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Air Quality Criteria for Carbon Monoxide

Notice

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

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National Center for Environmental Assessment
Office of Research and Development
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Preface

The U.S. Environmental Protection Agency (EPA) promulgates the National Ambient Air Quality Standards (NAAQS) on the basis of an up-to-date compilation of scientific knowledge about the relationship between various concentrations of ambient air pollutants and their adverse effects on man and the environment. These air quality criteria are published in criteria documents. In 1970, the first air quality criteria document for carbon monoxide (CO) was issued by the National Air Pollution Control Administration, a predecessor of EPA. On the basis of scientific information in that document, NAAQS were promulgated for CO at levels of 9 ppm for an 8-h average and 35 ppm for a 1-h average. Periodic scientific assessments of the published literature were completed by EPA in 1979 and, again, in 1984. The last full-scale CO criteria document revision was published in 1991. Although the air quality criteria have changed over the past two decades, the NAAQS for CO have remained the same. This revised criteria document consolidates and updates the current scientific basis for another reevaluation of the CO NAAQS in accordance with the provisions identified in Sections 108 and 109 of the Clean Air Act.

This document was prepared and reviewed by experts from state and federal government offices, academia, and industry for use by EPA in support of decision making on potential public health risks of CO; it describes the nature, sources, distribution, measurement, and concentrations of CO in both the outdoor (ambient) and indoor environments and evaluates the latest data on the health effects in exposed human populations. Although not intended to be an exhaustive literature review, this document is intended to cover all pertinent literature through 1998.

The National Center for Environmental Assessment—Research Triangle Park, NC, acknowledges the contributions provided by the authors, contributors, and reviewers and the diligence of its staff and contractors in the preparation of this document.

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EXECUTIVE SUMMARY

Air Quality Criteria for Carbon Monoxide

External Review Draft

The purpose of this document is to present air quality criteria for carbon monoxide (CO), in accordance with Sections 108 and 109 of the Clean Air Act (CAA), that reflect the latest scientific information useful in indicating the kind and extent of all identifiable effects on public health and welfare that may be expected from the presence of CO in ambient air. This document is an update of *Air Quality Criteria for Carbon Monoxide*, published by the U.S. Environmental Protection Agency (EPA) in 1991, and will be used as the scientific basis for reevaluating the current national ambient air quality standards (NAAQS) for CO. This executive summary concisely summarizes key findings from the present document.

Summary Findings

Monitoring

Reliable methods are identified in Chapter 2 for monitoring CO concentrations in ambient air to determine compliance with the NAAQS and the potential effects on overall air quality and for monitoring the impact of ambient CO exposure on human populations.

- Several adequate techniques exist for highly reliable monitoring of CO to ensure compliance with the NAAQS. The most reliable method for continuous measurement of CO in ambient air is the nondispersive infrared (NDIR) optical transmission technique, the technique on which the EPA-designated analytical reference methods are based. One category of NDIR monitors, the gas filter correlation monitor, is still the single most widely used analyzer for fixed-site monitoring stations.

- Determining CO levels at many nonurban locations requires substantially better performance than that required to demonstrate compliance with the NAAQS. Commercial CO-monitoring instruments, sometimes with minor modifications, can meet the measurement needs for supplying useful data on the distribution and trends of ambient CO and for modeling photochemical smog in places where ambient levels are significantly below the NAAQS.

- There are at this time commonly used and accepted procedures for generating CO measurement standards that are accurate to better than ±2% in the parts-per-million range and about ±10% in the range of concentrations found in the clean troposphere. Several CO measurement techniques have been intercompared and found reliable.

- Several electrochemical and passive sampling methods are available. These techniques are currently inadequate for compliance monitoring or precise measurements in ambient air but are useful for personal exposure studies. Further work to improve stability and specificity is necessary.

- Blood carboxyhemoglobin (COHb) level and CO concentration in exhaled breath are biological indicators of CO exposure. Although the use of optical methods (e.g., CO-Oximetry [CO-Ox]) is common for population sampling and clinical analyses of COHb, gas chromatography is the method of choice for measuring low COHb saturations (<5%) that are expected to occur with ambient CO exposures. The measurement of CO in exhaled breath has practical advantages for population exposure sampling but has a greater potential than COHb for measurement error.

Global Tropospheric Chemistry

Current information about the abundance and distribution, the nature of sources and sinks, and the chemistry of CO in environments ranging from the global background to indoor air is summarized in Chapter 3. The importance of CO for atmospheric chemistry also is discussed in this chapter.

- In nonurban areas, tropospheric CO has a significant role in affecting the oxidizing capacity of the earth's atmosphere. Reaction with CO is a principal process by which hydroxyl radicals are removed from the atmosphere. Reaction with hydroxyl radicals is also the primary process for removing many other man-made and natural compounds, including CO, from the atmosphere.

- Carbon monoxide is linked closely to the cycle of tropospheric ozone and may be responsible for 20 to 40% of the ozone formed in nonurban areas. Ozone is an oxidant, a greenhouse gas, and a precursor of hydroxyl radicals. On balance, if CO increases, the net effect is to decrease hydroxyl radicals.

- Carbon monoxide is, therefore, an intermediary in determining the future concentrations of many environmentally important trace gases. The future of methane, a greenhouse gas, cannot be evaluated adequately or predicted without an accurate understanding of the global CO budget, which is not presently available. Similarly, predicting future concentrations of other environmentally important gases, such as the hydrochlorofluorocarbons that can deplete stratospheric ozone, depends on how well we understand the CO budget.

- Global background CO concentrations average about 130 and 50 ppb in remote areas of the Northern and Southern Hemispheres, respectively, that are not affected by local sources. Results from flask and in situ monitoring stations show no discernible trend in CO levels over the past 10 years.

- The average lifetime of CO in the atmosphere is about 2 mo, longer at high latitudes and shorter at low latitudes.

- In addition to direct emissions from fossil fuel and biomass burning, CO is produced in the atmosphere by the photochemical oxidation of anthropogenic and biogenic hydrocarbons. Because of uncertainties in reaction kinetics, the identification of reaction products, and the effects of heterogeneous processes, the accuracy of estimates of photochemical sources of CO are limited.

- The global emissions of CO are about 2.3×10^9 metric tons per year, amounting to an annual source of about 1.0×10^9 metric tons of carbon in the atmosphere, compared with a global anthropogenic input of 7.1×10^9 metric tons per year of carbon in carbon dioxide. Estimates of individual CO sources are uncertain by a factor of two or more; however, the total production of CO is known to within 25%, based on its estimated rate of destruction because of reactions with hydroxyl radicals.

- Emissions from various sources in developing countries are likely to be very significant but are not known at present.

Regional and Urban Air Quality

Emissions, concentrations, and effects of CO on air quality within the United States are discussed in Chapter 3 and its appendix.

- Carbon monoxide plays an important role in atmospheric photochemistry in regional and urban environments. In urban areas, CO either can produce or destroy ozone, depending on the concentrations of nitrogen oxides and hydrocarbons. In numerical simulations of several urban air sheds, CO was found to be responsible for production of 10 to 20% of the ozone.

- The nationwide average annual second highest 8-h ambient CO concentration decreased from 11 ppm in 1977 to 4 ppm in 1996. Between 1987 and 1996, this statistic decreased by 37% at 190 urban sites, 37% at 142 suburban sites, and 48% at 10 rural sites. During this same period, the nationwide average annual 24-h CO levels decreased by about 40%, from 2.0 ppm to about 1.2 ppm.

- On- and off-road mobile sources account for approximately 80% of the 1996 nationwide emissions inventory for CO. Declines in ambient CO levels in the United States follow approximately the decline in motor vehicle emissions of CO.

- There were 51 exceedances of the 8-h NAAQS for CO at nine U.S. monitoring sites in 1996. These sites, in descending order, were located in Lynwood, CA; Calexico and Hawthorne, CA; Anchorage, AK (two sites); Las Vegas, NV; Phoenix, AZ; Kalispell, MT; and El Paso, TX.

- Carbon monoxide levels in the four geographically diverse metropolitan statistical areas (MSAs) of Denver, CO; Los Angeles, CA; New York, NY; and Phoenix, AZ, have decreased from 1986 through 1995. However, the nature of the diurnal and seasonal variations has remained essentially the same. These variations result largely from the interaction among motor vehicle emissions, traffic patterns, and meteorological parameters, such as wind speed and mixing height.

- In general, the spatial distribution of CO within these four air sheds was highly heterogeneous. For instance, correlations between time series of daily 8-h average maximum CO concentrations at different monitoring sites in the Denver, New York, and Los Angeles MSAs ranged from about zero to 0.7, whereas corresponding correlations ranged from about 0.3 to 0.7 in the Phoenix MSA.

Indoor Air Quality

Indoor CO exposure may represent a significant portion of the total human exposure to CO. The sources, emissions, and concentrations of CO found in indoor microenvironments also are discussed in Chapter 3.

- Carbon monoxide occurs indoors directly through emissions from various indoor combustion sources or indirectly as a result of infiltration or ventilation from outdoor sources. In the absence of indoor sources, average CO concentrations generally will equal those in the surrounding ambient environment.

- Emissions of CO from the use of adequately vented combustion appliances (e.g., gas and oil furnaces, gas water heaters, gas dryers) will not contaminate indoor air unless the units or venting systems are malfunctioning.

- The major sources of CO in residential microenvironments are unvented and partially vented combustion appliances. Factors affecting emissions of CO from the use of combustion appliances in the home include the type of source (e.g., gas cooking stoves, unvented space heaters, wood stoves, fireplaces), appliance design, manufacturer, type of fuel used, fuel consumption rate, and source operating condition. Carbon monoxide concentrations in the indoor environment will vary based on the source emission rate, use pattern, ambient CO concentration, air exchange rate, building volume, and air mixing within the indoor compartments.

- Carbon monoxide emissions from gas stoves depend on their use pattern, operating condition, and fuel consumption rate. Ranges with standing pilot lights emit more CO than ranges with electronic pilot lights. The contribution of gas cooking stoves to CO concentrations in the indoor environment is expected to be negligible because of the intermittent nature of the stoves' use, unless gas stoves are used as a heat source.

- Carbon monoxide emissions from unvented space heaters vary as a function of unit design and operating condition, type of fuel used and consumption rate, air currents near the space heater, and use pattern. Carbon monoxide concentrations in environments using space heaters depend on the type of space heater, emission rate, air exchange/infiltration rate, and frequency and duration of use. Reported indoor CO concentrations are higher in homes using space heaters as the primary source of heat.

- Wood stoves and fireplaces emit CO during fire start-ups and maintenance, through leaks in the stove or venting system, and from back drafting. Carbon monoxide emissions are higher during the first stage of a fire because of increased fuel usage and lower combustion temperatures.

- Carbon monoxide emissions from tobacco smoke depend on the type of tobacco product (e.g., cigarette, cigar) and the degree to which tobacco is actively smoked. Concentrations of CO from the use of tobacco products will exceed background concentrations, but will vary

based on differences in ventilation, the number of cigarettes or cigars smoked, and the smoking rate.

Population Exposure

The reduction in automotive emissions brought about by the CAA have reduced in-traffic CO exposures and traffic-related ambient CO concentrations well below those measured in the past decade. Chapter 4 describes the impact on human populations of lower ambient CO exposures and the remaining risks to CO exposure above the level of the NAAQS in areas of high traffic density and in other, indoor locations where combustion devices (e.g., stoves, heaters) are not properly vented.

- Fixed site monitors often are used in urban areas to measure the ambient concentrations to which individuals in the surrounding areas may be exposed. These measurements tend to overestimate 8-h exposure values for people living in areas of lower traffic and underestimate the exposure of people living in areas of higher traffic.

- Fixed-site ambient CO monitoring may provide a reasonable estimate of the average CO exposures for some people who are not exposed to tobacco smoke or other sources of CO in their homes and occupations.

- Nonsmokers exposed to tobacco smoke, heavy traffic fumes, and indoor sources of CO will have higher body burdens of CO (COHb) than would be predicted from ambient data alone.

- Emission reductions in CO mandated by the CAA amendments have led to significant reductions in ambient CO concentrations and lower traffic-related exposures to CO from motor vehicle exhaust, suggesting that estimates of current population exposure based on pre-1990 exposure studies may no longer apply. There currently is not a good estimate of CO exposure distribution for the population.

- Personal CO exposures that exceed the level of the NAAQS will still occur in some nonsmokers exposed to sources of CO not controlled by the CAA (e.g., recreational vehicles, poorly vented or malfunctioning indoor combustion sources) or exposed in their occupations or hobbies to CO or to organic solvents that are metabolized to CO (e.g., methylene chloride).

- Modern CO exposure models adequately predict the average general population exposure but still underpredict high CO exposures, indicating that further work is required to understand the activities and emissions associated with these higher exposures.

Pharmacokinetics and Mechanisms of Action

The action of CO in the body and the factors influencing its uptake, distribution to vital tissues, and elimination, provide the foundation for measuring or predicting effects on organ function. In Chapter 5, the basic principles of CO pharmacokinetics are reviewed, and the possible mechanisms for pathophysiologic effects at the cellular level are discussed.

- The most prominent pathophysiological effect of CO is hypoxemia caused by the binding of CO to hemoglobin. The formation of COHb reduces the oxygen-carrying capacity of blood and impairs release of oxygen from red blood cells to tissues. The brain and heart are especially sensitive to CO-induced hypoxia and cytotoxicity because these tissues have the highest resting oxygen requirements.

- The amount of COHb formed is dependent on the CO concentration and duration of exposure, minute ventilation, lung diffusion capacity, and ambient pressure, as well as the health status and metabolism of the exposed individual. The formation of COHb is reversible, but, because of a small blood-to-air CO pressure gradient and tight binding of CO to Hb, the elimination half-time is quite long, varying from 2 to 6.5 h.

- The physical and physiological variables affecting the rate of COHb formation and elimination have been integrated into empirical and mathematical models for estimating COHb levels from different conditions of exposure. The nonlinear Coburn-Forster-Kane equation is the most widely used predictive model of COHb formation and is still considered the best all-around model for COHb prediction.

- Intracellular binding of CO to hemoproteins, particularly myoglobin (Mb) found in heart and skeletal muscle, would be favored under conditions of low intracellular oxygen tension as COHb levels rise. The impact of ambient CO on intracellular CO uptake by Mb is not well understood.

- New investigations have expanded on the physiological effects of CO in two areas. First, there is a growing recognition that CO may play a role in normal neurotransmission and in microvascular vasomotor control. Second, there also is increased interest in the ability of CO to cause free-radical-mediated changes in tissues. The impact of ambient CO on these processes and the role they may have in pathophysiology is not well understood.

Health Effects

Concerns about the potential health effects of exposure to CO are addressed in Chapter 6 by examining the published results of extensive controlled-exposure studies and more limited population-exposure studies. Emphasis is placed on the current understanding of quantifiable health effects that are likely to occur in humans at the low COHb levels (<5 %) that are predicted to result from typical ambient CO exposures.

- Blood COHb levels are the best indicator of potential health risk; however, the lowest-observed-effect levels depend on the method used for analysis. Gas chromatography (GC) generally is regarded as more accurate than CO-Ox for measuring low COHb saturations (<5%).

- Maximal exercise duration and performance in healthy individuals has been shown to be reduced at COHb levels of ≥2.3 and ≥4.3% (GC), respectively. Performance decrements are small, however, and likely to affect only competing athletes. No effects were observed during submaximal exercise in healthy individuals at COHb levels as high as 15 to 20%.

- Decreased exercise tolerance has been observed consistently in patients with coronary artery disease (CAD) and reproducible exercise-induced angina (chest pain) at COHb levels of 3 to 6% COHb (CO-Ox). The indicators of myocardial ischemia during exercise, such as electrocardiographic changes and associated chest pain, were statistically significant in one large multicenter study at ≥2.4% COHb (GC) and showed a dose-response relationship with increasing COHb.

- An increase in the number and complexity of exercise-related arrhythmias (irregular heart beats) has been observed at ≥6% COHb (CO-Ox) in some people with CAD and a high level of baseline ectopy (chronic arrhythmia) that may present an increased risk of sudden death.

- In epidemiologic studies, daily fluctuations in ambient CO concentration have been associated consistently with fluctuations in hospital admissions for congestive heart failure. This association has been observed at ambient CO levels at or below the current CO standards. The influence on this association of ambient CO exposure, relative to CO exposure from nonambient sources, has not been determined.

- Epidemiologic studies also suggest associations of short-term ambient CO exposure with total daily cardiovascular hospital admissions and with total nonaccidental daily mortality, the great majority of which occurs in people at least 65 years of age. As above, the relative influences on these associations of ambient and nonambient CO have not been determined.

- Recent analyses indicate that significant behavioral impairments in healthy individuals should not be expected until COHb levels exceed 20%; however, mild central nervous system effects have been reported in the historical CO literature at COHb levels between 5 and 20%.

- Acute CO poisoning can affect the growth and function of the developing fetus, infant, and child; however, it is very unlikely that ambient levels of CO typically encountered by pregnant women would cause increased fetal risk.

- Ambient levels of CO are not known to have any direct effects on lung tissue.

- Carbon monoxide has the potential to interact with other stressors. These include (1) visitation to high altitudes, especially for patients with CAD; (2) use of psychoactive drugs or alcohol; (3) use of specific medications, especially nitric oxide and calcium channel blockers; (4) prolonged exposure to heat; and (5) exposure to other pollutants.

Subpopulations Potentially At Risk

On the basis of monitored ambient CO concentrations and quantifiable CO concentration-response relationships for health effects demonstrated in humans, the following conclusions are made in Chapter 7 regarding subpopulations potentially at risk from exposure to ambient CO.

- Young, healthy nonsmokers are not at immediate risk from ambient CO exposure because only limitations at maximal exercise performance have been demonstrated at low COHb levels (<5%) that are predicted to result from ambient exposures. Effects have not been demonstrated

on healthy individuals performing submaximal exercise that is more typical of daily human activity.

- Patients with reproducible exercise-induced angina (chest pain) are a sensitive group within the general population that is at increased risk of experiencing decreased exercise tolerance because of exacerbation of cardiovascular symptoms at ambient or near-ambient CO-exposure concentrations that result in COHb levels of 2.4% (GC) or higher.

1. INTRODUCTION

This document is an update of *Air Quality Criteria for Carbon Monoxide*, published by the U.S. Environmental Protection Agency (EPA) in 1991, and will serve as the basis for reevaluating the current National Ambient Air Quality Standards (NAAQS) for carbon monoxide (CO) set in 1994. Carbon monoxide is one of six ubiquitous ambient air pollutants covered by the Federal Clean Air Act (CAA) requiring an assessment of the latest scientific knowledge as a requisite step in the development of standards to protect public health and welfare. The present document is not intended as a complete and detailed literature review, but it does summarize relevant key information from the previous 1991 document and evaluates new information relevant to the CO NAAQS criteria development, based on pertinent published literature available through 1998.

Carbon monoxide, a trace constituent of the troposphere, is produced by both natural processes and human activities. Because plants can both metabolize and produce CO, trace levels are considered a normal constituent of the natural environment. Although ambient concentrations of CO in the vicinity of urban and industrial areas can exceed global background levels, there are no reports of these currently measured levels of CO producing any adverse effects on plants or microorganisms. Ambient concentrations of CO, however, can be detrimental to human health and welfare, depending on the levels that occur in areas where humans live and work and on the susceptibility of exposed individuals to potentially adverse effects.

This chapter presents a brief summary of the legislative and regulatory history of the CO NAAQS and the rationale for the existing standards and gives an overview of the issues, methods, and procedures utilized in the preparation of the present document.

1.1 LEGISLATIVE REQUIREMENTS

Two sections of the CAA govern the establishment, review, and revision of NAAQS. Section 108 (U.S. Code, 1991) directs the Administrator of EPA to identify and issue air quality

criteria for pollutants that may reasonably be anticipated to endanger public health or welfare. 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, 1991) 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 that 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 that 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, 1991) requires periodic review and, if appropriate, revision of existing criteria and standards. If, in the Administrator's judgment, EPA'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). Alternatively, the Administrator may find that revision of the standards is inappropriate and conclude the review by leaving the existing standards unchanged.

1.2 REGULATORY BACKGROUND

On April 30, 1971, EPA promulgated identical primary and secondary NAAQS for CO at levels of 10 mg/m^3 (9 ppm) for an 8-h average and 40 mg/m^3 (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).

In accordance with Sections 108 and 109 of the CAA, EPA periodically has reviewed and revised the criteria on which the existing NAAQS for CO (Table 1) are based. On August 18,

TABLE 1. NATIONAL AMBIENT AIR QUALITY STANDARDS FOR CARBON MONOXIDE

Date of Promulgation	Primary NAAQS	Averaging Time
August 1, 1994	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 at 25 °C, 760 mm Hg.
[b]Not to be exceeded more than once per year.

Source: Federal Register (1994).

1980, EPA proposed certain changes in the standards 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 no longer should be considered as 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%. On August 18, 1980, EPA proposed changes to the standard (Federal Register, 1980) based on the findings of the revised criteria. 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 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. In its report (Horvath et al., 1983), the committee concluded

that EPA should not rely on Dr. Aronow's data because of concerns regarding the research that substantially limited the validity and usefulness of the results.

An addendum to the 1979 criteria document for CO (U.S. Environmental Protection Agency, 1984) 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 findings reported subsequent to those previously reviewed. 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.

The criteria review process was initiated again on July 22, 1987, and notice of availability of the revised draft criteria document was published in the Federal Register (Federal Register, 1990) on April 19, 1990. This draft document included discussion of several new studies of effects of CO on angina patients that had been initiated in light of the controversy discussed above. The Clean Air Scientific Advisory Committee (CASAC) reviewed the draft criteria document at a public meeting held on April 30, 1991. The EPA carefully considered comments received from the public and from CASAC in preparing the final criteria document (U.S. Environmental Protection Agency, 1991). On July 17, 1991, CASAC sent to the EPA Administrator a "closure letter" outlining key issues and recommendations and indicating that the document provided a scientifically balanced and defensible summary of the available knowledge of effects of CO. A revised "staff paper" based on the scientific evidence was released for public review in February 1992, followed by two CASAC review meetings held on March 5 and on April 28, 1992. The CASAC came to closure on the final staff paper (U.S. Environmental Protection Agency, 1992) in a letter to the Administrator dated August 11, 1992, indicating that it provided a scientifically adequate basis for EPA to make a regulatory decision on the appropriate primary NAAQS for CO. On August 1, 1994, EPA issued a final decision (Federal Register, 1994) that revisions of the NAAQS for CO were not appropriate at that time.

In keeping with the requirements of the CAA, EPA's National Center for Environmental Assessment has begun to review and once again revise the criteria for CO.

1.3 RATIONALE FOR THE EXISTING CARBON MONOXIDE STANDARDS

The following discussion describing the bases for the existing CO NAAQS set in 1994 has been excerpted and adapted from "National Ambient Air Quality Standards for Carbon Monoxide—Final Decision" (Federal Register, 1994). The discussion includes the rationale for selection of the level and averaging time for the NAAQS that would be protective of adverse effects in the most sensitive subpopulation and EPA's assessment that led to a decision not to revise the existing standards for CO.

1.3.1 Carboxyhemoglobin Levels of Concern

In selecting the appropriate level and averaging time for the primary NAAQS for CO, the EPA Administrator must first determine the COHb levels of concern, taking into account a large and diverse health effects database. Based on the assessments provided in the criteria document (U.S. Environmental Protection Agency, 1991) and in the staff paper (U.S. Environmental Protection Agency, 1992), judgments were made to identify the most useful studies for establishing a range of COHb levels to be considered for standard setting. In addition, the more uncertain or less quantifiable evidence was reviewed to determine the lower end of the range that would provide an adequate margin of safety from effects of clear concern. The following discussion summarizes the most critical considerations for the Administrator's 1994 decision on the CO NAAQS.

The Administrator of EPA concluded that cardiovascular effects, as measured by decreased time to onset of angina pain and by decreased time to onset of significant electrocardiogram (ECG) ST-segment depression, were the health effects of greatest concern to be clearly associated with CO exposures at levels observed in the ambient air. These effects were demonstrated in angina patients at postexposure COHb levels that were elevated to 2.9 to 5.9% (CO-Oximetry [CO-Ox] measurement), representing incremental increases of 1.5 to 4.4% from baseline levels. Time to onset of significant ECG ST-segment change, which is indicative of myocardial ischemia in patients with documented coronary artery disease and a more objective indicator of ischemia than angina pain, provided supportive evidence of health effects occurring at exposures as low as 2.9 to 3.0% COHb (CO-Ox). The clinical importance of cardiovascular effects associated with exposures to CO resulting in COHb levels less than 2.9% remains less

certain and was considered only in evaluating whether the current CO standards provide an adequate margin of safety.

The Administrator of EPA also considered the following factors in evaluating the adequacy of the current CO NAAQS.

- Short-term reductions in maximal work capacity were measured in trained athletes exposed to CO sufficient to produce COHb levels as low as 2.3%.
- The wide range of human susceptibility to CO exposures and ethical considerations in selecting subjects for experimental purposes, taken together, suggest that the most sensitive individuals have not been studied.
- Animal studies of developmental toxicity and human studies of the effects of maternal smoking provide evidence that exposures to high concentrations of CO can be detrimental to fetal development, although little is known about the effects of ambient CO exposures on the developing human fetus.
- Although little is known about the effects of CO on other potentially sensitive populations besides those with coronary artery disease, there is reason for concern about visitors to high altitudes, individuals with anemia or respiratory disease, and the elderly.
- Impairment of visual perception, sensorimotor performance, vigilance, and other central nervous system effects have not been demonstrated to be caused by CO concentrations commonly found in ambient air; however, short-term peak CO exposures may be responsible for impairments that could be a matter of concern for complex activities such as automobile driving.
- Limited evidence suggests concern for individuals exposed to CO concurrently with drug use (e.g., alcohol), heat stress, or coexposure to other pollutants.
- Large uncertainties remain regarding modeling COHb formation and estimating human exposure to CO that could lead to over- or underestimation of COHb levels associated with attainment of a given CO NAAQS in the population.
- Measurement of COHb made using the CO-Ox technique may not reflect the COHb levels in angina patients studied, thereby creating uncertainty in establishing a lowest effects level for CO.

The Administrator concluded that the lowest COHb level at which adverse effects have been demonstrated in persons with angina is around 2.9 to 3.0%, representing an increase of 1.5% COHb above baseline when using the CO-Ox to measure COHb. These data serve to establish the upper end of the range of COHb levels of concern. Taking into account the above data uncertainties, the less significant health endpoints, and less quantifiable data on other potentially sensitive groups, the lower end of the range was established at 2.0% COHb.

