induced ST segment depression, angina, or abnormal ejection fraction response (i.e., all patients had documented evidence of ischemia).

Patients were exposed to CO (100 ppm) or air during a three-day, randomized double-blind protocol to achieve a postexposure level of 4% COHb (CO-Ox measurement). Resting preexposure levels were 1.7%, and postexposure levels averaged 3.8% on the CO exposure day, thus the study examined acute elevation of COHb levels from 1.7% to an average of 3.8%, or an average increase of 2.2% from resting values. Comparing exposure to CO to exposure to air, there was no significant difference in time to onset of angina, maximal exercise time, maximal ST segment depression (1.5 mm for both), or time to significant ST segment depression. The conclusion of this study was that 3.8% COHb produces no clinically significant effects on this patient population.

Interestingly, further analysis of the time to onset of angina data in this paper demonstrated that 3 of the 30 patients experienced angina on the CO exposure day but not on the air control day. These patients had to be deleted from the classical analysis of differences between time to onset of angina that was reported in the publication. However, actuarial analysis of time to onset of angina including these patients revealed a statistically significant difference in time to onset of angina favoring an earlier time under the CO-exposure conditions (Bissette et al., 1986). None of the patients had angina only on the air exposure day.

Subsequent work from these same investigators (Adams et al., 1988) focused on repeating the study at 6% COHb (CO-Ox measurement) using an identical protocol and a similar patient population. Postexposure COHb levels averaged $5.9 \pm 0.1\%$ compared to $1.6 \pm 0.1\%$ after air exposure, representing an increase of 4.3%. The mean duration of exercise was significantly longer after air compared to CO exposure (626 ± 50 s for air vs. 585 ± 49 s for CO, $p<0.05$). Actuarial methods suggested that subjects experienced angina

earlier during exercise on the day of CO exposure ($p<0.05$). In addition this study showed that, at a slightly higher level of CO exposure, both the level and change in ejection fraction at submaximal exercise were greater on the air day than on the CO day. The peak exercise left ventricular ejection fraction, however, was not different for the two exposures.

These results demonstrated earlier onset of ventricular dysfunction and angina and poorer exercise performance in patients with ischemic heart disease after acute CO exposure sufficient to increase COHb to 6%. It is of interest that in both the 4% study and the 6% study reported by this group, some of the patients experienced angina on the CO day, but not on the air exposure day. There were no patients who experienced angina in the reverse sequence.

Kleinman and Whittenberger (1985) and Kleinman et al. (1989) studied nonsmoking male subjects with a history of stable angina pectoris and positive exercise tests. All but two of the 26 subjects had additional confirmation of ischemic heart disease, such as previous myocardial infarction, positive angiogram, positive thallium scan, prior angioplasty, or prior bypass surgery. Subjects were exposed for one hour in a randomized double-blind crossover fashion to either 100 ppm CO or to clean air on two separate days. Subjects performed an incremental exercise test on a cycle ergometer to the point at which they noticed the onset of angina. For the study group, the one-hour exposure to 100 ppm CO resulted in an increase of COHb from 1.4% after clean air to 3% (CO-Ox measurement) after CO. For the entire study group ($n = 26$), the one-hour exposure to 100 ppm resulted in a decrease of the time to onset of angina by 6.9% from 6.5 to 6.05 min (Kleinman and Whittenberger, 1985). This difference was significant in a one-tailed paired T-test ($p = 0.03$). When using a two-tailed test the difference loses statistical significance at the $p = 0.05$ level.

In a subsequent publication of results from this study (Kleinman et al., 1989), the two subjects with inconsistencies in their medical records and histories were dropped from the analysis. For this study group ($n = 24$), the one-hour exposure to 100 ppm CO (3% COHb by CO-Ox measurement) resulted in a decrease of time to onset of angina by 5.9% ($p = 0.046$). There was no significant effect on the duration of angina but O_2 uptake at angina point was reduced 2.7% ($p = 0.04$). Only eight of the subjects exhibited depression in the ST segment of their EKG traces during exercise. For this subgroup, there was a 10%

reduction ($p<0.036$) in time to onset of angina and a 19% reduction ($p<0.044$) in the time to onset of 0.1 mV ST segment depression.

A multicenter study of effects of low levels of COHb has been conducted on a relatively large sample (n = 63) of individuals with coronary artery disease from three different cities (Allred et al., 1989a,b). The purpose of this study was to determine the effects of 2.0% and 3.9% COHb (GC measurement) on time of onset of significant ischemia during a standard treadmill exercise test. Significant ischemia was measured subjectively by the time of exercise required for the development of angina (time of onset of angina) and objectively by the time required to demonstrate a 1-mm change in the ST segment of the ECG (time to ST). Male subjects, ages 41 to 75 (mean = 62.1 years) with stable exertional angina pectoris and positive stress test, as measured by >1-mm ST segment change, were studied. Further evidence that these subjects had coronary artery disease was provided by the presence of at least one of the following criteria: angiographic evidence of ≥70% narrowing of at least one coronary artery, documented prior myocardial infarction, or a positive stress thallium demonstrating an unequivocal perfusion defect. Thus, as opposed to some previous studies reported, this study critically identified patients with documented coronary artery disease.

The protocol for this study was similar to that used in the Aronow studies because two exercise tests were performed on the same day. The two tests were separated by a recovery period and double-blind exposure period. On each of the three exposure days the subject performed a symptom-limited exercise test on a treadmill, then was exposed for 50 to 70 min to the test environment (clean air, 117 ppm CO, or 253 ppm CO), and then performed a second symptom-limited exercise test. The time to the onset of angina and the time to 1-mm ST change was determined for each test. The percent change following exposure at both 2.0 and 3.9% COHb (GC measurement) then were compared to the same subject's response to the randomized exposure to room air (less than 2 ppm CO.)

When potential exacerbation of the exercise-induced ischemia by exposure to CO was tested using the objective measure of time to 1-mm ST segment change, exposure to 2.0% COHb resulted in a 5.1% decrease ($p = 0.01$) in the time to attain this level of ischemia. At 3.9% COHb the decrease in time to the ST criterion was 12.1% ($p\leq0.0001$) relative to the air–day results. At the 3.9% COHb level this reduction in time to ST depression was accompanied by a significant ($p = 0.03$) reduction in the heart rate-blood pressure product

(double product), an index of myocardial work. The maximal amplitude of the ST segment change also was significantly affected by the CO exposures: at 2% COHb the increase was 11% ($p = 0.002$) and at 3.9% COHb the increase was 17% relative to the air day ($p \leq 0.0001$).

When the individual center data in the Allred et al. (1989a,b) study were analyzed for covariates that may have influenced the results of this study, only the absolute level of COHb was found to have had a significant effect. This finding is not surprising given the dose-response relationship between CO and time to ST. This analysis compared the slopes for each individual subject: the three times to ST were plotted against the three actual COHb levels. The 62 individual slopes then were combined to yield a significant ($p < 0.005$) regression: change in time to ST = -3.85 ± 0.63 (%COHb) + 8.01% ± 2.48%. This dose-response relationship indicates that there is a 3.9% decrease in the time to ST criterion for every 1% increase in COHb.

The time to the onset of angina also was significantly reduced in these subjects. At 2.0% COHb the time to angina was reduced by 4.2% ($p = 0.027$) and at 3.9% COHb the time was reduced by 7.1% There were no significant changes in the double products at the time of the onset of angina in either exposure condition. The regression analysis for the time to angina data also resulted in a significant relationship ($p < 0.025$.) The average regression was time to angina = -1.89% + 0.81% (%COHb) + 1.00% ± 2.11%. The lower level of significance and the larger error terms for the angina regression relative to the ST analysis indicate that the angina endpoint is more variable. This may be due to the subjective nature of this endpoint and the variability in the ability of subjects to clearly recognize the onset of the pain.

The two endpoints (time to angina and time to ST change) in the Allred study also were highly correlated: the Spearman rank correlation coefficient = 0.49, $p \leq 0.0001$. The conclusion of all of the analyses from this multicenter study is that the response of the myocardium in these patients with coronary artery disease is consistent, although the effects are relatively small.

The analysis of the covariates in this multicenter study also provides answers to ancillary questions that have been raised elsewhere in this document. The medication being used by these subjects did not significantly influence the results (i.e., there does not appear to be any

drug interaction with the effects of CO). The major medications being used in this group were betablockers (38/63), nitrates (36/63), and calcium-channel blockers (40/63). The other major concern was the influence of the severity of the disease. The simplest approach to this was to evaluate the influence of the duration of the exercise because the subjects with more severe disease were limited in their exercise performance. No significant correlation was found between duration of exercise and the change in the time to angina or ST criterion. There also was no relationship between the average time of exercise until the onset of angina and either of the endpoints. There also was no relationship between the presence of a previous myocardial infarction and the study endpoints.

The duration of exercise was significantly shortened by the 3.9% COHb but not by the 2.0% level. This finding must be used cautiously because these subjects were not exercised to their maximum capacity in the usual sense. The major reason for termination of the exercise was the progression of the angina (306/376 exercise tests.) The subjects were to grade their angina on a four-point scale, and when the exercise progressed beyond level two they were stopped. Therefore this significant decrease in exercise time of 40 s at the 3.9% COHb level is undoubtedly due to the earlier onset of angina followed by the normal rate of progression of the severity of the angina.

The individual center data provides insight into the interpretation of other studies that have been conducted in this area. Each of the centers enrolled the numbers of subjects that have been reported by other investigators. The findings reported above were not substantiated in all instances at each center. When one considers the responses of the group to even the 3.9% COHb, it is clear as to why one might not find significance in one parameter or another. For the decrease in ST segment at 3.9%, only 49 of 62 subjects demonstrated this effect on the day tested. The potential for finding significance at this effect rate with a smaller sample size is reduced. Random sampling of this population with a smaller sample easily could provide subjects that would not show significant effects of these low levels of CO on the test day.

The recent report (Allred et al., 1989b) of the multicenter study conducted by the Health Effects Institute (HEI) discusses some reasons for differences between the results of the studies cited above (also see Table 10-2 and Table 10-3). The studies have different designs, types of exercise tests, inclusion criteria (and, therefore, patient populations), exposure

TABLE 10-3. COMPARISON OF SUBJECTS IN STUDIES OF THE EFFECT OF CARBON MONOXIDE EXPOSURE ON OCCURRENCE OF ANGINA DURING EXERCISE

	Subject Characteristics					
Study	Number of Subjects	Gender	Medication	Smoking History	Description of Disease	Age (years)
Anderson et al. (1973)	10	male	1 subject took digitalis; drug therapy basis for exclusion	5 smokers (refrained for 12 h prior to exposure)	Stable angina pectoris, positive exercise test (ST changes); reproducible angina on treadmill	(mean = 49.9)
Kleinman et al. (1989)	24	male	14 on betablockers; 19 on nitrates; 8 on Ca-channel blockers	No current smokers	Ischemic heart disease, stable exertional angina pectoris	49 - 66 (mean = 59)
Allred et al. (1989a,b)	63	male	38 on betablockers; 36 on nitrates; 40 on calcium antagonists	No current smokers	Stable exertional angina and positive exercise test (ST changes) plus 1 or more of the following: (1) $\geq$70% lesion by angiography in 1 or more major vessels, (2) prior MI, (3) positive exercise thallium test	41 - 75 (mean = 62.1)
Sheps et al. (1987)	30 (23 with angina)	25 male 5 female	26 subjects on medication; 19 on beta blockers; 11 on Ca-channel blockers; 1 on long-acting nitrates	No current smokers	Ischemia during exercise (ST changes or abnormal ejection fraction response) and 1 or more of the following: (1) angiographically proven CAD, 2) prior MI, (3) typical angina	36 - 75 (mean = 58.2)
Adams et al. (1988)	30	22 male 8 female	25 subjects on medication; 13 on beta blockers + Ca-channel blockers; 6 on beta blockers; 5 on Ca-channel blockers; 1 on long-acting nitrates	No current smokers	Ischemia during exercise (ST changes or abnormal ejection fraction response) and 1 or more of the following: (1) angiographically proven CAD, (2) prior MI, (3) typical angina	36 - 75 (mean = 58)

Source: Adapted from Allred et al. (1989b)

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conditions, and means of measuring COHb. All of the studies have shown an effect of COHb elevation on the time to onset of angina (see Figure 10-2). Results form the Kleinman et al. (1989) study showed a 6% decrease in exercise time to angina at 3.0% COHb (CO-Ox measurement) measured at the end of exposure. Allred et al. (1989a,b) reported a 5 and 7% decrease in time to onset of angina after increasing COHb levels to 3.2 and 5.6% (CO-Ox measurement), respectively, at the end of exposure. Both Sheps et al. (1987) and Adams et al. (1988) reported a significant decrease in the time to onset of angina on days when COHb levels at the end of exposure were 3.8 and 5.9% (CO-Ox measurement), respectively, if the data analysis by actuarial method included subjects who experienced angina on the CO but not the air day.

The multicenter study (Allred et al., 1989a,b) demonstrated a dose-response effect of COHb on time to onset of angina. The only other single study that investigated more than a single target level of COHb was Anderson et al. (1973) and their results did not show a dose response for angina.

The time to onset of significant ECG ST-segment changes, which are indicative of myocardial ischemia in patients with documented cornary artery disease (CAD), is a more objective indicator of ischemia than angina. Allred et al. (1989a,b) reported a 5.1 and 12.1% decrease in time to ST depression at COHb levels of 2.0 and 3.9% (GC measurement), respectively, measured at the end of exercise. An additional measurement of the ST change was made by Allred et al. (1989b) to confirm this response – all the leads showing ST segment changes were summed. This summed ST score also was significantly affected by both levels of COHb. The significant finding for the summed ST score indicates that the effect reported for time to ST was not dependent upon changes observed in a single EKG lead.

The differences between the results of these five studies on exercise-induced angina can largely be explained by differences in experimental methodology and analysis of data and, to some extent, by differences in subject populations and sample size. For example, the Kleinman study and the Allred study used one-tailed p values. The Sheps and Adams studies used two-tailed p values. If a two-sided p value was utilized on the time to onset of angina variable observed at the lowest COHb level in the Allred study, it would become 0.054 rather than 0.027, a result that would be considered borderline significant. If a two-sided p value

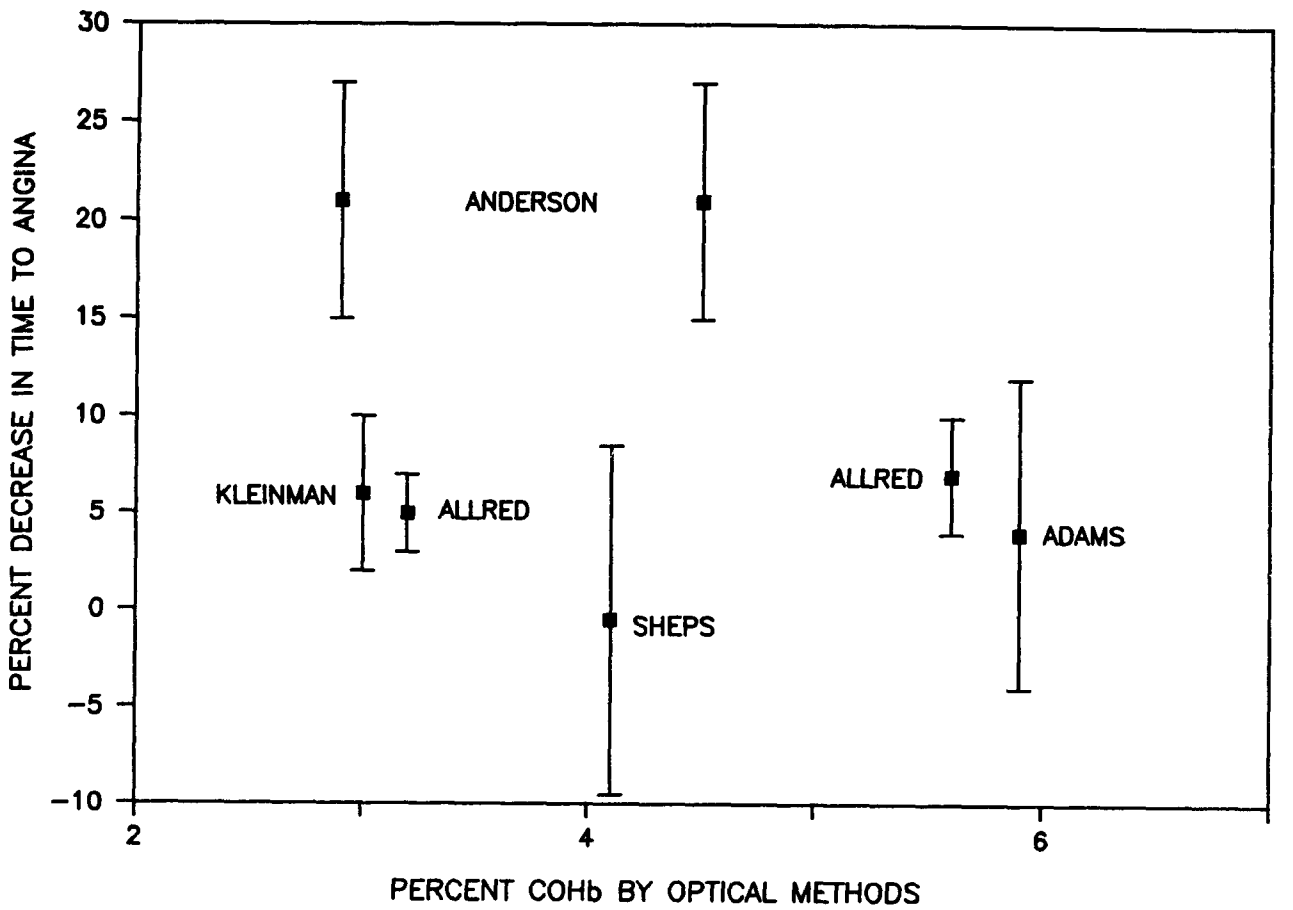

Figure 10-2. The effect of CO exposure on time to onset of angina. For comparison across studies, data are presented as the mean percent differences between air and CO exposure days for individual subjects that were calculated from each of the studies. Bars indicate calculated standard errors of the mean. (See text and Table 10-2 and Table 10-3 for more detailed information).

Source: Adapted from Allred et al. (1989b).

were used in the Kleinman study, the difference in time to onset of angina would lose significance at the $p = 0.05$ level.

The entry criteria in the Allred study were more rigorous than in the other studies. All subjects were required to have stable exertional angina and *reproducible* exercise-induced ST depression and angina. Besides these criteria, all subjects were required to have either a previous myocardial infarction (MI), angiographic disease, or a positive thallium stress test. In addition, only men were studied. These strict entry criteria were helpful in allowing the investigators to measure more precisely an adverse effect of CO exposure. However, because of the difficulty the investigators had in recruiting subjects, some questions remain about how representative the study population is of all patients in the United States with exercise-induced ischemia. In addition, the protocol for the multicenter study was slightly different from some of the protocols previously reported. On each test day, the subject performed a symptom-limited exercise test on a treadmill, then was exposed for approximately one hour to air or one of two levels of CO in air, and then underwent a *second* exercise test. Time to the onset of ischemic EKG changes and time to the onset of angina were determined for each exercise test. The percent difference for these endpoints from the pre- and postexposure test then was determined. The results on the 2% target day and then the 4% target day were compared to those on the control day.

The statistical significance reported at the low-level CO exposure is only present when the *differences* between pre- and postexposure exercise tests are analyzed. Analysis of only the postexposure test results in a loss of statistical significance for the 2% COHb level. Some of the differences between the results of this multicenter study and previous studies may be related to the fact that the exposure was conducted shortly after patients exercised to angina. Because the effects of ischemia may have a variable duration (radionuclide studies have shown metabolic effects of ischemia to last for over an hour), differences between pre- and postexposure tests may have been due to effects of CO exposure on *recovery* from a previous episode of exercise-induced ischemia rather than detrimental effects only during exercise.

In conclusion, five key studies have investigated the potential for CO exposure to enhance the development of myocardial ischemia at ≤6% COHb during progressive exercise tests. Despite differences between these studies, it is impressive that Figure 10-2 shows a consistent relationship in percent decrease in time to onset of angina across multiple studies.

Therefore, there are clearly demonstrable effects of low-level CO exposure in patients with ischemic heart disease. The decrements in performance that have been described at the lowest levels (≤3% COHb) are probably in the range of reproducibility of the test and would not be alarming to most physicians. The adverse health consequences of these types of effects, however, are very difficult to project.

Effects in Individuals with Chronic Obstructive Lung Disease

Aronow et al. (1977) studied the effects of a one-hour exposure to 100 ppm CO on exercise performance in 10 men, aged 53 to 67 years, with chronic obstructive lung disease. The resting mean COHb levels increased from baseline levels of 1.4% to 4.1% after breathing CO. The mean exercise time until marked dyspnea significantly decreased (33%) from 218 s in the air-control period to 147 s after breathing CO. The authors speculated that the reduction in exercise performance was due to a cardiovascular limitation rather than respiratory impairment.

Only one other study in the literature by Calverley et al. (1981) looked at the effects of CO on exercise performance in older subjects with chronic lung disease. They evaluated 15 patients with severe reversible airway obstruction due to chronic bronchitis and emphysema. Six of the patients were current smokers but they were asked to stop smoking for 12 h before each study. The distance walked within 12 min was measured before and after each subject breathed 0.02% CO in air from a mouthpiece for 20 to 30 min until COHb levels were 8 to 12% above their initial levels. A significant decrease in walking distance was reported when the mean COHb concentration reached 12.3%, a level much higher than most of those reported in the studies on healthy subjects.

Thus, while it is possible that individuals with hypoxia due to chronic lung diseases such as bronchitis and emphysema may be susceptible to CO during submaximal exercise typically found during normal daily exercise, these effects have not been studied adequately at relevant COHb concentrations of <5%.

Effects in Individuals with Chronic Anemia

An additional study by Aronow et al. (1984) on the effect of CO on exercise performance in anemic subjects found a highly significant decrease in work time (16%)

induced by a 1.24% increase in COHb. The magnitude of change seems to be very unlikely, however, even considering the report by Ekblom and Huot (1972). The study was double-blind and randomized, but with only 10 subjects. The exercise tests were done on a bicycle in the upright position with an increase in workload of 25 watt every 3 min. However, no measure of maximal performance such as blood lactate was used. The mean maximal heart rate was only 139 to 146 beats/min compared to a predicted maximal heart rate of 170 beats/min for the mean age of the subjects. A subject repeating a test within the same day, which was the case in the Aronow et al. (1984) study, often will remember the time and work load and try to do the same in the second test. Normally, however, some subjects will increase while others will decrease the time. This situation was apparent on the air-control day, with an increase demonstrated in 6 out of 10 subjects, despite the high reproducibility for such a soft, subjective endpoint. Also, comparing the control tests on the air day with the CO day, 7 out of 10 subjects increased their work time. After CO exposure, however, every subject decreased their time between 29 and 65 s. These data appear to be implausible given the soft endpoint used, when two to three of the subjects would be expected to increase their time even if there was a true effect of CO.

10.3.2.2 Arrhythmogenic Effects

The literature until recent years has been confusing with regard to potential arrhythmogenic effects of CO.

Davies and Smith (1980) studied the effects of moderate CO exposure on healthy individuals. Six matched groups of human subjects lived in a closed, environmental-exposure chamber for 18 days and were exposed to varying levels of CO. Standard 12-lead electrocardiograms were recorded during five control, eight exposure, and five recovery days, respectively. P-wave changes of at least 0.1 mV were seen in the electrocardiograms during the CO exposure period in 3 of 15 subjects at 2.4% COHb and in 6 of 15 at 7.1% COHB compared to none of 14 at 0.5% COHb. The authors felt that CO had a specific toxic effect on the myocardium in addition to producing a generalized decrease in O_2 transport to tissue.

Several methodological problems create difficulties of interpretation for this study. The study design did not use each subject as his own control. Thus, only one exposure was conducted out for each subject. Half of the subjects were tobacco smokers who were required

to stop and certainly some of the ECG changes could have been due to the effects of nicotine withdrawal. Although the subjects were deemed to be normal, no screening stress tests were performed to uncover latent ischemic heart disease or propensity to arrhythmia. Most importantly, no sustained arrhythmias or measurable effects on the conduction system were noted by the authors. If p-wave changes of clinical significance are representative of a toxic effect of CO on the atrium, then an effect on conduction of arrhythmias should be demonstrated.

Knelson (1972) reported that 7 of 26 individuals, aged 41 to 60 years, had abnormal electrocardiograms after exposure to 100 ppm CO for four hours (COHb levels of 5 to 9%). Two of them developed arrhythmias. No further details were given regarding specifics of these abnormalities. Among 12 younger subjects aged 25 to 36 years, all electrocardiograms were normal.

Hinderliter et al. (1989) reported on effects of low-level CO exposure on resting and exercise-induced ventricular arrhythmias in patients with CAD and no baseline ectopy. They studied 10 patients with ischemic heart disease and no ectopy according to baseline monitoring. After an initial training session, patients were exposed to air, 100 ppm CO, or 200 ppm CO on successive days in a randomized, double-blinded crossover fashion. Venous COHb levels after exposure to 100 and 200 ppm CO averaged 4 and 6%, respectively. Symptom-limited supine exercise was performed after exposure. Eight of the ten patients had evidence of exercise-induced ischemia – either angina, ST segment depression, or abnormal left ventricular ejection fraction response – during one or more exposure days. Ambulatory electrocardiograms were obtained for each day and analyzed for arrhythmia frequency and severity. On air- and CO-exposure days, each patient had only zero to one ventricular premature beat per hour in the two hours prior to exposure, during the exposure period, during the subsequent exercise test, and in the five hours following exercise. The authors concluded that low-level CO exposure is not arrhythmogenic in patients with CAD and no ventricular ectopy at baseline.

When patients with other levels of ventricular ectopy were studied (Sheps et al., 1989), there was an increase in exercise-related arrhythmia (both simple and complex). Although no definite evidence exists to date relating effects of CO exposure and lethal arrhythmias, the recent epidemiologic study of Stern and colleagues (Stern et al., 1988) indicates that an excess

of cardiovascular mortality in tunnel workers could be due to exposure to high levels of CO (see Section 10.3.3.1). Their findings that risk decreased after job cessation and that risk was not related to length of exposure suggest an acute effect of CO exposure maybe the causative factor (perhaps due to arrhythmia production). These findings are consistent with the general lack of effect of CO exposure on the development or progression of atherosclerosis.

10.3.2.3 Effects on Coronary Blood Flow

The effects of breathing CO on myocardial function in patients with and without coronary heart disease have been examined by Ayres et al. (1969; 1970). Acute elevation of COHb from 0.98 to 8.96% by a bolus exposure using either 1000 ppm CO for 8 to 15 min or 5000 ppm for 30 to 45 s caused a 20% average decrease in coronary sinus O_2 tension without a concomitant increase in coronary blood flow in the patients with coronary artery disease. Observations in patients with coronary disease revealed that acute elevation of COHb to approximately 9% decreased the extraction of O_2 by the myocardium. However, overall myocardial O_2 consumption did not change significantly because an increase in coronary blood flow served as a mechanism to compensate for a lower overall myocardial O_2 extraction. In contrast, patients with noncoronary disease increased their coronary blood flow with an insignificant decrease in coronary sinus O_2 tension as a response to increased COHb. The coronary patients also switched from lactate extraction to lactate production. Thus, a potential threat exists for patients with coronary heart disease who inhale CO because of their inability to increase coronary blood flow to compensate for the effects of increased COHb.

Although in this study the coronary sinus PO_2 dropped only slightly (reflecting average coronary venous O_2 tension), it is certainly possible that, in areas beyond a significant coronary arterial stenosis, tissue hypoxia might be precipitated by very low tissue PO_2 values. Tissue hypoxia might be further exacerbated by a coronary-steal phenomena whereby increased overall coronary flow diverts flow from areas beyond a stenosis to other normal areas. Therefore the substrate for the worsening of ischemia and consequent precipitation of arrhythmias is present with CO exposure.

10.3.3 Relationship between CO Exposure and Risk of Cardiovascular Disease in Man

10.3.3.1 Risk of Ischemic Heart Disease

Epidemiologic studies on the relation between CO exposure and ischemic heart disease are scarce. Earlier epidemiological data were summarized by Kuller and Radford (1983). They concluded that mortality and morbidity studies have been negative or equivocal in relating CO levels to health effects, but studies in human subjects with compromised coronary circulation support an effect of acute exposure to CO at blood levels equivalent to about 20 ppm over several hours. They calculate that based on health surveys, probably over 10 million subjects in the United States are exposed to potentially deleterious levels of CO and that perhaps 1250 excess deaths related to low-dose environmental CO exposure occur each year.

Stern et al. (1981) reported a study performed by the NIOSH. They investigated the health effects of chronic exposure to low concentrations of CO by conducting a historical prospective cohort study of mortality patterns among 1558 white, male motor vehicle examiners in New Jersey. The examiners were exposed to 10 to 24 ppm. The COHb levels were determined in 27 volunteers. The average COHb level before a work shift was 3.3% and the post-shift level was 4.7% in the whole group and 2.1 and 3.7%, respectively, in nonsmokers only. The death rates were compared to the rates in the U.S. population based on vital statistics. The cohort demonstrated a slight overall increase in cardiovascular deaths but a more pronounced excess was observed within the first 10 years following employment. The study has several important limitations, however, including the use of historical controls. A second limitation is the lack of knowledge about smoking habits. A third is that the individuals' values of COHb were not known.

Stern et al. (1988) published coronary heart disease mortality data among bridge and tunnel officers exposed to CO. They investigated the effect of occupational exposure to CO on mortality from arteriosclerotic heart disease in a retrospective study of 5529 New York City bridge and tunnel officers. There were 4317 bridge officers and 1212 tunnel officers. Among former tunnel officers, the standardized mortality ratio was 1.35 (90% confidence interval 1.09 to 1.68) compared to the New York City population. Using the proportional hazards model, the authors compared the risk of mortality from arteriosclerotic heart disease

among tunnel workers with that of the less-exposed bridge officers. They found an elevated risk in the tunnel workers that declined within as little as five years after cessation of exposure. The 24-h average CO level in the tunnel was around 50 ppm in 1961 and around 40 ppm in 1968. However, higher values were recorded during rush hours. In 1971 the ventilation was further improved and the officers were allowed clean-air breaks. Although the authors concluded that CO exposure may play an important role in the pathophysiology of cardiovascular mortality, other factors must be taken into consideration. Mortality from arteriosclerotic heart disease has a complex multifactor etiology. The presence of other risk factors, such as cigarette smoke, hypertension, hyperlipidemia, family history of heart disease, obesity, socioeconomic status, and sedentary living all can increase the risk of developing coronary heart disease. In addition, detailed exposure monitoring was not done in this study. The bridge and tunnel workers were not only exposed to CO but also were exposed to other compounds emitted from motor vehicle exhaust and to the noise and stress of their environment. These other factors could have contributed to the findings.

Intoxication with CO that induces COHb levels around 50 to 60% is often lethal. However, even levels around 20% COHb have been associated with death, mainly coronary events, in patients with severe coronary artery disease. Balraj (1984) reported on 38 cases of individuals dying immediately or within a few days following exposure to 10 to 50% COHb, usually nonlethal levels of CO. All of the subjects had coronary artery disease, and 29 of them had severe cases. The author concluded that the CO exposure, between 10 to 30% COHb in 24 cases, triggered the lethal event in subjects with a restricted coronary flow reserve. Similar associations between CO exposure and death or myocardial infarction have been reported by several other authors. Atkins and Baker (1985) reported two cases with 23 and 30% COHb; McMeekin and Finegan (1987) reported one case with 45% COHb; Minor and Seidler (1986) reported one case with 19% COHb; and Ebisuno et al. (1986) reported one case with 21% COHb.

Forycki et al. (1980) described electrocardiographic changes in 880 patients treated for acute poisoning. Effects were observed in 279 cases, with the most marked changes in cases with CO poisoning. In those, the most common change was a T-wave abnormality and in six cases a pattern of acute myocardial infarction was present. Conduction disturbances also were common in CO poisoning but arrhythmias were less common.

The association between smoking and cardiovascular disease (CVD) is fully established. Although little is known about the relative importance of CO compared to nicotine, most researchers consider them to be equally important. The nicotine component clearly aggravates the decrease in O_2 capacity induced by CO through an increase in the O_2 demand of the heart. This is exemplified in the study by Deanfield et al. (1986) using positron emission tomography. They found that smoking one cigarette induced perfusion abnormalities in six out of eight patients with CAD and exercise-induced angina. However, the smoke-induced ischemia was without angina or silent ischemia in all of the patients and without ST depression in seven of the patients. This raises an important question regarding analyses of the effect of CO. Ischemia is not always associated with angina and/or ST depression. However, most of the reports used to develop the guidelines for CO exposure have used angina and/or ST depression as a sign of ischemia. Only the two studies by Sheps et al. (1987) and Adams et al. (1988) used additional techniques to diagnose ischemia (see Section 10.3.2). Both used gated radionuclide angiography to measure changes in ejection fraction and wall motion induced by exercise, allowing the detection for signs of ischemia in the absence of angina and/or ST depression. Positron emission tomography is even more sensitive, however. Future studies on the effects of CO in patients with CVD, therefore, will need to include more sensitive measures of ischemia than angina and/or ST depression.

Passive smoking exposes an individual to all components in the cigarette smoke, but the CO component dominates heavily because only 1% or less of the nicotine is absorbed from sidestream smoke compared to 100% in an active smoker (Wall et al., 1988; Jarvis, 1987). Therefore, exposure to sidestream smoke will be the closest to pure CO exposure even if the resultant levels of COHb are low (about 2 to 3%). Two recent studies report on the relationship between passive smoking and risk of coronary heart disease (CHD). Svendsen et al. (1987) report from the multiple risk factor intervention trial (MRFIT) study on 1245 married, never-smoking men and 286 men married to women who smoke. The relative risk for exposure to sidestream smoke was 1.48 ($p = 0.13$, 95% confidence interval [CI] = 0.89 to 2.47) for nonfatal and fatal coronary events and 1.96 ($p = 0.08$, 95% CI = 0.93 to 4.11) for all causes of mortality. Even more significant results were reported by Helsing et al. (1988) who studied 4162 men and 14,873 women that were nonsmokers, some of which had been exposed to sidestream smoke. The relative risk for exposure to passive smoke was

1.31 (95% CI = 1.1 to 1.6) in men and 1.24 (95% CI = 1.1 to 1.4) in women for arteriosclerotic heart disease death. Even though it is impossible to rule out an effect of the other component in sidestream smoke, the data suggest an increase in risk of CHD associated with a prolonged exposure to low levels of CO. In the United States, a population study by Cohen et al. (1969) suggested an association between atmospheric levels of CO and increased mortality from myocardial infarction in Los Angeles, but potential confounders were not effectively controlled. In contrast, a similar study in Baltimore (Kuller et al., 1975) showed no association between ambient CO levels and myocardial infarction or sudden death. In a Finnish study (Hernberg et al. 1976), the prevalence of angina among foundry workers showed an exposure-response relationship with regard to CO exposure, but no such result was found for ischemic EKG findings during exercise.

In a cross-sectional study of 625 smokers, age 30 to 69, Wald et al. (1984) reported that the incidence of CVD was higher in subjects with COHb >5% compared to subjects below 3%, a relative risk of 21.2 (95% CI = 3.3 to 34.3). Even if all of the subjects were smokers, the association between COHb and CVD might be due to the fact that percent COHb is a measure of smoke exposure.

Low to intermediate levels of COHb might interfere with the early course of an acute myocardial infarction. The increase in COHb can be due to recent smoking or environmental exposure. Mall et al. (1985) reported on a prospective study in smoking and nonsmoking patients with acute myocardial infarction who were separated by their baseline COHb levels. A total of 66 patients were studied. Thirty-one patients presented with a COHb level of 1.5% and 35 with a level of 4.5%. In the group with elevated COHb, more patients developed transmural infarction, but the difference was not significant. Patients with transmural infarction had higher maximum creatine phosphokinase values when COHb was over 2%. During the first six hour after admission to the hospital, these patients needed an antiarrhythmic treatment significantly more frequently. Differences in rhythm disorders were still present at a time when nicotine, due to its short half-life, was already eliminated. The authors concluded that moderately elevated levels of COHb may aggravate the course of an acute myocardial infarction.

10.3.3.2 Risk of Hypertension

Because short-term exposure to CO does not change the arterial blood pressure, it is unlikely that a prolonged CO exposure will induce hypertension. However, in a study by Ahmad and Ahmad (1980), a higher prevalence of hypertension in the population was observed in a large city compared to a small village where COHb levels were 16.4 and 5.6%, respectively. The main difference between the two locations was that greater exposures to noise and CO in the large city are known to induce hypertension, which might explain the findings. On the other hand, laboratory animal studies (see Section 10.3.4) indicate that prolonged CO exposure induces cardiac hypertrophy. If a similar effect occurs in humans, it may be significant because hypertension increases the risk of developing left ventricular hypertrophy (Frohlich, 1987). Therefore, it is important to study further the association between CO exposure and risk of hypertension, which should be one of the research tasks identified for future investigation.

10.3.4 Studies in Laboratory Animals

10.3.4.1 Introduction

The mechanisms by which CO exerts its toxic effects are detailed in Chapter 9. In brief, CO combines with blood Hb to form COHb; this decreases the O_2-carrying capacity of the blood and shifts the O_2Hb dissociation curve to the left. The cardiovascular system is sensitive to alterations in O_2 supply, and because inhaled CO limits O_2 supply, it might be expected to adversely affect the cardiovascular system; the degree of hypoxia and the extent of tissue injury will be determined by the dose of CO. The effect of CO on the cardiovascular system has been the subject of several recent reviews (Turino, 1981; McGrath, 1982; Penney, 1988). This section will discuss studies in animals that have evaluated the effects of CO on ventricular fibrillation, hemodynamics, cardiomegaly, hematology, and atherosclerosis. In this review, CO concentrations, times of exposure, and COHb levels are provided whenever they were mentioned in the original manuscript. An attempt has been made to focus, where possible, on those studies that have used the most relevant concentrations of CO. For a more detailed treatment of the effects of higher concentrations of CO the reader is referred to the review by Penney (1988).

10.3.4.2 Ventricular Fibrillation Studies

Data obtained from animal studies suggest that CO can disturb cardiac conduction and cause cardiac arrhythmias (see Table 10-4). In dogs exposed for six weeks in environmental chambers to CO (50 and 100 ppm; COHb = 2.6 to 12.0%) intermittently and continuously, Preziosi et al. (1970) reported abnormal electrocardiograms; the changes appeared during the second week and continued throughout the exposure. The blood cytology, hemoglobin, and hematocrit values were unchanged from control values. DeBias et al. (1973) studied the effects of breathing CO (96 to 102 ppm; COHb = 12.4%) continuously (23 h/day; for 24 weeks) on the electrocardiograms of healthy monkeys and monkeys with myocardial infarcts induced by injecting microspheres into the coronary circulation. The authors observed higher P-wave amplitudes in both the infarcted and non-infarcted monkeys and a higher incidence of T-wave inversion in the infarcted monkeys. The authors concluded there was a greater degree of ischemia in the infarcted animals breathing CO. Although there was a greater incidence of T–wave inversion in the infarcted monkeys the effects were transient and of such low magnitude that accurate measurements of amplitude were not possible.

In other long-term studies, however, several groups have reported no effects of CO either on the EKG or on cardiac arrhythmias. Musselman et al. (1959) observed no changes in the EKG of dogs exposed continuously to CO (50 ppm COHb = 7.3%) for three months. These observations were confirmed by Malinow et al. (1976) who reported no effects on the EKG in cynomolgus monkeys exposed to CO (500 ppm-pulsed; COHb = 21.6%) for 14 mo.

Several research groups have investigated the effects of CO on the vulnerability of the heart to induced ventricular fibrillation. DeBias et al. (1976) reported that CO (100 ppm inhaled for 16 h; COHb = 9.3%) reduced the threshold for ventricular fibrillation induced by an electrical stimulus applied to the myocardium of monkeys during the final stage of ventricular repolarization. The voltage required to induce fibrillation was highest in normal animals breathing air and lowest in infarcted animals breathing CO. Infarction alone and CO alone each required significantly less voltage for fibrillation; when the two were combined the effects on the myocardium were additive. These observations were confirmed in both anesthetized, open-chested dogs with acute myocardial injury (Aronow et al., 1978) and in normal dogs (Aronow et al., 1979) breathing CO (100 ppm; COHb = 6.3 to 6.5%) for two hours. However, Kaul et al. (1974) reported that anesthetized dogs inhaling 500 ppm

TABLE 10-4. VENTRICULAR FIBRILLATION AND HEMODYNAMIC STUDIES IN LABORATORY ANIMALS

Exposure[a,b]	COHb[c]	Animal	Dependent Variable[d]	Results	Comments	Reference
CO = 50 ppm continuously for 3 mo	--	Dog (n = 4) Rabbit (n = 4) Rat (n = 100)	EKG, heart rate	No effects		Musselman et al. (1959)
CO = 50-100 ppm for 6 weeks intermittently or continuously	2.6-12%	Dog (n = 28)	EKG and pathology	Abnormal EKG, heart dilation, myocardial thinning, some subjects showed scarring and degeneration in heart muscle		Preziosi et al. (1970)
CO = 100 ppm for 24 wk, 23 h/day; CO = 100 ppm for 6 h	12.4%; 9.3%	Cynomolgus monkey (n = 52; 20)	EKG and susceptibility to induced fibrillation	Abnormal EKG and increased sensitivity to fibrillation voltage	Infarcted animals showed greatest effect of COHb on both dependent variables	DeBias et al. (1973)
CO = 500 ppm, pulsed 12 h/day for 14 mo	21.6%	Cynomolgus monkey (n = 26)	EKG, arterial pressure, left ventricular pressure, dP/dt, V_{max}	No effects	Subjects on normal and high cholesterol diets	Malinow et al. (1976)
CO = 100 ppm, 2 h Coronary artery ligated; normal	6.3%	Dog (n = 21, 20)	Ventricular fibrillation threshold (VFT)	Reduced VFT in normal and ligated dogs	Studies were conducted blind	Aronow et al. (1978, 1979)
CO = 5,000 ppm 5 sequential exposures to produce desired COHb; Coronary artery ligated	4.9-17.0%	Dog (n = 11)	EKG, coronary blood flow	Elevated ST segment; increased flow to non-ischemic myocardium	CO can augment ischemia in acute myocardial infarction	Becker and Haak (1979)
CO = 100 ppm Coronary artery occluded briefly	6.8-14.6%	Dog (n = 14)	Arrhythmia; conduction slowing in ischemic myocardium	No changes	Concluded CO is not arrhythmogenic during early minutes of infarction	Foster (1981)
CO = 200 ppm for 60 and 90 min; Paced hearts and introduced premature stimulus	1.64-6.30%	Dog (n = ?)	Threshold for ventricular arrhythmias and refractory period	No effects		Hutcheon et al. (1983)

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TABLE 10-4 (cont'd). VENTRICULAR FIBRILLATION AND HEMODYNAMIC STUDIES IN LABORATORY ANIMALS

Exposure[a,b]	COHb[c]	Animal	Dependent Variable[d]	Results	Comments	Reference
CO = 3,000 ppm for 15 min followed by 130 ppm for 1 h; coronary artery ligated	13-15%	Dog (n = 10)	ST-segment elevation	Increased S-T segment elevation	CO increases ST-segment elevation and ischemia more than ligation alone	Sekiya et al. (1983)
CO = ?; previous myocardial infarction and 2 min coronary artery occlusion	10 and 20%	Dog (n = 9)	Arrhythmias	Arrhythmia worsened at 20% COHb in 2 of 9 animals	Could not reproduce results	Vanoli et al. (1986)
CO = 160-200 ppm for 6 weeks chronically instrumented	20%	Goats (n = 6)	Cardiac index, stroke volume, heart rate contractility	No changes		James et al. (1979)

[a]Exposure concentration and duration.
[b]1 ppm = 1.145 mg/m^3; 1 mg/m^3 = 0.873 ppm at 25°C, 760 mm Hg; 1% = 10,000 ppm.
[c]Measured blood carboxyhemoglobin (COHb) levels.
[d]See glossary of terms and symbols for abbreviations and acronyms.

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CO (COHb = 20 to 35%) for 90 min were resistant to direct electrocardiographic changes. At 20% COHb there was evidence of enhanced sensitivity to digitalis-induced ventricular tachycardia but there was no increase in vulnerability of the ventricles to hydrocarbon/epinephrine or to digitalis-induced fibrillation following exposure to 35% COHb.

Several workers have investigated the effect of breathing CO shortly after cardiac injury on the electrical activity of the heart. Becker and Haak (1979) evaluated the effects of CO (five sequential exposures to 5,000 ppm, producing COHb = 4.9 to 17.0%) on the electrocardiograms of anesthetized dogs one hour after coronary artery ligation. Myocardial ischemia, as judged by the amount of ST-segment elevation in epicardial electrocardiograms, increased significantly at the lowest COHb levels (4.9%) and increased further with increasing CO exposure; there were no changes in heart rate, blood pressure, left atrial pressure, cardiac output, or blood flow to the ischemic myocardium. Similar results were noted by Sekiya et al. (1983) who investigated the influence of CO (3,000 ppm for 15 min followed by 130 ppm CO for one hour, COHb = 13 to 15%) on the extent and severity of myocardial ischemia in dogs. This dose of CO inhaled prior to coronary artery ligation increased the severity and extent of ischemic injury, and the magnitude of ST segment elevation, more than did ligation alone. There were no changes in heart rate or arterial pressure. Vanoli et al. (1986) reported that CO (COHb = 10 and 20%) worsened the arrhythmia, following a two minute coronary artery occlusion, in two of nine dogs with one-month-old anterior myocardial infarcts. They were unable, however, to reproduce their results. The authors conclude that while acute exposure to CO is unlikely to produce detrimental effects in post-MI dogs, the CO-dependent tachycardia may enhance the risks and consequences of any ischemic episode.

On the other hand, several groups have reported no effects of CO on the EKG or on cardiac arrhythmias. Musselman et al. (1959) observed no changes in the EKG of dogs exposed continuously to CO (500 ppm) for three months. Their observations were confirmed by Malinow et al. (1976) who reported no effects on the EKG in cynomolgus monkeys exposed to CO for 14 mo (500 ppm-pulsed; COHb = 21.6%). Foster (1981) concludes that CO (100 ppm CO for six to nine minutes; COHb = 10.4%) is not arrhythmogenic in dogs during the early minutes of acute myocardial infarction following occlusion of the left anterior descending coronary artery. This level of CO did not effect either slowing of conduction

through the ischemic myocardium or the incidence of spontaneous ventricular tachycardia. These results were confirmed by Hutcheon et al. (1983) in their investigation of the effects of CO on the electrical threshold for ventricular arrhythmias and the effective refractory period of the heart. They conclude that CO (200 ppm CO for 60 and 90 min; COHb = 5.1 to 6.3%) does not alter the effective refractory period or the electrical threshold for ventricular arrhythmias in dogs. These results are consistent with those of Mills et al. (1987), who studied the effects of 0 to 20% COHb on the electrical stability of the heart in chloralose-anesthetized dogs during coronary occulsion. There were no major effects on heart rate, mean arterial blood pressure, effective refractory period, vulnerable period, or ventricular fibrillation threshold.

The effects of CO (1500 ppm, COHb = 15%) during acute myocardial ischemia on arrhythmias in dogs with a healed anterior myocardial infarction and at low or high risk for ventricular fibrillation were investigated by Vanoli et al. (1989). Following a two minute coronary artery occlusion, malignant arrhythmias occurred in two dogs at low risk but in none of the dogs at high risk for ventricular fibrillation. The authors conclude that, in dogs at high risk for ventricular fibrillation, arrhythmogenic effects seldom can be expected from acute exposure to CO.

On balance the results from animal studies suggest that inhaled CO can cause disturbances in cardiac rhythm in both healthy and compromised hearts. Depending on the exposure regime and species tested, the threshold for this response varies between 50 and 100 ppm CO (COHb = 2.6 to 12%) in dogs and 100 ppm (COHb = 12.4%) in monkeys inhaling CO for 6 to 24 weeks; and 500 ppm CO (COHb = 4.9 to 17.0%) in dogs and 100 ppm (COHb = 9.3%) in monkeys inhaling CO for 0.6 to 16 h.

10.3.4.3 Hemodynamic Studies

The effects of CO on coronary flow, heart rate, blood pressure, cardiac output, myocardial O_2 consumption, and blood flow to various organs have been investigated in laboratory animals. The results are somewhat contradictory (partly because exposure regimes differed); however, most workers agree that CO in sufficiently high doses can affect many hemodynamic variables.

Adams et al. (1973) described increased coronary flow and heart rate and decreased myocardial O_2 consumption in anesthetized dogs breathing 1500 ppm CO for 30 min (COHb = 23.1%). The decreased O_2 consumption indicates that the coronary flow response was not great enough to compensate for the decreased O_2 availability. The authors noted that although there was a positive chronotropic response, there was no positive inotropic response. The authors speculated that (1) the CO may have caused an increase in the endogenous rhythm or blocked the positive inotropic response or (2) the response to CO was mediated reflexly through the cardiac afferent receptors to give a chronotropic response without the concomitant inotropic response. When they used β-adrenergic blocking agents, the heart-rate response to CO disappeared, suggesting possible reflex mediation by the sympathetic nervous system.

In a later study in chronically-instrumented, awake dogs exposed to 1000 ppm CO producing COHb levels of 30%, Young and Stone (1976) reported an increase in coronary flow with no change in myocardial O_2 consumption. The increased coronary flow occurred in animals with hearts paced at 150 beats/min, as well as in nonpaced animals, and in animals with propranolol and atropine blockade. Because the changes in coronary flow with arterial O_2 saturation were similar whether the animals were paced or not, these workers conclude that the increase in coronary flow is independent of changes in heart rate. Furthermore, the authors reasoned that if the coronary vasodilation was caused entirely by the release of a metabolic vasodilator, associated with decreased arterial O_2 saturation, the change in coronary flow in animals with both β-adrenergic and parasympathetic blockade should be the same as in control dogs. Young and Stone conclude that coronary vasodilation observed with an arterial O_2 saturation reduced by CO is mediated partially through an active neurogenic process.

Increased myocardial blood flow after CO inhalation in dogs was confirmed by Einzig et al. (1980), who also demonstrated the regional nature of the blood flow response. Using labeled microspheres, these workers demonstrated that whereas both right and left ventricular beds were dilated maximally at COHb levels of 41% (CO = 15,000 to 20,000 ppm for 10 min), subendocardial/subepicardial blood flow ratios were reduced. The authors conclude that in addition to the global hypoxia associated with CO poisoning, there is also an underperfusion of the subendocardial layer, which is most pronounced in the left ventricle.

These results were confirmed by Kleinert et al. (1980) who investigated the effects of lowering O_2 content by about 30% with low O_2 or CO gas mixtures (CO = 10,000 ppm for three minutes, COHb = 21 to 28%) on regional myocardial relative tissue PO_2, perfusion and small vessel blood content. In anesthetized, thoracotomized rabbits, both hypoxic conditions increased regional blood flow to the myocardium, but to a lesser extent in the endocardium. Relative endocardial PO_2 fell more markedly than epicardial PO_2 in both conditions. Small vessel blood content increased more with CO than with low PO_2, whereas regional O_2 consumption increased under both conditions. The authors conclude that the response to lowered O_2 content (whether by inhaling low O_2 or CO gas mixtures) is increased flow, metabolic rate, and the number of open capillaries, and the effects of both types of hypoxia appear more severe in the endocardium.

A decrease in tissue PO_2 with CO exposure also has been reported by Weiss and Cohen (1974). These workers exposed anesthetized rats to 80 and 160 ppm CO for 20-min periods and measured tissue O_2 tension as well as heart rate. A statistically significant decrease in brain PO_2 occurred with inhalation of 160 ppm CO, but there was no change in heart rate.

Horvath (1975) investigated the coronary flow response in dogs with COHb levels of 6.2 to 35.6% produced by continuous administration of precisely measured volumes of CO. Coronary flow increased progressively as blood COHb increased and was maintained for the duration of the experiment. However, when animals with complete atrioventricular block were maintained by cardiac pacemakers and exposed to COHb levels of 6 to 7%, there was no longer an increase in coronary blood flow. These results are provocative, because they suggest an increased danger from low COHb levels in cardiac-disabled individuals.

Patajan et al. (1976) exposed unanesthetized rats to 1500 ppm CO for 80 min to achieve COHb levels of 60 to 70%. After a slight transient increase, heart rate as well as blood pressure decreased throughout the exposure. The authors interpret their data as indicating that the lowering of blood pressure was more important than the degree of hypoxia to the neurological impairment seen in their studies.

The effects of CO hypoxia and hypoxic hypoxia on arterial blood pressure and other vascular parameters also were studied in carotid baroreceptor and chemoreceptor-denervated dogs (Traystman and Fitzgerald, 1977). Arterial blood pressure was unchanged by CO hypoxia but increased with hypoxic hypoxia. Similar results were seen in carotid

baroreceptor-denervated animals with intact chemoreceptors. Following carotid chemodenervation, arterial blood pressure decreased equally with both types of hypoxia.

In a subsequent report from the same laboratory (Sylvester et al., 1979), the effects of CO hypoxia (CO = 10,000 ppm followed by 1000 ppm for 15 to 20 min; COHb = 61 to 67%) and hypoxic hypoxia, were compared in anesthetized, paralyzed dogs. Cardiac output and stroke volume increased during both CO and hypoxic hypoxia whereas heart rate was variable. Mean arterial pressure decreased during CO hypoxia, but increased during hypoxic hypoxia. Total peripheral resistance fell during both hypoxias, but the decrease was greater during the CO hypoxia. After resection of the carotid body, the circulatory effects of hypoxic and CO hypoxia were the same and were characterized by decreases in mean arterial pressure and total peripheral resistance. In a second series of closed-chest dogs, hypoxic and CO hypoxia caused equal catecholamine secretion before carotid body resection. After carotid body resection, the magnitude of the catecholamine response was doubled with both hypoxias. These workers conclude that the responses to hypoxic and CO hypoxia are different and that the difference is dependent on intact chemo- and baroreflexes and on differences in arterial O_2 tension, but not on differences in catecholamine secretion or ventilatory response.

In cynomolgus monkeys exposed to 500 ppm intermittently for 12 h a day for 14 mo (COHb = 21.6%), Malinow et al. (1976) reported no changes in arterial pressure, left ventricular pressure, dp/dt, and Vmax. On the other hand, Kanten et al. (1983) studied the effects of CO (150 ppm, COHb up to 16%) for 0.5-2 h on hemodynamic parameters in open–chest, anesthetized rats, and reported that heart rate, cardiac output, cardiac index, dF/dtmax (aortic), and stroke volume increased significantly, whereas mean arterial pressure, total peripheral resistance, and left ventricular systolic pressure decreased. These effects were evident at COHb levels as low as 7.5% (0.05 h). There were no changes in stroke work, left ventricular dp/dtmax, and stroke power.

The effects of CO on blood flow to various vascular beds has been investigated in several animal models, and most of the studies have been conducted at rather high CO or COHb levels. In general, CO increases cerebral blood flow. However, the effects of CO on the cerebral circulation are discussed in detail in Section 10.4.1.

In recent studies Oremus et al. (1988) reported that in the anesthetized rat breathing CO (500 ppm; COHb = 23%) for one hour that CO reduces mean arterial pressure through

peripheral vasodilation predominantly in the skeletal muscle vasculature. There were no differences in heart rate or mesenteric or renal resistances between the CO-exposed and control groups. This was confirmed by Gannon et al. (1988) who reported that in the anesthetized rat breathing CO (500 ppm; COHb = 24%) for one hour that CO increased inside vessel diameter (36 to 40%), increased flow rate (38 to 54%), and decreased mean arterial pressure to 79% of control in the cremaster muscle. There was no change in the response of 3A vessels to topical applications of phenylephrine as a result of CO exposure.

King et al. (1984, 1985) compared whole-body and hindlimb blood flow responses in anesthetized dogs exposed to CO or anemic hypoxia. Arterial O_2 content was reduced by moderate (50%) or severe (65%) CO-hypoxia (produced by dialysis with 100% CO) or anemic hypoxia (produced by hemodilution). These workers noted that cardiac output was elevated in all groups at 30 min and in the severe CO group at 60 min. Hindlimb blood flow remained unchanged during CO hypoxia in the animals with intact hindlimb innervation but was greater in animals with denervated hindlimbs. There was a decrease in mean arterial pressure in all groups associated with a fall in total peripheral resistance. Hindlimb resistance remained unchanged during moderate CO hypoxia in the intact groups but was increased in the denervated group. The authors concluded that the increase in cardiac output during CO was directed to nonmuscle areas of the body and that intact sympathetic innervation was required to achieve this redistribution. However, aortic chemoreceptor input was not necessary for the increase in cardiac output during severe CO hypoxia, nor for the diversion of the increased flow to nonmuscle tissues.

King et al. (1987) investigated the effects of severe CO (1000 to 10,000 ppm to lower arterial O_2 content to 5 to 6 vol) and hypoxic hypoxia on the contracting gastrocnemius muscle of anesthetized dogs. Oxygen uptake decreased from the normoxic level in the CO group but not in the hypoxic hypoxia group. Blood flow increased in both groups during hypoxia but more so in the CO group. Oxygen extraction increased further during contractions in the hypoxic group but fell in the CO group. The authors observed that the O_2 uptake limitation occurring during CO hypoxia and isometric contractions was associated with a reduced O_2 extraction and concluded that the leftward shift in the O_2Hb dissociation curve during CO hypoxia may have impeded O_2 extraction.

Melinyshyn et al. (1988) investigated the role of β-adrenoreceptors in the circulatory responses to severe CO (about a 63% decrease in arterial O_2 content obtained by dialyzing with 100% CO) of anesthetized dogs. One group was β blocked with propanolol (β_1 and β_2 blockade), a second with ICI 118,551 (β_2 blockade), and a third was a time control. Cardiac output increased in all groups during CO hypoxia with the increase being greatest in the unblockaded group. Hindlimb blood flow rose during CO hypoxia only in the unblockaded group. The authors conclude that 35% of the rise in cardiac output occurring during CO hypoxia (COH) depended on peripheral vasodilation mediated through β_2-adrenoreceptors.

Thus, the results from animal studies indicate that inhaled CO can adversely affect several hemodynamic parameters. The threshold for these effects may be near 150 ppm CO (COHb = 7.5%).

10.3.4.4 Cardiomegaly

The early investigations of cardiac enlargement following prolonged exposure to CO have been confirmed in different animal models and extended to characterize the development and regression of the cardiomegaly (see Table 10-5). Theodore et al. (1971) reported cardiac hypertrophy in rats breathing 500 ppm CO (COHb = 32 to 38%) for 168 days, but not in dogs, baboons, or monkeys. Penney et al. (1974a) also noted cardiomegaly in rats breathing 500 ppm CO; heart weights were one-third greater than predicted within 14 days of exposure, and 140 to 153% of controls after 42 days of exposure. The cardiomegaly was accompanied by changes in cardiac lactate dehydrogenase (LDH) isoenzyme composition that were similar to those reported in other conditions that cause cardiac hypertrophy (e.g., aortic and pulmonary artery constriction, coronary artery disease, altitude acclimation, severe anemia).

To further characterize the hypertrophy and determine its threshold, Penney et al. (1974b) measured heart weights in rats exposed continuously to 100, 200, and 500 ppm CO (COHb = 9.26, 15.82, and 41.14%), for various times (20 to 46 days); they noted significant increases in heart weights at 200 and 500 ppm CO, with changes occurring in the left ventricle and septum, right ventricle, and atria especially. The authors concluded that whereas the threshold for the Hb response is 100 ppm CO (COHb = 9.26%), the threshold

TABLE 10-5. CARDIAC HYPERTROPHY STUDIES IN LABORATORY ANIMALS

Exposure[a,b]	COHb[c]	Animal	Dependent Variable[d]	Results	Comments	Reference
400-500 ppm for 168 days	32-38% (dogs and monkeys only)	Monkey (n = 9) Baboon (n = 3) Dog (n = 16) Rat (n = 136) Mouse (n = 80)	Cardiovascular damage in rat heart	No changes except slight hypertrophy		Theodore et al. (1971)
100 ppm, 46 days 200 ppm, 30 days 500 ppm, 20-42 days	9.2% 15.8% 41.12%	Rat (n = 32)	Heart size; LDH	Hypertrophy of both left and right ventricles; LDH increases	Threshold for cardiac enlargement near 200 ppm	Penney et al. (1974a,b)
CO = 60, 125, 250, 500 ppm for 21 days gestation	--	Fetal rats (n = 75)	Hb, Hct, HW	Hb and Hct depressed with 60 ppm and elevated by 250 and 500 ppm; HW increased at all concentrations	HW increase probably not due to increased viscosity or pulmonary hypertension	Prigge and Hochrainer (1977)
CO = 400 ppm, or 500 ppm increased to 1,100 ppm	35-58%	Rat (n = 30)	Cardiomegaly (HW/BW) and LDH	HW/BW and %M LDH subunits increased with low and high CO; after removal of CO HW/BW and %M LDH remained high		Styka and Penney (1978)
CO = 500 ppm until 50 days of age	38-42%	Rat (n > 200) 5 and 25 days old	HW Right ventricle (RV) Left ventricle (LV)	HW, LV, and RV increased response greater in younger group	Potential for cardiac DNA synthesis and hyperplasia ends between 5-25 days postnatal life	Penney and Weeks (1979)
CO = 500 ppm for 1-42 days. Open-chest, anesthetized preparation.	38-42%	Rat (n = 25)	Stoke index (SI), Mean stroke power (SP), Mean cardiac output (CO), Systemic resistance (SR), Pulmonary resistance (PR).	SI, SP, CO increased; SR and PR decreased	Concluded that increased CO via increased stroke volume is compensation for CO intoxication; increased work may cause cardiomegaly	Penney et al. (1979)
CO = 150 ppm throughout gestation	(15% in adult rats)	Rat (n = 88)	BW Wet-Heart Weight (WHW)	BW depressed; WHW increased	Increased HW due to increased water content	Fechter et al. (1980)

TABLE 10-5 (cont'd). CARDIAC HYPERTROPHY STUDIES IN LABORATORY ANIMALS

Exposure[a,b]	COHb[c]	Animal	Dependent Variable[d]	Results	Comments	Reference
CO = 500 ppm for 32 days (1982)	38-42%	Rat (n = 140)	Cardiomegaly	HW/BW higher after 70 days of exposure and after 30 days of recovery; both RV and LV were affected	Cannot be explained by changes in DNA or hydroxyproline	Penney et al. (1982)
CO = 157-200 ppm last 17 days gestation	21.8-33.5%	Rat (n = 96)	RBC count, HW, placental weight (PW), cardiac LDH M subunit, Mb	Depressed RBC; HW and PW increased; LDH(M) increased; Mb increased	Cardiomegaly not due to elevated water content (Disagrees with Fechter et al., 1980)	Penney et al. (1983)
CO = 500 ppm for 38-47 days	38-40%	Rat (n = 25)	Cardiac compliance and dimensions	No change in compliance; LV length and outside diameter increased	Chronic COHb produces eccentric cardiomegaly with no change in wall stiffness	Penney et al. (1984a)
CO = 200 ppm from Day 7 of pregnancy until parturition, and for 28 days following parturition	--	Rat (n > 180)	HW, RV, and LV weight	RV increased with CO during fetal period, HW and LV increased with CO during postnatal period	Hemodynamic load caused by CO during fetal period results in cardiomegaly due to myocyte hyperplasia	Clubb et al. (1986)

[a]Exposure concentration and duration.
[b]1 ppm = 1.145 mg/m^3; 1 mg/m^3 = 0.873 ppm at 25°C, 760 mm Hg; 1% = 10,000 ppm.
[c]Measured blood carboxyhemoglobin (COHb) levels.
[d]See glossary of terms and symbols for abbreviations and acronyms.