1.3.2 Relationship Between Carbon Monoxide Exposure and Carboxyhemoglobin Levels

In order to set ambient CO standards based on an assessment of health effects at various COHb levels, it is necessary to estimate the ambient CO concentrations that are likely to result in COHb levels of concern. The best all-around model for predicting COHb levels is the Coburn, Foster, Kane (CFK) differential equation (U.S. Environmental Protection Agency, 1991). Baseline estimates of COHb levels expected to be reached by nonsmokers exposed to various constant concentrations of CO can be determined by the CFK equation (U.S. Environmental Protection Agency, 1992). There are, however, two major uncertainties involved in estimating COHb levels resulting from exposure to CO concentrations. First, the large distribution of physiological parameters used in the CFK equation across the population of interest is sufficient to produce noticeable deviations in the COHb levels. Second, predictions based on exposure to constant CO concentrations can under- or overestimate responses of individuals exposed to widely fluctuating CO levels that typically occur in the ambient environment.

1.3.3 Estimating Population Exposure

The EPA review included an analysis of CO exposures expected to be experienced by residents of Denver, CO, under air quality scenarios where the 8-h NAAQS is just attained. Although the exposure analysis included passive smoking and gas stove CO emissions as indoor sources of CO, it did not include other sources that may be of concern to high-risk groups (e.g., wood stoves, fireplaces, faulty furnaces). The analysis indicated that, at the 8-h standard, fewer than 0.1% of the nonsmoking cardiovascular-disease population would experience a COHb level $\geq$2.1% (U.S. Environmental Protection Agency, 1992). A smaller population was estimated to exceed higher COHb percentages.

1.3.4 Decision on the Primary Standards

Based on the exposure analysis results described above, the Administrator of EPA concluded that relatively few people of the cardiovascular sensitive population group analyzed would experience COHb levels ≥2.1% when exposed to CO levels in the absence of indoor sources when the current ambient standards were attained. Although indoor sources of CO may be of concern to high-risk groups, their contribution cannot be effectively mitigated by ambient air quality standards.

The Administrator of EPA also determined that both the 1-h and 8-h averaging times for CO were valid because the 1-h standard provided reasonable protection from health effects that might be encountered from very short duration peak (bolus) exposures in the urban environment, and the 8-h standard provided a good indicator for tracking continuous exposures that occur during any 24-h period. The Administrator concurred with staff recommendations (U.S. Environmental Protection Agency, 1992) that both averaging times be retained for the primary CO standards.

For these reasons, the EPA Administrator determined under CAA Section 102(d)(1) that revisions to the current 1-h (35 ppm) and 8-h (9 ppm) primary standards for CO were not appropriate at that time (Federal Register, 1994).

1.4 ISSUES OF CONCERN FOR THE CURRENT CRITERIA DEVELOPMENT

The following is a brief summary of scientific issues that are addressed in the revised air quality criteria document for CO. These issues are based on findings presented at symposia and workshops that were convened to assess the current state of understanding of the sources, atmospheric cycle, and health effects of CO and revised, as appropriate, by peer review comments received on earlier draft chapters of the criteria document.

1.4.1 Sources and Emissions

Detailed descriptions of the processes forming CO during combustion were presented in the previous CO document. These descriptions have been reviewed for accuracy in the revised document; however, a good deal of uncertainty exists regarding the correct values for CO

emissions from transportation sources. Emissions from transportation have been revised upward in the current emissions and trends report (U.S. Environmental Protection Agency, 1996) from those used in the previous document. Emissions estimates for CO from various sources are highly uncertain, especially those for transportation sources. The potential of relatively new techniques (e.g., inverse modeling) for testing and improving emissions estimates needs to be evaluated.

1.4.2 Atmospheric Chemistry

Much of the material discussed in the previous criteria document is already available in standard textbooks and does not need to be reviewed. New information, however, is needed in this current review regarding the chemistry of CO formation from the oxidation of methane and nonmethane hydrocarbons (NMHCs). For example, the fractional yields of CO resulting from the oxidation of NMHCs, especially isoprene and monoterpenes, need to be established. The importance of CO for ozone formation in the urban and nonurban atmosphere also needs to be highlighted.

1.4.3 Global Cycle

Global trends in tropospheric CO concentrations declined from about 1988 to 1993 after several years of annual increases, as determined by different networks of surface observations. Carbon monoxide levels apparently have stabilized since 1993. The reasons for the changes in CO trends still need to be determined.

1.4.4 Measurement Technology

The discussion on measurement methods for CO in the previous document has been reviewed, older methods have been removed, and newer methods for monitoring CO from various environmental sources are presented.

1.4.5 Ambient Air Quality

Because of the everchanging nature of atmospheric concentrations, levels in various environments (rural, urban, and suburban) have been reanalyzed for different regions of the

United States. The temporal variability of CO levels from daily to seasonal time scales also has been characterized. Relations between urban concentrations of CO and regional and global background levels also are examined, as well as background levels of CO for use in different applications.

1.4.6 Indoor Emissions and Concentrations

Indoor concentrations of CO are a function of outdoor concentrations, indoor sources, infiltration, ventilation, and air mixing. In the absence of indoor sources, concentrations of CO in the indoor environment are similar to those in ambient air; however, personal CO exposure studies have shown that CO concentrations in excess of 9 ppm can occur in certain indoor and in-transit microenvironments associated with transportation sources that are not considered part of the ambient air. Unvented, improperly installed, or poorly maintained combustion appliances, downdrafts during unstable weather conditions, and depressurization from the operation of exhaust systems and fireplaces also may contribute to potentially high CO concentrations indoors. Further research is still needed, however, to determine the contribution of nonambient sources to total human exposure to CO.

1.4.7 Exposure Assessment

Compliance with the NAAQS is determined by measurements taken at fixed-site, ambient monitors, yet exposure monitoring in the field and modeling studies indicate that individual personal exposure does not correlate directly with CO concentrations determined by the fixed-site monitors alone. This is because of the mobility of people and the spatial and temporal variability of CO concentrations across a given area. The nature of differences between fixed-site and personal monitoring results should be given greater attention, especially in regard to interpreting the results of epidemiology studies.

Data from population 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. New information from field monitoring studies needs to be incorporated into exposure models to better capture the observed personal exposure distributions, including the higher exposures found in the tail of exposure distribution.

A unique feature of CO exposure is that the dose an individual receives can be estimated by measuring COHb. It has been shown, however, that the method chosen for measurement of COHb can be a source of considerable error, particularly at the low end of the CO dissociation curve, where COHb levels are <5%. The sensitivity of COHb measurement techniques will, therefore, have an influence on the lowest-observed-effect level for CO.

1.4.8 Mechanisms of Action

The principle cause of CO toxicity is tissue hypoxia caused by CO binding to hemoglobin. Secondary mechanisms related to intracellular uptake of CO have been the focus of recent research. Current knowledge summarized in this document suggests that the most likely protein other than hemoglobin to be inhibited functionally at relevant levels of COHb is myoglobin, found in heart and skeletal muscle. The extent of effects caused by free oxygen radicals and lipid peroxidation needs to be evaluated in relation to typical ambient CO exposures in the population.

1.4.9 Health Effects

There are many published studies on acute experimental and accidental exposures to CO; however, there is not enough reliable information on chronic exposures to low concentrations from either ambient population-exposure studies or from occupational studies. Further work is needed, therefore, to determine potential long-term exposures in the population and to develop reliable dose-response relationships for at-risk groups. This information currently is missing from the published literature. Some of the issues associated with acute CO exposures are discussed below.

Cardiovascular Effects

Maximal exercise performance is reduced in young, healthy, nonsmoking individuals at COHb levels as low as 2.3%, but this effect is small and would be of concern mainly for competing athletes. Clinical studies on subjects with reproducible exercise-induced angina have confirmed that adverse effects occur with postexposure COHb levels as low as 3%. Thus, aggravation of coronary artery disease continues to provide the best scientific basis in support for the current (9-ppm, 8-h and 35-ppm, 1-h) NAAQS for CO. More recent epidemiology studies in

the United States, Canada, and Europe have suggested that day-to-day variations in ambient CO concentrations are related to cardiovascular hospital admissions and daily mortality, especially for individuals over 65 years of age. It is not clear, however, if the observed association results from CO or from combustion-related particles or, perhaps, from some other, unmeasured pollutant exposure that covaries in time with CO.

Cerebrovascular Effects

Carbon monoxide hypoxia increases cerebral blood flow in healthy subjects, even at very low exposure levels. Thus, effects of CO on behavior are not consistent. Behaviors that require sustained attention or performance are most sensitive to levels of COHb >5%. Disease or injury that impairs compensatory increases in blood flow may increase the probability of effects, but little is known about the susceptibility of compromised individuals to ambient levels of CO. Accidental exposures to CO have been shown to cause neurological problems weeks after recovery from the acute episode. It is not known, however, if these late neurological sequelae, described as intellectual deterioration; memory impairment; and cerebral, cerebellar, and mid-brain damage, result from long-term exposure to low ambient levels of CO.

Developmental Toxicity

Relatively high CO exposures of 150 to 200 ppm during gestation, leading to approximately 15 to 25% COHb, produce reductions in birth weight, cardiomegaly, delays in behavioral development, and disruption in cognitive function in newborn laboratory animals of several species. Little data exist on humans exposed to CO for predicting a lowest-observed-effect level for developmental effects. Studies relating human CO exposures from ambient sources or cigarette smoking to reduced birth weight are of concern because of the risk for developmental disorders; however, many of these studies have not considered all sources of CO. Nevertheless, some health professionals have considered this evidence sufficient to identify pregnant women, and the developing fetus, as at risk to ambient levels of CO.

High-Altitude Effects

There are relatively few reports on the effects of inhaling CO at high altitudes. Current knowledge supports the possibility that the effects of hypoxic hypoxia and CO-hypoxia are at

least additive. The potential additive effects of CO exposure in sensitive individuals visiting at high altitudes needs to be highlighted.

1.4.10 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 on psychoactive drugs that suggest cause for concern.

1.4.11 Subpopulations at Risk

On the basis of 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 of concern at ambient or near-ambient CO exposure concentrations resulting in COHb levels <5%. Certain other groups are at potential risk from exposure to CO, but further research is required to specify health effects associated with ambient or near-ambient CO exposures in these probable risk groups.

1.5 METHODS AND PROCEDURES FOR DOCUMENT PREPARATION

The procedures that were followed for developing the revised criteria document for CO are different from those that have been used for recent criteria documents. For example, the previous CO criteria document (U.S. Environmental Protection Agency, 1991) was a more comprehensive scientific review of available information on the nature, sources, distribution, measurement, and concentrations of CO in the environment and on the known and anticipated health effects that CO would have on at-risk population groups. In lieu of a comprehensive review of the literature, emphasis in the present criteria document has been placed on the development of a concise summary of key information and a more interpretative discussion of the new scientific and technological data available since the previous criteria were evaluated. The resulting document is more of an update, in accordance with the recommendations made by CASAC.

The main focus of this revised criteria document is on the evaluation and interpretation of more recent air quality, human exposure, and health effects issues. Therefore, the techniques

used to present this information vary according to the state-of-science for the respective topics. For example, the analysis of ambient air quality is based on newly obtained air monitoring data and utilizes the previous analysis only for showing trends over time. As a result of the relatively dramatic decrease in ambient CO concentrations, population exposure to ambient CO also has declined. Human exposure studies conducted in the early 1980s and earlier distributions of COHb levels in the U.S. population that were relied on heavily in the previous assessment are no longer relevant to the current picture of ambient CO exposure in the 1990s. Thus, key information on population exposure must focus on the newer studies and on modeling results. On the other hand, the health effects literature on CO has remained relatively static since the previous 1991 assessment, except for provocative publications on cellular mechanisms of CO action and on epidemiologic associations of ambient CO with mortality and morbidity in the elderly population. Newly published studies on most of the other health outcomes reconfirm the conclusions made in the last document and are incorporated into the previous summaries by reference only.

One of the first steps used in the development of this revised document was to convene symposia or workshops to review the key scientific issues and to focus on the selection of material that could be included in the document as the basis for the development of standard-setting criteria. Both EPA and non-EPA scientific experts were utilized for this effort.

An interdisciplinary scientific symposium was held in Portland, OR, in December 1997, to assess current scientific understanding of the atmospheric cycle of CO, including its sources, sinks, and distribution. The three main subject areas covered in the symposium relate to the distribution and spatial and temporal variability of CO, the atmospheric budget of CO, and direct or indirect effects of CO on human health. Results from papers presented at the symposium are included, by reference, in this revised criteria document.

A mini workshop, jointly organized by EPA, the Gas Research Institute, and the Health Effects Institute, was convened in Chicago, IL, on April 24 and 25, 1998, to provide expert scientific discussion on the public health significance of exposures to low levels (<50 ppm) of CO. The three main topics covered in the meeting were human exposure patterns and trends in CO exposure, pharmacokinetics and mechanisms of action of CO, and health effects. A summary of the discussion by participants and conclusions drawn from the meeting were used by authors in preparation of the draft criteria document chapters.

Finally, a public peer-review workshop was convened on September 17 and 18, 1998, to define key issues, to review early drafts of the present criteria document chapters, and to ascertain and discuss any pertinent new literature. The respective authors of the draft chapters or sections of the document revised them on the basis of the workshop recommendations. The revised chapters of the document have been incorporated into this first external review draft being released for public comment and review by CASAC. Necessary revisions will be made in response to public comments and CASAC recommendations before the final version of the criteria document is released.

1.6 ORGANIZATION AND CONTENT OF THE DOCUMENT

The updated air quality criteria document for CO critically evaluates and assesses scientific information on air quality, human exposure, and health effects associated with exposure to the concentrations found in the environment. Emphasis has been placed on the development of a concise review of key information and a more interpretative discussion of the new scientific and technological data available since completion of the previous criteria document (U.S. Environmental Protection Agency, 1991). The references cited in the document should be reflective of the state of knowledge through 1998 on those issues most relevant to review of the NAAQS for CO.

To aid in the concise development of this document, summaries of the relevant published literature and selective discussion of the literature has been undertaken. Studies that were presented in the previous criteria document and whose data were judged to be significant because of their usefulness in deriving the current NAAQS are discussed briefly in the text. The reader, however, has been referred to the more extensive discussion of these “key” studies in the previous document. Other, older studies are discussed in the text if they are open to reinterpretation because of newer data, or potentially useful in deriving revised standards for CO. Generally, only published information that has undergone scientific peer review has been included in the revised criteria document. However, some newer studies not yet published in the open literature but meeting high standards of scientific reporting have been included for a few areas.

The structure of the present document follows the general outline of the previous criteria document (U.S. Environmental Protection Agency, 1991), especially for topics that have changed little since the last criteria review. The resulting sequence of discussion should help the reader to find and contrast similar sections. There are, however, a few exceptions where some topics have been consolidated into a single chapter in order to present a more concise document. The executive summary at the beginning of the document provides a concise presentation of key information and conclusions from all subsequent chapters.

The document begins with this introduction (Chapter 1), which provides the regulatory history of CO and an understanding of the scientific basis for the current CO NAAQS. Information on analytical methods for monitoring CO (Chapter 2) covers the measurement of CO in ambient (outdoor) and indoor air, as well as methods for measuring breath CO and blood CO levels in exposed individuals. Chapter 3 provides information on the atmospheric chemistry of CO and typical sources, emissions, and concentrations found in the ambient and indoor environments, topics addressed in separate chapters of the previous document. The remaining chapters are similar to the previous document, covering topics on population exposure to CO (Chapter 4), pharmacokinetics and mechanisms of action (Chapter 5), and health effects (Chapter 6). The last chapter (Chapter 7) provides an overall integrative summary of key findings and an evaluation of subpopulations potentially at risk from exposure to CO.

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2. ANALYTICAL METHODS FOR MONITORING CARBON MONOXIDE

2.1 INTRODUCTION

Investigations into relationships between ambient carbon monoxide (CO) levels and human health outcomes and public health warnings of potentially harmful CO levels require accurate, precise, and representative measurements of CO. Reliable measurement methods also are needed to evaluate the effects of ambient CO on overall air quality. This chapter will review methods for monitoring CO in ambient air for conditions ranging from clean continental environments to polluted urban ones. Biological methods for monitoring the impact of ambient CO exposure on human populations also will be reviewed.

To promote uniform enforcement of the air quality standards set forth under the Clean Air Act as amended (U.S. Code, 1991), the U.S. Environmental Protection Agency (EPA) has established provisions under which analytical methods can be designated as "reference" or "equivalent" methods (Code of Federal Regulations, 1991a). Either a reference method or equivalent method for air quality measurements is required for acceptance of measurement data for National Ambient Air Quality Standards (NAAQS) compliance. 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.

The EPA-designated reference methods are automated methods utilizing the nondispersive infrared (NDIR) technique, generally accepted as being the most reliable, continuous method for the measurement of CO in ambient air. The official EPA reference methods (Code of Federal Regulations, 1991a) include eleven reference methods designated for use in determining compliance for CO. 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, 1991a), including the gas filter correlation (GFC) technique, which was

developed through EPA-sponsored research (Burch et al., 1976). No equivalent method using a principle other than NDIR has been designated for measuring CO in ambient air.

2.2 OVERVIEW OF TECHNIQUES FOR MEASUREMENT OF AMBIENT CARBON MONOXIDE

The NDIR technique is an automated and continuous method that is 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 near atmospheric pressure, and the most sensitive analyzers are able to detect minimum CO concentrations of about 0.02 ppm. Interferences because of carbon dioxide (CO_2) and water vapor can be dealt with so as not to affect the data quality; a particle filter (Teflon® or nylon composition is recommended), and desiccant in the inlet line improves reliability. Nondispersive infrared analyzers are relatively insensitive to flow rate, require no wet chemicals, are sensitive over wide concentration ranges, and have short response times. Nondispersive infrared analyzers of the newer GFC type have overcome zero and span problems, as well as minor problems caused by 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., 1975; Swinnerton et al., 1968; Tesarik and Krejci, 1974). This technique is an automated, semicontinuous method where CO is separated from water, CO_2, and hydrocarbons other than methane (CH_4) 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. Mercury liberation detectors offer greater sensitivity and ease of operation than FID's (see Section 2.3.4.3). These methods have no known interferences and can be used to measure levels from 0.02 to 45 ppm.

Whichever method or instrument is used, it is essential that the results be evaluated by frequent calibration with samples of known composition (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.

The performance specifications for automated CO analyzers currently in use are shown in Table 2-1. The normal full-scale operating range for reference methods is 0 to 50 ppm (0 to 57 mg/m^3). Some instruments offer higher ranges, typically 0 to 100 ppm (0 to 115 mg/m^3), or lower ranges such as 0 to 20 ppm (0 to 23 mg/m^3). Higher ranges up to 1,000 ppm (1,145 mg/m^3) are used to measure CO concentrations in vehicular tunnels and parking garages.

Although CO is one of the criteria pollutants, it is also a precursor to ozone and a useful tracer of combustion-derived pollutants (Carter, 1991; Ryan et al., 1998). These additional roles for CO make its detection at levels well below the NAAQS highly desirable. At many existing monitoring sites, the mixing ratio is frequently below the lower detectable limit specified in Table 2-1. Chemical Transport Models (CTMs) developed to understand air pollution and often required to test abatement strategies for photochemical smog, rely on accurate data for concentrations of source gases including nitrogen oxides, non-methane hydrocarbons, and CO. Boundary layer CO mixing ratios in urban areas are typically 100s of ppb (Seinfeld and Pandis, 1998; Dickerson et al., 1992; Morales, 1998). A CO monitor with precision of 500 ppb would be adequate to prove compliance with the CO standard, but would not provide adequate input data for CTMs. This chapter, therefore, will review methods for measuring CO in ambient air that provide sensitivity adequate to quantify the content of clean continental boundary layer air, that is with uncertainty on the order of 10 ppb and has a detection limit around 50 ppb in addition to methods in current use. Suggested performance specifications for monitoring CO in nonurban environments are shown in Table 2-2.

2.3 GAS STANDARDS FOR CALIBRATION

There are basically two different types of calibration gas mixture, pre-made blends and mixtures prepared in the laboratory. Certain types of pre-made blends can be purchased with recognized and accepted certification and traceability information. Other pre-made blends can be purchased without certification or with certification of limited acceptance. There is no mechanism to provide accepted certification for mixtures made in the laboratory. The EPA accepts only the first four types of gas mixtures described below.

TABLE 2-1. PERFORMANCE SPECIFICATIONS FOR AUTOMATED ANALYTICAL METHODS FOR CARBON MONOXIDE

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

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 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.

Source: Code of Federal Regulations (1991a).

TABLE 2-2. SUGGESTED PERFORMANCE SPECIFICATIONS FOR MONITORING CARBON MONOXIDE IN NONURBAN ENVIRONMENTS

Range	0 to 50 ppm (0 to 57 mg/m^3)
Noise	0.05 ppm (0.06 mg/m^3)
Lower detectable limit	0.05 ppm (0.06 mg/m^3)
Interference equivalent	
Each interfering substance	±0.05 ppm (±0.06 mg/m^3)
Total interfering substances	0.10 ppm (0.12 mg/m^3)
Zero drift	
12 h	±0.1 ppm (±0.12 mg/m^3)
24 h	±0.1 ppm (±0.12 mg/m^3)
Zero interval,[a] maximum	1 h
Span drift, 24 h	
20% of upper range limit	±5.0%
80% of upper range limit	±2%
Lag time	1 min
Rise time	5 min
Fall time	5 min
Precision	
20% of upper range limit	0.2 ppm (0.24 mg/m^3)
80% of upper range limit	0.2 ppm (0.24 mg/m^3)

[a]Zero interval is the interval between measuring chemical zeros.

Source: Adapted from Code of Federal Regulations (1991a).

2.3.1 Pre-made Mixtures

2.3.1.1 Standard Reference Materials

Calibration gas standards of CO in air (certified at levels of approximately 12, 23, and 46 mg/cm^3 or (10, 20, and 40 ppm, respectively) or in nitrogen (N_2; 10 ppm to 13%) are obtainable from the Standard Reference Material Program of the National Institute of Standards and Technology (NIST), formerly the National Bureau of Standards, Gaithersburg, MD 20899. These Standard Reference Materials (SRMs) are supplied as compressed gas mixtures at about 135 bar (1,900 psi) in high-pressure aluminum cylinders containing 800 L (28 ft^3) of gas at standard temperature and pressure, dry (STPD) (National Bureau of Standards, 1975; Guenther

et al., 1996). Each cylinder is supplied with a certificate stating concentration and uncertainty. The concentrations are certified to be accurate to ±1% relative to the stated values. Because of the resources required for their certification, SRMs are not intended for use as daily working standards, but rather as primary standards against which transfer standards can be calibrated.

2.3.1.2 National Institute of Standards and Technology Traceable Reference Materials

Calibration gas standards of CO in air or N_2, in the concentrations indicated above, are obtainable from specialty gas companies. Information as to whether a specialty gas company supplies such mixtures is obtainable from the specific company, or the information may be obtained from the Standard Reference Material Program of NIST. These NIST Traceable Reference Materials (NTRMs) are purchased directly from industry and are supplied as compressed gas mixtures at about 135 bar (1,900 psi) in high pressure aluminum cylinders containing 4,000 L (140 ft^3) of gas at STPD. Each cylinder is supplied with a certificate stating concentration and uncertainty. The concentrations are certified to be accurate to ±1% relative to the stated values (Guenther et al., 1996).

2.3.1.3 U.S. Environmental Protection Agency Protocol Gases

Calibration gas standards of CO in air or CO in N_2 at approximately the same concentrations as SRMs and NTRMs can be purchased from specialty gas companies as EPA Protocol Gases. These gases are blended and analyzed according to an EPA protocol document and are supplied as gas mixtures in high pressure aluminum cylinders. These mixtures are supplied with certificates stating concentration and uncertainty (U.S. Environmental Protection Agency, 1997).

2.3.1.4 Dutch Bureau of Standards

Calibration gas standards of CO in air over a wide concentration range also can be purchased from the Dutch Bureau of Standards, which is the Nederland Meetinstituut (NMi) Holland (fax 31-15-261-2971). These are Primary Reference Materials (PRMs) or Certified Reference Materials (CRMs). These Reference Materials (PRMs or CRMs) are supplied as compressed gas mixtures at about 135 bar (1,900 psi) in high pressure aluminum cylinders containing 800 L of gas at STPD. Each cylinder is supplied with a certificate stating

concentration and uncertainty. The NIST and EPA recognize the equivalency of specific NMi standards with NIST standards on the strength of the NIST/NMi Declaration of Equivalency Document.

2.3.1.5 Commercial Blends

Calibration gas mixtures of CO in air or N_2 over a wide concentration range also can be purchased commercially from many specialty gas companies. Some mixtures may have "certification" documentation and some may not. These mixtures can be ordered in cylinders of almost any size. Mild steel cylinders are to be avoided (U.S. Environmental Protection Agency, 1991).

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 NIST SRM's, commercial gas blends, and an extensive set of standard gas mixtures prepared by gravimetric blending at EPA (Paulsell, 1976). Results of the comparison showed that commercial gas blends are within ±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.

2.3.2 Laboratory Blended Mixtures

Mixtures of CO in almost any matrix gas can be blended in the laboratory. One can start with gaseous CO or mixtures of CO and dilute these to any concentration desired. The three common procedures for blending mixtures into containers are the gravimetric (weighing) procedure, the manometric (pressure) technique, and the volumetric method. One also can use dynamic dilution to prepare standards that are not stored in containers but are used at the time of preparation. There are advantages and disadvantages to each procedure, and one must evaluate the application, standards requirements, and laboratory equipment before choosing the method of standards preparation.

Standard samples of CO in air also can be prepared by flowing gas dilution techniques. In a versatile system designed for this purpose (Hughes et al., 1973), air at a pressure of about 0.7 to 7.0 bars (about 10 to 100 psi) above ambient is first purified and dried by passage through

cartridges of charcoal and silica gel, then is 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.

Dynamic dilution employed to make CO standards often relies on mass flow controllers. When performing a calibration with this technique, care should be taken to control the temperature and pressure of the flow controllers. Investigations into the performance of several brands of mass flow controllers on aircraft has revealed that, for large pressure changes, some instruments experience errors in the output well beyond the specifications (Weinheimer and Ridley, 1990).

2.3.3 Other Methods

Permeation tubes have been used for preparing standard mixtures of such pollutant gases as sulfur dioxide (SO_2) and nitrogen dioxide (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 [$Ni(CO)_4$]. 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).

2.3.4 Intercomparisons of Standards

Initial efforts to establish the absolute uncertainty of CO standards and to put various research groups around the world on the same scale revealed systematic errors in some of the standards. Careful preparation of gas standards and repeated intercomparison of calibration gases and measurements on ambient air have since led to general agreement within the international community on both a reference scale and on analytical methods. Calibration standards now generally agree to within 5%, and atmospheric measurements made with a variety of analytical techniques agree to 10 ppb or better.

The National Aeronautics and Space Administration (NASA), as part of the Chemical Instrumentation Test and Evaluation Project, intercompared a tunable diode laser spectroscopy (TDLS) technique and several "grab"-sample gas chromatography-flame ionization detection (GC-FID) techniques (Hoell et al., 1984, 1985). Initial results indicated a high degree of correlation among the various instruments, but agreement on the absolute concentration was only about 15%; differences were as large as 38%. When the intercomparison was repeated (Hoell et al., 1987), calibration standards agreed within 95% confidence levels. Measurements of ambient air samples under actual field conditions demonstrated agreement within experimental uncertainty (on the order of 10 ppb) for CO mixing ratios from 60 to 170 ppb. When data from the various instruments were regressed, however, slopes again differed from unity by as much as 14%.

Careful intercomparisons of calibration gases indicate that accurate and consistent standards can be made. Hughes et al. (1991) compared primary gas standards of CO in N_2 produced by NIST and the National Physical Laboratory in the United Kingdom. These standards, prepared gravimetrically, contained mixing ratios ranging from 10 ppm to 8%. In a blind intercomparison, the mean difference was 0.2%, well within the experimental uncertainty of the techniques. Novelli et al. (1991) gravimetrically produced CO in zero air in the range of 25 to 1,000 ppb from both pure CO and a NIST SRM; they found agreement to within 1%. Agreement with commercially available NIST-traceable standards was within 3%. Reasonable consistency (6% or better) was found with standards used by Australian, German, Brazilian, and several American institutions. One Australian standard was found to be 22% lower, although trouble with this standard had been reported previously (Weeks et al., 1989). A reevaluation of the reference scale in the range of nonurban ambient concentrations (Novelli et al., 1994) confirmed agreement to within 5% or better for the National Oceanic and Atmospheric Administration (NOAA), NASA, and German groups.

Intercomparisons of TDLS and NDIR GFC techniques (Poulida et al., 1991; Fried et al., 1991) indicated agreement within experimental uncertainty (better than 10% for typical tropospheric concentrations of 100 to 1,000 ppb), when NIST-based standards were used to calibrate both instruments. These experiments demonstrated good agreement in ambient and compressed air. These results, as well as results form spiking tests, indicated no significant

interferences in either monitor. The intercomparisons also established linearity for both techniques in the range from 100 ppm to 10 ppb.

Recent standards normalization and intercomparisons of TDLS, mercury liberation, GC-FID, and NDIR techniques are described by Novelli et al. (1998). For mixing ratios down to the lowest expected in the boundary layer, about 50 ppb, agreement among groups was typically better than 10 ppb; for higher mixing ratios the typical agreement was about 5%.

2.3.5 Infrared Absorption

The TDLS can provide an independent measurement of the concentration of a CO standard. Fried et al. (1991) used the high-resolution transmission (HITRAN) molecular absorption database for the line parameters to calculate the concentration based on direct absorption. Their results agreed with a NIST-certified gas standard to within 1.6%, well within the uncertainty of the absorption measurement.

2.4 MEASUREMENT IN AMBIENT AIR

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.

2.4.1 Sampling System Components

Carbon monoxide monitoring requires a sample introduction system, an analyzer system, and a data recording system. 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 periodically check 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 fluorinated ethylene propylene Teflon® (Code of Federal

Regulations, 1991b) 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 such as a Nafion® drying tube 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 caused by particulate buildup in the sample lines or analyzer inlet. The sample preconditioning system also may include a flow metering and control device to control the sampling rate to the analyzer.

2.4.2 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; the procedures should be 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 air containing no CO along with several known concentrations of CO in air or N_2 contained in high-pressure gas cylinders and verified by NIST-certified SRMs wherever possible (Code of Federal Regulations, 1991a). The CO can be removed from an air stream by oxidation to CO_2 on a catalyst (Dickerson and Delany, 1988; Parrish et al., 1994). 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, 1991b; 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.

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. For high-sensitivity measurement, hourly zeros and weekly calibrations are recommended.

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, 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 ±9%, and the 95% national probability limits for accuracy are within ±1.5% for all audit levels

up to 85 ppm. The results (accuracy) for CO exceed comparable results for other criteria pollutants with national ambient air quality standards (Rhodes and Evans, 1987).

2.4.3 Sampling Schedules

Carbon monoxide concentrations in the atmosphere exhibit large temporal variations because of changes in the time and rate that CO is emitted by different sources and because of changes in meteorological conditions that govern the amounts of transport and dilution that take place. During a 1-year period, an urban CO station may monitor hourly concentrations of CO ranging from below the minimum detection limit to as high as 45 ppm (52 mg/m^3). The NAAQS for CO are based on the second highest 1- and 8-h average concentrations; violations represent extreme events. In order to measure the highest two values from the distribution of 8,760 hourly values in a year, the "best" sampling schedule to employ is continuous monitoring 24 h per day, 365 days per year. Even so, continuous monitors rarely operate for long periods without data losses because of malfunctions, upsets, and routine maintenance. Data losses of 5 to 10% are common. Consequently, the data must be interpreted in terms of the likelihood that the NAAQS were attained or exceeded. Statistical methods can be employed to interpret the results (Garbarz et al., 1977; Larsen, 1971).

Compliance with 1- and 8-h 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.

2.4.4 Continuous Analysis

2.4.4.1 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. Gas filter correlation spectroscopy analyzers are used most frequently now in documenting compliance with ambient air standards.

Gas-Filter Correlation Spectroscopy

A GFC monitor (Burch et al., 1976) has 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. A top schematic view of the GFC monitor is shown in Figure 2-1, showing the components of the optical path for CO detection. During operation, air flows continuously through the sample cell. Radiation from the source is directed by optical transfer elements through the two main optical subsystems: (1) the rotating gas filter and (2) 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.

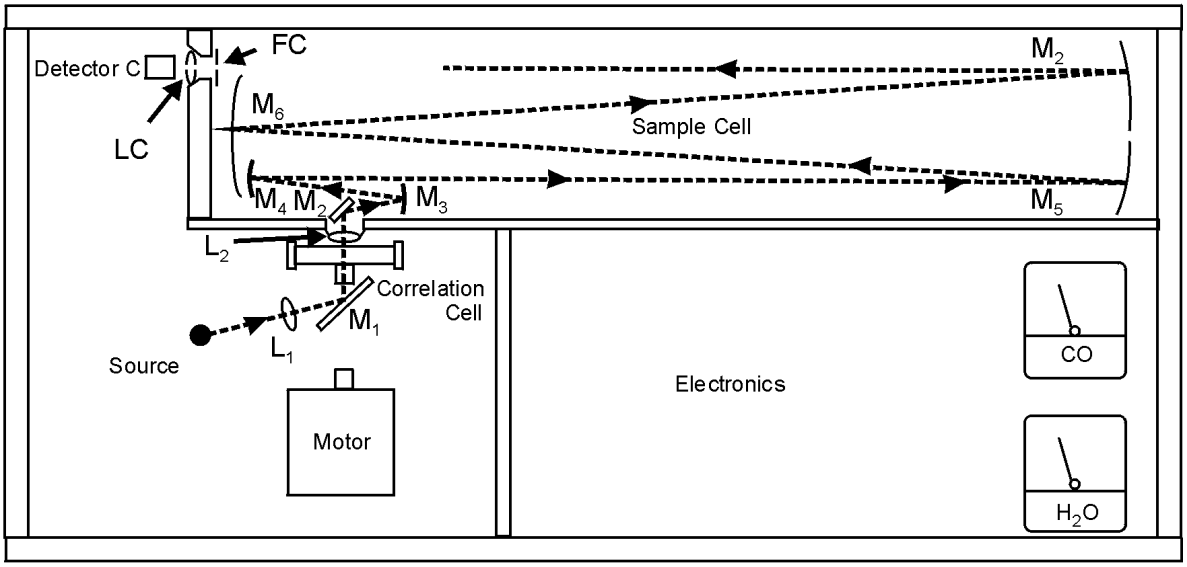
The gas correlation cell is constructed with two compartments: one compartment is filled with 0.5 atm CO, and the second compartment is filled with pure N_2. Radiation transmitted through the CO is completely attenuated at wavelengths where CO absorbs strongly. The radiation transmitted through the N_2 is reduced by coating the exit window of the cell with a neutral attenuator so that the amounts of radiation transmitted by the two cells are made approximately equal in the passband that reaches the detector.

In operation, radiation passes alternately through the two cells as they are rotated to establish a signal modulation frequency. If CO is present in the sample, the radiation transmitted through the CO is not appreciably changed, whereas that through the N_2 cell is changed. This imbalance is linearly related to CO concentrations in ambient air.

Enhanced Performance

Although commercial CO monitors were designed to meet the performance specifications shown in Table 2-1, several instruments have the potential for much greater sensitivity.

A.



B.

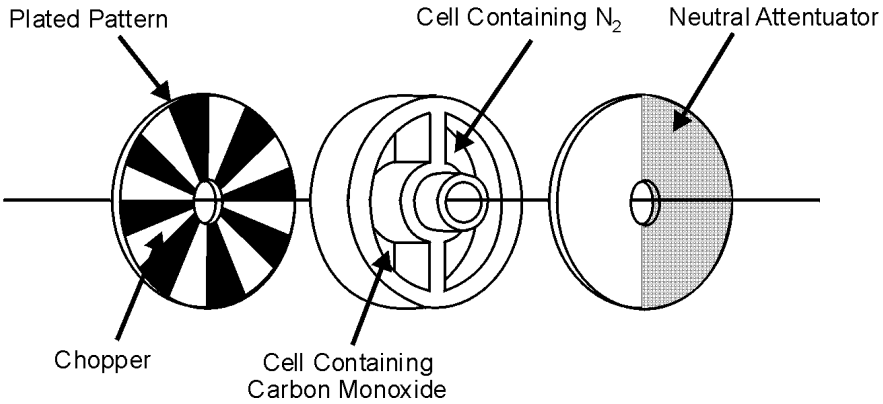


Figure 2-1. Schematic diagram of GFC monitor for CO. A = optical layout (M denotes mirror reflector, and L denotes lens); B = detail of correlation cell.

Source: Chaney and McClenny (1977).

Modifications of commercially available NDIR monitors (Dickerson and Delany, 1988; Parrish et al., 1994) have been made to enhance their performance, but the manufacturers have continued to improve instruments and offer "high sensitivity" options that could meet the requirements of monitoring clean continental air (i.e., a detection limit of about 50 ppb and resolution of 10 ppb).

The principal constraints on the lower detectable limits of commercially available NDIR CO monitors are detector noise, water vapor interference, and drift in the background. Several methods have been developed by researchers to improve detector noise, such as cooling the preamplifier and improving the optics. More recent improvements made by the manufacturers, such as gold-coated mirrors and selected infrared (IR) radiation detectors have been effective in reducing detector noise.

Water vapor produces a negative artifact such that a volume mixing ratio of 1% would reduce apparent CO mixing ratio measurement by 50 ppb. This interference can be reduced to within tolerances by drying the sample air with a cold trap, desiccant, or drying tube (Dickerson and Delany, 1988). Alternatively, the zero can be checked frequently enough so that changes in ambient humidity are unlikely to produce a significant error (Parrish et al., 1994).

The greatest source of potential error in monitoring CO in the 0.1-ppm range is background drift. The stability of the instruments with respect to changes in calibration (span) is adequate, but the background (zero) drifts on time scales of minutes to hours in response to, among other factors, instrument temperature. This drift can be accounted for most easily by frequent chemical zeroing with a oxidizer that converts CO to CO_2.

2.4.4.2 Gas Chromatography-Flame Ionization

Carbon monoxide can be measured in either ambient air samples collected every few minutes or in air from grab samples stored under pressure in inert canisters. Carbon monoxide in air samples is dried, preconcentrated, reduced to methane, and detected by flame ionization (Heidt, 1978; Greenberg et al., 1984; Hoell et al., 1987). Uncertainty on the order of 10 ppb or 10% of the observation can be obtained routinely.

2.4.4.3 Mercury Liberation

This technique, involving reaction with hot mercuric oxide to give elemental mercury vapor, was developed early this century (Moser and Schmid, 1914; Beckman et al., 1948; McCullough et al., 1947; Mueller, 1954; Palanos, 1972; Robbins et al., 1968) and is now available commercially (e.g., Trace Analytical Inc., Menlo Park, CA). The method is temperature and pressure sensitive, and operation in the continuous mode requires elimination of interferences from sulfur dioxide, hydrogen, and hydrocarbons (Seiler et al., 1980). Successful

continuous operation has been reported with response time on the order of 20 s and detection limits near 20 ppb (Fishman et al., 1980; Brunke et al., 1990).

As a GC detector, mercury liberation offers high sensitivity, without the interferences inherent in continuous measurements (e.g., Novelli et al., 1991, 1998). Air samples are collected in glass bottles and injected into a gas chromatograph with two columns. The CO is then detected with a commercial mercuric oxide reduction detector (e.g., Trace Analytical Inc., Menlo Park, CA). The system is linear from 10 to over 1,000 ppb, has a detection limit below 10 ppb, and the reported uncertainty is about 2%.

2.4.4.4 Tunable Diode Laser Spectroscopy

Tunable diode lasers (TDLs) produce IR radiation with a line width that is narrow compared with typical absorption lines of atmospheric trace gases. Absorption of IR radiation by a single rotational line in the 4.6-µm band can be exploited to measure CO with high precision and rapid response and without interferences; the sharp focus on a narrow spectral region provides great selectivity. Ambient air samples are measured over open paths through the ambient air (Chaney et al., 1979) or by pulling air samples through an orifice into a long-path cell maintained at a pressure well below ambient (Sachse et al., 1987; Fried et al., 1991; Roths et al., 1996). Radiation from a TDL is modulated over a very narrow wavelength region such that absorption by CO produces an AC signal. The background is measured by catalytic oxidation of CO to CO_2.

Instruments based on TDLS are currently the fastest and most sensitive extant, with a typical detection limit of a few ppb and a response time of a few seconds. For long-term monitoring, the high cost and need for a skilled operator on site are disadvantages.

2.4.4.5 Resonance Fluorescence

Resonance fluorescence of CO in the vacuum UV has been used for a highly sensitive and rapidly responding instrument (Volz and Kley, 1985; Gerbig et al., 1996). Excitation is represented by the following reaction (Equation 2-1):

$$CO\,(X^1\Sigma) + h\nu \rightarrow CO\,(X^1\Pi). \qquad (2\text{-}1)$$

Atmospheric CO absorbs radiation in the 150-nm range from a radio frequency discharge lamp, and fluorescence from the excited CO is detected by a photo-multiplier tube. The lamp generates a plasma in a continuous flow of CO_2 in argon. Limits to the sensitivity of this instrument are set by interference from water vapor, continuum Raman scattering by oxygen (O_2), and by drift in the lamp intensity. The pressure in the fluorescence chamber must be maintained between 7 and 9 mbar air to balance interference from O_2 and signal from CO.

Recent improvements (Gerbig et al., 1998) have reduced the detection limit to 3 ppb for a response time of 1 s. The high sensitivity and small size of the instrument are desirable for measurements from aircraft. Before the instrument is practical for air pollution monitoring, its stability must be improved. As the lamp window degrades, sensitivity is lost, such that after about 200 h of operation, a factor of two loss in the span can be expected.

2.4.5 Intercomparisons of Standards

Several techniques have been evaluated in rigorous intercomparisons under field conditions. For unpolluted tropospheric air, a number of instruments employing different analytical principles have consistently measured mixing ratios that agree within experimental uncertainty. These techniques include TDLS, NDIR/GFC, GC-FID, and GC-ML (Hoell et al., 1987; Fried et al., 1991; Poulida et al., 1991; Novelli et al., 1998). Additional details can be found in Section 2.2.4.

2.4.6 Other Methods of Analysis

Color changes induced by reaction of a solid or liquid date back to Haldane (1897-1898) and were reviewed extensively in the previous criteria document. Examples include the colored silver sol method, the NIST colorimetric indicating gel, the length-of-stain indicator tube, and frontal analysis (U.S. Environmental Protection Agency, 1991). More recently developed electrochemical techniques show improved resolution and specificity (e.g., Ott et al., 1994; Wallace et al., 1988). These techniques are inadequate for ambient air monitoring to demonstrate compliance but have use in personal exposure studies. Further research on the selectivity, stability, and sensitivity of these methods is needed.

2.5 MEASUREMENT USING PERSONAL MONITORS

Monitors at fixed locations provide useful information on ambient CO concentrations and their variability and trends, but cannot measure personal exposure. Information on personal exposure, including home, in-transit, and work-related concentrations is needed for epidemiological studies. The previous criteria document (U.S. Environmental Protection Agency, 1991) reviewed the state of the science of personal monitors as of about 1986. Since that time, the devices have been further developed and refined.

One technique involves an ion-exchange Y-type zeolite, with zinc ion as the adsorbent. The adsorbent is desorbed thermally, converted to methane, and analyzed using GC-FID (e.g., Lee et al., 1992a,b; Lee and Yanagisawa, 1992; 1995).

Apte (1997) reviewed several of these devices and described passive samplers based on transition metal compound color changes measured spectrochemically. The method suffers an interference from ethylene, but provides adequate performance (sensitivity of 10 ppm-h and precision of 20% or better) for health studies. Substantial work remains for most passive samplers on stability and response to temperature, humidity, and interferences. These techniques lack the response speed and sensitivity for ambient air monitoring.

2.6 BIOLOGICAL MONITORING

A unique feature of CO 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 end-tidal exhaled breath after a standardized breathhold maneuver, with a required correction for the background CO inhaled prior to a breathhold (Smith, 1977; Wallace, 1983). The measurement methods for COHb and breath CO were reviewed extensively in the previous criteria document (U.S. Environmental Protection Agency, 1991). This section provides an update on advances in analytical methods for measuring blood COHb and breath CO that have been published in the literature since the previous review. New studies reporting breath CO or blood COHb in population studies are discussed in Chapter 4, along with other new CO exposure assessments.

2.6.1 Carboxyhemoglobin Measurements

Direct reading of COHb is usually performed in the clinical or hospital setting through the use of a direct-reading spectrophotometer, such as a CO-Oximeter (CO-Ox). For this use, precision on the order of ±1% COHb is not of primary importance, because of the need to differentiate between conditions of low levels of COHb and much higher levels of COHb that indicate treatment for CO poisoning. The concern in this setting, for example, is to rapidly distinguish between 1 and 10% COHb, not between 1 and 2% COHb.

The performance of various CO-Ox instruments for measuring blood COHb was investigated by Vreman et al. (1993) and Mahoney et al. (1993) after the previous review (U.S. Environmental Protection Agency, 1991). They confirmed that considerable difficulties still were encountered for COHb concentrations below 5% (a region with which most environmental studies of nonsmokers are concerned), and the authors concluded that CO-Ox is unreliable for environmental studies. The CO-Ox also was found to be influenced by bilirubin and by fetal hemoglobin, presenting difficulty in diagnosing newborn infants with jaundice (Stevenson and Vreman, 1997); however, a new commercial device was found to be unaffected by these two problems (Vreman and Stevenson, 1994).

Marshall et al. (1995) showed a very wide range of "threshold" COHb values (measured in the blood by CO-Ox, not estimated from breath CO) was used to determine treatment in a sample of 23 Boston, MA, area laboratories. For example, eight laboratories accepted values of 5 to 6 % COHb as normal in nonsmokers, a value that cannot be supported by the scientific literature. The authors recommended the use of threshold limits of 3% COHb for nonsmokers and 10% COHb for smokers when classifying subjects for treatment.

For a research study, the method of choice is GC for analysis of the CO gas released from the blood when COHb is dissociated (U.S. Environmental Protection Agency, 1991). The reader is alerted to the difference between breath CO-blood COHb relationships when the COHb is determined by CO-Ox or by GC, and a calibration curve relating exhaled breath CO to COHb should be based on a standard breathhold maneuver for the CO collection and the GC method of COHb analysis.

2.6.2 Breath Carbon Monoxide Measurements

Carbon monoxide in the breath can be measured by all techniques used to measure ambient CO concentrations, as described in U.S. Environmental Protection Agency (1991). A common type of instrument in use for rapidly screening large numbers of people for CO exposures or measuring breath CO distributions is the electrochemical analyzer. The subject performs an inhalation-breathhold maneuver and exhales through a mouthpiece into the instrument inlet. The end tidal breath is retained for analysis, and the reading in ppm CO can be converted to COHb through a calibration curve or nomogram provided with the instrument.

Vreman et al. (1993) presented evidence to show that a serious positive interferent in the electrochemical method (hydrogen gas) is present in the exhaled breath of some persons as a result of metabolism of certain foods. Because this could have affected many previous studies, including the very large EPA studies in Washington, DC, and Denver, CO (Akland et al., 1985), it would be desirable to determine the fraction of the population so affected. Because of the general decline of ambient CO, this potential interference takes on more importance in any future studies, which must account for this problem if employing electrochemical devices to measure breath CO.

Lee et al. (1991) developed a TDLS system that was well suited for measuring low levels of CO in breath. The system also can detect the abundance of isotopic CO ($^{13}C^{16}O$), with a preliminary finding of a slight enrichment over atmospheric abundance in breath. Lee et al. (1994) employed the instrument in a study correlating breath CO and blood COHb in people living near Boulder, CO (described in Chapter 4).

The passive CO sampler developed by Lee and Yanagisawa (1992, 1995) (see Section 2.5) has a reusable sampling system that allows the collection of only the last 5 mL of a breath expelled after breath holding for 20 s, thus obtaining alveolar air undiluted by dead space air. The sampler was unaffected by humidity; however, the rather low efficiency of collection (50%) and the resulting fairly high detection limit of 3.2 ppm may limit the utility of the sampler for environmental studies.

2.6.3 Relationships of Breath Carbon Monoxide to Blood Carboxyhemoglobin

The end-tidal breath CO versus COHb relationships reviewed in the previous criteria document (see Table 8-14 in U.S. Environmental Protection Agency, 1991) and in studies published in the literature since then are often at variance because they use either a 10-s, 15-s, or 20-s breathhold step in the breath collection; use either GC or CO-Ox for the blood COHb measurements; or may not correct for the CO content of the inhaled air. The use of a 20-s breathhold, as recommended by Jones et al. (1958), with a correction for the CO content of the inhaled air (Smith, 1977; Wallace, 1983), would improve the reproducibility of the CO breath measurements, and the use of GC would improve the accuracy of the corresponding COHb measurement. The 20-s breathhold is preferable, because it maximizes the approach to equilibrium and minimizes the magnitude of the required correction for CO in inhaled air. Therefore, specific details regarding the length of the breathhold, corrections for inhaled CO, and the method of COHb analysis should be provided in the published discussions of studies of the CO-COHb relationship so that differences among study results can be evaluated.

One comprehensive review article on CO-COHb relationships (Vreman et al., 1995) discusses physical and chemical properties, endogenous and exogenous sources of CO, body burden and elimination, toxicity and treatment, clinical chemistry, measurement methods, and the relationship of CO and COHb to bilirubin and jaundice in neonates. A second, less comprehensive review from the same investigators focuses on the production of CO and bilirubin in equal amounts by heme degradation and on the physiological significance of CO as a neuronal messenger (Rodgers et al., 1994).

Lee et al. (1994) performed a study of CO-COHb relationships at altitude in Boulder. A total of 13 nonsmoking adults were exposed to 9 ppm CO for both 1 and 8 h. Blood was sampled and end-tidal breath samples were taken after a 10-s breathhold. Mean COHb values prior to exposure were 0.65% and, after exposure for the 1- and 8-h periods were 1.2 and 2.2%, respectively. The corresponding mean CO levels in the breath samples were about 2.4, 4.4, and 8.2 ppm (uncorrected for the ≈0 ppm ambient CO in inhaled air), respectively, as shown in Figure 2-2. The slope of 3.65 ppm per 1% COHb saturation after a 10-s breathhold at altitude is somewhat smaller than previous estimates of about 5 ppm CO per 1% COHb, but the previous

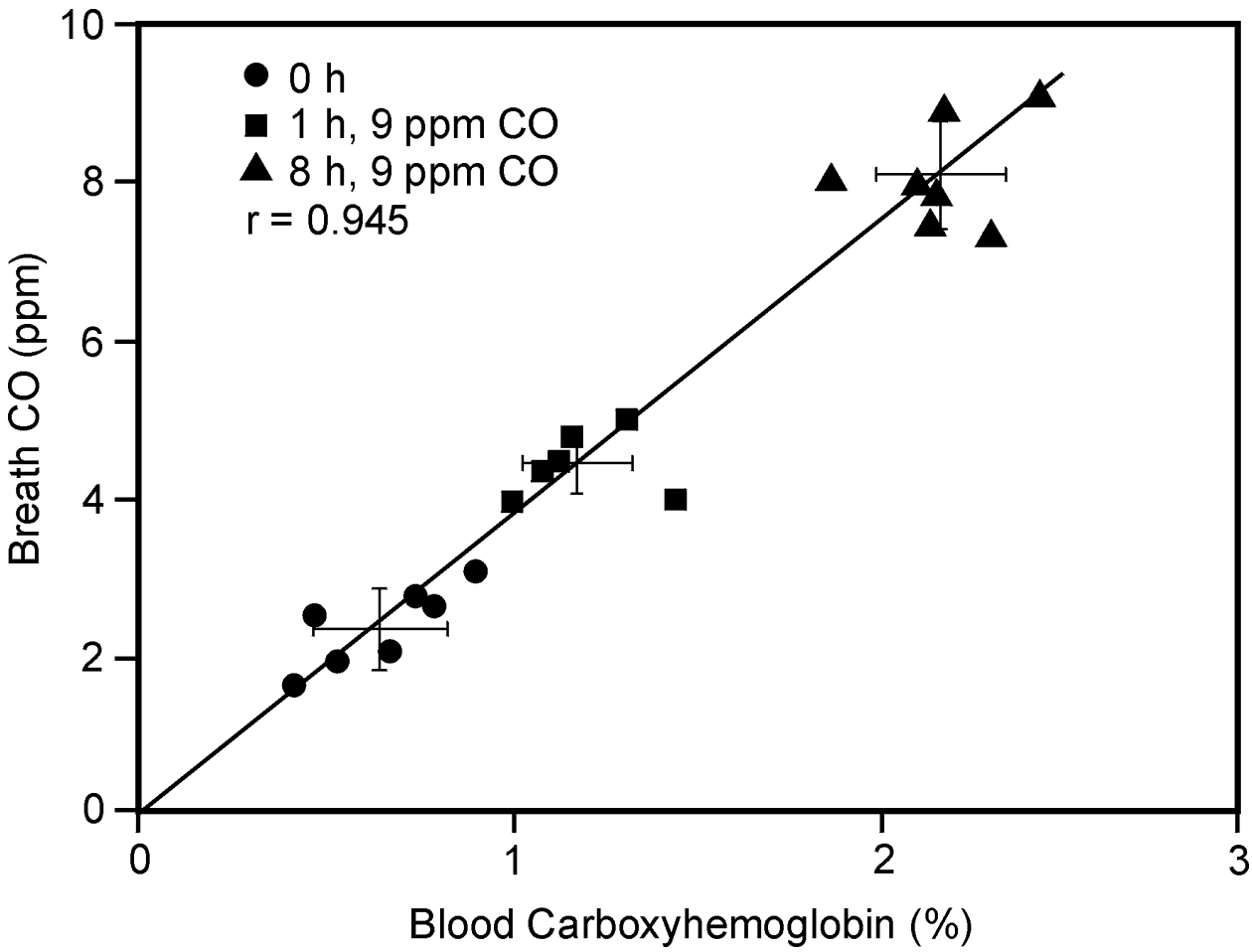


Figure 2-2. The correlation between an end-tidal breath CO concentration after a 10-s breathhold and blood COHb levels expressed as individual data points as well as mean ± standard deviation. The breath concentration was not corrected for the concentration of CO in the inhaled air (Smith, 1977; Wallace, 1983).