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for cardiac enlargement is near 200 ppm CO (COHb = 12.03%), and unlike cardiac hypertrophy caused by altitude, which primarily involves the right ventricle, cardiac hypertrophy caused by CO involves the whole heart.

The regression of cardiac hypertrophy in rats exposed continuously to moderate (400 ppm; COHb = 35%) or severe (500-1100 ppm; COHb = 58%) CO for six weeks was followed by Styka and Penney (1978). Heart weight to body weight ratio (HW/BW) increased from 2.65 in controls, to 3.52 and 4.01 with moderate and severe CO exposure, respectively. Myocardial LDH M subunits (M LDH) were elevated 5 to 6% by moderate and 12 to 14% by severe CO exposure. Forty-one to 48 days after terminating the CO exposure, Hb concentrations among groups did not differ significantly; HW/BW ratios were similar in the control and moderately exposed animals, but remained significantly elevated in the severely exposed animals.

In addition to cardiomegaly, Kjeldsen et al. (1972) has reported ultrastructual changes in the myocardium of rabbits breathing 180 ppm CO (COHb = 16.7%) for two weeks. The changes included focal areas of necrosis of myofibrils and degenerative changes of the mitochondria. In addition, varying degrees of injury were noted in the blood vessels. These included edema in the capillaries; stasis and perivascular hemorrhages on the venous side; and endothelial swelling, subendothelial edema, and degenerative changes in myocytes on the arterial side.

The hemodynamic consequences of prolonged CO exposure have been examined in rats breathing 500 ppm CO (COHb = 38 to 42%) for 1 to 42 days, (Penney et al., 1979) and in goats breathing 160 to 220 ppm CO (COHb = 20%) for two weeks (James et al., 1979). In rats, cardiomegaly developed and stroke index, stroke power, and cardiac index increased; total systemic and pulmonary resistances decreased. Left and right ventricular systolic pressures, mean aortic pressure, maximum left ventricular dp/dt, and heart rate did not change significantly. Penney et al. concluded that enhanced cardiac output, via an increased stroke volume, is a compensatory mechanism to provide tissue oxygenation during CO intoxication and that increased cardiac work is the major factor responsible for the development of cardiomegaly. In chronically-instrumented goats, James et al. noted that cardiac index, stroke volume, left ventricular contractility, and heart rate were all unchanged during exposure to CO, but were depressed significantly during the first week following

termination of the exposure. Discrepancies between the Penney and James studies may be caused by differences in the CO concentrations or in the species used.

Penney et al. (1984a) studied the compliance and measured the dimensions of hypertrophied hearts from rats breathing 500 ppm CO (COHb = 38 to 40%) for 38 to 47 days. Heart weight to body weight ratios increased from 2.69 to 3.34. Although compliance of the right and left ventricles was higher in the CO group, the differences disappeared when the heart weight was normalized by body weight. Left ventricular apex-to-base length and left ventricular outside diameter increased 6.4% and 7.3%, respectively; there were no changes in left ventricle, right ventricle, or septum thickness. The authors conclude that chronic CO exposure produces eccentric cardiomegaly with no intrinsic change in wall stiffness.

The consequences of breathing CO also have been investigated in perinatal animals. Prigge and Hochrainer (1977) reported elevated heart weights in fetuses from pregnant rats exposed for 21 days to CO concentrations as low as 60 ppm. Because these animals developed anemia rather than polycythemia, these workers discounted increased blood viscosity as a cause of the cardiomegaly. Penney and Weeks (1979) examined the effects of inhaling 500 ppm CO (COHb = 38 to 42%) until 50 days of age on cardiac growth in young (5 days) and old (25 days) rats. They observed that the younger rats experienced the greatest change in heart weight and DNA synthesis and concluded that the potential for cardiac DNA synthesis and muscle cell hyperplasia ends in rats during the 5th through 25th days of postnatal development.

Fechter et al. (1980) reported elevated wet-heart weights at birth in neonatal rats from dams exposed throughout gestation to 150 ppm CO (COHb = 15%). There were no differences in dry-heart weight, total protein, or RNA or DNA levels; the differences between groups in wet-heart weight disappeared after four days. These workers concluded that the increased heart weight seen at birth in the CO-exposed rats is caused by cardiac edema.

These results were not verified by Penney et al. (1983) in offspring of pregnant rats exposed to 157, 166, and 200 ppm CO (COHb = 21.8 to 33.5%) for the last 17 of 22 days gestation. These workers observed that wet- and dry-heart weights increase proportionately and conclude that cardiomegaly, present at birth, is not due to elevated myocardial water content. They also determined that cardiac LDH M subunit composition and Mb

concentration were elevated at 200 ppm CO. They conclude that maternal CO inhalation exerts significant effects on fetal body and placental weights, heart weight, enzyme constituents, and composition. Moreover, in newborn rats inhaling 500 ppm CO (COHb = 38 to 42%) for 32 days and then developing in air, Penney et al. (1982) observed that HW/BW ratio increased sharply after birth, peaked at 14 days of age, and then fell progressively; it remained higher in rats exposed prenatally to CO than in control rats for up to 107 days of age. The persistent cardiomegaly could not be explained by changes in DNA or hydroxyproline.

Ventricular weights (wet and dry) and myocyte size and volume were measured in perinatal rats exposed to 200 ppm CO by Clubb et al. (1986). Pregnant rats were exposed to air or CO, and, at birth, pups from these two groups were subdivided into four groups: (1) control group (air/air), maintained in air *in utero* and postpartum; (2) air/CO group, received CO only postpartum; (3) CO/CO group; received CO *in utero* and postpartum; and (4) CO/air group, received CO *in utero*, but in air postpartum. Right ventricle weights were increased in animals exposed to CO during the fetal period, but left ventricular weights were increased by CO during the neonatal period. Although HW/BW ratios increased to that of the CO/CO group by 12 days of age in animals exposed to CO postnatally only (air/CO), HW/BW ratios decreased to that of controls (air/air) by 28 days of age in animals exposed to air postnatally following fetal CO exposure (CO/air). There was no difference in myocyte volume between groups at birth. Left ventricle plus septum and right ventricle cell volumes of the CO/CO group were smaller than the controls at 28 days of age despite the heavier wet and dry weights of the CO/CO neonates. At birth, the CO-exposed animals had more myocytes in the right ventricle than the air-exposed controls; CO exposure after birth resulted in left ventricular hyperplasia.

Clubb et al. (1986) concluded that the increased hemodynamic load caused by CO during the fetal period results in cardiomegaly, characterized by myocyte hyperplasia, and this cellular response is sustained throughout the early neonatal period in animals exposed to CO postpartum.

Thus, results from animal studies indicate that inhaled CO can cause cardiomegaly, and that the threshold for this response is near 200 ppm (COHb = 12%) in adult rats, and 60 ppm in fetal rats.

10.3.4.5 Hematology Studies

Increase in Hb concentration, as well as hematocrit ratio, is a well-documented response to hypoxia, which serves to increase the O_2 carrying-capacity of the blood. Guyton and Richardson (1961) and Smith and Crowall (1967) however, suggest that changes in hematocrit ratio not only affect the O_2-carrying capacity of the blood, but blood flow as well. Therefore, when hematocrit ratios increase much above normal, O_2 delivery to the tissues may be reduced because the resultant decrease in blood flow can more than offset the increased O_2 carrying capacity of the blood. Smith and Crowall conclude that there is an optimum hematocrit ratio at sea level that shifts to a higher value with altitude acclimation. Presumably a similar compensation would occur when O_2 transport is reduced by CO.

Changes in Hb concentration and hematocrit ratio have been reported in numerous animal studies (see Table 10-6). In dogs exposed to 50 ppm CO (COHb = 7.3%) for three months, Musselman et al. (1959) reported a slight increase in Hb concentration (12%), hematocrit ratio (10%), and in red blood cells (10%). These observations were extended by Jones et al. (1971) to include several species of animals exposed to 51 ppm or more CO (COHb = 3.2 to 20.2%), intermittently or continuously, for up to 90 days. There were no significant increases in the Hb and hematocrit values observed in any of the species at 51 ppm CO (COHb = 3.2 to 6.2%). At 96 ppm CO (COHb = 4.9 to 12.7%), significant increases were noted in the hematocrit value for monkeys (from 43 to 47%) and in the Hb (from 14.0 to 16.49%) and hematocrit values (from 46 to 52%) for rats. Hemoglobin and hematocrit values were elevated in rats (14 and 10%, respectively) guinea pigs (8 and 10%, respectively), and monkeys (34 and 26%, respectively) exposed to 200 ppm CO (COHb = 9.4 to 12.0%); they also were elevated in dogs, but there were too few animals to determine statistical significance. However, in dogs exposed to CO (195 ppm; COHb = 30%) for 72 h, Syvertsen and Harris (1973) reported that hematocrit and Hb increased from 50.3 to 57.8% and 15.0 to 16.2 g%, respectively. The differences in hematocrit and Hb occurred after 72 h exposure and were attributed to increased erythropoiesis. Penney et al. (1974b) observed significant increases in Hb (from 15.6 to 16.7 g%) in rats exposed to 100 ppm CO over several weeks and conclude that the threshold for the Hb response is close to 100 ppm (COHb = 9.26%).

TABLE 10-6. HEMATOLOGY STUDIES IN LABORATORY ANIMALS

Exposure[a,b]	COHb[c]	Animal	Dependent Variable[d]	Results	Comments	Reference
CO = 50 ppm continuously for 3 mo	7.3% 3.2% 1.8%	Dog (n = 4) Rabbit (n = 40) Rat (n = 100)	Hb, Hct, and RBC, EKG	Hb, Hct, RBC increased in dogs and rabbit; no change in EKG in dog	No toxic signs in dogs, rabbits or rats	Musselman et al. (1959)
CO = 51, 96, or 200 ppm for 90 days	3.2-6.2% 4.9-12.7% 9.4-20.2% depending upon species	Rat (n = 35) Guinea pig (n = 35) Monkey (n = 9) Dog (n = 6)	Hb	Increases in rats at 96, 106, and 200 ppm; increases in all animals at 200 ppm		Jones et al. (1971)
CO = 67.5 ppm 22 h/day, 7 day/ for 2 years	1.9-5.5% and 2.8-10.2%	Cynomolgus monkey (n = 27)	Hct, Hb RBC counts	No effects	Unusual variation in COHb	Eckhardt et al. (1972)
CO = 195 for 72 h	~30%	Dog (n = 12)	Hct and Hb	Both increased	Increase due to erythropoiesis	Syvertsen and Harris (1973)
CO = 100 ppm, 46 days; 200 ppm, 30 days; 500 ppm, 20-42 days	9.20% 15.82% 41.12%	Rat (n = 32)	Hb	Increased at all levels	About 30 days until Hb approached asymptotic values	Penney et al. (1974b)
CO = 200 ppm last 18 days gestation	27%	Rat	Hb, Hct, and RBC	Hb, Hct, and RBC all lower		Penney et al. (1980)
50 and 100 ppm for 6 weeks on various intermittent daily schedules	2.6-12%	Dog (n = 46)	Hb	No effects		Preziosi et al. (1970)
CO = 50 ppm, 95 h/week whole natural life expectancy up to 2 years (also short-term)		Rat (n = 336) Mouse (n = 767)	EKG, organ weights, Hb, Hct, and RBC	No effects	Also showed no effects on other variables	Stupfel and Bouley (1970)

[a]Exposure concentration and duration.
[b]1 ppm = 1.145 mg/m^3; 1 mg/m^3 = 0.873 ppm at 25°C, 760 mm Hg; 1% = 10,000 ppm.
[c]Measured blood carboxyhemoglobin (COHb) levels.
[d]See glossary of terms and symbols for abbreviations and acronyms.

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Several groups have reported no change in Hb or hematocrit following CO exposure. Thus, Preziosi et al. (1970) observed no significant change in Hb concentration in dogs exposed to 50 and 100 ppm CO (COHb = 2.6 to 12.0%) for six weeks. In monkeys, exposed to 20 and 65 ppm CO (COHb = 1.9 to 10.2%) for two years, Eckardt et al. (1972) noted no compensatory increases in Hb concentration or hematocrit ratio. In mice exposed 5 days a week to 50 ppm CO for one to three months, Stupfel and Bouley (1970) observed no signfiicant increase in Hb.

Interestingly, in fetuses removed from pregnant rats after 21 days exposure to CO, Prigge and Hochrainer (1977) reported a significant increase in fetal hematocrit (from 33.3 to 34.5%) at 60 ppm and a significant decrease in Hb and hematocrit at 250 ppm (from 9.1 to 8.0 g% and from 33.3 to 28.4%, respectively) and 500 ppm (from 9.1 to 6.5 g% and from 33.3 to 21.9%, respectively). These results were confirmed by Penney et al. (1980) who reported significantly lower Hb (12.6 vs. 15.8 g%), hematocrit (46.2 vs. 54.4%), and RBC counts (27.2 vs. 29.1%) in newborns from pregnant rats exposed to 200 ppm CO (COHb = 27.8%) for the final 18 days of development than in controls. However, in a later study, Penney et al. (1983) reported that although RBC count was depressed in neonates from pregnant rats exposed to 157, 166, and 200 ppm CO (COHb = 21.8 to 33.5%) for the last 17 out of 22 days gestation, mean corpuscular Hb and volume were elevated.

The results from animal studies indicate inhaled CO can increase Hb concentration and hematocrit ratio and that the threshold for this response, at least in rats, appears to be near 100 ppm (COHb = 9.26%). Small increases in Hb and hematocrit probably represent a compensation for the reduction in O_2-transport caused by CO. At higher CO concentrations, excessive increases in Hb and hematocrit may impose an additional workload on the heart and compromise blood flow to the tissue. The O_2 transport system of the fetus is especially sensitive to CO inhaled by the mother, and it may be affected by CO concentrations as low as 60 ppm.

10.3.4.6 Atherosclerosis and Thrombosis

The section dealing with cholesterol and atherosclerosis in the previous air quality criteria document for CO (U.S. Environmental Protection Agency, 1979) described about

12 publications. These studies generally utilized animal models of atherosclerosis or animal models describing arterial wall cholesterol uptake in response to COHb concentrations ranging from 4.5 to 41.1% (see Table 10-7). The conclusion was that the evidence failed to support conclusively a relationship between CO exposure and atherosclerosis in animal models. Since completion of the 1979 air quality criteria document, a number of additional studies have been published (Table 10-7). However, taken in aggregate, the studies still fail to conclusively prove an atherogenic effect of exposure to low doses of CO.

Astrup et al. (1967) described atheromatosis as well as increased cholesterol accumulation in aortas of rabbits fed cholesterol and exposed to CO (170 to 350 ppm; COHb = 17 to 33%) for 10 weeks. These observations were not verified, however, by Webster et al. (1970) who observed no changes in the aorta or carotid arteries or in serum cholesterol levels in squirrel monkeys fed cholesterol and exposed intermittently to CO (100 to 300 ppm; COHb = 9 to 26%) for seven months; they did note enhanced atherosclerosis in the coronary arteries. Davies et al. (1976) confirmed that coronary artery atherosclerosis was significantly higher in rabbits fed cholesterol and exposed intermittently to CO for 10 weeks (250 ppm; COHb = 20%); but they also reported no significant differences between groups in aortic concentrations of triglycerides, cholesterol, phospholipids, or plasma cholesterol.

In cynomolgus monkeys fed cholesterol and exposed intermittently to CO for 14 mo (50 to 500 ppm; COHb = 21.6%), Malinow et al. (1976) observed no differences in plasma cholesterol levels or in coronary or aortic atherosclerosis. Armitage et al. (1976) confirmed that intermittent CO (150 ppm; COHb = 10% for 52 and 84 weeks) did not enhance the extent or severity of atherosclerosis in the normal White Carneau pigeon. While CO exposure did increase the severity of coronary artery atherosclerosis in birds fed cholesterol; the difference between groups, noted at 52 weeks, was not present after 84 weeks.

Stender et al. (1977) exposed rabbits that were fed high levels of cholestrol to CO for six weeks continuously and intermittently (200 ppm; COHb = 17%). In the cholesterol-fed group, CO had no effect on free- and esterified-cholesterol concentrations in the inner layer of the aortic wall. In the normal group, CO increased the concentration of cholesterol in the aortic arch, but there was no difference in the cholesterol content of the total aorta.

Hugod et al. (1978), using a blind technique and the same criteria to assess intimal damage as was used in earlier studies (Kjeldsen et al., 1972; Thomsen, 1974; Thomsen and

TABLE 10-7. ATHEROSCLEROTIC STUDIES IN LABORATORY ANIMALS

Exposure[a,b]	COHb[c]	Animal	Dependent Variable[d]	Results	Comments	Reference
CO = 170 ppm for 8 week, then 350 ppm for last 2 week, fed cholesterol	17-33%	Rabbit (n = 24)	Atherosclerotic changes	Increased aortic atheromatosis and cholesterol; Local degenerative signs and hemorrhages in hearts	Not verified in subsequent studies	Astrup et al. (1967)
CO = 100-300 ppm 4 h/day, 5 days/week for 7 mo, fed cholesterol	9-26%	Squirrel monkey	Atherosclerosis in various blood vessels plus serum cholesterol	Increased coronary atherosclerosis but no effects on aorta or carotid arteries or serum cholesterol		Webster et al. (1970)
CO = 250 ppm continuously for 2 week	20.6%	Cynomolgus monkey (n = 20)	Coronary artery pathology	Subendothelial edema, gaps between endothelial cells, infiltration cells containing lipid droplets	Lipid-laden cell findings suggest greater sensitivity of monkeys than of rabbits	Thomsen (1974)
CO = 50, 100, and 180 ppm for periods ranging from 30 min - 24 h, and from 2-11 days	4.5% 9.0%	Rabbit (n = 61)	Aortic damage	Increased aortic intimal lesions at 180 ppm CO for 4 h or more	Postulates 180 ppm CO for 4 h is threshold for injury	Thomsen and Kjeldsen (1975)
CO = 150 ppm 6 h/day, 5 day/week for 52 and 84 weeks, fed cholesterol	10%	White carneau pigeon (n = 180)	Severity of atherosclerosis	No effect in normocholesterolemic birds; coronary artery atherosclerosis significantly enhanced in hypercholesterolemic birds at 52 weeks	No significant changes in coronary arteries after 84 weeks	Armitage et al. (1976)
CO = 250 ppm 4 h/day, 7 day/week, 10 week	20%	Rabbit (n = 24)	Blood cholesterol; coronary artery atherosclerosis; aortic cholesterol content	Increased atherosclerosis in coronary arteries but no differences in aortic or plasma cholesterol	Study disagrees with Astrup et al. (1967)	Davies et al. (1976)

TABLE 10-7 (cont'd). ATHEROSCLEROTIC STUDIES IN LABORATORY ANIMALS

Exposure[a,b]	COHb[c]	Animal	Dependent Variable[d]	Results	Comments	Reference
CO = 50-500 ppm, 12 h/day for 14 mo	21.6%	Cynomolgus monkey (n = 26)	Aortic and coronary atherosclerosis	No effects	Subjects on high- and low-cholesterol diets; disagrees with Astrup et al. (1967).	Malinow et al. (1976)
CO = 200 ppm, continuously or 12 h/day for 6 week	17%	Rabbit (n = 30)	Cardiovascular pathology	No differences in atherosclerosis but CO produced higher serum cholesterol levels	Serum cholesterol was controlled by adjusting individual diets; apparently coronary atherosclerosis in Astrup et al. (1967) was caused by increased serum cholesterol	Stender et al. (1977)
CO = 200 ppm for 5-12 weeks, 2,000 ppm for 320 min; 4,000 ppm for 205 min	--	Rabbit (n = 150)	Coronary artery and aortic damage	No effect	Inability to reproduce earlier results may be due to lack of blind technique and smaller number of animals in earlier studies	Hugod et al. (1978)
CO = 400 ppm for 10 alternate half-hours of each day for 12 mo	23%	Cynomolgus monkey (n = 11)	Cholesterol content of vessels and plasma	No effect on plasma-free cholesterol, cholesterol ester, tri- and diglycerides, and phospholipids; no significant increase in cholesterol content of aorta; no histologic damage and no fat deposition	Agrees with Malinow et al. (1976)	Bing et al. (1980)
Smoked 43 cigarettes per day for 14-19 mo; fed cholesterol	0.6-1.9%	Baboons (n = 36)	Serum cholesterol	No significant differences in serum total cholesterol, VLDL + LDL cholesterol, HDL cholesterol, or triglyceride concentrations		Rogers et al. (1980)
CO = 200-300 ppm continuously for	---	Rabbits (n = 140)	Myocardial morphology using electron microscopy	No histotoxic effects		Hugod (1981)

TABLE 10-7 (cont'd). ATHEROSCLEROTIC STUDIES IN LABORATORY ANIMALS

Exposure[a,b]	COHb[c]	Animal	Dependent Variable[d]	Results	Comments	Reference
Smoked 43 cigarettes per day for up to 33 mo; fed cholesterol	0.64-2.0% 0.35-1.13%	Male baboons (n = 36) Female baboons (n = 25)	Serum cholesterol	No significant differences in serum total cholesterol, VLDL + LDL cholesterol, HDL cholesterol, or triglyceride concentrations; slightly enhanced plague formation in carotid artery; no difference in lesions or vascular content of lipid or prostaglandin in aorta or coronary arteries		Rogers et al. (1988)
CO = 100 ppm 8 h/day, 5 day/week for 4 mo, fed cholesterol	6.8-7.6%	Pigs (n = 38) (normal or homozygous and heterozygous for von Willebrand's disease) with balloon-catheter injury of coronary arteries	Coronary artery and aortic lesions	No significant changes		Sultzer et al. (1982)

[a]Exposure concentration and duration.
[b]1 ppm = 1.145 mg/m^3; 1 mg/m^3 = 0.873 ppm at 25°C, 760 mm Hg; 1% = 10,000 ppm.
[c]Measured blood carboxyhemoglobin (COHb) levels.
[d]See glossary of terms and symbols for abbreviations and acronyms.

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Kjeldsen, 1975), noted no histologic changes in the coronary arteries or aorta in rabbits exposed to CO (200, 2000, or 4000 ppm) for 0.5 to 12 weeks. These workers suggested that the positive results obtained earlier were due to the non-blind evaluation techniques and the small number of animals used in the earlier studies. Later, Hugod (1981) confirmed these negative results using electron microscopy.

Only a few of the studies published since completion of the 1979 criteria document have demonstrated a significant atherogenic effect of low-level CO exposure. Turner et al. (1979) showed that CO enhanced the development of coronary artery lesions in White Carneau pigeons that were fed a diet of 0.5 and 1%, but not 2%, cholesterol. The exposure was to 150 ppm for six hours, five days each week for 52 weeks (COHb = 10%-20%). Plasma cholesterol levels may have been increased slightly by the CO, but this was significant ($p<0.5$) only at Week 11. Marshall and Hess (1981) exposed minipigs to 160, 185, and 420 ppm CO for four hours per day for 1 to 16 days (COHb = 5 to 30%). The higher concentrations were associated with adhesion of platelets to arterial endothelium and to fossae of degenerated endothelial cells. Additional changes at the higher concentration included an increased hematocrit, an increase in blood viscosity, and an increase in platelet aggregation.

Alcindor et al. (1984) studied rabbits with induced hypercholesterolemia. Three sets of rabbits were studied. The first was a control group receiving a normal diet and breathing air. The second group was given a 2% cholesterol diet. The third group was given the same diet and exposed to 150 ppm CO. COHb levels were not reported. Low-density lipoprotein particles in the CO-exposed rabbits were richer in cholesterol and had a higher cholesterol-to-phospholipid molar ratio than did the particles from the nonexposed rabbits after 45 days ($p<0.01$).

Other animal studies have given generally negative results. Bing et al. (1980) studied cynomolgus monkeys (*Macaca fascicularis*). Four animals were used as controls. Seven were exposed to CO at a level of 400 ppm for 10 alternate half-hours of each day during 12 mo. Carboxyhemoglobin levels showed a gradual increase to a peak at five hours of 20%. The monkeys had no histologic evidence of atherosclerosis, vessel wall damage, or fat deposition in the arterial wall. There was no significant change in cholesterol or in lipoprotein levels. High density to total cholesterol ratios did not differ between the CO-exposed and air-exposed animals. These animals were on a normal diet with no augmentation of cholesterol

or fat content. The study demonstrated that even high levels of CO exposure are not invariably followed by arterial injury or abnormal lipid accumulation.

Similar negative results were reported by Sultzer et al. (1982) who studied swine. Pigs with and without von Willebrand's disease were divided into groups that were exposed to intermittent, low-level CO or to air. CO was delivered at 100 ppm for eight hours each week day for four months. COHb levels averaged 7% after five hours of exposure. The degree of coronary and aortic atherosclerotic lesion development in response to a 2% cholesterol diet was similar in the two exposure groups. There was no effect of the ambient CO on the degree of hypercholesterolemia induced by the diet. The findings showed no obvious effect of CO on atherogenesis in hypercholesterolemic pigs.

A number of studies have examined the contribution of CO in cigarette smoke to the purported effects of smoking on atherogenesis and thrombosis. Rogers et al. (1980) fed a high-cholesterol diet to 36 baboons for up to 81 weeks. The animals were taught to puff either cigarette smoke or air by operant conditioning using a water reward. Half of the baboons smoked 43 cigarettes each day. The baboons were given a cigarette or sham every 15 min during a 12-h day except during times of blood drawing. Average COHb levels in smokers were about 1.9%. Only slight differences in the very low-density lipoprotein (VLDL), LDL and high-density lipoprotein (HDL) levels were noted between the smokers and nonsmokers. Additionally, platelet aggregation with adenosine 5'-phosphate (ADP) and collagen was similar in the two groups.

Rogers et al. (1988) extended their previous study of male baboons for an additional 1.2 years of diet and smoking (total diet, 3.2 years; total smoking, 2.8 years). They also studied a separate group of 25 female baboons that received the diet for 2.6 years and were exposed to cigarette smoke for 1.6 years. Blood levels of COHb were determined by GC and reported both as total concentration in milligrams per deciliter and as percent saturation of Hb, as calculated by a validated linear regression equation. Levels of COHb in the male baboons averaged 0.64% at baseline, whereas COHb was on an average of 0.35% in female baboons at baseline. The weekly averages of COHb levels determined after 57 weeks were 2.01 and 1.13% in male and female baboons, respectively. The baseline cholesterol levels were 105 mg/dL and 88 mg/dL in the two groups of baboons. Levels at 16 weeks were 226 mg/dL in males and 291 mg/dL in females. There were no significant differences in total

cholesterol, HDL cholesterol, or LDL cholesterol between smokers and controls. There were slightly more fatty streaks and fibrous lesions in the carotid arteries of smokers than in controls. No differences in lesion prevalence, vascular content of lipids, or prostaglandins were seen in aorta or coronary arteries.

The results reported by Rogers et al. (1980; 1988) suggest little if any effect of cigarette smoking on atherosclerotic lesion development in baboons. How these findings can be extrapolated to effects of smoking in humans is difficult to know. The COHb levels attained in the experimental animals were barely 2%. Levels in human smokers are probably 4% or more during the waking hours of the day. On the other hand, the findings are consistent with most studies of the effects of low levels of CO on atherogenesis.

A study of cockerels by Penn et al. (1983) has shown negative results as well. Three groups of cockerels, each including seven animals, were used to determine if the atherogenic effect of cigarette smoke could be separated from an effect due solely to CO. Cockerels develop aortic fibromuscular atherosclerotic lesions spontaneously. Various agents, including some carcinogens, have been shown to accelerate the growth in thickness and extent of these lesions. The authors used this model by exposing one group of animals to the smoke from 40 cigarettes each day for five days each week. The cockerels were exposed from about six weeks of age until about 22 weeks of age. A similar group of animals was exposed to CO calibrated to give a similar COHb level to that achieved in the animals exposed to cigarette smoke. The third group of animals was exposed to filtered air. Carboxyhemoglobin levels following an exposure session were measured at 6, 9, 12, and 15 weeks. The average level in the air-exposed animals was 1.6%. Levels in the cigarette smoke and CO groups were 6.7 and 7.2%, respectively. Atherosclerosis was quantified both by the extent of the aorta involved and by the cross-sectional area of the intimal thickening. The cigarette smoke-exposed group had more aortic lesions and lesions with greater cross-sectional area than did either the CO-exposed group or the air-exposed group. This difference was significant at $p < 0.05$ in a one-tailed chi-square test. The data suggest that atherogenic effects of cigarette smoke are not solely attributable to CO.

It has been postulated that a possible atherogenic effect of CO may be mediated through an ability of CO to enhance platelet aggregation or some other component of thrombosis. This possibility was raised in the study by Marshall and Hess (1981) noted above. Other

studies, however, have demonstrated that the effect of CO is to depress platelet aggregation. In one study (Mansouri and Perry, 1982), platelet aggregation to epinephrine and arachidonic acid was reduced in *in vitro* experiments in which CO was bubbled through platelet-rich plasma. Similarly, platelets from smokers aggregated less well than platelets from nonsmokers, although this inhibition of aggregation was not correlated with the level of COHb.

Madsen and Dyerberg (1984) extended these observations by studying effects of CO and nicotine on bleeding time in humans. Smoke from high-nicotine cigarettes caused a significant shortening of the bleeding time. Smoke from low-nicotine cigarettes caused no significant change in bleeding time. CO inhalation sufficient to raise the COHb to 15% was followed by a shortening of the bleeding time (6.0 minutes to 4.8 min), but for a short period of time (< 1.5 h). After administration of aspirin, neither nicotine nor CO affected bleeding times or platelet aggregation. The findings suggest that the proaggregating effects of cigarette smoke are mediated through an inhibitory effect of nicotine on prostacyclin (PGI_2) production. Effects of CO in the smoke seem to be minor and short lived.

These findings were corroborated by Renaud et al. (1984). The effects of smoking cigarettes of varying nicotine content on plasma clotting times and on aggregation of platelets with thrombin, ADP, collagen, and epinephrine were studied in 10 human subjects. Both the clotting functions and platelet aggregation were increased with increasing nicotine content in cigarettes. There was no correlation of these parameters, however, with COHb levels. COHb levels, reported as percent increase from baseline, achieved about a 60% increase.

Effeney (1987) has provided convincing evidence that these effects of nicotine and CO on platelet function are mediated through opposing effects on PGI_2 production. Four rabbits were exposed to CO in an exposure chamber at 400 ppm for 7 to 10 days. Carboxy-hemoglobin levels averaged about 20%. Ten rabbits received an infusion of nicotine for 7 to 10 days. Full-thickness samples of atrial and ventricular myocardium were incubated with arachidonic acid for determination of PGI_2 production by radioimmunoassay of 6-keto-$PGF_{1\alpha}$ and by inhibition of platelet aggregation. Carbon monoxide exposure increased PGI_2 production which was significant in ventricular myocardium. Nicotine exposure reduced PGI_2 production in all tissues examined. The combination of nicotine and CO caused a net

increase in PGI_2 production. The effect of CO may be to induce hypoxemia, a known stimulant of PGI_2 production. This effect of CO would serve to reduce aggregation.

Another explanation for the antiaggregatory effect of CO exposure recently has been provided by Brune and Ullrich (1987). These investigators bubbled CO through platelet-rich plasma and then challenged the platelets with various agonists. The CO exposure was much greater than that encountered in physiologic or even toxic states. The results, however, indicated that inhibition of aggregation was related to enhancement of guanylate cyclase action and associated increased cyclic guanosine monophosphate (cGMP) levels.

10.3.5 Summary and Conclusions

The 1984 Addendum to the 1979 Air Quality Criteria Document for Carbon Monoxide (U.S. Environmental Protection Agency, 1984) reported what appears to be a linear relationship between level of COHb and decrements in human exercise performance, measured as maximal O_2 uptake. Exercise performance consistently decreases at a blood level of about 5.0% COHb in young, healthy, nonsmoking individuals (Klein et al., 1980; Stewart et al., 1978; Weiser et al., 1978). Some studies have even observed a decrease in performance at levels as low as 2.3 to 4.3% COHb (Horvath et al., 1975; Drinkwater et al., 1974; Raven et al., 1974a); however, this decrease is so small as to be of concern mainly for competing athletes rather than for ordinary people conducting the activities of daily life. Cigarette smoking has a similar effect on cardiorespiratory response to exercise in nonathletic human subjects indicating a reduced ability for sustained work (Hirsch et al., 1985; Klausen et al., 1983).

Since the 1979 Air Quality Criteria Document, several important studies appearing in the literature have expanded the cardiovascular data base. Adverse effects in patients with reproducible exercise-induced angina (Allred et al., 1989a,b) have been noted with postexposure COHb levels (CO-Ox measurement) as low as 3.2% (corresponding to an increase of 2.0% from baseline). Sheps et al. (1987) also found a similar effect in a group of patients with angina at COHb levels of 3.8% (representing an increase of 2.2% from baseline). Kleinman et al. (1989) studied subjects with angina and found an effect at 3% COHb representing an increase of 1.5% from baseline. Thus, the lowest observed adverse effect level in patients with stable angina is somewhere between 3 and 4% COHb (CO-Ox

measurement), representing an increase from baseline of from 1.5 to 2.2%. Effects on silent ischemia episodes, which represent the majority of episodes in these patients, have not been studied (see Chapter 12).

Exposure sufficient to achieve 6% COHb recently has been shown to adversely affect exercise-related arrhythmia in patients with CAD (Sheps et al., 1989). This finding combined with the epidemiologic work of Stern et al. (1988) in tunnel workers is suggestive but not conclusive that CO exposure may provide an increased risk of sudden death from arrhythmia in patients with CAD.

There is also strong evidence from both theoretical considerations and experimental studies in animals that CO can adversely affect the cardiovascular system. Tables 10-4 through 10-7 are summaries of the data pertinent to the effects of CO on the cardiovascular systems of experimental animals. Accordingly, disturbances in cardiac rhythm and conduction have been noted in healthy and cardiac-impaired animals at CO concentrations of 50 to 100 ppm (COHb = 2.6 to 12%); alterations in various hemodynamic parameters have been observed at CO concentrations of 150 ppm (COHb = 7.5%); cardiomegaly has been reported at CO concentrations of 200 ppm (COHb = 12%) and 60 ppm in adult and fetal animals, respectively; changes in Hb concentrations have been reported at CO concentrations of 100 ppm (COHb = 9.26%) and 60 ppm in adult and fetal animals, respectively.

There is conflicting evidence that CO exposure will enhance development of atherosclerosis in laboratory animals; and most studies show no measurable effect. Similarly, the possibility that CO will promote significant changes in lipid metabolism that might accelerate atherosclerosis is suggested in only a few studies. Any such effect must be subtle at most. Finally, CO probably inhibits rather than promotes platelet aggregation. Except for the studies by Rogers et al. (1980, 1988) on baboons, the CO exposures used in the studies on atherosclerosis created COHb levels of 7% or higher; sometimes much higher. While occupational exposures in some workplace situations might regularly lead to COHb levels of 10% or more, such high-exposure levels are almost never encountered in the nonoccupationally exposed general public. In this general population, exposures are rarely as much as 25 to 50 ppm, and COHb levels typically are below 3% in nonsmokers (see Chapter 8). When examined in this context, this review, therefore, provides little data to

indicate that an atherogenic effect of exposure would be likely to occur in human populations at commonly encountered levels of ambient CO.

10.4 CEREBROVASCULAR AND BEHAVIORAL EFFECTS OF CARBON MONOXIDE

10.4.1 Control of Cerebral Blood Flow and Tissue PO_2 with Carbon Monoxide and Hypoxic Hypoxia

10.4.1.1 Introduction

The effect of CO on cerebral blood flow (CBF) and cerebral O_2 consumption ($CMRO_2$) is complicated by the relationship between CBF and cerebral O_2 delivery or availability. Alterations in cerebral neurological function, as evaluated by neurological symptoms or changes in evoked potential responses, are particularly difficult to correlate with changes in CBF or cerebral O_2 delivery. One of the most fundamental challenges to the organism is to obtain O_2 from its environment and deliver it to the tissues. However, each tissue or organ may have regulatory mechanisms to obtain O_2 which differ from other tissues or organs. Literature concerning the cerebrovascular effects of CO is incomplete and in many cases conflicting, and, despite the enormous literature concerning hypoxia and the cerebrovasculature, the mechanisms that regulate the cerebral vessels during hypoxia are unclear.

Kety and Schmidt (1948) demonstrated that $CMRO_2$ is about 3.5 mL of O_2 per 100 g of brain (cerebral hemispheres) per minute in normal adult man. This consumption of O_2 is virtually unchanged under a variety of conditions. About one-half of $CMRO_2$ is dedicated to synaptic transmission (Astrup, 1982; Donegan et al., 1985) and this remains relatively constant under all conditions. Half of the remaining, vegetative O_2 consumption, a quarter of the overall value, maintains resting neuronal membrane potentials. The remaining quarter is consumed by a variety of unidentified, but presumably irreducible, processes (Astrup, 1982). In order for the brain to maintain its $CMRO_2$ it has but two adaptations: (1) the brain could extract more O_2 from the blood or (2) CBF could increase. In fact, the brain generally relies largely on increasing CBF for its major adaptability mechanism to provide more O_2 to the tissue. Thus, the following discussion concerns the regulation of CBF with hypoxia, with little discussion of the regulation of O_2 extraction.

The cerebral vasculature responds to decreases in O_2 availability by increasing CBF in order to maintain cerebral O_2 delivery and/or by increasing O_2 extraction in order to maintain cerebral O_2 utilization when cerebral O_2 delivery is limited. Compared with other forms of cerebral O_2 deprivation, such as hypoxic hypoxia (lowered inspired O_2 concentration) and anemia, CO hypoxia may interfere with O_2 delivery and cerebral O_2 utilization through effects on the Hb dissociation curve and on the cytochrome oxidase system. During O_2 deprivation (hypoxia) CBF and cerebral O_2 delivery may be altered by hemodynamic responses, specifically changes in cerebral perfusion pressure, as well as the absolute amount of O_2 limitation (arterial O_2 content). Because hypoxia adversely effects cerebral autoregulation, hypertension during hypoxia may result in an increased CBF and, hence, cerebral O_2 availability. Conversely, hypotension during hypoxia may decrease CBF and cerebral O_2 delivery. In the following sections, the effects of hypoxia (hypoxic and CO) on the cerebro-vasculature will be demonstrated and the potential mechanisms of action of hypoxia on cerebral blood vessels will be examined. The effects of CO on global and regional CBF, and the effects of both high and low levels of CO on CBF and $CMRO_2$ also will be examined. An attempt will be made to demonstrate the potential mechanisms of action of hypoxia on the cerebrovasculature, and the synergistic effects of CO and cyanide hypoxia on the cerebral circulation will be examined.

10.4.1.2 Effects on Global Cerebral Blood Flow

At the present time, there is conflicting information concerning whether the cerebrovascular response to CO is similar to other forms of cerebral hypoxia, such as hypoxic hypoxia and anemic hypoxia. Few studies are available in which other types of hypoxia have been compared to CO hypoxia, especially at similar levels of O_2 deprivation. In addition, comparison of cerebrovascular effects of CO and other types of hypoxia from laboratories of different investigators is difficult because of differences in anesthetic techniques, use of different animal species, and use of different CBF techniques. An important point to emphasize when comparing CO hypoxia to hypoxic hypoxia is that although arterial O_2 content is reduced with both hypoxic and CO hypoxia, there is no reduction in arterial O_2 tension with CO hypoxia. Comparisons of the equivalent effects of both CO and hypoxic hypoxia on CBF and $CMRO_2$ in the same animal preparations have been made by Traystman's

laboratory in several studies (Traystman and Fitzgerald, 1977; Traystman et al., 1978; Fitzgerald and Traystman, 1980; Traystman and Fitzgerald, 1981; Koehler et al., 1982; Koehler et al., 1984; Koehler et al., 1983; Koehler et al., 1985). The concept of equivalent effects of both types of hypoxia (hypoxic and CO) has been described by Permutt and Farhi (1969) and involves the comparison of physiologic effects of elevated COHb and low O_2 at equal reductions in Hb, arterial O_2 content, arterial or venous O_2 tension, or blood flow. The focus of investigation of several laboratories, including Traystman's, concerning the effects of hypoxia on the cerebral vasculature is not merely to describe the well-known vasodilation that occurs, but to examine the mechanism that produces this vasodilation. This is where much of the controversy lies. Here issues focus on the importance of local mechanisms in controlling CBF such as tissue acidosis (Kety and Schmidt, 1948; Molnar and Szanto, 1964) and the direct effect of hypoxia on vascular smooth muscle (Detar and Bohr, 1968). Some years ago it also had been postulated that O_2-sensitive carotid arterial chemoreceptors might play a role in the CBF response during hypoxia (Ponte and Purves, 1974). Other groups of investigators additionally suggested that carotid baroreceptor stimulation produces cerebral vasoconstriction (James and MacDonnell, 1975; Ponte and Purves, 1974). This vasoconstrictor response to an elevation in blood pressure could contribute to the autoregulatory responses of the cerebral vessels. Because the carotid and aortic chemoreceptors are stimulated by certain forms of hypoxia, as is systemic arterial blood pressure, the underlying mechanism of the cerebral vasodilator response to hypoxia is complicated.

Traystman et al. (1978) previously reported that the increase in CBF in dogs during a reduction in arterial O_2 content, produced by breathing the animal with a low O_2 gas mixture (hypoxic hypoxia), was not different from the increase in CBF when O_2 content was decreased by adding CO to the breathing gas mixture (CO hypoxia) (Figure 10-3). This was true both before and after carotid sinus chemodenervation. This study also demonstrated that with hypoxic hypoxia mean arterial blood pressure increased, whereas it decreased with CO hypoxia. Because the CBF increase with CO and hypoxic hypoxia was similar, cerebrovascular resistance actually decreased more with CO hypoxia. This represents the effect of the carotid chemoreceptors on systemic blood pressure during each type of hypoxia. When the carotid chemoreceptors were denervated, cerebrovascular resistance decreased to the

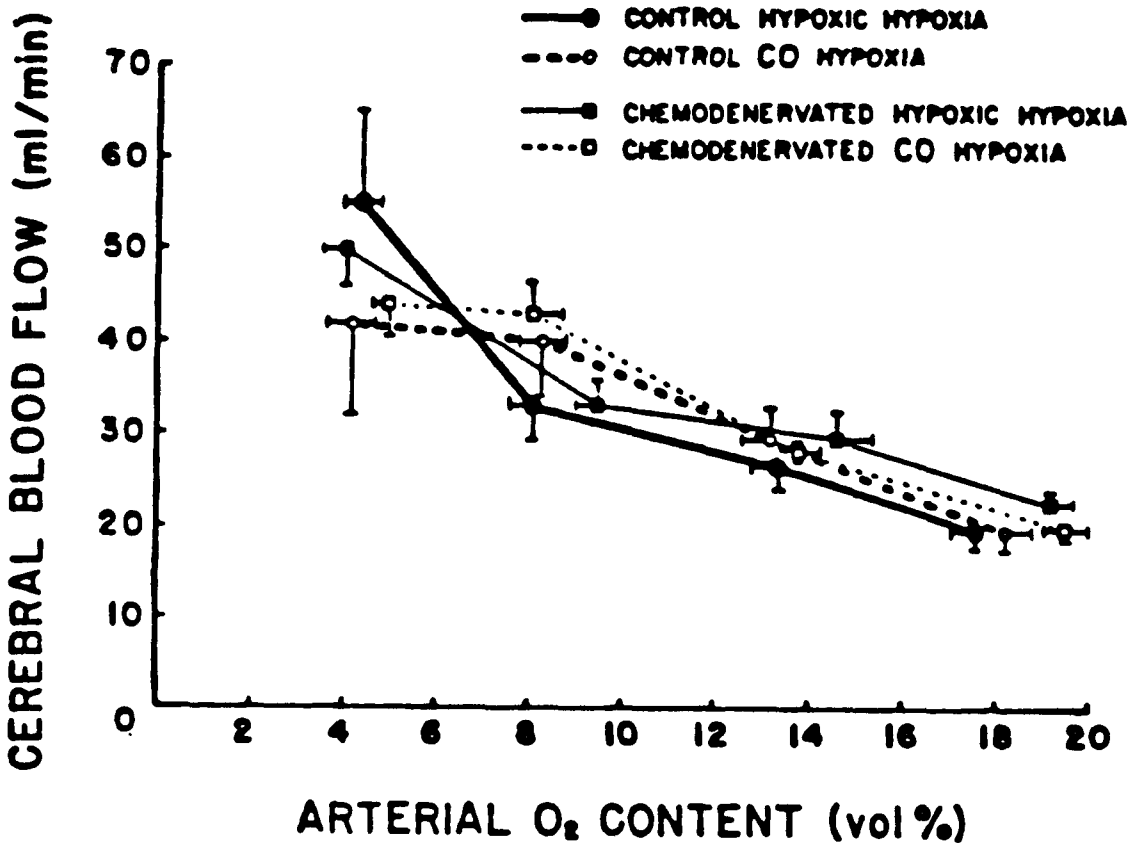

Figure 10-3. Effect of hypoxic hypoxia and CO hypoxia on cerebral blood flow in 13 control and 9 chemodenervated dogs. Each point represents the mean ± SE. Analysis of variance showed that the four slopes were not significantly different from each other. Point-by-point analysis using Student's t-test showed that the minimum difference that was significant was between chemodenervated hypoxic hypoxia and chemodenervated CO hypoxia at 8 vol. % ($p = 0.05$).

Source: Traystman et al. (1978).

same level as with CO hypoxia. They concluded that the carotid chemoreceptors do not play an important role in the global cerebral vasodilator response to either CO or hypoxic hypoxia.

There were two important limitations of that study, however. One involved the possibility that the aortic chemoreceptors (aortic bodies) might have a role in controlling CBF, and this was not considered at that time. The aortic bodies have been reported to have a role in the control of pulmonary blood flow (Stern et al., 1964). The other involved the fact that sectioning of the carotid sinus nerves denervated not only the carotid chemoreceptors, but also the carotid sinus baroreceptors. Because hypoxic hypoxia and CO hypoxia affect blood pressure, they therefore could modulate chemoreceptor input by baroreceptor input. Traystman and Fitzgerald (1981) demonstrated that the carotid and aortic chemoreceptors are not necessary for the increase in CBF with hypoxia and that the increase in CBF is not modified by the carotid and aortic baroreceptors (Figure 10-4). They also showed that the cerebral vasodilation to hypoxia in carotid chemoreceptor-denervated animals and in carotid sinus nerve sectioned and vagotomized animals resembles that occurring in animals exposed to CO hypoxia, with intact chemoreceptors in which both the arterial O_2 tension is high and the chemoreceptors may not be activated (Figure 10-5). $CMRO_2$ remained at control values under both hypoxic hypoxia and CO hypoxia conditions and was unchanged by any denervation condition. These data support the notion that the brain increases its blood flow in response to its O_2 needs with both hypoxic and CO hypoxia in control or baroreceptor and chemoreceptor denervated dogs in order to maintain $CMRO_2$ constant. The cerebral blood vessels appear to be relatively unresponsive to reflex stimuli (Heymans and Bouckaert, 1932; Heistad and Marcus, 1978; Heistad et al., 1976), and the CBF responses to low-inspired O_2 or elevated CO are not dependent on either the carotid or aortic chemoreceptors. These responses also are not modified by either the carotid or aortic baroreceptors. These findings would be most compatible with the idea that control of the cerebral vasculature during hypoxia is mediated locally, however it remains possible that central (brainstem) mechanisms are involved. These brainstem mechanisms concerning the CBF responses to hypoxic hypoxia have been studied little, and their possible involvement in CBF responses to CO have not been examined at all.

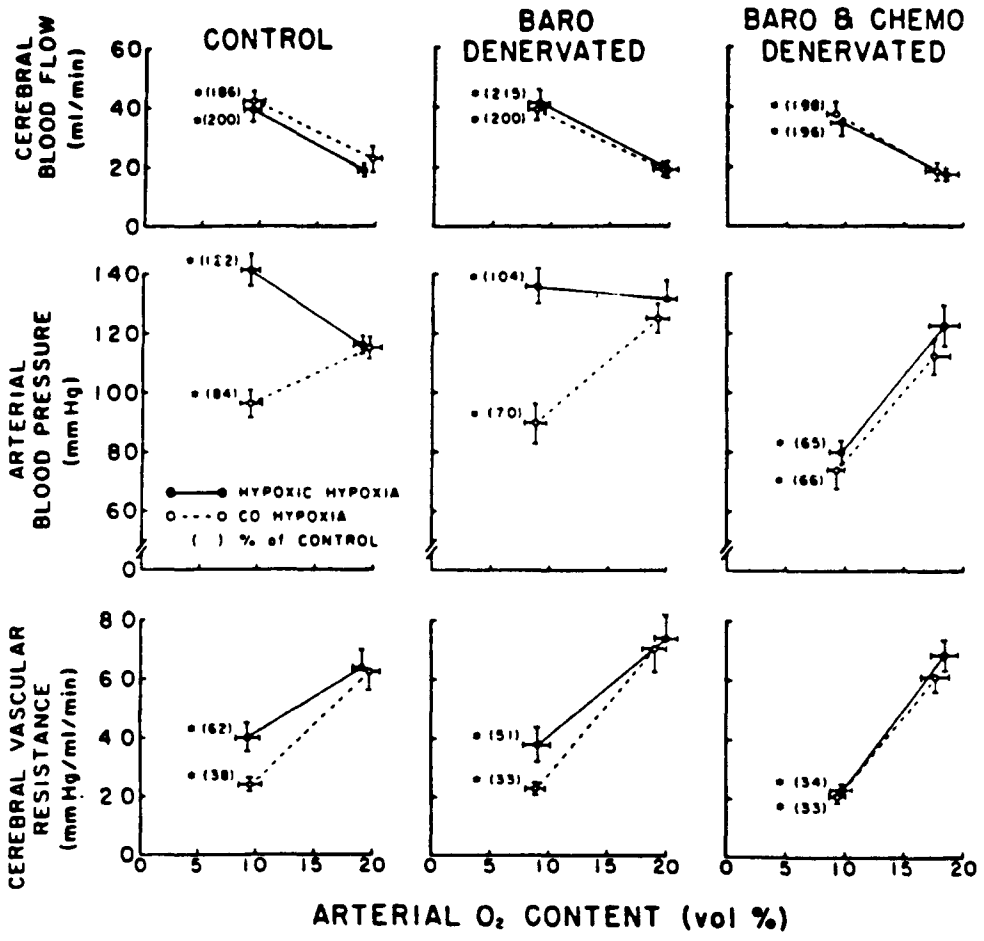

Figure 10-4. Effects of hypoxic and carbon monoxide hypoxia on cerebral blood flow, mean arterial blood pressure, and cerebral vascular resistance in control, carotid baroreceptor-, and chemoreceptor-denervated animals. Data points and bars represent means ± SE of nine animals. Numbers in parentheses are percent of control. *$p<0.05$.

Source: Traystman and Fitzgerald (1981).

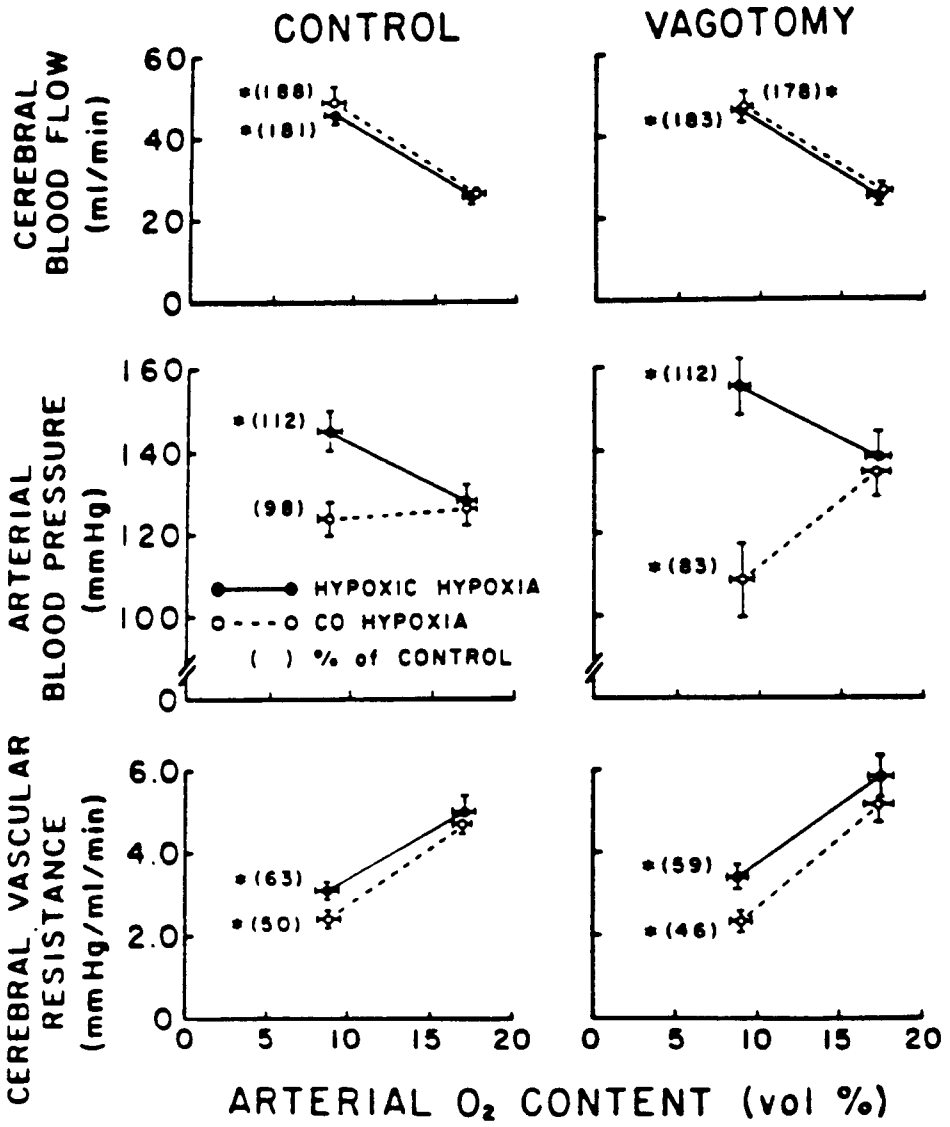

Figure 10-5. Effects of hypoxic and carbon monoxide hypoxia on cerebral blood flow, mean arterial blood pressure, and cerebral vascular resistance in control and vagotomized animals. Data points and bars represent means ± SE of five animals. Numbers in parentheses are percent of control. *$p<0.05$.

Source: Traystman and Fitzgerald (1981).

The idea, however, that CBF responses to CO are always similar to those of hypoxic hypoxia is not universal. Studies on fetal (Jones et al., 1978) and newborn lambs (Jones et al., 1981) have demonstrated that CBF increases during hypoxic hypoxia may correlate better with decreased arterial O_2 content than with decreased arterial O_2 partial pressure. The description of hypoxia in terms of arterial O_2 content rather than arterial O_2 partial pressure is more than simply an arbitrary choice between two similar variables. When one considers hypoxic hypoxia as a fall in arterial O_2 content, this emphasizes the importance of cerebral O_2 delivery to the microvascular exchange site, whereas O_2 partial pressure emphasizes diffusion from the exchange site to the parenchyma. The studies previously mentioned (Jones et al., 1978; Jones et al., 1981) demonstrated that the relationship between CBF and arterial O_2 content is such that the product of CBF and arterial O_2 content, which equals cerebral O_2 delivery, is essentially constant as arterial O_2 partial pressure falls. The study in newborn lambs (Jones et al., 1978) demonstrated that arterial fractional O_2 extraction ($CMRO_2$ per amount of O_2 delivered) was well maintained in both anemic and hypoxic hypoxia conditions. The maintenance of cerebral O_2 delivery and fractional O_2 extraction during anemic and hypoxic hypoxia is not unique to the lamb and does apply to adults of other species (Jones et al., 1981).

Koehler et al. (1982), working with a newborn-lamb model, tested the hypothesis that CBF and $CMRO_2$ bear relationships to arterial O_2 content during CO hypoxia that are not different from those occurring during hypoxic hypoxia. They reasoned that if these relationships differ between hypoxic hypoxia and CO hypoxia, then other effects of CO exposure, such as the shift in the O_2Hb dissociation curve or histotoxic effects, need to be considered. Koehler et al. (1982) found that CO hypoxia causes a 47% greater increase in CBF compared with hypoxic hypoxia for a similar reduction in arterial O_2 content (Figure 10-6). A greater CBF response to CO hypoxia than to anemic hypoxia also has been reported in humans (Paulson et al., 1973). In the study of Koehler et al. (1982), $CMRO_2$ and O_2 delivery were constant during hypoxic hypoxia. Thus, fractional O_2 extraction, which equals O_2 consumption divided by O_2 delivery, remained constant with hypoxic hypoxia. During CO hypoxia, although $CMRO_2$ remained constant, O_2 delivery increased and fractional O_2 extraction decreased. This decline in fractional O_2 extraction was correlated with the leftward shift of the O_2Hb dissociation curve that accompanied CO hypoxia. In this situation,

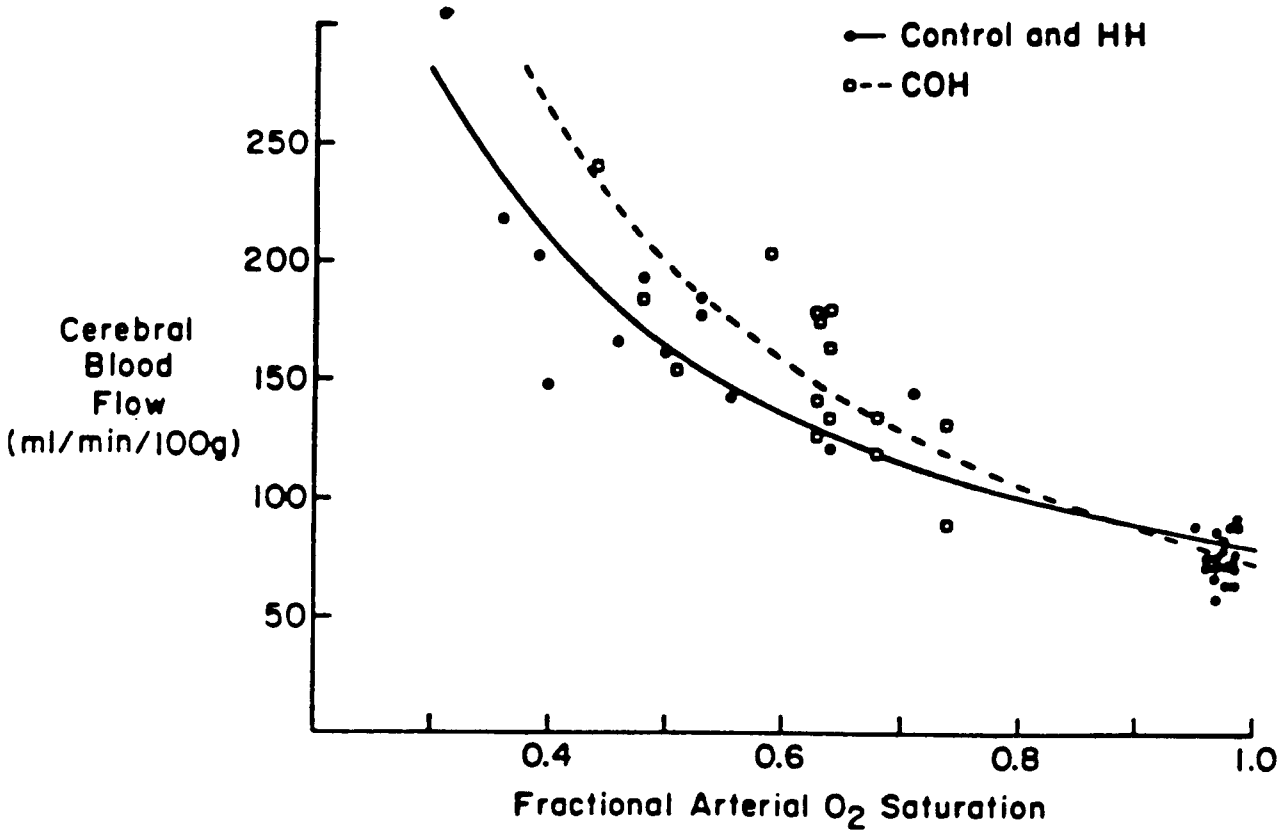

Figure 10-6. Cerebral blood flow as a function of fractional arterial O_2 saturation. Circles represent control or hypoxic hypoxia; squares represent CO hypoxia.