Source: Lee et al. (1991, 1994).

estimates were based on a 20-s breathhold near sea level that maximizes the end-tidal CO if the inhaled air had a CO concentration below the 20-s end-tidal breath CO (Jones et al., 1958).

2.6.4 Summary of the Relationship Between Biological Measurements of Carbon Monoxide

The use of CO-Ox to measure COHb provides useful information regarding values of COHb in populations being studied for clinical diagnosis. However, the range of COHb values

obtained with this optical method for blood collected from nonsmokers is greater than that obtained from a split sample analyzed for COHb by research laboratory GC. Therefore, the greater potential exists with the CO-Ox for having an incorrect absolute value for COHb, as well as an incorrectly broadened range of values, when used in population studies. In addition, it is not clear exactly how sensitive the CO-Ox techniques are to small changes in COHb at the low CO end of the COHb dissociation curve. Interferences (e.g., from variable levels of oxygen saturation of hemoglobin [O_2Hb]) and nonlinear phenomena appear to have a very significant influence on the COHb reading at low COHb concentrations in a sample, suggesting nonlinearity or a disproportionality in the absorption spectra of different species of Hb (e.g., HbA [adult], HbF [fetal], HbS [sickle], HbZH [Zurich]). Gas chromatography continues to be the method of choice for measuring COHb in a research setting, although, with care, a CO-Ox can be specially calibrated by GC analysis of calibration-standard blood samples prepared with low COHb concentrations (Dahms and Horvath, 1974).

The measurement of exhaled breath CO has the advantages of ease, speed, precision (provided the required correction for CO in the inhaled air is made), and greater subject acceptance than the invasive measurement of blood COHb. Breath CO measurement on randomly chosen people can be related to the blood COHb by use of an empirical relationship developed by simultaneous measurements of COHb (preferably by GC) and breath CO using the identical procedure for the breath collection that is used in the population study. The empirical relationships developed with different breath holding techniques will differ from the theoretical Haldane equilibrium relationship for the reaction $CO + O_2Hb \leftrightarrow O_2 + COHb$, which depends on the ratio of adult- to fetal-hemoglobin (HbA:HbF). This is because the Haldane relationship is for static equilibrium, and the empirical end-tidal breath CO-blood COHb relationship is for a dynamic equilibrium that depends on how long the breath is held and on the correction for the CO in inhaled air.

2.7 SUMMARY

The review of the state of the science for this criteria document yields several major points concerning analytical techniques for CO measurement.

Several adequate techniques exist for highly reliable monitoring of CO to ensure compliance with the NAAQS. Determination of the actual mean ambient air concentration requires substantially better performance than does the minimum required to demonstrate compliance with the NAAQS. Commercial instruments, sometimes with minor modifications, can meet the measurement needs for supplying useful data on the emission, distribution, and trends of ambient CO and for modeling photochemical smog.

Use of enhanced instruments for monitoring of actual CO concentrations with reasonable precision is needed if CO levels in clean continental air outside of urban environments are to be quantified adequately. Commonly used calibration standards and measurement techniques have in the past failed to meet the criteria of precise measurement, but there is now general agreement on procedures for generating standards with absolute accuracy better than about 2% in the parts per million range and about 10% in the range of mixing ratios found in the clean troposphere. Several monitoring techniques have been intercompared and found reliable.

Several electrochemical and passive sampling methods have become available. These techniques are inadequate for compliance monitoring or precise measurements in ambient air, but may prove useful for personal exposure studies. Further work on the stability and specificity of these methods is warranted. Accepted methods of analytical chemistry should be applied, and the results should be published in the reviewed scientific literature.

The level of COHb in the blood may be determined directly by blood analysis or indirectly by measuring CO in exhaled breath. The use of CO-Ox to measure COHb can provide useful information regarding mean values in populations being studied or as an aid in clinical diagnosis. It has been shown, however, that the range of values obtained with this optical method will be greater than that obtained with other more accurate methods, especially at COHb levels <5%. Gas chromatography continues to be the method of choice for measuring COHb.

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 still remains in question, especially at low environmental CO concentrations.

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3. SOURCES, EMISSIONS, AND CONCENTRATIONS OF CARBON MONOXIDE IN AMBIENT AND INDOOR AIR

3.1 INTRODUCTION

Current information about the abundance and distribution, the nature of sources and sinks and the chemistry of carbon monoxide (CO) in various environments, ranging from the global background to indoor air, is summarized in this chapter. Carbon monoxide is studied in each of these widely varied environments for very different reasons. In indoor environments with sources such as malfunctioning or misused combustion appliances, automobile exhaust from attached garages, and cigarettes and, in outdoor environments such as urban areas where emissions from motor vehicles or wood burning can cause high concentrations to exist, carbon monoxide is of direct concern because of health effects resulting from human exposure to these high concentrations. Human exposures to CO are discussed in Chapter 4.

Carbon monoxide in the atmosphere outside of these situations is of interest because of its importance to atmospheric chemistry. Carbon monoxide can affect the formation of ozone (O_3) and other photochemical oxidants in the atmosphere. Carbon monoxide strongly influences the abundance of hydroxyl radicals (OH), thus affecting the global cycles of many biogenic and anthropogenic trace gases, such as methane (CH_4), that affect the abundance of stratospheric O_3 and the energy budget of the atmosphere. Changes in CO levels, therefore, may contribute to widespread changes in atmospheric chemistry and indirectly affect global climate. In this chapter, the global scale aspects of CO are discussed first, and then the discussion proceeds to successively smaller scales. An overview of the major sources and sinks of CO and the resulting CO distribution on a global basis and the importance of CO to tropospheric chemistry is presented in Section 3.2, followed by a discussion of nationwide emissions of CO in Section 3.3. Nationwide trends in ambient CO levels and related discussions on CO air quality are presented in Section 3.4, and concentrations and sources of CO in indoor environments are discussed in Section 3.5.

3.2 THE GLOBAL CYCLE OF CARBON MONOXIDE

The major sources and sinks of CO are summarized in Table 3-1. Examples of major activities leading to the emissions of CO from each source category are shown in the second column of Table 3-1. Many of these sources have natural components. As can be seen from Table 3-1, CO is produced as a primary pollutant during the combustion of fossil and biomass fuels. Vegetation also can emit CO directly into the atmosphere as a metabolic byproduct.

TABLE 3-1. SUMMARY OF MAJOR SOURCES AND SINKS OF CARBON MONOXIDE

Sources and Sinks	Notes
Sources	
Fossil fuel combustion	Transportation and coal, oil, and natural gas burning.
Biomass burning	Agricultural clearing, wood and refuse burning, and forest fires.[a]
CH_4 oxidation	Wetlands,[a] agriculture (rice cultivation, animal husbandry, and biomass burning), landfills, coal mining, and natural gas and petroleum industry.
NMHC oxidation	Transportation (alkanes, alkenes, aromatic and compounds) and vegetation[a] (isoprene and terpenes).
Organic matter oxidation[a]	Humic and other organic substances in surface waters and soils.
Vegetation[a]	Metabolic by-product.
Sinks	
Reaction with OH radicals	Hydroxyl radicals are ubiquitous scavengers of many atmospheric pollutants.
Soil microorganisms[a]	Responsible microorganisms still need to be catalogued.

[a]Sources and sinks that have large natural components.

Carbon monoxide is formed as an intermediate product during the photochemical oxidation of methane and non-methane hydrocarbons (NMHCs) to CO_2. Major sources of methane are summarized in the second column of Table 3-1. Likewise, major sources of NMHCs, whose oxidation produces CO, are given. In addition, the photooxidation of organic matter in surface

waters (oceans, lakes, and rivers) and on the soil surface occurs. Carbon monoxide is lost primarily by reaction with atmospheric OH radicals and by uptake by soil microorganisms.

More detailed descriptions of the nature of individual sources of primary CO shown in Table 3-1 and estimates of the strengths of these sources, along with similar material for nonchemical sinks of CO, are given in Section 3.2.2. Carbon monoxide concentrations and trends in the background atmosphere are discussed in Section 3.2.1, and the atmospheric chemistry of CO, including the formation of secondary CO, is discussed in Section 3.2.3.

3.2.1 Global Background Concentrations of Carbon Monoxide

In common usage, the term "background levels" refers to concentrations observed in remote areas relatively unaffected by local pollution sources. However, several definitions of background levels are possible (see Chapter 6, U.S. Environmental Protection Agency, 1996). The two definitions chosen in that document as being most relevant for regulatory purposes and for providing corrections to assessments of the health risks posed by exposure to CO are based on estimates of contributions from uncontrollable sources that can affect CO levels in the United States. The first definition includes anthropogenic and natural sources outside North America, and natural sources within North America. The second definition includes only natural sources within and outside North America. These background levels refer to concentrations that would be present because of the presence of these sources alone. Because of long-range transport from anthropogenic source regions in North America, it may be impossible to obtain background levels defined above solely on the basis of direct measurement. However, some inferences about what these levels may be can be made with the help of numerical models and historical data.

Surface measurements of CO concentrations are made routinely as part of the National Oceanic and Atmospheric Administration's Climate Monitoring Diagnostics Laboratory (NOAA/CMDL) Global Cooperative Air Sampling Network (e.g., Hofmann et al., 1996). Carbon monoxide flask samples are collected weekly in flasks or continuously with in situ gas chromatographs at about 40 remote sites around the world. These sites are located primarily in the marine boundary layer, with a few located in continental areas. The latitudinal and seasonal variations in CO levels are summarized in the three-dimensional diagram shown in Figure 3-1 (Novelli et al., 1998). Annual average CO mixing ratios are about 130 ppb in the Northern

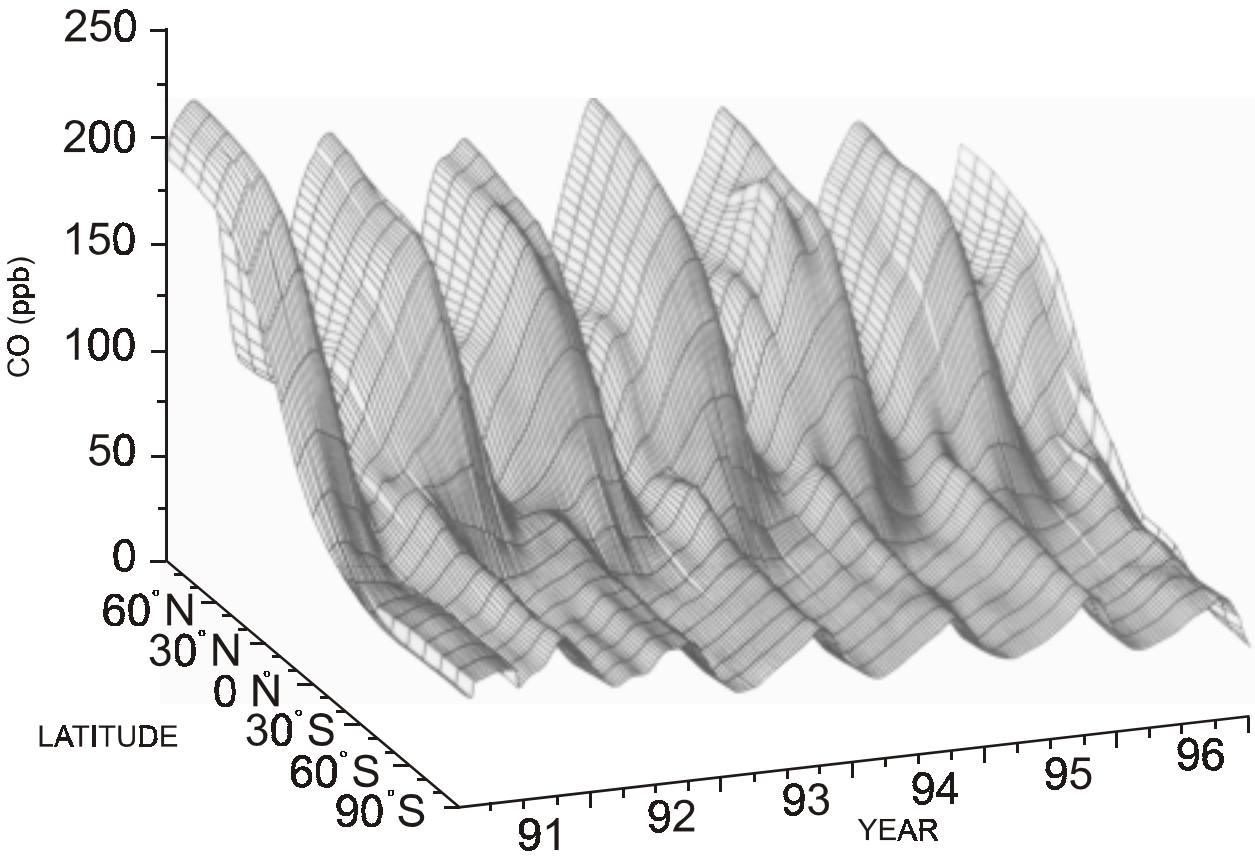

Figure 3-1. Latitudinal and seasonal variability in CO concentrations obtained in the NOAA/CMDL monitoring network.

Source: Novelli et al. (1998).

Hemisphere and about 50 ppb in the Southern Hemisphere. Seasonal maxima in CO mixing ratios occur during late winter in both hemispheres, and minima occur during late summer, with about a factor of two variation between maximum and minimum values. Carbon monoxide is well mixed in high latitudes of both the Northern Hemisphere and the Southern Hemisphere. A steep gradient in CO mixing ratios exists between about 30° north (N) latitude and about 10° south (S) latitude. Carbon monoxide concentrations range from a minimum of about 45 ppb during summer in the Southern Hemisphere to about 220 ppb at high latitudes in the Northern Hemisphere during winter. Thus, CO concentrations in remote areas of the Northern Hemisphere are only a small fraction (≈1 to 2%) of those of concern to human health (as given by the

National Ambient Air Quality Standards [NAAQS] for CO of 9 ppm for the second highest, nonoverlapping 8-h average concentration).

During the 1980s, there were sufficient data on tropospheric air quality trends to suggest that CO concentrations measured in remote areas were increasing globally at approximately 1% per year, based on data collected by the Oregon Graduate Institute (OGI) (Khalil and Rasmussen, 1988). This increase presumably resulted from anthropogenic activities. From about 1988 until 1992, global average CO concentrations declined rapidly at a rate of about $-2.6 \pm 0.8\%$ per year (Khalil and Rasmussen, 1994), perhaps caused by reductions in fossil fuel combustion and tropical biomass burning. Possible increases in tropospheric OH levels resulting from enhanced transmission of solar ultraviolet radiation caused by stratospheric O_3 depletion may have been an additional factor. Since 1993, these investigators have found that CO concentrations have leveled off. However, these results differ from those reported by NOAA/CMDL. Taken collectively over the last 10 years (as of December 1997), data collected at in situ and flask monitoring stations by OGI and NOAA/CMDL show no significant trend (Hard et al., 1998).

Because direct measurements of sufficient precision for defining trends have come into use only within the last 15 to 20 years, estimates of longer term trends in CO levels must come from indirect means. Rinsland and Levine (1985) derived an increase in the mean tropospheric CO abundance of about 2% per year from 1950 to 1984, based on an examination of solar spectra captured on photographic plates in Europe. Carbon monoxide concentrations measured in air bubbles trapped in the ice sheets of Greenland and Antarctica have been used as proxies for CO concentrations in ambient air at the time the air bubbles were sealed from the atmosphere (Haan et al., 1996). Carbon monoxide concentrations derived this way for the preindustrial era (roughly corresponding to the year 1850, when anthropogenic activities should not have influenced significantly the atmospheric composition) are about 90 ppb for the high-latitude Northern Hemisphere and are about 50 ppb for the high-latitude Southern Hemisphere. However, it should be noted that the CO in the trapped air bubbles also may result from the decomposition of organic compounds also trapped in the same air bubbles, and that it is difficult to extract CO from the air bubbles without contamination. Both factors tend to cause positive artifacts in the CO concentrations reported. In addition, the Northern Hemispheric value derived from the ice cores is higher than that predicted by atmospheric model studies of the preindustrial era that

indicate CO mixing ratios of about 50 ppb (Thompson and Cicerone, 1986; Pinto and Khalil, 1991; Thompson et al., 1993). Some enhancement of Northern Hemispheric values over Southern Hemispheric values during the preindustrial era is likely because of the greater mass of vegetation that can emit NMHCs in the Northern Hemisphere.

3.2.2 Sources and Global Emissions Estimates of Carbon Monoxide

Global CO emission estimates are summarized in Table 3-2. By far, the largest contribution from fossil fuel combustion on the global scale arises from motor vehicles. Variables controlling the formation of CO during combustion of any fuel are oxygen concentration, flame temperature, gas residence time at high temperature, and mixing in the combustion zone. In general, increases in all four factors result in lower amounts of CO produced relative to carbon dioxide (CO_2). Carbon monoxide is produced primarily during conditions of incomplete combustion. The estimates for fossil fuel emissions by stationary sources, shown in Table 3-2, do not include significant contributions from power plants, because fuels are burned with high efficiency in modern power plants. Rather, they are based on estimates of CO emitted in small, hand-fired furnaces used for domestic purposes (e.g., cooking, heating, water sterilization) and in inefficient boilers and furnaces used in small-scale industrial operations. This latter source is of significance only in eastern Europe and in developing countries of Africa and Asia (especially China). For example, Pinto and Rasmussen (1998) have estimated that as much as 50% of CO observed during a severe air pollution episode in Prague, Czech Republic, in February 1993 may have come from inefficient coal burning. However, it also should be noted that the importance of this source has been declining as heating needs are met increasingly by centralized power plants.

Biomass burning consists of burning vegetation to clear new land for agriculture and population resettlement; to control the growth of unwanted plants on pasture land; to dispose of agricultural and domestic waste; and as fuel for cooking, heating, and water sterilization. Biomass burning exhibits strong seasonality, with most biomass burned during the local dry season. The smoldering phase of combustion yields higher emissions factors than the flaming phase. Lobert et al. (1991) found, in controlled combustion chamber experiments with a wide variety of vegetation types, that, on average, 84% of CO was produced during the smoldering phase and 16% during the flaming phase of combustion. Smoldering conditions are more

TABLE 3-2. ANNUAL GLOBAL CARBON MONOXIDE EMISSIONS ESTIMATES (in teragrams [Tg] per year)

	Allen et al. (1996)	Logan et al. (1981)	Seiler and Conrad (1987)	Pacyna and Graedel (1995)	Dignon et al. (1998)
Sources					
Fossil fuel combustion	329	450[a]	640 ± 200	440 ± 150	600[b] (2.1)[c]
Biomass burning	370	655	1,000 ± 600	700 ± 200	600 (2.7)
Natural NMHC oxidation	618	560	900 ± 500	800 ± 400	300 (2.3)
Anthropogenic NMHC oxidation	—	90	—	—	200 (2.3)
Methane oxidation	722	810	600 ± 300	600 ± 200	600 (2)
Oceans	—	40	100 ± 90	50 ± 40	10
Soils	—	—	—	—	30
Vegetation	—	130	75 ± 25	75 ± 25	200 (4)
Total	2,039	2,735	3,315 ± 1,700	2,700 ± 1,000	2,500 (1.5)
Sinks					
Soils					300 (3)
OH reaction					2,300 (1.4)
Total					2,600

[a]Estimate includes 150 Tg/year from stationary sources.
[b]Estimate includes 100 Tg/year from stationary sources.
[c]Values in parentheses represent ratio of maximum to minimum estimate of source term.

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prevalent during the burning of large pieces of vegetation, such as trees, compared with grasses. Nonetheless, most CO is produced in the tropics by savanna burning (mainly in Africa), followed by burning forests, fuel wood, and agricultural waste. Less than 20% of the CO produced by biomass burning originates in middle and high latitudes (Andreae, 1991; Levine and Pinto, 1998).

The other sources of CO shown in Table 3-2 all have large natural components. Carbon monoxide may be evolved from the photodecomposition of organic matter in surface waters (such as oceans, rivers, and lakes) and the soil surface. Soils can act as a source or a sink for carbon monoxide, depending on soil moisture, the intensity of sunlight reaching the soil surface, and soil temperature (e.g., Inman et al., 1971; Conrad and Seiler, 1985). Soil uptake of CO occurs because of anaerobic bacteria and potentially can be an important sink, as soils exposed to test atmospheres containing 100 ppm CO could reduce the CO concentrations to near zero within a few hours (Inman et al., 1971). Emissions of CO from soils appear to occur by abiotic processes, such as thermodecomposition or photodecomposition of organic matter. In general, warm and moist conditions favor CO uptake, whereas hot and dry conditions favor the release of CO. Liebl and Seiler (1976) have estimated a mean deposition velocity of 0.04 cm/s for CO. However, despite the small mean value for the deposition velocity of CO, uptake by soil microbes still may be capable of depleting CO in the stable nocturnal boundary layer (Moxley and Cape, 1997). The value reported for soil emissions in Table 3-2 is based on very limited data, and hence it is difficult even to assign uncertainty bounds (Conrad, 1996).

Estimates of the magnitude of the soil sink range from 250 to 640 Tg/year (Logan et al., 1981; Cicerone, 1988), with a current "best"estimate of 300 Tg/year, with an uncertainty range of a factor of three (Dignon et al., 1998). More extensive field measurements, perhaps based on the eddy correlation technique (Ritter et al., 1994), are needed to characterize the variability and the direction of the CO flux to the soil surface. Most CO in the atmosphere is lost by its oxidation to CO_2 by OH radicals. Reaction with OH radicals accounts for a loss of 2,300 Tg/year, with an uncertainty factor of 1.4 (Dignon et al., 1998). Because of large uncertainties in individual sources and sinks, the imbalance between sources (2,500 Tg/year) and sinks (2,600 Tg/year) is not significantly different from zero.

3.2.3 The Atmospheric Chemistry of Carbon Monoxide

Carbon monoxide is produced by the photooxidation of CH_4 and other organic compounds (including NMHCs) in the atmosphere and of organic molecules in surface waters and soils (Table 3-1 and 3-2). Estimates of CH_4 emissions from the various source categories shown in Table 3-1 can be found in the Intergovernmental Panel on Climate Change report (1996). Methane oxidation can be summarized by the following sequence of reactions:

$$CH_4 + OH \rightarrow CH_3 + H_2O$$
$$CH_3 + O_2\ (+M) \rightarrow CH_3O_2\ (+M)$$
$$CH_3O_2 + NO \rightarrow CH_3O + NO_2$$
$$CH_3O + O_2 \rightarrow CH_2O + HO_2$$
$$CH_2O + h\upsilon \rightarrow H_2 + CO,$$
$$\text{or} \quad CH_2O + h\upsilon \rightarrow HCO + H,$$
$$\text{or} \quad CH_2O + OH \rightarrow HCO + H_2O$$
$$HCO + O_2 \rightarrow CO + HO_2,$$

where M is a mediator (e.g., nitrogen, O_2, argon, CO_2). The photolysis of formaldehyde (CH_2O) proceeds by two pathways, the first yields molecular hydrogen (H_2) plus CO (55%), and the second yields atomic hydrogen (H) plus the formyl radical (HCO) (45%), where the percentages are given for overhead sun conditions (Rogers, 1990). Formyl radicals then react with molecular oxygen (O_2) to form the hydroperoxy radical (HO_2) plus CO. In addition, the reaction of the methyl peroxy radical (CH_3O_2) with HO_2 radicals, forming methyl hydroperoxide (CH_3OOH), needs to be considered, especially in low nitrogen oxide (NO_x) environments. The heterogeneous removal of soluble intermediate products, such as CH_3OOH, CH_2O, and radicals, decreases the yield of CO from the oxidation of CH_4.

Althought the oxidation of CH_2O nearly always results in CO formation (except for the formation of small quantities of formic acid in the reaction of CH_2O with HO_2), the oxidation of acetaldehyde (CH_3CHO) does not always yield two CO molecules. The photolysis of CH_3CHO also involves pathways that produce molecules and radicals, namely CH_4 + CO and CH_3 + HCO. Estimates of the yield of CO from the photooxidation of CH_4 and CH_3 are subject to the same considerations outlined above. The reaction of CH_3CHO with OH radicals can yield acetyl

radicals (CH_3CO). The acetyl radicals then will participate with O_2 in a termolecular recombination reaction to form acetyl peroxy radicals, which then can react with nitric oxide (NO) to form $CH_3 + CO_2$ (or the acetyl peroxy radicals can react with nitrogen dioxide (NO_2) to form peroxy acetyl nitrate [PAN]). Thus, one of the carbon atoms can be oxidized directly to CO_2 without passing through CO. The yield of CO depends on the OH concentration and the photolysis rate of CH_3CHO, as well as on the abundance of NO, as acetyl peroxy radicals also can react with HO_2 and other hydrogen-bearing radicals.

Estimates of the yield of CO from the oxidation of more complex hydrocarbons requires the calculation of the yields of CH_2O, CH_3CHO, CH_3CO, and analogous radicals from the oxidation of the parent molecule. Likewise, the extent of heterogeneous removal of soluble intermediate products needs to be considered in the oxidation of more complex hydrocarbons. However, in contrast to simple hydrocarbons containing one or two carbon atoms, detailed kinetic information is lacking about the gas phase oxidation pathways of many anthropogenic hydrocarbons (e.g., aromatic compounds, such as benzene and toluene), biogenic hydrocarbons (e.g., isoprene, the monoterpenes), and their intermediate oxidation products (e.g., epoxides, nitrates, carbonyl compounds). As much as 30% of the carbon in hydrocarbons in many urban areas is in the form of aromatic compounds (Grosjean and Fung, 1984; Seila et al., 1989). Yet mass balance analyses performed on irradiated smog chamber mixtures of aromatic hydrocarbons indicate that only about one-half of the carbon is in the form of compounds that can be identified. Reactions that have condensible products, such as those occurring during the oxidation of terpenes, also need to be considered because these reactions produce secondary organic particulate matter, thereby reducing the potential yield of CO.

The yield of CO from the oxidation of CH_4 is about 0.9, and it is about 0.4 from the oxidation of ethane and propane, on a per carbon basis from estimates based on atmospheric model results (Kanakidou et al., 1991). Jacob and Wofsy (1990) estimated that 1 mole of CO is produced by the oxidation of 1 mole of isoprene (corresponding to a conversion factor of 0.2 on a per carbon basis) for low NO_x levels. For higher NO_x levels, they estimated that 3 moles of CO are produced per mole of isoprene oxidized (corresponding to a conversion factor of 0.6 on a per carbon basis). Isoprene accounts for most of the CO produced by the photochemical oxidation of NMHCs shown in Table 3-2. An indication of the possible importance of the oxidation of isoprene as a source of CO is provided by Yarwood and Morris (1998). They found that the

oxidation of isoprene accounted for over 50% of the CO in many rural areas in a simulation of an O_3 episode (July 7 to 18, 1995) in the eastern half of the United States.

Although the source of secondary CO may be important on regional and global scales, it may not be as important when considering CO in urban areas. In analyzing the results of a numerical simulation of an O_3 episode in California's San Joaquin Valley from August 3 to 4, 1990, Jeffries (1998) found that the peak photochemical oxidation of NMHCs produced only 2.5 ppb CO per hour, compared with an average CO mixing ratio of 260 ppb. Thus, it would take about 100 h of uninterrupted oxidation of NMHCs under optimal conditions to produce the observed CO. The lack of importance of photochemical sources in this air shed reflects the combination of concentrated, local, automotive emissions and the lack of complete oxidation of the NMHCs emitted in the model domain.

The major pathway removing CO from the atmosphere is by its reaction with OH radicals. There have been numerous determinations of the rate coefficient for this reaction. The most recent evaluation of kinetics data for use in atmospheric modeling (National Aeronautics and Space Administration, Panel for Data Evaluation, 1997) recommends a value of 1.5×10^{-13} $(1 + 0.6\ P_{atm})$ cm^3 $molecules^{-1}$ s^{-1}, with a value of 0 ± 300 K for *E/R* for the reaction

$$OH + CO \rightarrow Products.$$

This reaction proceeds through two channels. The bimolecular channel yields $H + CO_2$, whereas the addition channel leads to the formation of a carboxyl radical (HOCO). In the presence of O_2, the HOCO intermediate is converted to $HO_2 + CO_2$. Therefore, for atmospheric purposes, the products of the reaction OH + CO can be taken to be HO_2 and CO_2.

Estimates of OH radical concentrations can be used along with the rate coefficient given above to calculate the lifetime of CO in the atmosphere. Measurements of OH radical concentrations in situ (Hard et al., 1992; Mount and Williams, 1997; Poppe et al., 1994) in the lower troposphere show that their levels are highly site specific and are highly variable in space and time. Typical mid-latitude noontime values during summer (when OH concentrations are at their highest levels) range from about 5 to 10×10^6 OH/cm^3 and are much lower during other times of the day and during other seasons. As a result, it is difficult to derive average values that would be meaningful for use in calculating the atmospheric lifetime of long-lived species that

react with OH radicals, based on direct measurements. Modeling the atmospheric distribution of methyl chloroform (CH_3CCl_3) has been used to derive diurnal and global average OH values for calculating the atmospheric lifetimes of long-lived species by comparing predictions to observations (Prinn et al., 1992). Average OH values derived in this manner are about 8×10^5 OH/cm^3. By further adjusting the OH fields derived in a simulation of the CH_3CCl_3 distribution, to optimize the fit between the measurements and simulations of CH_3CCl_3 concentrations, Krol et al. (1998) derived concentrations of 1.00×10^6 OH/cm^3 in 1978 and 1.07×10^6 OH/cm^3 in 1993. The resulting trend in OH values is estimated to be $0.46 \pm 0.5\%$ year^{-1}. The resulting atmospheric lifetime of CO is approximately 2 mo in middle latitudes (range, 1 to 4 mo, depending on latitude and season, with highest values during winter and at higher latitudes). These lifetimes are shorter than the characteristic time scale for mixing between the hemispheres (about 1 year), and hence a large gradient in concentrations can exist between the hemispheres (see Figure 3-1). In addition, the chemical lifetime of CO at high latitudes is long enough to result in much smaller gradients between 30° latitude and the pole of either hemisphere.

Reaction with CO, is in turn, the major reaction of OH radicals. The reaction of CO with OH radicals constitutes at least 50% of the tropospheric sink of OH radicals (e.g., Collins et al., 1997). Thus, changes in the abundance of CO could lead to changes in the abundance of a number of trace gases whose major loss process involves reaction with OH radicals. These trace gases can absorb infrared radiation from the earth's surface and contribute to the greenhouse effect (e.g., CH_4) or can deplete stratospheric O_3 (e.g., methyl chloride [CH_3Cl], methyl bromide [CH_3Br], and hydrochlorofluorocarbons, such as difluorochloromethane). Because of the importance of CO in determining OH levels, interest has focused on the possible effects of increases in anthropogenic CO emissions on the concentrations of gases such as CH_4 (Sze, 1977; Chameides et al., 1977; Thompson and Cicerone, 1986). For instance, Thompson and Cicerone (1986) found in numerical simulations, in which the CO mixing ratio at the surface was allowed to increase by 1% per year from 1980 to 2000, while holding CH_4 emissions constant, that the mixing ratio of CH_4 at the surface increased by about 12% (corresponding to a mean increase of 0.56% per year), and that the mixing ratio of CH_4 at the surface increased by about 30% (corresponding to a mean increase of 1.3% per year) for an increase in surface CO mixing ratio of 2% per year. However, based on the trend results reported earlier, Brühl and Crutzen (1998)

have examined the consequences of decreases in CO levels for atmospheric chemistry. They found, by decreasing CO emissions linearly by about 20% between 1990 and 2000, that the CO reductions could lead to a significant decrease (≈25%) in the growth rate of CH_4 and even to a decrease in CH_4 levels in the case of constant CH_4 emissions. An accurate knowledge of the sources and sinks of carbon monoxide in the atmosphere is therefore necessary for assessing the effects of future increases in anthropogenic CO emissions on the concentrations of the above-mentioned radiatively and photochemically important trace species. However, because of nonlinearities introduced into the calculation of OH radical concentrations by short-lived NO_x (e.g., Hameed et al., 1979), an accurate assessment of these effects awaits the development of three-dimensional chemistry and transport models incorporating the spatial variability of NO_x (e.g., Kanakidou and Crutzen, 1993).

In the free troposphere, in the absence of significant quantities of NMHCs, the effects of CO on tropospheric O_3 can be summarized as shown below.

Atmospheric Reactions Leading to O_3 Production

$$\begin{array}{ll} & CO + OH \rightarrow CO_2 + H \\ & H + O_2\,(+M) \rightarrow HO_2\,(+M) \\ & HO_2 + NO \rightarrow NO_2 + OH \\ & NO_2 + h\nu \rightarrow O + NO \\ & O + O_2\,(+M) \rightarrow O_3\,(+M) \\ \hline \text{Net} & CO + 2O_2 \rightarrow CO_2 + O_3 \end{array}$$

Atmospheric Reactions Leading to O_3 Destruction

$$\begin{array}{ll} & CO + OH \rightarrow CO_2 + H \\ & H + O_2\,(+M) \rightarrow HO_2\,(+M) \\ & HO_2 + O_3 \rightarrow OH + 2O_2 \\ \hline \text{Net} & CO + O_3 \rightarrow CO_2 + O_2 \end{array}$$

The oxidation of CO by OH could lead to the production or destruction of O_3, depending on the ratio of NO to HO_2 concentrations. Based on current values of rate coefficients for the reactions of HO_2 with NO and O_3, in regions where NO levels are greater than about 10 ppt, the oxidation of CO leads to O_3 formation, whereas, in areas where NO levels are less than about 10 ppt, the oxidation of CO leads to O_3 destruction. Nitric oxide levels less than 10 ppt typically are found over the tropical oceans (Carroll et al., 1990). A rough estimate of the fraction of

O_3 production resulting from CO in the remote troposphere can be made by taking the overall rate of the reaction of CO with OH radicals and then correcting for the fraction of HO_2 radicals that do not react with NO, based on free radical balances presented by Collins et al. (1997). This quantity (i.e., the rate of conversion of NO to NO_2 by HO_2 radicals produced by the reaction of CO with OH radicals) represents 20 to 40% of the production of O_3 on a global basis.

The effects of CO on O_3 photochemistry in environments with abundant hydrocarbons (e.g., cities, tropical rain forests) require a much more complex treatment that includes the competition for OH radicals by CO and NMHCs and the effects of this competition on the overall budget of hydrogen-containing radicals (i.e., OH, HO_2). In urban environments, reaction with OH radicals represents the major loss process for NMHCs and initiates the sequence of further reactions leading to the formation of O_3 and CO itself. Detailed analyses of the radical balances (i.e., production and loss rates in each reaction) in urban air chemistry models, as performed by Jeffries (1998), can give the amount of O_3 formed because of the reaction of CO. However, only a few such analyses have been performed. Jeffries (1998), in a numerical simulation of an O_3 episode in the San Joaquin Valley from August 3 to 4, 1990, found that reaction with CO constituted 27% of the loss of OH radicals. It was found, by tracking sources of various radicals produced by the oxidation of VOCs and that oxidize NO to NO_2, that CO accounted for about 14% of the O_3 formed in this example (compared to about 86% for VOCs). He found that CO was responsible for 18% of the O_3 production in another simulation of an O_3 episode in Charlotte, NC. Methane accounted for 6%, paraffins (with more than three carbon [C] atoms) for 25%, ethane for 6%, olefins for 4%, toluene for 2%, xylenes for 3%, isoprene for 10%, aldehydes for 21%, methylglyoxyl for 1%, PAN for 3%, and other species for about 1% of the O_3 produced in this episode. In examining grid cells downwind of New York City, NY, during an O_3 episode, Jeffries (1998) also found that CO accounted for about 11% of the O_3 formed. Obviously, more analyses of this sort are needed to characterize regional differences in the importance of CO in different cities in the United States, which may have very different combinations of CO, NMHC, and NO_x concentrations than those used in these examples. Because of nonlinearities in the production rate of O_3 involving each of the above species, caution should be exercised in attempting to estimate the effects of variations in CO levels on O_3 production rates in the case studies cited above.

3.3 NATIONWIDE CARBON MONOXIDE EMISSIONS ESTIMATES

Total primary CO emissions were estimated for the period of 1987 through 1996 using the National Emissions Inventory Trends database (U.S. Environmental Protection Agency, 1998). These emissions (see Table 3-3) are shown in the original units used in their calculation (i.e., thousands of short tons per year). A short ton is equal to 2,000 lb or 9.08×10^5 g. Table 3-3 shows that total CO emissions decreased by 18.4% from 1987 to 1996; however, the fractional contribution of transportation (the major source of CO both then and now) remained constant at 79%. In addition, there are several categories, such as fuel consumption by electric utilities and industry and nonroad mobile sources, in which emissions have increased over the same period. Total CO emissions for the United States were reported to be 66,189 thousand short tons for 1990, the last year reported in the previous air quality criteria document (AQCD) for CO. It can be seen from inspection of Table 3-3 that the values for 1990 have been revised upward in the interim to 96,535 thousand short tons. The upward revision in values for 1990 is primarily the result of changes in the methods for calculating motor vehicle emissions. The MOBILE5 emissions factor model (U.S. Environmental Protection Agency, 1993) replaced the earlier MOBILE4.1 version (U.S. Environmental Protection Agency, 1991a). Changes were made in methods for calculating inputs to the model (e.g., temperatures and operating mode) and in the method for calculating vehicle miles traveled. Additional differences relate to the use of county-level statistics for vehicle registration, as well as the use of temperature data from individual counties.

In addition, emissions of secondary CO, such as from the oxidation of isoprene also should also be mentioned. Annual emissions of isoprene in the contiguous United States are about 17.2 Tg/year (Pierce and Dudek, 1996). A source of CO of 8.9 Tg/year is calculated using the conversion factor of 0.25 for C in isoprene to C in CO estimated by Yarwood and Morris (1998). This value represents about 11% of the estimated U.S. emissions for CO in 1995, as shown in Table 3-3. The oxidation of anthropogenic and other natural NMHCs may supply an additional 2 to 3 Tg CO per year.

A number of techniques, such as roadside tunnel sampling and the remote sensing of individual motor vehicle emissions have been applied in the past several years at a number of locations throughout the United States to test CO emissions estimates and to derive emissions factors (i.e., emissions per unit distance traveled). Two major points have been realized on the

TABLE 3-3. NATIONWIDE CARBON MONOXIDE EMISSIONS ESTIMATES, 1987 to 1996
(thousands of short tons per year)

Source Category	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
Fuel Combustion	**6,967**	**7,379**	**7,449**	**5,510**	**5,856**	**6,155**	**5,586**	**5,519**	**5,934**	**5,962**
Electric Utilities	307	320	327	363	349	350	363	370	372	377
Coal	223	236	239	234	234	236	246	247	250	263
Oil	20	25	26	20	19	15	16	15	10	11
Gas	53	48	51	51	51	51	49	53	55	44
Internal combustion	10	11	11	57	45	47	51	55	58	59
Industrial	649	669	672	879	920	955	1,043	1,041	1,056	1,072
Coal	85	87	87	105	101	102	101	100	98	99
Oil	46	46	46	74	60	64	66	66	71	72
Gas	252	265	271	226	284	300	322	337	345	348
Other	171	173	173	279	267	264	286	287	297	305
Internal combustion	96	98	96	195	208	227	268	251	245	247
Other	6,011	6,389	6,449	4,269	4,587	4,849	4,181	4,109	4,505	4,513
Residential wood	5,719	6,086	6,161	3,781	4,090	4,332	3,679	3,607	3,999	3,993
Other	292	303	288	488	497	517	502	502	506	520
Industrial Processes	**6,851**	**7,034**	**7,013**	**5,852**	**5,740**	**5,683**	**5,898**	**5,839**	**5,790**	**5,817**
Chemical and Allied Processing	1,798	1,917	1,925	1,183	1,127	1,112	1,093	1,171	1,223	1,223
Metals Processing	1,984	2,101	2,132	2,640	2,571	2,496	2,536	2,475	2,380	2,378
Petroleum and Related Industries	455	441	436	333	345	371	371	338	348	348

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TABLE 3-3 (cont'd). NATIONWIDE CARBON MONOXIDE EMISSIONS ESTIMATES, 1987 to 1996
(thousands of short tons per year)

Source Category	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
Other Industrial Processes	713	711	716	537	548	544	594	600	624	635
Solvent Utilization	2	2	2	5	5	5	5	5	6	6
Storage and Transport	50	56	55	76	28	17	51	24	25	25
Waste Disposal and Recycling	1,850	1,806	1,747	1,079	1,116	1,138	1,248	1,225	1,185	1,203
Transportation	**86,209**	**86,861**	**81,832**	**73,965**	**78,114**	**76,233**	**76,794**	**78,706**	**70,947**	**69,946**
On-Road Vehicles	71,250	71,081	66,050	57,848	62,704	59,859	60,202	61,833	54,106	52,944
Nonroad Sources	14,959	15,780	15,781	16,117	16,040	16,374	16,592	16,873	16,841	17,002
Miscellaneous	**8,852**	**15,895**	**8,153**	**11,208**	**8,751**	**7,052**	**7,013**	**9,614**	**7,050**	**7,099**
Structural Fires	242	242	242	164	166	168	169	170	171	172
Agricultural Fires	483	612	571	415	413	421	415	441	465	475
Prescribed Burning	4,332	4,332	4,332	4,668	4,713	4,760	4,810	4,860	4,916	4,955
Forest Wildfires	3,795	10,709	3,009	5,928	3,430	1,674	1,586	4,114	1,469	1,469
Other	NA	NA	NA	32	28	30	34	28	28	27
Total All Sources	**108,879**	**117,169**	**104,447**	**96,535**	**98,461**	**95,123**	**95,291**	**99,677**	**89,721**	**88,822**

Note: Some columns may not sum to totals because of rounding.

Source: U.S. Environmental Protection Agency (1998).

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basis of these studies: first, that a small percentage of motor vehicles are responsible for most of the emissions, and, second, that CO and hydrocarbon emissions have been systematically underestimated by as much as a factor of two in emissions factor models.

Roadside remote sensing data indicate that about 50% of CO and NMHC emissions are produced by only about 10% of the vehicles (Lawson et al., 1990; Stephens and Cadle, 1991). These "superemitters" are typically older, poorly maintained vehicles. There are also a surprising number of newer vehicles that are classified as superemitters. Possible reasons are related to tampering with emissions control systems to improve milage, the use of contaminated fuels that may interfere with the proper operation of emissions control systems, and the lack of maintenance of emissions control equipment. In addition to the above activities, so-called off-cycle operations also can result in enhanced emissions relative to those conditions for which emissions testing is usually done. For example, rapid accelerations have been shown to increase emissions relative to less stressful driving modes.

A comparison of emissions factors computed on the basis of tunnel measurements in Van Nuys, CA, during the South Coast Air Quality Study in 1987 with those calculated by emissions inventory models indicated that CO emissions were underpredicted by emissions models (i.e., the Emissions Factor 7C [EMFAC7C] model, which is similar to MOBILE3) by a factor of 2.7, and hydrocarbon emissions were underestimated by a factor of 3.8 (Ingalls et al., 1989; Pierson et al., 1990). A reinterpretation of the Van Nuys tunnel data by Pollack et al. (1998) indicated that emissions factors calculated using MOBILE5a were only a few percent more than the ambient tunnel data indicated (21.3 versus 20.9 g/mi), compared with a factor of two difference using EMFAC7F (9.6 versus 20.9 g/mi). Likewise, a comparison of emission factors computed on the basis of measurements in the Fort McHenry, MD, and Tuscarora, PA, tunnels with those calculated by emissions models (MOBILE4.1 and MOBILE5) illustrated the extent of model dependence on the intercomparisons (Pierson et al., 1996). In general, both versions of the model gave predictions within ±50% of observations most of the time. However, both versions showed different tendencies to either over- or underpredict, suggesting that the model predictions were within the range of uncertainty of the model.

Comparisons of ambient air quality data with predictions of emissions factor models have been made for conditions when ambient concentrations result primarily from local emissions with minimal photochemical processing and minimal transport from locations with different

source characteristics. The optimal time to obtain such conditions is during the early morning, when ambient concentrations of CO, non-methane organic compounds (NMOCs), and NO_x typically peak and are dominated by local mobile source emissions (Fujita et al., 1992). These comparisons have been performed in California for the Los Angeles Basin (Fujita et al., 1992), the San Joaquin Valley, and San Francisco Bay Area (Magliano et al., 1993), and for the Lake Michigan air quality region (Korc et al., 1993). A fairly consistent picture of underpredictions of ambient CO to NO_x and NMOC to NO_x ratios by emissions factor models, after allowing for correction for the artifacts mentioned above, emerges from these studies. In the Los Angeles Basin study, ambient CO to NO_x ratios were factors of 1.3 to 2.9 higher than corresponding emissions inventory ratios during summer, and factors of 1.2 to 2.4 higher than predicted by emissions models during fall. In the San Joaquin Valley study, ambient CO to NO_x ratios ranged from factors of 1.1 to 7.2 higher than predicted by emission models. In the Lake Michigan area study, ambient CO to NO ratios ranged from factors of 1.7 to 4.7 higher than predicted by emissions models. However, more recent comparisons between ambient and emission inventory CO/NO_x for Los Angeles and the San Joaquin Valley show better agreement than in previous studies (Croes et al., 1996; Ipps and Popejoy, 1998; Haste et al., 1998).

3.4 CARBON MONOXIDE CONCENTRATIONS IN AMBIENT AIR

The U.S. Environmental Protection Agency's (EPA's) Aerometric Information Retrieval System (AIRS) receives data from the National Air Monitoring Stations (NAMS) and the State and Local Air Monitoring Stations (SLAMS). Current NAAQS define 1- and 8-h average concentrations that should not be exceeded more than once per year. The standards are met if the second highest 1-h value is less than 35 ppm (40 mg/m^3), and the second highest nonoverlapping 8-h value is less than 9 ppm (10 mg/m^3). Nationwide trends in ambient CO concentrations are presented in Section 3.4.1, diurnal variations in ambient CO levels are presented in Section 3.4.2, and a more detailed characterization of the spatial and temporal variability in ambient CO concentrations in selected urban areas are presented in Appendix 3-A. The analyses in Appendix 3-A were performed for the Denver, CO; Los Angeles; New York City, NY; and Phoenix, AZ, Metropolitan Statistical Areas.

3.4.1 Nationwide Trends in Ambient Carbon Monoxide Concentrations

In 1996, 554 monitoring sites reported ambient CO air quality data to EPA's AIRS. Most CO monitoring stations in the United States are located in larger urban areas. Figure 3-2 displays the geographic locations of the monitoring sites reporting CO data to AIRS for 1996. On the map, the sites are identified as NAMS, SLAMS, or "other". The NAMS were established by EPA to ensure a long-term national network for urban-area-oriented ambient monitoring and to provide a systematic, consistent database for air quality comparisons and trends analysis. The SLAMS allow state or local governments to develop networks tailored for their immediate monitoring needs. These NAMS and SLAMS sites conform to uniform criteria for monitor siting, instrumentation, and quality assurance. "Other" monitors may be Special Purpose Monitors, monitors at industrial sites, monitors on tribal lands, etc. Although state and local air programs may require extensive monitoring to document and measure the local impacts of CO emissions, only two NAMS sites are required in urbanized areas with populations greater than 500,000. Two categories of NAMS sites are required: (1) peak concentration areas (microscale), such as major traffic corridors, street canyons, and major arterial streets, and (2) areas with high population and traffic densities (middle scale or neighborhood scale).

Only nine of the sites shown in Figure 3-2 failed to meet the 8-h standard of 9 ppm, and none of the 554 monitoring sites exceeded the 1-h standard of 35 ppm in 1996. The locations of these nine sites, along with the second highest 8-h CO concentration and the number of exceedances for 1996, are given in Table 3-4.

Figure 3-3 shows the consistent, downward trend in the nationwide composite average of the annual second highest 8-h CO concentration during the past 20 years (1977 through 1996). This statistic relates directly to the averaging time and form of the current CO NAAQS and complies with the recommendations of the Intra-Agency Task Force on Air Quality Indicators (U.S. Environmental Protection Agency, 1981). The dashed curve in Figure 3-3 tracks the trend in the composite mean of the annual second highest 8-h average concentration for 102 monitoring sites that reported ambient air quality data in at least 17 of the past 20 years, 1977 to 1996. All monitoring sites are weighted equally when computing the nationwide composite mean concentration. This selection criterion maximizes the number of sites available for trend analyses. This subset of sites yields good geographical coverage with sites from more than 50 cities in 28 states. Each year, site leases are lost, or sites are discontinued, and new sites come

Figure 3-2. Locations of sites in the nationwide ambient CO monitoring network, 1996.

online; therefore, the 102 long-term-trend sites compose less than 20% of the currently active CO monitors. The solid line in Figure 3-3 shows the trend in the composite mean for a larger database of 345 sites that have reported ambient CO monitoring data in at least 8 of the past 10 years. Missing annual second-highest CO concentration data for the second through ninth years are estimated by linear interpolation from the surrounding years. Missing endpoints are replaced with the nearest valid year of data. This latter procedure explains the discrepancy between the two curves in 1987 and 1988. Specific computational details are described elsewhere (U.S. Environmental Protection Agency, 1998). This larger data set permits the examination of the inter-site variability in peak CO concentrations. Figure 3-4 presents the 10th, 50th, and 90th percentile concentrations and the composite mean concentrations across these 345 sites. The 10th, 50th, and 90th percentile concentrations CO concentrations for each year are

TABLE 3-4. SITES NOT MEETING THE CARBON MONOXIDE NATIONAL AMBIENT AIR QUALITY STANDARDS IN 1996

		1996	
Location	AIRS Site ID No.	2nd Max[a]	No. Exc.[b]
Lynwood, CA[c]	06 037 1301	14.5	22
Calexico, CA	06 025 0005	14.1	9
Kalispell, MT	30 029 0045	11.1	2
Hawthorne, CA[c]	06 037 5001	10.5	5
Anchorage, AK	02 020 0037	10.5	3
El Paso, TX	48 141 0027	10.3	2
Las Vegas, NV	32 003 0557	10.1	3
Phoenix, AZ	04 013 0022	10.0	2
Anchorage, AK	02 020 0017	9.6	3

[a]Second highest 8-h average CO concentration.
[b]Number of exceedances of CO NAAQS.
[c]Both sites are located in Los Angeles County.

indicated, respectively, by the bottom, middle, and top lines of each box. For example, 10% of the 345 trends sites reported 1987 second highest 8-h CO concentrations lower than the bottom of the first bar in Figure 3-4. The yearly composite mean across all 345 sites is indicated by the "×" in each bar. Figure 3-5 shows trends in CO concentrations in each of the different sampling environments (urban, suburban, and rural sites). As can be seen from Figure 3-5, the downward trend in ambient CO concentrations occurred at monitoring sites in urban, suburban, and rural environments.