Source: Koehler et al. (1982).

the additional increase in CBF with CO hypoxia could be explained because the shift in the curve lessens the O_2 diffusion gradient into the tissue and further lowers the arterial O_2 partial pressure. In other words, while increases in CBF maintain O_2 availability at the micro-vascular exchange site, overall O_2 transport to the cells becomes relatively more diffusion-dependent with CO hypoxia. Although these investigators believe that the best explanation for the difference in the CBF response to hypoxic hypoxia and CO hypoxia is the leftward shift of the O_2Hb dissociation curve, they cannot completely rule out a potential histotoxic effect of CO resulting from the competition of CO and O_2 for cytochrome aa_3 oxidase. This effect generally is considered to be insignificant at low CO levels because *in vitro* cytochrome oxidase remains completely oxidized until very low tissue O_2 partial pressure levels are reached. However, Hempel et al. (1977) has shown that cerebral cytochrome aa_3 *in vivo* is in a substantially reduced state, raising the possibility that CO may readily compete with O_2 at relatively low CO levels. This binding relationship between CO and the oxidase also has been demonstrated by Piantadosi et al. (1985; 1987). On the other hand, if CO were exerting a histotoxic effect, $CMRO_2$ would be expected to fall, and this was not observed in Koehler's experiments. It also is possible, however, that CO could have a direct histotoxic effect on cerebral vascular smooth muscle, independently of brain tissue metabolism.

In a subsequent study, Koehler et al. (1984) compared the effect of hypoxic hypoxia and CO hypoxia on CBF in adult and newborn sheep in which arterial O_2 content was reduced to 50 to 60% of control with both types of hypoxia. During hypoxic hypoxia, CBF increased to maintain cerebral O_2 delivery in both adults and newborns; however $CMRO_2$ did not change. Although $CMRO_2$ was higher in newborns, the responses of CBF/$CMRO_2$ to hypoxic hypoxia was not different in newborns and adults. In newborns and adults, CBF increased to a greater extent with CO hypoxia than with hypoxic hypoxia for similar reductions in arterial O_2 content (Figure 10-7). This resulted in an increase in cerebral O_2 delivery with CO hypoxia. As discussed previously, the degree to which CO hypoxic differed from hypoxic hypoxia correlated with the magnitude of the leftward shift of the O_2Hb dissociation curve that accompanies CO hypoxia. In the adult animals with CO hypoxia, $CMRO_2$ was reduced by 16%, however, $CMRO_2$ was maintained in the newborns. These data allowed for the conclusion that maintenance of cerebral O_2 delivery during hypoxic hypoxia is a property of CBF regulation common to both newborn and adult sheep. During CO hypoxia, the position

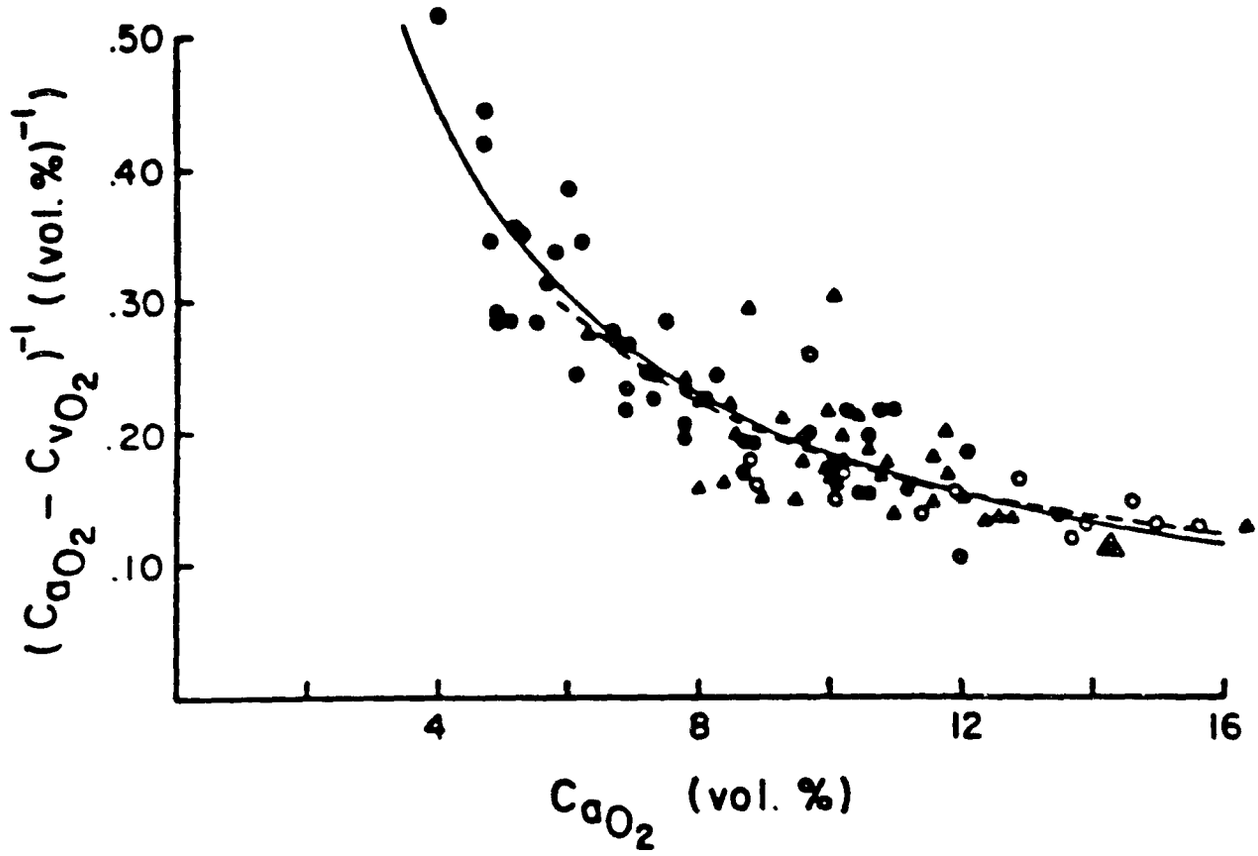

Figure 10-7. Comparison of newborn and adult responses of the reciprocal of the cerebral arteriovenous O_2 content difference (C_aO_2 - C_vO_2)-1 to a reduction in arterial O_2 content (C_aO_2) during hypoxic hypoxia (HH). Open circles, room-air control in newborns; solid circles, HH in newborns; open triangles, room-air control in adults; solid triangles, HH in adults. Regression lines were fitted to the reciprocal of C_aO_2. For newborns (solid line), (C_aO_2 - C_vO_2)-1 = 1.74 C_aO_2-1 + 0.01 (r = 0.91). For adults (dashed line), (C_aO_2 - CvO2)-1 = 1.64 C_aO2 + 0.02 (r = 0.67). Responses of blood flow per unit O_2 consumption are not significantly different between newborns and adults.

Source: Koehler et al. (1985).

of the O_2Hb dissociation curve is an additional factor that sets the level of O_2 delivery. The fetal conditions of low arterial-O_2 content and a left-shifted O_2Hb dissociation curve may have provided the newborn with a microcirculation better suited for maintaining $CMRO_2$ during CO hypoxia.

Some points need to be considered when comparing the cerebrovascular effects of hypoxic hypoxia and CO hypoxia as described in the dog studies (Traystman and Fitzgerald, 1981; Traystman et al., 1978) with those described in the newborn and adult sheep. In the studies concerning the anesthetized dogs, the CBF response to hypoxic hypoxia and CO hypoxia was not statistically different although the mean blood flows tended to be higher with moderate levels of CO. This response was statistically significant in the newborn and adult sheep experiments. One likely explanation for the different result is that arterial blood pressure declined during CO hypoxia in the anesthetized dog, whereas it was well maintained in the unanesthetized sheep. Because cerebral autoregulation is impaired during severe hypoxia (Haggendal and Johannsson, 1965), a drop in perfusion pressure during CO hypoxia may have limited the increase in CBF in the dog. A reexamination of data from the dog study indicated that cerebral O_2 delivery increased and fractional O_2 extraction decreased during CO hypoxia. Thus, the dog study is consistent with the data obtained in the sheep study. Similar results have been reported in humans (Paulson et al., 1973) and in goats (Doblar et al., 1977). Another possible explanation for the differences in CBF responses to hypoxia in the dogs versus the sheep is that the dogs were anesthetized with sodium pentobarbital, whereas the sheep were studied in the unanesthetized state. Pentobarbital anesthesia reduces CBF and $CMRO_2$ so that differences in flow would be minimized in the dog studies. Finally, the P_{50} of sheep Hb is considerably higher than in the dog (44 mmHg for sheep vs. 27 mmHg for dogs) so that the leftward shift of the O_2Hb dissociation curve would be larger in sheep and therefore result in a greater increase in CBF with CO hypoxia versus hypoxic hypoxia. Evidence supporting a role for P_{50} in the CBF response to CO was obtained by Koehler et al. (1983) in experiments in which lambs were first exchange transfused with high-P_{50} donor blood, which resulted in an increase in cerebral fractional O_2 extraction. With the induction of CO hypoxia to return P_{50} to the pretransfusion level, cerebral O_2 delivery and O_2 extraction also returned to pretransfusion levels. These investigators suggested that since P_{50} can affect capillary and tissue O_2 partial pressure

independent of arterial O_2 content, the position of the O_2Hb dissociation curve appears to set the level of cerebral O_2 delivery about which CBF is regulated when arterial O_2 content is reduced. These data, taken together with the previously mentioned work from this group, are consistent with the existence of a tissue O_2 tension-dependent mechanism controlling the cerebral vasculature in which tissue O_2 tension is a function of $CMRO_2$, cerebral O_2 delivery to the microcirculation, the position of the O_2Hb dissociation curve, and microcirculatory morphology.

10.4.1.3 Effects on Regional Cerebral Blood Flow

Both human and animal histopathology studies have suggested that there are regional differences in tissue injury following severe CO exposure. One potential source of these differences is regional differences in the CBF response to CO exposure. Two logical comparisons of the regional CBF response to CO hypoxia are (1) anatomical, (i.e., rostral to caudal [cortex to brainstem] comparison) and (2) physiological (i.e. brain areas with a functional blood brain barrier versus brain areas without an intact blood brain barrier). Koehler et al. (1984) observed interesting regional CBF responses to hypoxic and CO hypoxia in newborn lambs and adult sheep (Table 10-8; Figure 10-8). In adults, regions with high normoxic blood flows such as the caudate nucleus and midbrain showed a large response to hypoxia, whereas lower blood flow regions with large white matter tracts, such as the cervical spinal cord, pons, diencephalon, and piriform lobe, showed a relatively lower response. Other brain regions were essentially homogeneous in their responses. CO hypoxia increased CBF to a greater extent than hypoxic hypoxia in all brain regions, but the overall pattern of regional CBF was similar for the two types of hypoxia in the adults. In Table 10-8 the regions are listed in order from highest to lowest responsivity, and the particular groups of regions that are significantly different are separated by pairs of vertical brackets. In the newborns, regional responses differed for each type of hypoxia. With hypoxic hypoxia in the newborns, the brainstem regions had a significantly greater response than all other regions except the caudate nucleus, whereas all cerebral lobes responded significantly less than all other regions. With CO hypoxia, the difference between brainstem responses and those of other regions was less marked. In the adults, in contrast, there was no significant interactive effect between the type of hypoxia and the pattern of regional response. With both types of

TABLE 10-8. BRAIN REGIONS RANKED FROM GREATEST TO LEAST IN RESPONSE TO HYPOXIA[a]

Hypoxic Hypoxia	Carbon Monoxide Hypoxia
Adult sheep	
Caudate nucleus	Caudate Nucleus
Midbrain	Midbrain
Medulla	Occipital lobe
Parietal lobe	Medulla
Occipital lobe	Cerebellum
Frontal lobe	Temporal lobe
Cerebellum	Frontal lobe
Temporal lobe	Parietal lobe
Fusiform lobe	Diencephalon
Diencephalon	Fusiform lobe
Pons	Pons
Spinal cord	Spinal cord
Newborn lambs	
Medulla	Midbrain
Midbrain	Caudate nucleus
Pons	Cerebellum
Caudate nucleus	Medulla
Cerebellum	Pons
Diencephalon	Diencephalon
Spinal cord	Occipital lobe
Frontal lobe	Temporal lobe
Occipital lobe	Parietal lobe
Temporal lobe	Frontal lobe
Parietal lobe	Spinal cord
Fusiform lobe	Fusiform lobe

[a]Multiple-range tests were performed within each type of hypoxia and each age group. Each pair of vertical brackets encloses two groups of brain regions that have significantly different responses.

hypoxia, the caudate nucleus had a significantly greater response than all other regions and the cervical spinal cord responded significantly less than all other regions.

MacMillan (1975) studied CO hypoxia in rats and did not demonstrate any gross regional CBF differences, in contrast to the studies of Koehler et al. (1982; 1984). However, in MacMillan's study, far fewer brain regions were studied, and the caudate nucleus and midbrain regions, which Koehler's group found to have large responses, were not individually

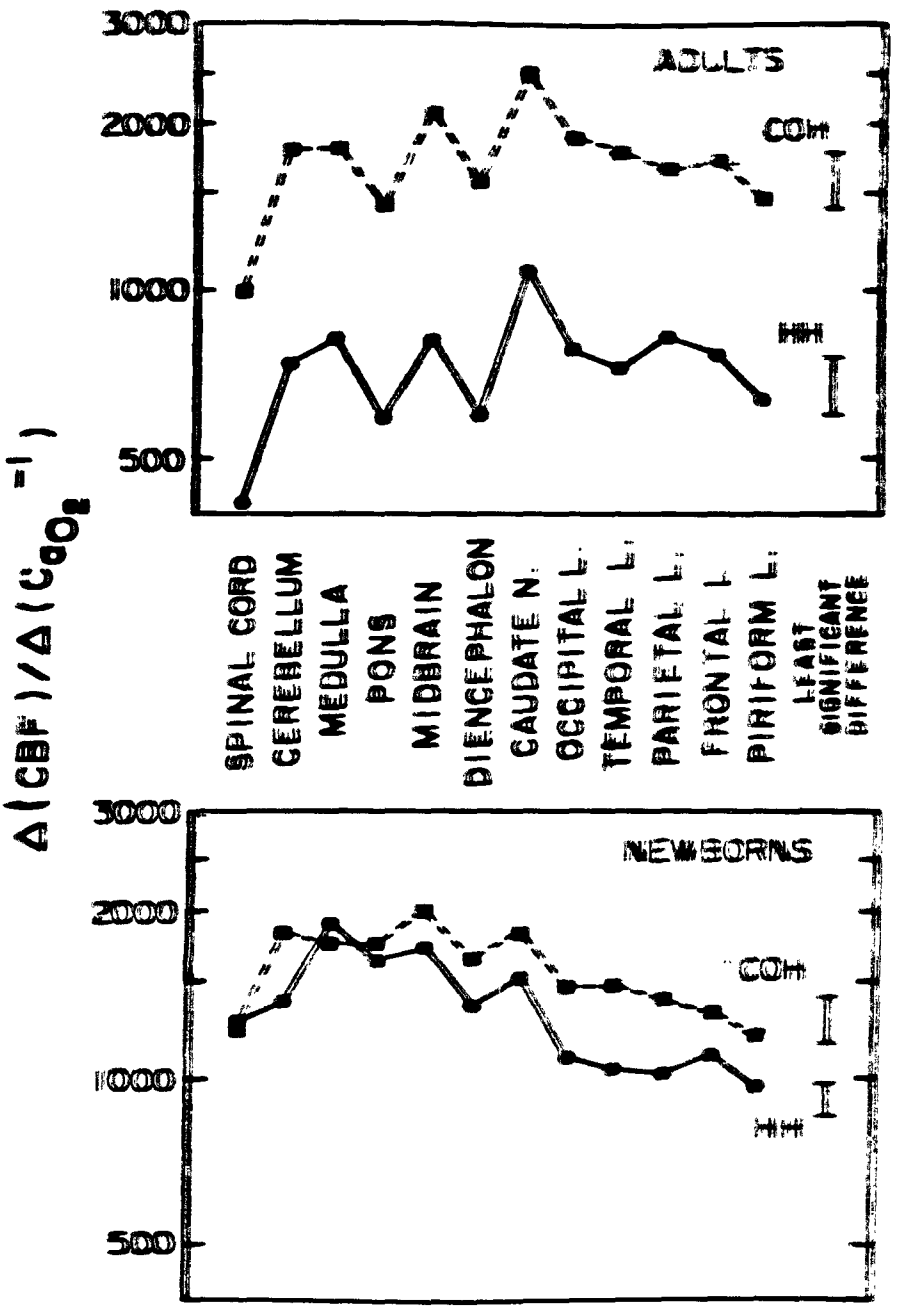

Figure 10-8. Profiles of slopes of regional blood flow responses to hypoxic hypoxia (HH, solid lines) and CO hypoxia (COH, dashed lines) in adults (top) and newborns (bottom). Slopes were calculated from the change in flow (in mL/min/100g 100 g) per change in the reciprocal of the arterial O_2 content (reciprocal of milliliters of oxygen per 100 mL blood) to achieve linearity. Least significant differences for multiple comparisons of regions within each age and type of hypoxia group are given by the bars on the right, as calculated by the K-ratio procedure. (Points along the profile line separated in height by more than the height of the bars are significantly different.))

Source: Koehler et al. (1985).

reported. Okeda et al. (1987) also demonstrated CO-induced regional CBF differences in cats. This group attempted to demonstrate that there is a selective vulnerability of the pallidum and cerebral white matter and showed low CBF values for these brain areas. In the newborn lambs (Koehler et al., 1984), unlike the adult sheep, the patterns of regional CBF responses were not similar with the two types of hypoxia. Brainstem regions, especially the medulla, had marked responses relative to the cerebrum during hypoxic hypoxia. Peeters et al. (1979) also have made this observation in unanesthetized fetal lambs. Rosenberg et al. (1982) found in the fetal and neonatal lamb, but not in the adult sheep, that the brainstem also had a greater CBF response to arterial CO_2 than other regions, and Cavazzuti and Duffy (1982), in newborn dogs, observed results consistent with those in the lamb in that brainstem regions displayed a greater blood flow response to hypoxic hypoxia and to hypercapnia. The most likely explanation in the puppy for the higher brainstem response to hypoxia and hypercapnia is that this region has a higher $CMRO_2$. Normoxic glucose consumption *in vivo* (Cavazzuti and Duffy, 1982) and O_2 consumption *in vitro* (Himwich and Fazekas, 1941) are relatively high in the brainstem of the neonatal puppy. This also may be true in the neonatal lamb. However, if this were the only explanation, there should be a much greater CBF response in brainstem regions relative to the rest of the brain during CO hypoxia, as well as hypoxic hypoxia, but this has not been observed. The larger CBF response of caudate nucleus with hypoxia compared with cortical lobes may be explained by the high fraction of grey matter in the caudate nucleus. The large response of the brainstem region also may be partly explained by a relatively high proportion of grey matter. It also is likely that increased activation of cardiovascular and respiratory centers in the brainstem during hypoxia produces local increases in metabolism and O_2 demand, which in turn would produce an additional increase in blood flow in this area. The capability of the central nervous system to increase $CMRO_2$ during hypoxic hypoxia has been demonstrated in certain strains of rats (Berntman et al., 1979). An alternative explanation for the regional differences in sensitivity to hypoxia is that stimulation of the peripheral chemoreceptors by hypoxia produced sympathetic vasoconstriction preferentially in the cerebral hemispheres. This explanation is considered unlikely because previous studies have shown that neither carotid nor aortic chemoreceptor denervation alters CBF from cortical regions during hypoxic or CO hypoxia (Traystman and Fitzgerald, 1981; Traystman et al., 1978).

There is at least one area of the brain that does not respond to alterations in arterial O_2 content and partial pressure as do other brain areas, the neurohypophysis. The neurohypophysis is an anatomically unique region of the brain, and the regulation of blood flow to this area appears to be different from other areas of the brain. Hanley et al. (1986) demonstrated that when arterial O_2 content was reduced equivalently with hypoxic hypoxia and CO hypoxia, global CBF increased by 239 and 300%, respectively. Regional CBF also showed similar responses for all brain areas except the neurohypophysis. With hypoxic hypoxia, neurohypophysis blood flow increased markedly (320%), but it was unchanged with CO (Figure 10-9). These blood flow responses of the neurohypophysis occur independently of alterations in blood pressure.

Wilson et al. (1987) determined the role of the chemoreceptors in the neurohypophyseal response to hypoxia and found that chemoreceptor denervation completely inhibited the increase in neurohypophyseal blood flow associated with hypoxia. The response to CO was unaltered (Figure 10-10). These data (Hanley et al., 1986; Wilson et al., 1987) demonstrated that the mechanism responsible for the increase in neurohypophyseal blood flow with hypoxia is unique when compared to other brain regions. The only animals in which neurohypophyseal blood flow did not respond were the denervated animals and those given CO. Both of these conditions are ones in which the chemoreceptors have been shown to be inactive (Traystman and Fitzgerald, 1981; Comroe, 1974). Although for most brain regions the blood flow response to hypoxia does not involve the peripheral chemoreceptors, this is not true for the neurohypophysis. Thus, here is an example of one regional brain area that does not respond to CO hypoxia (i.e., a change in arterial O_2 content) but does respond to a change in arterial O_2 tension. This suggests that the chemoreceptor represents the mechanism involved in the neurohypophyseal response to hypoxic hypoxia and that local changes in arterial O_2 content are not involved in this response, because the neurohypophysis does not respond to CO. It is unclear whether other regional brain areas have similar responses and mechanisms to hypoxic and CO hypoxia.

10.4.1.4 Effect of Low Levels of Carbon Monoxide on Cerebral Blood Flow

Little information is available concerning the effects of low levels of CO on the cerebral vasculature. This is particularly unfortunate because many investigators have shown

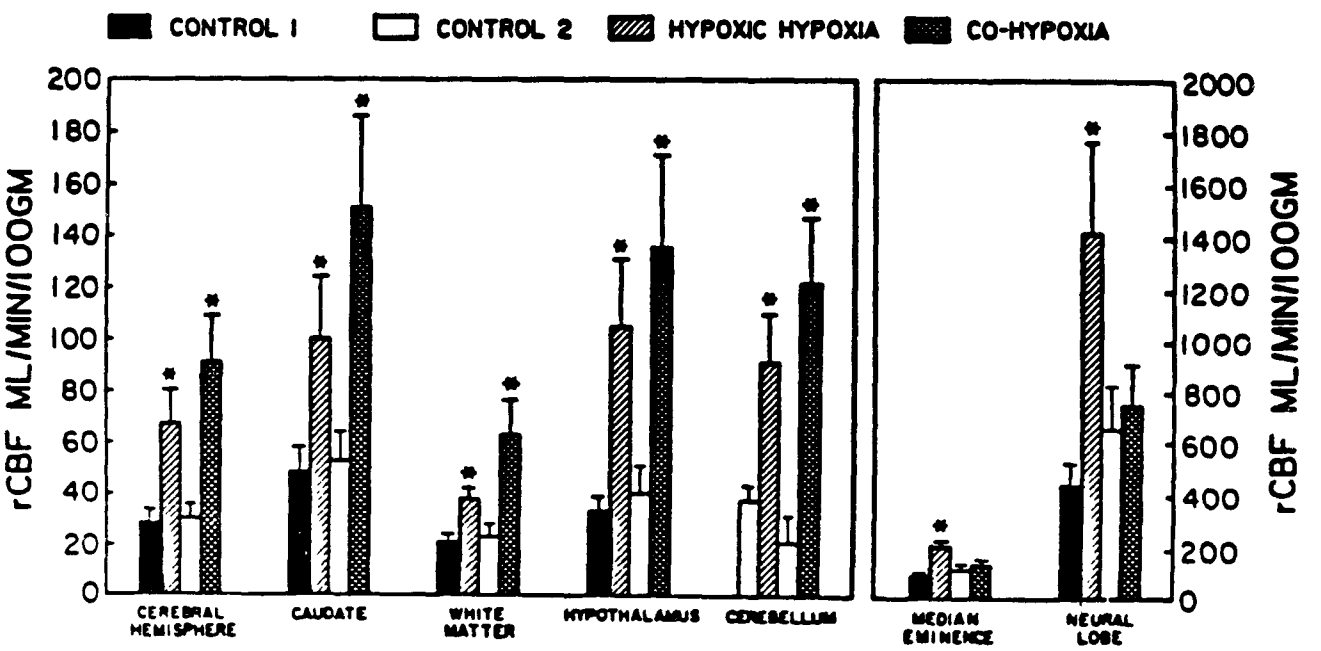

Figure 10-9. Effect of hypoxic hypoxia and carbon monoxide (CO) hypoxia on neurohypophyseal and regional cerebral blood flow (rCBF). Each bar represents mean ± SE of five dogs. Both types of hypoxia (diagonal and cross-hatched bars) produced significant increases from control (open and dark bars) in blood flow to all regions except neurohypophysis. Both parts of neurohypophysis, median eminence and neural lobe, showed no change from control with CO hypoxia but did not have significant flow responses to hypoxic hypoxia. Note changes in vertical axis at right for median eminence and neural lobe blood flow.

Source: Hanley et al. (1986).

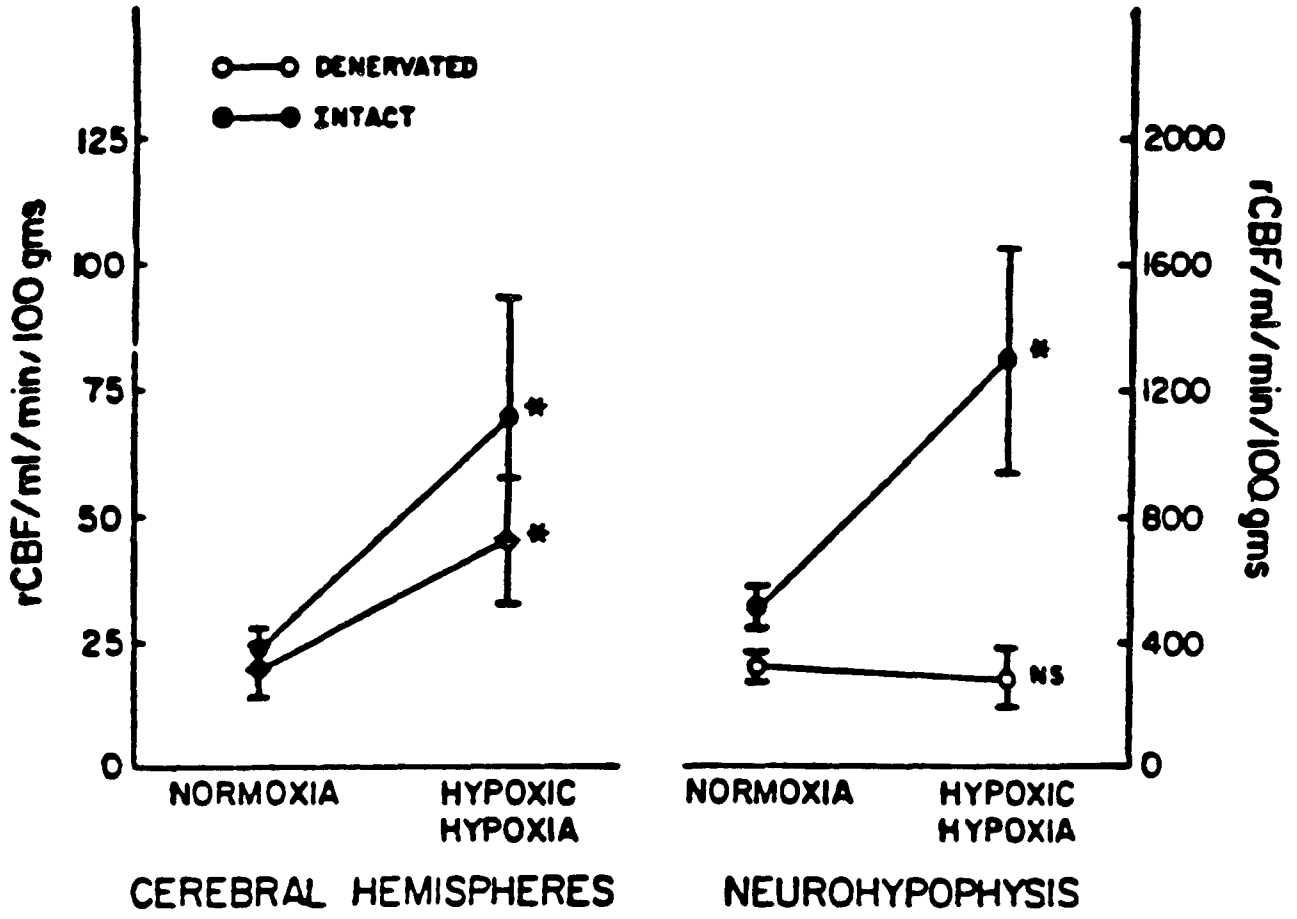

Figure 10-10. Effect of complete chemoreceptor denervation on total cerebral and neurohypophyseal blood flow. Each line represents mean ± SEM of six dogs. (Note change in y axis for neurohypophyseal blood flow.)

Source: Wilson et al. (1987).

behavioral and electrophysiological abnormalities with various levels of CO exposure (Xintaras et al., 1966; Beard and Wertheim, 1967; Fodor and Winneke, 1972; Horvath et al., 1971), and it is conceivable that these effects could result from abnormalities of CBF. Carbon monoxide hypoxia results in an increase in CBF, and this has been demonstrated by a number of investigators (Traystman and Fitzgerald, 1981; Traystman et al., 1978; Sjostrand, 1948; Haggendal and Norbeck, 1966; Paulson et al., 1973). However, many difficulties have been encountered in these experiments such as extracranial contamination of the measured CBF, surgical trauma to the cerebral vasculature, inadequate control of blood gases, and failure to measure COHb concentrations.

Traystman (1978) examined the CBF responses to CO hypoxia in anesthetized dogs, particularly in the range of COHb less than 20% (Figure 10-11). A COHb level as low as 2.5% resulted in a small, but significant, increase in CBF to 102% of control. With reductions in O_2-carrying capacity of 5, 10, 20, and 30% (COHb 5, 10, 20, and 30%) CBF increased to approximately 105, 110, 120, and 130% of control, respectively. At each of these levels, $CMRO_2$ remained unchanged. At COHb levels above 30%, CBF increased out of proportion to the decrease in O_2-carrying capacity, but the brain could no longer maintain $CMRO_2$ constant. At a COHb level of 50%, CBF increased to about 200% of control. These findings are in general agreement with those of MacMillan (1975) who demonstrated that as COHb increased to 20, 50, and 65%, CBF increased to 200, 300, and then 400%, respectively, in cats. These CBF increases at 20% COHb are higher than those reported in Traystman's (1978) study but the reason for this is not known. Haggendal and Norbeck (1966) demonstrated a 50 to 150% of control increase in CBF with COHbs of 30 to 70%, and Paulson et al. (1973) showed a 26% increase in CBF with a COHb of 20%. These findings also indicate that CBF increases progressively with increasing COHb concentrations, and that $CMRO_2$ is maintained constant even at a COHb level of 30%. This has important implications regarding the behavioral and electrophysiological consequences of CO exposure. These findings also would be consistent with those of Dyer and Annau (1978) who found that superior colliculus-evoked potential latencies are not affected by COHb levels up to 40%. At levels above this, the brain cannot increase blood flow enough to compensate for decreased tissue O_2 delivery. At these high COHb levels, then, behavioral and neurophysiological abnormalities should be quite evident. At lower COHb levels, these abnormalities should not

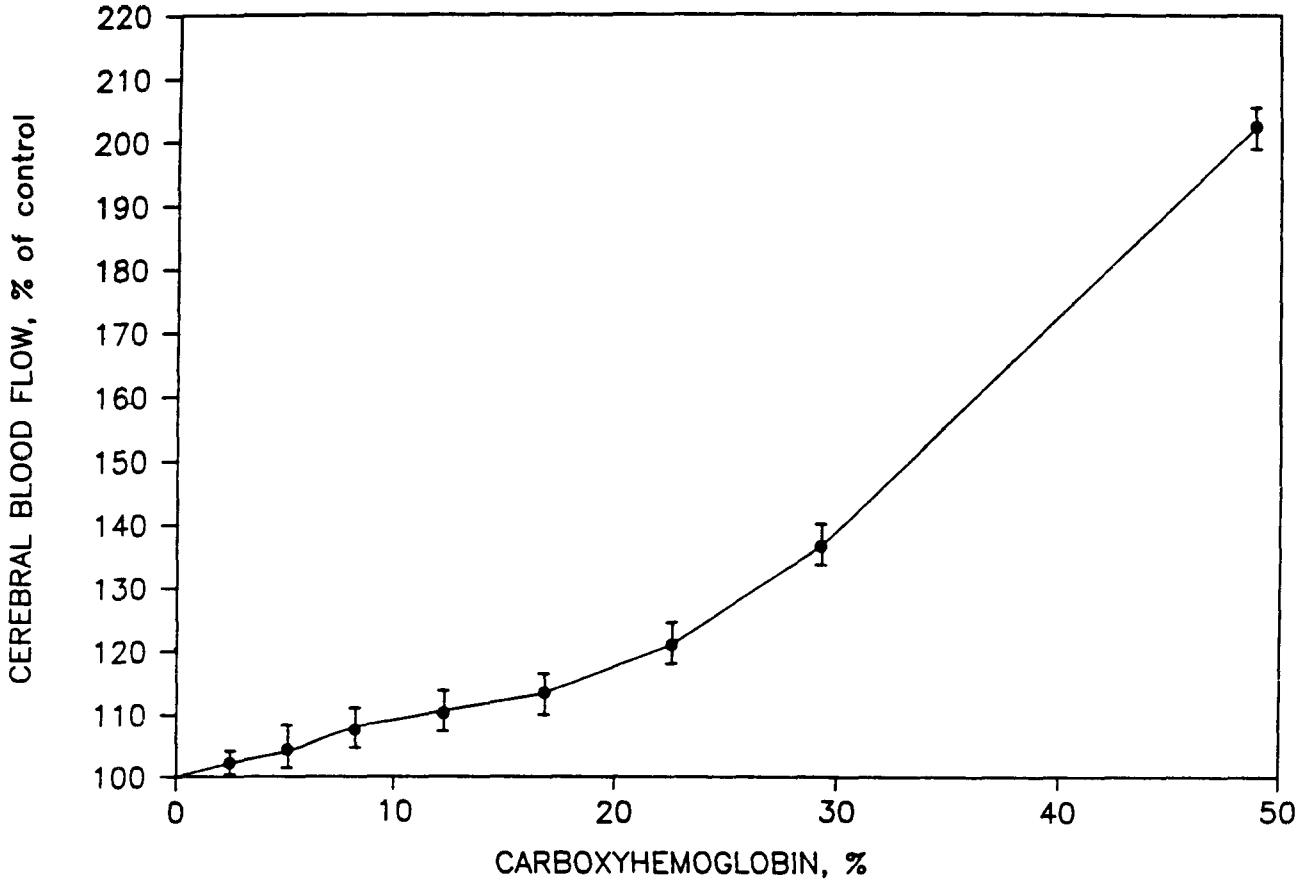

Figure 10-11. Effect of increasing carboxyhemoglobin levels on cerebral blood flow, with special reference to low-level administration (below 20% COHb). Each point represents the mean ± SE of 10 dog preparations.

Source: Traystman (1978).

be seen because the brain can increase its blood flow and/or O_2 extraction to maintain $CMRO_2$ constant. Obviously, in a compromised cerebral vasculature (i.e., patients with stroke, head injury, atherosclerosis, hypertension) these abnormalities would be evident because the brain perhaps could not increase its blood flow or extraction enough to maintain a constant $CMRO_2$. These data lead to the suggestion that as long as the brain can compensate for the decrease in O_2 availability by increasing its blood flow or O_2 extraction to maintain $CMRO_2$ constant, there should be no detrimental effects of hypoxia at these levels (i.e., up to a COHb of 30% or more). However, once these compensatory mechanisms fail, the detrimental effects on behavioral or electrophysiological aspects should be observed. This is a completely different hypothesis from the one that suggests there are behavioral or neurophysiological effects at COHb levels of less than 10%, or even 5%.

In addition, the idea of a threshold level below which changes in COHb would not invoke increases in CBF (Otto and Reiter, 1978) was unsubstantiated by Traystman's work (Traystman, 1978). A threshold level such as this would have nicely accounted for behavioral and electrophysiological decrements observed by some investigators at COHb levels of less than 5% (Xintaras et al., 1966; Beard and Wertheim, 1967). Because Traystman (1978) showed increased CBF and stable $CMRO_2$ up to COHb levels of 30%, this suggests almost perfect compensation of the cerebral circulation to levels of rather severe hypoxia. Several investigators, however, have dealt with whether there is a threshold arterial O_2 tension for alterations in CBF with hypoxic hypoxia. McDowall (1966) reported a threshold arterial O_2 tension of 50 mmHg in anesthetized dogs. CBF began to increase as arterial O_2 tension approached 50 mmHg, and at 30 mmHg had increased to 220% of control. Kogure et al. (1970) confirmed McDowall's findings using a venous outflow technique. However, Borgstrom et al. (1975) reported a significant increase in CBF at arterial O_2 tensions as high as 85 mmHg. Other investigators have shown that CBF increases even with decreases in arterial O_2 content, or O_2 tension within the normoxic range (Jones et al., 1981; Traystman et al., 1978). There is little reason to think that a critical O_2 tension exists at the present time, primarily because of the experiments described above, but also because of a better understanding of how O_2 exerts itself on cellular metabolism in intact biologic systems (Rosenthal et al., 1976; Wilson et al., 1979). A threshold response to a decrease in arterial O_2 tension or the parenchymal O_2 tension (probably parenchymal [Kontos et al., 1978]) is the

major determinant of CBF. Also, because of loss of O_2 from larger arterioles (Duling et al., 1979) and the sigmoid shape of the O_2Hb dissociation curve, large changes in arterial O_2 tension will result in relatively small changes in O_2 tension in small arterioles and tissues. In addition, any changes in CBF that occur at high levels of arterial O_2 tension will be on the flat portion of the hyperbolic CBF response curve (Jones and Traystman, 1984) and will be difficult to measure. Thus, it is probably more correct to consider the CBF response to hypoxic hypoxia as a continuous hyperbolic function that applies over a wide range of O_2 tension values.

10.4.1.5 Synergistic Effects of Carbon Monoxide

There has been some work regarding the synergistic effects of CO with other toxicologic substances, most of these investigating the by-products of combustion (also see Chapter 11, Section 11.3.2.). In spite of the complex nature of fire, it is clear that CO absorption is a major contributing factor in fire deaths (Radford et al., 1976). Cyanide also has been demonstrated to be present as a result of combustion and the combination, or interaction, of this agent with CO is of specific interest in the cerebral vasculature because the combined effects of these agents may be one of the underlying causes of mental confusion, unconsciousness, or death in fire victims (Smith et al., 1976b).

Numerous experimental studies have shown that intoxication by cyanide compounds can lead to damage to the brains of rats, rabbits, cats, dogs, and monkeys (for reviews see Levine and Stypulkowski, 1959; Meyer, 1963; Brierly et al., 1976). Comatose states and deep depression of electrical activity have been observed in a variety of species following cyanide administration (Ward and Wheatley, 1947; Brierly, 1975). Cyanide appeared to selectively damage cerebral white matter (Smith et al., 1963; Levine, 1967), but it is unclear whether this neuropathology was due to direct effects of cyanide on the white matter, or if it was secondary to anoxia or ischemia. This neuropathology also may have been due to regionally inadequate cerebral circulation during cyanide hypoxia.

The action of cyanide on the cerebral vasculature and on $CMRO_2$ has not been studied in any great detail under controlled conditions. Differences in methods, animal species, dosages, failure to measure blood or tissue cyanides, lack of control in regard to other variables such as respiration and consequently CO_2, and difficulty in securing pure cerebral

venous samples, have led to some inconsistencies in observations and interpretations of cyanide and the cerebral circulation. This has been so for CO as well. McGinty (1929) observed an increase in the outflow from the sagittal sinus of anesthetized dogs following a small dose of sodium cyanide. Paulet (1958) observed an increase in cerebrospinal fluid pressure following a bolus injection of cyanide, and concluded that CBF must have increased. Studies in cats and rabbits showed large increases in blood flow through the sagittal sinus without any alteration in the arterio-venous O_2 content difference across the blood brain barrier (Russek et al., 1963). Russek observed an increase in $CMRO_2$ to 300% of control in these experiments. He concluded that stimulation of the carotid chemoreceptors caused the increase in $CMRO_2$ and that the increase in CBF was secondary to the metabolic change. Brierly et al. (1976) speculated that CBF decreased during cyanide administration due to cyanide's depressive effect on the myocardium. However, he never actually measured CBF, but rather he made speculations on CBF that were based upon vascular pressure changes in the sagittal sinus of monkeys. Aliukhin et al. (1974) also observed increases in CBF following acute cyanide poisoning in rats.

The cerebral metabolic response to cyanide has been studied *in vitro* and *in vivo*. McGinty (1929) observed an outpouring of lactic acid into the cerebral venous drainage during moderate cyanide intoxication, and this was the first indication of an altered cerebral aerobic metabolism in cyanide hypoxia. Fazekas et al. (1939) reported a decreased $CMRO_2$ in dogs following administration of potassium cyanide, however, these workers did not measure CBF. Doses of cyanide sufficient to decrease cerebral cytochrome oxidase activity by 50% in rats led to increases in lactate, inorganic phosphate, and triphosphate (Albaum et al., 1946). Olsen and Klein (1947) reported similar metabolic findings in rats and calculated that glucose consumption must have increased to account for the rise in lactic acid. They also discussed how the addition of cyanide to brain slices, *in vitro*, failed to decrease O_2 consumption until high cyanide levels were achieved. Gasteva and Raize (1975) demonstrated a reduction in $CMRO_2$ with cyanide.

Early studies of the combined effects of CO and cyanide were inconclusive in describing any interaction of these two agents (Hofer, 1926; Moss et al., 1951). Two inhalation toxicological studies have reported no interaction between CO and cyanide with respect to lethal-dose levels (Higgins et al., 1972; Yamamoto, 1976). Smith et al. (1976b) using

behavioral assessments reported at least an additive effect of cyanide and CO on the time to cause incapacitation and death in exercising rats. However, few studies have ever examined the combined effects of these agents on the cerebrovasculature. Pitt et al. (1979) examined individual and combined effects of cyanide and CO on CBF and $CMRO_2$ because many of the deleterious effects of the fire environment may be due to altered cerebral nervous system function. They found that CBF increases during CO hypoxia and it also increases with cyanide hypoxia. $CMRO_2$ remained unchanged until the higher levels of either cyanide or CO were reached. These data are consistent with those previously presented for CO. When CO and cyanide were administered simultaneously, CBF increased in an additive manner (Figure 10-12), but significant decreases in $CMRO_2$ occurred at the combination of the lower concentrations (Figure 10-13). These data suggest that CO and cyanide are physiologically additive in producing changes in CBF, but may act synergistically on $CMRO_2$.

Figure 10-14 (from Pitt et al., 1979) demonstrates the relationship between CBF and $CMRO_2$ (VEO_2) in CO and cyanide hypoxia. Three aspects of this figure suggest that cyanide and CO may act through similar mechanisms with respect to changes in CBF and $CMRO_2$. First, low doses of either agent alone produce increases in CBF that maintain $CMRO_2$ constant. Second, higher doses of CO or cyanide increase CBF to 200% of control while $CMRO_2$ decreased to around 80% of control. Finally, combinations of cyanide and CO hypoxia result in an increased CBF with a decreased $CMRO_2$ that would be predicted on the basis of an additive effect. Although CO binds to nonhemoglobin proteins, including cytochrome oxidase *in vitro*, it is unlikely that *in vivo* this binding contributes to the hypoxic effect of CO (Root, 1965). Because we demonstrated previously that the effect of CO hypoxia on the brain was similar to an equivalent reduction in arterial O_2 content with hypoxic hypoxia, it may be that the mechanism that mediates the increase in CBF to maintain $CMRO_2$ relatively constant with CO and hypoxic hypoxia, may be similarly affected by blocking cellular respiration with cyanide hypoxia. The nonspecificity of the hypoxic response suggests a common mechanism of cerebral vasodilation with hypoxia, and it lends support to a metabolic control of cerebral vessels although the precise mediator is unknown.

As Pitt et al. (1979) explains, there are several explanations for the loss of maintaining $CMRO_2$ constant when CBF increased to 200% of control, or more, for combinations of CO and cyanide hypoxia. First, it is possible that the cortical cells themselves were damaged by

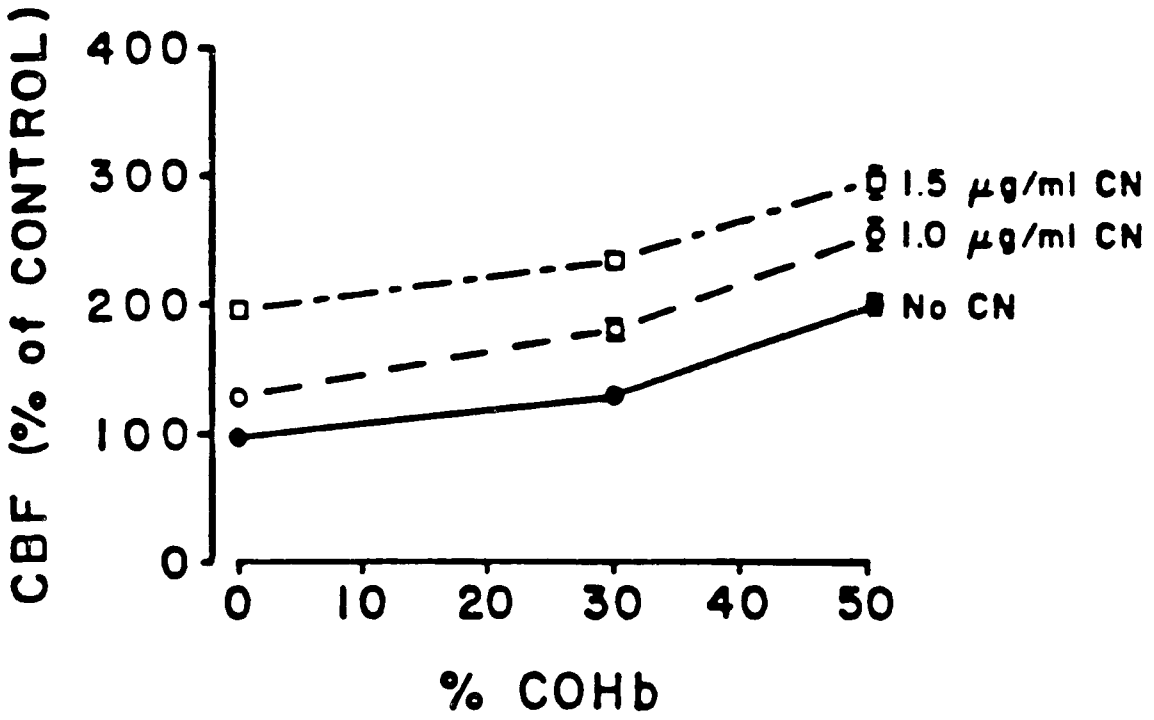

Figure 10-12. Effect of cyanide (CN) and CO hypoxia, alone and in combination, on cerebral blood flow. Each point represents mean ± SE. Closed circles = CO alone (19 animals); open circles = 1.0 μg/mL blood CN (12 animals); and open squares = 1.5 μg/mL blood CN (seven animals).

Source: Pitt et al. (1979).

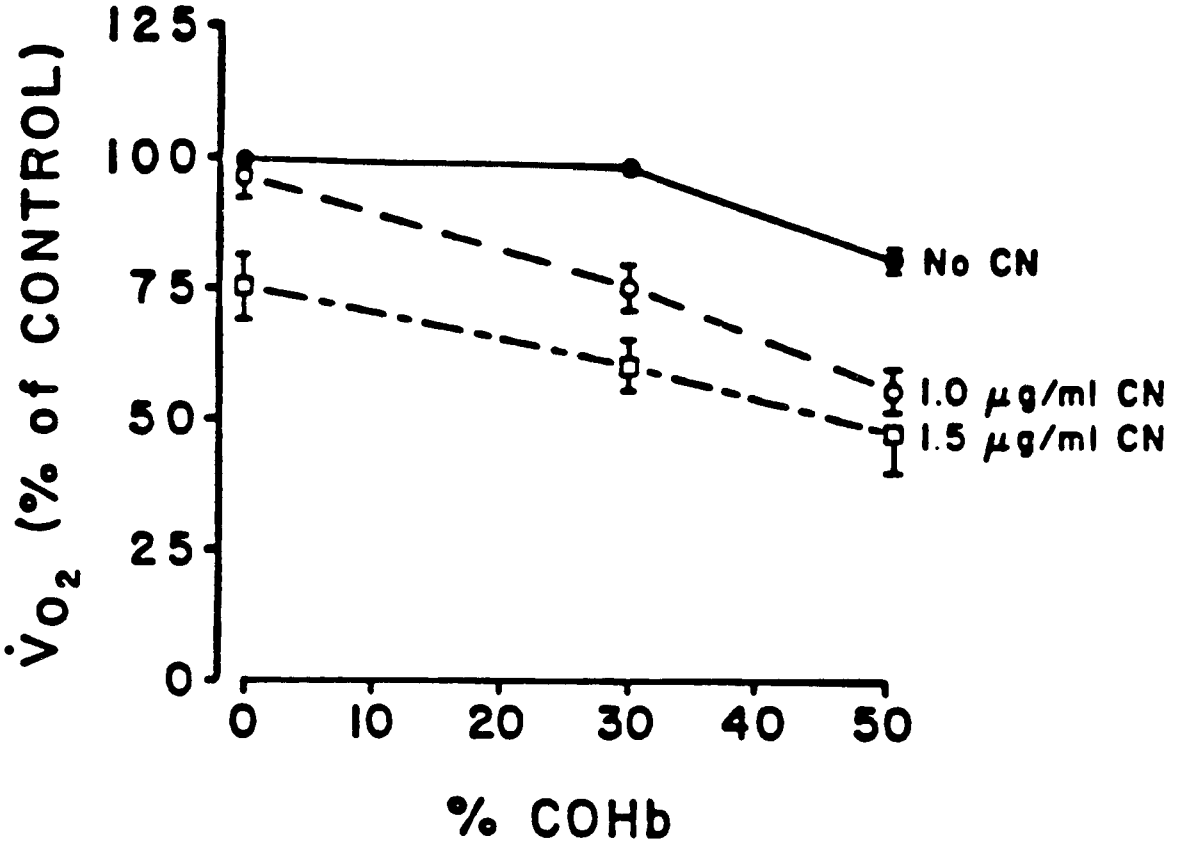

Figure 10-13. Effect of CN and CO hypoxia, alone and in combination, on cerebral oxygen consumption. Each point represents mean ± SE. Closed circles = CO alone (19 animals); open circles = 1.0 μg/mL blood CN (12 animals); and open squares = 1.5 μg/mL blood CN (seven animals).

Source: Pitt et al. (1979).

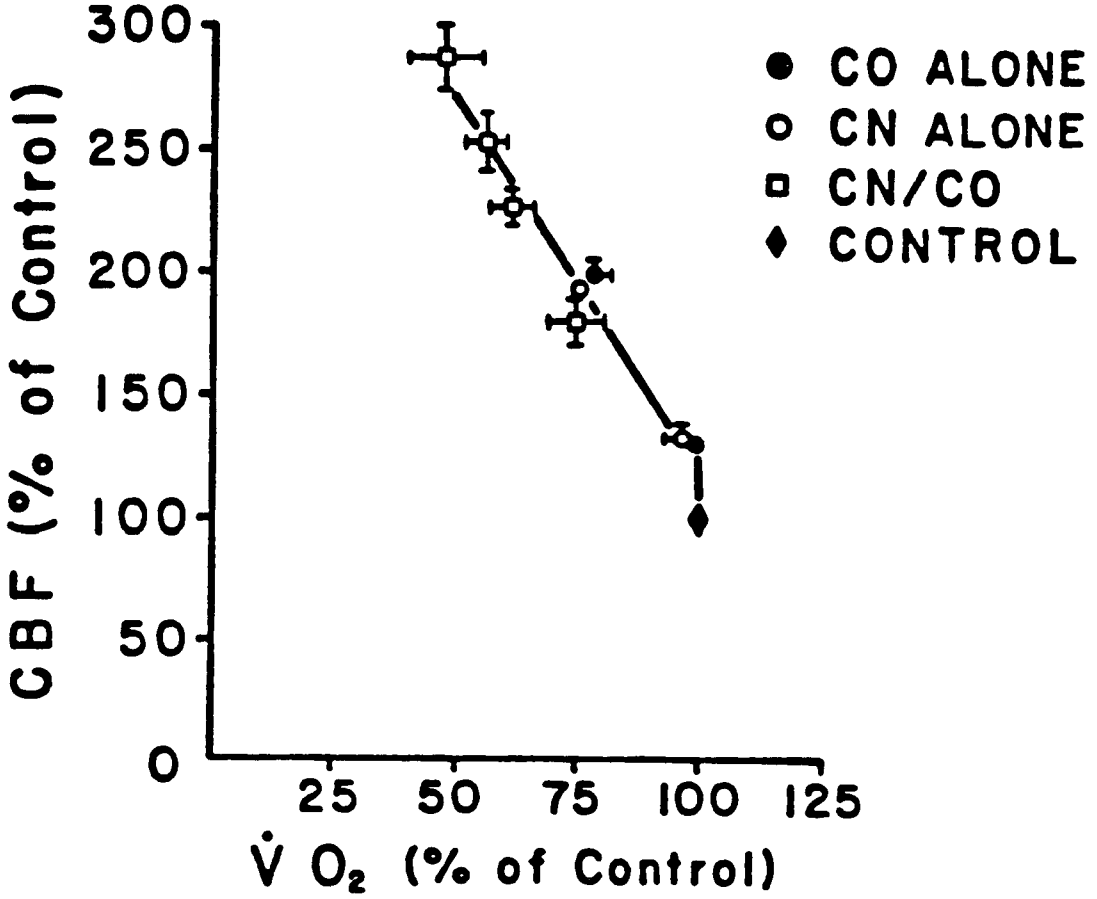

Figure 10-14. Relationship of CBF to cerebral O_2 consumption ($\dot{V}O_2$) during CN and CO hypoxia. The mean ± SEM of CBF (percent of control) and $\dot{V}O_2$ (percent of control) is plotted for the groups previously described. A straight line was fitted by regression for the effects of CO or CN alone, and extended up to a CBF of 300% of control.

Source: Pitt et al. (1979).

combination of cyanide and CO and were rendered incapable of utilizing the O_2 and substrate delivered. Because the observed physiological parameters returned to control when blood cyanide and COHb levels were returned to control, the cortical cell damage was temporary and reversible. Second, it is possible that within the brain, regional inequalities existed between the increase in CBF and the metabolic demands of the tissue. Third, it is possible that in severe hypoxia, although the energy state of the brain may be normal and CBF increases in an apparent adequate manner, a compensatory decrease in neuronal activity is produced (Duffy et al., 1972). Finally, a fourth mechanism of how cyanide and CO hypoxia could act to synergistically reduce $CMRO_2$ is based on the characteristics of the multi-enzyme cellular respiratory chain (Chance et al., 1970). Under normal metabolic conditions, cerebral mitochondrial respiration is zero order with respect to O_2, until mitochondrial arterial O_2 tension is less than 1 mmHg (Chance et al., 1962). During low levels of cyanide hypoxia, the abundance of cytochrome oxidase (Lubbers, 1968), the ability of unblocked respiratory chains to branch out and oxidize cyanide blocked chains, and the ability of a multi-enzyme system to maintain a constant electron flow for a wide range of steady-state changes in the terminal oxidase (Chance et al., 1970) enable the brain to maintain $CMRO_2$ constant by increasing CBF. However, further reduction in O_2 supply with the addition of CO result in a further reduction in the enzyme system.

10.4.1.6 Mechanism of Regulation of Cerebral Blood Flow in Hypoxia

Although it is clear that hypoxia produces cerebral vasodilation and an increase in CBF, the precise mechanism by which this occurs is not clear. Hypotheses to explain this mechanism include direct effects of O_2, neurogenic (which was referred to earlier in this chapter), and chemical or metabolic theories. Little evidence exists concerning the direct effects of O_2 on cerebral vessels, however, there is some evidence that O_2 may act directly on the smooth muscle of cerebral vessels, with a high O_2 tension leading to vasodilation. Garry (1928) showed that spirals of carotid artery of sheep contract with high O_2 tension. This response was confirmed later by Smith and Vane (1966) and Detar and Bohr (1968), and in addition, Detar and Bohr (1968) showed that isolated rabbit aortas dilated when perfused with blood or saline with low O_2 tension. The dependence of the contractile response to O_2 tension is explained if one assumes that O_2 plays a metabolic role within the mitochondria of smooth

muscle cells. It has been documented that the mechanical tension of some vascular smooth muscle is sensitive to altered O_2 tension (*in vitro*), however, Fitzman and Duling (1973) have calculated that arterioles 10 μm in diameter would be unaffected by O_2 tensions greater than 2 mmHg. They suggested that the large-artery *in vitro* experiments showing a direct relationship between smooth muscle tension and O_2 tension may be misleading because of the high O_2 consumption and large diffusion gradients of the strips. Coburn (1977) suggested the possibility that receptors sensitive to O_2 tension could exist in vascular smooth muscle but indicated that these receptors do not appear to work through a cytochrome a3-ATP model. Finally, in a study of pial vessels, *in vivo*, Kontos et al. (1978) demonstrated that local hypoxia, administered by application of cerebrospinal fluid containing no O_2 on the surface of the brain, produced only slight arteriolar vasodilation. This group postulated that the effects of hypoxia on cerebral arterioles is mediated via local mechanisms because the vasodilation was reversed completely by supplying O_2 via topical application of fluorocarbons to the brain surface.

Extracellular acidosis, secondary to cerebral lactate production, also has been suggested to be the mechanism of cerebral vasodilation with hypoxia (Betz, 1972; Skinhoj, 1966). Reducing the arterial O_2 tension to less than 50 mmHg increases CBF and the concentration of intracellular and extracellular cerebral lactate (Siesjo and Nilsson, 1971). Wahl et al. (1970) suggested that cerebral metabolic acidosis affects the cerebral vascular smooth muscle by altering pH within the cell. Kogure et al. (1970) reported that cerebral vasodilation with hypoxemia correlated well with cerebral cortical acidosis and concluded that hypoxia exerted its influence secondary to the formation of parenchymal lactate from anaerobic glycolysis. Other results, however, have challenged this hypothesis (Borgstrom et al., 1975; Nilsson et al., 1976; Norberg and Siesjo, 1975). These reports demonstrated that during the initial, rapid, nonsteady-state increases in CBF during hypoxia there is only a slight increase in lactate, or none at all. Also, this increase in CBF leads to a reduction in tissue CO_2 tension and a subsequent increase in pH. The actual measurements of cerebral parenchymal pH show a transient alkalotic shift of 0.02 pH units at a time when the CBF increase has reached its maximal level. Thus, Nilsson et al. (1976) concluded that the increased blood flow must be related to some aspect of cellular metabolism less sluggish than lactate formation.

The relationship between organ blood flow and the metabolism of that organ is an old physiologic issue (Pflüger, 1875), and a close relationship between CBF and metabolic by-products of the brain's interstitial fluid was proposed over a century ago (Gaskell, 1880; Roy and Brown, 1879). One such metabolic by-product, adenosine, has been proposed to be involved with metabolic increase in coronary blood flow (Rubio and Berne, 1969). Berne et al. (1974) postulated that some aspect of adenosine metabolism may be involved in the CBF increase with hypoxia. These investigators reported that brain adenosine levels increase rapidly (2 to 3 s) and this results in cerebral vasodilation with cerebral ischemia. Rubio et al. (1975) demonstrated that hypoxia increased brain adenosine levels markedly, and Winn et al. (1981) reported a 500% increase in brain adenosine levels within 30 s of hypoxia. In addition, Wahl and Kuschinsky (1976) showed that adenosine dilates pial arterioles when applied to the perivascular space. These alterations in adenosine levels with hypoxia, and the fact that adenosine causes cerebral vasodilation, support the potential role of adenosine as a chemical link between metabolism and CBF during hypoxia; however, Wahl and Kuschinsky (1979) point out the speculative nature of the role of this metabolite.

Other metabolic substrates, such as oxygenase, also may play a role in hypoxic vasodilation because oxygenase inhibitors can attenuate the increase in CBF that occurs with hypoxia (Traystman et al., 1981). Enzyme systems may play an important role in O_2 delivery to brain tissue through alterations in CBF (Harik et al., 1979; Jobsis and Rosenthal, 1978; Sokoloff, 1978). The precise nature and location of these oxygenases is unclear, although Traystman et al. (1981) suggested that these receptors for hypoxia are located close to the cerebrospinal fluid. The idea of a special O_2 sensor is not new. Opitz and Schneider (1950) proposed the existence of O_2 receptors in cerebral parenchyma. Other investigators (Bicher et al., 1973; Burgess and Bean, 1970; Mchedlishvili et al., 1976) hypothesized that tissue O_2 receptors participate in a neural feedback loop originating with cerebral tissue to produce cerebral dilation with hypoxia. The neurogenic aspects of cerebral circulatory control during hypoxia have been discussed earlier in this chapter, and to summarize briefly, the prevailing opinion is that the peripheral carotid and aortic chemoreceptors and baroreceptors probably are not involved in the CBF response to hypoxia. Central (brainstem) neurogenic mechanisms may be involved, however, much less is known about these control mechanisms than for the peripheral systems. The importance of the pons and mesencephalon in mediating the

increased CBF with hypercapnia has been demonstrated (Shalit et al., 1967). Other investigators also have demonstrated the potential involvement of higher brain centers in the regulation of CBF (Langfitt and Kassell, 1968; Molnar and Szanto, 1964; Stavraky, 1936), and it remains possible that these central neurogenic centers may be involved in the CBF response to hypoxia.