3.4.2 Circadian Patterns in Carbon Monoxide Concentrations

The diurnal variation in winter time, composite, hourly CO concentrations is shown in Figure 3-6 from 1987 through 1996 (Cohen and Iwamiya, 1998). It can be seen that hourly mean CO concentrations peak during the morning rush hours (7 to 9 a.m.). This peak results mainly from CO emitted into the relatively shallow morning boundary layer by motor vehicles (e.g., Fujita et al., 1992). The CO mixing ratios decline towards mid-afternoon, as the height of the

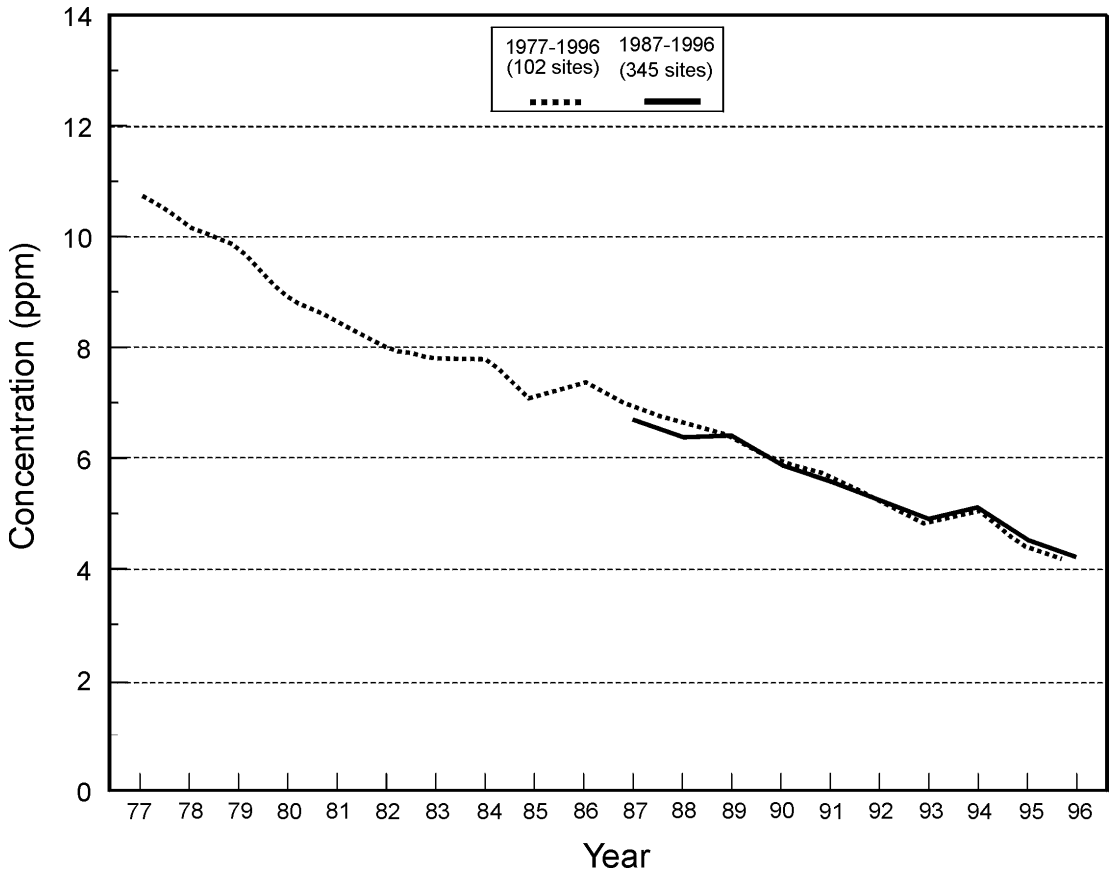

Figure 3-3. Nationwide composite average of the annual second highest 8-h CO concentrations, 1977 to 1996.

Source: U.S. Environmental Protection Agency (1998).

atmospheric mixing layer increases and then increase again with the onset of the evening rush hour. Carbon monoxide levels fall off less rapidly after the afternoon peak because the mixing layer height decreases during evening and nighttime. There is a general decrease in CO levels during the night because of a lack of fresh emissions combined with processes such as mixing with CO-poor areas and deposition to the surface. The downward trend in CO concentrations from 1987 to 1996 is apparent for all times of the day. Especially notable is the decease in 7 to 9 a.m. CO concentrations, which is consistent with the decrease in motor vehicle emissions that was noted earlier for the same period. During the period from 1987 to 1996, the 24-h nationwide composite average CO concentration decreased from 2.0 to 1.2 ppm.

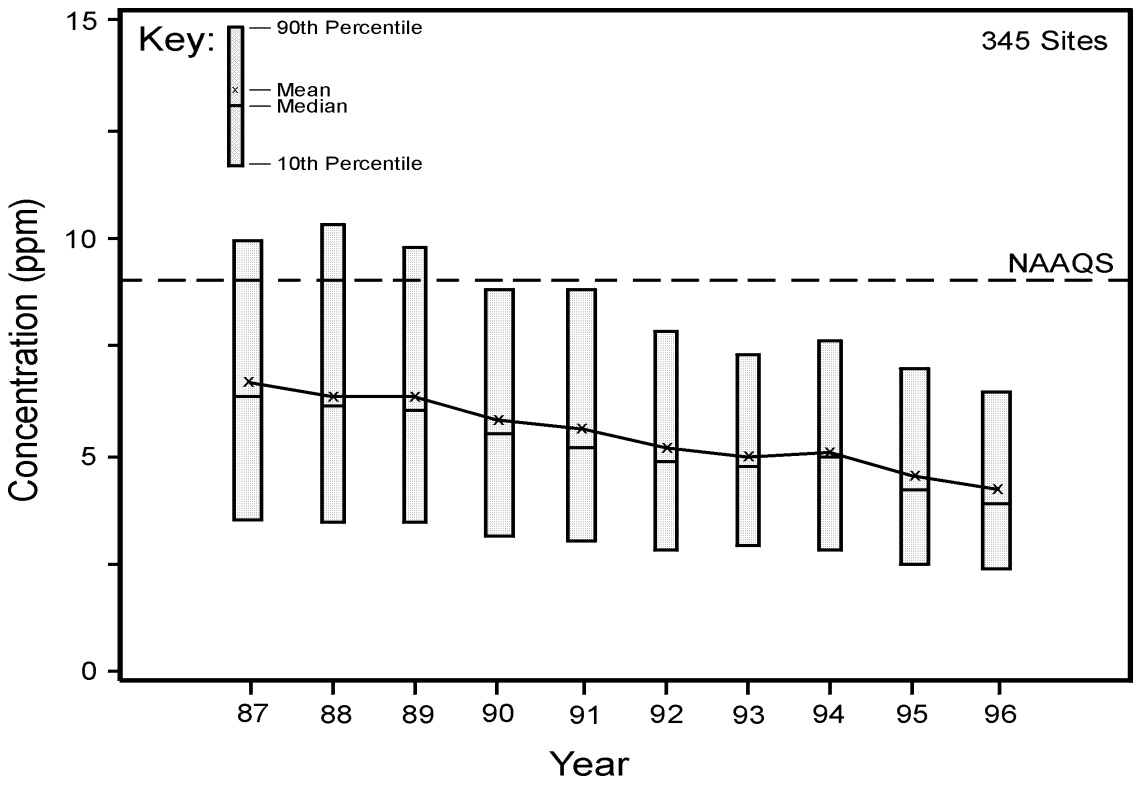

Figure 3-4. Variability in the annual second highest 8-h CO concentrations across all sites in the United States, 1987 to 1996.

Source: U.S. Environmental Protection Agency (1998).

The diurnal pattern of 8-h average CO concentrations that exceed 9.5 ppm is somewhat different from the hourly average concentration pattern shown in Figure 3-6. One way to estimate the time of day when 8-h average CO concentrations are likely to exceed 9.5 ppm is to sum the numbers of these events by hour of the day over the course of a year. Hourly average CO data were taken from AIRS to construct running 8-h averages for 1996.

In the previous AQCD for CO (U.S. Environmental Protection Agency, 1991b), which summarized ambient monitoring data through 1988, six stations in six major cities, with prominent patterns of 8-h exceedances, were selected to demonstrate the variability in the circadian patterns of exceedances using the above technique; some peaked in daylight hours and

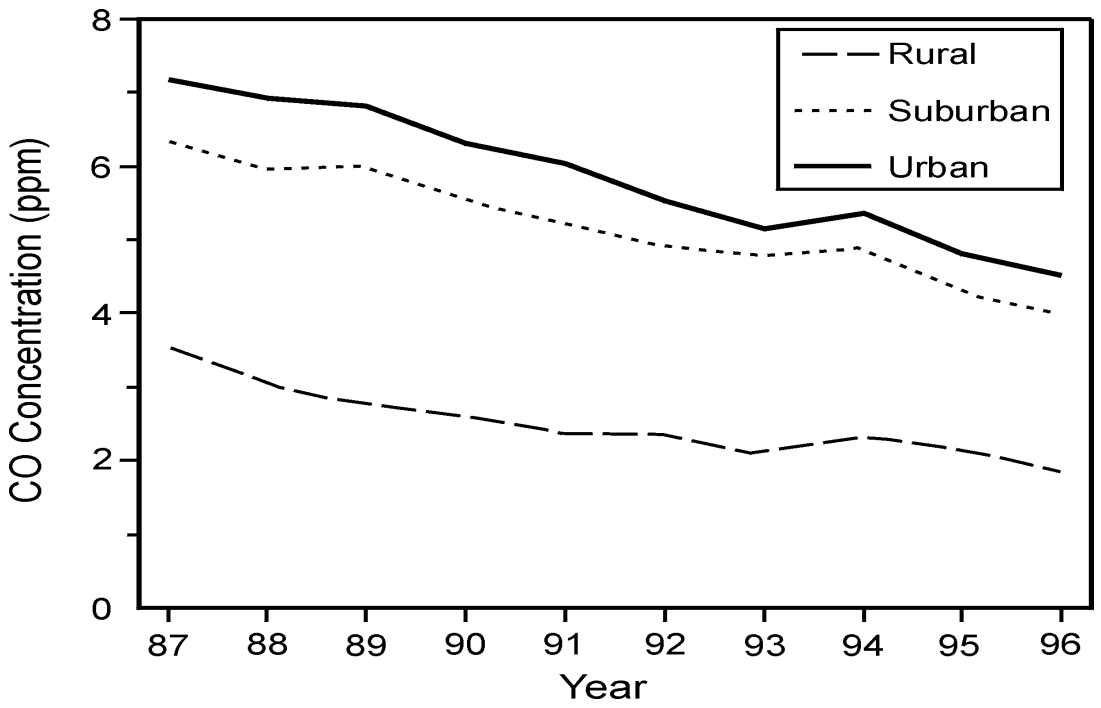

Figure 3-5. Composite average of the annual second highest 8-h CO concentrations for rural, suburban, and urban sites, 1987 to 1996.

Source: U.S. Environmental Protection Agency (1998).

others in nighttime hours. Five of those six monitors are still in operation; Table 3-5 summarizes and compares their 1988 record with 1996 data.

Note that in Table 3-5 and in the analysis of 1996 data shown in Table 3-6 a "running-average" exceedance is defined as any hour that culminates in an 8-h average higher than 9.5 ppm. This definition differs from that used in the construction of Table 3-4 in that the number of nonoverlapping exceedances was used in Table 3-4. A formal violation of the 8-h standard occurs when, in a given year, a second 8-h average exceeds 9.5 ppm but does not overlap the first 8-h exceedance. Exceedances culminating in any hour are treated here because an individual's cumulative exposure to a level greater than 9.5 ppm could occur in any hour.

At the Lynwood station, the running-average exceedances have declined from 392 in 1988 to 110 in 1996 (22 nonoverlapping exceedances); the majority of exceedances in 1996 occurred

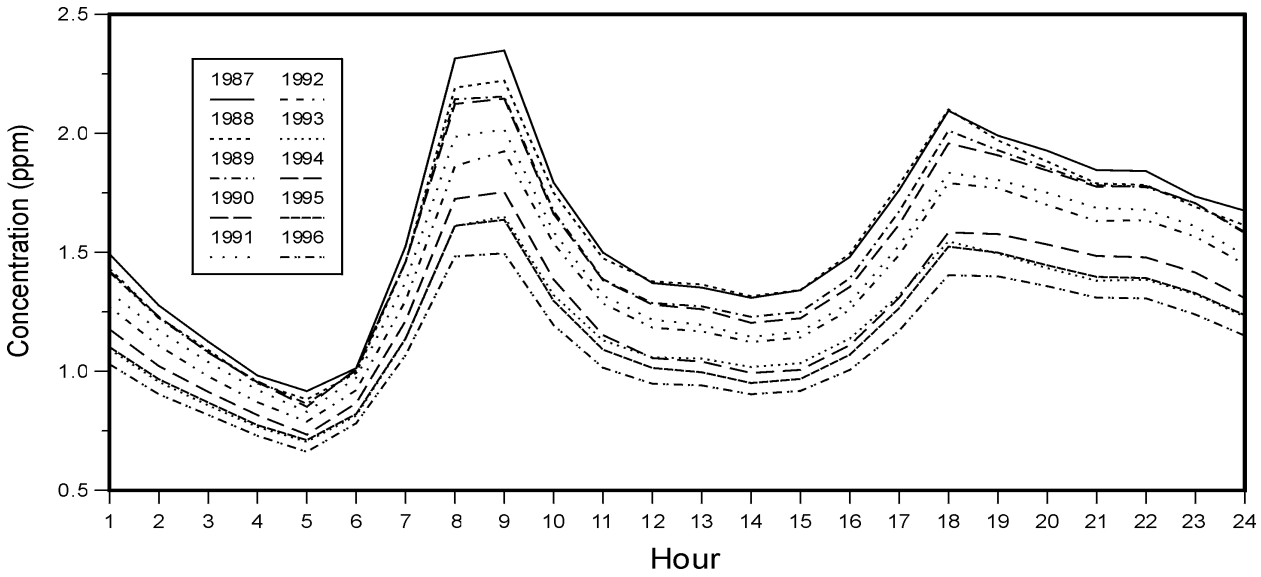

Figure 3-6. Diurnal variation of nationwide composite hourly average CO concentrations for winter (December to February), from 1987 to 1996.

Source: Cohen and Iwamiya (1998).

TABLE 3-5. RUNNING-AVERAGE EXCEEDANCES OF THE 9 ppm 8-HOUR CARBON MONOXIDE STANDARD, 1988 VERSUS 1996

Location	AIRS Site ID No.	1988	1996
Lynwood, CA	06 037 1301	392	110
Hawthorne, CA	06 037 5001	163	19
Las Vegas, NV	32 003 0557	102	3
New York City, NY	36 061 0081	123	NA[a]
Steubenville, OH	39 081 1012	152	0
Spokane, WA	53 056 0040	169	1

[a]NA = not available.

TABLE 3-6. ANNUAL CIRCADIAN PATTERN OF 8-HOUR AVERAGE CARBON MONOXIDE CONCENTRATIONS CULMINATING IN VALUES GREATER THAN 9.5 ppm IN LYNWOOD AND HAWTHORNE, CA, DURING 1996

Ending of 8-h Period	Lynwood	Hawthorne
Midnight	9	0
1 a.m.	9	0
2 a.m.	10	2
3 a.m.	11	3
4 a.m.[a]	8	4
5 a.m.	7	4
6 a.m.	8	2
7 a.m.	7	2
8 a.m.	8	1
9 a.m.	8	1
10 a.m.	6	0
11 a.m.	3	0
Noon	2	0
1 p.m.	1	0
2 p.m.	1	0
3 p.m.	0	0
4 p.m.	0	0
5 p.m.	0	0
6 p.m.	0	0
7 p.m.	0	0
8 p.m.	1	0
9 p.m.	1	0
10 p.m.	4	0
11 p.m.	6	0
Total	110	19

[a]Calibrations normally are done at 4 a.m., thus values are interpolated.

in the hours between midnight and sunrise, as they had in 1988. They occurred in the months of January, February, November, and December.

At the Hawthorne station, running-average exceedances have declined from 163 in 1988 to 19 in 1996 (five nonoverlapping exceedances). These are clustered around sunrise when dispersion is most likely to be at a minimum. The exceedances at this station also occur in the winter quarter.

Only a small number of stations have several running-average exceedances; however, these recurrent high levels are attributed to unusual local situations. A prime example is the monitoring station in Calexico, which is several blocks away from a major U.S.-Mexico border crossing and the route leading to it; nine nonoverlapping exceedances were recorded in 1996. Reportedly, there are often long lines of idling vehicles waiting to cross the border, including vehicles of Mexican registration that are not equipped with the emission control equipment required on vehicles sold in the United States. Such situations will need to be addressed on a local, case-by-case basis.

3.5 SOURCES, EMISSIONS, AND CONCENTRATIONS OF CARBON MONOXIDE IN INDOOR ENVIRONMENTS

The general U.S. population spends up to 85% of its time indoors. In recent years, more emphasis has been placed on the evaluation of pollutant sources, emissions, and concentrations in indoor environments to aid in the evaluation of total human exposure. It is particularly important to evaluate carbon monoxide concentrations in indoor environments because indoor exposure may represent a significant portion of the total CO exposure.

The proceeding sections focus on the sources and emission rates of CO in indoor environments. Concentrations of CO in various indoor environments also will be discussed. Emphasis is placed on the evaluation of those currently accepted uses of combustion appliances and consumer products and the resulting CO emissions and concentrations. Accidental or unintentional sources and concentrations will be mentioned only briefly.

3.5.1 Unvented Combustion Sources and Estimated Emissions Rates

Carbon monoxide occurs in indoor environments directly through emissions from various indoor combustion sources or indirectly as a result of infiltration or ventilation from outdoor sources. Unvented, partially vented, and improperly vented combustion appliances and consumer products represent the primary sources of CO emissions in the indoor environment. Table 3-7 lists the various sources of CO in the indoor environment. Emissions of CO from use of combustion appliances will depend on several factors. These factors include the source (e.g.,

TABLE 3-7. SOURCES OF CARBON MONOXIDE IN THE INDOOR ENVIRONMENT

Source	Comments
Outdoor (ambient air)	Carbon monoxide is produced as a primary pollutant during the combustion of fossil and biomass fuel and as a secondary gas in the photochemical oxidation of methane and other organic compounds in the atmosphere. Carbon monoxide enters indoor compartments through mechanical ventilation systems and infiltration through the building envelope.
Gas cooking ranges	Emissions of CO from gas ranges depends on the use pattern, unit operating condition, and fuel consumption rate. Gas ranges with standing pilots emit more CO than do units with electronic pilots. Poorly tuned burners emit more CO than well-tuned burners.
Gas space heaters	Emissions of CO from gas space heaters are affected by the fuel type and consumption rate, type of burner (convective, radiant, or catalytic), operating condition, and duration of use.
Kerosene space heaters	Emissions vary based on unit type (convective, radiant, or two-stage), operating condition, and duration of use.
Environmental tobacco smoke	The majority of CO entering indoor compartments from the combustion of tobacco products is through sidestream smoke.
Fireplaces and woodstoves	Carbon monoxide is emitted during fire start-ups, leaks in stoves and pipes, and during backdrafting resulting from depressurization.
Gas furnaces, clothes dryers, and water heaters	Gas furnaces and dryers generally are vented and do not emit CO in the indoor environment unless the unit is malfunctioning.
Motor vehicles	Operating motor vehicles in enclosed spaces can be significant sources of CO in indoor environments.

gas cooking stoves, unvented space heaters, woodstoves, fireplaces), appliance design, manufacturer, type of fuel used, fuel consumption rate, use pattern, and operating condition.

Two different approaches are used to evaluate CO emissions for combustion appliances: the direct or sampling-hood approach and the mass-balance/chamber approach. For details on these two approaches, see U.S. Environmental Protection Agency (1991b).

3.5.1.1 Gas Cooking Ranges and Ovens and Furnaces

Emissions of CO from gas top ranges will depend of the use pattern, operating condition, fuel consumption rate, and air infiltration into the microenvironment. Average annual household fuel consumption has been estimated at 5,000 ft^3 for ranges with standing pilots (Johnson et al.,

1992). Menkedick et al. (1993) reported annual household fuel consumption of 2,180 ft^3 (±890 ft^3) for burners, based on actual fuel consumption measurements taken on 103 gas ranges individually metered over a 2-year period in Illinois. Fuel consumption for burner and standing pilots was 5,710 ft^3 (±1,830 ft^3). The average fuel consumption also was affected by the age of the occupants (older adults used the range more frequently for preparing meals than did young adults) and the presence or absence of a standing pilot, and it showed a seasonal trend. Figure 3-7 illustrates the seasonal trend for daily gas stove fuel consumption. Carbon monoxide emissions from gas ranges (burners and ovens) are summarized in Table 3-8 as a function of operating conditions.

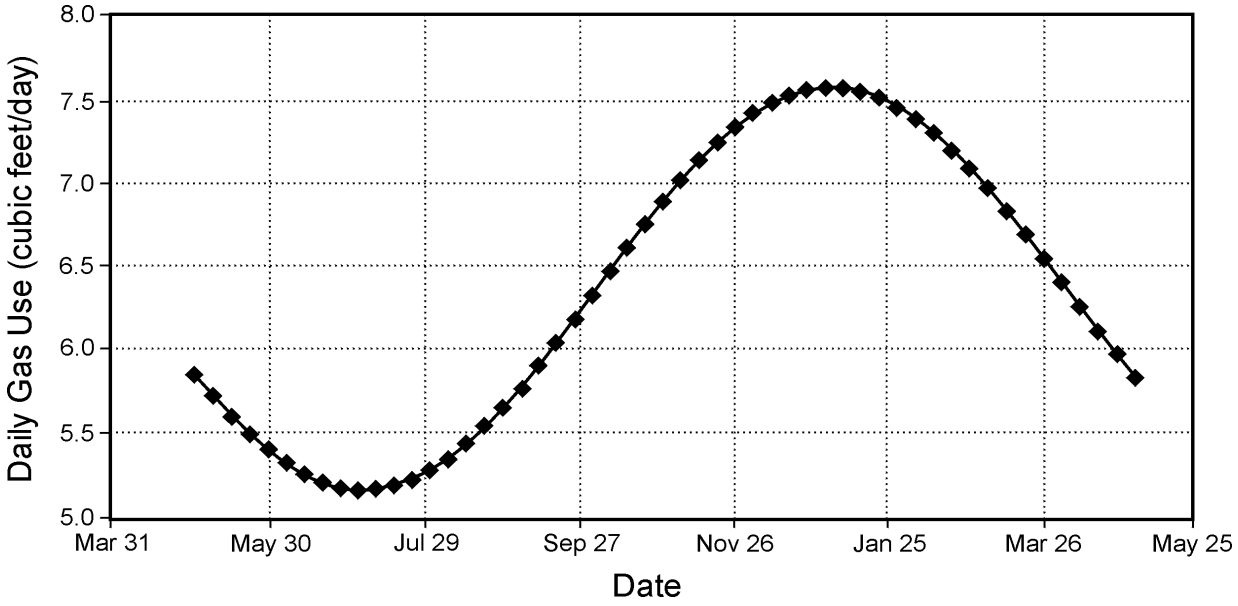

Figure 3-7. Annual trend in gas stove burner fuel use.

Source: Menkedick et al. (1993).

Carbon monoxide emissions from vented gas furnaces are generally negligible (Borrazzo et al., 1987); however, emissions may vary based on the working condition and efficiency of the unit. Ryan and McCrillis (1994) evaluated CO emissions from two gas furnaces; one furnace

TABLE 3-8. RANGES IN AVERAGE CARBON MONOXIDE EMISSION RATES FOR RESIDENTIAL SOURCES

Unit Type	Fuel Type[a]	Fuel Consumption Rate (kJ/min[b])	Flame	Ranges in Average Emission Rates (μg/kJ)	Source
Gas Ranges[c]					
Top burners	NG	—	Blue	16-200	Himmel and DeWerth (1974) Traynor et al. (1982) Borrazzo et al. (1987) Cote et al. (1974) Moschandreas et al. (1985) Spicer and Billick (1996) Billick et al. (1984)
		—	Yellow-tipping	92-197	Himmel and DeWerth (1974) Cote et al. (1974) Moschandreas et al. (1985)
Ovens	NG	—	Blue	16-622	Himmel and DeWerth (1974) Traynor et al. (1982) Borrazzo et al. (1987)
		—	Yellow-tipping	62	Himmel and DeWerth (1974)
Burner pilots	NG	—	Blue	28-56	Himmel and DeWerth (1974)
Oven pilots	NG	—	Blue	209-322	Himmel and DeWerth (1974)
Gas Space Heaters					
Convective	NG	131-784	Blue	3-192	Traynor et al. (1984, 1985) Moschandreas et al. (1985) Thrasher and DeWerth (1979) Zawacki et al. (1984) Hedrick and Krug (1995) Spicer and Billick (1996) Zawacki et al. (1986)
	P	351-703	Blue	16	Traynor et al. (1984, 1985) Zawacki et al. (1986)
Infrared	NG	260-368	Infrared	5-69	Traynor et al. (1984, 1985) Moschandreas et al. (1985) Spicer and Billick (1996) Zawacki et al. (1986)
	P	258-264	Infrared	4-45	Traynor et al. (1984, 1985) Zawacki et al. (1986)
Catalytic	NG	207	Blue	9-14	Moschandreas et al. (1985)

TABLE 3-8 (cont'd). RANGES IN AVERAGE CARBON MONOXIDE EMISSION RATES FOR RESIDENTIAL SOURCES

Unit Type	Fuel Type[a]	Fuel Consumption Rate (kJ/min[b])	Flame	Ranges in Average Emission Rates (μg/kJ)	Source
Kerosene Heaters					
Convective		37-193	—	4-272	Leaderer (1982) Traynor et al. (1983) Moschandreas et al. (1985) Traynor et al. (1990) Mumford et al. (1991)
Radiant		85-168	—	43-264	Leaderer (1982) Traynor et al. (1983) Moschandreas et al. (1985) Traynor et al. (1990) Mumford et al. (1991)
Two-stage		132-182	—	54-9	Traynor et al. (1983)
Furnaces	NG	—	—	6->1,000	Ryan and McCrillis (1994)
Woodstoves and Fireplaces	—	—	—	2.0-1,748.6 g/h	Traynor et al. (1987) Mueller Associates (1985) Jaasma et al. (1995)
Tobacco Smoke					
Cigarette		—	—	<0.5-78 mg/cigarette	National Research Council (1986) Klepeis et al. (1995, 1996) Ott et al. (1992) Löfroth et al. (1989)
Cigar		—	—	130-200 mg/g[d]	Klepeis et al. (1999)

[a]NG = natural gas, P = propane.
[b]One kJ (kiloJoule) is the equivalent of 3.485 ft^3 of natural gas.
[c]Fuel consumption rates not provided for most studies.
[d]Emission rate based on cigar mass of 4.9 to 8.8 g.

was an older model with an energy efficiency of 60 to 70% and the other was a newer furnace with an energy efficiency of 94%. The furnaces were operated for 10 min then allowed to cool for 5 to 10 min. The cycle was repeated 12 to 18 times during the course of each test. The CO emission rate was >1,000 μg/kJ for the older unit, compared with 6 μg/kJ for the newer, more efficient model.

3.5.1.2 Emissions from Unvented Space Heaters

Carbon monoxide emissions from unvented space heaters will vary as a function of appliance design and condition, manner of operation, and fuel type and consumption rate. Higher emissions have been reported for infrared gas space heaters versus the convective or catalytic units. Other factors that may affect emissions from unvented space heaters include air circulation near the heater, primary aeration, air infiltration and exchange, and use pattern.