Carbon monoxide can compromise tissue oxygenation in three ways: a fall in arterial O_2 content, an increase in O_2Hb affinity, and theoretically, a direct cellular effect (Coburn, 1979). Arterial O_2 content falls as CO occupies O_2-binding sites, but when CO occupies binding sites, the O_2 affinity of the remaining sites increases (Paulson et al., 1973; Coburn, 1979; Roughton and Darling, 1944). As a result, cerebral venous O_2 tension, and presumably tissue O_2 tension, decrease. Both types of hypoxia, hypoxic and CO, produce essentially identical decreases in cerebral venous O_2 tension. This reduction in cerebral venous O_2 tension could be translated into an increased CBF via some of the mechanisms previously described (i.e., adenosine, O_2 receptors, neurogenic mechanisms, etc). Because arterial O_2 tension falls only with hypoxic hypoxia, one has difficulty in ascribing changes in CBF to alterations in arterial O_2 tension. In CO hypoxia, arterial O_2 content is reduced, not O_2 tension, thus one must consider the possibility of O_2 content-type receptors, which is unlikely. Another controversial potential effect of CO is an identifiable direct effect of CO on cellular metabolism. If the CO/O_2 tension ratio in the mitochondrion is sufficiently high, CO can combine with cytochrome a3 (Coburn, 1979). This would prevent oxidation at the terminal electron transport chain and would be equivalent to a lack of molecular O_2. Whether this potential mechanism operates *in vivo* is unclear at the present time.

10.4.1.7 Summary

The data reviewed indicate that CO hypoxia increases cerebral blood flow, even at very low exposure levels. Cerebral O_2 consumption is well maintained until levels of COHb reach upwards of 30%. The overall responses of the cerebrovasculature are similar in the fetus, newborn, and adult animal; however, the mechanism of the increase in cerebral blood flow is still unclear. In fact, several mechanisms working simultaneously to increase cerebral blood flow appear likely and these may involve metabolic and neural aspects as well as the O_2Hb dissociation curve, tissue O_2 levels, and even a histotoxic effect of CO. These potential

mechanisms of CO-induced alterations in the cerebral circulation need to be investigated further. The interaction of CO with cyanide (additive and synergistic) on the cerebral vasculature is clear, however the interaction of CO with other agents and their combined effects on brain blood vessels is unknown. This also is true for the long-term (chronic) effects of CO alone, or in combination with other agents in low- or high-dose levels on the cerebral vasculature. Finally, under normal circumstances the brain can increase its blood flow or its O_2 extraction in order to compensate for a reduced O_2 environment. Whether these compensatory mechanisms continue to operate successfully in a variety of conditions where the brain, or its vasculature are compromised (i.e., stroke, head injury, atherosclerosis, hypertension) is unknown and requires further investigation.

10.4.2 Behavioral Effects of Carbon Monoxide

10.4.2.1 Introduction

The following is an evaluative review of the literature concerning the behavioral and nervous system effects of elevated COHb. An effort was made to organize the findings by subject matter, devoting a section of the review to each of several subtopics. Such an organizational scheme is always arbitrary and therefore occasionally strained. The organization of the material is, however, a benefit which outweighs the disadvantages.

Extensive use is made of tables in each subtopic to help summarize the findings and give a critique of each study. For each published report the following information is given: duration of CO exposure, range of COHb achieved, number of subjects studied (n), the dependent variable studied, the authors' conclusions about effects, a comment about the features of the study, and technical critique notes.

The technical critique notes refer to technique problems that frequently exist in studies in the CO literature concerned with behavior. A critique code has been devised to facilitate reference to two of the most common problems - blinding and multiple statistical tests conducted on the same data base. The following paragraphs describe the problems and a table is given to define the codes used.

One of the features of a study is the so-called blinding of subjects and experimenters to the exposure conditions. To avoid the effects of suggestion and expectation on the part of the subject, the subject should not be informed about his own exposure condition until after the

completion of the study (i.e., the subject should be kept 'blind' regarding exposure. To avoid unintentional bias in the handling of subjects or making unintentional suggestions to the subjects, experimenters who deal directly with subjects also should be blind. All subjective scoring of data should be performed blindly. An experiment in which both subjects and experimenters were blind is called 'double blind.' When only subjects are blind, a single-blind condition is said to exist. When no blinding was used, the study will be called nonblind.

The other technical aspect of an experiment that was included in the summary tables involves the statistical significance test methodology that was employed. When many individual tests are conducted on the same data set the probability is increased that at least one of them will be significant by chance alone. Thus, the 'experiment-wise' Type I error rate is increased (Muller et al., 1984). Studies in which data were analyzed in the above manner will have an increased probability of reporting a significant effect even when no effect exists in the population. This bias toward significant effect worsens with the number of tests conducted. Statistical methods exist that can be used to test multiple hypotheses for each data set without increased probability of false significant effects.

The two technical problems, blinding and statistical methods, are noted in the summary tables by use of the following code letters in the column labeled 'Technical Critique.1' If nothing appears in the Technical Critique column, the experiment was conducted double-blind and multiple significance testing was not done. The following list defines the code.

A - No or unspecified statistical test

B - Multiple-significance tests on the same data set

C - Single-blind study

D - Nonblind study

Examination of the summary tables reveals that many of the same references appear repeatedly. These were instances in which the experimenters measured several variables in the same study. Thus, the reader should recognize that the number of experiments reported in the literature is considerably smaller than the number of summary table entries.

10.4.2.2 Sensory Effects

Vision

Absolute Threshold. Studies of the effects of COHb on absolute visual threshold are summarized in Table 10-9. In an experiment using four well-trained young subjects it was demonstrated that visual sensitivity was decreased in a dose-related manner by COHb levels of 4.5, 9.4, 15.8, and 19.7% (McFarland et al., 1944). Various aspects of these data were subsequently reported by Halperin et al. (1959) and McFarland (1970). COHb elevations were accomplished by inhalation of boluses of high-concentration CO. Visual thresholds were measured repeatedly over a five-minute period at each COHb level. Experimenters were not blind to the exposure conditions and the subjects could have easily deduced the conditions from the experimental design, because no air-only condition was included to control for the effects of the testing scheme itself. Data from only one typical subject were presented. Thresholds were measured at only one level of dark adaptation (0.002 foot candles).

The McFarland et al. (1944) study (above) stands in disagreement with several other studies of absolute threshold effects of COHb. An early study of dark adaptation was reported by Abramson and Heyman (1944) in which effects were inconsistent and not statistically significant. Nine subjects were tested and the COHb level ranged up to 30%. Documentation of the study was, however, very sparse so that it was difficult to consider the study critically but the power was apparently quite low. McFarland (1973), in a scantly documented article, reported that similar threshold shifts occurred at the end of a CO-exposure period (17% COHb) and an air-only session. Thus it is possible that the effects reported by McFarland et al. (1944) were due to fatigue or some other time-on-task related variable. Von Restorff and Hebisch (1988) found no dark adaptation effects on subjects with COHb levels ranging from 9 to 17%. Luria and McKay (1979) found no effect of 9% COHb on scotopic visual threshold.

The effect of 17% COHb (bolus administration, followed by maintenance CO level for 135 min) on the entire dark adaptation curve was studied by Hudnell and Benignus (1989) using 21 young men in a double-blind study. No difference between CO and air groups was observed. A power of 0.7 was calculated for the test employed so that the conclusions are reasonably defensible. From the above evidence, it appears that if COHb elevation affects visual sensitivity, it remains to be demonstrated.

TABLE 10-9. EFFECTS OF COHb ON ABSOLUTE VISUAL THRESHOLD

Exposure Duration, min	Elevated COHb Range %	n	CO Effect	Comment	Technical Critique[a]	Reference
?	10.0 - 30.0	9	No	Stimuli, methods not well specified. No statistics given. Only one subject at 10% COHb.	A,D	Abramson and Heyman (1944)
Bolus	17.0 +135	21	No	Power for McFarland-size effect was *ca.* 0.7. Entire dark adaptation curve was measured. Stimulus was 10.0 deg visual angle p31 phosphor CRT with neutral density filters.		Hudnell and Benignus (1989)
18	9.0	18	No	Measured only scotopic sensitivity.	B,C	Luria and McKay (1979)
0.5	4.5 - 19.7	4	Yes	No control group for air only. Only typical data for one subject. Tested only at adaptation to 0.002 ft candle. Effect was COHb-ordinal, beginning at *ca.* 5%.	A,C	McFarland et al. (1944); Halperin et al. (1959) McFarland (1970)
Various	6.0 - 17.0	27	No	Smokers and nonsmokers tested, n not given. Few methods, specifications, or statistics. Minutes of exposure (not given) adjusted to target COHb.	A,C	McFarland (1973)
Bolus	9.0 17.0 +60	5	No	Dependent variables were time to adaptation and sensitivity after adaptation.	C	Von Restorff and Hebisch (1988)

[a]Technical problems: A=No or unspecified statistical tests; B=Multiple-significance tests on the same data; C=Single-blind study; D=Nonblind study. If no technical problems are noted, the experiment was conducted under double-blind conditions and multiple-significance testing was not done.

Temporal Resolution. The temporal resolution of the visual system has been studied in the form of critical flicker fusion (CFF). In the CFF paradigm, subjects report the frequency at which light flashes begin to appear as a continuous light. Studies of the effects of COHb on CFF are summarized in Table 10-10.

Seppanen et al. (1977) reported dose-ordinal decreases of CFF for COHb values of *ca.* 4.0, 6.1, 8.4, 10.7, and 12.7%. The experiment was conducted with 22 healthy subjects whose age ranged from 20 to 62 yrs. COHb was induced by breathing high concentrations of CO from a Douglas bag. Subjects were blind as to the condition but apparently experimenters were informed. Appropriate controls for fatigue were included and the exposure levels were randomized.

A study was reported by Von Post-Lingen (1964) in which COHb levels ranged up to 23%. COHb was induced in 100 subjects by breathing CO-contaminated air from a spirometer for about seven minutes in a single-blind procedure. One group of subjects was given an injection of Evipan (sodium hexobarbitone, see Reynolds, 1982), a drug previously shown to have produced decreases in CFF only if patients had demonstrable brain damage. In the nondrug group, CFF was unaffected until *ca.* 14% COHb. In the drug group, however, effects began at COHb levels as low as 6% and were dose proportional up to the highest COHb value. When the drug + CO study was repeated in a small (n=15) double–blind replication, no effects were seen. The latter replication study was given only one paragraph in the report and thus it is not clear exactly what was done.

Beard and Grandstaff (1970) reported significant effects on CFF in an earlier study in which four subjects had been exposed to CO level of 50, 150, or 250 ppm for one hour. COHb was estimated to have reached 3.0, 5.0, and 7.5%, respectively, by the end of the exposure. Documentation was extremely sparse and with only four subjects, power was probably low. Even though the elevated COHb groups had decreased CFF, the results were not dose ordinal. There is a comparatively large literature published before the Seppanen et al. (1977) article, in which the effect of elevated COHb on CFF was tested. In none of the earlier studies was CFF found to be affected, even though much higher levels of COHb were tried. The studies and their maximum COHb levels were Fodor and Winneke (1972) - 7.5%, Guest et al. (1970) – 8.9%, Lilienthal and Fugitt (1946) - 15.4%, O'Donnell et al.

TABLE 10-10. EFFECTS OF COHb ON CRITICAL FLICKER FUSION

Exposure Duration, min	Elevated COHB Range %	n	CO Effect	Comment	Technical Critique[a]	Reference
60	1.8 - 6.7	4	Yes	Test specification, methods, and statistics not given. Effects disordinal in COHb. COHb estimated from breath sample.	A,D	Beard and Grandstaff (1970)
780	5.3[b]	12	No	Few test specifications, only brand name of test device. COHb estimated from exposure by original authors.	B,C	Fodor and Winneke (1972)
65	8.9	8	No	Tested with red neon lamp, 0.7 deg visual angle, viewed binocularly. Luminance not given.	B	Guest et al. (1970)
Bolus	12.0 - 17.0	5	No	Tested with neon lamp, 1 deg visual angle, viewed monocularly. Luminance not given. Minutes of exposure adjusted to target COHb.	A,D	Lilienthal and Fugitt (1946)
540	5.9 - 12.7	4	No	Tested with red light, 1.3 deg visual angle, viewed binocularly. Luminance not given. Tested in noisy environment after CO exposure during sleep.	B	O'Donnell et al. (1971a)
45	7.6 - 11.2	60	No	No specifications for CFF test.	B	Ramsey (1973)
30	5.0 - 12.7	22	Yes	Tested with white light, 5.8 deg visual angle, apparently viewed binocularly. Luminance = 50 lux. Effect was significant beginning at 5% COHb.	B,C	Seppanen et al. (1977)
5	7.5 - 17.5	17	No	Tested with red neon lamp, 1 deg visual angle viewed binocularly. Luminance not given.	B,C	Vollmer et al. (1946)

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TABLE 10-10 (cont'd). EFFECTS OF COHb ON CRITICAL FLICKER FUSION

Exposure Duration, min	Elevated COHB Range %	n	CO Effect	Comment	Technical Critique[a]	Reference
7	4.0 - 23.0	100	Yes	No effects in poorly described double-blind part of same study (n=15). Effects of COHb ordinal beginning at *ca.* 14% and at *ca.* 6% with Evipan drug challenge. Tested with green light, 2 deg visual angle. Intensity of light was adjusted to produce fusion, not frequency.	B,C	Von Post-Linqen (1964)
300	10.0[c]	18	No	Few test specifications, only brand name of test device.	A,C	Winneke (1974)

[a]Technical problems: A=No or unspecified statistical tests; B=Multiple-significance tests on the same data; C=Single-blind study; D=Nonblind study. If no technical problems are noted, the experiment was conducted under double-blind conditions and multiple-significance testing was not done.
[b]The original authors estimated COHb from expired air.
[c]COHb estimated from exposure by original authors.

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(1971a) - 12.7%, Ramsey (1973) -11.2%, Vollmer et al. (1946) - 17.5%, and Winneke (1974) - 10.0%. To be sure, there was much variation in size of the subject group, method, and experimental design among the above studies, but no pattern emerges as to why the Seppanen et al. (1977), Beard and Grandstaff (1970), and Von Post-Lingen (1964) studies found significant effects when the others did not. It is noteworthy that the studies reporting significant effects were all conducted in a single- or nonblind manner.

Miscellaneous Visual Functions. A number of researchers reported the results of experiments in which visual parameters other than absolute threshold or CFF were measured as part of a battery of tests. Many of these experiments studied a large group of subjects. Table 10-11 summarizes these studies.

Beard and Grandstaff (1970) reported a study in which four subjects were exposed to CO sufficient to produce estimated COHb levels of 3.0, 5.0, and 7.5%. The measurements made were CFF (see above), brightness-difference thresholds, visual acuity, and absolute threshold. Data for the latter variable were unreliable and not reported. Dose-related impairments in acuity and brightness-difference sensitivity were reported. The scant documentation of methods, plus the few subjects, make the results difficult to evaluate.

Five other reports of significant visual function effects by COHb elevation are extant. Two of the studies (Bender et al., 1972; and Fodor and Winneke, 1972) reported that tachistoscopic pattern detection was impaired by COHb levels of 7.3 and 5.3%, respectively. Weir et al. (1973), Ramsey (1972), and Salvatore (1974) reported that brightness discrimination was adversely affected by COHb levels of 6 to 20%.

Tests of visual function after COHb elevation conducted by other authors have been uniformly nonsignificant. Table 10-11 summarizes these data. Especially noteworthy are studies by Hudnell and Benignus (1989) and Stewart et al. (1972) both of which found no acuity effects as reported by Beard and Grandstaff (1970). Brightness discrimination was similarly not found to be affected (Ramsey, 1973), in contradiction with the reports of others. The latter study is especially interesting in that it represents a failure to replicate an earlier study by the same author (Ramsey, 1972). The first of the pair of studies by Ramsey was conducted in a single-blind manner, the second was double blind.

TABLE 10-11. EFFECTS OF COHb ON MISCELLANEOUS VISUAL FUNCTIONS

Exposure Duration, min	Elevated COHb Range %	n	Dependent Variable	CO Effect	Comment	Technical Critique[a]	Reference
60	1.8 - 6.7[b]	4	Brightness	Yes	Test specification, methods, and statistics not given. Effects and acuity disordinal in COHb (both variables). COHb estimated from breath sample.	A,D	Beard and Grandstaff (1970)
150	7.3[c]	42	Pattern	Yes	Pattern displayed for unspecified short time. COHb estimated from breath sample.	B,C	Bender et al. (1972)
780	5.3[c]	12	Pattern	Yes	Pattern displayed for 0.1 s. COHb estimated by original authors from exposure.	B,C	Fodor and Winneke (1972)
60	27.0 - 41.0	5	See comment	No	Tested detection of dim objects in glare and approach/recession comments of objects. No specifications or statistics given.	A,D	Forbes et al. (1937)
Bolus	17.0	21	Acuity and motion	No	Stimulus was ×× deg p 31 phosphor CRT. Tested both photopic + 135 and scotopic.		Hudnell and Benignus (1989)
Various	6.0 - 17.0	27	Peripheral vision %	No	Few methods, specifications, or statistics. Minutes of exposure (not given), adjusted to target COHb.	A,C	McFarland (1973)
45	5.0	20	Brightness and depth	Yes	No specification for tests. Only brightness discrimination affected.	B,C	Ramsey (1972)
45	7.6 - 11.2	60	Brightness and depth	No	No specifications for tests. Results did not support previous study by Ramsey (1972).	B	Ramsey (1973)
390	5.4	6	Brightness discrimination	Yes	None.	D	Salvatore (1974)
30	4.0 - 12.7	22	Perceptual speed	No	Test not well specified.	B,C	Seppanen et al. (1977)

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TABLE 10-11 (cont'd). EFFECTS OF COHb ON MISCELLANEOUS VISUAL FUNCTIONS

Exposure Duration, min	Elevated COHb Range %	n	Dependent Variable	CO Effect	Comment	Technical Critique[a]	Reference
Var up to 1440	Continuous distribution	11	See comment	No	Little documentation. Tested acuity, depth, color, and phoria using clinical instruments.	B	Stewart et al. (1970)
150-300	Continuous distribution up to 20.0	27	Defect detection	No	Subject inspected small parts. Not well specified.		Stewart et al. (1972)
5	7.5 - 17.5	17	Red field size	No	Tested with perimeter bar and red sample patch.	B,C	Vollmer et al. (1946)
90-120	2.0	15	Brightness discrimination	Yes	Tested intensity matching with red, green, and white.	B	Weir et al. (1973)
Bolus	5.6[c]	50	See comment	No	Poor documentation. Tested target detection in "dim" light, during glare, recovery after glare, and depth.	B	Wright et al. (1973)

[a]Technical problems: A=No or unspecified statistical tests; B=Multiple-significance tests on the same data; C=Single-blind study; D=Nonblind study. If no technical problems are noted, the experiment was conducted under double-blind conditions and multiple-significance testing was not done.
[b]Values of COHb were not reported by the original authors. Values given in the table were estimated by the present author using exposure parameters and the method of Coburn et al. (1965).
[c]The original authors estimated COHb from expired air.

The most thorough modern tests of visual function was performed by Hudnell and Benignus (1989) who tested absolute threshold (see above), acuity, and motion detection with COHb levels of 17% and found no effects due to COHb. The acuity and motion detection were tested at both scotopic and photopic levels.

It would appear that the results of studies of the effects of COHb elevation on miscellaneous visual function are not supportive of significant effects. Results that were significant in two studies (Beard and Grandstaff, 1970; Weir et al., 1973) were contradicted by other reports using relatively large groups of subjects. One author (Ramsey, 1972, 1973) failed to confirm his own findings.

Audition

Surprisingly little work has been done concerning the effects of COHb on auditory processes. Table 10-12 is a summary of the studies. Stewart et al. (1970) reported that the audiogram of subjects exposed to as high as 12.0% COHb was not affected. Haider et al. (1976) exposed subjects to a 105 dB, one-octave bandwidth random noise (center frequency of 2 kHz) for 15 min while COHb level was elevated to 13%. Under continued COHb elevation, the temporary threshold shifts (TTS) were measured after noise cessation. No effects of COHb on TTS was observed. Guest et al. (1970) tested the effects of elevated COHb (8.9%) on auditory flutter fusion and found no significant effect. The flutter fusion test is analogous to CFF in vision and was tested by having the subject judge the rate at which an interrupted white noise became apparently continuous. From these data it would appear that the functioning of the auditory system is not comparatively sensitive to COHb elevation, but little research has been done.

10.4.2.3 Motor and Sensorimotor Performance

Fine Motor Skills

Bender et al. (1972) found that manual dexterity and precision (Purdure pegboard) were impaired by 7% COHb. Winneke (1974) reported that hand steadiness was affected by 10% COHb, but no supportive statistical test was presented.

Similar motor functions were evaluated by a number of other investigators and found not to be affected, even at higher COHb levels. Table 10-13 summarizes the literature.

TABLE 10-12. EFFECTS OF COHb ON MISCELLANEOUS AUDITORY FUNCTIONS

Exposure Duration, min	Elevated COHb Range %	N	Dependent Variable	CO Effect	Comment	Technical Critique[a]	Reference
65	8.9	8	Flutter fusion	No	Auditory flutter fusion was measured by rapid interruption of white noise, varying frequency of interruption until continuous sound occurred.	B	Guest et al. (1970)
120 - 240	3.0 - 13.0	20	TTS	No	Measured temporary threshold shift after exposure to 105 dB noise.	A	Haider et al. (1976)
Var up to 480	Continuous distribution up to 12.0	11	Audiogram	No	Little documentation of procedure or results.	B	Stewart et al. (1970)

[a]Technical problems: A=No or unspecified statistical tests; B=Multiple-significance tests on the same data; C=Single-blind study; D=Nonblind study. If no technical problems are noted, the experiment was conducted under double-blind conditions and multiple-significance testing was not done.

TABLE 10-13. EFFECTS OF COHb ON FINE MOTOR SKILLS

Exposure Duration, min	Elevated COHb Range %	n	Dependent Variable	CO Effect	Comment	Technical Critique[a]	Reference
150	7.3[b]	42	Tapping and pegboard	Yes	Some aspect of each task declared affected. COHb estimated from breath sample.	B,C	Bender et al. (1972)
780	5.3[b]	12	Tapping, pegboard, and steadiness	No	COHb estimated by original authors from exposure.	B,C	Fodor and Winneke (1972)
150	5.5	16	Tapping	No	Tested tapping with and without simultaneous arithmetic task.	C	Mihevic et al. (1983)
180	3.0 - 12.4	9	Ataxia	No	No data above 6.6% COHb shown, only results of significance tests. Noisy environment.	B	O'Donnell (1971b)
30	4.0 - 12.7	22	Tapping	No	None.	B,C	Seppanen et al. (1977)
Var up to 480	Continuous distribution up to 12.0	11	See comments	No	Little documentation of procedure or results. Tested collar/pin, screw, Flanagan coordination, tapping, and hand steadiness.	B	Stewart et al. (1970)
Var up to 1440 up to 20.0	Continuous distribution	27	See comment	No	Tested collar/pin, spiral drawing, and hand steadiness.		Stewart et al. (1972)
5	7.5 - 17.5	17	Postural stability	No	Tested both eyes open and closed.	B,C	Vollmer et al. (1946)
300	10.0[b]	18	See comments	Yes	Tested tapping, steadiness, and Purdue hand precision. Only steadiness declared affected.	A,C	Winneke (1974)
90 - 120	20.0	15	See comment	No	Tested tapping, star tracing, and rail walking.	B	Weir et al. (1973)
Bolus	5.6[b]	50	Steadiness	No	None.	B	Wright et al. (1973)

[a]Technical problems: A=No or unspecified statistical tests; B=Multiple-significance tests on the same data; C=Single-blind study; D=Nonblind study. If no technical problems are noted, the experiment was conducted under double-blind conditions and multiple-significance testing was not done.
[b]Originial authors estimated COHb from expired air.

Vollmer et al. (1946) reported that 20% COHb did not affect postural stability. O'Donnell et al. (1971b) used the Pensacola Ataxia Battery to measure various aspects of locomotion and postural stability. Subjects with 6.6% COHb were not affected. Stewart et al. (1970, 1972) tested the ability of subjects to manipulate small parts using the Crawford collar and pin test and screw test, the AAA hand steadiness test and the Flanagan coordination test. COHb levels up to 15% had no effect on any of the measures. Two subjects were taken to 33% and 40% COHb, however, and in these subjects, the collar and pin performance was impaired and the subjects reported hand fatigue. Manual dexterity (Purdue Pegboard), rapid precision movement (Purdue hand precision), and static hand steadiness (pen in hole) and tapping tests were not affected by COHb levels of *ca.* 5.3% (Fodor and Winneke, 1972). Wright et al. (1973) reported that hand steadiness was not affected by COHb levels of 5.6%. Weir et al. (1973) found no effects of 14% COHb on tapping, star tracing, and rail walking. Mihevic et al. (1983) discovered no effect on tapping when the task was performed alone or simultaneously with an arithmetic task. Finally, Seppannen et al. (1977) demonstrated that tapping speed was unaffected by 12.7% COHb. Most of the above nonsignificant studies used a moderate-to-large number of subjects. The overwhelming evidence in the area of fine motor control indicates that COHb levels below *ca.* 20% (the highest level tested) do not produce effects.

Reaction Time

Table 10-14 summarizes the literature with respect to the effects of elevated COHb on reaction time. Of the 11 experiments that studied reaction time, only one reported a significant result (Weir et al., 1973), and that effect occurred only at 20% COHb. A number of the nonsignificant effects were from studies using a large number of subjects. The pervasive finding that COHb elevation does not affect reaction time is especially impressive because of the wide range of COHb levels employed (5.3 to 27.8%).

Tracking

Tracking is a special form of fine motor behavior and hand-eye coordination that requires a subject to either follow a moving target or compensate for a moving target's motion by manipulation of a lever, for example. The literature on tracking is summarized in

TABLE 10-14. EFFECTS OF COHb ON REACTION TIME

Exposure Duration, min	Elevated COHb Range %	n	Type	CO Effect	Comment	Technical Critique[a]	Reference
780	5.3	12	Simple and choice	No	COHb estimated by original authors from exposure.	B,C	Fodor and Winneke (1972)
60	27.0 - 41.0[b]	5	Simple	No	Brake-reaction time in auto simulator. No statistics given.	A,D	Forbes et al. (1937)
210	5.3	5	Choice	No	Both young (n=33) and elderly (n=22) subjects. Age for young: 22.8 years, and for old: 68.7 years.		Harbin et al. (1988)
18	9.0	18	Simple and choice	No	None.	B,C	Luria and McKay (1979)
Various	6.0 - 17.0	27	Choice	No	Few methods or statistics. Minutes of exposure (not given), adjusted to target COHb.	A,C	McFarland (1973)
45	5.0	20	Choice	No	None.	B,C	Ramsey (1972)
45	4.6 - 11.2	60	Choice	No	None.	B	Ramsey (1973)
20	7.6	7	Simple	No	Tested in auto simulator. Task was to press foot pedal as quickly as possible.	B,C	Rummo and Sarlanis (1974)
Var up to 480	Continuous distribution up to 12.0	11	Choice	No	None.	B	Stewart et al. (1970)
90 - 120	7.0 - 20.0	15-25	Choice	Yes	Effects were only seen in the 20% COHb group.	B	Weir et al. (1973)

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TABLE 10-14 (cont'd). EFFECTS OF COHb ON REACTION TIME

Exposure Duration, min	Elevated COHb Range %	n	Type	CO Effect	Comment	Technical Critique[a]	Reference
300	10.0[c]	18	Simple and choice	No	COHb estimated from exposure by original authors.	A,C	Winneke (1974)
Bolus	5.6[c]	50	Simple	No	None.	B	Wright et al. (1973)

[a]Technical problems: A=No or unspecified statistical tests; B=Multiple-significance tests on the same data; C=Single-blind study; D=Nonblind study. If no technical problems are noted, the experiment was conducted under double-blind conditions and multiple-significance testing was not done.
[b]Original authors estimated COHb from expired air.
[c]COHb estimated from exposure by original authors.

Table 10-15. Of the 11 studies on the topic, four reported significant effects and one of those found effects only at 20% COHb. The matter is more complicated, however, and the literature in the area offers some clues to the reasons for the diversity among the reports.

O'Donnell et al. (1971a,b) used critical instability compensatory tracking in which the task was to keep a meter needle centered. Simultaneous performance of detection tasks also was required in one of the studies. No effects were demonstrated for COHb levels of 12 to 13%. The critical instability tracking task also was used by Gliner et al. (1983) in conjunction with peripheral light detection. COHb levels up to 5.8% had no effect on performance. Pursuit rotor tracking also was reported to be unaffected at 5.3% COHB (Fodor and Winneke, 1972). Weir et al. (1973) reported that pursuit rotor performance was slightly affected beginning at 20% COHb. In a 1988 study, Bunnell and Horvath used a two-dimensional tracking task in which the stimulus was presented on a CRT and controlled with a joystick. No effect of COHb or exercise or combination of the two was seen for COHb levels up to 10.2%. Schaad et al. (1983) reported that pursuit and compensatory tracking were not affected by COHb of 20% even during simultaneous performance of monitoring tasks.

In a pair of careful studies of different design, Putz et al. (1976, 1979) studied compensatory tracking by having the subject try to keep a vertically moving spot in the center of an oscilloscope screen. The tracking was performed while simultaneously performing a light-brightness detection task. In both studies, tracking was significantly affected by COHb levels of 5%. The fact that both studies demonstrated significant results despite differences in experimental design lends credibility to the finding. Additional credibility was gained when the Putz et al. (1976) study was replicated with similar results by Benignus et al. (1987). The consistency of the compensatory tracking results in the Putz et al. (1976) protocol was not continued when Benignus et al. (1989a) attempted to demonstrate a dose-effect relationship using the same experimental design. In the latter study, independent groups were exposed to CO sufficient to produce COHb levels of control, 5, 12, and 17% COHb. CO was administered via Douglas bag breathing and then COHb was maintained by low-level CO in room air. A fifth group was exposed to CO in the chamber only and this group served as a positive control because it was treated in exactly the same ways as the subjects in Putz et al. (1976) and in Beningus et al. (1987). No significant effects were demonstrated on tracking in

TABLE 10-15. EFFECTS OF COHb ON TRACKING

Exposure Duration, min	Elevated COHb Range %	n	Type	CO Effect	Comment	Technical Critique[a]	Reference
240	8.2	22	Compensatory	Yes	CRT display with simultaneous monitoring, same task as Putz et al. (1976, 1979).		Benignus et al. (1987)
Bolus + 240	5.6 - 17.0	74	Compensatory	No	CRT display with simultaneous monitoring, same task as Putz et al. (1976, 1979).		Benignus et al. (1989a)
Bolus + 55	7.0 - 10.0	15	Compensatory	No	Two-dimensional tracking test performed for 9 min using CRT and joystick.	C	Bunnell and Horvath (1988)
780	5.3[b]	12	Pursuit rotor	No	COHb estimated from exposure by original authors.	B,C	Fodor and Winneke (1972)
150	5.8	15	Compensatory	No	Critical instability method using a line on a CRT screen.	C	Gliner et al. (1983)
540	5.9 - 12.7	4	Compensatory	No	Task was to keep meter needle centered while monitoring other meters and lights. Tested in noisy environment. CO exposure during sleep.	B	O'Donnell et al. (1971a)
180	3.0 - 12.4	9	Compensatory	No	Critical instability method using a meter needle centering. Noisy environment.	B	O'Donnell et al. (1971b)
240	3.0 - 5.1	30	Compensatory	Yes	CRT display with simultaneous monitoring. Significant at 5.1% COHb only.		Putz et al. (1976)
240	3.5 - 4.6	30	Compensatory	Yes	CRT display with simultaneous monitoring. Significant at 4.6% COHb only.		Putz et al. (1979)

TABLE 10-15 (cont'd). EFFECTS OF COHb ON TRACKING

Exposure Duration, min	Elevated COHb Range %	n	Type	CO Effect	Comment	Technical Critique[a]	Reference
270	20.0	10	Pursuit and compensatory	No	Light-monitoring and arithmetic tasks performed simultaneously.	B,D	Schaad et al. (1983)
90 - 120	7.0 - 20.0	15-25	Pursuit	Yes	No consistent effects until 20% COHb.	B	Weir et al. (1973)

[a]Technical problems: A=No or unspecified statistical tests; B=Multiple-significance tests on the same data; C=Single-blind study; D=Nonblind study. If no technical problems are noted, the experiment was conducted under double-blind conditions and multiple-significance testing was not done.
[b]Original authors estimated COHb from expired air.

any group. The means for the tracking error were elevated in a nearly dose-ordinal manner but not to a statistically significant extent.

At present there is no apparent reason for the lack of consistency among the reports of tracking performance. The largest study, with the widest dose range (Benignus et al., 1989a), appears to be the strongest indicator of no significant effects of COHb elevation. However, it is difficult to ignore the several other studies which were controlled well and did demonstrate significant effects. At this point the best summary seems to be that COHb elevation produces small decrements in tracking which are sometimes significant. The possible reasons for such high variability are unclear. Benignus et al. (1989b) discussed the issues in a speculative manner. The latter article will be reviewed later in the present document.

10.4.2.4 Vigilance

A dependent variable, which is possibly affected by elevated COHb, is the performance of extended, low-demand tasks characterized as vigilance tasks. Because of the low-demand characteristic of vigilance tasks, they are always of a single-task type. Table 10-16 is a summary of the literature on the subject. Of the eight reports, four reported significant effects. Despite the seemingly greater unanimity in this area, it is noteworthy that for each report of significant effects, there exists a failed attempt at direct replication.

Horvath et al. (1971) reported a significant vigilance effect at 6.6% COHb. A second study, conducted in the same laboratory (Christensen et al., 1977), failed to find significant effects of 4.8% COHb on the same task. To be sure, the second study used slightly lower COHb levels, but the means left no suggestion of an effect. Roche et al. (1981) reported that performance of the same task using bolus exposure to produce 5% COHb was not affected.

Fodor and Winneke (1972) reported a study in which 5.3% COHb significantly impaired performance of a vigilance task. The same task and protocol were tried again in the same laboratory (Winneke, 1974). In the replication attempt, no significant effects were found, even for COHb levels up to 10%.

Groll-Knapp et al. (1972) reported dose-related significant effects of COHb ranging from estimated values of 3 to 7.6%. Effects were large but apparently the study was not blind. Haider et al. (1976) reported similar effects at low COHb levels but not at higher levels. The authors have mentioned twice failures to replicate the results (Haider et al., 1976;

TABLE 10-16. EFFECTS OF COHb ON VIGILANCE

Exposure Duration, min	Elevated COHb Range %	n	Type	CO Effect	Comment	Technical Critique[a]	Reference
120	4.8	10	Light	No	None.		Christensen et al. (1977)
780	5.3[b]	12	White noise	Yes	Effect disordinal in COHb. COHb estimated from exposure by original authors.	B,C	Fodor and Winneke (1972)
120	3.0 - 7.6[b]	20	Tone	Yes	Effects were significant at 3% COHb and increased with dose.	A,D	Groll-Knapp et al. (1972)
210	6.0 - 12.0	20	Click	No	None.	B	Groll-Knapp et al. (1978)
120 - 240	3.0 - 13.0	20	Tone	Yes	Two experiments were reported, one gave effect at *ca.* 7.6% COHb and the other gave no effect at 13%. No data presented, only conclusions.	A	Haider et al. (1976)
135	2.3 - 6.6	15	Light	Yes	No effect at 2.3% COHb.	C	Horvath et al. (1971)
Bolus +60	5.0	18	Light	No	None.		Roche et al. (1981)
300	10.0[c]	18	White	No noise	COHb estimated from exposure by original authors.	A,C	Winneke (1974)

[a]Technical problems: A=No or unspecified statistical tests; B=Multiple-significance tests on the same data; C=Single-blind study; D=Nonblind study. If no technical problems are noted, the experiment was conducted under double-blind conditions and multiple-significance testing was not done.
[b]Original authors estimated COHb from expired air.
[c]COHb estimated from exposure by original authors.

Groll-Knapp et al., 1978). A similar experiment using a different stimulus failed to produce significant effects at 12% COHb (Groll-Knapp et al., 1978).

The fact that all replication attempts for each of the reported significant effects of COHb on vigilance have failed to verify the original reports is evidence for some unreliability or the operation of unknown and uncontrolled variables. That the non-verifications were conducted by the original researchers, as well as by others, makes the case for unreliability even more binding. If vigilance is affected by COHb elevation, a convincing demonstration remains to be made. Perhaps a case may be made for small effects similar to the argument advanced in Benignus et al. (1989b).

10.4.2.5 Miscellaneous Measures of Performance

Continuous Performance

Continuous performance is a category of behavior which is related to vigilance. The difference is that many tasks that are performed over a long period of time are more demanding and involve more than simple vigilance. Sometimes the continuous performance tasks are not performed for a sufficiently long period of time to involve decrements in vigilance or are interrupted too frequently. Table 10-17 is a summary of the literature regarding the effects of COHb on continuous performance.

Putz et al. (1976, 1979) reported that monitoring performed simultaneously with tracking was impaired at COHb values as low as 5%. In a replication attempt of the Putz et al. studies, Benignus et al. (1987) failed to find any effects of *ca.* 8% COHb. O'Donnell et al. (1971a) also failed to find effects of COHb on a monitoring task performed simultaneously with tracking. Schaad et al. (1983) found no effects on monitoring simultaneously with tracking even when COHb was 20%. Gliner et al. (1983) reported that signal detection was affected by 5.8% COHb when performed singly, but not when performed simultaneously with tracking. The latter results are in conflict with Putz et al. (1976, 1979).

Isogna and Warren (1984) reported that the total game score on the performance of a multi-task video game was reduced by COHb levels of 4.2%. Separate task scores were not collected. Schulte (1963) reported that letter, word, and color detection tasks were dose-ordinally impaired by COHb levels of as low as 5% and ranging up to 20%. Reported COHb

TABLE 10-17. EFFECTS OF COHb ON CONTINUOUS PERFORMANCE

Exposure Duration, min	Elevated COHb Range %	n	Type	CO Effect	Comment	Technical Critique[a]	Reference
240	8.2	22	Light	No	Light monitoring simultaneously with tracking.		Benignus et al. (1987)
200	4.6 - 12.6	52	Numeric display	No	Task was to detect numerals of unmatched parity in a series of three.		Benignus et al. (1977)
150	5.8	15	Light	Yes	Same task as Putz et al. (1976, 1979) but under one condition performed without tracking. Only the latter condition was affected.	C	Gliner et al. (1983)
120	2.1 - 4.2	9	Complex target detection	Yes	Video game. Targets tracked and "shot down."	C	Insogna and Warren (1984)
540	5.9 - 12.7	4	Meters and lights	No	Monitoring meters and lights while tracking.	B	O'Donnell et al. (1971a)
240	3.0 - 5.1	30	Light and tone tasks	Yes	Light monitoring simultaneously with tracking. Tone monitoring as separate task. Only light tasks affected. No effect at 3.0% COHb.		Putz et al. (1976)
240	3.5 - 4.6	30	Light and tone tasks	Yes	Light monitoring simultaneously with tracking. Tone monitoring as separate task. Both light and tone task affected. No effect at 3.5% COHb.		Putz et al. (1979)
270	20.0	10	Light monitoring	No	Peformed simultaneously with tracking.	B,D	Schaad et al. (1983)

TABLE 10-17 (cont'd). EFFECTS OF COHb ON CONTINUOUS PERFORMANCE

Exposure Duration, min	Elevated COHb Range %	n	Type	CO Effect	Comment	Technical Critique[a]	Reference
?	0 - 20.0	49	Letter, word, and color detection	Yes	COHb values larger than expected asymptotic value. All values affected even for low COHb.	B,C	Schulte (1963)

[a]Technical problems: A=No or unspecified statistical tests; B=Multiple-significance tests on the same data; C=Single-blind study; D=Nonblind study. If no technical problems are noted, the experiment was conducted under double-blind conditions and multiple-significance testing was not done.

levels were at considerable variance with values expected from the exposure parameters (Laties and Merigan, 1979). Benignus et al. (1977) reported that 8.2% COHb did not effect a numeric monitoring task.

Again, there is disturbing lack of replicability in the literature. The two most credible studies showing effects of COHb on continuous performance (Putz et al., 1976, 1979) were not verified by Benignus et al. (1987). In the latter study, the tracking effects of the Putz et al. work were verified. Similar studies of monitoring during tracking (O'Donnell et al., 1971a; Schaad et al., 1983; Gliner et al., 1983) also reported no effects of COHb, even with levels of up to 20%. It seems necessary to suspend judgment regarding the continuous performance results until further data and understanding are available. Perhaps the best judgment is to hypothesize small effects.

Time Estimation

In 1967 Beard and Wertheim reported that COHb produced a dose-related decrement in single-task time estimation accuracy beginning at 2.7%. Various versions of the same task were tested by others (see Table 10-18) with COHb levels ranging up to 20% without effects being demonstrated (Stewart et al., 1970, 1972, 1973b; O'Donnell et al., 1971b; Weir and Rockwell, 1973, Wright and Shephard, 1978b). An exact replication was conducted by Otto et al. (1979) which also did not find significant results. It seems safe to assume that time estimation is not affected by COHb elevation.

Cognitive Effects. Table 10-19 is a summary of the literature concerning the effects of COHb elevation on the performance of cognitive tasks. Five of the 11 experiments that have been reported found cognitive effects of COHb. Bender et al. (1972) reported effects of 7.3% COHb on a variety of tasks. Groll-Knapp et al. (1978) reported memory to be affected after exposure to CO during sleep (11% COHb), but a very similar study performed by the same group later found no effects of 10% COHb (Groll-Knapp et al., 1982). Arithmetic performance was affected slightly in a nondose-ordinal manner when a simultaneous tapping task was performed (Mihevic et al., 1983). Schulte (1963) reported a dose-ordinal effect on arithmetic performance beginning at 5% and ranging to 20% COHb. COHb levels in the latter study were at considerable variance with expected values from the exposure parameters (Laties and Merigan, 1979). Similar variables were tested by others, sometimes at higher

TABLE 10-18. EFFECTS OF COHb ON TIME ESTIMATION

Exposure Duration, min	Elevated COHb Range %	n	Type	CO Effect	Comment	Technical Critique[a]	Reference
120	2.7 - 12.5[b]	18	Duration discrimination	Yes	Effects were COHb ordinal beginning at *ca.* 2.7% COHb.	B,C	Beard and Wertheim (1967)
180	3.0 - 12.4	9	Duration and time	No	Tone duration discrimination and time interval estimation. Noisy environment.	B	O'Donnell et al. (1971b)
120	3.7 - 7.8	13	Duration discrimination	No	Replication of Beard and Wertheim (1967).		Otto et al. (1979)
Var up to 1440	Continuous distribution up to 12.0	11	Duration discrimination	No	Tone duration compared to light duration.	B	Stewart et al. (1970)
150 - 300	Continuous distribution up to 20.0	27	See comment	No	Used duration discrimination, time estimation, and Marquette test.		Stewart et al. (1972, 1973b)
90	20.0	15	Duration estimation	No	Various tone duration judgments were used.	B	Weir et al. (1973)
2	2.0 - 8.0[c]	13	Duration discrimination	No	Results of three experiments.	D	Wright and Shephard (1978b)

[a]Technical problems: A=No or unspecified statistical tests; B=Multiple-significance tests on the same data; C=Single-blind study; D=Nonblind study. If no technical problems are noted, the experiment was conducted under double-blind conditions and multiple-significance testing was not done.
[b]COHb values were not reported by the originial authors. Values given in the table were estimated by the present authors using exposure parameters and the method of Coburn et al. (1965).
[c]Original authors estimated COHb from expired air.

TABLE 10-19. EFFECTS OF COHb ON MISCELLANEOUS COGNITIVE TASKS

Exposure Duration, min	Elevated COHb Range %	n	Task	CO Effect	Comment	Technical Critique[a]	Reference
150 - 300	7.3[b]	42	Digit span, nonsense syllables, intelligence test	Yes	Some aspect of each declared affected. COHb estimated from breath sample.	B,C	Bender et al. (1972)
>55	7.0 - 10.0	15	Memory, stroop test, visual search, and arithmetic	Yes	Stroop test affected in nondose-ordinal manner. Visual search affected interactively by CO and exercise.	C	Bunnell and Horvath (1988)
210	6.0 - 12.0	20	Arithmetic, nonsense syllables, mood scale	No	None.	B	Groll-Knapp et al. (1978)
410	11.0[c]	10	Memory, mood	Yes	Only memory declared affected. Exposure during sleep.	B	Groll-Knapp et al. (1978)
480	10.0	20	Verbal learning and memory	No	Tested before and after exposure. Was exposed during sleep.	B	Groll-Knapp et al. (1982)
120 - 240	3.0 - 13.0	20	Attention, memory, arithmetic.	No	None.	A	Haider et al. (1976)
150	5.5	16	Arithmetic	Yes	Effect was present only during multiple-task performance and was not dose ordinal.	C	Mihevic et al. (1983)
540	5.9 - 12.7	4	Arithmetic	No	Tested in noisy environment.	B	O'Donnell et al. (1971a)
270	20.0	10	Arithmetic	No	Performed simultaneously with tracking.	B,D	Shaad et al. (1983)

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TABLE 10-19 (cont'd). EFFECTS OF COHb ON MISCELLANEOUS COGNITIVE TASKS

Exposure Duration, min	Elevated COHb Range %	n	Task	CO Effect	Comment	Technical Critique[a]	Reference
?	0.0 - 20.0	49	Arithmetic	Yes	COHb values larger than expected asymptotic value. Significant effects even at low COHb.	B,C	Schulte (1963)
150 - 300	Continuous	27	Arithmetic distribution up to 20.0	No	None.		Stewart et al. (1972)

[a]A=No or unspecified statistical tests; B=Multiple-significance tests on the same data; C=Single-blind study; D=Nonblind study.
[b]Original authors estimated COHb from expired air.
[c]Original authors estimated COHb via Coburn, Forster, and Kane equation.

levels of COHb and with relatively large groups of subjects, without finding effects (O'Donnell et al., 1971a; Stewart et al., 1972; Haider et al., 1976; Groll-Knapp et al., 1978; Schaad et al., 1983). The conclusions are, at best, equivocal.

A recent study by Bunnell and Horvath (1988) utilized a wide range of cognitive effects involving short-term memory, manikin rotation, stroop word-color tests, visual search, and arithmetic problems (the latter as part of a divided attention task performed simultaneously with tracking). COHb was formed by bag breathing followed by a CO level in room air designed to maintain a constant COHb level. Subjects were exercised at either 0, 35, or 60% of $\dot{V}O_2$ max before cognitive tests were performed. The stroop test performance was slightly but significantly affected by either 7 or 10% COHb by the same amount but exercise had no effect. The authors suggested that negative transfer effects (difficultly in reversing instructional sets) were responsible for the decrement. Visual searching improved for both COHb levels at rest and at medium exercise. At the high exercise level, however, COHb produced dose-ordinal impairments in performance. The authors conjectured that hypoxic depression of cortical function interacted with hypoxic stress and exercise stress to produce the effects.

Most of the data on cognitive effects of COHb elevation are not sufficiently consistent to consider. The study by Bunnell and Horvath (1988), however, is suggestive of potentially important effects of interactions of COHb and exercise. Before any conclusions may be drawn about the results, the study must be expanded to unravel the mechanisms by which the interactions were produced.

10.4.2.6 Automobile Driving

Complex behavior, in the form of automobile driving, has been tested a number of times for effects of COHb elevation. Not only is automobile driving potentially more sensitive to disruption because of its complexity, but it is an inherently interesting variable because of its direct applicability to nonlaboratory situations. The well-practiced nature of the behavior, on the other hand, may make performances more resistant to disruption. The complexity of the behavior also leads to methodological difficulties. To exhaustively measure the complex behaviors usually leads investigators to measure many dependent variables. Statistically

analyzing a large number of variables in a defensible way requires many subjects and leads to greater expense.

Table 10-20 is a summary of the studies of automobile driving as affected by COHb. In an early study by Forbes et al. (1937), using only five subjects, steering accuracy in a simulator was investigated with COHb levels of up to 27.8%. No effects were demonstrated. A sparsely documented experiment by Wright et al. (1973), using 50 subjects with 5.6% COHb, tested a number of functions of simulator performance but found no effects. Weir et al. (1973) performed an experiment with actual automobile driving on a highway in which a great number of variables were measured and tested. None of the variables were reliably affected until COHb exceeded *ca.* 20%. Wright and Shephard (1978a) failed to find effects of 7% COHb on driving. In the latter study, the authors reported effects but only after misapplication of the chi-square test. The only effect of COHb on driving at a lower level (7.6%) was reported by Rummo and Sarlanis (1974), who found that the ability to follow another car at a fixed distance was impaired.

The difference between the experiments of Rummo and Sarlanis (1974) and Weir et al. (1973) is troubling. Both measured following distance but only the experiment employing the lower-level COHb found effects. If automobile driving is affected by COHb elevation, it remains to be demonstrated in a conclusive manner.

10.4.2.7 Brain Electrical Activity

Electrical activity of the brain (see review by Benignus, 1984) offers the possibility of testing the effects of COHb without the problem of selecting the most sensitive behavioral dependent variable. It is less dependent upon subject cooperation and effort and may be a more general screening method. The major disadvantage of the measures is the lack of functional interpretability. The area has been plagued with poor quantification and, frequently, a lack of statistical significance testing.

The electroencephalogram (EEG) is a recording of the continuous voltage fluctuations emitted by the intact brain. The slow-evoked potential originally called the contingent negative variation (CNV) is computed by averaging over trials and was linked to (among other things) cognitive processes or expectancy (Donchin et al., 1977). The evoked potential (EP) is the electrical activity in the brain resulting from sensory stimulation, either auditory

TABLE 10-20. EFFECTS OF COHb ON AUTOMOBILE DRIVING TASKS

Exposure Duration, min	Elevated COHb Range %	n	Task	CO Effect	Comment	Technical Critique[a]	Reference
60	27.0 - 41.0	5	Steering accuracy	No	In auto simulator (unspecified).	A,D	Forbes et al. (1937)
20	7.6	7	Steering wheel reversals and following distance	Yes	Only following distance was affected. Tested in auto simulator.	B,C	Rummo and Sarlanis (1974)
90 - 120	7.0 - 20.0	12	See comments	Yes	Instrumented automobile driven on highway. Many measures of control functions plus measures of driving stability and information processing load were utilized. The latter was affected at 20% but not reliably below that. Authors debated functional importance of findings.	B	Weir et al. (1973)
Bolus	5.6[b]	50	See comment	No	Poor documentation. Tested automobile simulator performance--brake, accelerator, steering, and signals.	B	Wright et al. (1973)
Bolus	7.0	10	Brake-reaction time	No	None.	C	Wright and Shephard (1978a)

[a]Technical problems: A=No or unspecified statistical tests; B=Multiple-significance tests on the same data; C=Single-blind study; D=Nonblind study. If no technical problems are noted, the experiment was conducted under double-blind conditions and multiple-significance testing was not done.
[b]Original authors estimated COHb from expired air.

(AEP) or visual (VEP). EEG, CNV, and EPs have been studied with COHb elevation. Table 10-21 is a summary of results from these studies.

Groll-Knapp et al. (1972) reported that the CNV was decreased in amplitude in a dose-related manner for COHb values ranging from 3 to 7.6%. In a second study, Groll-Knapp et al. (1978) again reported that CNV amplitude was reduced by 12% COHb when subjects missed a signal in a vigilance task. More evidence is required before the functional significance of such an effect can be deduced but it is a potentially important finding.

Clinical EEGs were analyzed by visual inspection by Stewart et al. (1970, 1973a) and Hosko (1970) after exposure to sufficient CO to produce COHb levels ranging up to 33%. No effects were noticed. Groll-Knapp et al. (1978) reported similar results using spectrum analysis on EEGs from subjects with 12% COHb. Haider et al. (1976) reported slight changes in the EEG spectrum for COHb levels of 13%, but no tests of significance were conducted. In view of the above studies, it seems reasonable to assume that no EEG effects of COHb levels below at least 10% should be expected.

O'Donnell et al. (1971b) reported that sleep stages (as determined from the EEG) were not distributed by COHb levels up to 12.4%. Groll-Knapp et al. (1978) and Haider et al. (1976), however, both reported distributed sleep stages at similar COHb levels using EEG spectra. Groll-Knapp et al. (1982) repeated their earlier study and found essentially the same effects.

The VEP was consistently not affected by COHb elevation below *ca.* 22% and usually the lowest level for effects was higher (see Table 10-21). At higher levels the effects were dose-related (Dyer and Annau, 1977; Stewart et al., 1970; Hosko, 1970). The above is true for both rats and man.

A single study of visual electrophysiology has reported low-level effects of COHb (Ingenito and Durlacher, 1979). The electroretinogram (ERG) of anesthetized cats was reported to have exhibited a reduced β-wave amplitude beginning at 7.5%. Effects were dose-ordinal up to 42% COHb. The contribution of the anesthesia (chloralose) to the effect as a possible potentiator of COHb effects was not tested in the study. The authors reported that the effect outlasted the COHb elevation and possibly was due to direct cellular CO toxicity.

TABLE 10-21. EFFECTS OF COHb ON BRAIN ELECTRICAL ACTIVITY

Exposure Duration, min	Elevated COHb Range %	n	Dependent Variable	Species	CO Effect	Comment	Technical Critique[a]	Reference
120	6.0 - 55.0	15	VEP	Rat	Yes	First significant effect increased amplitude at 22% COHb in cortex (at 38% in superior colliculus). Changes were dose related.		Dyer and Annau (1977)
Injection	10.0 - 75.0	10	Tone AEP	Rat	Yes	COHb-ordinal effects beginning at *ca.* 45% in rat. Small effect possible near 25% when CO was injected ip.		Fechter et al. (1987)
120	3.0 - 17.6[b]	20	CNV	Human	Yes	Significant differences at all COHb levels above endogenous.	A,D	Groll-Knapp et al. (1972)
210	6.0 - 12.0	20	VEP, click AEP, CNV, and EEG spectra	Human	Yes	CNV only declared affected. No data given, only conclusions stated.	B	Groll-Knapp et al. (1978)
410	11.0	10	Click, AEP, and EEG sleep stages	Human	Yes	Both affected.	B	Groll-Knapp et al. (1978)
480	10.0	20	EEG sleep stages	Human	Yes	Same conclusions as Groll-Knapp et al. (1978)	B	Groll-Knapp et al. (1982)
420	12.0	20	Sleep stages and EEG spectra	Human	Yes	Both changed slightly (no significance test).	A	Haider et al. (1976)
210	5.3	55	VEP	Human	No	Both young (n = 33) and elderly (n = 22) were tested. Mean age for young: 22.8, and for old: 68.7.		Harbin et al. (1988)
120	7.5 - 42.0	6	ERG	Cat	Yes	Decreased β-wave amplitude. Dose-related effect beginning at 7.5% COHb.		Ingenito and Durlacher (1979)

TABLE 10-21 (cont'd). EFFECTS OF COHb ON BRAIN ELECTRICAL ACTIVITY

Exposure Duration, min	Elevated COHb Range %	n	Dependent Variable	Species	CO Effect	Comment	Technical Critique[a]	Reference
18	9.0	18	VEP	Human	No	None.	B,C	Luria and McKay (1974)
180	3.0 - 12.4	9	Sleep stages	Human	No	No data above 6.6% COHb shown only results of signficance tests. Noisy environment.	B	O'Donnell et al. (1971b)
Var up to 1440	Continuous distribution up to 33.0	11	VEP and EEG	Human	Yes	No effects until COHb *ca.* 21%. Only 2 subjects were tested in the high range. Effect was an increased amplitude of peaks N1, P2, and N2. No statistical tests.	B	Stewart et al. (1970); Hosko (1970)
Var (<10)	3.2 - 15.2	6	VEP and EEG	Human	No	None.	B,D	Stewart et al. (1973a)
240	3.0 - 5.1	30	Tone AEP	Human	Yes	p-p Amplitude of N1-P1 peak increased in COHb-ordinal manner beginning at 3%.		Putz et al. (1976)
120	7.0 - 62.0[c]	6	VEP	Rat	Yes	Increased amplitude at both cortex and superior colliculus at 62% COHb. Late component amplitude decreased at 7% COHb in superior colliculus. No statistics, only typical data given.		Xintaras et al. (1966)

[a]Technical problems: A=No or unspecified statistical tests; B=Multiple-significance tests on the same data; C=Single-blind study; D=Nonblind study. If no technical problems are noted, the experiment was conducted under double-blind conditions and multiple-significance testing was not done.
[b]COHb was estimated by comparison to a separate series of animals.
[c]COHb was estimated from exposure by published data (Montgomery and Rubin, 1971) by present author.

Groll-Knapp et al. (1978) found no effect of COHb (8.6%) on auditory (click)-evoked potentials during waking, but reported increased positive-peak amplitudes when subjects were tested during sleep at *ca.* 11% COHb. The finding was verified by Groll-Knapp et al. (1982). The fact that the data were collected during sleep is potentially important.

Putz et al. (1976) conducted a double-blind study in which 30 persons were exposed to 70 ppm CO for 240 min (5% COHb at the end of the session). Among other variables, the auditory-evoked potential was measured. The peak-to-peak amplitude of the N1-P1 components was increased in a dose-ordinal manner beginning at *ca.* 3% COHb.

Ten millisecond tone bursts were used by Fechter et al. (1987) to produce AEPs in rats exposed to graded doses of injected CO. COHb levels ranged up to 75%. Slight evaluations of the mean threshold began at about 25% COHb. Effects were first seen at higher frequencies. All effects were reversible. During the exposure, normal body temperature was maintained to avoid hypothermia (Annau and Dyer, 1977).

Many of the brain electrical activity measures seem to be altered by COHb elevation. The functional significance of these changes is not clear. Sometimes an alteration is not an indication of a deleterious effect but merely implies some change in processing. When induced by low levels of COHb, however, any change should be viewed as potentially serious.

10.4.2.8 Schedule-Controlled Behavior

Because of the high levels of COHb that can be employed in studies of laboratory animals, using schedule-controlled behavior, effects of COHb are reported in all articles on the subject. Table 10-22 is a summary of the literature. There are a number of problems with the published literature, however, as seen in Table 10-22. Only a few investigators measured COHb; instead, they simply specified the exposure parameters. Another problem is that of hypothermia, which occurs in rats when COHb levels rise (Annau and Dyer, 1977; Mullin and Krivanek, 1982). If hypothermia develops as a consequence of COHb elevation, behavioral effects may be secondary to the hypothermia, not the COHb directly. None of the experimenters attempted to control for hypothermia effects. Thus behavioral effects of COHb may be overestimated in the rat.

TABLE 10-22. EFFECTS OF COHb ON SCHEDULE-CONTROLLED BEHAVIOR

Exposure Duration, min	Elevated COHb Range %	n	Scheds.	Species	CO Effect	Comment	Reference
120	9.0 - 58.0[a]	5	CRF	Rat	Yes	Rates fell inversely at COHb beginning at *ca.*20%	Annau (1975)
1,440	9.0 - 58.8[a]	8	Body weight	Rat	Yes	Weight fell inversely at COHb beginning at 22%. Food and water consumption also fell.	Annau (1975)
75	35.0 - 55.0[a]	15	MULT combinations of FI3 and FR30	Rat	Yes	Rates fell inversely at COHb beginning between 32 and 48% for schedules.	Ator (1982)
90	8.0 - 54.0[a]	4	DRL21	Rat	Yes	Rates fell inversely at COHb beginning at *ca.* 37%. Temporal discrimination was undisturbed.	Ator et al. (1976)
48	15.0 - 55.0[a]	?	FI3, FR25 VI25, VR15 VR25, DRL	Rat	Yes	Effects were COHb ordinal beginning at *ca.* 14%. DRL was affected at COHb < 1%. Methods were poorly described	Beard and Wertheim (1967)
Injection	9.0 - 58.0	22	CRF brain stimulation	Rat	Yes	CO was injected ip. Effects were first noted near 45% COHb.	Fountain et al. (1986)
240	12.2 - 54.9	6	Behavioral screen	Rat	Yes	Behavioral screen included reflexes, grasping, and conditioned avoidance. Lowest level effect was on conditioned avoidance at 12.2%. COHb levels measured by authors were much lower than predicted from data of Montgomery and Rubin (1971).	Mullin and Krivanek (1982)
30	Continuous distribution up to 32.0	3	Appetitive shuttling	Monkey	Yes	Shuttling velocity decreased as COHb beginning at 16 - 22%.	Purser and Berrill (1983)
90	34.0 - 53.0	3	MULT FR 30, DRL 18	Rat	Yes	Rates fell beginning *ca.* 45% COHb.	Schrot and Thomas (1986)
90	40.0 - 66.0	3	Multiple sequential responses	Rat	Yes	Rats repeated relearned response chain after extinction. More time to relearn was required beginning *ca.* 50% COHb.	Schrot et al. (1984)
Variable	15.0 - 40.0[a]	4	FCN	Rat	Yes	Rates fell inversely at COHb beginning between 20 and 28%	Smith et al. (1976a)

[a]COHb was estimated from exposure by published data (Montgomery and Rubin, 1971) by present author.

The level of COHb may be estimated for studies in which it was not given by use of the data from Montgomery and Rubin (1971). The latter-published normative curves can be used for such estimates. Schrot and Thomas (1986) and Schrot et al. (1984) have published corroborating curves. For all rat studies in which COHb was not measured, the present reviewer estimated the levels from exposure parameters.

With one exception (Mullin and Krivanek, 1982), effects of COHb did not occur on schedule-controlled behavior until COHb exceeded *ca.* 20%. In some studies no effect was observed until even higher levels. It is possible, however, that a number of the studies were insensitive because of the small numbers of subjects employed. In the study by Mullin and Krivanek (1982), it was reported that conditioned-avoidance behavior was affected at COHb levels as low as 12.2%. The COHb level reported in the latter study is, however, about half of the value that would be estimated from the Montgomery and Rubin (1971) data. It seems likely that either exposure or COHb values were erroneous in the report. If the exposure data were correct, the effects threshold would fit the other data in the literature. It thus appears that COHb does not affect schedule-controlled data in laboratory animals until levels exceed 20%.