Tables 7-5 and 7-6 in the previous AQCD for CO (U.S. Environmental Protection Agency, 1991b) summarize the available emissions data from earlier studies on gas and kerosene space heaters. The available data show variability in CO emissions based on unit design, maintenance, and the type of fuel used. Several recent studies on CO emissions evaluated emissions from prototype units; a brief discussion of the results of these studies follows.

The Gas Research Institute evaluated the emissions of CO, NO, NO_2, and unburned hydrocarbons (UHC) from a vented and an unvented prototype space heater. The heater design was a Pyrocore ceramic fiber radiant burner. Emission goals were 5.5 μg/kJ (20 ppm) CO, 4.0 μg/kJ (13.5 ppm) NO, 0.7 μg/kJ (1.5 ppm) NO_2, and 0.8 μg/kJ (5.0 ppm) UHC. Both units had cross-flow room air circulation fans. The samples collected from the unvented space heater were corrected for dilution effects. Emission rates were estimated using a single-equation mass-balance model. Carbon monoxide emissions ranged from 0.6 to >27.5 μg/kJ (2.0 to >100 ppm), based on the amount of excess air and the firing rate values (Duret and Tidball, 1990).

Apte and Traynor (1993) determined the emission rates of combustion pollutants for a radiant-fiber-matrix gas burner prototype. Fuel consumption ranged from 333 to 527 kJ/min. Carbon monoxide emission rates were generally low, with an average of 3.0 μg/kJ when the unit was operated with 10% excess air, and 7.4 μg/kJ with 40% excess air.

The Institute of Gas Technology, along with Maxon Corporation, designed and tested an air heater based on the cyclonic combustion concept. This technology included premixed high-excess air, and cyclonic combustion with flame stabilization, in conjunction with optimized nozzle velocity control. Carbon monoxide emissions were 1.6 to 5.9 μg/kJ (1.0 to 3.6 ppm at 15% O_2) (Xiong et al., 1991). Carbon monoxide emissions from unvented space heaters are summarized in Table 3-8 as a function of unit type, fuel type and consumption rate, and appliance operating condition.

3.5.1.3 Woodstoves and Fireplaces

A few studies have evaluated the emission of CO from woodstove or fireplace use. Carbon monoxide may enter the indoor environment during fire start-up and tending and through leaks in the stove or venting system. Carbon monoxide emissions are higher during the first stage of a fire because of increasing amounts of fuel being burned and inadequate temperature conditions. Such intermittent emissions makes it difficult to accurately determine CO emission rates. In an early study by Traynor et al. (1987), the average CO source strength for three airtight stoves was found to be 0.13 to 0.175 g/h (104 to 140 cm^3/h), whereas the average source strengths for a nonairtight stove ranged from 0.275 to 2.25 g/h (220 to 1,800 cm^3/h). Mueller Associates (1985) reported CO emission ranges of 0.07 to 0.375 g/h for wood heaters. Jaasma et al. (1995) conducted a study designed to evaluate the effectiveness of custom-built glass doors for fireplaces in reducing CO emissions under conditions of negative pressure. The glass doors decreased spillage of CO; however, decreasing the leakiness of the glass doors did not always reduce CO spillage. Tests with the glass doors closed had CO emission rates of 2 to 36 g/h (highest levels represented leaking glass doors). Carbon monoxide emissions on the order of 70 g/h were noted for glass- door-opened tests under negative pressure.

Carbon monoxide also may enter the indoor environment through backdrafting when the natural draft is overcome by depressurization. Depressurization generally occurs during fire start-up, but also may occur during operation of other equipment such as kitchen and bathroom exhaust fans and clothes dryers. Nagda et al. (1996) summarized the results of several studies on emissions of pollutants into living compartments as a result of house depressurization. Carbon monoxide emissions were found to be insignificant. Tiegs and Bighouse (1994) evaluated CO spillage from a woodstove under chamber and in-house conditions. They reported CO leakage into the indoor environment by nonairtight woodstoves during conditions of negative pressure.

3.5.1.4 Environmental Tobacco Smoke

Carbon monoxide emissions from the combustion of tobacco occurs in the indoor environment when smokers exhale the inhaled or mainstream smoke and from the emission of sidestream smoke from smoldering tobacco products. The majority of the CO comes from the sidestream smoke. The amount of CO emitted will vary based on the type of tobacco product

(cigarette/cigar), the degree to which tobacco is actively smoked, and the amount of smoke being absorbed by the lungs (Klepeis et al., 1996; Akbar-Khanzadeh and Greco, 1996).

The National Academy of Science report on environmental tobacco smoke estimated a CO emission range of 40 to 67 mg per cigarette (National Research Council, 1986). The Federal Trade Commission compiled data on 933 varieties of cigarette manufactured and sold in the United States in 1992. These data were provided by the various cigarette manufacturers. Carbon monoxide emission rates for the brands of cigarettes reported ranged from <0.5 to 23.0 mg per cigarette (cigarettes emitting 23.0 mg were unfiltered brands) (Federal Trade Commission, 1994). Klepeis et al. (1995, 1996) measured CO concentrations in airport smoking lounges under real life conditions. They estimated CO emissions to be 78 mg per cigarette on the basis of an average CO emission rate of 11.1 mg/min and a smoking duration of 7 min. An estimated total CO emission rate of 81.2 mg for three cigarettes was reported by Ott et al. (1992). Löfroth et al. (1989) estimated an emission rate of 67 mg per cigarette based on a cigarette weight of ≈1.2 g and a smoking duration of 12 min. Large cigars emit substantially more CO than do cigarettes. Emission rates of 130 to 200 mg CO/g (mass smoked) were reported by Klepeis et al. (1999) (smoked by machine and by a person). Cigar mass ranged from 4.9 to 8.8 g, and the smoking time was 7.8 to 24 min for the machine-smoked test and 76 min for the test measuring emissions for a cigar being smoked by a person.

3.5.2 Indoor Concentrations of Carbon Monoxide

3.5.2.1 Factors Affecting Carbon Monoxide Concentrations

A number of factors can affect indoor CO concentrations: the presence of a source and its use pattern, pollutant emission rate, ambient air concentrations, infiltration through the building envelope, air exchange rate (AER), building volume, air mixing within the indoor compartments, and the presence and effectiveness of a pollutant removal system.

The major sources of CO in residential environments are unvented gas or kerosene appliances. Because gas cooking ranges are used intermittently, it is not likely that the use of gas ranges would result in substantial increases in CO over long periods of time, except in households where gas cooking stoves are used improperly as a primary or secondary source of heat. Also, the replacement of gas ranges with standing pilots lights with ranges with electronic pilots likely will have an influence on the CO concentrations from gas range usage. Koontz et al.

(1992) reported the results of a survey conducted in 1985 and 1991. The purposes of the survey were to determine the prevalence of kitchen fans and the factors affecting their use and to determine the impact of other cooking appliances (i.e., microwave ovens, toaster ovens, hot plates) on the use of the range for cooking. The authors reported a 35% increase in the use of gas ranges without standing pilot lights between 1985 and 1991 and a 20% reduction in the use of stoves for cooking. Ninety-five percent of the households surveyed reported having another form of cooking appliance in addition to the gas range, and, of this number, 55 to 65% reported using the stove less often. There were, however, more people using a gas range for purposes of supplemental heating than there were using electric ranges for that purpose (11% versus 3.6%). Estimates of gas cooking stove usage range from 30 to 60 min/day. Table 3-9 contains information on the prevalence of gas cooking stoves in the United States.

Data from the National Health and Nutrition Examination Survey estimated that 13.7 million adults used unvented combustion space heaters between 1988 and 1994. Based on the information obtained in the survey, an estimated 13.2% of the adult population in the southern United States used unvented combustion space heaters. An estimated 5.9% of the adult population in the Midwest, 4.2% in the Northeast, and 2.5% in the West used unvented space heaters (Figure 3-8) (Slack and Heumann, 1997). The use of more combustion space heaters in the South also was reported in earlier studies by U.S. Department of Housing and Urban Development (1987), U.S. Environmental Protection Agency (1992), and Williams et al. (1992). This may be because, in areas with relatively mild winters, combustion space heaters are used frequently as the primary source of heat. The U.S. Environmental Protection Agency (1990) estimated that kerosene heaters are used 16.7 h/day in southern states and, in regions where the heaters are used as secondary heat sources, estimated a use range of 2.6 to 10.7 h.

The AER, the balance of the flow of air in and out of a microenvironment, is based on the fraction of air that enters the microenvironment through infiltration through unintentional openings in the building envelope, natural ventilation through any designed opening in the building envelope (doors, windows), and forced ventilation systems. Infiltration is the dominant mechanism for residential air exchange. Forced ventilation is typically the dominant mechanism for air exchange in nonresidential buildings. Natural ventilation, airflow through doors and opened windows, is seasonal (Koontz and Rector, 1995). Air exchange rates for residential

TABLE 3-9. PREVALENCE OF GAS COOKING RANGES

Fuel	Region	Number of Households (total)	Percentage of Households	Comments	Reference
Gas	U.S. households (1985)	959 (2,323)	41	Twenty percent of households had electronic pilots in 1985. Twenty-seven percent of the households had electronic pilots in 1991, based on 886 respondents from the 1985 survey.	Koontz et al. (1992)
Natural gas	U.S. households (1993)	33,813,000 (94,363,000)	36		U.S. Census Bureau (1998)
Natural gas	California (1991, 1992)	150 (293)	52	Twenty-five percent of households had electronic pilots; 3% had combination pilots.	Wilson et al. (1993)
Natural gas	Los Angeles, CA (1995)	2,614,000 (3,165,200)	82		U.S. Census Bureau (1998)
	Denver, CO (1995)	151,300 (770,600)	20		
Natural gas	Washington, DC (1982-1993)	609,029 (953,714)	64	Results are based on a survey of 1987 participants in Washington and 1,139 participants in Denver.	Johnson (1984) Hartwell et al. (1984)
	Denver, CO (1982-1983)	85,542 (345,163)	25		

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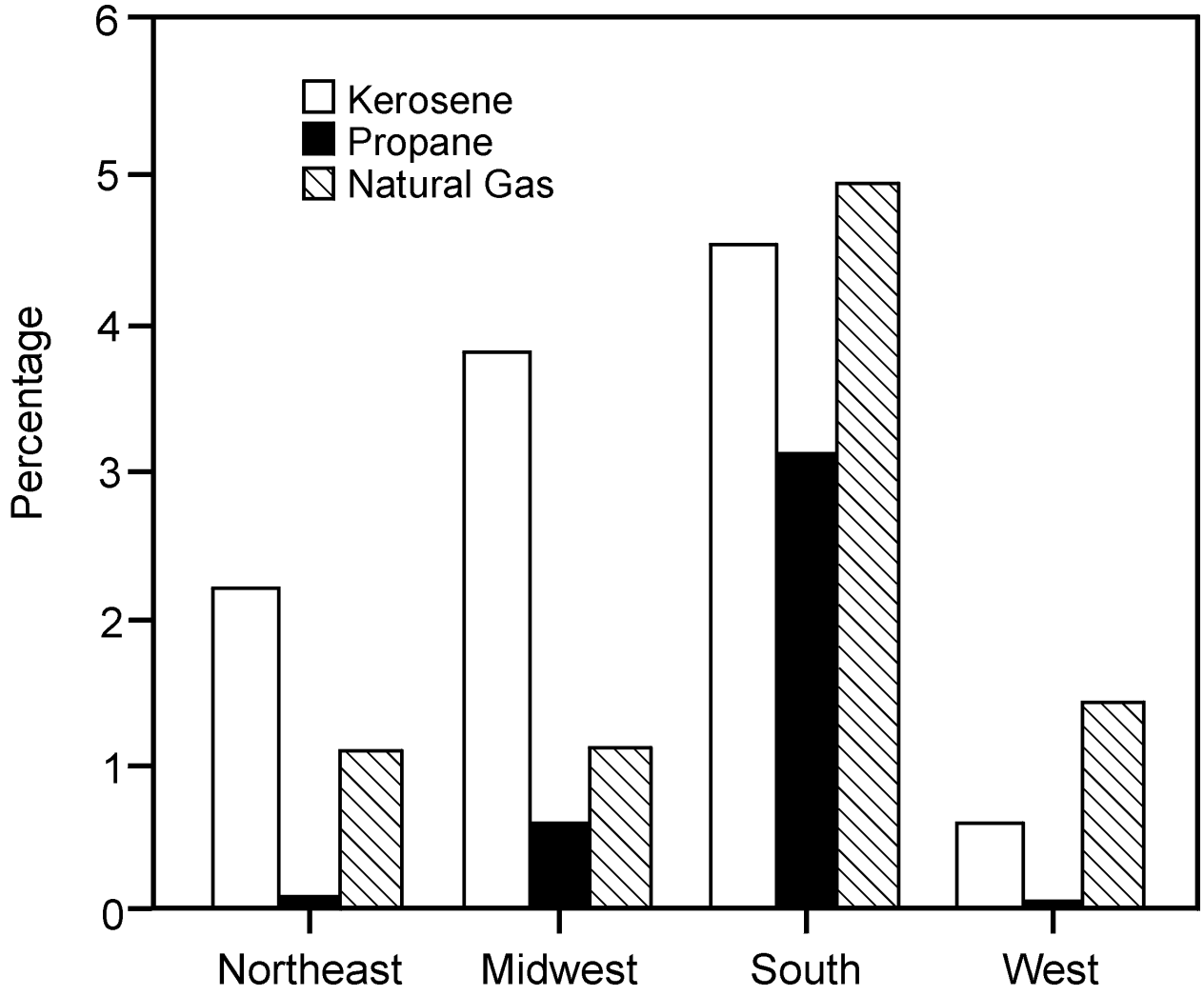

Figure 3-8. Percentage of U.S. households using unvented combustion heaters, by type of fuel, stratified by region (Third National Health and Nutrition Examination Survey, 1988 to 1994).

Source: Slack and Heumann (1997).

buildings are in Table 3-10. Air exchange rates vary depending on the outside temperature, geographical location, type of cooking fuel used, type of heating system used, and building type (Colome et al., 1994).

TABLE 3-10. RESIDENTIAL AIR EXCHANGE RATES

Geographic Location	Sample Size	AER (h^{-1})	Type	Standard Deviation	Reference
Riverside, CA	175	0.87 (day) 0.75 (night)	Arithmetic	—	Sheldon et al. (1992)
Los Angeles, CA	571 (1 week)	0.62 0.78 (March)	Geometric Arithmetic	1.95 0.63	Wilson et al. (1996)
	426 (1 week)	1.05 1.51 (July)	Geometric Arithmetic	2.39 1.47	
	372 (2 days)	0.47 0.58 (January)	Geometric Arithmetic	1.97 0.47	
	75 (2 days)	0.63 0.79 (winter)	Geometric Arithmetic	1.97 0.57	
Northern California	128 (2 days)	0.41 (winter)	Arithmetic	0.34	
San Diego, CA	85 (2 days)	0.46 (winter)	Arithmetic	0.34	
United States	2,844	0.76 (all seasons)	Arithmetic	0.88	Murray and Burmaster (1995)
		0.55 (winter)		0.46	
		0.65 (spring)		0.57	
		1.50 (summer)		1.53	
		0.41 (fall)		0.58	
California	293	0.58	Arithmetic	0.43	Colome et al. (1994)
New York (Suffolk and Onondaga Counties)	245	0.59	Arithmetic	0.03	Research Triangle Institute (1990)

Air exchange rates for nonresidential microenvironments also have been measured. Lagus Applied Technology, Inc. (1995) reported AERs for 49 nonresidential buildings (14 schools, 22 offices, and 13 retail establishments) in California. Average mean (median) AERs 2.45 (2.24), 1.35 (1.09), and 2.22 (1.79)/h for schools, offices, and retail establishments,

respectively. Air infiltration rates for 40 of the 49 buildings were 0.32, 0.31, 1.12/h for schools, offices, and retail establishments, respectively. Air exchange rates for 40 nonresidential buildings in Oregon and Washington (Turk et al., 1989) averaged 1.5/h (mean [median = 1.3/h]). Park et al. (1998) reported AERs for three stationary cars (cars varied by age) under different ventilation conditions. Air exchange rates ranged from 1.0 to 3.0/h for windows closed and fan off, 13.3 to 23.5/h for window opened and fan off, 1.8 to 3.7/h for window closed and fan on recirculation (two cars tested), and 36.2 to 47.5/h for windows closed and fan on fresh air (one car tested). An average AER of 13.1/h was reported by Ott et al. (1992) for a station wagon moving at 20 mph with the windows closed.

3.5.2.2 Models for Carbon Monoxide Concentrations

The concentration of CO in indoor environments will depend on the source emission rate, source use characteristics, building characteristics, outdoor concentrations and the rate of penetration into indoor compartments, distribution between compartments, and the pollutant removal rate.

Indoor concentrations of CO can be estimated using the mass-balance model. The mass-balance model estimates the concentration of a pollutant over time. The simplest form of the model is represented by the following differential equation for a perfectly mixed microenvironment.

$$\frac{dC_{IN}}{dt} = (1 - F_B)\, v\, C_{OUT} + \frac{S}{(c\,V)} - v\, C_{IN} - F_d C_{IN} - \frac{q\, F\, C_{IN}}{(c\,V)}, \qquad (3\text{-}1)$$

where C_{IN} is the indoor pollutant concentration in mass per unit volume, F_B is the deposition fraction of outdoor pollutant infiltration through the building envelope, v is the AER in 1/time, C_{OUT} is the outdoor pollutant concentration in mass/volume, S is the indoor pollutant source emission rate in mass/time, c is the effective indoor volume fraction and is assumed to equal 1, V is the volume of microenvironment (national mean residential volume is 380 m^3; Murray and Burmaster, 1995), F_d is the coefficient for decay in 1/time (zero for CO), q is the flow rate into the air cleaning device in volume/time, and F is the efficiency of the air cleaning device.

Equation 3-1 can be simplified because the deposition and decay rates for CO are negligible, and assuming the absence of an air cleaning device, the equation becomes

$$\frac{dC_{IN}}{dt} = vC_{OUT} + \frac{S}{V} - vC_{IN}. \tag{3-2}$$

A more in-depth discussion of the mass-balance model may be found in U.S. Environmental Protection Agency (1991b) and Nagda et al. (1987).

Traynor et al. (1989) used a macromodel to predict CO concentrations in residential environments for one pollutant source. Model inputs included ambient air concentrations, source emission rates and usage characteristics, compartment volume, AERs, and outside temperatures. The macromodel combined the steady-state version of the mass-balance model used in indoor air quality studies, a source-usage model for space heating appliances, and an air exchange model. A combination of the Monte Carlo and deterministic techniques was used to predict indoor concentration distributions.

The mass-balance model for CO is expressed as

$$C_{IN} = C_{OUT} + S / vV. \tag{3-3}$$

The source-strength model was expressed as

$$S = QEF_v, \tag{3-4}$$

where Q is the source usage rate, same as house heating requirements for space heaters, in kiloJoules per hour or cigarettes per hour; E is the source emission rate in micrograms per kiloJoule or micrograms per cigarette; and F_v is the appliance venting factor (unitless; 1 = 100% unvented). The space heater source usage rate (Q) is based on the heating requirements of the heater and is equal to the heat loss through conduction and infiltration minus the “free” heat, modified by the unit efficiency and the occupant life-style factor (under- or overheating and heating only certain rooms). The source usage rate was expressed as

$$Q = \frac{b}{\epsilon}\left(UA\Delta T + vVq\Delta T - Q_f\right), \tag{3-5}$$

where b is the life-style factor (unitless), ϵ is the appliance efficiency (unitless; 1 = 100% efficient), U is the building envelope thermal conductance in kiloJoules per hour per square meter per degree centrigrade, $UA\Delta T$ accounts for the conduction losses through the building envelope, A is the total house surface area including ceiling and floor in square meters, ΔT is the indoor/outdoor temperature difference in degrees centigrade, V is the house volume in cubic meters, q is the heat content of dry air (1.2 kJ/m^3 °C), and Q_f is the house free heat in kiloJoules per hour. House free heat includes solar heat gain, internal-appliance heat, and human generated heat; it was expressed as

$$Q_f = Q_s + Q_{appl} + Q_{people}, \tag{3-6}$$

where Q_s is the solar heat gain in kiloJoules per hour, Q_{appl} is the interior heat generated by appliances (the American Society of Heating, Refrigerating, and Air Conditioning Engineers standard is 2,000 kJ/h), and Q_{people} is the interior heat generated by people (estimated to be 1,000 kJ/h for a house with two adults and two children). The air exchange model included an additional term to account for increased AERs because of the use of woodstoves and was expressed as

$$v = \frac{\left(ELA^2 f_s^2 \Delta T + ELA^2 f_w^2 u^2 + Z^2_{appl}\right)^{0.5}}{V} \tag{3-7}$$

and

$$ELA = SLA \times A_f,$$

where ELA is the effective leakage area in square meters, f_s is the reference stack parameter for the infiltration model (430 m/h °C$^{0.5}$), f_w is the reference wind parameter for the infiltration model (120,000 m^2/km^2), u is the wind speed in kilometers per hour, Z_{appl} is the woodstove-flue

flow rate (76 m^3/h), SLA is the specific leakage area (unitless), and A_f is the floor surface area in square meters. Based on the modeled results, the use of kerosene heaters, unvented gas space heaters, and gas ovens and ranges for heating produced the highest concentrations of CO in the indoor environment (see Figure 3-9). The model input parameters are given in Table 3-11.

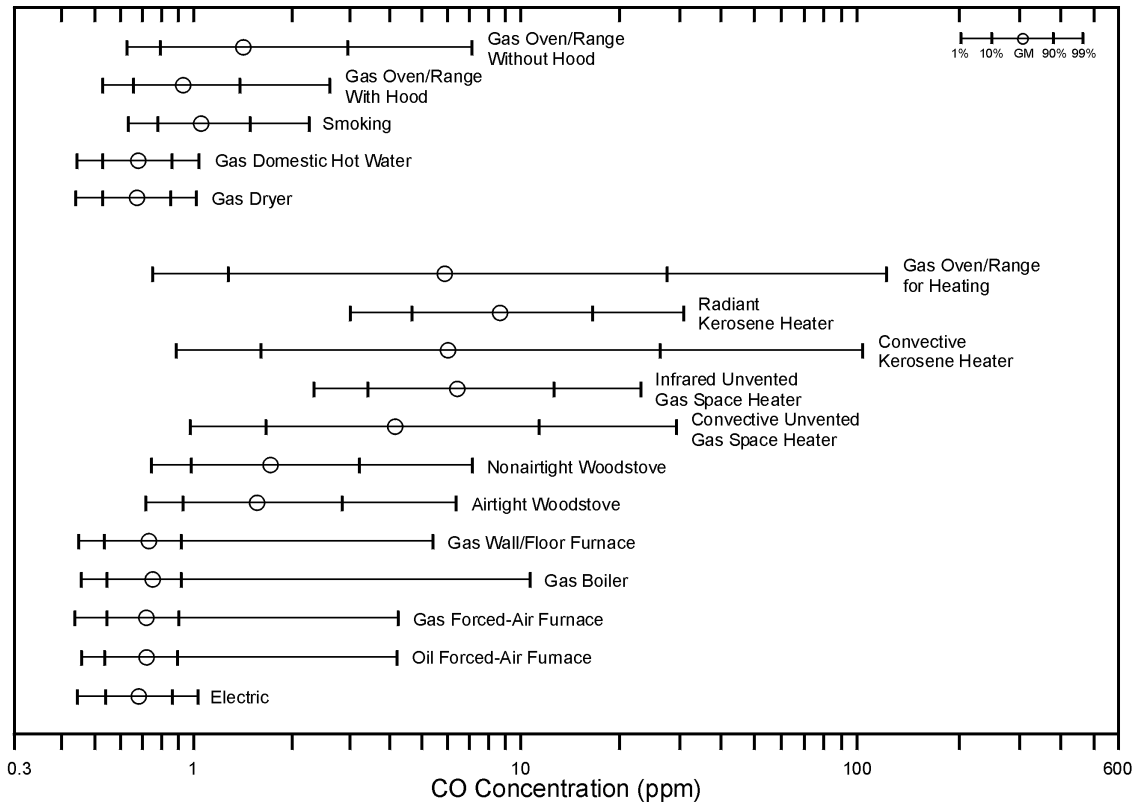

Figure 3-9. Modeled indoor CO concentration distributions in houses with only one indoor combustion pollutant source.

Source: Traynor et al. (1989).

3.5.2.3 Microenvironmental Monitoring Studies

Residential Carbon Monoxide Concentrations Related to Indoor Sources

Peak CO concentrations of 5.0 ppm (over ambient concentrations) from the use of gas ranges and stoves were reported by Davidson et al. (1987), based on a survey of the literature.

TABLE 3-11. INPUT PARAMETERS FOR CARBON MONOXIDE

Input Parameter	Data Points	Geometric Mean	Geometric Standard Deviation	Empirical Distribution Range
HEATING APPLIANCE EFFICIENCY (%)				
Gas forced-air furnace (FAF)				55-95
Gas boiler				60-95
Gas wall/floor (W/F) furnace				75-85
Oil FAF				70-90
Airtight Woodstove				45-65
Nonairtight Woodstove				35-45
SMOKING FREQUENCY (cigarettes/h)	—	0.8	1.5	
POLLUTANT EMISSION RATES (μg/kJ or μg/cigarette)				
Gas FAF	11	11.4	6.4	
Gas boiler	32	4.4	1.8	
Gas W/F	—	8.4	2.3	
Unvented gas space heater (UVGSH) infrared	4	4.6	1.1	
UVGSH convective	12	27.9	2.4	
Gas stove top	53	81.3	3.1	
Gas stove oven	56	38.6	4.1	
Gas dryer	2	52.0	1.5	
Gas water heater	55	5.8	1.9	
Oil FAF	30	6.3	11.7	
Wood airtight	12	3.9	2.1	
Wood nonairtight	4	3.2	2.0	
Kerosene radiant	7	67.9	1.4	
Kerosene convective	4	42.1	3.4	
Cigarettes	6	714.0	1.3	
NONZERO VENT FACTORS FOR VENTED GAS/OIL SPACE HEATERS	5			6.8%
RANGE HOOD VENT FACTOR (unitless)	1			0.3
POLLUTANT PENETRATION FACTORS (unitless)	—	1.0		

TABLE 3-11 (cont'd). INPUT PARAMETERS FOR CARBON MONOXIDE

Input Parameter	Data Points	Geometric Mean	Geometric Standard Deviation	Empirical Distribution Range
MARKET PENETRATION OF APPLIANCE (%)	[a]			[b]
PRIMARY HEATING APPLIANCE DISTRIBUTION (%)	[a]			[b]
NONHEATING APPLIANCE DISTRIBUTION (%)	[a]			[b]
NON-SPACE-HEATING APPLIANCE FUEL USAGE (kJ/h)	—			[b]
HOUSE VOLUME (m^3)	48			325-775
OUTDOOR POLLUTANT CONCENTRATION (ppm)	2	0.7	1.2	
BUILDING U-VALUES (kJ/h m^2 °C)				
Walls and ceilings	—			[b]
Floors	—			[b]
Windows and storm windows	—			[b]
Doors and storm doors	—			[b]
OUTDOOR TEMPERATURE (°C)	—			–9-25
WIND SPEED (m/s)	—			4.4-16.2
SOLAR GAIN[c] (kJ/h m^2)	—			39-455
NUMBER OF STORIES	—			1-2
SPECIFIC LEAKAGE AREA (10^{-4} m^2/m^2)	50	2.84	1.44	

[a]RASS sample size = 350 responses out of 2,074 possible (17%).
[b]Data details found in Traynor et al. (1989).
[c]Range of solar gain in houses with and without storm windows.