When there were frank effects on schedule-controlled behavior, they seemed all to be in the direction of a slowing of rate or speed of response. Schedule-produced patterns of behavior were not disrupted, in general. Thus, it appears that the effect of elevated COHb is on some general aspect of behavioral control having to do with the rate of processing.

10.4.2.9 Summary and Discussion of Behavioral Literature

The literature regarding the effects of COHb on behavior, as seen in the above review, does not allow clear-cut conclusions. Results of studies frequently were not replicable or were not supported by related studies. In this section an attempt will be made to discover what, if any, general conclusions can be made.

Analysis of Technical Problems

It is possible that the many technical problems that were noted in the summary tables in the 'technical critique' column may account for some of the lack of agreement among experimental results. In the following analysis, tabulations were made of all of the studies in which

either blinding or statistical analysis problems occurred. Studies were cast into 2 × 2 tables according to the presence or absence of a particular condition and according to the occurrence (or not) of a COHb effect. If multiple-dependent variables were measured in a particular experiment, that experiment was tallied as having reported a significant effect if any one or more of the variables was reported as affected. A study was tallied as having reported a significant effect only if the effect occurred below 10% COHb to avoid the inclusion of frank effects that will occur if COHb is made sufficiently high. All studies were included, regardless of what dependent variables were studied. Only human studies were included. To decide whether the technical problem in question can be inferred to have influenced the results, a Fisher's exact test was conducted on each table. Two such tests were conducted; therefore, the alpha level selected for each test was 0.05/2 or 0.025. Given signficant results, exploratory tests also were conducted.

Table 10-23 is a tabulation of studies according to their blinding practices. Non-blind and single-blind studies were pooled because of the few non-blind studies. The Fisher test yielded significant results, $p = 0.0154$. It is impressive that the rate of reported COHb effects was about 2.24 times as high for studies not using a double-blind design. When the five non-blind studies were dropped and the data reanalyzed in an exploratory manner, the rate of finding significant effects for single-blind studies was 2.275 times as high as for double-blind studies ($p = 0.0172$).

TABLE 10-23. EFFECT OF BLIND CONDITIONS

	Non-Double Blind	Double Blind
Effects	16	6
No Effects	9	15

Fisher's exact test, $p = 0.0154$.

Table 10-24 is a tabulation of studies according to the employment of multiple-significance tests on the same data set. The Fisher test was not significant (p = 0.221).

TABLE 10-24. EFFECT OF STATISTICAL METHODOLOGY

	Multiple-Significance Test Methods	Conservative-Significance Test Methods
Effects	13	9
No Effects	13	11

Fisher's exact test, p = 0.221.

From the above analyses it may be concluded that studies that were not conducted in a double-blind manner tend to demonstrate more apparent COHb effects. It may be argued that the bias thus introduced into the study is added to whatever COHb effect may be present. No evidence was demonstrated, however, for the hypothesis that multiple statistical tests tended to produce an inflated Type I experiment-wise error rate.

Evaluation of the Literature

In the evaluation of the literature on the behavioral effects of COHb it is not clear how to treat the results from studies not conducted in a double-blind manner. Although they are biased toward reporting COHb effects, they clearly contain useful information. In the following summary, results from double-blind studies will be tabulated separately from results of studies not conducted in a double-blind manner.

Table 10-25 summarizes literature on the behavioral effects of COHb. Both double-blind and non-double-blind studies are tabulated. For each family of dependent variables, the table gives the number of studies in the double-blind and non-double-blind categories. Finally, the proportion of studies reporting a COHb effect, p(E), is given for both double-blind and non-double-blind studies. Several conclusions may be drawn from Table 10-25.

TABLE 10-25. PROBABILITY OF EFFECTS OF COHb[a]

Dependent Variable	Non-Double Blind (n)	Double Blind (n)	Non-Double Blind, p(E)	Double Blind p(E)
Absolute visual threshold	4	1	.20	.00
Critical flicker fusion	7	3	.33	.00
Misc. visual functions	9	5	.55	.00
Misc. auditory functions	0	3	N/A	.00
Fine motor skills	6	4	.33	.00
Reaction time	7	5	.00	.00
Tracking	4	7	.00	.43
Vigilance	4	4	.75	.25
Continuous performance	4	5	.75	.40
Time estimation	2	4	.50	.00
Misc. cognitive function	5	5	.80	.00
Automobile driving	3	2	.33	.00
Brain electrical activity	3	6	.33	.50

[a]Based on numbers of studies in each category.

Those conclusions are as follows:

A. Non-double-blind studies produce a greater proportion of reported effects, even for the individual dependent variables. This is true with the exception of tracking and brain electrical activity. This observation supports the previous inference that non-double-blind studies are biased toward finding more effects than justified.

B. Studies using double-blind procedures found effects on four of the 14 dependent variable families: tracking, vigilance, continuous performance, and brain electrical activity.

C. In the five dependent variable categories where COHb was found to affect behavior, usually less than half of the reported studies found effects in double-blind studies.

D. Sensory and cognitive effects were not found to be affected by COHb in double-blind studies.

E. In most instances, the rate of finding COHb effects in non-double-blind studies was high in the same dependent variables where the double-blind studies reported effects. This observation lends further support to the findings in the double-blind studies.

Continuous Performance. It may be argued that the dependent variables of tracking, vigilance, and continuous performance are related functionally. Each of the dependent variables in the three categories require the continuous performance of some sort of behavior. The response rate and/or attention demand in vigilance behavior is low compared to the other two groups, otherwise, the behaviors are similar. Tracking is clearly a particular form of continuous performance which was categorized separately simply because of the homogeneity of a group of studies that existed in the literature. It also may be argued that, despite the high response rates in the tracking and continuous performance studies, both of these behaviors require a strong component of sustained attention. It seems fair to conjecture, therefore, that behaviors that require sustained attention and/or sustained performance are most sensitive to disruption by COHb.

The group of studies of tracking, vigilance, and continuous performance offer the most consistent and defensible evidence of COHb effects on behavior. The results across studies is, however, far from consistent. Further examination of the three areas seems appropriate.

Compensatory tracking was studied by two groups of investigators using virtually identical task parameters and equipment (Putz et al., 1976, 1979; Benignus et al., 1987, 1989a). Both of the studies by Putz et al. (1976, 1979) found significant and moderately large effects of 5% COHb. Benignus et al. (1987) reported similar but smaller significant effects in a nearly identical experiment to Putz et al. (1976). However, in a dose-effects study including another direct replication group, Benignus et al. (1989a) found no significant effects, even for COHb levels of 17%. In the latter study, the means were nearly dose ordinal but too small to be statistically significant. It is particularly puzzling why the latter study, using a large number of subjects on an identical task, should find no significant effects for even 17% COHb when three other studies found effects at lower levels. Three other

double-blind tracking studies of various methods found no effects of COHb levels of 12% or greater.

As discussed in the above literature review, there is a similar disunity among studies on the effects of COHb on vigilance. Because of the many failed attempts at direct replication, the conclusions seem weaker than for tracking.

Of the five double-blind experiments in which continuous performance was measured, three were mentioned earlier in the discussion of tracking. In these studies (direct replications), continuous performance was measured simultaneously with tracking (Putz et al., 1976, 1979; Benignus et al., 1987). The latter of the three found no effects. A small study reported continuous performance effects that were disordinal in COHb (O'Donnel et al., 1971a). The remaining study (Benignus et al., 1977) used a different task and obtained no COHb effects.

Multiple Performance. It is possible that COHb impairs task performance more when multiple tasks are performed simultaneously, thus decreasing the amount of behavioral reserve capacity. To test this exploratory hypothesis, behavioral studies (sensory and electrophysiological excluded) were tabulated according to single/multiple task performance and significant/nonsignificant effects of COHb. If any given study used both single-task and multiple-task behaviors, the study was tabulated according to the multiple-task results only. For studies in which only single tasks were required, the study was classed as having shown significant results if one or more variables were significant, otherwise as nonsignificant. The above rules prevented any study from being tabulated more than once.

Table 10-26 is the result of the above tabulation. The exploratory Fisher's exact test yielded $p = 0.081$. While the result would have been nonsignificant by *a priori* rules, the table shows a slight tendency toward more multitask studies showing a significant effect, whereas more of the single-task studies found no effect.

The question of multitask vs. single-task performance sensitivity to COHb disruption would be answered best by experiments in which the tasks were performed singly and together within the same study. In the literature there were only two cases in which this was done. In both of these, one of the single tasks alone was affected more than multitask performance (Bender et al., 1972; Gliner et al., 1983). Experiments designed to specifically

TABLE 10-26. EFFECT OF SINGLE VS. MULTIPLE TASK PERFORMANCE

	Single Task	Multiple Task
Effects	7	8
No Effects	14	5

Fisher's exact test, p = 0.081.

answer the question of single-task vs. multitask performance sensitivity need to be done.

COHb Formation Rate. It is possible that the rate at which COHb is formed is an important variable in the effects of COHb on the CNS. To explore this possibility, studies were cast into a table according to their rate of COHb formation (fast or slow) and whether effects were found or not. When COHb was formed to its target value in 10 min or less, the study was tabulated as fast. Studies in which effects were found only above 10% COHb were tabulated as no effects to avoid consideration of frank effects.

Table 10-27 is the result of the above classification. The exploratory two-sided Fisher's exact test yielded p = 0.002. It appears that studies using slow COHb formation are more likely to find significant effects. Experiments explicitly designed to test the hypothesis would be needed before firm conclusions can be drawn.

TABLE 10-27. EFFECT OF RATE OF COHb FORMATION

	Slow	Fast
Effects	20	2
No Effects	12	9

Fisher's exact test, p = 0.002.

10.4.2.10 Hypotheses

Dose-Effect Function

An effort has been made to unify the dose-effects literature concerning CO and behavior (Benignus et al., 1989b). The analyses and hypotheses of the latter article will be reviewed below. Both laboratory animal and human data were considered. Only dose-effects studies were considered so that comparisons and extrapolations could be made. The literature concerning dose-effects functions in humans, as above, was found to be inconsistent. As has been pointed out in the present review, effects of COHb elevation do not become significant until *ca.* 20% in laboratory animals. The literature for such higher levels of COHb is quite consistent. Nonlinear, positively-accelerated functions were fitted to the laboratory animal data to describe dose-effects relationships.

To compare the human data to the laboratory animal data, it was necessary to select from the divergent group of human dose-effects studies. The argument was made that the most accurate estimate of the dose-effects function was that the effects below *ca.* 20% COHb were either zero or very small in size. This argument was based on the observations about nonverification of findings in the literature as well as upon the findings of Benignus et al. (1989a), which demonstrated small but nonsignificant elevations in mean tracking error in a large study (n=74) with COHb levels up to 17%.

The data from Benignus et al. (1989a) were fitted with the same form of function as fitted to the laboratory animal data. Extrapolation of the curve projected the human data as passing through laboratory animals curves. The latter observation was used to imply that the human and laboratory animal findings were similar and that frank effects of COHb elevation in humans should not be expected below *ca.* 20% COHb.

An argument was made for the possibility and importance of small effects for low COHb levels but no unimpeachable evidence could be marshalled. The possibility of small effects below *ca.* 20% COHb was supported by the observation that in many studies, using both laboratory animals and humans, means were usually shifted in the direction of deleterious effects at low levels, but not in a statistically significantly manner. Means were much more rarely shifted in directions implying improvement of behavioral abilities with small levels of COHb. Thus, there may exist small effects below 20% COHb (or some

individuals are affected while most are not). The latter possibility cannot be ignored but it cannot be confirmed.

Compensatory Mechanisms

As discussed above in Section 10.4.1, a proportional vasodilation occurs in the brain in response to COHb elevation. This vasodilation is sufficient, on the average, to keep the cerebral O_2 consumption from being reduced even though the COHb has reduced the blood's O_2-carrying capacity 20 to 30% and the presence of COHb has shifted the O_2Hb dissociation curve to the left. The cerebral vasodilation may be viewed, teleologically, as a closed-loop compensatory mechanism to assure adequate oxygenation of the brain in the presence of elevated COHb.

If the cerebral vasodilation is adequate in any individual and if the vasodilation is homogeneous for all cerebral tissue, then that individual should not be behaviorally impaired by COHb elevation. This statement assumes that the sole mechanism for CO toxicity is the hypoxic effect of COHb.

The agreement between the behavioral literature and the compensatory mechanism hypothesis is noteworthy. According to the compensatory mechanism data, O_2 consumption in the brain does not begin to decrease until COHb exceeds 20 to 30%. Data from behavioral studies in laboratory animals demonstrate that significant effects in schedule-controlled behavior do not occur below 20 to 30% COHb. Behavioral effects in humans have not been unambiguously demonstrated below 20 to 30% COHb.

10.4.2.11 Conclusions

At the present stage of evidence, it seems unfounded to conclude that COHb elevation below *ca.* 20% is deleterious to the behavioral abilities in humans. It seems unwise, however, to ignore the frequent evidence in favor of effects. Even if effects are small or occasional, they might be important to the performance of critical tasks.

Some of the differences among studies of the effect of COHb on the behavior of humans is due apparently to technical problems in the execution of experiments, because single-blind or nonblind experiments tend to yield a much higher rate of significant effects than do double-blind studies. Even when non-double-blind experiments are eliminated from consideration,

however, a substantial amount of disparity remains among results of studies. It is possible that such residual disagreement is due to the action of an unsuspected variable that is not being controlled across experiments.

If the compensatory CNS blood flow hypothesis has validity, it is possible that there exist groups that are at higher risk to COHb elevation than the usual subjects who were studied in the behavioral experiments. Disease or injury might either impair the compensatory mechanism or reduce the non-exposed O^2 delivery. Aging increases the probability of such injury and disease. It also is possible that there exist individual differences with regard to COHb sensitivity and/or compensatory mechanisms. Too little is known about the compensatory process to make conjectures, but the matters seem important to investigate.

The literature on the behavioral effects of COHb elevation has grown considerably since the last Criteria Document was written (U.S. Environmental Protection Agency, 1979). It seems safe to state that the effect of the new information did not increase the certainty about COHb effects. Unless some key piece of information is uncovered by new research, there does not seem to be much hope of gaining clarification in the conflicting findings. The solution to the puzzle would seem to lie in the conduct of more research into mechanisms of action of CO rather than in further attempts to show reliable behavioral effects. The latter approach, which has not been successful in the past, should be resumed only when mechanisms of toxicity are understood better. More findings of behavioral effects of COHb would not appreciably alter the conclusions of the present section unless future studies were to show an unusual unanimity.

10.5 DEVELOPMENTAL TOXICITY OF CARBON MONOXIDE

10.5.1 Introduction

Developmental toxicity has been described in the U.S. Environmental Protection Agency's Guidelines for the Health Assessment of Suspect Developmental Toxicants (Federal Register, 1986) as including death of the developing organism, structural abnormalities, altered growth, and functional deficits resulting from toxic exposures that occur prior to the subject's attaining sexual maturity. The appearance of toxic effects may occur at any time

throughout life. Concern for special vulnerability of immature organisms to toxic compounds focuses on the possibilities that (1) a toxic exposure that is not sufficient to produce maternal toxicity or toxicity in the adult organism will adversely affect the fetus or neonate or (2) at a level of exposure that does produce a toxic consequence to the adult or mother that the fetus or neonate suffers a qualitatively different toxic response. Toxic responses that occur early in life, but which are not permanent, may or may not be a cause of concern. In some cases they truly may be transient events with no persisting consequences. However, in other cases such results may have their own consequences for development of the organism or may reappear under conditions of ill health produced by other toxic exposures, environmental stresses, or exposure to pathogenic agents. Therefore, even seemingly transitory toxic effects must be viewed as serious consequences of exposure when they occur in humans. In this section, data are presented that describe the toxic consequences of CO exposure early in development. These data describe the types of toxic outcomes that the immature subject may show and also help to identify the dosage at which such toxicity is seen.

There are theoretical reasons and supporting experimental data that suggest that the fetus and developing organism are especially vulnerable to CO. One reason for approaching the fetus as a separate entity for purposes of regulation is that the fetus is likely to experience a different CO exposure than the adult given identical concentrations of the gas in air. This is due to differences in uptake and elimination of CO from fetal hemoglobin which are documented below. Less studied is the possibility that tissue hypoxia may differ between the fetus and adult even at equivalent carboxyhemoglobin concentrations as a result of differences in perfusion of critical organs, in maturation of adaptive cardiovascular responses to hypoxia and as a result of tissue requirements for oxygen. Inferences concerning these factors are obtained principally from experimentation performed in laboratory animals in which the immature organism does show enhanced toxicity relative to the adult. Concern must be expressed, too, for the development of sensitive and appropriate animal models. It is necessary to bear in mind the relative state of development of the human and laboratory animal in question at the time of birth in developing useful animal models. For example, the neonatal rat is very immature relative to the neonatal human at birth, with respect to development of the central nervous system, (Fechter et al., 1986) and so a combined prenatal and neonatal exposure model may be more accurate in predicting consequences of prenatal

exposure in the human. Further, differences appear to exist among species in the relative affinity of fetal and adult hemoglobin for CO. These data are reviewed by Longo (1970).

There exist a variety of relevant data bases that will be reviewed. These include experimental investigations conducted using laboratory animals (and these are most numerous), case report data collected in offspring of women exposed to generally high-level, acute CO poisoning during pregnancy, and epidemiological data. One large, but problematical, literature from the standpoint of this document concerns maternal cigarette smoking.

Cigarette smoking constitutes a major source of exposure of the individual to CO and this is particularly relevant for the fetus because of the high affinity of fetal hemoglobin for CO (Longo, 1977). Maternal smoking has been associated with a variety of untoward consequences ranging from increased incidence of placenta previa, abruptio placentae, spontaneous abortion and subsequent fetal deaths to depressed birthweight, and increased numbers of hospital admissions for a broad range of complaints during at least the first 5 years of life, to poorer than predicted school performance during the first 11 years of life. This literature has been thoroughly reviewed as a report to the U.S. Surgeon General (National Institute of Child Health and Human Development, 1979). These outcomes should be cause for significant concern. However, it is not easy to determine the extent to which CO is a causative factor. Cigarette smoke contains a large number of toxic chemicals other than CO and these other agents either alone or in combination may be responsible for the untoward outcomes that are readily associated with maternal smoking. A few epidemiological reports are reviewed below in which it is concluded that CO, either from ambient sources or cigarette smoke, is responsible for developmental disruption. However, these reports generally are deficient in characterizing the level of CO exposure or in ruling out potential contributions by other toxic agents contained in smoke. Investigations with laboratory animals exposed to CO rather than cigarette smoke early in development have demonstrated developmental anomalies and persisting neurobehavioral disorders that are most relevant to this document and that are reviewed below. Because such effects are seen at CO levels approaching values observed in the offspring of cigarette smokers, this must be cause for serious concern. However, it is not possible to use the cigarette smoker literature in establishing criteria for permissible CO exposure.

10.5.2 Theoretical Basis for Fetal Exposure to Excessive Carbon Monoxide and for Excess Fetal Toxicity

Hill et al. (1977) aptly described mathematical models for predicting fetal exposure to CO based upon placental transport and the differences between maternal and fetal hemoglobin affinity for CO and O_2. They predicted that for any maternal CO exposure of moderate duration that fetal COHb levels would lag behind maternal COHb levels for several hours, but would, given sufficient time, surpass maternal COHb levels by as much as 10% (in humans) due to the higher affinity of fetal hemoglobin for CO than adult hemoglobin. Moreover, they predicted a far longer wash-out period for the fetal circulation to eliminate CO following termination of exposure than that found in the adult. Data, accumulated in both laboratory animal and human studies, support these conclusions.

10.5.2.1 Evidence for Elevated Fetal Carboxyhemoglobin Relative to Maternal Hemoglobin

A fairly wide range of neonatal and maternal COHb levels has been published for humans, probably due to wide differences in cigarette smoking patterns prior to and during labor. In one recent study, measurement of fetal cord blood in the offspring of cigarette smokers who smoked during labor showed fetal COHb levels 2.55 times higher than in maternal blood. Cord blood averaged 10.1% COHb at delivery while maternal blood averaged 5.6% on the mother's arrival at the hospital and 4.1% at delivery (Bureau et al., 1982). These values for fetal COHb are fairly high relative to other published sources (Longo, 1977 - Table IV). However, greater fetal COHb levels have been found in laboratory studies across a broad range of animal species if sufficient time was allowed for COHb to equilibrate in the fetal compartment. Christensen et al. (1986) ultimately observed higher CO levels in fetal guinea pigs than in their dams following CO exposure given near term. Immediately following maternal exposure, at gestational age 62 to 65 days, to a bolus of CO (5 mL given over 65 seconds), they reported a faster elevation in maternal COHb levels than in fetal levels, a finding consistent with the models of Hill et al. (1977).

Anders and Sunram (1982) exposed gravid rats to 22 ppm CO for one hour on Day 21 of gestation and reported that fetal COHb levels averaged 12% higher than levels taken at the same time period in the dam. These results are consistent with those of Garvey and Longo (1978) whose study involved chronic CO exposures in rats. Dominick and Carson (1983)

exposed pregnant sows to CO concentrations of 150 to 400 ppm for 48 to 96 h between gestation days (GDs) 108 to 110. They reported fetal COHb levels that exceeded maternal levels by 3 to 22% using a CO-oximeter.

Longo and Hill (1977) similarly reported that COHb levels in fetal lambs do exceed maternal levels once equilibrium is reached in the fetal compartment and that this washout from the fetal blood exceeds that observed for maternal blood.

Fetal COHb kinetics may not be static throughout pregnancy. Bissonnette and Wickham (1977) studied transplacental CO uptake in guinea pigs at approximate gestational ages 45 to 68 days. They report that placental diffusing capacity increases significantly with increased gestational age and appears to be correlated with fetal weight rather than placental weight. Longo and Ching (1977) also showed increases in CO diffusion rates across the placenta of the ewe during the last trimester of pregnancy. However, they did not find a consistent increase when diffusion rate was corrected for fetal weight (i.e., when diffusing capacity was expressed on a per kilogram fetal weight basis).

10.5.2.2 Effect of Maternal Carboxyhemoglobin on Placental O_2 Transport

Gurtner et al. (1982) studied the transport of O_2 across the placenta in the presence of CO by cannulating both the maternal and fetal vessels of anesthetized sheep preparation. They measured the transport of O_2 across the placenta compared to transport of argon, urea, and tritiated water when CO was introduced. They showed a reduction in O_2 diffusing capacity relative to Ar that appeared to be related to the level of maternal COHb. Reduction of O_2 transport was observed below 10% COHb and O_2 transport approached zero at COHb values of 40 to 50%. They interpreted these data as supporting the role of carrier-mediated transport for O_2 and suggest that CO competitively binds to this carrier. An alternative explanation is that the introduction of CO simply reduces the amount of fetal hemoglobin available to bind O_2. Moreover, Longo and Ching (1977), for example, were unable to alter CO diffusing capacity across the placenta by administration of a series of drugs that bind to cytochrome P-450. Gilbert et al. (1979) have underscored the low concentration of cytochrome P-450 in human placenta, as compared to liver and to the very low levels found in many other species.

Christensen et al. (1986) suggest that maternal CO exposure may independently impair O_2 diffusion across the placenta due to the enhanced affinity of maternal hemoglobin for O_2 in the presence of COHb (the Haldane effect). Using the guinea pig, these authors demonstrated an initial almost instantaneous fall in fetal paO_2 levels and an increase in fetal pCO_2, which subsequently was followed by an increase in fetal COHb between approximately 5 to 10 min (the last time point studied but a time when fetal COHb values were still far below maternal values). They calculated that the decrease in fetal O_2 transfer was due mostly to a decrease in maternal O_2-carrying capacity, but also, perhaps up to one-third, by the increased affinity of hemoglobin for O_2 in the presence of CO. This model assumes that uterine perfusion remains constant under the experimental conditions used. Longo (1976) also showed a significant dose related drop in fetal O_2 levels in blood taken from the fetal descending artery and fetal inferior vena cava after pregnant ewes were exposed to variable levels of CO for durations sufficient to yield COHb equilibration in both the fetal and maternal compartments. To summarize, it has been demonstrated that the presence of maternal COHb over a range of values results in depressed O_2 levels in fetal blood. The simplest explanations for the inverse relationship between maternal COHb and fetal O_2 levels are reduced maternal O_2-carrying capacity, impaired dissociation of O_2 from maternal hemoglobin (the Haldane effect), and reduced availability of free fetal hemoglobin able to bind O_2.

10.5.3 Measurement of Carboxyhemoglobin Content in Fetal Blood

Zwart et al. (1981) and Huch et al. (1983) have called into question the accuracy of spectrophotometric measurements of COHb in fetal blood using the IL 182 and 282 CO-oximeters. The CO-oximeter is effectively a spectrophotometer preset to read samples at specific wavelengths that correspond to absorbance maxima for oxy- carboxy- and met-hemoglobin determined using adult blood samples. Different plug-in modules (IL 182) or programmed absorbance values (IL 282) can be used to correct for species differences in the absorbance spectrum of rat, human, dog, and cow. Some investigators have used these instruments for estimating COHb levels in species for which the instrument has not been calibrated such as the pig and guinea pig. Typically, individual investigators have calibrated the CO-oximeter using blood standards fully saturated with CO and with O_2. The adequacy of such a procedure is not certain. (See Chapter 8, Section 8.5 for more details on the

measurement of COHb.) Further, the correspondence of absorbance maxima between adult and fetal hemoglobin for species upon which the CO–oximeter is calibrated at the factory is an empirical question for which little data are published. Noting the finding of higher apparent COHb levels in the venous cord blood of humans than in the uterine artery, Huch et al. (1983) examined the possibility that oxyhemoglobin in fetal blood might interfere with accurate measurement of COHb levels in the fetus due, presumably, to different absorbance maxima for fetal than adult blood. Working *in vitro*, Huch et al. (1983) deoxygenated fetal and maternal blood by flushing a tonometer with nitrogen and 5% CO_2. They introduced a "small volume" of CO gas, measured the blood gases using the IL 282 CO-oximeter, and then studied the effect of stepwise addition of O_2 to the apparent COHb levels. They showed little influence of O_2 saturation upon maternal COHb, but indicate that O_2 saturation did affect readings of fetal COHb so as to overestimate COHb. This confound is particularly likely at high oxyhemoglobin concentrations. Zwart et al. (1981) suggest an apparent elevation of COHb levels of approximately 2% with 40% oxyhemoglobin saturation and of approximately 6% with oxyhemoglobin levels of 90 to 95%. Such errors do not invalidate the finding that fetal COHb exceeds maternal values, but do bring into question the magnitude of this difference. Whether similar errors also occur in measuring fetal COHb levels in animal blood is uncertain and should be subjected to experimental test. The calibration of spectrophotometers based upon fetal hemoglobin absorbance spectra rather than automated analysis based upon adult absorbance spectra is recommended to achieve greater accuracy in determining absolute levels of CO in fetal blood. Vreman et al. (1984) have described a gas chromotographic method for measuring COHb which has been applied to human neonates. Because of the very small volume of blood needed to make these measurements and because they eliminate the problem of absorbance spectra of fetal hemoglobin, this may be considered a useful means of accurately assessing COHb in developing organisms. There also is a new model of the Co-oximeter (#482) which apparently allows for use of absorbance spectra based on calibration of fetal blood.

10.5.4 Consequences of Carbon Monoxide in Development

This section presents the evidence that CO exposure during early development has the potential of producing untoward effects. The four types of toxic outcomes – fetotoxicity,

gross teratogenicity, altered growth, and functional deficiencies in sensitive organ systems – are considered in order. As is the case in adult organisms, the nervous and cardiovascular systems appear to be most sensitive to CO exposure.

10.5.4.1 Fetotoxic and Teratogenic Consequence of Prenatal Carbon Monoxide Exposure

There is clear evidence from human and animal studies that very high levels of CO exposure may be fetotoxic. However, there exists some question concerning the level of exposure that causes fetal death as both the duration and concentration of maternal exposure are critical values in determining fetal exposure. More important for the setting of ambient air standards is the suggestion of a causal relationship between sudden infant death syndrome (SIDS) and ambient CO levels. These data are extremely limited at present and no conclusive correlation can be drawn between SIDS and CO.

The lowest-observed-effect level (LOEL) for fetotoxicity in laboratory animals appears to be in the range of 500 ppm for rodents, but one experiment conducted in pigs suggests that this species may be especially sensitive to this effect showing significant fetotoxicity at 250 ppm for 2 to 4 days late in gestation. Evidence of fetotoxicity in animals also has come from acute, high-dose experiments that are not included here because they are not directly relevant to standard setting.

The data that suggest that prenatal CO exposure produces terata is extremely limited and, again, comes largely from quite high exposure levels. Table 10-28 presents the reported effects of prenatal CO exposure on fetotoxicity, teratogenicity, and growth abnormalities.

Perinatal Carbon Monoxide Exposure and Sudden Infant Death Syndrome (SIDS)

It has been suggested that CO may be a causative factor in SIDS. Hoppenbrouwers et al. (1981) reported a statistical association between the frequency of SIDS and levels of several airborne pollutants including CO, sulfur dioxide (SO_2), NO_2, and hydrocarbons. SIDS was reported more commonly in the winter, at a time when the burning of fossil fuels for heating would be greatest. It is interesting to note that there is a phase lag of approximately 7 weeks between the increase in pollutant levels and the increase of SIDS cases. Whether this phase lag for SIDS represents a failure to identify the true cause of SIDS or a lag with some meaning in terms of the physiology is uncertain. Further correlations

TABLE 10-28. TERATOGENIC CONSEQUENCES OF PRENATAL CARBON MONOXIDE EXPOSURE IN LABORATORY ANIMALS

Species (Strain)	Maternal Treatment	Maternal Toxicity	Development Abnormality	References
Mouse (strain NR)	5,900 or 15,000 ppm CO for 5-8 min every other day of gestation	Acute effects: unconsciousness (no COHb levels)	Abortions, resorptions, and abnormal growth of survivors	Wells (1933)
Rat (Ames-Wilson)	3,400 ppm CO for 1 h/day for 3, 6, or 8.3 mo	Decreased body weight, appetite, and muscle tone; lack of grooming (COHb levels of 60-70%)	Decrease of litter size, decrease of preweaning survival (50% reduction of pregnancy at 3 mo, no pregnancies induced with longer exposures; 19% increase of estrous cycle)	William and Smith (1935)
Rat (Sprague-Dawley)	750 ppm CO for 3 h/day on GDs 7, 8, or 9	NR (no COHb levels)	Absorptions, stillbirths, and skeletal anomalies, decreased fetal body weight and crown-rump length	Choi and Oh (1975)
Rabbit (strain NR)	90 or 180 ppm CO from mating to the day before parturition	NR (COHb levels of 8-9% and and 16-18%)	180 ppm: 35% mortality of neonates, 11% decrease in birth weights, and increase in malformations 90 ppm: 9.9% mortality of neonates, 13% decrease in birth weights	Astrup et al. (1972)
Mouse (CF-1) and Rabbit (New Zealand)	7 or 24 h/day of 250 ppm CO on GDs 6-15 for mice and on GDs 6-18 for rabbits	Transient increase in body weight for mice in 7-h/day group; COHb levels of 10-11% (mice) and 13-15% (rabbits) for 7-h/day exposures	Mice: increase in resorptions and body weight w/7-h/day exposure, decrease in body weight and crown-rump length w/24-h day exposure; both exposures increased skeletal anomalies (GD 18) Rabbits: increase in body weight and crown-rump length w/7-h/day exposure	Scwetz et al. (1979)

TABLE 10-28 (cont'd). TERATOGENIC CONSEQUENCES OF PRENATAL CARBON MONOXIDE EXPOSURE IN LABORATORY ANIMALS

Species (Strain)	Maternal Treatment	Maternal Toxicity	Development Abnormality	References
Rat (Long-Evans)	0, 30, or 90 ppm CO or 13% oxygen in nitrogen on GDs 3-20	Decrease in successful pregnancies; COHb levels of 4.8 and 8.8%	13% oxygen: 12% decrease in body weight 90 ppm CO: 14% increase in brain weight, 24% decrease in lung weight, serotonin concentration decrease in brain	Garvey and Longo (1978)
Mice (CD-1)	125 250 500 ppm CO GDs 8-18	–	Increased fetal mortality significant w/500 ppm, no effect on number of implantation sites	Singh and Scott (1984)
Mice (CD-1)	0, 65, 125 ppm CO GDs 7-18	None	Impaired righting reflex on PD 1 for 125-ppm group, impaired negative geotaxis on PD 10 for 125-ppm group, impaired serial righting on PD 14 for both 65- and 125-ppm CO groups	Singh (1986)
Pig	150-450 ppm for 48-96 h between GDs 108-110	–	Linear increase in number of stillbirths significant when maternal COHb exceeded 23% (approximately 2500 ppm)	Dominick and Carson (1983)
Rabbit	12 "puffs" of 2700-5400 ppm CO daily from GDs 6-18	Decreased maternal respiration rate Significant maternal death rate	Larger number of fetal deaths No terata	Rosenkrantz et al. (1986)
Rat (Wistar)	1,000-6,000 ppm CO 2×/day for 2 h 40 min total from GDs 0-6 7-13 14-20 0-20	–		Tachi and Aoyama (1983)
			Decreased fetal weight at GD 21	Tachi and Aoyama (1986)

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were obtained between SIDS and the predicted level of CO and lead for the child's birth month and between SIDS and the level of pollution at the reporting station closest to the infant's home. These correlations are not compelling without more information on the methods by which other possible risk factors were controlled in making the geographical correlations. While it is technically difficult, it would be very useful to obtain COHb levels close to the time of death in SIDS victims as this would greatly assist in determining the incidence of elevated CO exposure in such cases.

There have been several studies linking maternal cigarette smoking with SIDS (these are reviewed in the National Institute of Child Health and Human Development, 1979 report on "Smoking and Health"), but it is uncertain what the role of CO might be in such a relationship. Thus, it is clear that severe, acute CO intoxication can be fetotoxic although specification of maternal and fetal COHb levels is difficult because such exposures rarely involve the achievement of steady-state COHb levels or permit careful and rapid determination of COHb levels. More relevant to the issue of standards for ambient exposure is the possible link between CO and SIDS, but this literature currently is insufficient to determine whether such a relationship exists.

Fetotoxicity in Laboratory Animals

Working with CD-1 strain mice, Singh and Scott (1984) found significant increases in the number of dead or resorbed fetuses per litter and an increase in fetal mortality with continuous CO exposure of 500 ppm from Gestation Day (GD) 8 until subjects were sacrificed at GD 18. Although not statistically significant, they found a dose-related trend in these measures beginning at approximately 125 ppm. The no-observed-effect level (NOEL) for these measures was 250 ppm. There was no effect of CO on the number of implantation sites suggesting a fetotoxic rather than an embryopathic event. Schwetz et al. (1979) also exposed mice to 250 ppm CO for 7 and 24 h per day on GDs 6 to 15. They found no effect on number of implantation sites or number of live fetuses per litter but did show a significant elevation in resorptions with the 7-h exposure (10 to 11% COHb) but not with 24-h per day exposures.

Dominick and Carson (1983) exposed pregnant sows to CO concentrations of 150 to 400 ppm for 48 to 96 h between GDs 108 to 110 (average gestation was 114 days). They

showed a significant linear increase in the number of stillbirths as a function of increasing CO exposure. Stillbirths were significantly elevated above control levels when the maternal COHb levels exceeded 23% saturation. These saturation levels were obtained at approximately 250 ppm. COHb levels were measured using an IL 182 CO-oximeter equipped with a human blood board; pig blood fully saturated with CO and with O_2 were run each day to calibrate the instrument. There was a very large variability among litters at a given concentration level in the percentage of stillbirths that occurred. Penney et al. (1980) found evidence of reduced litter size in rats exposed for the last 18 days of gestation to 200 ppm CO (maternal COHb levels averaged 28%). However, Fechter et al. (1987) did not observe similar effects on litter size in rats exposed to levels of CO as high as 300 ppm (maternal COHb levels of 24%).

Teratogenicity

There are very limited data (Astrup et al., 1972) suggesting increased fetal mortality and malformations among rabbits exposed to 180 ppm CO throughout gestation (COHb levels = 16 to 18%). The frequency of malformations reported was very small, the historical rate of such anomalies in the laboratory undocumented, and so these results require replication by other workers before they can be considered as the basis for regulation. Rosenkrantz et al. (1986) exposed rabbits to high doses (12 puffs of 2,700 to 5,400 ppm CO) for short time periods daily from GDs 6 to 18. COHb levels were estimated at 16% although animals had not equilibrated with the inhaled mixture. Despite a large number of fetal deaths, there was no evidence of terata in the CO-exposed animals.

Choi and Oh (1975) reported skeletal anomalies in rats exposed to 750 ppm CO for 3 h per day on GDs 7, 8, or 9. They also reported an excess in fetal absorptions and stillbirths and a decrease in body length. Schwetz et al. (1979) reported no teratogenic effects but an increase in minor skeletal variants in CF-1 mice exposed to 250 ppm CO for 24 h per day from GDs 6 to 15.

10.5.4.2 Carbon Monoxide and Body Weight

One of the best studied and possibly one of the most sensitive measures of early CO exposure is a depression in birthweight. The effect seen in animals following fetal CO

exposure is generally transitory and occurs despite the fact that maternal body weight growth through pregnancy does not appear to be adversely affected. The LOEL is in the range of 150 to 200 ppm in laboratory animals. In as much as the depressed birthweight observed is a transient event, its significance is not clear. However, in humans, low birthweight babies may be at particular risk for many other developmental disorders so that the effect cannot be disregarded casually. Moreover, in humans there is a strong correlation between maternal cigarette smoking and reduced birthweight. Whether the causative agent here is CO, nicotine, or a combination of these or other agents is uncertain.

Studies relating human CO exposure from ambient sources or cigarette smoking to reduced birthweight frequently have failed to take into account all sources of CO exposure. Alderman et al. (1987), for example, studied the relationship between birthweight and maternal CO exposure based upon neighborhood ambient CO data obtained from stationary air monitoring sites in Denver. They failed to show a relationship between these factors, but failed to control for maternal cigarette smoking or possible occupational exposures to CO. COHb measurements were not made either among the mothers or their offspring to estimate net exposure levels. A similar design problem is found in the study of Wouters et al. (1987) where cord blood COHb and birthweight were correlated. The authors report a significant correlation between cigarette smoking and reduced birthweight, but no correlation between cord blood COHb and birthweight. Such data might be interpreted to mean that CO is not the component in cigarette smoke responsible for reduced birthweight. Such a conclusion appears to be unjustified based upon Wouters et al. (1987), because COHb is a good estimate of recent CO exposure only. Thus it may indicate only how recently women in this study smoked their last cigarette before delivery of the child rather than estimating smoking rates or history throughout pregnancy.

Other studies have related indirect exposure to smoke in pregnancy with reduced birthweights. Martin and Bracken (1986) showed an association between passive smoking (exposure to cigarette smoke for at least 2 h per day) and reduced birthweight. Unfortunately, side-stream smoke contains significant nicotine as well as CO and so it is not possible to relate this effect to CO exposure.

Mochizuki et al. (1984) attempted to evaluate the role of maternal nicotine intake in reduced birthweight and did present evidence of possibly impaired utero-placental circulation

among smokers. These changes were not related specifically to the nicotine content of the cigarettes and failed, moreover, to take into account the possible synergistic effects between reduced perfusion that might have resulted from the vasoconstrictive effects of nicotine and the reduced O_2 availability that might have resulted from CO exposure. As noted in the section of this report that deals with the effects of high altitude, many of the outcomes of maternal CO exposure also are observed in offspring of women living at high altitude. These include reduced birthweight, increased risk of perinatal mortality, and increased risk of placental abnormalities. Limited data exist on the possibility of increased risk of CO exposure to the fetus being carried at high altitude. Such findings are considered in the section on high altitude.

Fechter and Annau (1980) replicated earlier data from their laboratory showing significantly depressed birthweights in pigmented rats exposed throughout gestation to 150 ppm CO. Penney et al. (1980) also found a significant depression in birthweight among rats exposed for the last 18 days of gestation to 200 ppm CO. Penney et al. (1983) showed a trend toward divergence in bodyweight among fetuses exposed to 200 ppm CO, which developed progressively during the last 17 days of parturition suggesting that late gestational exposure to CO may be essential to observe the effect. Storm et al. (1986) reported that in the following CO exposure from the beginning of gestation through postnatal day (PD) 10 that body weight was depressed in a dose-dependent fashion at 75, 150, and 300 ppm CO. Moreover, these values were all significantly lower than air-control subjects. By age 21 days no significant body weight differences were seen among the test groups. At no time have Fechter and colleagues observed evidence of maternal toxicity as identified by death, reduced maternal weight gain, or gross physical appearance. Morris et al. (1985b) exposed neonatal piglets chronically to CO for 21 days starting at approximately 28 days of age (200- and 300-ppm COHb levels averaged 16 and 21%, respectively). They reported a significant impairment in weight gain in pigs exposed to 300 ppm, but no effect in pigs exposed to 200 ppm CO.

10.5.4.3 Alteration in Cardiovascular Development following Early Carbon Monoxide Exposure

It is known that a variety of cardiovascular and hematopoietic changes can accompany hypoxia in neonates and adult subjects including elevation in hemoglobin, hematocrit, and

heart weight. Data gathered in adult laboratory animals suggest that these changes may be related. Cardiomegaly resulting from hypoxia reflects the amount of work performed to extract an adequate supply of O_2. Whether the same processes occur in prenatal and neonatal CO-induced hypoxia has been the subject of several reports (these reports are summarized in Table 10-29). For prenatal exposure, the accumulated laboratory animal data suggest that CO-induced cardiomegaly may be proportionately greater than in adult animals at a given maternal CO-exposure level. Whether this is due to higher fetal COHb levels, as a consequence of fetal hemoglobin's affinity for CO is not clear. While the cardiomegaly may resolve when the neonatal subject is placed in a normal air environment, there is evidence for a persisting increase in the number of muscle fibers. The functional significance of these changes, if any, is uncertain. The LOEL for fetal cardiomegaly has not been well determined. One experiment has shown significant elevation of heart weight following CO exposures as low as 60 ppm (Prigge and Hochrainer, 1977) and there are no published dose-response experiments that provide a NOEL. Chronic prenatal CO exposure at approximately 200 ppm results in a significant increase in the number of muscle fibers in the heart. The NOEL for this change has not been determined.

Fechter et al. (1980) measured wet-and-dry heart weight and protein and nucleic acid levels at several time points between birth and weaning in rats prenatally exposed to 150 ppm CO or to air. They reported that neonates had significantly elevated wet-heart weights despite a slightly reduced body weight at birth. Groups did not differ at birth in dry-heart weight, total protein, or RNA or DNA levels in whole heart. No significant differences between groups on any measure were present at PD 4 or subsequent ages studied. The data were interpreted as evidence for cardiac edema rather than a change in heart muscle mass itself. The finding of a heavier heart at birth replicated the finding of Prigge and Hochrainer (1977), who exposed rats prenatally to CO at levels as low as 60 ppm and observed a similar increase in heart weight. Clubb et al. (1986) have conducted a comprehensive experiment in which rats were exposed to 200 ppm CO either prenatally from GD 7 (CO/air), prenatally and postnatally until age 28 days (CO/CO), only postnatally for various durations (air/CO), or to air (air/air). Subjects were sacrificed at different ages and ventricular wet and dry weights and myocyte volume and number were measured histologically so that estimates of cell size and cell number could be made. They observed increases in right ventricular weight due to

TABLE 10-29. CONSEQUENCES OF PRENATAL CARBON MONOXIDE EXPOSURE ON CARDIOVASCULAR DEVELOPMENT IN LABORATORY RATS

Exposure	COHb (%)	Body Weight	Wet-Heart Weight	Heart/Body Weight	Dry-Heart Weight	Hematocrit	Total Hemoglobin	Other	References
150 ppm CO, GDs 1-21	15	--	Increased	Increased	Decreased	ND	ND	Nucleic acid protein unchanged, no significant differences at PDs 4-21	Fechter et al. (1980)
230 ppm CO, GD 2-PD 21	24 24	Decreased	ND	Increased PD 5	ND	Increased PD 5	Increased PD 5		Hoffman and Campbell (1977)
60, 125, 250, 500 ppm CO	ND	Decreased	Increased	Increased	ND	Decreased, 250-500 ppm	Decreased, 250-500 ppm		Prigge and Hochainer (1977)
157, 166, 200 ppm CO, GDs 5-22	24.9	Decreased	Increased ventricles	Increased	Increased	--	--	Increased LDH M subunit, increased DNA content	Penney et al. (1983)
200 ppm CO	27.8	Decreased	Increased	Increased	ND	--	--	No lasting effects of prenatal exposure	Penney et al. (1980)
30, 90 ppm CO	4.8-8.8	--	--	--	ND	--	--		Garvey and Longo (1978)
200 ppm CO from GD 7-PD 28	ND	--	Increased at birth	Increased	--	ND	ND	Prenatal CO increased myocytes in right ventricle, postnatal CO	Clubb et al. (1986)
GD 7-PD 1		Decreased at PD 28		Increased	--	ND			

TABLE 10-29 (cont'd). CONSEQUENCES OF PRENATAL CARBON MONOXIDE EXPOSURE ON CARDIOVASCULAR DEVELOPMENT IN LABORATORY RATS

Exposure	COHb (%)	Body Weight	Wet-Heart Weight	Heart/Body Weight	Dry-Heart Weight	Hematocrit	Total Hemoglobin	Other	References
PD 1-PD 28		Decreased at PD 21 and PD 28	Increased at birth	Increased	--	ND		increased myocytes in left ventricle	
500 ppm CO PDs 1-32 (CO gradually increased from PDs 1-7)	ND	--	Elevated in adulthood	Elevated in adulthood	ND	Increase at some ages in adulthood	ND	Heart rate elevated 10-15% in adulthood. No effect on blood pressure	Penney et al. (1984)
300 and 700 ppm CO PDs 1-32 (CO gradually increased from PDs 1-7)	Approximately 30 and 50%	Decreased in 700-ppm CO group only in adulthood	Increased in 700-ppm CO group only in adulthood	Increase in 700-ppm CO group only in adulthood	Decrease in dry/wet heart weight in females	Increased in females in adulthood	ND	No consistent effect on heart rate at either exposure level. Elevated ventricular DNA levels in adulthood	Penney et al. (1988)
500 ppm CO PDs 1-32 (CO gradually increased from PDs 1-7)	ND	Decreased only during CO exposure	ND	Increased during exposure	ND	ND	ND		Clubb et al. (1989)

TABLE 10-29 (cont'd). CONSEQUENCES OF PRENATAL CARBON MONOXIDE EXPOSURE ON CARDIOVASCULAR DEVELOPMENT IN LABORATORY RATS

Exposure	COHb (%)	Body Weight	Wet-Heart Weight	Heart/Body Weight	Dry-Heart Weight	Hematocrit	Total Hemoglobin	Other	References
500 ppm CO PDs 1-32 (CO gradually increased from PDs 1-7)	ND	Decreased during CO exposure	Increased during CO exposure	Increased during CO exposure	ND	Increased during CO exposure	ND	Exercise in adulthood increased atrium to body weight ratio. CO in neonatal period produced small additional effect	Penney et al. (1989)

fetal CO exposure, and increases in left ventricular weight following neonatal CO exposure. As in the case of Fechter et al. (1980), they showed a gradual return to normal heart weight when prenatally exposed neonates were placed in an air environment neonatally. They attributed the reversal of cardiomegaly in the CO/air group to a loss in cell volume rather than a loss in cell number (which remains elevated). Myocyte volume did not differ between CO and air subjects at birth. Left ventricle plus septum and right ventricle cell volumes of the CO/CO group were smaller than controls at 28 days of age despite the heavier wet heart weight shown by the CO/CO subjects. Clubb et al. (1986) report that prenatal CO increased right ventricular myocyte number and that neonatal CO exposure increased left ventricular myocytes suggesting that cardiomegaly in early development is related to increased hemodynamic load. This possibility is supported by reports from Penney et al. (1983) showing that prenatal exposures to CO levels between 157 and 200 ppm during the last 17 days of gestation did lead to a significant elevation in DNA content among treated subjects. Moreover, hydroxyproline content, an indicator of collagen, also was increased following the CO exposure as was cardiac lactate dehydrogenase M (LDH M) subunit among the 200-ppm CO subjects.

Penney et al. (1980) compared the effects of prenatal CO exposure at a dose of 200 ppm with exposure both prenatally and neonatally until age 29 days. Neonatal CO concentrations were elevated to 500 ppm. Cardiomegaly and depressed hemoglobin, hematocrit, and red blood cell counts were found following CO exposure. In subjects allowed to survive until young adulthood, the heart weight to body weight ratio of subjects receiving CO both prenatally and neonatally still was elevated, while those in the prenatal CO condition did not differ from control subjects in this measure. Penney and colleagues have published a series of papers that propose that the neonatal period is a time when CO exposure might produce persisting cardiovascular consequences. Typically their experimental protocol involves exposure of rats to CO from soon after birth until PD 33. CO levels are increased in step-wise fashion during the first week of neonatal life reaching the nominal CO exposure level by PD 7. Spectrophotometric determination of COHb levels were reported in one manuscript published by these authors to be approximately 30% for subjects exposed to peak CO values of 350 ppm, 40% for subjects receiving 500 ppm, and 50% for those exposed to 700 ppm CO. (Penney et al., 1988). The treatment produces significant reductions in body weight

(Penney et al., 1988), elevated hematocrit (Penney et al., 1988; Penney et al., 1989), and significant increases in heart weight (left ventricle plus septum and right ventricle) above control subjects at the end of CO exposure to 350 ppm (Penney et al., 1989). The elevation in heart weight partially recovers as subjects mature although in some studies (e.g., Penney et al., 1984) persistent effects were observed into adulthood when neonatal CO levels were 500 ppm. In other studies, the elevation in heart weight or the heart weight:body weight ratio resulting from 500-ppm CO exposure neonatally was no longer present in adulthood (e.g., Clubb et al., 1989). Penney et al. (1984) also suggested a 10-15% increase in adult heart rates associated with neonatal exposure to 500 ppm CO, but this effect was not replicated using 350- and 750-ppm CO exposure (Penney et al., 1988). Further, there was no evidence for an increase in blood pressure or other functional changes that might explain the tachycardia associated with 500-ppm CO exposure. Finally, a recent paper (Penney et al., 1989) suggested possible additive effects of neonatal exposure to 500 ppm CO and exercise-induced changes on adult heart size. Analysis of these effects are complicated by particularly large effects of exercise on atrial weight rather than ventricular weight.

To summarize, there is good evidence for the development of severe cardiomegaly following early life CO exposure at doses between 60 to 200 ppm. These effects are transitory if exposure is prenatal and it is not clear whether they alter cardiac function or produce latent cardiovascular effects that may become overt later in life. Persisting elevation in heart weight results from combined prenatal CO exposure at 200 ppm and neonatal exposure at 500 ppm. The LOEL for this effect has not been determined.

There are many published reports suggesting some residual increase in heart weight associated with neonatal CO exposures of 500 ppm and greater, maintained over the first 33 days of life. Even granting a small (10-15%) increase in heart rate found in one study among subjects exposed to 500 ppm CO neonatally, there is no evidence that neonatal CO exposure has functional consequences for experimental subjects.

10.5.4.4 Neurobehavioral Consequences of Perinatal Carbon Monoxide Exposure

The Developmental Toxicology Guidelines published by the U.S. Environmental Protection Agency (Federal Register 1986) recognized the importance of neurobehavioral investigations as a means of assessing nervous system function. Behavior is an essential

function of the nervous system and abnormalities in this outcome can be diagnostic for particular neurological disorders or for nervous system dysfunctions. The LOEL for such effects appears to be in the range of 125 to 150 ppm using a variety of behavioral tasks in experimental animals, though isolated studies suggest possible anomalies in the range of 60 to 65 ppm. These studies are summarized in Table 10-30. There are a limited number of human case reports that also are described here (see Table 10-31 for summary). However, those reports generally are not adequate for evaluating a threshold for persisting neurobehavioral impairments in children.

Crocker and Walker (1985) reported on the consequences of acute CO exposure in 28 children of which 16 had COHb levels over 15% and were considered to have had "potentially toxic" COHb levels. These children were between the ages of 8 mo and 14 years. The authors report nausea, vomiting, headache, lethargy, and syncope to be the most common signs and symptoms. A very limited follow-up investigation was performed with these children and so no conclusions can be drawn from this work concerning persisting effects. In addition to very large differences in the nature (dose and duration) of exposure, the extreme variability in patient age limits the potential value of the data presented in this work. The absence of any reports from children having COHb levels of 15% or less (a very significant COHb level) is regrettable because these are the children one must study to develop an understanding of the relationship between dose and effect for the purpose of setting standards for ambient air.

Klees et al. (1985) conducted a more comprehensive study of the consequences of childhood CO exposure on subsequent behavioral development. They report that the age atwhich exposure occurred, its severity, and also the child's intellectual level at the time of exposure also play a role in the outcome. Younger children tended to show somewhat milder symptoms if they did recover fully than did children who were older at the time of CO exposure. Subjects who had higher intellectual function prior to accidental exposure also appeared to fare better after CO exposure. However, the authors stress that long-term perceptual and intellectual consequences of CO exposure may occur that are not identified well in short-term cursory examinations. Of 14 children followed up for 2 to 11 years after intoxication only 1 showed no sequelae (despite COHb levels of 42% on admission to hospital at the age of 9 years 10 mo). Seven children had impairment of visual memory and

TABLE 10-30. NEUROBEHAVIORAL CONSEQUENCES OF PRENATAL CARBON MONOXIDE EXPOSURE IN LABORATORY ANIMALS

Species (strain)	Maternal/Neonatal Treatment	Maternal/Embryonic Toxicity	Developmental Abnormality	References
Rat (Sprague-Dawley)	10,000 ppm CO for 2 or 3 h on GD 15; no cross-fostering	Acute effects: loss of righting reflex followed by coma. Litter size normal; COHb levels of approximately 50%	26% increase in exploratory activity in figure-8 maze at PD 30 (3-h exposure)	Daughtrey and Norton (1983)
Rat (Long-Evans)	150 ppm CO throughout gestation; no cross-fostering	No difference in litter size or fetal mortality; COHb levels of 12.2-14%	3.3% decreased birth weights and decrease in preweaning weights; decreased locomotor response to L-dopa in open field (PD 4 and PD 14); increased rate of habituation (PD 14)	Fechter and Annau (1976)
Rat (Long-Evans)	150 ppm CO throughout gestations; no cross-fostering	Litter size normal; no differences in neonatal mortality; COHb levels of 15%	4.9% decreased birth weights and decrease in preweaning weights; decreased response to L-dopa (in open field) at PD 1, PD 4 (also decreased dopamine levels); increase in rate of habituation of activity (PD 14)	Fechter and Annau (1977)
Mouse (Swiss-Webster)	CO exposure throughout gestation; no cross-fostering	ND Maternal COHb levels of 6-11%	Increased errors in heat-motivated Y-maze at PD 40	Abbatiello and Mohmann (1979)
Rat (Long-Evans)	CO exposure throughout gestation; no cross-fostering	Maternal weight gain, gestation length, and litter size normal; COHb levels of 15.6%	Decreased acquisition and (24-h) retention of two-way active avoidance (PD 30); neither multiple measures nor use of pseudo-conditioning controls similarly affected	Mactutus and Fechter (1984)

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TABLE 10-30 (cont'd). NEUROBEHAVIORAL CONSEQUENCES OR PRENATAL CARBON MONOXIDE EXPOSURE IN LABORATORY ANIMALS

Species (strain)	Maternal/Neonatal Treatment	Maternal/Embryonic Toxicity	Developmental Abnormality	References
Rat (Long-Evans)	CO exposure throughout gestation; no cross-fostering	ND COHb levels of 15.6%	Normal two-way avoidance acquisition with moderate or difficult task requirements (PD 120), but minimal (24-h) and pronounced (28-day) decreased retention; decreased acquisition and retention of two-way avoidance (PDs 300-360)	Mactutus and Fechter (1985)
Rat (Long-Evans)	150 ppm CO throughout gestation; cross-fostering for weight measures	ND (no COHb levels)	7.6% decrease in birth weights and decreased preweaning weights; decreased negative geotaxis (PD 3); decreased homing behavior (PDs 3-5)	Fechter and Annau (1980)

TABLE 10-31. CONSEQUENCES OF HUMAN CARBON MONOXIDE INTOXICATION DURING EARLY DEVELOPMENT

Characterization of Exposure[1]	Approximate COHb Level	Immediate Symptoms and Their Frequency	Persisting Symptoms and Their Frequency After Hyperbaric O_2 and Normobaric O_2 Therapy	References
Light	4-27%	Hyperreflexia (1/3) auditive memory impairment and spatial orientation problems (1/3)	Auditive and visual memory impairment (1/3)	Klees et al. (1985)
Medium	6-36%	ND (6/12) Coma (1/12) Unconscious (1/12) Normal (2/12)	Anxiety or emotional instability (3/12) Memory impairment (2/12) Spatial/temporal disorganization and perceptual problems (3/12) None or questionable effect (4/12)	Klees et al. (1985)
Severe	37%	Coma-developmental level Regression (language and motor) Violent anger/nervousness (1/1)	Persistent emotional instability (1/1)	Klees et al. (1985)
Accidental at 13 weeks of age	60%	Convulsion, hypotonic, unconscious (1/1)	Recovery of minor neurologic deficits by 6 weeks (1/1)	Venning et al. (1982)
Accidental at 21 days' old	6.7% 4 h after exposure (>15% at time of removal from CO)	Lethargy, vomiting (1/1)	None	O'Sullivan (1983)
28 pediatric exposures	Threshold value at which symptom was first observed in any subject 15% 16.7% 19.8% 18.6% 24.5% 36.9%	 Asymptomatic Nausea/headache Vomiting Lethargy Visual symptoms/syncope Seizures	Headaches, memory deficit, decline in school performance (3/28)	Crocker and Walker (1985)

TABLE 10-31 (cont'd). CONSEQUENCES OF HUMAN CARBON MONOXIDE INTOXICATION DURING EARLY DEVELOPMENT

Characterization of Exposure[1]	Approximate COHb Level	Immediate Symptoms and Their Frequency	Persisting Symptoms and Their Frequency After Hyperbaric O_2 and Normobaric O_2 Therapy	References
Light (6/14)	19-42%	Somnolence (2/6) Headache/nausea (3/6)	Perceptual (2/6) Memory (3/6) Emotional (1/16) Psychomotor (1/16) Cognitive (3/6)	Klees et al. (1985)
Medium (5/14)	16-42%	Incontinent (1/5) Unconscious (4/5)	Perceptual (1/5) Memory (1/5) Emotional (2/5) Cognitive (2/5)	Klees et al. (1985)
Severe (3/14)	?-13%	Vigil coma (3/3)	Perceptual (2/3) Cognitive (3/3)	Klees et al. (1985)

Notes: Exposure duration and level of CO exposure are poorly defined in all studies. Exposures are grouped according to authors' descriptive characterization when available rather than COHb level. The latter varies widely with group.

See glossary of terms and symbols for abbreviations and acronyms.

concentration, but normal IQ scores. These children had "slight or medium" exposure (COHb levels in the low to mid-twenties) and no coma. The six children with serious learning disorders did not have more severe CO exposures as judged from their COHb levels. They include several cases where exposures did occur at a young age and in children who had psychological difficulties prior to CO exposure. This study leaves some question concerning the relative vulnerability of children to CO as a function of their age as several of the youngest children did make full recovery while others did not. It seems likely that the child's age may have an influence on the duration of CO exposure which is survivable and perhaps also on the promptness with which either hospitalization or measurement of COHb levels is made. Further study of the outcomes of childhood CO exposures will be useful in determining whether there are differences with respect to vulnerability to CO level. Venning et al. (1982) report on a case of acute CO poisoning in a 13-week-old baby who had profoundly elevated COHb levels (60% 2 h after removal from the automobile in which she accidentally was exposed to CO). Her parents had much lower COHb values though this may reflect differences in concentration of CO inhaled. The child was reported to be unconscious for 48 h, to go through convulsions over the next 18 days, but, again, to show recovery from "minor neurological abnormalities" by 6 weeks later. There have been a series of experiments reported in rodents that identify both persistent neurobehavioral effects of prenatal CO exposure and also transient effects that may be symptomatic of functional delays in development. Fechter and Annau (1980) reported delays in the development of negative geotaxis and homing in rats exposed prenatally to 150 ppm CO (maternal COHb levels were not reported in this paper, but levels previously reported in this laboratory under that exposure regimen are 15 to 17% [Fechter and Annau, 1977]). These data were replicated by Singh (1986) using CD-1 mice exposed from GD 7 to 18 to 0, 65, and 125 ppm CO. He found that exposure at 125 ppm significantly impaired the righting reflex on PD 1 and negative geotaxis on PD 10. He also reported impaired aerial righting among subjects exposed prenatally to 65 or 125 ppm CO. Morris et al. (1985a) studied the consequences of moderate CO exposure given very late in gestation. They exposed pigs to 200 and 250 ppm CO (COHb levels of 20 and 22%) from GD 109 until birth. They found impairment of negative-geotaxis behavior and open field activity 24 h after birth in pigs exposed to 250 ppm. Activity in the open field was significantly reduced in subjects exposed to both 200

and 250 ppm 48 h after birth. The significance of these behavioral dysfunctions is that they point to delays in behavioral development that may themselves contribute to impairments in the way in which the individual interacts with its environment.

There also are reports of impaired cognitive function produced by prenatal CO which may be related to permanent neurological damage. Mactutus and Fechter (1984) showed poorer acquisition and retention of a learned active avoidance task in rats of 30 to 31 days of age that had received continuous prenatal exposures of 150 ppm CO. This study is noteworthy because very careful efforts were made to distinguish cognitive deficits and performance deficits such as motivational, emotional, or motoric factors. These findings were replicated and extended by Mactutus and Fechter (1985). They studied the effects of prenatal exposures to 150 ppm CO (16% maternal COHb) on learning and retention in weanling, young adult, and aging (1-year-old) rats. They found that both the weanling and young adult rats showed significant retention deficits, while in aging adults impairments were found in both learning and retention relative to control subjects. They interpreted these results to mean that there are permanent neurological sequelae of prenatal CO exposure. They raise the important issue that sensitivity of tests for consequences of early toxic exposure may reflect the developmental status of the test subject and complexity of the task. In this case, a learning impairment not observed in the early adult period was detected by working with aged subjects. No systematic attempts have been made to replicate these effects using lower levels of CO. One earlier study (Abbatiello and Mohrmann, 1979) suggested an increase in the number of errors made by mice prenatally exposed to CO throughout gestation (maternal COHb levels were 6 to 11%) and required to learn a maze discrimination task at 6 weeks of age. The absence of many details concerning the manner in which the control subjects were handled during pregnancy and the absence of details in the exposure protocol make it difficult to draw firm conclusions from this paper.

10.5.4.5 Neurochemical Consequences of Prenatal and Perinatal Carbon Monoxide Exposure

A significant number of studies have appeared concerning the consequence of acute and chronic prenatal and perinatal CO exposure upon a variety of neurochemical parameters. These experiments are important because the transmission of information between nerve cells is based upon neurochemical processes. Neurotransmitters can sometimes serve as markers

for the development of specific neurons in the brain, thereby serving as a sensitive alternative to histopathologic investigation particularly when the toxic agent selectively lesions neurons based upon a biochemical target. The absence of a specific cell group identified by neurochemical methods may have important consequences for subsequent brain development because the absence of targets for synapse formation can have additional consequences on brain development. Altered neurochemical development has been observed at CO-exposure levels lower than those necessary to produce signs of maternal toxicity or gross teratogenicity in the neonates. Chronic prenatal and perinatal exposures to 150-300 ppm CO have been shown to yield persisting alterations in norepinephrine, serotonin, and GABA levels and in GABA uptake in rats. There also are a substantial number of acute exposure studies that have demonstrated neurochemical effects of CO. However, these generally have been conducted at life-threatening levels and are not particularly relevant to setting ambient air standards for CO.

Storm and Fechter (1985a) and Storm et al. (1986) have carefully studied the developing cerebellum because this structure shows a rather slow developmental pattern and has been shown to be sensitive to hypoxic injury. The cerebellum plays prominent roles in many diverse functions. It is a part of the extra-pyramidal motor system, and it plays an important role in maintaining balance. The cerebellum also receives diverse sensory inputs and plays a role in sensory-motor integration. The cerebellar cortex contains a diverse group of neurons whose organization has been studied very well. The intrinsic neurons of the cerebellum – those having their cell bodies and axonal processes within this structure – consist of the granule, pyramidal, stellate, basket, and Golgi cells. The granule cells use the excitatory amino acid, glutamate, as their neurotransmitter and synapse on the pyramidal cells. The other intrinsic cells of the cerebellum appear to use the inhibitory amino acid, GABA, as their neurotransmitter. The Purkinje cells, being extremely large in size, probably contribute considerably to the total GABA levels found in the cerebellum.

The cerebellum receives several different neurotransmitter inputs from other brain regions. Most important of these is a noradrenergic input from the brainstem, a cholinergic link via mossy fibers and possibly aspartate or glutamate climbing fibers.

Storm and Fechter (1985a) reported that chronic prenatal CO exposures of 150 ppm CO (approximately 16 to 18% COHb based upon other research in this laboratory) decreased

cerebellar wet weight, but increased norepinephrine levels in this structure when expressed either in terms of concentration (nanograms per milligram wet weight) or total cerebellar content above control values between the ages of 14 to 42 days. This period represented the duration of the experiment. While this persisting elevation in norepinephrine cannot be considered permanent, it is the case that rats do obtain normal adult values of monoamine neurotransmitters at about the age of 40 to 45 days. There was no effect of CO treatment on norepinephrine levels in the cerebral cortex. Since noradrenergic neurons have their cell bodies outside of the cerebellum and project axons that terminate on cell bodies in this structure, Storm and Fechter's data may reflect an effect of increased noradrenergic innervation secondary to toxic injury to target neurons in the cerebellum. Consistent with this hypothesis, Storm et al. (1986) reported deficits in cerebellar weight, but more importantly deficits in markers of GABA-ergic activity in the cerebellum following prenatal and perinatal CO exposures. GABA is thought to be an inhibitory neurotransmitter present in several neurons that are endogenous to the cerebellum. Subjects in this experiment received 0, 75, 150, and 300 ppm CO (corresponding maternal COHb levels were 2.5, 11.5, 18.5, and 26.8%) from the beginning of gestation until PD 10. Neurochemical measurements were made either on PD 10 or PD 21. They showed reduced total GABA levels in the cerebellum following either 150- or 300-ppm CO exposure at both measurement times. They also reported a significant reduction in total GABA uptake, but not glutamate uptake in synaptosomes prepared from cerebella of 21-day-old neonates. Glutamate is an excitatory neurotransmitter found within the cerebellum. Histological markers of cerebellar toxicity also were obtained that were compatible with the neurochemical data and these are described below under histopathology.

In a subsequent paper, Storm and Fechter (1985b) evaluated norepinephrine and serotonin levels at PDs 21 and 42 in four different brain regions (pons/medulla, neocortex, hippocampus, and cerebellum) following chronic prenatal exposures to 75, 150, and 300 ppm CO. They reported that norepinephrine and serotonin concentrations decreased linearly with dose in the pons/medulla at 21 but not 42 days of age (i.e., evidence of a transient effect) the; LOEL was 150 ppm. Norepinephrine increased linearly with CO dose in neocortex at 42, but not at 21 days of age. They also showed that cerebellar weight was significantly reduced at

150 and 300 ppm CO when measured on PD 21 and for the 300-ppm-exposed rats at 42 days of age.

10.5.4.6 Morphological Consequences of Acute Prenatal Carbon Monoxide

Profound acute CO exposures do result in obvious neurological pathology that can be predicted to be inconsistent with life or with normal neurological development. These data are not as relevant to setting standards for ambient air quality as they are in demonstrating both the danger of accidental high-level CO exposures and in providing possible insight into the susceptibility of the developing brain to toxic exposure. The one possible exception is a study conducted in fetal pigs exposed via the mother to 300 ppm CO for 96 h (Dominick and Carson, 1983). The authors reported quite marked sensitivity to the CO as reflected in fetotoxicity, but also identified multifocal hemorrhages and vacuolation of the neuropile throughout the cortical white matter and brain stem. They also observed cerebellar edema with swollen oligodendrocytes and astrocytes, two non-neuronal cell types that have important roles in supporting neural function.

Okeda et al. (1986) studied the effects of 2,000- to 3,000-ppm CO exposure for 76 to 150 min in cats of different gestational ages. They suggest a different pattern of neurological damage in cats exposed late versus those exposed early to the CO. In late gestation, the primary changes were seen in cerebral white matter and brain stem. Basal ganglia and thalamus were affected less and cerebral cortex even less affected. Kittens exposed to CO at an early gestational age show less histopathology than those exposed later. Cerebral white matter and the basal ganglia tended to be most affected by early CO exposure.

Daughtrey and Norton (1982) studied the effect of exposing pregnant rats (GD 15) to 1,000 ppm CO exposure for 3 h upon central nervous system development of the fetuses on GD 16. Estimated maternal COHb levels reached about 50%. They reported 13 to 28% fetotoxicity (lethality) and described hemorrhagic infarcts and the most consistent damage to the ventral germinal matrix overlying the caudate nucleus. Further study (Daughtrey and Norton, 1983) indicated damage to the dendritic branches of Golgi type II neurons in the CO exposed fetuses.

Storm et al. (1986) showed that exposure of rats to 300 ppm CO (maternal COHb levels of 26.8%) throughout gestation and until day 10 after gestation resulted in a noticeably

smaller cerebellum at PD 21. The cerebellum of exposed neonates had fewer fissures than normal controls.

10.5.5 Summary

The data reviewed provide strong evidence that CO exposures of 150 to 200 ppm produce reductions in birthweight, cardiomegaly, delays in behavioral development, and disruption in cognitive function in laboratory animals of several species. Isolated experiments suggest that some of these effects may be present at doses as low as 60 to 65 ppm maintained throughout gestation. The current data from human children suggesting a link between environmental CO exposures and SIDS are weak, but further study should be encouraged. Human data from cases of accidental high dose CO exposures are difficult to use in identifying a LOEL or NOEL for this agent because of the small numbers of cases reviewed and problems in documenting levels of exposure. However, such data if systematically gathered and reported could be useful in identifying possible ages of special sensitivity to CO and cofactors or other risk factors that might identify sensitive subpopulations.

10.6 OTHER SYSTEMIC EFFECTS OF CARBON MONOXIDE

Studies (see Table 10-32) reviewed in the previous criteria document (U.S. Environmental Protection Agency, 1979) and again in Chapter 9 of this document suggest that enzyme metabolism and the P-450-mediated metabolism of xenobiotic compounds may be affected by CO exposure (Montgomery and Rubin, 1971; Kustov et al., 1972; Pankow and Ponsold, 1972, 1974; Martynjuk and Dacenko, 1973; Swiecicki, 1973; Pankow et al., 1974; Roth and Rubin, 1976a,b). Most of the authors have concluded, however, that effects on metabolism at low COHb levels (≤15%) are attributable entirely to tissue hypoxia produced by increased levels of COHb because they are no greater than the effects produced by comparable levels of hypoxic hypoxia. At higher levels of exposure, where COHb concentrations exceed 15 to 20%, there may be direct inhibitory effects of CO on the activity of mixed-function oxidases but more basic research is needed (see Chapter 9, Section 9.4). The decreases in xenobiotic metabolism shown with CO exposure might be important to

TABLE 10-32. OTHER SYSTEMIC EFFECTS OF CARBON MONOXIDE

Exposure[a,b]	COHb[c]	Subject(s)	Observed Effects[d]	Conclusions	Reference
Increasing exposure to 3000 ppm at 100 days	ND n = 36-45	Rat	Slightly few weight gains during first 100 days; increased weight gain in last 200 days	No significant body weight effect	Campbell (1934)[e]
0.8 or 3.0% until death group	71.3% or 79.2%	Rat n = 5 per group	Increased plasma levels of leucine aminopeptidase. No change in state-4 respiration of mitochondria; decreased state-3 rate in CO-exposed rats	Acute CO poisoning caused damage to liver mitochondria	Katsumata et al. (1980)
250, 500, and 1000 ppm for 24 h	ND	Rat n = 36	Decreased food and water intake; decreased weight gain	Significant body weight effect	Koob et al.[e] (1974)
Accidental exposure	3.4% to 32%	Man n = 6	Increased serum phosphocreatine-kinase	Diffuse myolysis indicative of acute renal failure	Kuska et al. (1980)
50 ppm	ND	Rat n = 92	Decreased liver cytochrome oxidase; increased liver succinate dehydrogenase	Tissue hypoxia	Kustov et al.[e] (1972)
17 ppm	ND	Rat n = 95	Increased aspartate and alanine amino transferase activity	Tissue hypoxia	Martynjuck and[e] Dacenko (1973)
250-3000 ppm for 90 min	20-60%	Rat n = 10-20 per group	Prolonged response to hexobarbital at 1000 ppm and to zoxazolamine at 250 ppm	Decreased xenobiotic metabolism	Montgomery and[e] Rubin (1971)
50 ppm for 3 mo	ND	Rat n = 100; Rabbit n = 40; Dog n = 4	No effect on body weight	No significant body weight effect	Musselman[e] et al. (1959)
Subcutaneous CO at 7.2 and 9.6 mol/kg; 40 injections in 53 days	50%	Rat n = 20-30	Increased leucine aminopeptidase activity in the liver with single and repeated injections; increased liver weight with repeated injections		Pankow and Ponsold (1972, 1974)[e]

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TABLE 10-32 (cont'd). OTHER SYSTEMIC EFFECTS OF CARBON MONOXIDE

Exposure[a,b]	COHb[c]	Subject(s)	Observed Effects[d]	Conclusions	Reference
CO exposure combined with 1% ethanol	40-50%	Rat n = 110	Increased leucine aminopeptidase activity in the liver; enlarged liver with ethanol		Pankow and Ponsold (1974)[e] Pankow et al. (1974)[e]
500 ppm	ND	Rat n = 7-8 per group	Decreased rate of hexobarbital metabolism; no effect on hepatic blood flow	Hypoxic hypoxia more effective than CO-hypoxia in inhibiting drug metabolism *in vivo*	Roth and Rubin (1976b)
	ND	Rat	Decreased rate of hexobarbital metabolism in isolated liver; CO hypoxia more effective than hypoxic hypoxia	No direct inhibition of drug metabolism by CO binding to liver cytochrome P-450	Roth and Rubin (1976b)
5,000 and 10,000 ppm for 3 min; 6 to 12 times daily for 3 to 4 weeks	ND	Guinea pig n = 7-9 per group	Increased number of alveolar macrophages and PMNs in lung lavage; reduced number of plague-forming cells in spleen with high exposure	Altered immune capacity with CO exposure	Snella and Rylander (1979)
50 ppm for 95 h/week up to 2 years; 1- to 3-mo exposures	ND	Rat n = 336; Mouse n = 767	No effect on body weight	No significant body weight effect	Stupfel and Bouley (1970)[e]
1% for 15 min	ND	Rat n = 60	Stimulation of adrenergic system	Increased carbohydrate metabolism	Swiecicki (1973)[e]
400-500 ppm for 168 days	ND	Rat n = 136	Trend toward lower body weight	No significant body weight effect	Theodore et al. (1971)[e]
0.24% for 42 to 180 days	ND	Mice n = 81	Planimetric measurement of increased bone tissue in parietal bones, sternum, lumbar vertebrae, and ribs; expansion of marrow cavities in ribs; parietal bones, and femurs	CO-induced increased blood flow caused excessive bone formation	Zebro et al. (1983)

[a]Exposure concentration, duration, and activity level
[b]1 ppm = 1.145 mg/m^3; 1 mg/m^3 = 0.873 ppm @ 25°C, 760 mm Hg; 1% = 10,000 ppm
[c]Estimated or measured blood carboxyhemoglobin (COHb) level; ND = not determined
[d]See glossary for definition of symbols
[e]Cited in U.S. Environmental Protection Agency (1979)

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individuals receiving treatment with drugs. The implications of this effect are discussed in Chapter 12, Section 12.3.

The effects of CO on tissue metabolism noted above may partially explain the body weight changes associated with CO. Short-term exposure to 250-1000 ppm for 24 h was reported previously to cause weight loss in laboratory rats (Koob et al., 1974) but no significant body weight effects were reported in long-term exposure studies in laboratory animals at CO concentrations ranging from 50 ppm for 3 mo to 3000 ppm for 300 days (Theodore et al., 1971; Musselman et al., 1959; Campbell, 1934; Stupfel and Bouley, 1970). It is quite probable that the initial hypoxic stress resulted in decreased weight gain followed by compensation for the hypoxia with continued exposure by adaptive changes in the blood and circulatory system (see Section 10.3). It is known, however, that CO-induced hypoxia during gestation will cause a reduction in the birthweight of laboratory animals. While a similar effect has been difficult to demonstrate in humans exposed to CO alone, there is a strong correlation between maternal cigarette smoking and reduced birthweight. (See Section 10.5 for a more complete discussion of fetal effects of CO exposure.)

Inhalation of high levels of CO, leading to COHb concentrations greater than 10 to 15%, have been reported to cause a number of systemic effects in laboratory animals as well as effects in humans suffering from acute CO poisoning. Tissues of highly active oxygen metabolism, such as heart, brain, liver, kidney, and muscle, may be particularly sensitive to CO poisoning. The impairment of function in the heart and brain caused by CO exposure is well known and has been described in other sections of this chapter. Other systemic effects of CO poisoning are not as well known and are, therefore, less certain. There are reports in the literature (see Table 10.6-1) of effects on liver (Katsumata et al., 1980), kidney (Kuska et al., 1980), and bone (Zebro et al., 1983). Results from one additional study in adult guinea pigs suggest that immune capacity in the lung and spleen was affected by intermittent exposure to high levels of CO for 3 to 4 weeks (Snella and Rylander, 1979). It generally is agreed that these systemic effects are caused by the severe tissue damage occurring during acute CO poisoning due to (1) ischemia resulting from the formation of COHb, (2) inhibition of O_2 release from HbO_2, (3) inhibition of cellular cytochrome function (e.g., cytochrome oxidases), and (4) metabolic acidosis.

The effects of CO on visual acuity and dark adaptation, caused primarily by CNS alterations, were described previously (see Section 10.4). Besides central effects, however, acute CO exposure can cause damage at the sensory end-organ level. Observed ocular effects from acute CO poisoning range from retinal hemorrhages (Dempsey et al., 1973; Kelley and Sophocleus, 1978) to blindness (Duncan and Gumpert, 1983; Katafuchi et al., 1985). In addition, peripheral neuropathy and tortuous retinal vessels have been described after chronic, intermittent exposure to low levels of CO over a 16-mo period (Trese et al., 1980). The authors of the latter report speculated that increased blood flow from low-level, chronic exposure to CO may lead to the development of a compensatory retinal vascular tortuosity. With high-level, acute exposures to CO, the compensation will not take place and localized vascular hemorrhages result.

Finally, exposure to CO has been associated with direct and indirect mutagenic activity (van Houdt et al., 1987), as measured by the Salmonella/microsome test (Ames et al., 1975). When tested in human populations living in the San Francisco Bay area, however, no significant association was found between ambient levels of CO and site-specific cancer incidence (Selvin et al., 1980). A case-control study of persons with newly diagnosed multiple myeloma living in four geographical locations of the United States found an increased risk for self-respondents reporting an exposure to combustion products including CO (Morris et al., 1986). The difference in number of cases was small when compared to geographically matched controls and the exposure was not defined well. Given the limited information available at this time, it is unlikely that exposure to CO would contribute significantly to the development of cancer in nonoccupationally exposed individuals.

10.7 ADAPTATION, HABITUATION, AND COMPENSATORY RESPONSES TO CARBON MONOXIDE EXPOSURE

This section considers whether exposure to CO eventually will lead to the development of physiological responses that tend to offset some of the deleterious effects. While there is possibly a temporal continuum in such processes, in this review the term "adaptation" will be used to refer to long-term phenomena, and the term "habituation" will refer to short-term processes. Allusions will be made, where possible, to the physiological chain of events by

which adaptation and habituation come about, but extensive reductive explanations will be avoided. The term "compensatory mechanism" will be used to refer to those physiological responses that tend to ameliorate deleterious effects, whether in the long-term or short-term case.

10.7.1 Short-Term Habituation

Arguments have been made for the possibility that there exist short-term compensatory mechanisms for CO exposure. These hypothetical mechanisms have been (1) based upon physiological evidence, and (2) used to account for certain behavioral findings reported in the literature.

There is physiological evidence for responses that would compensate for the deleterious effects of CO in a very short time span. As discussed in Section 10.4, CO exposure has been demonstrated to produce an increased cerebral blood flow which is apparently produced by cerebrovascular vasodilation. It also has been shown (Doblar et al., 1977; Miller and Wood, 1974; Traystman, 1978; Zorn, 1972), however, that the tissue PO_2 values for various CNS sites fall in proportion to COHb, despite the increased blood flow. Apparently, the PO_2 values would fall considerably more without the increased blood flow. Although the published graphs of these data do not show very short time intervals, it appears that tissue PO_2 falls immediately and continuously as COHb rises. Although there is no evidence for time delays or for threshold effects in these data, it is noteworthy that only very high CO levels were employed. Thus, the saturation rates were high, and time lags or thresholds would be difficult to detect.

As discussed in Section 10.3, both coronary blood flow and O_2 extraction in the peripheral musculature increase as COHb rises. These, too, are compensatory mechanisms, but mechanisms that have been shown to be only partly effective. None of the studies present evidence of time lags or threshold effects, because only terminal or near-asymptotic values were reported.

The behavioral work upon which short-term habituation hypotheses have been predicated are mostly human studies, where CO exposure at very low levels or at very early exposure times (well before asymptotic saturation) have shown performance decrements that were not apparent with higher or longer exposures (Section 10.4). Depending upon the particular

version, the habituation hypothesis holds that there might exist some threshold value of CO below which no compensation would be initiated, or that there might be some time lag in the compensatory mechanism so that the early effects of CO exposures would later subside. The behavioral data to support this contention have been controversial and need to be examined closely.

Most of the hypotheses about compensatory mechanisms were based, however, upon post hoc reasoning to explain empirical findings, not upon results form experiments to test the existence or nature of such mechanisms. Disregarding hypothesized time lags and thresholds, without the compensatory mechanisms CO would apparently have even more deleterious effects and the threshold for such effects would be lower.

10.7.2 Long-Term Adaptation

Adaptation is an all-inclusive term that incorporates all of the acute or chronic adjustments of an organism to a stressor. It does not indicate (or predict) whether the adjustments are initially or eventually beneficial or detrimental. Acclimatization is an adaptive process that results in reduction of the physiological strain produced by exposure to a stressor. Generally, the main effect of repeated, constant exposure to the stressor is considered to result in an improvement of performance or a reduced physiological cost. Both of these phenomenon tend to exploit the reserve potential of the organism.

It generally is agreed that adaptation to lowered levels of oxygen tension and oxygen-carrying capacity can occur with continued hypoxic exposure. This is evident especially in healthy individuals living for lengthy periods of time at high terrestrial altitudes. It should be noted, however, that there is no assurance that individuals moving from low altitudes to higher ones will attain the physiological status to the higher altitudes that is observed in natives (viz. natives of the Andes and Himalayas). Prominent features of prolonged altitude exposures are increases in hemoglobin concentration and hematocrit. Additional alterations are right ventricular hypertrophy, pulmonary artery vasoconstriction, possible changes in cardiac output, and increased blood volume due to increases in the red cell mass.

Whether or not adaptation can occur in individuals chronically exposed to various ambient concentrations of CO remains unresolved. Concern for CO intoxication in England and Scandinavia led to the speculation that adaptational adjustments could occur in man (Grut,

1949; Killick, 1940). These concerns were directed to situations where high ambient CO concentrations were present. There are only a few available studies conducted in humans.

Killick (1940), using herself as a subject, reported that she developed acclimatization as evidenced by diminished symptoms, slower heart rate, and the attainment of a lower COHb equilibrium level following exposure to a given inspired CO concentration. Interestingly, Haldane and Priestly (1935) already had reported a similar finding as to the attainment of a different COHb equilibrium following exposure to a fixed level of CO in the ambient air.

Killick (1948) repeated her CO-exposure studies in an attempt to obtain more precise estimations of the acclimatization effects she had noted previously. The degree of acclimatization was indicated by (1) a diminution in severity of symptoms during successive exposure to the same concentrations of CO, and (2) a lower COHb level after acclimatization than that obtained prior to acclimatization during exposure to the same concentrations of inhaled CO.

Before using herself as a subject, Killick (1937) studied the effects of CO on laboratory animals. Mice were exposed to successively higher concentrations of CO, which in a period of 6 to 15 weeks reached levels of 2300 to 3275 mg/m^3 (2000 to 2850 ppm) CO and produced 60 to 70% COHb. The nonadapted mice exhibited much more extreme symptoms when exposed to such levels. A control group was used to partially rule out effects of selection of CO-resistant animals.

Clark and Otis (1952) exposed mice to gradually increasing CO levels over a period of 14 days until a level of 1380 mg/m^3 (1200 ppm) was reached. When exposed to a simulated altitude of 34,000 ft, survival of the CO-adapted groups was much greater than controls. Similarly, Clark and Otis (1952) acclimatized mice to a simulated altitude of 18,000 ft and showed that these altitude-adapted mice survived 2875 mg/m^3 (2500 ppm) CO better than controls. Wilks et al. (1959) reported similar effects in dogs.

Gorbatow and Noro (1948) showed that rats given successive daily short-term exposures could tolerate, without loss of consciousness, longer and longer exposures. Their CO-exposure levels were 2875 to 11,500 mg/m^3 (2000 to 10,000 ppm). Increases in tolerance to CO began to be evident as early as the fourth or fifth day of exposure and still were occurring as late as the 47th day. Nonexposure for several days eliminated some of the adaptation. Similar results were reported by Zebro et al. (1976).

Chronic CO exposure of rats increases hemoglobin concentration, hematocrit, and erythrocyte counts via erythropoietin production (see Section 10.3.4). Penney et al. (1974) concluded that the threshold for the erythropoietin response was 100 ppm (9.26% COHb). Cardiac enlargement, involving the entire heart during CO exposure (compared to right ventricular hypertrophy with high-altitude exposure), is induced when ambient CO is near 200 ppm, producing COHb levels of 15.8% (Penney et al., 1974). Blood volume of the rat exposed for 7.5 weeks to CO exposures peaking at 1300 ppm nearly doubled while erythrocyte mass more than tripled (Penney et al., 1988). After 42 days of continuous exposure to 500 ppm, rat blood volume almost doubled, primarily as a consequence of increases in erythrocytes (Davidson and Penney, 1988). It should be noted that all the demonstrated effects on tissues and fluids are induced by long-term exposures to high CO concentrations. McGrath (1989) exposed rats for 6 weeks to altitudes ranging from 3,300 ft (ambient) to 18,000 ft and to concentrations of CO ranging from 0 to 500 ppm. At 9 and 35 ppm CO, where COHb levels ranged from 0.9 to 3.3%, there were no significant changes in body weight, right ventricular weight, hematocrit, or hemoglobin. Small but nonsignificant changes in these variables were measured when the CO concentration was 100 ppm and COHb levels ranged from 9.4 to 10.2%. This is consistent with the observations noted above (Penney et al., 1974) – that the threshold for erythropoietin effects was 100 ppm.

Besides the level of exposure, the time course of exposure to CO also is important. As discussed in Section 10.3.4, Hb increases in laboratory animals exposed to CO after about 48 h, and continues to increase in the course of continued exposure until about 30 days, depending perhaps upon exposure level. This hemopoietic response to long-term CO exposure is similar to that shown for long-term hypoxic hypoxia, except that it is slower to start and tends to offset CO hypoxic effects.

Most investigators have at least implied that increased Hb level is the mechanism by which adaptation occurs. Certainly this explanation is reasonable for the studies showing increased survival in groups adapted for several days. Little has been done, however, to elucidate the extent to which such increases offset the deleterious effects of CO. The probability that some adaptation occurs is supported theoretically due to Hb increases, and

empirically in the findings of laboratory animal studies measuring survival time. But adaptation has not been demonstrated for specific health effects other than survival time.

Compensatory increases in Hb are not without deleterious consequences of their own, such as cardiac hypertrophy (see Section 10.3.4). The Hb increases also are not entirely compensatory at all CO levels in view of the fact that deleterious effects still occur at some CO levels for many physiological systems. It is possible, however, that without such mechanisms as Hb increases, CO effects would be worse or would occur at lower exposure concentrations.

10.7.3 Summary

The only evidence for short- or long-term COHb compensation in man is indirect. Experimental animal data indicate that COHb levels produce physiological responses that tend to offset other deleterious effects of CO exposure. Such responses are (1) increased coronary blood flow, (2) increased cerebral blood flow, (3) increased hemoglobin through increased hemopoiesis, and (4) increased O_2 consumption in muscle.

Short-term compensatory responses in blood flow or O_2 consumption may not be complete or might even be lacking in certain persons. For example, from laboratory animal studies it is known that coronary blood flow is increased with COHb, and from human clinical studies it is known that subjects with ischemic heart disease respond to the lowest levels of COHb (5%, or less). The implication is that in some cases of cardiac impairment, the short-term compensatory mechanism is impaired.

From neurobehavioral studies, it is apparent that decrements due to CO have not occurred consistently in all subjects, or even in the same studies, and have not demonstrated a dose-response relationship with increasing COHb levels. The implication from this data suggests that there might be some threshold or time lag in a compensatory mechanism such as increased cerebral blood flow. Without direct physiological evidence in either laboratory animals or, preferably humans, this concept only can be hypothesized. The observed results from the neurobehavioral studies could be explained by differences or problems in experimental protocols or due to possible nonrandom sampling.

The idea of a threshold or a time lag in compensatory mechanisms should not be rejected entirely, however. There simply is no direct evidence. Studies need to be performed

to (1) measure cerebral blood flow and tissue PO_2 with low COHb levels at various ambient concentrations of CO to determine early and low level effects accurately, and (2) design behavioral studies where threshold effects or time lags are factors in the experimental protocols that can be explicitly studied.

The mechanism by which long-term adaptation would occur, if it could be demonstrated in humans, is assumed to be an increased Hb concentration via a several-day increase in hemopoiesis. This alteration in Hb production has been demonstrated repeatedly in animal studies but no recent studies have been conducted indicating or suggesting that some adaptational benefit has or would occur. Furthermore, even if the Hb increase is a signature of adaptation, it has not been demonstrated to occur at low ambient concentrations of CO. The human studies of the 1940s have not been replicated, so the question of adaptation remains unresolved.

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11. COMBINED EXPOSURE OF CARBON MONOXIDE WITH OTHER POLLUTANTS, DRUGS, AND ENVIRONMENTAL FACTORS

11.1 HIGH ALTITUDE EFFECTS OF CARBON MONOXIDE

11.1.1 Introduction

Precise estimates of the number of people exposed to CO at high altitude are not readily available. As of 1980, however, more than 4.2 (Lindsey, 1989) million people were living at altitudes in excess of 1524 m (5000 ft). Moreover, estimates obtained from several states with mountainous regions (i.e. California, Nevada, Hawaii, and Utah) indicate that more than 35 million tourists may sojourn in high altitude areas during the summer and winter months.

The potential effects on human health of inhaling CO at high altitudes are complex. Whenever CO binds to Hb it reduces the amount of Hb available to carry O_2. People at high altitudes already live in a state of hypoxemia, however, because of the reduced partial pressure of oxygen (PO_2) in the air. Carbon monoxide, by binding to Hb, intensifies the hypoxemia existing at high altitudes by further reducing transport of O_2 to the tissues. Hence, the effects of CO and high altitude usually are considered to be additive.

This consideration does not take into account the fact that within hours (perhaps sooner) of arrival at high altitude, however, hemoconcentration occurs which increases the Hb concentration. The increased Hb concentration offsets the decreased O_2 saturation and restores O_2 concentration to pre-ascent levels. Consequently, the simple additive model of COHb and altitude hypoxemia may be valid only during early altitude exposure.

The visitor newly arrived to higher altitudes may be at greater risk from CO than the adapted resident, however, because of a noncompensated respiratory alkalosis from hyperventilation, lower arterial Hb saturation without a compensatory absolute polycythemia (therefore greater hypoxemia) and hypoxia-induced tachycardia. (See Chapter 12, Section 12.5 for further discussion of this topic.)

Several factors tend to exacerbate ambient CO levels at high altitude (Kirkpatrick and Reeser, 1976). For example, in mountain communities, automobile emissions are higher. Automobiles tuned for driving at 1610 m (5280 ft) emit almost 1.8 times more CO when

driven at 2438 m (8000 ft). Automobiles tuned for driving at sea level emit almost four times more CO when driven at 2438 m. Moreover, automobile emissions are increased by driving at reduced speeds, along steep grades, and under poor-driving conditions. Therefore, large influxes of tourists driving automobiles tuned for sea-level conditions into high-altitude resort areas may drastically increase pollutant levels in general, and CO levels in particular (National Research Council, 1977). Newer automobile engine technologies, however, should significantly reduce CO emissions in general, as well as CO emissions at high altitude. Heating devices (space heaters and fireplaces) used for social effect, as well as warmth, are a second factor contributing to CO emissions in mountain resort areas. Finally, population growth in mountain areas is concentrated along valley floors; this factor combined with the reduced volume of air available for pollutant dispersal in valleys causes pollutants, including CO, to accumulate in mountain valleys. As a result of these factors, the NAAQS for CO of 9 ppm is exceeded frequently in Denver, CO, (altitude 1610 m) during the winter months (Haagenson, 1979).

Because of concern for CO exposure at high altitudes, it has been suggested that the NAAQS for CO set at sea level is probably too high for altitudes of 1500 m and above. An example of supporting data for this opinion were studies conducted before 1950 on the psychophysiological effects of high altitude and CO-induced hypoxia. These studies provided evidence for a concept that there are physiologically equivalent altitudes dependent on the ambient concentration of CO. In 1976, the states of California and Nevada adopted ambient standards for the Lake Tahoe air basin (1900 m; 6231 ft), which were more stringent than the NAAQS (i.e., 6 ppm rather than 9 ppm).

Mitchell et al. (1979) justified this concept by stating that "equivalent carboxyhemoglobin levels observed at sea level would occur during exposure to lower ambient CO concentrations at 1500 m." The high-altitude standard was calculated from the model developed by Coburn et al. (1965). This model was developed for quasi-steady-state responses to low CO concentrations, such as those produced endogenously, however, and was not intended to apply to other, exogenous sources of CO (see Chapter 9 for a description of the model). Collier and Goldsmith (1983) acknowledged that an error was made in the original calculations for the California-Nevada high-altitude standard. They expanded the

computations to include factors relating to the ambient CO concentrations and altitude and concluded, based on their model calculations, that the expected altitude effect would be small.

11.1.2 Carboxyhemoglobin Formation

The effects of high altitude on COHb formation have been considered in a theoretical paper by Collier and Goldsmith (1983). Transforming and rearranging the Coburn-Foster-Kane equation (Coburn et al., 1965), these workers derived an equation expressing COHb in terms of endogenous and exogenous sources of CO. Thus,

$$SCO = \frac{FICO\,(P_B\text{-}47)}{10^6\,K} + \frac{\dot{V}CO\,Z}{K} \qquad (11\text{-}1)$$

where:

SCO	=	COHb (%)
FICO	=	Fraction inspired CO (ppm)
P_B	=	Barometric Pressure (torr)
$\dot{V}CO$	=	Rate of CO production (mL•min^{-1} STPD)
K	=	$P_{\bar{c}}O_2/(M \times SO_2)$
Z	=	$1/D_LCO + (P_B\text{-}47/(\dot{V}_A)$

and

$P_{\bar{c}}O_2$	=	mean partial pressure of pulmonary capillary O_2 (torr)
M	=	Haldane constant
SO_2	=	O_2 Hb (%)

and

D_LCO	=	CO diffusing capacity (mL•min^{-1}•torr^{-1})
$(\dot{V}_A)$	=	alveolar ventilation (mL•min^{-1} STPD)

According to this relationship, a given PCO will result in a higher percent COHb at high altitudes (where PO_2 is reduced). Thus, Collier and Goldsmith calculate that humans breathing 8 ppm CO will have equilibrium COHb levels of 1.4% at sea level and 1.6, 1.8, and 1.8%, respectively, at 1530, 3050, and 3660 m (Table 11-1). Moreover, these workers calculate an increase in COHb at altitude even in the absence of inhaled CO (due to endogenous production of CO).

TABLE 11-1. CALCULATED EQUILIBRIUM VALUES OF PERCENT COHb AND PERCENT O_2Hb IN HUMANS EXPOSED TO AMBIENT CO AT VARIOUS ALTITUDES

Ambient CO (ppm)	Sea level		530 m		3050 m		3660 m	
	% COHb	% O_2Hb	% COHb	% O_2Hb	% COHb	% O_2Hb	% COHb	% O_2Hb
0	0.20	97.3	0.26	93.6	0.35	82.4	0.37	73.3
4	0.8	96.8	0.9	93.0	1.1	82.1	1.1	73.1
8	1.4	96.2	1.6	92.5	1.8	81.7	1.8	72.9
12	2.1	95.6	2.3	91.9	2.5	81.3	2.5	72.7
16	2.7	95.1	2.9	91.4	3.2	80.9	3.2	72.5

Notes: The table is for unacclimatized, sedentary individuals at one level of activity ($\dot{V}O_2$ = 500 ml•min^{-1}).

Source: Adapted from Collier and Goldsmith (1983).

11.1.3 Cardiovascular Effects

There are studies comparing the cardiovascular responses to CO with those to high altitude, but there are relatively few studies of the cardiovascular responses to CO at high altitude (see Table 11-2). Forbes et al. (1945) reported that CO uptake increased during six minutes of exercise of varying intensity on a bicycle ergometer at 4877 m (16,000 ft). The increased CO uptake was caused by altitude hyperventilation stimulated by decreased arterial O_2 tension and not by diminished barometric pressure.

Pitts and Pace (1947) reported that pulse rate increased in response to the combined stress of high altitude and CO. The subjects were 10 healthy men who were exposed to simulated altitudes of 2134, 3048 and 4572 m (7000, 10,000, and 15,000 ft) and inhaled 3000 or 6000 ppm CO to obtain COHb levels of 6 or 13%, respectively. The mean pulse rate during exercise and the mean pulse rate during the first five minutes after exercise were correlated with and increased with the COHb concentration and simulated altitude. The authors concluded that the response to a 1% increase in COHb level was equivalent to that

TABLE 11-2. SUMMARY OF EFFECTS OF CARBON MONOXIDE AT ALTITUDE

Exposure	COHb	Subject	Dependent Variable	Results	Comments	Reference
Alt = 4,877 m 3,000-4,000 ppm CO 6 min exercise	–	Human (n=3	Blood CO	CO uptake increased with altitude	Caused by altitude hyperventilation.	Forbes et al. (1945)
Alt = 1,524 - 1,848 m CO = 1,500-2,000 ppm	5-10%	Human (n=5)	Flicker fusion frequency (FFF)	FFF decreased with CO at altitude	FFF not affected by altitude or COHb alone; 8-10% COHb reduced altitude tolerance by 1,215 m.	Lillianthal & Fugitt (1946)
Alt = 3,070-4,555 m CO = 2,800-5,600 ppm	5-22%	Human (n=20)	Critical flicker frequency (CFF), body sway (BS), red visual field (RVF)	CFF, BS, and RVF impaired by altitude; no added effect of CO	No correlation of any response with COHb. Effects of CO may be masked by compensatory effect.	Vollmer et al. (1946)
Simulated alt = 2,134, 3,048, 4,572 m (16, 14, 11% O_2 + N_2) 3,000 or 6,000 ppm CO treadmill exercise	6 and 13%	Human (n=10)	Pulse rate	Pulse rate during and 5 min after exercise increased with altitude and COHb	Response to 1% COHb equivalent to increase in altitude of 335 ft. The effects of CO and altitude are additive.	Pitts & Pace (1947)
Alt = 2,134-4,877 m CO = 100-300 ppm	1.1 - 20.5%	Human (n=4)	Visual sensitivity	CO decreased visual sensitivity	Recovery from the detrimental effects of CO lagged behind elimination of CO from blood.	Halperin et al. (1959)
^{14}CO in rebreathing system P_aO_2 varied from 650 to 40 mm Hg	–	Dog (n=31)	^{14}CO in blood	No change in ^{14}CO activity in blood when P_aO_2 varied from 40 to 650 mmHg; ^{14}CO decreased to 50% control when P_aO_2 decreased below 40 mmHg	With severe arterial hypoxemia (P_aO_2 <40 mmHg) ^{14}CO shifts into extravascular tissue.	Luomanmaki & Coburn (1969)
CO administered at constant rate	2-75%	Dog (n=4)	Rate of increase in COHb	COHb increased at constant up to 50%; at 50%, rate of COHb formation decreased	Suggests that at high COHb levels CO shifts into extravascular space.	Luomanmaki & Coburn (1969)
Alt = 305-3,109 m smokers	4.77-6.66%	Human (n=62)	COHb levels	COHb in smokers higher at altitude than at sea level		Brewer et al. (1970)

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TABLE 11-2 (cont'd). SUMMARY OF EFFECTS OF CARBON MONOXIDE AT ALTITUDE

Exposure	COHb	Subject	Dependent Variable	Results	Comments	Reference
Alt = 2,438 m	5%	Human	Visual sensitivity	Visual sensitivity decreased by CO at altitude	5% COHb depresses visual sensitivity as much as 2,438-3,048 m. The effects of altitude and CO are additive.	McFarland (1970); McFarland et al. (1944)
Alt = 4,500 m CO = 4,300 ppm every second hour for 3-5 hours	20%	Human (n=16)	Capillary permeability to protein (CP)	CP increased with CO but not with altitude; plasma volume decreased with altitude	Increase in CP appears unique to CO (nonhypoxic effect).	Parving (1972)
Alt = 3,109 m Smokers	0.4-7.14%	Human (n=49)	COHb and O_2 affinities	COHb levels and O_2 affinities decreased in polycythemic smokers on cessation of smoking	O_2 dropped to lower than normal sea level values in polycythemic smokers on cessation of smoking.	Brewer et al. (1974)
Alt = 3,048 m CO bolus followed by 40 ppm. Bicycle exercise	4.2%	Human (n=12)	Cardiac output, stroke volume (SV), arterial-mixed venous O_2 difference (A-V)	At altitude, cardiac output increased and SV and A-V decreased in nonsmokers; no effect on smokers.	Smokers may be partially adapted to hypoxic environments and CO.	Wagner et al. (1978)
Alt = 1,610 m CO = 100% bolus	5%	Human (n=9)	Work performance	Increased working HR, and shortened post-exercise LV ejection time; lowered anaerobic threshold	CO impaired exercise performance to same degree as at sea level.	Weiser et al. (1978)
Alt = 1,524 m CO = 160-200 ppm 6 weeks	20%	Goat (n=6)	Cardiac index (CI), Stoke volume (SV), Heart rate (HR), Ventricular contractility (V_{max})	No effect on CI, SV, HR, and V_{max} during exposure	After removal from CO, both HR and V_{max} were depressed.	James et al. (1979)
Alt = 3,100 m Smokers	1.8-6.2%	Human (n=44)	Infant birth weights	Maternal smoking associated with 2-3 times greater reduction in infant birth weight than at sea level	COHb levels measured in mothers were inversely related to infant birth weight.	Moore et al. (1982)

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TABLE 11-2 (cont'd). SUMMARY OF EFFECTS OF CARBON MONOXIDE AT ALTITUDE

Exposure	COHb	Subject	Dependent Variable	Results	Comments	Reference
Alt = 4,572 m CO = 500 ppm 6 weeks	36.2% and 34.1%	Rat (n=24)	Hematocrit (Hct), mean electrical axis (MEA), HW/BW ratios	Hct increased by altitude and CO; MEA shifted left with CO, right with altitude	Effects of altitude and CO on Hct, MEA, and HW/BW were additive.	Cooper et al. (1985)
Alt = 5,486 m CO = 50, 100, 500 ppm 6 weeks	5.8, 11.1, and 4.26%	Rat (n=22)	Cardiac hypertrophy, coronary capillarity	RV hypertrophy and coronary capillarity increased with altitude	Increase in coronary capillarity was blocked by CO.	McDonagh et al. (1986)
Alt = 4,572 m CO = 100 ppm 6 weeks	8.4%	Rats (n=24)	Hct ratio and weights: BW, HW, RV, LV+S, Pituitary (PiT)	Alt ↓BW, ↑Hct, ↑RV, ↑HT, ↑PiT; CO ↑Hct, ↑LV+S	Effects produced by altitude were not intensified by 100 ppm CO.	McGrath (1988)
Alt = 55, 1,524, 2,134, and 3,048 m; CO = 0, 50, 100, and 150 ppm	2.56 - 4.42%	Human (n=23) (11 men; 12 women)	Maximum aerobic capacity ($\dot{V}O_2$ max)	$\dot{V}O_2$ max decreased at 2,134m (4%) and 3,048m (8%); $\dot{V}O_2$ max decreased slightly with increasing ambient CO.	Altitude- and CO-hypoxia independently affect $\dot{V}O_2$ max; decreased COHb with increasing altitude was due, in part, to decreased driving CO pressure	Horvath et al. (1988 a,b)
Alt = 55 and 2,134 m; CO = 0 and 9 ppm for 8 h	0.2 - 0.7%	Human (n=17)	Maximum aerobic capacity ($\dot{V}O_2$ max)	$\dot{V}O_2$ max decreased 7-10% with increasing altitude at 0 ppm CO; similar effects were found after 8-h exposure to 9 ppm CO, regardless of exercise level	$\dot{V}O_2$ max was reduced in all subjects at altitude regardless of the ambient CO level	Horvath and Bedi (1989)

obtained by raising a normal group of men 102 m (335 ft) in altitude. This relationship was stated for a range of altitudes from 2134 to 3048 m (7000 to 10,000 ft) and for increases in COHb up to 13%.

Weiser et al. (1978) studied the effects of CO on aerobic work at 1610 m (5280 ft) in young subjects inhaling 100% CO until COHb levels reached 5%. They reported that this level of COHb impaired exercise performance at high altitude to the same extent as that reported at sea level (Horvath et al., 1975). Because these subjects were Denver residents and fully adapted to this altitude, however, they would have had an arterial O_2 concentration the same as at sea level (about 20 mL O_2/dL). Hence, 5% COHb would lower arterial O_2 concentration about the same amount at both altitudes and impair work performance at altitude to the same extent as at sea level. In the Weiser study, breathing CO during submaximal exercise caused small but significant changes in cardiorespiratory function; the working heart rate increased and the postexercise left ventricular ejection time shortened, but not to the same extent as when filtered air was breathed. CO lowered the anaerobic threshold and, at work rates heavier than the anaerobic threshold, increased minute ventilation.

Wagner et al. (1978) studied young smokers and nonsmokers who exercised at 53% of their $\dot{V}O_2$ max at 760 and 523 torr. Carboxyhemoglobin levels were raised to 4.2%. While at altitude with these elevated COHb levels, nonsmokers increased their cardiac output and decreased their arterial-mixed venous O_2 differences. Smokers did not respond in a similar manner. Smokers, with their initial higher Hb concentrations, may have developed some degree of adaptation to CO and/or high altitude.

Horvath et al. (1988) in a complex study involving four altitudes (up to 3050 m) and four ambient CO concentrations (up to 150 ppm) evaluated COHb levels during a maximal aerobic capacity test. They concluded that $\dot{V}O_2$ max values determined in men were only slightly diminished due to increased ambient CO. Carboxyhemoglobin concentrations attained at maximum were highest at 55 m (4.42%) and lowest at 3035 m (2.56%) while breathing 150 ppm CO (Figure 11-1). This was attributed to the reduced partial pressure of CO at high altitude. No additional effects that could be attributed to the combined exposure to high altitude and CO were found. Independence of the altitude and CO hypoxia was demonstrated under the condition of performing a maximum aerobic capacity test. The reductions in $\dot{V}O_2$

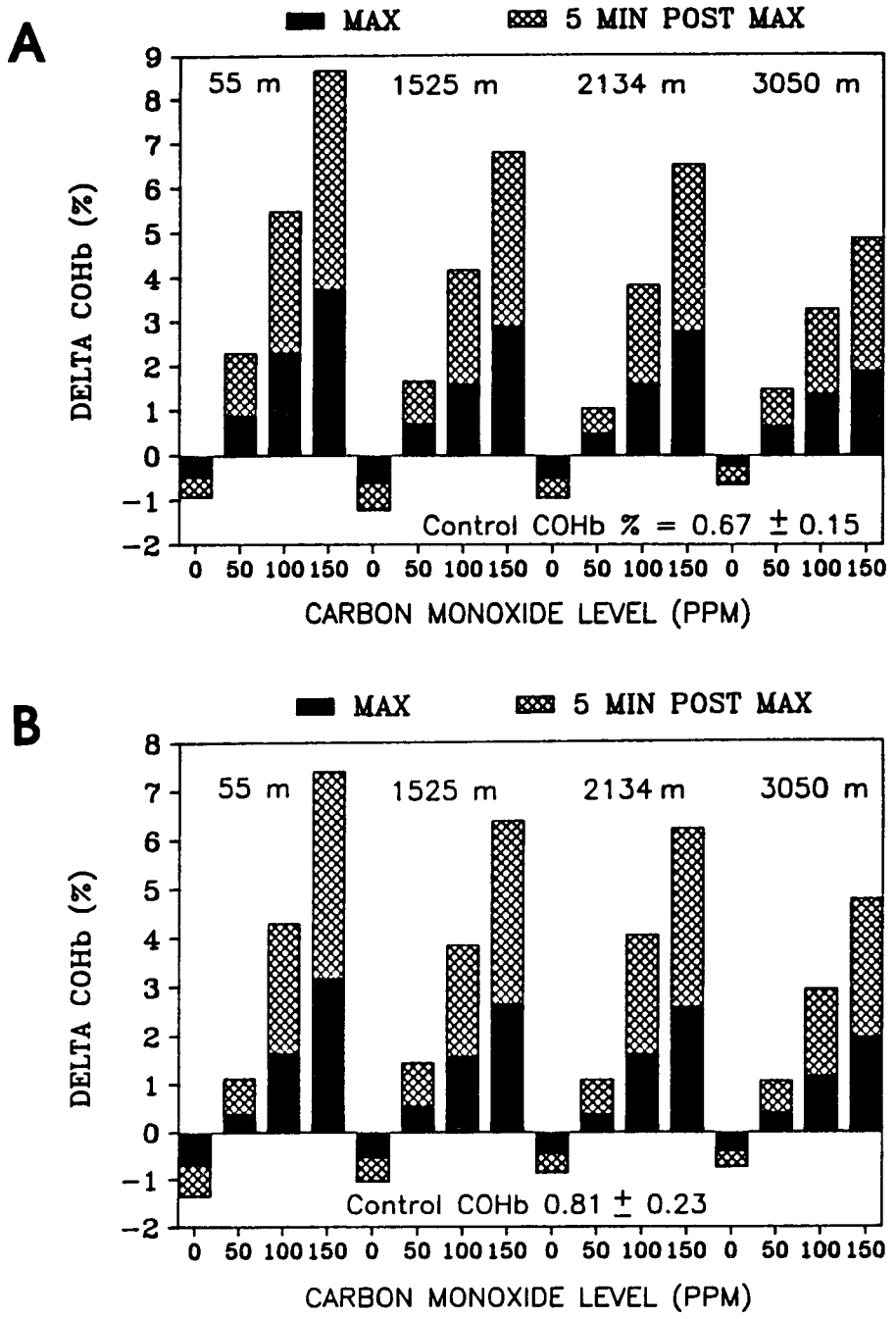

Figure 11-1. Increment in percent carboxyhemoglobin (Δ% HbCO) over basal (control) levels at the end of a maximum aerobic capacity test and at the 5th min of recovery from a test in a typical (A) male and (B) female subject. Altitudes are 55, 1524, 2134, and 3048 m, whereas exercise was conducted with ambient concentrations of 0, 50, 100, and 150 ppm CO.

Source: Horvath et al. (1988).

max due to high altitude and to the combined exposure of ambient CO and high altitude were similar.

Horvath and Bedi (1989) studied 17 nonsmoking young men to determine the alterations in COHb during exposure to 0 or 9 ppm ambient CO for eight hours at sea level or an altitude of 2134 m (7000 ft). Nine subjects rested during the exposures and eight exercised for the last 10 minutes of each hour at a mean ventilation of 25 L (BTPS). All subjects performed a maximal aerobic capacity test at the completion of their respective exposures. At the low CO concentrations studied, the Coburn, Forster, and Kane (CFK) equation estimated COHb levels to be 1.4% (Petersen and Stewart, 1975). Carboxy-hemoglobin concentrations fell in all subjects during their exposures to 0 ppm CO at sea level or 2134 m. During the eight hour exposures to 9 ppm CO, COHb levels rose linearly from approximately 0.2 to 0.7% (Figures 11-2). No significant differences in uptake were found whether the subjects were resting or intermittently exercising. Levels of COHb were similar at both altitudes. A portion of the larger estimate of COHb determined by the CFK equation could be accounted for by the use of an assumed blood volume. Maximal aerobic capacity was reduced approximately 7 to 10% consequent to altitude exposure during 0 ppm CO. These values were not altered following eight-hour exposure to 9 ppm CO in either resting or exercising individuals.

11.1.4 Chronic Studies

There have been few studies of the long-term effects of CO at altitude (see Table 11-2). James et al. (1979) studied cardiac function in six unsedated goats that were chronically instrumented and exposed to 160 to 200 ppm CO (COHb = 20%) for six weeks at 1524 m. Cardiac index and stroke volume were unchanged during and after the exposure. Heart rate and contractility (V_{max}) of the left ventricular myocardium were unchanged during exposure to CO, but both were depressed during the first week after removal of the CO. The authors concluded that if there was a decrease in intrinsic myocardial function during the CO exposure, it may have been masked by increased sympathetic activity.

McGrath (1988; 1989) studied cardiovascular, body, and organ weight changes in rats exposed continuously for six weeks to (1) ambient altitude, (2) ambient altitude + CO,

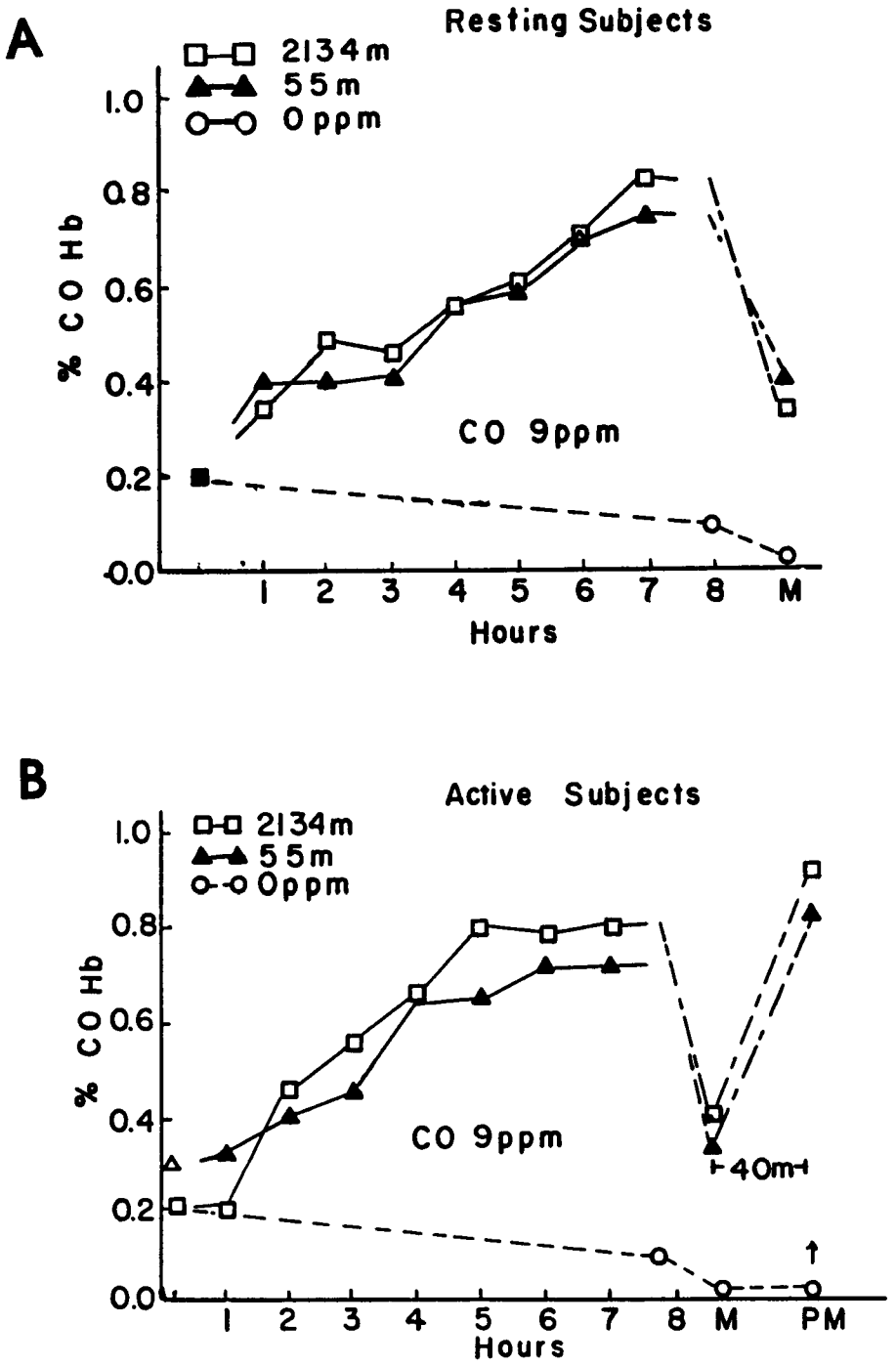

Figure 11-2. Change in carboxyhemoglobin concentration (% COHb) during eight-hour exposures to 0 to 9 ppm CO for (A) resting and (B) exercising subjects. Altitudes are sea level (55 m) and 2134 m (7000 ft).

Source: Horvath and Bedi (1989).

(3) simulated high altitude, and (4) CO at high altitude. Altitudes ranged from 3300 ft (1000 m) to 18,000 ft (5486 m) and CO concentrations from 0 to 500 ppm.

Carbon monoxide had no effect on body weight at any altitude. There was a tendency for hematocrit to increase even at the lowest concentration of CO (9 ppm), but the increase did not become significant until 100 ppm. At 10,000 ft, there was a tendency for the total heart weight to increase in rats inhaling 100 ppm CO. Although its effects on the heart at high altitude are complex, CO, in concentrations of 500 ppm or less, had little effect on the right ventricle; it did not exacerbate any effects due to altitude. There was a tendency for the left ventricle weight to increase with exposure to 35 ppm carbon monoxide at high altitude, but the increase was not significant until 100 ppm CO. Heart rate, blood pressure, cardiac output, and peripheral resistance were unaffected by exposure to 35 ppm CO or 10,000-ft altitude, singly or in combination. The author concluded that six weeks of exposure to 35 ppm CO does not produce measurable effects in the healthy laboratory rat, nor does it exacerbate the effects produced by exposure to 10,000-ft altitude.

The data reported by McGrath (1988; 1989) are generally in agreement with findings reported by other investigators. Carboxyhemoglobin obtained at the end of the six weeks of exposure to CO are presented in Figure 11-3. The COHb concentrations were (at 3300 ft) 0.6, 0.9, 2.4, 3.7, and 8.5% for ambient CO levels of 0, 9, 35, 50, and 100 ppm, respectively. This relationship can be expressed as:

$$\%COHb = 0.115 + 0.08x \qquad (11\text{-}2)$$

where x is the CO exposure, in ppm. The correlation coefficient (r) for this relationship was 0.99. The changes at other altitudes were not sufficient to calculate the rate of increase. Exposure of rats to 500 ppm and altitudes up to 18,000 ft resulted in COHb levels of 40 to 42%. An interesting, but not unexpected, finding in this study was that high altitude residence in the absence of exogenous CO resulted in increased basal COHb concentrations. These values were 0.6, 1.3, 1.7, and 1.9% for altitudes from 3300 to 18,000 ft. These increases can be expressed as:

$$\%COHb = 0.0000914 + 0.26687x \qquad (11\text{-}3)$$

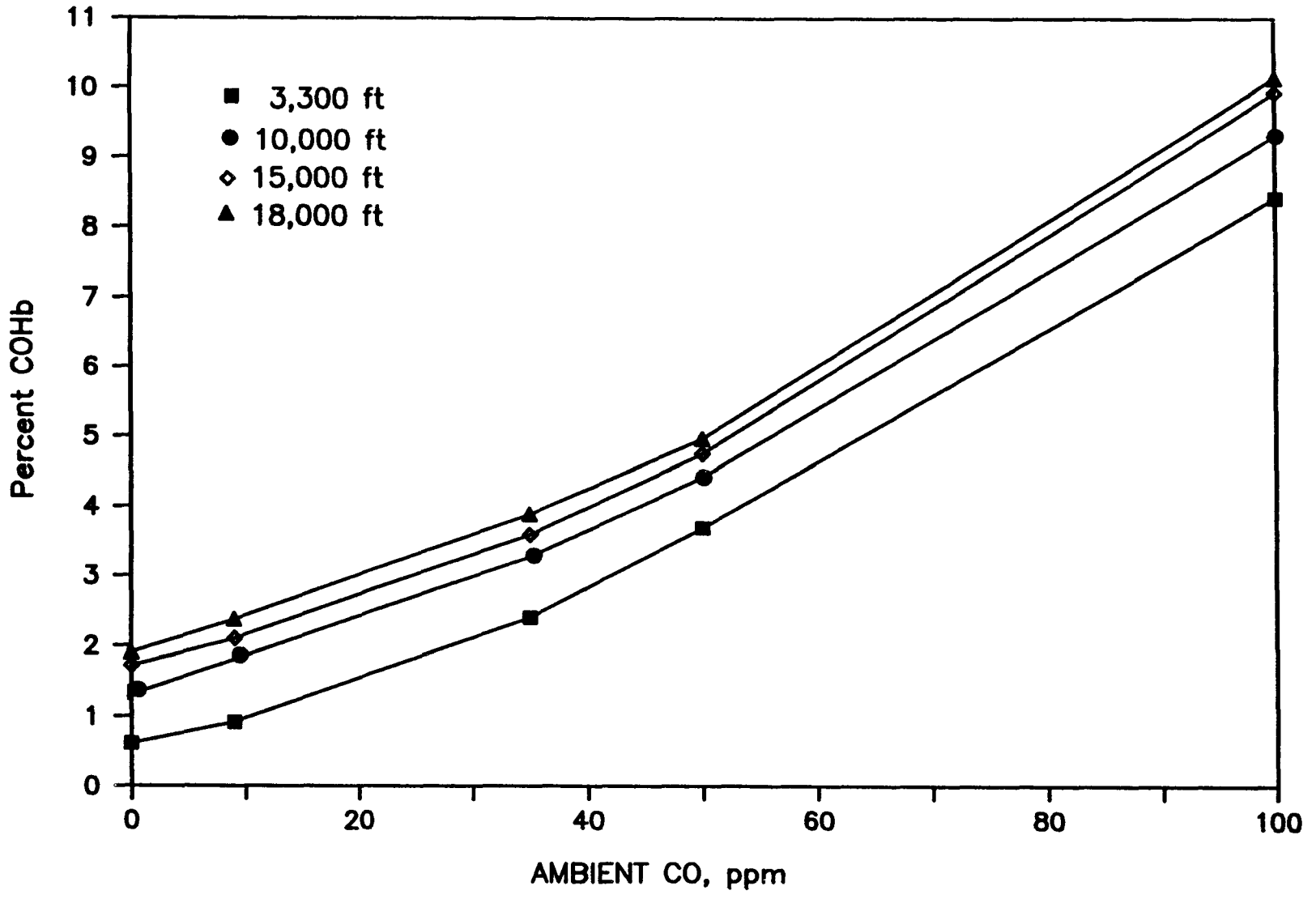

Figure 11-3. The effects of altitude and ambient CO exposure on COHb in Fischer 344 rats.

where x is altitude, in feet. The correlation coefficient (r) for this relationship was 0.99. Whether similar increases in basal COHb concentrations would be observed in humans adapted to altitude needs to be determined. Presumably, because there are marked elevations in Hb and Hct in residents of high altitudes, a greater endogenous CO production might be present. In this study, 100 ppm CO had no effect on body, right ventricle, total heart, adrenal, spleen, or kidney weights, but it did increase Hct ratios and left ventricle weights. There was no significant interaction between altitude and CO on any parameter except kidney weight. The author concluded that although there was a tendency for hematocrit ratios, spleen weights, and total heart weights to be elevated by combined CO-altitude exposure, the results were not significant and, in general, the effects produced by 4572-m altitude were not intensified by exposure to 100 ppm CO.

McDonagh et al. (1986) studied cardiac hypertrophy and ventricular capillarity in rats exposed to 5486 m (18,000 ft) and 50, 100, and 500 ppm CO. Coronary capillarity increased after exposure to 5486 m for six weeks, but this response was blocked by CO. Right ventricular thickness was increased by altitude, but was not increased further by CO. At 500 ppm, CO the right ventricular hypertrophy was attenuated, but the results are uncertain due to the high mortality in this group. Left ventricular thickness also was increased at 5486 m (18,000 ft) and increased further by CO. The authors concluded that because the ventricular thickness is increased while capillarity is reduced, it is possible that the myocardium can be underperfused in the altitude plus CO group.

Cooper et al. (1985) evaluated the effects of CO at altitude on EKGs and cardiac weights in rats exposed for six weeks to (1) ambient (amb), (2) ambient + 500 ppm CO (amb+CO), (3) 4572 m (15,000 ft) (alt), and (4) 4572 m + 500 ppm CO (alt+CO). COHb values were 36.2 and 34.1% in the amb+CO and alt+CO groups, respectively. Hematocrits were 54 $\pm$ 1, 77$\pm$ 1, 68 $\pm$ 1, and 82$\pm$ 1%, in the amb, amb+CO, alt, and alt+CO groups, respectively. In the amb+CO, alt, and alt+CO groups, respectively, the mean electrical axis shifted 33.2° left, 30° right, and 116.4° right. Heart weight to body weight ratios were 2.6, 3.2, 3.2, and 4.0 $\times$ 10^{-3} in the amb, amb+CO, alt, and alt+CO groups, respectively. Whereas CO increased left ventricular weight, and alt increased right ventricular weight, alt+CO increased both. EKG changes were consistent with changes in cardiac weight.

These results indicate that whereas CO inhaled at ambient altitude causes a left electrical axis deviation, CO inhaled at 4572 m exacerbates the well-known phenomenon of right electrical axis deviation. Thus, the results from chronic animal studies indicate that there is little effect of CO on the cardiovascular system of rats exposed to CO concentrations of 100 ppm or less and altitudes up to 3030 m (10,000 ft).

Exposure to CO from smoking may pose a special risk to the fetus at altitude. Moore et al. (1982) reported that maternal smoking at 3100 m is associated with a two- to threefold greater reduction in infant birth weight than has been reported at sea level. Moreover, COHb levels of 1.8 to 6.2% measured in all pregnant subjects, were inversely related to infant birth weight. Earlier, Brewer et al. (1970, 1974) reported that the mean COHb level in smokers at altitude is higher than smokers at sea level, and that subjects who smoked had greater O_2 affinities than nonsmokers. Moreover, cessation of smoking by polycythemic individuals at altitude results in a marked reduction in COHb and a decrease in hemoglobin-O_2 affinity to values less than those reported for normal individuals at sea level. The chronic effects of altitude and CO exposure are summarized in Table 11-3.

TABLE 11-3. CHRONIC EFFECTS OF ALTITUDE AND CARBON MONOXIDE EXPOSURE

Effect	Altitude	Carbon Monoxide
Hemoglobin	↑	↑
Hematocrit	↑	↑
Pulmonary arterial pressure	↑	-
Cardiac hypertrophy		
Right ventricle	↑	-
Both ventricles	-	↑
Cardiac output[a]	↑↑	?
Blood volume	↑	↑
Body weight	↓	-

[a]Initial increase that later returns to baseline value.

11.1.5 Neurobehavioral Effects

The neurobehavioral effects following CO exposure are controversial and are described in detail in Chapter 10, (Section 10.4). Those neurobehavioral studies specifically concerned with CO exposure at altitude are reviewed briefly in this section.

McFarland et al. (1944) reported changes in visual sensitivity occurring at a COHb concentration of 5% or at a simulated altitude of approximately 2432 m (8000 ft). Later, McFarland (1970) expanded on the original study and noted that a pilot flying at 1829 m (6000 ft) breathing 0.005% CO in air is at an altitude physiologically equivalent to approximately 3658 m (12,000 ft). McFarland stated that sensitivity of the visual acuity test was such that even the effects of small quantities of CO absorbed from cigarette smoke were clearly demonstrable. In subjects inhaling smoke from three cigarettes at 2286 m (7500 ft), there was a combined loss of visual sensitivity equal to that occurring at 3048 to 3353 m (10,000 to 11,000 ft). This report was confirmed by Halperin et al. (1959), who also observed that recovery from the detrimental effects of CO on visual sensitivity lagged behind elimination of CO from the blood.

Lilienthal and Fugitt (1946) reported that combined exposure to altitude and CO decreased flicker-fusion frequency (FFF) (i.e., the critical frequency in cycles per second at which a flickering light appears to be steady). Whereas mild hypoxia (that occurring at 2743 to 3658 m (9000 to 12,000 ft)) alone impaired FFF, COHb levels of 5 to 10% decreased the altitude threshold for onset of impairment to 1524 to 1829 m (5000 to 6000 ft).

The psychophysiological effects of CO at altitude are a particular hazard in high-performance aircraft (Denniston et al., 1978). Acute ascent to altitude increases ventilation via the stimulating effects of a reduced PO_2 on the chemoreceptors. The increased ventilation causes a slight increase in blood pH and a slight leftward shift in the O_2Hb dissociation curve. Although such a small shift would probably have no physiological significance under normal conditions, it may take on physiological importance for aviators required to fly under a variety of operational conditions and to perform tedious tasks involving a multitude of cognitive processes. The leftward shift of the O_2Hb dissociation curve may be further aggravated by the persisting alkalosis caused by hyperventilation resulting from anxiety. The potential for this effect has been reported by Pettyjohn et al. (1977), who reported that respiratory minute volume may be increased by 110% during final landing approaches

requiring night-vision devices. Thus, the hypoxia-inducing effects of CO inhalation would accentuate the cellular hypoxia caused by stress and altitude-induced hyperventilation.

11.1.6 Compartmental Shifts

Studies by Luomanmaki and Coburn (1969) suggest that CO in very high concentrations may pose a special threat at higher altitudes. These workers report that during hypoxia, in anesthetized dogs, CO shifts out of the blood and into the tissues. In experiments using ^{14}CO, they observed that radioactivity in blood did not change when arterial O_2 tension increased from 50 to 500 mmHg. However, ^{14}CO activity in blood decreased to 50% of control levels when arterial PO_2 decreased below 40 mmHg; ^{14}CO shifted back into the blood when arterial PO_2 returned to normal. Because there was no significant difference between splenic and central venous ^{14}CO radioactivity either before or after the ^{14}CO shift, these workers excluded the possibility that the ^{14}CO had been sequestered in the spleen.

Luomanmaki and Coburn (1969) also studied the shift of CO out of the blood during hypoxia by administering CO into a rebreathing system and measuring the rate at which blood COHb increased. They reasoned that if the partition of CO between vascular and extravascular stores remained constant, the increase in blood COHb should be proportional to the amount of CO administered. They found that COHb increased at a constant rate up to a saturation of 50%. With additional CO, there was a decrease in the rate at which COHb increased; this suggests that proportionally greater amounts of CO were entering the extravascular stores. At 50% COHb (corresponding to an arterial PO_2 of 90 mmHg), the rate of COHb formation became nonlinear. Agostoni et al. (1980) presented a theoretical model supporting these observations; they developed equations predicting that decreasing venous PO_2 causes CO to move out of the vascular compartment and into skeletal and heart muscle. This increases the rate at which COMb is formed in the tissues.

The shift of CO out of the blood has been further demonstrated in studies (Horvath et al., 1988) conducted on both men and women undergoing maximal aerobic capacity tests at altitudes of 55, 1524, 2134, and 3058 m and CO concentrations of 0, 50, 100, and 150 ppm. Carbon monoxide at maximum work shifted into extravascular spaces and returned to

the vascular space within five minutes after exercise stopped (Figure 11-4). This liberation of CO was related to the concentration of COHb achieved as noted by the regression equation:

$$y = 0.0017 + 0.3047x \tag{11-4}$$

where x is the COHb concentration at exhaustion.

11.1.7 Conclusions

While there are many studies comparing and contrasting inhaling CO with exposure to altitude, there are relatively few reports on the effects of inhaling CO at altitude. There are data to support the possibility that the effects of these two hypoxia episodes are at least additive. These data were obtained at CO concentrations that are too high to have much meaning for regulatory concerns. There also are data that indicate decrements in visual sensitivity and flicker-fusion frequency in subjects exposed to CO (COHb = 5 to 10%) at higher altitudes. These data, however, are somewhat controversial.

There are even fewer studies of the long-term effects of CO at high altitude. These studies generally indicate few changes at CO concentrations below 100 ppm and altitudes below 4572 m (15,000 ft). A provocative study by McDonagh et al. (1986) suggests that the increase in ventricular capillarity seen with altitude exposure may be blocked by CO. The fetus may be particularly sensitive to the effects of CO at altitude; this is especially true with the high levels of CO associated with maternal smoking.

11.2 CARBON MONOXIDE INTERACTIONS WITH DRUGS

11.2.1 Introduction

There is little direct information on the possible enhancement of CO toxicity by concomitant drug use or abuse; however, there are some data suggesting cause for concern. There is evidence that interactions of drug effects with CO exposure can occur in both directions, that is, CO toxicity may be enhanced by drug use and the toxic or other effects of drugs may be altered by CO exposure. Nearly all the published data that are available on CO combinations with drugs concern psychoactive drugs. Possible interactions of CO with

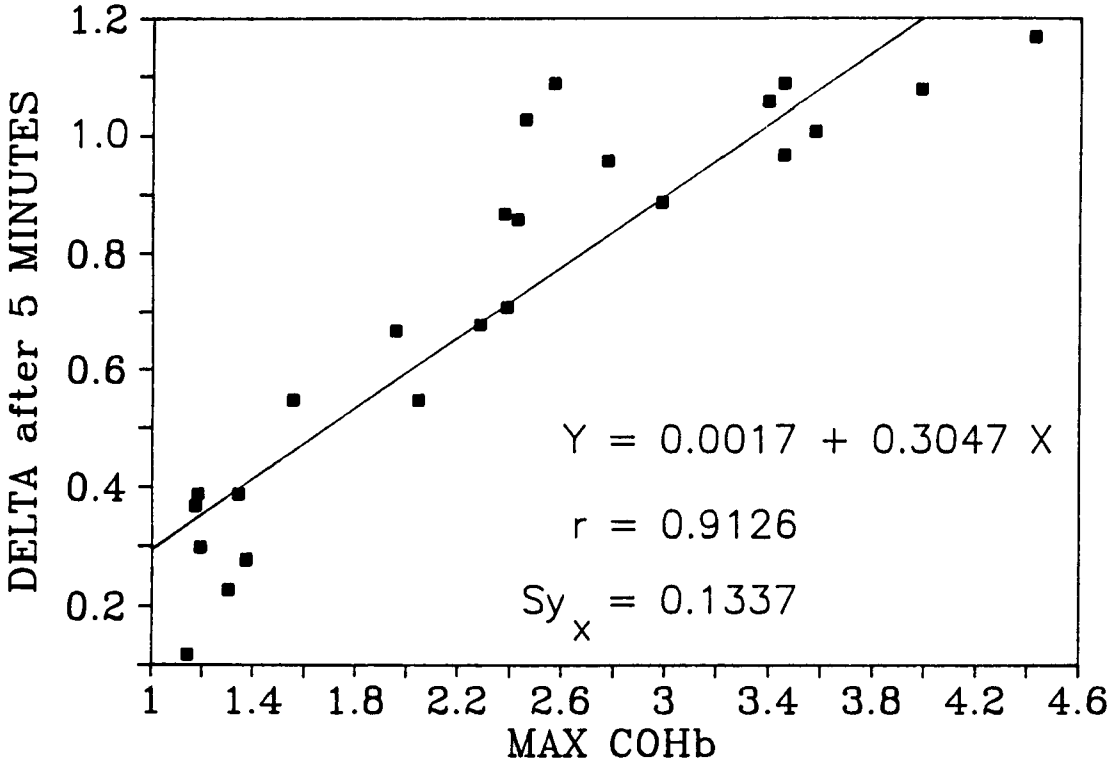

Figure 11-4. Higher concentrations of COHb observed at the end of a five-minute recovery period after attainment of the subject's maximum aerobic capacity indicate that liberation of CO from tissue stores is linearly related to COHb concentration present at exhaustion.

Source: Horvath et al. (1988).

other classes of drugs (e.g., those likely to be used in patients with cardiovascular disease who also are at risk for CO exposure) will be discussed elsewhere in this document (see Chapter 12, Section 12.4). Another related area of concern that will be reviewed elsewhere is interactions of CO with other toxicants (see Section 11.3).

The use and abuse of psychoactive drugs and alcohol is ubiquitous in society. Because of CO's well-established effects on brain functioning, interactions between CO and psychoactive drugs could be anticipated. Unfortunately, very little systematic research has addressed this question. In addition, very little of the research that has been done has utilized models for expected effects for treatment combinations. Thus, often it is not possible to assess whether the combined effects of drugs and CO exposure are additive or differ from additivity. It is important to recognize that even additive effects of combinations can be of clinical significance, especially when the individual is unaware of the combined hazard.

11.2.2 Alcohol

The effects of combined CO exposure and alcohol (ethanol) administration have been the most extensively studied interaction. The previous criteria document (U.S. Environmental Protection Agency, 1979) reviewed two human studies which examined combinations of CO and alcohol. A study from the Medical College of Wisconsin (1974) found no effects of alcohol doses resulting in blood alcohol levels of about 0.05% and COHb levels in the general range of 8 to 9%, either alone or in combination, on a number of psychomotor behavioral tasks. The lack of sensitivity of these measures to alcohol doses known to affect performance under many other conditions, as well as other problems in the study design, raises the question of the adequacy of this study to detect interactive effects. Rockwell and Weir (1975) studied the interaction of CO exposures resulting in nominal 0, 2, 8, and 12% COHb levels with alcohol doses resulting in nominal 0.05% blood alcohol levels for effects on actual driving performance in young, nonsmoking college students. Dose-related effects of CO for perceptual narrowing and decreased eye movement were observed. In addition, effects were observed on some measures by this dose of alcohol alone. An effect-addition model was used to evaluate the alcohol-CO interaction. In combination, the effects of CO and alcohol were often additive, and there was a supra-additive alcohol-CO interaction at 12% COHb levels. Although the 1979 review highlighted the lack of an interaction effect except at high COHb

concentrations, it should be noted that interaction effects for this study were defined as effects greater than the sum of the effects of the treatments alone. Thus, this extensive study in human subjects provides some evidence that driving-related performances already disrupted by alcohol could be further compromised by CO exposure.

Because of a concern that persons exposed to CO may not be able to detect odors that would indicate a fire or other hazardous condition, especially when consuming alcohol, Engen (1986) conducted a carefully controlled study of combined CO-alcohol exposure in human subject volunteers. The detection of a threshold concentration of the smoky odor of quaiacol was evaluated using signal-detection analysis. The dose of alcohol given resulted in blood alcohol levels of about 0.04 to 0.07% and CO exposure resulted in COHb values of 7.0 to 7.7%. In signal detection studies, d' is a measure of detection threshold, with higher values reflecting greater detection. The average *d'* for the four treatment conditions was as follows: air only (1.95), CO only (2.34), alcohol + air (2.20), and alcohol + CO (1.64). Although not statistically significant, there was a tendency for both alcohol and CO to improve odor detection compared to air only. When alcohol and CO were combined, the odor detection was significantly poorer than after either treatment alone, but it was not significantly poorer than the air control. One of the features of signal detection analysis is that it allows the separation of treatment effects on sensory sensitivity from effects on performance that would influence the reporting of the signal. Thus, in this study it was found that these changes in odor detection produced by alcohol and CO occurred in the absence of an effect of any of the experimental treatments on reporting bias. Thus, one could conclude that the results of combined alcohol and CO exposure was to eliminate the small improvement in odor sensitivity produced by exposure to either treatment alone. The relevance and importance of these small changes in odor detection are not readily apparent, especially because none of the treatments were significantly different from air control; however, they do suggest that a CO-alcohol interaction on odor thresholds may exist. An incidental finding of this study was that alcohol did not alter COHb concentrations after exposure to CO; nor did CO exposure affect blood alcohol levels produced by a fixed dose of oral alcohol.

There also have been a number of animal studies of combinations of alcohol and CO. Although there is some evidence that alcohol metabolism can be reduced in rat liver *in situ* by a COHb level of 20% (Toppling et al., 1981), an *in vivo* study in mice found no effects of

CO exposure on alcohol metabolism (Kim and Carlson, 1983). Compared to levels in control mice, either 1, 3, or 5 days of eight hour per day exposure to 500 ppm CO (COHb levels averaged 28%) had no effect on blood alcohol levels when 2.2 g/kg of alcohol was administered ip after 5.5 h of exposure on each of these days. On the other hand, Pankow et al. (1974) provide some evidence that high doses of CO associated with COHb levels of greater than 50% decreased blood alcohol levels in rats 30 min after a very large dose of alcohol (4.8 g/kg). They also reported that this dose of alcohol significantly lowered COHb levels associated with a very large subcutaneous dose of CO. These high-dose combinations were also associated with additive effects on enzyme markers of hepatotoxicity, but no interactions were observed when lower doses of CO were given.

In contrast to the inconsistent metabolic effects seen with combinations of CO and alcohol, results of two behavioral studies in animals have both shown substantial effects. Mitchell et al. (1978) studied the interaction of inhaled CO with two doses of alcohol (0.6 and 1.2 g/kg) in rats using two behavioral measures. Sensorimotor incapacitation was assessed by failure to remain on a rotating rod. An additional measure of motor effects was the inability to withdraw the leg from a source of electric shock. The length of exposure to about 2000 ppm CO before the animals failed in these performances was decreased in a dose-dependent manner by alcohol. Carboxyhemoglobin determinations made at the time of behavioral incapacitation was inversely related to alcohol dose. For example, nearly 50% COHb levels were required to impair rotorod performance in the absence of alcohol, whereas after 1.2 g/kg ethanol, less than 45% COHb levels produced the same effect. Unfortunately, data was not provided on the effects of these doses of alcohol in the absence of CO exposure to help determine the nature and magnitude of the interaction effects.

Knisely et al. (1989) recently reported a large interaction of CO exposure and alcohol administration on operant behavior in animals. Mice that had been trained to lever press for water reinforcement were tested with 1.1 g/kg alcohol and various doses of CO, alone and in combination. An unusual feature of this study was that the both the alcohol and CO were administered by ip injection. The authors provide evidence that this route of CO exposure results in COHb formation and behavioral effects comparable to those seen after inhalation exposure. The results of the study were evaluated by comparing the effects of the combinations to those expected by summing the effects of each treatment alone. A dose of

alcohol that had little effect on rates of lever pressing when given alone resulted in large rate-decreasing effects when given in combination with doses of CO that also had no effects when given alone. Supra-additive effects with alcohol were obtained by a dose of CO as low as 7.5 mL/kg, which when given alone was associated with COHb levels of about 20%. Significant supra-additive effects also were obtained with higher doses of CO. Typically, behavioral effects of CO alone were not seen under these test conditions until COHb saturations greater than 40 to 50% were obtained (Knisely et al., 1989). Thus, alcohol about doubled the acute toxicity of CO in this study.

11.2.3 Barbiturates

There has been some interest in the interaction of CO with barbiturates because prolongation of barbiturate effects can reflect effects of toxicants on drug metabolism. In an early evaluation of the functional significance of the binding of CO to cytochrome P-450, Montgomery and Rubin (1971) examined the effects of CO exposure on the duration of action of hexobarbital and the skeletal muscle relaxant zoxazolamine in rats. Both drugs are largely deactivated by the hepatic mixed-function oxidase (MFO) system. Although CO was found to dose-dependently enhance both hexobarbital sleeping time and zoxazolamine paralysis, subsequent research indicated that this was probably not due to a specific inhibition of the MFO system by CO, but rather a nonspecific effect of hypoxia, because even greater effects could be produced at a similar level of arterial O_2 produced by hypoxic hypoxia (Montgomery and Rubin, 1973; Roth and Rubin, 1976). In support of the lack of effects of CO on drug metabolism, Kim and Carlson (1983) found no effect of CO exposure on the plasma half-life for either hexobarbital or zoxazolamine in mice. This would suggest that something other than a metabolic interaction may be responsible for the enhancement of *in vivo* effects of these drugs by CO.

There have been two studies of the interaction of CO and pentobarbital using operant behavior in laboratory animals. McMillan and Miller (1974) found that exposure of pigeons to 380 ppm CO, a concentration that had little effect on behavior when given alone, reduced the response rate of schedule-controlled behavior, thereby increasing the effect of an intermediate dose of pentobarbital. On the other hand, the disruptive effects of all doses of pentobarbital on the temporal patterning of fixed-interval responding was enhanced markedly

by 1030 ppm CO. This concentration of CO by itself did not alter response patterning, but did lower overall rates of responding. In the study described more fully above in the section on alcohol interactions (11.2.2), Knisely et al. (1989) found generally additive effects of ip CO administration with the effects of pentobarbital in mice responding under a fixed-ratio schedule. In that study the interaction of CO with pentobarbital was not as evident as the interaction with alcohol, suggesting that general conclusions about CO interactions with central nervous system depressant drugs may not be possible.

11.2.4 Other Psychoactive Drugs

Even more limited data are available on interactions of CO exposure with other psychoactive drugs. In the study by Knisely et al. (1989), described above (Section 11.2.2), of interactions of ip CO administration with psychoactive drugs on operant behavior of mice, *d*-amphetamine, chlorpromazine, nicotine, diazepam, and morphine were studied in addition to alcohol and pentobarbital. As with alcohol, a suggestion of greater than additive effects were obtained from combinations of CO with both *d*-amphetamine and chlorpromazine; however, in these cases the differences from additivity did not reach statistical significance. Effects of CO in combination with nicotine, caffeine, and morphine were additive. McMillan and Miller (1974) also found evidence for an interaction of CO and *d*-amphetamine on operant behavior in pigeons. In this study, CO concentrations as low as 490 and 930 ppm were able to modify the behavioral effects of *d*-amphetamine.

11.3 COMBINED EXPOSURE TO CARBON MONOXIDE AND OTHER AIR POLLUTANTS AND ENVIRONMENTAL FACTORS

Exposure to a single air pollutant at ambient concentrations may have no harmful biological effects. In real life, however, exposure occurs not only to a single agent but also to multiple agents, resulting in potential interactions between them. The result of the interactions may be of an additive, synergistic, or antagonistic nature. Another possible interaction is potentiation, a condition in which a pollutant that is noneffective at a given exposure level may enhance the toxicity of another pollutant given simultaneously. Exposure

to CO frequently occurs in the natural environment in combination with other combustion products and air pollutants.

In this section both human and animal effects associated with combined exposure to CO and other air pollutants and environmental factors are reviewed. Although a number of studies in the literature have tested exposure to combined pollutants, fewer studies actually have been designed to test specifically for interactions between CO and the other exposure components. Therefore, this section emphasizes only those studies providing a combined treatment group where pollutant exposure levels are reported. The COHb levels resulting from CO exposure also are given if they were reported in the original manuscripts. The toxicity data discussed stress the newer literature published since 1979 in order to update the information reviewed in the previous Air Quality Criteria Document (U.S. Environmental Protection Agency, 1979).

11.3.1 Exposure in Ambient Air

Photochemical air pollution usually is associated with two or more pollutants, consisting mainly of CO, sulfur oxides, ozone, nitric oxides, peroxyacetyl nitrates, and organic peroxides. The gaseous compounds that constitute tobacco smoke are CO, hydrogen cyanide, and nitric oxide. As urban living, industrial employment, and cigarette smoking bring man into direct contact with CO and other pollutants, it seems appropriate to determine if combined exposure to these pollutants has detrimental health effects.

Several studies have been conducted to determine the effects resulting from combined exposure to CO and other pollutants. The experimental details (e.g., concentrations and duration of treatment) and the associated effects for each study are summarized in Table 11-4. A brief discussion of the major findings follows.

Murphy (1964) observed an increase in blood COHb levels in mice and rats exposed to $CO+O_3$ for six hours as compared with mice exposed to CO alone. However, another study (DeLucia et al., 1983) in adults exposed to $CO+O_3$ during exercise, showed no synergistic effects on blood COHb levels or pulmonary or cardiorespiratory thresholds. Similarly, simultaneous exposure to $CO+O_3+NO_2$ for two hours produced no consistent changes (synergistic or additive) in pulmonary function indices and physiological parameters in young, male subjects (Hackney et al., 1975a,b).

TABLE 11-4. COMBINED EXPOSURE TO CARBON MONOXIDE AND OTHER POLLUTANTS

Pollutant	Concentration	No./sex/species	Treatment	Observed Effects	Reference
CO O_3	300 ppm 0.75 ppm	9-10/-[a]/mouse and rat	Exposed to 300 ppm CO alone or 0.75 ppm O_3 + 300 ppm CO for 6 h; blood COHb levels were determined	Simultaneous exposure produced higher COHb levels (30.4% in rats and 18.9% in mice) than exposure to CO alone (25.8% in rats and 14.8% in mice).	Murphy (1964)
CO O_3	280 ppm 3 ppm	9/-/mice	Exposed to 280 ppm CO alone or 3 ppm O_3 + 280 ppm CO for 6 h	COHb levels were 24.3% in mice exposed CO + O_3 compared with 19.2% in mice exposed to CO alone.	Murphy (1964)
CO O_3	100 ppm 0.3 ppm	24/M/human 24/F/human (smokers and nonsmokers)	Exposed during exercise (four 1-h rides on a bicycle to filtered air only; 0.3 ppm O_3 alone; 100 ppm CO alone; or 0.3 ppm O_3 + 100 ppm CO); blood COHb, pulmonary function, cardiorespiratory performance, blood lactate levels, and subjective symptoms were examined	Exposure to O_3 + CO did not elicit a synergistic effect. Combined exposure did not alter the threshold(s) of any subject for appearance of adverse effects due to O_3 alone. Exposure to CO alone caused a mean increase in COHb (5.8%) levels compared with exposure not involving CO.	DeLucia et al. (1983)
CO O_3 NO_2	30 ppm 0.25 ppm 0.30 ppm	8/M/human	Exposed to O_3 alone and in combination with NO_2 and CO for 2 h with secondary stress of heat and intermittent light exercise; subjective symptoms were recorded; pulmonary function, and physiological studies were conducted	No consistent synergistic or additive effects were observed in subjects exposed to O_3 + NO_2 + CO in any parameter measured, except for increases in blood COHb (levels not reported).	Hackney et al. (1975 a,b)
CO Peroxy-acetyl-nitrate (PAN)	50 ppm 0.27 ppm	10/M/human (smokers) 10/F/human (nonsmokers)	Subjects exposed to filtered air only; 50 ppm CO alone; 0.27 ppm PAN alone; or 50 ppm CO + 0.27 ppm PAN for 5 min at two different temperatures, 25° and 35°C (relative humidity 30%); were tested for maximal aerobic power, metabolic temperature, and cardio-respiratory responses	Maximal aerobic power was not affected by any pollutant conditions. The heart rate was significantly ($p<0.05$) greater in the CO group compared with the filtered-air group. Metabolic and thermo-regulatory responses were not different in the various pollutant environments. Increases in COHb levels of smokers during the CO or CO + PAN exposures were observed.	Drinkwater et al. (1974); Gliner et al. (1975); Raven et al. (1974a,b)

TABLE 11-4 (cont'd). COMBINED EXPOSURE TO CARBON MONOXIDE AND OTHER POLLUTANTS

Pollutant	Concentration	No./sex/species	Treatment	Observed Effects	Reference
CO NO	100 ppm 500 ppm 10 ppm 50 ppm	15/M/rat (Long-Evans)	Exposed to clean air only; 100 or 500 ppm CO alone; 10 or 50 ppm NO alone; 100 ppm CO + 10 ppm NO; or 500 ppm CO + 50 ppm NO for 3 h; changes in discrimination learning and brain activity were measured	No significant changes were observed in COHb levels between any treatment groups. Exposure to 100 ppm CO + 10 ppm NO signinificantly ($p<0.01$) increased mean metHb levels when compared to NO (10 ppm) alone. Combined exposure caused significant behavioral effects at both levels. Combined exposure also affected early auditory-evoked potential components (P_{10} and N_{30}; the effect was more pronounced at higher dose level (500 ppm CO + 50 ppm NO) than at the lower levels, indicating a dominant role for NO.	Groll-Knapp et al. (1988)
CO NO HCN	200 ppm 5 ppm 0.5 ppm	12/M/rabbit (New Zealand white)	Exposed to 0.5 ppm HCN + 5 ppm NO + 200 ppm CO for 2 weeks	Combined exposure to the three noxious gases caused no morphological changes in the lung, pulmonary, and coronary arteries, or aorta.	Hugod (1979)
CO NO_2	20 ppm 67.5 ppm 0.5 ppm 7.5 ppm	24/M/rat 24/F/rat (Sprague-Dawley)	Exposed to clean air only; 0.5 or 7.5 ppm NO_2 alone; 20 or 67.5 ppm CO alone; 0.5 ppm NO_2 + 67.5 ppm CO; or 7.5 ppm NO_2 + 20 ppm CO continuously, 24 h/day, 7 days/week for 52 weeks; chronic toxicity was assessed	No consistent changes in pulmonary function indices were observed in any of the groups exposed to the pollutants alone or in combination with CO. Hematological and biochemical changes were within the normal range. Combined exposure to CO + NO_2 did not increase the severity of the histopathological changes observed in the lungs of rats exposed to NO_2 alone.	Busey (1972)
CO SO_2	20 ppm 67.5 ppm 0.5 ppm 10 ppm	24/M/rat 24/F/rat (Sprague-Dawley)	Exposed to clean air only, 0.5 ppm or 10 ppm SO_2 alone; 20 or 67.5 ppm CO alone; 0.5 ppm SO_2 + 67.5 ppm CO; or 10 ppm SO_2 + 20 ppm CO continuously, 24 h/day, 7 days/week for 52 weeks; chronic toxicity was assessed	Combined exposures caused no consistent changes in pulmonary function indices, hematology, or biochemical or histological parameters.	Busey (1972)
CO SO_2	250 ppm 25 ppm	32-40/F/mouse (CF-1)	Exposed to filtered air only; 25 ppm SO_2 alone; or 25 ppm SO + 250 ppm CO for 7 h/day during Days 6 through 15 gestation; teratogenic potential was evaluated	Exposure to SO_2 alone or SO_2 + CO caused no teratogenic effects.	Murray et al. (1978)

TABLE 11-4 (cont'd). COMBINED EXPOSURE TO CARBON MONOXIDE AND OTHER POLLUTANTS

Pollutant	Concentration	No./sex/species	Treatment	Observed Effects	Reference
CO SO_2	250 ppm 70 ppm	20/F/rabbit (New Zealand white)	Exposed to filtered air only, 70 ppm SO_2 alone, or 70 ppm SO_2 + 250 ppm CO for 7 h/day during Days 6 to 18 of gestation; teratogenic potential was evaluated	No teratogenicity was observed.	Murray et al. (1978)
CO SO_2	3 mg/m^3 6 mg/m^3 0.5 mg/m^3	3/-/human	Exposed to pure air for 5 min; 6 mg/m^3 CO for 20 min; 6 mg/m^3 CO + 0.5 mg/m^3 SO_2 for 5 min; 0.5 mg/m^3 SO for 25 min; 6 mg/m^3 CO + 0.5 mg/m^3 for 25 min; or 3 mg/m^3 CO +0.5 mg/m^3 SO_2 for 25 min; variations in ocular sensitivity to light and color vision were tested	Inhalation of 6 mg/m^3 CO + 0.5 mg/m^3 SO_2 for 5 min or CO alone for 20 min caused significant differences in light and color sensitivity when compared to controls.	Mamatsashvili (1967)
CO PbClBr	67.5 ppm 0.6 ppm	24/M/rat 24/F/rat (Sprague-Dawley)	Exposed to clean air alone, 67.5 ppm CO alone; 0.6 ppm PbClBr alone; or to 0.6 ppm + 67.5 ppm CO continuously 24 h/day, 7 days/week for 52 weeks; chronic toxicity was assessed	No consistent changes in pulmonary function, hematology, or biochemistry were observed between the treatment groups. Combined exposure to CO + PbClBr did not increase the incidence of histological changes observed in the kidneys of rats exposed to PbClBr alone.	Busey (1972)
CO CH_2Cl_2	100 ppm 1,000 ppm	5/M/rat (Wistar)	Exposed to clean air only; 100 ppm CO alone; 1,000 ppm CH_2Cl_2 only; or 100 ppm CO + 1,000 ppm CH_2Cl_2 for 3 h; mixed-function oxidase activity and blood COHb levels were examined	Combined exposure had an additive effect. Blood COHb was significantly ($p<0.001$) increased in rats exposed to CO + CH2CL2 (14.6%) compared with with CO alone (8.8%). Combined exposure significantly ($p<0.005$) increased the ethoxycoumarin-*O*-deethylase activity in the kidneys. Treatment had no effect on liver microsomal oxidation.	Kurppa et al. (1981)
CO CH_2Cl_2	1,500 ppm 2,000 ppm	-/-/dog (Cowenose Mongrel)	Exposed to 1,500 ppm CO for 25 min followed by a 2-h exposure to 2,000 ppm CH_2Cl_2 in air also containing 150 ppm CO; effects on the cardiovascular system were evaluated	Combined exposure of CO + CH_2Cl_2 had no effect on the phsiologic response due to CO, instead CO antagonized the responses due to CH_2Cl_2.	Adams (1975)

[a] Information was not reported in the original manuscript.

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Combined exposure to CO and peroxyacetylnitrate (PAN) exerted no greater effect on the work capacity of healthy men (young and middle-aged smokers and nonsmokers) than did exposure to CO alone. Increases in blood COHb levels of smokers during the CO or CO+PAN exposures were observed (Drinkwater et al., 1974; Raven et al., 1974a,b; Gliner et al., 1975).

Groll-Knapp et al. (1988) reported that combined exposure of rats to CO+NO for three hours caused a significant ($p<0.01$) increase in mean methemoglobin (metHb) levels when compared with metHb levels in rats exposed to NO alone. No significant changes were observed in blood COHb levels as compared with exposure to CO alone or to CO+NO. Combined exposure also caused significant behavioral changes. Hugod (1979) reported that combined exposure to CO+NO+HCN for two weeks produced no morphological changes in the lungs, pulmonary arteries, coronary arteries, or aortas of rabbits.

In a one-year inhalation toxicity study, no adverse toxic effects were seen in groups of rats exposed to relatively low levels of $CO+NO_2$ or $CO+SO_2$ as compared with rats exposed to one of these pollutants alone (Busey, 1972). Murray et al. (1978) observed no teratogenic effects in offspring of mice or rabbits exposed to $CO+SO_2$ for 7 hours/day during gestation Days 6 to 15 or 18, respectively.

Halogenated hydrocarbons, such as polybrominated and polychlorinated biphenyls, are widely used as organic solvents. These chemicals are metabolized in the body to produce CO which is readily bound to Hb. Therefore, any additional exposure to CO, producing higher COHb levels, could possibly cause greater health effects. For example, up to 80% of inhaled methylene chloride (CH_2Cl_2) will be metabolized to CO. Inhalation of 500 to 1000 ppm, therefore, would result in COHb levels of over 14%. This elevation in COHb can not only have a significant effect when combined with CO exposure, but the CO resulting from metabolism generally requires a longer time to dissipate (Kurppa, 1984).

In one study, combined exposure to $CO+CH_2Cl_2$ for three hours had an additive effect on blood COHb levels in rats (Kurppa et al., 1981). On the other hand, Adams (1975) reported that combined exposure to $CO+CH_2Cl_2$ did not have an additive effect on the physiologic response in the cardiovascular systems of dogs due to CO, instead, CO antagonized the responses due to CH_2Cl_2.

11.3.2 Exposure to Combustion Products

A common condition in an atmosphere produced by a fire is the presence of a rapidly changing combination of potentially toxic gases (primarily, CO, CO_2, and HCN), reduced O_2 levels (hypoxic hypoxia), and high temperatures. Combined exposure to these gases occurs during smoke inhalation under conditions of hypoxic hypoxia. In addition, both CO and CO_2 are common products of carbon-containing materials; consequently, accidental exposure to high levels of CO will rarely occur without simultaneous exposure to CO_2. Exposure to CO and HCN is of concern because both CO and HCN produce effects by influencing tissue O_2 delivery. Increased COHb reduces O_2-carrying capacity and may interfere with tissue O_2 release, while HCN inhibits tissue respiration. Studies were conducted to determine the toxicological interactions of the combustion products with and without reduced O_2. (Also see Chapter 10, Section 10.4.1.5 for more discussion on CO and HCN.)

Several studies have investigated the effects resulting from combined exposure to CO and combustion products from fires. The experimental details and the associated effects for each study are summarized in Table 11-5. The following is a brief discussion of the major findings.

Rodkey and Collison (1979) reported a significant ($p<0.02$) decrease in mean survival time in mice jointly exposed until death to $CO+CO_2$ compared with mice exposed to CO alone. In contrast, Crane (1985) observed no differences in the times-to-incapacitation or times-to-death in rats exposed until death to various concentrations of $CO+CO_2$. In a recent study, Levin et al. (1987a) demonstrated a synergistic effect between CO and CO_2 in rats exposed to various concentrations of $CO+CO_2$. Simultaneous exposure to nonlethal levels of CO_2 (1.7 to 17.3%) and to sublethal levels of CO (2500 to 4000 ppm) caused deaths in rats both during and following (up to 24 h) a 30-min exposure. The rate of COHb formation was 1.5 times greater in rats exposed to $CO+CO_2$ than in rats exposed to CO alone.

Combined exposure to CO+HCN had an additive effect in rats as evidenced by increases in mortality rate and changes in COHb levels. COHb levels decreased as the CO level decreased and HCN level increased (Levin et al., 1987b). HCN had a depressive effect on CO uptake and COHb formation, an effect that may explain the reason for the low COHb levels (<50%) seen in some people who died in a fire (Levin et al., 1987b). In contrast,

TABLE 11-5. COMBINED EXPOSURE TO CARBON MONOXIDE AND COMBUSTION PRODUCTS

Combustion Product	Concentration	No./Sex/Species	Treatment	Observed Effects	Reference
CO CO_2	6,000 ppm 2.1, 2.3, 4.5, 5.4%	6/F/rat (NMRI)	Exposed to 6,000 ppm CO alone; 6,000 ppm CO + 2.1 or 4.5% CO_2; or 6,000 ppm CO + 2.3 or 5.4% CO_2 until death; O_2 concentrations were either 14 or 21%; mean survival time (MST) and fatal blood COHb level were measured	The MST was significantly ($p<0.02$) decreased in rats exposed to 6,000 ppm CO + 2.1% CO_2 (18.4 min) or 4.5% CO_2 (16.8 min) compared with CO alone (22.4 min) in the presence of 21% O_2. Exposure to 14% O_2 + 6,000 ppm CO decreased the MST to 9.6 min; addition of 2.3% or 5.4% CO_2 had no further effect on MST. Combined exposure (CO + CO_2) had no effect on fatal blood COHB.	Rodkey and Collison (1979)
CO CO_2	5,000-14,000 ppm 4-13%	[a]/-/rat	Exposed to concentrations ranging from 5,000 to 14,000 ppm CO alone or with CO_2 concentrations ranging from 4 to 13% continuously until death; synergistic effects (times-to-incapacitation ([ti]) or the times-to-death ([t_d]) were evaluated.	No synergistic effects were observed; no significant CO_2 changes were observed in the endpoints (t_i or t_d) for added CO_2 compared to endpoints for CO alone.	Crane (1985)
CO CO_2	1,470-6,000 ppm 1.7-17.3%	6/M/rat (Fischer 344)	Exposed to 1,470 to 6,000 ppm CO or 2,500 to 4,000 ppm CO + 1.7 to 17.3% CO_2 for 30 min; toxicological interactions (mortality and COHb formation) were evaluated	Exposure to CO alone caused deaths at levels of 4,600 to 6,000 ppm and at COHb levels of >83%. Deaths were primarily due to the high COHb, low O_2Hb, and hypoxia. Combined exposure to $\geq$2500 ppm CO + 1.7 to 17.3% CO_2 caused deaths during exposure and the follow-up period (24 h). No mortality occurred in rats at <2,500 ppm CO alone regardless of CO_2 concentrations. The rate of COHb formation was 1.5 times greater in rats exposed to 2,500 ppm CO + 5.25% CO_2 than in rats exposed to 2,500 ppm CO alone. The COHb equilibrium level was the same	Levin et al. (1987a)

TABLE 11-5 (cont'd). COMBINED EXPOSURE TO CARBON MONOXIDE AND COMBUSTION PRODUCTS

Combustion Product	Concentration	No./Sex/Species	Treatment	Observed Effects	Reference
				(78%) for the combined exposure, but was reached in 10 min in the presence of CO_2 and 20 min in the absence of CO_2. Combined exposure increased the concentration of COHb, caused severe acidosis, and prolonged the recovery of acidosis following cessation of exposure. Exposure to CO_2 alone produced no mortality or incapacitation.	
CO HCN	1,242-4,600 ppm 43.2-126.4 ppm	6/M/rat (Fischer 344)	Exposed to 4,600 ppm CO alone or 1,242 to 3,450 ppm CO + 43.2 to 126.4 ppm HCN for 30 min; lethality and COHb formation were measured as toxicological endpoints	Combined exposure to CO + HCN had an additive effect as evidenced by increased mortality. As the concentrations of HCN increased, the animals died at lower CO concentrations and presented lower levels of COHb at death. When rats were exposed to 1,470 ppm CO alone or 1,450 ppm CO + 100 ppm HCN, the initial rate of COHb formation was the same in the presence or absence of HCN; however, the final COHb level was lower in the presence of HCN, indicating a depressive effect of HCN on CO uptake and the low COHb formation.	Levin et al. (1987b)
CO HCN	200 ppm 0.5 ppm	12-24/M/rabbit (albino)	Exposed to 0.5 ppm HCN alone or 0.5 ppm HCN + 200 ppm CO for 1 or 4 weeks; morphological changes in the lung, pulmonary arteries, coronary arteries, or aorta were evaluated	Exposure to HCN alone or in combination with CO produced no morphological changes in the lung, pulmonary arteries, coronary arteries, or aorta.	Hugod (1979)
CO KCN	0.63-0.66% 0.325-0.375% 4-9 mg/kg 1-6.35 mg/kg	10/M/mouse (ICR)	Mice were exposed to clean air or to atmospheric concentrations of 0.63-0.66% CO for 3 min (pre-treatment) and then injected ip with 4-9 mg/kg KCN	The LD_{50} value was significantly ($p<0.05$) lower for KCN (6.51 mg/kg) in CO-pretreated mice than in air-pretreated mice (7.90 mg/kg).	Norris et al. (1986)

TABLE 11-5 (cont'd). COMBINED EXPOSURE TO CARBON MONOXIDE AND COMBUSTION PRODUCTS

Combustion Product	Concentration	No./Sex/Species	Treatment	Observed Effects	Reference
			In another experiment, mice were pretreated with either saline (0.1 mL/10, ip) or KCN (1 to 6.35 mg/kg, ip) and then were exposed via inhalation to CO in the range of 0.325 to 0.375% CO for 4 min; lethality and blood CO and cyanide concentrations were measured	Sublethal doses of KCN (3.5 to 6.35 mg/kg) produced a synergistic effect in mortality: 40-100% mortality in KCN pretreated mice compared to 10-20% in saline pretreated mice. There were no differences in CO or cyanide blood levels between these treatment groups.	
CO KCN	1,000 ppm 2,500 ppm 7.5 mg/kg	20/M/mouse (Swiss Webster)	Preexposed to 1,000 ppm CO for 4 h followed by a single ip injection of 7.5 mg/kg KCN, 24 h later; effects on KCN-induced letahlity were studied	No alterations in lethality in CO + KCN group as compared with control + KCN group.	Winston and Roberts (1975)
			Preexposed to 7.5 mg/kg KCN (ip) 24 h prior to exposure to 2,500 ppm CO for 2 h; effects on KCN-induced lethality were studied	Pretreatment with KCN had no significant effect on lethality associated with subsequent exposure to CO.	
CO (under con-ditions of hypoxic hypoxia)	CO: 6,000 ppm O_2: 14 or 21%	6/F/rat (NMRI)	Exposed to 6,000 ppm CO until death in the presence of either 14 or 21% O_2; MST and fatal blood COHb levels were measured	MST was significantly ($p<0.01$) decreased in the presence of low (14%) O_2 (9.6 min) compared to that of high (21%) O_2 (22.4 min) levels. A significantly ($p<0.01$) higher level of COHb was observed in rats treated with 14% O_2 (89.4%) compared with those treated with 21% O_2 (83.4%).	Rodkey and Collison (1979)
CO (under con-ditions of hypoxic hypoxia)	CO: 500, 1,000 or 2,500 ppm O_2: 7 or 10%	20/M/mouse (Swiss Webster)	Mice were preexposed to 500 or 1,000 ppm CO for 4 h and then exposed to 2,500 ppm for 2 h, 24 h later exposure to CO.	Preexposure to CO caused a significant ($p<0.05$) decrease in lethality during subsequent	Winston and Roberts (1975)
			Preexposed to 500 or 1,000 ppm CO for 4 h and then exposed to 7% O_2 for 2 h, 24 h later	Preexposure to CO followed by exposure to O_2 had no effect on lethality. Preexposure to CO had no protective effect against hypoxic hypoxia.	

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TABLE 11-5 (cont'd). COMBINED EXPOSURE TO CARBON MONOXIDE AND COMBUSTION PRODUCTS

Combustion Product	Concentration	No./Sex/Species	Treatment	Observed Effects	Reference
			Preexposed to 10% O_2 for 4 h and then exposed to 2,500 ppm CO for 2 h, 24 h later	Preexposure to O_2 followed by exposure to CO significantly ($p<0.05$) decreased lethality compared to controls.	
			Preexposed to 1,000 ppm CO or 10% O_2 for 4 h and then exposed to 2,500 ppm CO for up to 2 h, 24 h later	Preexposure to either CO or O_2 had no significant effect on O_2-consumption level. Alterations in CO lethality were not associated with alterations in COHb levels.	
CO (under conditions of hypoxic hypoxia)	CO: 500 or 1,000 ppm O_2: 6-21% or 11.8-20.5%	[a]-/M/mouse (Swiss Webster)	Exposed to reduced O_2 (6-21%) alone or reduced O_2 (11.8 to 20.5%) + 500 ppm CO, or 20.2% O_2 + 1,000 ppm CO for 20 min; animals were subjected to behavioral tests that determined reaction time and performance of the animals in a mouse pole-jump apparatus	Reaction time gradually increased with a decrease in O_2 to 10%. At <10% O_2, reaction time increased dramatically and animal performance decreased almost immediately. At reduced O_2 levels + CO, the decreases in performance were even greater than those seen in mice exposed to reduced O_2 levels only. At 20% O_2 (close to ambient level) + 1,000 ppm CO, performance was nearly completely degraded.	Cagliostro and Islas (1982)

[a]Data not provided in the published manuscript.

Hugod (1979) reported that exposure to HCN alone or to CO+HCN for one to four weeks produced no morphological changes in the lung, pulmonary and coronary arteries, or aorta of rabbits.

Combined exposures to CO+KCN have produced conflicting results. Norris et al. (1986) reported that the LD_{50} values were significantly lower in mice pretreated with CO prior to intraperitoneal injection of KCN. Sublethal doses of KCN produced a synergistic effect on mortality. On the other hand, Winston and Roberts (1975) observed no alterations in lethality in mice pretreated with CO and then treated with intraperitoneal injections of KCN.

A number of studies examined the effects of CO administered under conditions of hypoxic hypoxia. Rodkey and Collison (1979) observed a lower mean survival time and a higher level of COHb in mice exposed to CO in the presence of low O_2 (14%) than in those exposed to an ambient O_2 (21%) level. Winston and Roberts (1975) showed that preexposure of mice to CO, followed by exposure to 7% O_2 24 h later, had no effect on lethality as compared with controls exposed to 7% O_2 only. Thus, preexposure to CO had no protective effect against hypoxic hypoxia. However, preexposure to 10% O_2 caused a significant decrease in lethality in mice exposed 24 h later to CO. Alterations in colethality were not associated with alterations in COHb levels. In a behavioral study in mice, Cagliostro and Islas (1982) showed that reaction times gradually increased with a decrease in O_2 levels to 10%. At <10% O_2, reaction time increased dramatically. At reduced O_2 levels and in the presence of CO, the decreases in performance were even greater than those observed in mice exposed to reduced O_2 levels alone.

11.3.3 Exposure to Other Environmental Factors

11.3.3.1 Environmental Heat

Several of the studies (Drinkwater et al., 1974; Raven et al., 1974a,b; Gliner et al., 1975) describing the effects of CO exposure alone and CO combined with peroxyacetyl nitrate (PAN) on exercise performance in healthy adult men, reviewed in Sections 10.3.2 and 11.3.1, also evaluated the effects of heat stress. Subjects were exposed to 50 ppm CO and/or 0.27 ppm PAN in environmental exposure chamber conditions of 30% RH at 25 and 30°C. In these studies, O_2 uptake and exercise duration were assessed during both maximal and

submaximal exercise. Heat stress was more effective in reducing maximal exercise performance than exposure to the polluted environments. The combination of heat stress with CO exposure was found to be important, however, in producing symptom complaints during submaximal exercise at 35°C that were not found at 25°C. Further work in the same laboratory (Bunnell and Horvath, 1989) also demonstrated that subjects experienced significant levels of symptoms, particularly exertion symptoms, associated with elevated COHb when exercising in the heat. These studies suggest, therefore, that heat stress may be an important determinant of changes in exercise performance when combined with exposure to CO.

Yang et al. (1988) studied the combined effects of high temperature and CO exposure in laboratory mice and rats. They were exposed one hour per day for 23 consecutive days to environmental chamber temperatures of 25 and 35°C at CO concentrations ranging from 580 to 607 ppm. Carboxyhemoglobin levels after one hour of exposure ranged from 31.5 to 46.5%. The toxicity of CO to mice, based on the LC_{50} and survival time, was found to be three times higher at 35°C. High temperature also was found to enhance the effects of CO on the function of oxidative phosphorylation of liver mitochondria in rats. Body temperature regulation and heat tolerance also was affected by CO exposure. The authors speculate that these effects of combined exposure to CO and high temperature are due to the production of higher COHb, possibly due to hyperventilation.

11.3.3.2 Environmental Noise

Fechter et al. (1987; 1988) and Fechter (1988) speculated that the cochlea would be particularly susceptible to injury when exposed to both CO and environmental noise. The rationale for this potential effect was that CO exposure could impair cochlear oxygenation at a time when auditory metabolism was likely to be enhanced by noise exposure. Using laboratory rats exposed to high levels of CO (250 to 1200 ppm for 3.5 h) with and without broad-band noise (105 dBA for 120 min), the authors were able to show that CO acts in a dose-dependent manner to potentiate noise-induced auditory dysfunction. While CO or noise alone did not have an effect, CO combined with noise produced a more severe loss of hair cells at the basal end of the cochlea. Auditory threshold loss for the combined exposure was evident at all frequencies tested but was greatest for high-frequency tones. A previous pilot

study by Young et al. (1987) conducted at 1200 ppm CO also showed that combined exposure to noise and CO produced high-frequency shifts of greater magnitude than those produced by exposure to noise alone.

Results from the toxicologic studies in rats suggest that combined exposure to noise and CO may be important in evaluating potential risk to exposed individuals. The CO levels used in these studies, however, are much greater than those encountered in the typical ambient, or even in the typical occupational environment. Thus, it is difficult to predict how relevant these studies are to actual conditions of human exposure. An early epidemiologic study by Lumio (1948) in operators of CO-fueled vehicles found significantly greater permanent hearing loss than expected after controlling for possible confounding factors. More recently, Sulkowski and Bojarski (1988) studied age-matched workers with similar length of duty employed in foundry, cast iron, and cast steel positions of a mining devices factory where CO and noise exposure varied. Careful otological and audiometric examinations were performed on these workers. The group exposed to the combined effects of 95 dBA noise and a mean concentration of 41 ppm CO did not experience any greater hearing loss than the groups exposed only to noise (96 dBA) or CO (45 ppm). In fact, a permanent threshold shift was significantly larger in workers exposed to noise alone than those exposed to the combined influence of CO and noise. This study needs to be verified, however, at similar, relevant exposure levels before any definitive conclusions can be made regarding the potential of lower-level CO to potentiate noise-induced auditory loss in humans.

11.3.4 Summary

Much of the data concerning the combined effects of CO and other pollutants found in the ambient air are based on animal experiments. Only a few human studies are available. Early studies in healthy human subjects by Hackney et al. (1975a,b), Raven et al. (1974a,b), Gliner et al. (1975), and Drinkwater et al. (1974) on common air pollutants such as NO_2, O_3, or PAN and more recent work on CO + O_3 by DeLucia et al. (1983) failed to show any interaction from combined exposure.

In animal studies, no interaction was observed following combined exposure of CO and pollutants such as HCN, NO_2, SO_2, or PbClBr (Hugod, 1979; Busey, 1972; Murray et al., 1978). However, an additive effect was observed following combined exposure of high levels

of CO + NO (Groll-Knapp et al., 1988), and a synergistic effect was observed after combined exposure to CO and O_3 (Murphy, 1964).

Toxicological interactions of combustion products, primarily CO, CO_2, and HCN, from indoor and outdoor fires, have shown a synergistic effect following CO + CO_2 exposure (Rodkey and Collison, 1979; Levin et al., 1987a) and an additive effect with CO + HCN (Levin et al., 1987b). Additional studies are needed, however, to evaluate the effects of CO under conditions of hypoxic hypoxia.

Finally, laboratory animal studies (Yang et al., 1988; Fechter et al., 1988; Young et al., 1987) suggest that the combination of environmental factors such as heat stress and noise may be important determinants of health effects occurring in combination with exposure to CO. Of the effects described, the one potentially most relevant to typical human exposures is a greater decrement in exercise performance seen when heat stress is combined with 50 ppm CO (Drinkwater et al., 1974; Raven et al., 1974a,b; Gliner et al., 1975).

11.4 ENVIRONMENTAL TOBACCO SMOKE

A common source of CO for the general population comes from tobacco smoke, along with other primary sources arising from the environment. Exposure to tobacco smoke not only affects the COHb level of the smoker himself, but under some circumstances, such as in poorly ventilated spaces, tobacco smoke exposure also can affect nonsmokers. For example, acute exposure (1 to 2 h) to smoke-polluted environments has been reported to cause an incremental increase in nonsmokers' COHb of about 1% (Jarvis, 1987). In addition to CO, other products inhaled by the affected individuals, such as NO_2, HCN, nicotine, and potential carcinogens contained in tobacco smoke, may produce subtle physiological and biochemical effects in both the smoker and nonsmoker. Possible pathological changes due to the interaction of CO and these other constituents of tobacco smoke that may occur in the lungs and other tissues remain to be elucidated.

A detailed discussion of the possible health effects due to CO emitted from tobacco smoke is beyond the scope of this document. Those interested in the problems related to smoking tobacco (i.e., carcinogenesis and cardiovascular and pulmonary disease) should refer to review documents specifically concerned with these matters (U.S. Department of Health

and Human Services, 1983; U.S. Department of Health, Education and Welfare, 1979, 1972). In addition, a number of sources have reviewed the potential health effects of tobacco smoke on nonsmokers (Fielding and Phenow, 1988; Hulka, 1988; Mohler, 1987; Surgeon General of the United States, 1986; National Research Council, 1986).

Tobacco smoking has been found to result in higher COHb levels than exposure to ambient concentrations of CO. The actual quantity of CO entering the lung depends on the form in which tobacco is smoked, the pattern of smoking, and the depth of inhalation (Robinson and Forbes, 1975). Very little CO (approximately 5%) is absorbed in the mouth and larynx, therefore most of the CO available for binding to Hb must reach the alveoli in order to raise the level of COHb present in the blood. The CO concentration in tobacco smoke is approximately 4.5% (45,000 ppm). It has been estimated that a smoker may be exposed to 400 to 500 ppm CO for the approximately 6 min that it takes to smoke a typical cigarette, producing an average baseline COHb of 4%, with a typical range of 3 to 8%. Heavy smokers can have COHb levels as high as 15%. In comparison, nonsmokers average about 1% COHb in their blood. (See Chapter 8 for more information on CO exposure in the population.) As a result of the higher baseline COHb levels, smokers are actually excreting CO into the air rather than inhaling it from the ambient environment. Smokers may even show an adaptive response to the elevated COHb levels, as evidenced by increased red cell volumes or reduced plasma volumes (Smith and Landaw, 1978a,b). For these reasons, EPA previously has not considered active smokers in determining the need for a margin of safety for the CO NAAQS (Federal Register, 1980). This position was affirmed by the Clean Air Scientific Advisory Committee of EPA's Science Advisory Board during review of the previous CO criteria document (U.S. Environmental Protection Agency, 1979).

The effects of CO from tobacco smoke have been discussed in other sections of the document. Human experimental studies suggested that acute effects of tobacco smoke on maximal exercise performance are similar to those described for healthy subjects exposed to CO. Prospective and retrospective epidemiological studies identified tobacco smoke as one of the major factors in the development of cardiovascular disease. Tobacco smoke may contribute to the development and/or aggravation of effects in exposed individuals through the action of several independent or complementary mechanisms, one of which is the formation of significant levels of COHb. Unfortunately, attempts to separate the CO effects of tobacco

smoke from the potential effects of other substances present in the smoke have been unsuccessful. (For a discussion of these studies, see Section 10.3).

In summary, although tobacco smoke is another source of CO for smokers as well as nonsmokers, it is also a source of other chemicals with which environmental CO levels could interact. Available data strongly suggest that acute and chronic CO exposure attributed to tobacco smoke can affect the cardiopulmonary system, but the potential interaction of CO with other products of tobacco smoke confounds the results. In addition, it is not clear if incremental increases in COHb caused by environmental exposure would actually be additive to chronically elevated COHb levels due to tobacco smoke, because some physiological adaptation may take place. There is, therefore, a need for further research to describe these relationships better.

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12. EVALUATION OF SUBPOPULATIONS POTENTIALLY AT RISK TO CARBON MONOXIDE EXPOSURE

12.1 INTRODUCTION

Most of the information on the human health effects of carbon monoxide discussed in Chapter 10 of this document has concentrated on two carefully defined population groups – young healthy, predominantly male adults and patients with diagnosed coronary artery disease. On the basis of the known effects described, patients with reproducible exercise-induced angina appear to be best established as a sensitive group within the general population that is at increased risk for experiencing health effects (i.e., decreased exercise duration due to exacerbation of cardiovascular symptoms) of concern at ambient or near-ambient CO-exposure concentrations that result in COHb levels of ≤5%. A smaller sensitive group of healthy individuals experience decreased exercise duration at similar levels of CO exposure, but only during short-term maximal exercise. Decrements in exercise duration in the healthy population, therefore, would be mainly of concern to competing athletes rather than for nonathletic people carrying out the common activities of daily life.

It is known, however, from both theoretical work and from experimental research in laboratory animals that certain other groups in the population are at potential risk to exposure from CO. The purpose of this chapter is to explore the potential effects of CO in population groups that have not been studied adequately, but which could be expected to be susceptible to CO because of underlying physiological status either due to gender differences, aging, preexisting disease, or because of the use of medications or alterations in their environment. These probable risk groups include (1) fetuses and young infants; (2) pregnant women; (3) the elderly, especially those with compromised cardiopulmonary or cerebrovascular functions; (4) individuals with obstructed coronary arteries, but not yet manifesting overt symptomatology of coronary artery disease; (5) individuals with congestive heart failure; (6) individuals with peripheral vascular or cerebrovascular disease; (7) individuals with hematological diseases (e.g., anemia) that affect oxygen-carrying capacity or transport in the blood; (8) individuals with genetically unusual forms of hemoglobin associated with reduced

oxygen-carrying capacity; (9) individuals with chronic obstructive lung diseases; (10) individuals using medicinal or recreational drugs having CNS depressant properties; (11) individuals exposed to other pollutants (e.g., methylene chloride) that increase endogenous formation of CO; and (12) individuals who have not been adapted to high altitude and are exposed to a combination of high altitude and CO.

Little empirical evidence currently is available by which to specify health effects associated with ambient or near-ambient CO exposures in these probable risk groups. Where the previous chapters dealt with documented evidence of CO exposure through controlled or natural laboratory investigations, this chapter will be more speculative. An effort will be made to determine the anticipated effects of CO in special subpopulations that form a significant proportion of the population at large.

12.2 AGE AND GENDER AS RISK FACTORS

The fetus and newborn infant are theoretically susceptible to CO exposure for several reasons. Fetal circulation is likely to have a higher COHb level than the maternal circulation due to differences in uptake and elimination of CO from fetal hemoglobin. Because the fetus also has a lower oxygen tension in the blood than adults, any further drop in fetal oxygen tension due to the presence of COHb could have a potentially serious effect. The newborn infant with a comparatively high rate of oxygen consumption and lower hemoglobin blood oxygen-transport capacity than most adults also would be potentially susceptible to the hypoxic effects of increased COHb. Newer data from laboratory animal studies on the developmental toxicity of CO suggest that prolonged exposure to high levels (> 100 ppm) of CO during gestation may produce a reduction in birthweight, cardiomegaly, and delayed behavioral development (see Chapter 10, Section 10.5). Human data are scant and more difficult to evaluate, but further research is warranted. Additional studies, therefore, are needed in order to determine if chronic exposure to CO, particularly at low, near-ambient levels, can compromise the already marginal conditions existing in the fetus and newborn infant.

The effects of CO on maternal-fetal relationships are not understood well. In addition to fetuses and newborn infants, pregnant women also represent a susceptible group because

pregnancy is associated with increased alveolar ventilation and an increased rate of oxygen consumption that serves to increase the rate of CO uptake from inspired air. A perhaps more important factor is that pregnant women experience hemodilution due to the disproportionate increase in plasma volume as compared to erythrocyte volume. This group, therefore, should be studied to evaluate the effects of CO exposure and elevated COHb levels.

Seventy percent of the population of the United States survive to 65 years of age and 30% reach 80 years of age or more (Brody et al., 1987). In 1982 about 40% were 75 years of age or older, corresponding to about 10.7 million subjects. The percentage of the population reaching 75 years of age or older is expected to increase to 49% by the year 2000 and to 56% by the year 2080, making it one of the fastest growing segments of the population. Thus, the aging population represents a potentially large subgroup that may be at risk to CO exposure.

Changes in metabolic capability with age may make the aging population particularly susceptible to CO. Maximal oxygen uptake declines steadily with age at a rate of about 0.9 mL/kg/min/year on the average. However, the rate is only 0.65 in an active person and about 1.3 in an inactive person. Since inactivity is the most prevalent condition, especially in the elderly, the maximal oxygen uptake at age 65 will be about 16 to 21 mL/kg/min or 1.2-1.6 L/min. At age 75 the maximal oxygen uptake will be about 10 to 15 mL/kg/min or 0.75-1.1 L/min. Note that these values refer to a healthy but inactive male person.

A person needs about 1 L/min or 10 mL/kg/min in maximal oxygen uptake to meet daily metabolic requirements. Thus, at age 75 many healthy subjects are on the border line with respect to performing ordinary activities, implying that even a low level of COHb might be enough to critically impair oxygen delivery to the tissues and severely limit daily metabolic requirements.

The above given data refer to inactive males. However, the decline by age in maximal oxygen uptake seems to be the same in inactive females. Because females have about 25% lower maximal oxygen uptake expressed in milliliters per kilogram per minute, the critical age for a female will be about 70 years. If a person is physically active on a regular basis, the critical age with respect to maximal oxygen uptake would be expected to increase by 15 to 20 years. Because females have a longer life expectancy than males, the aging female

population potentially at risk to CO exposure would be expected to be larger than the aging male population.

12.3 RISK OF CARBON MONOXIDE EXPOSURE IN INDIVIDUALS WITH PREEXISTING DISEASE

12.3.1 Subjects with Coronary Artery Disease

Coronary heart disease remains the major cause of death and disability in the United States both in males and females. According to the most recent data compiled by the American Heart Association (1988), persons with diagnosed coronary artery disease numbered about 5.4 million in 1985 and current estimates are as high as seven million (U.S. Department of Health and Human Services, 1987; Collins, 1988). These individuals have myocardial ischemia, which occurs when the heart muscle receives insufficient oxygen delivered by the blood. For some, chest discomfort called angina pectoris can occur. The predominant type of ischemia, as identified by ST segment depression, in all patients with coronary artery disease, however, is asymptomatic (i.e., silent). Especially patients who experience angina usually have more ischemic episodes that are asymptomatic. About 10% of middle-aged men develop a positive exercise test, one of the signs of ischemia. Nationally, more than one million heart disease deaths occur each year, half of them being fatal. About 20% of all myocardial infarctions are silent. Of the 500,000 survivors of hospitalized myocardial infarction, about 10% are asymptomatic but have signs of ischemia. Thus, many more persons than currently known are not aware that they have coronary heart disease and may constitute a high-risk group.

Persons with both asymptomatic and symptomatic coronary artery disease have a limited coronary flow reserve and, therefore, will be sensitive to a decrease in oxygen-carrying capacity induced by CO exposure (see Section 10.3.2). In addition, CO might interfere with different vasomotor-active substances and thereby induce a vasoconstriction or prevent a vasodilation in the coronary arteries which will produce ischemia that is likely to be silent. Unfortunately, studies have not been performed specifically addressing the effect of CO exposure on asymptomatic ischemia.

12.3.2 Subjects with Congestive Heart Failure

Congestive heart failure is a major and growing public health problem in the United States. It has been estimated that approximately three million Americans suffer from heart failure, and moreover, because the prevalence of heart failure is known to increase with age, improvements in the average life expectancy of the general population would be expected to increase the magnitude of the problem over the next few decades.

Today about 75% of the patients with heart failure are above the age of 60 years (Brody et al., 1987). About 400,000 new cases of heart failure are diagnosed every year in the United States, resulting in about 1.6 million hospitalizations. The mortality rate is high, between 15 to 60% per year. The cause of death is often sudden death and because about 65% of heart failure patients have serious arrhythmias, sudden death is thought to be due to arrhythmia. Each year 200,000 patients die. The mortality is highest in Class 4 patients or in patients with a low maximal oxygen uptake (below 10 mL/kg/min).

Patients with congestive heart failure have a markedly reduced circulatory capacity and, therefore, may be very sensitive to any limitations in oxygen-carrying capacity. Thus, exposure to CO certainly will reduce their exercise capacity and even be dangerous, especially if CO is determined to be proarrhythmogenic (see Section 10.3.2). The etiology of heart failure is diverse but the dominating disease is coronary artery disease. The large portion of heart failure patients with coronary artery disease, therefore, might be even more sensitive to CO exposure.

12.3.3 Subjects with Other Vascular Diseases

Peripheral vascular disease is present in about 7% of both the male and female population and is more prevalent above age 65 years. Cerebrovascular disease also is present in about 6.6% of both the male and female population of the same ages. Both of these conditions often are found in subjects with coronary artery disease. Both conditions also are associated with a limited blood flow capacity and, therefore, should be sensitive to CO exposure. It is not clear, however, how low levels of exposure to CO will affect these individuals. Only one study (Aronow et al., 1974), reviewed in the previous criteria document (U.S. Environmental Protection Agency, 1979), has been reported on patients with peripheral vascular disease. Ten men with diagnosed intermittent claudication experienced a

significant decrease in time to onset of leg pain when exercising on a bicycle ergometer after breathing 50 ppm CO for 2 h (2.8% COHb). Further research is needed, therefore, to better determine the sensitivity of subjects with vascular disease to CO.

12.3.4 Subjects with Anemia and Other Hematologic Disorders

Clinically diagnosed low values of hemoglobin, characterized as anemia, is a relatively prevalent condition in the United States. If the anemia is mild to moderate, an inactive person is often asymptomatic. However, due to the limitation in the oxygen-carrying capacity resulting from the low hemoglobin values, an anemic person should be more sensitive to low-level CO exposure than a person with normal hemoglobin levels (see Section 10.3.2). If anemia is combined with other prevalent diseases, such as coronary artery disease, the individual also will be at an increased risk to CO exposure. Anemia is more prevalent in women and in the elderly, already two potentially "high" risk groups. An anemic person also will be more sensitive to the combination of CO exposure and high altitude. Additional studies are needed, therefore, in order to determine the susceptibility of this group to CO exposure.

Individuals with hemolytic anemia often have higher baseline levels of COHb because the rate of endogenous CO production from heme catabolism is increased. One of the many causes of anemia is the presence of abnormal hemoglobin in the blood. For example, in sickle-cell disease the average lifespan of red blood cells with abnormal hemoglobin S (Hb S) is 12 days compared to an average of 88 days in healthy individuals with normal hemoglobin (Hb A). As a result, baseline COHb levels can be as high as 4% (Solanki et al., 1988). In subjects with hemoglobin Zurich, where affinity for CO is 65 times that of normal hemoglobin, COHb levels range from 4 to 7% (Zinkham et al., 1980).

There are over 350 variants to normal human hemoglobin (Zinkham et al., 1980). In the Hb S variant, sickling takes place when deoxy Hb S in the red blood cell reaches a critical level and causes intracellular polymerization. Oxygenation of the Hb S molecules in the polymer, therefore, should lead to a change in molecular shape, breakup of the polymer, and unsickling of the cell. Carbon monoxide was considered at one time to be potentially beneficial because it ultimately would reduce the concentration of deoxy Hb S by converting

part of the hemoglobin to COHb. Exposure to CO, however, was not considered to be an effective clinical treatment because high COHb levels (>20%) were required.

Other hematologic disorders can cause elevated concentrations of COHb in the blood. Ko and Eisenberg (1987) studied a patient with Waldenström's Macroglobulinemia. Not only was the COHb saturation elevated, but the half-life of COHb was about three times longer than in a normal individual. Presumably, exogenous exposure to CO, in conjunction with higher endogenous CO levels, could result in critical levels of COHb. However, because CO also can modify the characteristics of unstable hemoglobin, as demonstrated in patients with Hb S it is not known how ambient or near-ambient levels of CO would affect individuals with these disorders.

12.3.5 Subjects with Obstructive Lung Disease

Chronic obstructive pulmonary disease (COPD) is a prevalent disease especially among smokers. It is estimated (U.S. Department of Health and Human Services, 1987; Collins, 1988) that 14 million persons (~6%) suffer from COPD in the United States and that a large number (>50%) of these individuals have limitations in their exercise performance demonstrated by a decrease in oxygen saturation during mild to moderate exercise. In spite of their symptoms, many of them (~30%) continue to smoke and already may have COHb levels of 4 to 8%. Subjects with hypoxia are also more likely to have a progression of the disease resulting in severe pulmonary insufficiency, pulmonary hypertension, and right heart failure. Studies by Aronow et al. (1977) and Calverley et al. (1981), reviewed in Chapter 10, suggest that individuals with hypoxia due to chronic lung disease such as bronchitis and emphysema may be susceptible to CO during submaximal exercise typically found during normal daily activity.

The prevalence of chronic asthma in the United States is estimated to be as high as 9 million persons or about 4% of the total population (U.S. Department of Health and Human Services, 1987; Collins, 1986, 1988). There has been evidence that hospital admissions for asthma have increased considerably in the past few years, particularly among individuals less than 18 years of age. Because asthmatics also can experience exercise-induced airflow limitation, it is likely that they also would be susceptible to hypoxia. It is not known, however, how exposure to CO would affect these individuals.

12.4 SUBPOPULATIONS AT RISK FROM COMBINED EXPOSURE TO CARBON MONOXIDE AND OTHER CHEMICAL SUBSTANCES

12.4.1 Interactions with Psychoactive Drugs

There is almost a complete lack of data on the possible toxic consequences of combined CO exposure and drug use. The most extensively studied interaction has been combined exposure to CO and alcohol. The previous criteria document (U.S. Environmental Protection Agency, 1979) reviewed an extensive human study of alcohol-CO interactions on driving performance (Rockwell and Weir, 1975). In this study of actual driving behavior, alcohol and CO effects were often additive, and at 12% COHb concentrations, combined effects were observed that were greater than the sum of the effects of CO and alcohol alone. Two animal studies of alcohol-CO combinations (Mitchell et al., 1978; Knisely et al., 1989) also provide evidence that the effects of alcohol on behavior can be enhanced by high concentrations of CO exposure.

Thus is seems prudent to tentatively conclude that the behavioral effects of alcohol may be exacerbated under some conditions of CO exposure. What is not known is the range of behavioral effects for which this occurs, the quantitative nature of the interaction, the mechanism of the combined effects, or the minimal COHb concentrations needed to see an interaction. Further research on this clearly is needed. This is particularly the case when one considers the role of alcohol in our society and the likelihood of frequent opportunities for combined alcohol use and CO exposure. Some statistics from the recent report to Congress on *Alcohol and Health* illustrate the potential problem (National Institute on Alcohol Abuse and Alcoholism, 1987). In 1984, the estimated per capita alcohol consumption per year in the United States was 2.65 gal of pure alcohol per person over the age of 14. The National Institute on Alcohol Abuse and Alcoholism estimates that two-thirds of the U.S. population over the age of 18 drink alcohol, and one-half of these are moderate to heavy drinkers. Nearly 50% of all accidental deaths are alcohol related. Even a small interaction of CO exposure with alcohol would be magnified by the high incidence of these combinations.

Other studies of interactions of CO and drugs have been conducted; however not nearly enough data exist upon which one could draw conclusions concerning populations at risk. Some evidence from animal research indicates that CO exposure may alter the effects of pentobarbital, *d*-amphetamine, and chlorpromazine (McMillan and Miller, 1974; Knisely

et al., 1989). Because these drugs represent diverse classes of psychoactive drugs, and many other classes have not been examined at all, it must be concluded that this is an area of concern for which it is difficult at the present time to make recommendations that will have an effect on air quality standards. The lack of data on possible interactions of CO exposure and drug use was identified in both the 1979 Criteria Document and an addendum to that document (U.S. Environmental Protection Agency, 1979, 1984). Little has changed since then.

12.4.2 Interactions with Cardiovascular Drugs

There are limited data currently available to determine if there is a possible interaction between CO exposure and different cardiovascular drugs. Drugs used to treat patients with coronary artery disease, such as betablockers, calcium channel blockers, and nitrates, should be tested for potential interaction with CO because those patients already are high-risk subjects. Patients with angina that were used as subjects in studies on the effects of CO exposure (see Chapter 10, Section 10.3) also were treated with these classes of drugs. Unfortunately, drug interactions were not investigated in most of the studies. Only Allred et al. (1989a,b) analyzed their data for potential medication effect and no interactions with CO were found. The only other available data dealt with the interaction of CO with betablockers and calcium blockers in smokers. Deanfield et al. (1984) studied 10 smoking patients with stable angina in a double-blind placebo controlled study. He studied two betablockers, atenolol and propranolol, and one calcium blocker, nifedipine. The patients underwent exercise tests and Holter monitoring both when they still were smoking and after they had stopped smoking for one month. The performance and results from Holter monitoring showed improvement after the patients refrained from smoking. The difference was largest for nifedipine. Blood levels of propranolol were increased when the patients stopped smoking; levels of nifedipine and atenolol were unchanged. Part of the decreased efficacy of the drugs while smoking might be due to lower plasma levels and part of it might be due to some interaction on a cellular level. However, it currently is not known if the interaction was due to nicotine and/or CO.

Another of the high risk groups using multiple medications are heart failure patients. They often use digitalis, diuretics, vasodilators, and recently, inhibitors of angiotension

converting enzyme. If CO exposure modifies the responses to those drugs, the patients' status may deteriorate when the plasma levels of a drug are lower or the patients may develop side effects when the plasma levels of a drug are higher. Due to the large number of high-risk patients with coronary artery disease and heart failure that use often very potent and multiple mediations, this area needs to be addressed carefully through further research.

12.4.3 Mechanisms of Carbon Monoxide Interactions with Drugs: Need for Further Research

Because data are generally lacking on CO-drug interactions, it should be useful to speculate on some of the mechanisms by which CO might be expected to alter drug effects, or vice versa, and discuss possible populations at risk due to these potential interaction effects.

12.4.3.1 Metabolic Effects

A mechanism by which CO might be expected to interact with many drugs is through the modification of drug metabolism. CO is known to bind to cytochrome P-450 *in vitro* (Gray, 1982), but the significance of this under physiological conditions is not known. Another section of this document (see Section 9.4) reviews the interactions of CO with oxidative metabolism and concludes that clinically relevant inhibition of these systems probably does not occur under most conditions of exposure. If further research provides evidence that these important drug-metabolizing systems are significantly compromised as a result of ambient CO exposure, then drugs dependent upon these systems for activation or deactivation would interact with CO exposures. If changes in drug metabolism occur as a result of CO exposure, this would be of considerable practical importance. It might be necessary to alter prescribing practices in heavily exposed populations. More research on this is needed.

12.4.3.2 Central Nervous System (CNS) Depression

In the absence of systematic data on the interactions of CO with psychoactive drugs, it is necessary to hypothesize mechanisms by which such interactions might occur. In the 1984 Addendum (U.S. Environmental Protection Agency, 1984), it was speculated that "drugs with primary or secondary CNS depressant effects should be expected to exacerbate the

neurobehavioral effects of CO," presumably because of the generally depressant effects on the nervous system of CO itself. On the other hand, one might also argue the converse (i.e., that CNS depressant drugs, because they might reduce cerebral metabolism and hence oxygen utilization, could lessen the neurobehavioral effects of CO). It should be obvious that speculation on these matters, in the absence of data, cannot be expected to yield answers upon which regulatory decisions could be made. On the other hand, because of the overall sensitivity of the CNS to perturbations, it is possible that interactions of these types could occur and may even be quite pronounced. Clearly, more research on this is needed because we cannot rely on scientific speculation.

12.4.3.3 Alteration in Cerebral Blood Flow

Another mechanism by which CO could be speculated to interact with certain drugs is through modification of cerebral blood flow. Brain hypoxia resulting from CO exposure may result in compensatory increases in cerebral blood flow (Dobler et al., 1977). Drugs that have vasoconstrictive effects on cerebral circulation could be hypothesized to interfere with this compensatory mechanism and thus exacerbate the neurobehavioral toxicity of CO. The methylxanthines, such as caffeine and theophylline, have well-established central vasoconstrictive effects (Rall, 1980) and thus could be hypothesized to enhance CO-induced brain hypoxia. On the other hand, their vasodilatory effects in the periphery (Rall, 1980) might enhance the vasodilatory effects of CO. Because of the widespread use of methylxanthines, these possible interactions may be of particular significance.

As the oxygen-carrying capacity of the blood decreases with CO poisoning, many organs, including the brain, will compensate their blood flow to try and maintain proper tissue oxygenation. Several studies using radiolabeled microspheres to measure cerebral blood flow have demonstrated autoregulation and increased blood flow in response to CO (Koehler et al., 1982). However, if the brain oxygen supply is inadequate despite increased blood flow, further metabolic changes will undoubtedly occur. The consequences of these metabolic changes with respect to their effect on the regulation of brain blood flow is uncertain. More simply, damage resulting from lack of proper brain oxygenation may alter the brain vasculature's ability to regulate brain blood flow. Damage to the vasculature previously has been shown to alter the vasculature's response to vasoactive agents. For

example, it is known that following ischemia-induced injury and other types of brain injury, the brain releases polyunsaturated fatty acids from its phospholipids (Gardiner et al., 1981). These free fatty acids may be metabolized enzymatically to compounds such as prostaglandins and leukotrienes with effects on the cerebral vasculature. For example, the metabolism of arachidonic acid generates prostaglandins and oxygen-free radicals that can cause cerebral vasodilation in normal animals. However, when these radicals are produced in excess, as in acute, extreme hypertensive episodes, the free radicals initiate peroxidation of other unsaturated fatty acids (Kukreja et al., 1986). These peroxides and oxygen radicals cause damage to the vascular endothelium and decrease the brain's capacity to regulate blood flow in response to changes in arterial CO_2 (Wei et al., 1981). Additionally, the vascular damage caused by these oxygen radicals alters the normal cerebral arterial response to vasoactive agents, including neurotransmitters. For example, acetylcholine, which is normally a dilator of cerebral arterioles, produces vasoconstriction after free radical-induced damage (Wei et al., 1985). Potentially, therefore, in an injured brain, acetylcholine may decrease an already inadequate blood flow.

Conceptually, tissue hypoxia produced by CO may stimulate arachidonic acid metabolism and production of prostaglandins and free radicals in a manner similar to hypoxia caused by ischemia or trauma. Production of vasodilator free radicals or vasodilator prostaglandins may be a mechanism by which the brain increases its blood flow in response to CO. Assuming this is the case, therapeutic agents or drugs of abuse that modify the arachidonic acid cascade may alter the brain's capacity to increase blood flow in response to CO. For example, if aspirin, indomethacin, or other cyclooxygenase inhibitors are present during exposure to CO, the brain's capacity to increase its flow may be diminished due to decreased capacity to form dilator prostanoids and free radicals. An instance where this sort of possibility is known to occur is in neonatal animals, and possibly in neonatal humans. Investigators recently have shown in neonatal animals that indomethacin markedly diminished the brain's capacity to increase its blood flow in response to hypoxia (Leffler and Busija, 1987).

A possible interaction between CO and nitrite exposure also might be predicted. Nitrites can be expected to oxidize hemoglobin to methemoglobin leaving less hemoglobin to bind either to O_2 or CO. However, since CO has a greater affinity than O_2 for hemoglobin, it is

most likely to expect additive effects in reduction of oxyhemoglobin. In addition, some organic nitrites such as amyl nitrite, used to relieve angina pain, and butyl nitrite, an abused substance, produce significant peripheral vasodilation and, consequently, an abrupt drop in blood pressure and subsequent tachycardia. These potent cardiovascular effect's which result from carbon monoxide exposure, might interfere with the enhanced cardiac output, particularly the output to sensitive organs such as the brain. To date there are no published data on the combined effect of CO and nitrite exposure. However, there are limited data showing reasonably parallel consequences on auditory function (Fechter et al., 1987, 1989) when CO and butyl nitrite are given individually to rats.

Additionally, recent evidence shows that acetylcholine stimulates arachidonic acid metabolism (Busija et al., 1987). Whether hypoxia increases arachidonic acid metabolism via stimulation of acetylcholine release is uncertain, however, exogenous acetylcholine is known to stimulate brain prostaglandin production. Assuming that endogenous acetylcholine release in response to CO-induced hypoxia is important, other agents such as atropine or scopolamine, which block muscarinic receptors, could reduce the vasodilator response to CO. In an opposite manner, cholinesterase inhibitors (e.g., organophosphate or carbamate insecticides) that penetrate the blood brain barriers may magnify the dilator response to CO. Other agents that may modify the capacity of the brain's blood flow to regulate in response to CO are agents that cause an acute, large increase in blood pressure, thus inducing excess free radical production, lipid peroxidation, and abnormal vascular reactivity. Such an agent might include for example, cocaine, which when administered in large doses causes acute transient hypertension.

While the above points are speculative, the possibility that therapeutic agents and drugs of abuse may alter the brain vasculature's capacity to respond to CO is a subject that bears further consideration and investigation.

12.4.4 Interactions with Other Chemical Substances in the Environment

Besides direct ambient exposure to CO, there are other chemical substances in the environment that can lead to increased COHb saturation when inhaled. Halogenated hydrocarbons used as organic solvents undergo metabolic breakdown by cytochrome P-450 to form CO and inorganic halide. Possibly the greatest concern regarding potential risk in the

population comes from exposure to one of these halogenated hydrocarbons, methylene chloride (CH_2Cl_2), and some of its derivatives. Almost a million kilograms are produced each year, making it the second highest source of CO in the environment. Although it is present in ambient air emissions, the highest concentrations of CH_2Cl_2 occur from various sources such as paint removers, cleaners, propellants, and from industrial manufacturing.

From available experimental studies (see Section 11-3), it is not clear if combined exposure to CO and CH_2Cl_2 would produce an additive effect in humans. Theoretically, acute CH_2Cl_2 exposure can result in a steady production of endogenous CO in tissues such as the lung, liver, kidney, heart, and brain that contain cytochrome P-450. Any histotoxic hypoxia produced at the tissue level combined with hypoxic hypoxia due to the formation of COHb from endogenous as well as exogenous CO exposure could place exposed individuals at risk.

12.5 SUBPOPULATIONS EXPOSED TO CARBON MONOXIDE AT HIGH ALTITUDES

For patients with coronary artery disease, restricted coronary blood flow limits oxygen delivery to the myocardium. Carbon monoxide also has the potential for compromising oxygen transport to the heart. For this reason, such patients have been identified as the subpopulation most sensitive to the effects of CO. A reduction in the partial pressure of oxygen (PO_2) in the atmosphere, as at high altitude, also has the potential for compromising oxygen transport. Therefore, patients with coronary artery disease who visit higher elevations might be unusually sensitive to the added effects of atmospheric CO.

Before considering the combined effects of CO and atmospheric hypoxia, it is important to distinguish between the long term resident of high altitude, as compared with the newly arrived visitor from low altitude. Specifically, the visitor will be more hypoxemic than the fully adapted resident for the following reasons. Initially, the visitor will exhibit relative hypoventilation, particularly during sleep, since ventilatory adaptation requires several days. The result will be a lowering of arterial PO_2, a fall in arterial O_2 saturation, and a reduction in arterial O_2 content. This hypoxemia will stimulate the sympathetic nervous system to increase heart rate, myocardial contractility, and systemic arterial blood pressure (Grover et al., 1986). These factors combine to increase cardiac work, calling for an increase in coronary blood

flow. In addition, the initial increase in ventilation will produce a respiratory alkalosis which, in turn, will increase the affinity of hemoglobin for oxygen and thereby interfere with oxygen release to the tissues.

Over several days following arrival at high altitude, a number of mechanism will operate to lessen the initial impact of atmospheric hypoxia. Ventilation will increase progressively, and this will evaluate arterial O_2 tension, saturation, and content. A decrease in plasma volume increases hematocrit (hemoconcentration), with an associated increase in the O_2-carrying capacity (hemoglobin concentration) of the blood; at this point, the polycythemia is only *relative* not *absolute*. Nevertheless, this will increase further the arterial O_2 content. Although increased sympathetic activity persists, cardiac beta receptor responsiveness decreases, mitigating the initial tachycardia. This combined with a decreased in cardiac stroke volume leads to a return of cardiac output to normal (or even subnormal) levels (Grover et al., 1986). Compensation for the initial respiratory alkalosis returns blood pH towards normal. Concurrently, there is an increase in the concentration of 2,3-disphosphoglycerate (2,3-DPG) within the red cells, the net effect being not only a return of hemoglobin-oxygen affinity to normal but actually to levels lower than prior to ascent. This facilitates the release of oxygen to the tissues, an effect that more than offsets the slight decrease in arterial O_2 saturation. For the heart, this is particularly important, for it removes the demands for increased coronary blood flow at moderate altitude (Grover et al., 1976).

For the long-term resident at high altitude, systemic blood pressure returns to (or below) values normal for sea level (Marticorena et al., 1969). Cardiac output remains at (or below) levels normal for sea level (Hartley et al., 1967). Tissue capillary density increases, thereby enhancing oxygen delivery. Consequently, demands on the coronary circulation are not increased. An *absolute* polycythemia develops, i.e., total red cell mass plateaus at levels greater than at sea level. As a consequence, the normal turn-over of this greater mass of red cells results in an increase in the endogenous production of CO (Johnson, 1968).

Based on these considerations, the population subgroup at greatest risk from CO exposure would be the newly-arrived transient visitors to high altitudes. By binding hemoglobin, CO would reduce further arterial O_2 content, i.e., increase hypoxemia. In addition, CO would augment the effect of alkalosis by increasing further the affinity of hemoglobin for oxygen, thereby impairing O_2 delivery even more. Both factors would

increase demands for greater coronary blood flow. These initial risks would decline progressively if the visitor remains long enough to complete physiological adaptation. The period of increased risk is probably prolonged in the elderly, since adaptation to high altitude proceeds more slowly with increasing age (Dill et al., 1963, 1985; Robinson et al., 1973).

Not surprisingly, the total number of transient visitors to high altitude far exceeds the resident population. Ironically, it is these same transient visitors who contribute most to atmospheric pollution with CO in the mountains (automobile engines not tuned to high altitude, inefficient wood burning fireplaces used for social effect in vacation cabins, etc.). In addition, newly arrived visitors are often unaware of the physiological effects of high altitude (plus CO), and hence are prone to over-exertion which would increase the potential hazard. For a variety of reasons, COHb concentrations tend to be higher in high altitude residents than seen at low altitude (Johnson, 1968).

One would postulate that the combination of high altitude with CO would pose the greatest risk to persons newly arrived at high altitude who have underlying cardiovascular disease, particularly since they are usually older individuals. Surprisingly, this hypothesis has never been tested adequately. In fact, there are virtually no data on how patients with known or suspected coronary artery disease responde to a sojourn at moderately high altitude (8,000 to 12,000 ft or higher) with or without added CO exposure. In two pilot studies, the risk from altitude alone at least appears to be minimal (Okin, 1970; Khanna et al., 1976). Among 148,000 persons (10% over 50 years of age) trekking in Nepal to altitudes up to 18,000 ft, there were no cardiac deaths and only three helicopter evacuations for cardiac problems (Shlim and Houston, 1989). Nevertheless, the need remains for a rigorous test of the hypothesis.

If the cardiovascular effects of atmospheric hypoxia at high altitude are augmented by added exposure to CO, then patients already hypoxic from chronic obstructive lung disease should also be at increased risk from CO at altitude. Paradoxically, this does not appear to be true, again at least for brief exposure to altitude alone, even though hypoxemia is exaggerated (Graham and Houston, 1978; Schwart et al., 1984). This may reflect the decrease in air density at high altitude which reduces both the work of breathing (Thoden et al., 1969) as well as the effective degree of airway obstruction in such patients (Kryger et al., 1978).

Although limited observations do not indicate an increased risk from exposure to moderate altitude (without added CO) for patients with either cardiovascular or obstructive airway disease, this does not imply that prolonged residence at altitude is well tolerated. Individuals with these disorders, while successfully living at higher altitudes initially, tend to leave these altitudes as they reach older age. Outward migration of older individuals with these disorders has been described for the higher elevations in the state of Colorado (Regensteiner and Moore, 1985). These elderly residents living at altitudes above 8,000 ft left primarily due to poor health. Heart disease and lung disease (each 41%) accounted for the majority of reasons for leaving their high altitude homes.

It is known that low birth weights occur in both infants born at altitudes above 6,000 ft as well as infants born near sea level whose mothers had elevated COHb levels due to cigarette smoking (see Chapter 11, Section 11.1). It has also been shown that COHb levels in smokers at high altitude are higher than in smokers at sea level (Brewer et al., 1970). While it is probable that the combination of hypoxic hypoxia and hypoxia resulting from ambient exposure to CO could further reduce birth weight at high altitude and possibly modify future development, no data are presently available to support this hypothesis. A study conducted in Colorado (Alderman et al., 1987) failed to find a strong relationship between risk of low birth weight and maternal exposure to neighborhood CO estimated from stationary monitors. The combination, however, of maternal smoking and 6,000 ft altitude did result in lower birth weights than those due to altitude alone.

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APPENDIX A: GLOSSARY OF TERMS AND SYMBOLS

Abbreviations and Acronyms

τ	Atmospheric lifetime
χ	Chi
$^{12}C^{16}O$	Carbon monoxide containing oxygen isotope 16
$^{12}C^{18}O$	Carbon monoxide containing oxygen isotope 18
^{131}I	Iodine-131
2,3-DPG	2,3-diphosphoglycerate
^{51}Cr	Chromium-51
7-mode	137 second driving cycle test
^{85}Kr	Krypton-85
^{99m}TcDTPA	Radiolabeled diethylene triamine pentacetic acid
A/F	Air-to-fuel ratio
a.k.a.	Also known as
A-aDO_2	Alveolar-arterial O_2 gradient
ACD	Acid citrate dextrose
ACGIH	American Conference of Governmental Industrial Hygienists
ADD (m)	Additive constant specification
AEP	Auditory evoked potential
AIRS	Aerometric Information Retrieval System (U.S. EPA)
Alt	Altitude above sea level
amb	Ambient
ANOVA	Analysis of variance
ANSI	American National Standards Institute
Ar	Argon
atm	Atmosphere
BEI	Biological exposure index
BF	Blue flame (heater)
BLIS	Bibliographic literature information system
BS	Body sway
BTPS	Body temperature, barometric pressure, and saturated
Btu	British thermal unit
C	Celsius
Ca	Calcium
CAA	Clean Air Act
CAD	Coronary artery disease
CALINE3 Model	A form of dispersion modeling
CASAC	Clean Air Scientific Advisory Committee
C_b	Concentration of carbon monoxide for a bulk mixture
CBF	Cerebral blood flow
cc	Cubic centimeter *(see also cm^3)
C_∞	Concentration of carbon monoxide in the sample

CEQ	Presidents Council on Environmental Quality
CFF	Critical flicker frequency
Cff	Critical flicker fusion
CFK	Coburn-Forster-Kane
CFKE	Coburn-Forster-Kane equation
cGMP	Cyclic guanosine monophosphate
CH_2Cl_2	Methylene chloride
CH_3CCl_3	Methylchloroform
CH_4	Methane
CHD	Coronary heart disease
CI	Confidence interval
$C_i(t)$	The air pollutant concentration to which an individual is exposed at any point in time t.
CID	Cubic inch displacement
cm	Centimeter(s)
cm^3	Cubic centimeter
$CMRO_2$	Cerebral O_2 consumption
CN	Cyanide
CNS	Central nervous system
CNV	Contingent negative variation (slow-evoked potential)
CO	Carbon monoxide
CO	Cardiac output
CO-Ox	CO-oximeter
CO_2	Carbon dioxide
COH	Carbon monoxide hypoxia
COHb	Carboxyhemoglobin
COMb	Carboxymyoglobin
COPD	Chronic obstructive pulmonary disease
CP	Capillary permeability to protein
CVD	Cardiovascular disease
CVS-72	Constant volume sample cold start test
CVS-75	Constant volume sample test including cold and hot starts
Cyt	Cytochrome
d'	Measure of detection threshold
dBA	Decibels (A-scale)
dF/dtmax	Derivative of maximal force
D_LCO	Diffusing capacity for CO, mL min^{-1} $torr^{-1}$ (STPD)
D_LO_2	Diffusing capacity for O_2, mL min^{-1} (STPD)
dP/dt	Derivative of pressure with time
D_pCO	Carbon monoxide diffusion coefficient across the placenta
DPG	Diphosphoglycerides
EDRF	Endothelium-derived relaxing factor
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalogram
EKG	Electrocardiogram (also ECG)
EP	Evoked potential
EPA	Environmental Protection Agency

ERG	Electroretinogram
ETS	Environmental tobacco smoke
f	Fetal
F_6	Flow rate of carbon monoxide for a bulk mixture
F_A	Air flow rate
f_B	Breathing frequency
F_{CO}	Carbon monoxide flow rate
FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV_1	Forced expiratory volume (at one minute)
FFF	Flicker-fusion frequency
F_ICO	Volumetric fractional concentration of CO in dry inspired air, ppm
FID	Flame ionization detector
F_{IO2}	Fraction of inspired O_2
FMVCP	Federal Motor Vehicle Control Program
FRC	Functional residual capacity
FVC	Forced vital capacity
g	Gram(s)
GC	Gas chromatograph
GD	Gestation day
GFC	Gas filter correlation
GMP	Guanosine monophosphate
h	Hour
H_2O	Water
HANES	Health and Nutrition Examination Survey
Hb	Hemoglobin concentration in blood, g dL^{-1}
Hb 5	Abnormal hemoglobin found in individuals with sickle-cell disease
Hb A	Normal hemoglobin
HBO	Hyperbaric oxygen
HbO_2	Oxyhemoglobin
HCN	Hydrogen cyanide
HCs	Hydrocarbons
Hct	Hematocrit
HDL	High-density lipoprotein
He	Helium
HEI	Health Effects Institute
Hg	Mercury
HgO	Mercuric oxide
HH	Hypoxic hypoxia
$HO_2^{\bullet}$	Hydroperoxyl radical
HR	Heart rate
HW/BW	Heart weight to body weight ratio
$H^{\bullet}$	Hydrogen atom
I_2O_5	Iodine pentoxide
ip	Intraperitoneal
K	Warburg partition coefficient
K_2HPO_4	Mono-hydrogen potassium arthrophosphate

$K_4Fe(CN)_6$	Potassium ferrocyanide
K_{eff}	The effective reaction rate constant
kg	Kilogram(s)
kJ	Kilo Joule, $1x10^{10}$ ergs, 0.948 Btu
km	Kilometer
K_m	Michaelis-Menten constant
KPM	Kilopondmeters per minute
L	Liter(s)
LC_{50}	Concentration that is lethal to 50% of test subjects (used in inhalation studies)
LD_{50}	Dose that is lethal to 50% of test subjects
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDV	Light-duty vehicle
LOEL	Lowest-observed-effect level
LPG	Liquefied petroleum gas
LV	Left ventricle
M LDH	Myocardial lactate dehydrogenase
M	Haldane constant
m	Maternal
m^3	Cubic meter
Mb	Myoglobin
MEA	Mean electrical axis
MEMs	Microenvironmental monitors
metHb	Methemoglobin
METS	Basal metabolic equivalent
MFO	Mixed-function oxidase
mg	Milligram(s)
mi	Mile
MI	Myocardial infarction
mL	Milliliter(s)
MMFR	Maximum mid-expiratory flow rate
mo	Month(s)
mol	Mole
MRFIT	Multiple risk factor intervention trial
MSA	Metropolitan Statistical Area
MSHA	Mine Safety and Health Administration
MST	Mean survival time
MULT (m)	Multiplicative constant specification
n	Number
N_2	Nitrogen
N_2O	Nitrous oxide
NAAQS	National Ambient Air Quality Standards
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
$NaHCO_3$	Acid sodium carbonate
NAMS	National Air Monitoring Stations
NASA	National Aeronautics and Space Administration

NBS	National Bureau of Standards, now NIST
ND	Not determined
NDIR	Nondispersive infrared
NEDS	National Emissions Data System
NEM	NAAQS Exposure Model
NG	Natural gas
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
nm	Nanometer
NO	Nitric oxide
NO_2	Nitrogen dioxide
NO_3	Nitrate
NOEL	No-observed-effect level
NO_x	Nitrogen oxides
NR	No response
O_2	Oxygen
O_2Mb	Oxymyoglobin
O_3	Ozone
$OH^{\bullet}$	Hydroxyl radical
P	Pressure in atmospheres
P	Propane
P_{50}	Partial pressure of O_2 at 50% saturation of hemoglobin
P_aCO_2	Partial pressure of CO_2 in arterial blood, torr
P_ACO_2	Partial pressure of CO_2 in alveolar gas, torr
PAH	Polyaromatic hydrocarbons
PAN	Peroxyacetyl nitrate
P_aO_2	Partial pressure of O_2 in arterial blood
P_B	Barometric pressure, torr
PCN	Potassium cyanide
P_{CO}	Partial pressure of CO
P_cO_2	Mean partial pressure of pulmonary capillary 0_2 (torr)
PCO_2	Partial pressure of CO_2
PD	Postnatal day
PEMs	Personal exposure monitors
P_fCO	Partial pressures of carbon monoxide in the fetal placental capillaries
PGI_2	Prostacyclin
P_iCO	Partial pressure of CO in humidified inspired air, torr
PiT	Pituitary
P_mCO	Partial pressures of CO in the maternal placental
PMN	Polymorphonuclear neutrophil leukocytes
PO_2	Partial pressure of O_2
ppbv	Parts per billion by volume
ppm	Parts per million by volume (milligrams per liter)
ppmm	Parts per million by mass (milligrams per kilogram)
PR	Pulmonary resistance
PW	Placental weight
$\dot{Q}$	Overall perfusion

r	Correlation coefficient
rCBF	Regional cerebral blood flow
R	CO/O_2 at 50% inhibition
R^2	Coefficient of determination
RBC	Red blood cell
RV	Right ventricle
RV	Residual volume
RVF	Red visual field
s	Second
SAROAD	U.S. EPA centralized data base; superceded by AIRS (q.v.)
scf	Standard cubic foot
SCO	Percent COHb of total Hb
SD	Standard deviation
SE	Standard error
SF_6	Sulfur hexafluoride
SHAPE	Simulation of Human Activity and Pollutant Exposure
SHED	Sealed housing for evaporative determination
SI	Stroke index
SIDS	Sudden infant death syndrome
SIPs	State Implementation Plans
SLAMS	State and Local Air Monitoring Stations
SO_2	$\%O_2$ Hb of total Hb
SO_2	Sulfur dioxide
SP	Mean stroke power
SR	Systemic resistance
SRMs	Standard Reference Materials
ST	Segment of the EKG (see definition of electrocardiogram)
STPD	Standard temperature and pressure, dry
SV	Stroke volume
t	Time, minute
t^1	Postexposure time in minutes
t_d	Times-to-death
TEAM	Total exposure assessment methodology
TEM	Transmission electron microscopy
Tg	Teragram(s); 10^{12} grams; 10^6 metric tons
TH	Total hydrocarbon
THC	Total hydrocarbon content
t_i	Times-to-incapacitation
TLC	Total lung capacity
torr	A unit of pressure equal to 1/760 of an atmosphere
TSP	Total suspended particulates
TTS	Temporary threshold shifts
TV	Tidal volume (also V_T)
TWA	Time-weighted average
UV	Ultraviolet
V_D	Physiological deadspace
VEP	Visual evoked potential

VFT	Ventricular fibrillation threshold
VLDL	Very low-density lipoprotein
V_{max}	Ventricular contractility
VMT	Vehicle-miles traveled
VPD	Vehicles per day
V_T	Tidal volume
$\dot{V}$	Ventilation
$\dot{V}_A$	Alveolar ventilation, mL min^{-1} (STPD)
$\dot{V}CO$	Rate of endogenous production of CO, mL min^{-1} (STPD)
$\dot{V}_E$	Minute ventilation; expired volume per minute
$\dot{V}O_2$	Oxygen uptake by the body
$\dot{V}O_2$	Oxygen consumption of tissues or cells (also, $\dot{Q}O_2$)
$\dot{V}O_2$ max	Maximal oxygen uptake
w/	With
WBC	White blood cell
WF	White flame (heater)
WHW	Wet heart weight
$\bar{x}$	Mean
[COHb]	Concentration of COHb in blood, as milliliters of CO per milliliter of blood (STPD)
$[CO]_{ave}$	Average concentration of CO
$[OH^{\bullet}]_{ave}$	Average concentration of the hydroxyl radical
Σ	Sigma (sum of terms)
Å	Angstrom
μm	Micrometer(s)

Definitions

Acclimatization: The physiological and behavioral adjustments of an organism to changes in its environment.

Adaptation: Changes in an organism's structure or habit that help it adjust to its surroundings.

Additivity: A pharmacologic or toxicologic interaction in which the combined effect of two or more chemicals is approximately equal to the sum of the effect of each chemical alone. (Compare with: antagonism, synergism.)

Adiabatic warming: The temperature increase produced in a descending air mass as pressure increases with decreasing altitude.

Air Pollutant: Any substance in air that could, if in high enough concentration, harm humans, other animals, vegetation, or material. Pollutants may include almost any natural or artificial composition of matter capable of being airborne. They may be in the form of solid particles, liquid droplets, gases, or in combinations of these forms. Generally, they fall into two main groups: (1) those emitted directly from identifiable sources and (2) those produced in the air by interaction between two or more primary pollutants, or by reaction with normal atmospheric constituents, with or without photoactivation. Exclusive of pollen, fog, and dust, which are of natural origin, about 100 contaminants have been identified and fall into the following categories: solids, sulfur compounds, volatile organic chemicals, nitrogen compounds, oxygen compounds, halogen compounds, radioactive compounds, and odors.

Air Pollution: The presence of contaminant or pollutant substances in the air that do not disperse properly and interfere with human health or welfare, or produce other harmful environmental effects.

Air Pollution Episode: A period of abnormally high concentration of air pollutants, often due to low winds and temperature inversion, that can cause illness and death.

Air Quality Criteria: The levels of pollution and lengths of exposure above which adverse health and welfare effects may occur.

Air Quality Standards: The level of pollutants prescribed by regulations that may not be exceeded during a specified time in a defined area.

Alveolar-arterial oxygen pressure difference [$P(A\text{-}a)O_2$]: The difference in partial pressure of oxygen in the alveolar gas spaces and that in the systemic arterial blood, measured in torr.

Alveolar carbon dioxide pressure (P_ACO_2): Partial pressure of carbon dioxide in the air contained in the lung alveoli.

Alveolar oxygen partial pressure (P_AO_2): Partial pressure of oxygen in the air contained in the alveoli of the lungs.

Alveolus: Hexagonal or spherical air cells of the lungs. The majority of alveoli arise from the alveolar ducts which are lined with the alveoli. An alveolus is an ultimate respiratory unit where the gas exchange takes place.

Ambient Air: Any unconfined portion of the atmosphere: open air, surrounding air.

Ambient Air Quality Standards: (See: Criteria Pollutants and National Ambient Air Quality Standards).

Anatomical dead space ($V_{D\ anat}$): Volume of the conducting airways down to the level where, during air breathing, gas exchange with blood can occur, a region probably situated at the entrance of the alveolar ducts.

Antagonism: A pharmacologic or toxicologic interaction in which the combined effect of two chemicals is less than the sum of the effect of each chemical alone; the chemicals either interfere with each other's actions, or one interferes with the action of the other. (Compare with: additivity, synergism).

Arrhythmia: Any variation from the normal rhythm of the heartbeat.

Arterial oxygen saturation (SaO_2): Percent saturation of dissolved oxygen in arterial blood.

Arterial partial pressure of carbon dioxide ($PaCO_2$): Partial pressure of dissolved carbon dioxide in arterial blood.

Arterial partial pressure of oxygen (PaO_2): Partial pressure of dissolved oxygen in arterial blood.

Atmosphere [*atm*]: A standard unit of pressure representing the pressure exerted by a 29.92-in column of mercury at sea level at 45° latitude and equal to 1000 g/cm^2. The whole mass of air surrounding the Earth, composed largely of oxygen and nitrogen.

ATPS condition (ATPS): Ambient temperature and pressure, saturated with water vapor. These are the conditions existing in a water spirometer.

BTPS conditions (BTPS): Body temperature, barometric pressure, and saturated with water vapor. These are the conditions existing in the gas phase of the lungs. For humans the normal temperature is taken as 37°C, the pressure as the barometric pressure, and the partial pressure of water vapor as 47 torr.

Carbon dioxide (CO_2): A colorless, odorless, non-poisonous gas, which results from fossil fuel combustion and is normally a part of the ambient air.

Carbon dioxide production ($\dot{V}CO_2$): Rate of carbon dioxide production by organisms, tissues, or cells. Common units: mL CO_2 (STPD)/kg•min.

Carbon monoxide (CO): An odorless, colorless, toxic gas formed by incomplete combustion, with a strong affinity for hemoglobin and cytochrome; it reduces oxygen absorption capacity, transport, and utilization.

Carboxyhemoglobin (COHb): Hemoglobin in which the iron is associated with carbon monoxide. The affinity of hemoglobin for carbon monoxide is about 240 to 250 times greater than for oxygen.

Central nervous system (CNS): The portion of the nervous system that includes the brain and spinal cord, and their connecting nerves.

Chronic obstructive lung disease (COLD): This term refers to diseases of uncertain etiology characterized by persistent slowing of airflow during forced expiration. It is recommended that a more specific term, such as chronic obstructive bronchitis or chronic obstructive emphysema, be used whenever possible. Synonymous with chronic obstructive pulmonary disease (COPD).

Combustion: Burning, or rapid oxidation, accompanied by release of energy in the form of heat and light. A basic cause of air pollution.

Combustion product: Substance produced during the burning or oxidation of a material.

Criteria: Descriptive factors taken into account by EPA in setting standards for various pollutants. These factors are used to determine limits on allowable concentration levels, and to limit the number of violations per year. When issued by EPA, the criteria provide guidance to the states on how to establish their standards.

Criteria pollutants: The 1970 amendments to the Clean Air Act required EPA to set National Ambient Air Quality Standards for certain pollutants known to be hazardous to human health. EPA has identified and set standards to protect human health and welfare for six pollutants: ozone, carbon monoxide, total suspended particulates, sulfur dioxide, lead, and nitrogen oxide. The term "criteria pollutants" derives from the requirement that EPA must describe the characteristics and potential health and welfare effects of these pollutants. It is on the basis of these criteria that standards are set or revised.

Diffusing capacity of the lung (D_L, D_LO_2, D_LCO_2, D_LCO): Amount of gas (O_2, CO, CO_2) commonly expressed as mL gas (STPD) diffusing between alveolar gas and pulmonary capillary blood per torr mean gas pressure difference per minute, that is, mL 0_2/(min-torr). Synonymous with transfer factor and diffusion factor.

Dose-response relationship: A relationship between (1) the dose, often actually based on "administered dose" (i.e., exposure) rather than absorbed dose, and (2) the extent of toxic injury produced by that chemical. Response can be expressed either as the severity of injury or proportion of exposed subjects affected.

Electrocardiogram (ECG, EKG): A graphic tracing of the variations in electrical potential caused by the excitation of the heart muscle and detected at the body surface. The normal electrocardiogram shows deflections resulting from arterial and ventricular activity. The first deflection, P, is due to excitation of the atria. The QRS deflections are due to excitation (depolarization) of the ventricles. The T wave is due to recovery of the ventricles (repolarization). The U wave is a potential undulation of unknown origin immediately following the T wave, seen in normal electrocardiograms and accentuated in hypokalemia.

Emission: Pollution discharged into the atmosphere from smokestacks, other vents, and surface areas of commercial or industrial facilities; from residential chimneys; and from motor vehicle, locomotive, or aircraft exhausts.

Emission factor: The relationship between the amount of pollution produced and the amount of raw material processed. For example, an emission factor for a blast furnace making iron would be the number of pounds of particulates per ton of raw materials.

Emission inventory: A list, by source, of the amount of air pollutants discharged into the atmosphere of a community. It is used to establish emission standards.

Emission standard: The maximum amount of air polluting discharge legally allowed from a single source, mobile or stationary.

Environment: The sum of all external conditions affecting the life, development, and survival of an organism.

EPA: The U.S. Environmental Protection Agency; established in 1970 by Presidential Executive Order, bringing together parts of various government agencies involved with the control of pollution.

Episode (pollution): An air pollution incident in a given area caused by a concentration of atmospheric pollution reacting with meteorological conditions that may result in a significant increase in illnesses or deaths. Although most commonly used in relation to air pollution, the term also may be used in connection with other kinds of environmental events such as a massive water pollution situation.

Exceedance: Violation of environmental protection standards by exceeding allowable limits or concentration levels.

Exposure: The amount of radiation or pollutant present in an environment that represents a potential health threat to the living organisms in the environment.

Fetus: The post-embryonic stage of the developing young. In humans, from the end of the second month of pregnancy up to birth.

Forced expiratory flow (FEFx): Related to some portion of the FVC curve. Modifiers refer to the amount of the FVC already exhaled when the measurement is made.

Forced expiratory volume (FEV): Denotes the volume of gas that is exhaled in a given time interval during the execution of a forced vital capacity. Conventionally, the times used are 0.5, 0.75, or 1 s, symbolized $FEV_{0.5}$, $FEV_{0.75}$, $FEV_{1.0}$. These values often are expressed as a percent of the forced vital capacity, e.g. $(FEV_{1.0}/VC) \times 100$.

Forced vital capacity (FVC): Vital capacity performed with a maximally forced expiratory effort.

Hematocrit (Hct): The percentage of the volume of red blood cells in whole blood.

Hemoglobin (Hb): A hemoprotein naturally occurring in most vertebrate blood, consisting of four polypeptide chains (the globulin) to each of which there is attached a heme group. The heme is made of four pyrrole rings and a divalent iron (Fe^{2+}-protoporphyrin) which combines reversibly with molecular oxygen.

Hydrocarbons (HC): Chemical compounds that consist entirely of carbon and hydrogen.

Hypoxemia: A state in which the oxygen pressure and/or concentration in arterial and/or venous blood is lower than its normal value at sea level. Normal oxygen pressures at sea level are 85 to 100 torr in arterial blood and 37 to 44 torr in mixed venous blood. In adult humans the normal oxygen concentration is 17 to 23 mL O_2/100 mL arterial blood; in mixed venous blood at rest it is 13 to 18 mL O_2/100 mL blood.

Hypoxia: Any state in which the oxygen in the lung, blood, and/or tissues is abnormally low compared with that of a normal resting human breathing air at sea level. If the P_{O2} is low in the environment, whether because of decreased barometric pressure or decreased fractional concentration of oxygen, the condition is termed environmental hypoxia. Hypoxia when referring to the blood is termed hypoxemia. Tissues are said to be hypoxic when their P_{O2} is low, even if there is no arterial hypoxemia, as in "stagnant hypoxia" which occurs when the local circulation is low compared to the local metabolism.

In vitro: 1. "In glass"; a test-tube culture. 2. Any laboratory test using living cells taken from an organism.

In vivo: In the living body of a plant or animal. In vivo tests are those laboratory experiments carried out on whole animals or human volunteers.

Indoor air: The breathing air inside a habitable structure or conveyance.

Indoor air pollution: Chemical, physical, or biological contaminants in indoor air.

Inversion: An atmospheric condition caused by a layer of warm air preventing the rise of cooling air trapped beneath it. This prevents the rise of pollutants that might otherwise be dispersed and can cause an air pollution episode.

Isotope: A variation of an element that has the same atomic number but a different weight because of its neutrons. Various isotopes of the same element may have different radioactive behaviors.

Lapse rate: Vertical temperature gradient in the atmosphere; usually negative (i.e., decreasing with altitude) (see "inversion").

Lowest-observed-adverse-effect level (LOAEL): The lowest dose or exposure level of a chemical in a study at which there is a statistically or biologically significant increase in the frequency or severity of an adverse effect in the exposed population as compared with an appropriate, unexposed control group.

Lowest-observed effect level (LOEL): In a study, the lowest dose or exposure level at which a statistically or biologically significant effect is observed in the exposed population compared with an appropriate unexposed control group.

Lung volume (V_L): Actual volume of the lung, including the volume of the conducting airways.

Maximal aerobic capacity (max $\dot{V}O_2$): The rate of oxygen uptake by the body during repetitive maximal respiratory effort. Synonymous with maximal oxygen consumption.

Methemoglobin (MetHb): Hemoglobin in which iron is in the ferric state. Because the iron is oxidized, methemoglobin is incapable of oxygen transport. Methemoglobins are formed by various drugs and occur under pathological conditions. Many methods for hemoglobin measurements utilize methemoglobin (chlorhemiglobin, cyanhemiglobin).

Minute ventilation ($\dot{V}_E$): Volume of air breathed in one minute. It is a product of tidal volume (V_T) and breathing frequency (f_B). (See ventilation)

Minute volume: Synonymous with minute ventilation.

Modeling: An investigative technique using a mathematical or physical representation of a system or theory that accounts for all or some its known properties. Models are often used to test the effect of changes of system components on the overall performance of the system.

Monitoring: Periodic or continuous surveillance or testing to determine the level of compliance with statutory requirements and/or pollutant levels in various media or in humans, animals, and other living things.

National Ambient Air Quality Standards (NAAQS): Air quality standards established by EPA that apply to outside air throughout the country. (See criteria pollutants)

Nitric oxide (NO): A gas formed by combustion under high temperature and high pressure in an internal combustion engine. It changes into nitrogen dioxide in the ambient air and contributes to photochemical smog.

Nitrogen dioxide (NO_2): The result of nitric oxide combining with oxygen in the atmosphere. A major component of photochemical smog.

Nitrogen oxides (NO_x): Compounds of nitrogen and oxygen in ambient air; that is, nitric oxide (NO) and others with a higher oxidation state of nitrogen, of which nitrogen dioxide is the most important toxicologically.

No-observed-adverse-effect level (NOAEL): The highest experimental dose at which there is no statistically or biologically significant increases in frequency or severity of adverse health effects, as seen in the exposed population compared with an appropriate, unexposed population. Effects may be produced at this level, but they are not considered to be adverse.

No-observed-effect level (NOEL): The highest experimental dose at which there is no statistically or biologically significant increases in frequency or severity of toxic effects seen in the exposed compared with an appropriate, unexposed population.

Oxygen consumption ($\dot{V}O_2$, $\dot{Q}O_2$): Rate of oxygen uptake of organisms, tissues, or cells. Common units: mL O_2 (STPD)/(kg•min) or mL O_2 (STPD)/(kg•hr). For whole organisms the oxygen consumption commonly is expressed per unit surface area or some power of the body weight. For tissue samples or isolated cells $\dot{Q}O_2$ = μL O_2/h/mg dry weight.

Oxygen saturation (SO_2): The amount of oxygen combined with hemoglobin, expressed as a percentage of the oxygen capacity of that hemoglobin. In arterial blood, SaO_2.

Oxygen uptake ($\dot{V}O_2$): Amount of oxygen taken up by the body from the environment, by the blood from the alveolar gas, or by an organ or tissue from the blood. When this amount of oxygen is expressed per unit of time one deals with an "oxygen uptake rate." "Oxygen consumption" refers more specifically to the oxygen uptake rate by all tissues of the body and is equal to the oxygen uptake rate of the organism only when the oxygen stores are constant.

Ozone (O_3): Found in two layers of the atmosphere, the stratosphere and the troposphere. In the stratosphere (the atmospheric layer beginning 7 to 10 miles above the Earth's surface) ozone is a form of oxygen found naturally which provides a protective layer shielding the earth from ultraviolet radiation's harmful health effects on humans and the environment. In the troposphere (the layer extending up 7 to 10 miles from the Earth's surface), ozone is a chemical oxidant and major component of photochemical smog. Ozone can seriously affect the human respiratory system and is one of the most prevalent and widespread of all the criteria pollutants for which the Clean Air Act required EPA to set standards. Ozone in troposphere is produced through complex chemical reactions of nitrogen oxides, which are among the primary pollutants emitted by combustion sources; hydrocarbons, released into the atmosphere through the combustion, handling and processing of petroleum products; and sunlight.

Peroxyacetyl nitrate (PAN): Pollutant created by action of UV component of sunlight on hydrocarbons and nitrogen oxides in the air; an ingredient of photochemical smog.

pH: A measure of the acidity or alkalinity of a liquid or solid material.

Photochemical smog: Air pollution caused by chemical reactions of various pollutants emitted from different sources.

Physiological dead space (V_D): Calculated volume that accounts for the difference between the pressures of carbon dioxide in expired and alveolar gas (or arterial blood). Physiological dead space reflects the combination of anatomical dead space and alveolar dead space, the volume of the latter increasing with the importance of the nonuniformity of the ventilation/perfusion ratio in the lung.

Pollutant: Generally, any substance introduced into the environment that adversely affects the usefulness of a resource.

Pollution: Generally, the presence of matter or energy whose nature, location or quantity produces undesired environmental effects. Under the Clean Water Act, for example, the term is defined as the man-made or man-induced alteration of the physical, biological, and radiological integrity of water.

Population: A group of interbreeding organisms of the same kind occupying a particular space. Generically, the number of humans or other living creatures in a designated area.

Respiratory frequency (f_R): The number of breathing cycles per unit of time. Synonymous with breathing frequency (f_B).

Smog: Air pollution associated with oxidants. (See photochemical smog)

Smoke: Particles suspended in air after incomplete combustion of materials.

Sulfur dioxide (SO_2): Colorless gas with pungent odor, primarily released from burning of fossil fuels, such as coal, containing sulfur.

Synergism: A pharmacologic or toxicologic interaction in which the combined effect of two or more chemicals is greater than the sum of the effect of each chemical alone. (Compare with: additivity, antagonism.)

STPD conditions (STPD): Standard temperature and pressure, dry. These are the conditions of a volume of gas at 0°C, at 760 torr, without water vapor. A STPD volume of a given gas contains a known number of moles of that gas.

Tidal volume (TV): That volume of air inhaled or exhaled with each breath during quiet breathing, only used to indicate a subdivision of lung volume. When tidal volume is used in gas exchange formulations, the symbol V_T should be used.

Time-weighted average (TWA): The average concentration to which a worker may be exposed continuously for 8 h without damage to health.

Torr: A unit of pressure equal to 1,333.22 dynes/cm^2 or 1.33322 millibars. The torr is equal to the pressure required to support a column of mercury 1 mm high when the mercury is of standard density and subjected to standard acceleration. These standard conditions are met at 0°C and 45° latitude, where the acceleration of gravity is 980.6 cm/s^2. In reading a mercury barometer at other temperatures and latitudes, corrections, which commonly exceed 2 torr, must be introduced for these terms and for the thermal expansion of the measuring scale used. The torr is synonymous with pressure unit mm Hg.

Total lung capacity (TLC): The sum of all volume compartments or the volume of air in the lungs after maximal inspiration. The method of measurement should be indicated, as with RV.

Ventilation: Physiological process by which gas is renewed in the lungs. The word ventilation sometimes designates ventilatory flow rate (or ventilatory minute volume) which is the product of the tidal volume by the ventilatory frequency. Conditions usually are indicated as modifiers; that is,

$\dot{V}_E$ = Expired volume per minute (BTPS),
and
$\dot{V}_I$ = Inspired volume per minute (BTPS).

Ventilation often is referred to as "total ventilation" to distinguish it from "alveolar ventilation". (See ventilation, alveolar)

Ventilation, alveolar ($\dot{V}_A$): Physiological process by which alveolar gas is removed completely and replaced with fresh gas. Alveolar ventilation is less than total ventilation because when a tidal volume of gas leaves the alveolar spaces, the last part does not get expelled from the body but occupies the dead space, to be reinspired with the next inspiration. Thus the volume of alveolar gas actually expelled completely is equal to the tidal volume minus the volume of the dead space. This truly complete expiration volume times the ventilatory frequency constitutes the alveolar ventilation.

Ventilation, dead-space ($\dot{V}_D$): Ventilation per minute of the physiologic dead space (wasted ventilation), BTPS, defined by the following equation:

$$\dot{V}_D = \dot{V}_E(PaCO_2 - P_ECO_2)/(PaCO_2 - P_ICO_2)$$

Ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$): Ratio of the alveolar ventilation to the blood perfusion volume flow through the pulmonary parenchyma. This ratio is a fundamental determinant of the oxygen and carbon dioxide pressure of the alveolar gas and of the end-capillary blood. Throughout the lungs the local ventilation/perfusion ratios vary, and consequently the local alveolar gas and end-capillary blood compositions also vary.

Vital capacity (VC): The maximum volume of air exhaled from the point of maximum inspiration.

Warbug partition coefficient (K): The carbon monoxide/oxygen ratio that produces 50% inhibition of the oxygen uptake of the enzyme or, in the case of myoglobin, a 50% decrease in the number of available oxygen-binding sites.

Wood-burning stove pollution: Air pollution caused by emissions of particulate matter, carbon monoxide, total suspended particulates, and polycyclic organic matter from wood-burning stoves.

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☆U.S. GOVERNMENT PRINTING OFFICE: 1990_748_159 00435