Source: Traynor et al. (1989).

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The Gas Research Institute, Pacific Gas and Electric Company, San Diego Gas and Electric Company, and Southern California Gas Company initiated indoor monitoring of 293 randomly selected homes. Monitoring was for a single 48-h period. Carbon monoxide levels indoors were reported to be closely associated with levels outdoors for most of the residences monitored. However, 13 homes had CO concentrations above 9 ppm, and concentrations in one home exceeded 35 ppm. Homes with gas ranges with standing pilot lights had higher CO concentrations than did homes with gas ranges with electronic pilot lights or electric ranges. Homes with standing pilots had a 0.56 ppm increase in net CO. Indoor minus outdoor CO concentrations for six averaging times were used to determine the highest ranked homes. Using that technique, 21 of the 293 homes studied were selected for case studies. The higher CO seen in these homes possibly was associated with occupant smoking, the use of gas stoves for heating purposes, infiltration from attached garages, the type of heating system used (homes with gas wall furnaces had higher CO), the building type and size (smaller multi-family homes had higher CO than larger single-family homes), use of gas appliances, and more than one CO source. The average AER varied by type of heating system (wall furnaces > forced-air > electric) and building type (multi-family units > single-family units) (Billick et al., 1994, 1996; Colome et al., 1994). The CO descriptive statistics for homes in this study are given in Table 3-12.

The Research Triangle Institute (1990) monitored CO concentrations in 400 homes for 3 days in Suffolk and Onondaga Counties, NY. The average room volume was assumed to be 50 m^3. The average AER was 0.59 h^{-1}. Carbon monoxide monitors were placed in the primary living space and close to the source. Approximately half of the homes used gas cooking stoves. Kerosene heaters had to be operated at least 3 h/day to qualify as a CO source, and the woodstove or fireplace had to be operated an average of 2 h/day. Any reported usage of gas stoves qualified them as sources. The average CO concentration in the primary living area was 2.23 ± 0.17 ppm (results for 209 homes). Use of both gas stoves and kerosene space heaters was associated with increased CO. Homes using woodstoves or fireplaces had lower CO than did homes without woodstoves or fireplaces (see Figure 3-10).

Hedrick and Krug (1995) reported CO concentrations from the use of unvented gas space heaters and pilot lights in a test house in Chicago, IL. The gas space heaters included blue-flame convective, radiant-tile, fan-forced blue-flame and perforated-tube convective units. Emission

TABLE 3-12. CARBON MONOXIDE DESCRIPTIVE STATISTICS FOR ALL HOMES (number = 277; in ppm)

All Homes	Indoor Average					Outdoor Average				
	48-h	Max 10-min	Max 30-min	Max1-h	Max 8-h	48-h	Max 10-min	Max 30-min	Max 1-h	Max 8-h
Arithmetic Mean	1.6	5.2	4.8	4.5	2.9	1.0	5.5	4.3	3.8	2.0
Standard Error	0.1	0.3	0.3	0.3	0.2	0.1	0.4	0.3	0.2	0.1
Mode	1.0	2.0	2.0	2.0	1.0	0.1	2.0	2.0	1.0	1.0
Percentiles										
Maximum	12.9	37.9	36.7	35.8	23.5	10.8	68.7	31.5	27.3	17.3
95th	4.3	15.1	14.2	13.2	8.3	2.7	16.1	12.3	10.6	6.3
75th	1.8	6.6	6.0	5.8	3.4	1.3	6.1	5.2	4.8	2.2
50th	1.2	3.5	3.1	3.0	2.0	0.8	3.3	2.9	2.6	1.4
25th	0.7	2.0	2.0	2.0	1.2	0.3	2.0	1.9	1.5	0.9
5th	0.1	1.0	1.0	1.0	0.5	0.1	1.1	1.0	1.0	0.3
Minimum	0.0	0.1	0.0	0.0	0.0	0.0	0.2	0.1	0.0	0.0

Source: Modified from Wilson et al. (1993).

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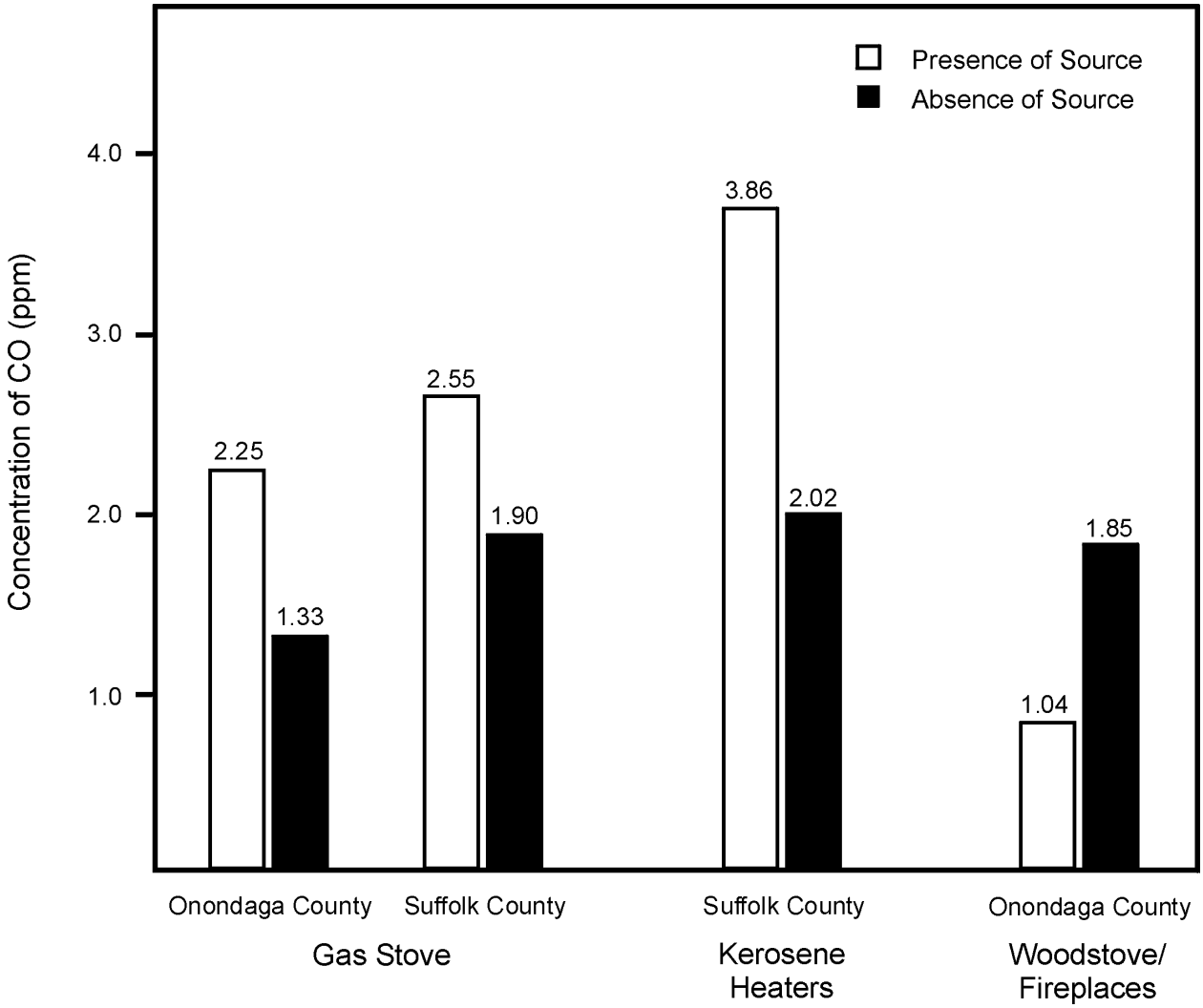

Figure 3-10. Arithmetic mean CO concentrations by presence or absence of combustion source.

Source: Research Triangle Institute (1990).

rates for the units are discussed in Section 3.5.1.2. The house was a single-family, one-story, three-bedroom dwelling with a full basement, comprising 1,150 ft^2 per level. Eight burner experiments and three pilot light experiments were conducted. Heaters were operated for 8 h followed by a 15-h decay period. The pilot studies were conducted over a 48-h period. Fans were used to distribute emissions throughout the house, excluding the basement. The highest CO concentrations were seen with the radiant-tile heater (13.4 ppm), and the lowest CO

concentrations were reported with the fan-forced unit (0.9 ppm). Two of the tests using the blue-flame convective units were affected by gas leakage, resulting in CO concentrations of 4.7 and 4.8 ppm. The test not affected by the leakage had a CO concentration of 2.7 ppm. The maximum CO concentration in the test house from use of the perforated-tube convective heater was 31.9 ppm. Carbon monoxide concentrations during the pilot light experiments did not exceed 2.0 ppm.

Koontz and Nagda (1988) reported CO concentrations in 82 homes using unvented gas space heaters as the primary heat source and in 29 homes using unvented gas space heaters as a secondary heat source. Forty-one of the homes monitored did not use a gas space heater. Carbon monoxide was monitored continuously (consisting of sequential 15-min averages) close to the geometric center of the house over an average period of 5 days. The highest CO concentrations were seen in homes using the space heaters as the primary heat source (highest concentration was 36.6 ppm). Carbon monoxide concentrations did not exceed 9.0 ppm in homes using space heaters as a secondary heat source or in homes without gas space heaters. Table 7-13 of the previous AQCD for CO presents a comparison of the CO concentrations in the homes studied (U.S. Environmental Protection Agency, 1991b).

Moderately high concentrations of CO have been reported in homes where unvented kerosene heaters are in use. Burton et al. (1990) monitored both the inside and outside of two mobile homes for pollutants emitted from the operation of a radiant and a convective unvented kerosene space heater. No other sources of combustion by-products were in the homes. Heaters were operated from 4:00 to 9:00 p.m. daily. Six random sampling periods were conducted, three with heaters on and three with heaters off. Measurements were made until 11:00 p.m. Average CO concentrations while the heaters were in operation were 12 ppm for the convective heater and 4 ppm for the radiant heater. When the heaters were not in use, average CO concentrations were 5 and 1 ppm, respectively. Ambient CO concentrations in the mobile home park were reported to be negligible.

Carbon monoxide concentrations in eight single-wide mobile homes (150 to 255 m^3) were reported by Mumford et al. (1990, 1991). Convective kerosene heaters were used in four of the homes. Three of the homes used radiant heaters, and one home used a convective/radiant heater. Monitoring was conducted 2.6 to 9.5 h/day (average 6.5 h/day) for 2 weeks with heaters on and 2 weeks with heaters off. Fuel consumption rates ranged from 252 to 295 kJ/min for convective

units, 105 to 168 kJ/min for radiant units, and 120 kJ/min for the convective/radiant unit. Average AERs were 0.47 h^{-1} with heater on and 0.48 h^{-1} with heater off. Monitoring began when heater use began and continued for 2 h after the heaters were turned off. Carbon monoxide concentrations were above 9 ppm in four of the eight homes. In one home with a convective heater, CO concentrations peaked at 51 ppm. The average CO concentration with heaters off was 1.4 ppm.

Williams et al. (1992) reported CO concentrations in eight all-electric mobile homes (each <100 m^2) from the use of kerosene heaters over a 6-day measurement period. The space heaters were used for an average of 4.5 h/day between 4:00 to 11:00 p.m. Background CO ranged from 0 to 8 ppm. Average CO during nonuse days was 1.4 ppm ± 0.3. Peak CO values ranged from 0.3 to 50.2 ppm. The 8-h average CO concentration in the homes was 7.4 ± 1.4 ppm. Peaks usually were observed at the end of the combustion period. The AER averaged 0.47 h^{-1} when the unit was in operation. Homes with the radiant and multistage units had higher CO than homes with convective heaters. Average 1-h levels of CO for convective units ranged from 1.3 to 5.3 ppm. One-hour average CO concentrations for radiant and multistage units ranged from 1.1 to 28.3 ppm and 16.0 to 50.0 ppm, respectively.

Carbon Monoxide Concentrations Related to Environmental Tobacco Smoke

Carbon monoxide concentrations in environments where smoking occurs exceed background CO concentrations. All the concentrations will depend on the size of the indoor space, number of cigarettes smoked, smoking rate, CO emission rate, differences in ventilation, and the ambient CO concentrations (Turner et al., 1992). Ott et al. (1992, 1995) conducted a series of monitoring experiments in a one-story house during development of a multi-compartment indoor mass-balance model to predict the pollutant concentrations from environmental tobacco smoke. Smoking time ranged from 6.5 to 9.5 min. Carbon monoxide concentrations were measured in three locations in the bedroom after three cigarettes were smoked over a 9-h period. Concentrations ranged from 0.4 to 0.6 ppm. The only ventilation was a partially opened window covered with a shade (AER = 1.2 h^{-1}). Klepeis et al. (1995) reported a range of 0.41 to 1.2 ppm CO (average 0.75 ppm CO) in airport smoking lounges based on 10 sampling periods ranging from 60 to 146 min. The average number of people smoking during the period ranged from 2.8 to 13.5. The room volumes ranged from 238 to 803 m^3, with AERs of

12.8 and 15.8 h^{-1}. Holcomb (1993) reviewed the literature on tobacco smoke in various indoor environments and evaluated those data the authors defined as generated under real-life conditions. Carbon monoxide concentrations ranged from 0.1 to 10.2 ppm depending on the indoor environment. The results are outlined in Table 3-13. Löfroth et al. (1989) reported CO concentrations in a chamber test for cigarettes (1 cigarette) smoked every 15 to 30 min. The chamber volume was 13.6 m^3, with a set AER of 3.55 h^{-1}. The cigarette mass was 1.2 g, and mass smoked was 0.9 to 1.0 g. Smoking duration was ≈12 min per cigarette. Carbon monoxide concentrations averaged 1.56 and 2.17 ppm for the 30-min tests and 4.16 ppm for the 15-min test.

TABLE 3-13. CARBON MONOXIDE CONCENTRATIONS (ppm) IN SMOKING (S) AND NONSMOKING (NS) AREAS IN REAL-LIFE SITUATIONS

			Smoking			Nonsmoking		Diff. in Means
Category	No. of Studies	Sample Size	Mean	Range	Sample Size	Mean	Range	S – NS
Offices and Public Buildings	13	697	2.95	0.1-8.7	275	2.99	0.7-4.0	–0.04
Restaurants	5	107	3.6	0.4-9.0	—		—	—
Taverns/Bars	2	5	6.4	—	—		—	—
Trains	2	18	2.2	1.0-5.2	10	1.30	0.5-2.9	0.90
Buses	1	35	6.0	3.7-10.2	—		—	—
Autos	1	—	—	—	213	11.6	8.8-22.3	—

Source: Holcomb (1993).

Carbon Monoxide Concentrations from the Operation of Motor Vehicles

Kern et al. (1990) measured CO concentrations in a poorly sealed, detached garage from operation of an emissions-controlled (catalytic reactor and oxygen sensor) and an emissions-uncontrolled vehicle (carbureted, without a catalytic reactor). Two tests were conducted: Test 1,

poorly sealed garage door with a 3-in. crack, and Test 2, garage door sealed with rags. Carbon monoxide concentrations in the poorly sealed garage reached 4,700 ppm for the uncontrolled car versus 2,000 ppm for the controlled car. When the garage was better sealed, CO concentrations, after 110 min of operation, reached 8,400 ppm for the uncontrolled vehicle versus 3,600 ppm for the controlled vehicle.

Amendola and Hanes (1984) evaluated the concentration of CO in automotive repair shops based on seasonal conditions and as a function of work environment size. Monitoring was conducted in a small service station (1 to 2 bays), a large service station (>2 bays), and an automobile dealership. The 8-h time-weighted average during warm weather ranged from 3.3 to 16.2 ppm, 3.4 to 21.6 ppm, and 12.1 to 20.8 ppm for the small and large service stations and the dealership; however, the authors noted that CO concentrations were affected by the type of ventilation used in the facility, volume and type of repairs, and employee work habits, such as minimizing engine run time.

3.6 SUMMARY

Carbon monoxide is produced by the incomplete combustion of burning fossil and biomass fuels. Approximately 80% of the CO produced globally is the result of anthropogenic activities. Carbon monoxide in the atmosphere is of both primary and secondary origin. The photochemical oxidation of CH_4 and NMHCs accounts for almost one-half of the total source strength of CO. The uncertainty in estimates of the magnitudes of individual CO sources ranges from a factor of two to three.

Atmospheric CO concentrations in remote areas of the world have been increasing at the rate of about 1% per year throughout most of the industrial era. This increase reflects the growth of anthropogenic emissions from the combustion of fossil and biomass fuels and increased agriculture to feed the expanding world population. However, CO levels decreased for several years from the late 1980s to the early 1990s. The reasons for this decline are not clear, although several factors may be involved. Levels of CO may have started increasing again over the past few years, although the significance of this trend is debatable.

Carbon monoxide plays an important role in atmospheric chemistry because it is the major reactant for OH radicals. Reaction with OH radicals is the loss mechanism for many trace gases

that are responsible for contributing to the greenhouse effect (e.g., CH_4) and for depleting stratospheric O_3 (e.g., CH_3Cl, and CH_3Br). Thus, increases in CO concentrations can suppress OH radical levels and allow the concentrations of these trace gases contributing to global-scale environmental problems to increase, even if trace gas emissions are constant. Conversely, decreases in global average CO concentrations can stabilize or even reverse the growth rates of the trace gases mentioned above.

Carbon monoxide may be responsible for 20 to 40% of the O_3 formed in the background or "clean" troposphere. In addition, CO may have been responsible for 10 to 20% of the O_3 formed during smog episodes in the few urban areas that have been examined. Obviously, the photochemistry must be examined in more cities before any more general statements about the importance of CO for urban air chemistry can be made.

Emissions from transportation dominate other sources of CO within the United States. Even though CO in urban areas results largely from motor vehicle emissions, a sizable fraction of the CO observed in rural air may be produced by the photochemical oxidation of isoprene and other NMHCs, at least according to one model study. The uncertainties in the nationwide and worldwide emission inventories are comparable (i.e., roughly a factor of between two and three).

There has been a consistent decrease in the nationwide annual second highest maximum 8-h composite average ambient CO concentration over the past 20 years, from about 11 ppm in 1977 to about 4 ppm in 1996. This improvement in CO quality occurred despite a 121% increase in vehicle miles traveled, a 29% increase in population, and a 104% increase in gross domestic product in the United States over the same period. During the past 10 years, the composite mean annual CO second maximum 8-h concentration decreased 37% at 190 urban sites, 37% at 142 suburban locations, and 48% at 10 rural monitoring sites. Hourly average CO concentrations decreased from 2.0 ppm to 1.2 ppm over the past 10 years. Despite uncertainties in the calculations of CO emissions, the decline in ambient CO concentrations in the United States reflects the controls placed on automotive emissions. These declines are seen clearly in the trends in CO levels during times of day when CO concentrations result mainly from mobile source emissions.

The patterns and trends of observed CO reflect reductions in the CO emissions of the past 11 years. However, it is important to note that the reported concentrations from the monitoring sites are representative only of the air quality in their neighborhoods. Also, although personal

exposure to CO from mobile sources also should be decreasing, the CO values from the monitoring sites are not equivalent to personal exposures. The same ratios of personal to monitored CO from past studies in urban areas with CO emissions dominated by mobile sources may remain applicable today, but continued validation is needed.

Carbon monoxide occurs in indoor environments directly through emissions from various indoor combustion sources or indirectly as a result of infiltration or ventilation from outdoor sources. Carbon monoxide concentrations in the indoor compartment is influenced by the CO emission rate of the unvented combustion appliance, the ambient CO concentration, infiltration through the building envelope, building volume, AER, and air mixing within the indoor compartments. In the absence of an indoor source, CO concentrations generally will equal those in the surrounding ambient environment.

Carbon monoxide emissions from gas ranges vary from range to range for both the top burners and the oven burners and will depend on the type of pilot light, the fuel consumption rate, the frequency of use, and the operating condition. Older gas ranges with standing pilot lights emit more CO than do newer units with electronic pilot lights. Estimates of fuel consumption range from 5,000 to 5,710 ft^3/year for burners and standing pilots. Annual pilot light fuel consumption for standing pilots has been estimated to be 3,530 ft^3. A steady decrease in the emission of CO from pilot lights likely will occur with the replacement of older gas ranges with new models without standing pilots. Also, with the advent of other cooking appliances (e.g., microwaves, toaster ovens, heating plates), the use of ranges in meal preparation is decreasing. Estimates of gas stove usage range from 30 to 60 min/day. Carbon monoxide emissions from furnaces are generally negligible, but less efficient models will emit more CO than the more efficient ones.

The use of well-maintained, energy-efficient gas stoves will result in only intermittent, small increases in CO concentrations. Carbon monoxide concentrations from gas stove usage have been reported to range from 0.65 to >9.0 ppm. The high levels of CO likely were associated with the presence of multiple CO sources, the use of the gas stove as a supplemental heat source, infiltration from ambient sources, and the building type (multi-family units versus single-family units).

Emissions from unvented space heaters are a function of the appliance design, combustion efficiency, length and frequency of use, and the fuel type and consumption rate. The combustion

appliances generating the highest CO emissions and concentrations are unvented gas and kerosene space heaters. Convective space heaters emit the smallest amount of CO. Radiant and infrared unvented space heaters emit higher amounts of CO. The CO concentration from the use of a radiant-tile gas unit was 13.4 ppm, compared with 0.9 ppm for a convective gas unit. However, CO concentrations also depend on the frequency and duration of use of the space heater. Higher CO is found in homes where space heaters are the primary heat source (up to 37 ppm) versus homes where space heaters are used to supplement another heat source (<9.0 ppm).

Available studies on woodstoves and fireplaces indicate that CO is emitted from fire start-up and maintenance, leaks in the stove and venting system, and through backdrafting when the natural draft is overcome by depressurization. The average CO source strength for airtight stoves ranged from 10 to 140 cm^3/h (9.7 to 136 g/h) versus 220 to 1,800 cm^3/h (213.7 to 1,748.6 g/h) for nonairtight stoves.

Carbon monoxide from the combustion of tobacco products occurs in the indoor environment primarily through sidestream smoke. Emissions will vary based on the type and brand of tobacco product. Concentrations of CO in environments where smoking occurs will exceed background concentrations but will be dependent on the CO emission rate of the tobacco product, number of cigarettes smoked, smoking rate, size of the indoor compartment, ventilation rate, and ambient CO concentrations.

Carbon monoxide emissions from the use of combustion engines may produce significant increases in CO in the microenvironments where the engines are being operated. Emissions from the operation of motor vehicles in enclosed, inadequately ventilated spaces such as garages and repair shops have resulted in 8-h time-weighted average CO concentrations of up to 22 ppm in the summer and 110 ppm during the winter.

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APPENDIX 3A:

The Spatial and Temporal Variability of Carbon Monoxide in Selected Urban Areas of the United States

3A.1 INTRODUCTION

The objective of this appendix is to present a general overview of the mean concentrations and the temporal and spatial variability of carbon monoxide (CO) in selected major metropolitan areas located in different geographic regions of the United States. Statistical analyses (Shadwick et al., 1997, 1998a,b,c) were performed on ambient CO data obtained in the Denver, CO; Los Angeles, CA; New York City, NY; and Phoenix, AZ, Metropolitan Statistical Areas (MSAs). These MSAs were chosen on the basis of their geographical diversity and their potential for showing exceedances of the CO National Ambient Air Quality Standards (NAAQS) during the years 1994 through 1996. The current NAAQS for CO was not met in the Los Angeles and Phoenix MSAs in 1996. In addition, the Denver and the New York City MSAs exceeded the CO NAAQS in 1995 and 1994, respectively. The analyses presented here focus on characterizing the variability in CO at different sites within the above MSAs for the winter season (defined as November 1 through the last day of February) for the years 1986 through 1996. Ambient CO levels are generally highest in the winter season because vehicle emissions are highest during cold weather, and there is a higher incidence of enhanced stability in the atmospheric boundary layer, leading to reduced vertical mixing (dilution) of emissions from the surface.

Carbon monoxide data were obtained from the U.S. Environmental Protection Agency's Aerometric Information Retrieval System (AIRS). Data from the network described in Section 3.4 are archived routinely in AIRS. Carbon monoxide data collected at the monitoring sites are meant to be used to characterize levels in environments ranging from "hot spots" (i.e., sites located at or very close to major sources) to ambient levels found in residential areas, and, hence, care should be exercised in matching the spatial scale over which the data obtained at a

monitoring site are meant to be representative with the spatial scale required by a particular use of the data.

Motor vehicle emissions are the major source of CO in each of these MSAs, and several of the sites in each MSA are located at or near roadways with high emissions. However, there are special siting criteria that guide the location of monitoring stations near source-specific high concentration clusters. Therefore, although CO concentrations at many monitoring stations in urban areas may be dominated by mobile sources, the concentrations are not at levels that a person would experience within or near an operating automobile. Time series in CO concentrations obtained at monitoring stations in urban areas could be used to monitor the progress in controlling emissions and to aid in evaluating relative changes in personal exposure to ambient CO, but they cannot be used alone to provide concentrations for estimating personal exposures.

3A.2 GENERAL METHODOLOGY FOR DATA COLLECTION AND ANALYSES

Hourly average CO data were used to calculate running 8-h averages for 1986 to1996. Only valid hourly average values were used to compose the 8-h average. In the case that less than six valid hourly average values were used to compose the 8-h average, the 8-h average was set to a missing value. The six valid hourly average values in an 8-h window corresponds to 75% data capture in the 8-h window.

The 24 running 8-h averages assigned to a day were used to compute the daily maximum 8-h average. A daily maximum 8-h average was considered to be valid if at least 18 of the 8-h running averages for the day were valid as described in the preceding paragraph. The 18 valid 8-h running averages in a day corresponds to a 75% data capture. In the case that a valid daily maximum 8-h running average could not be computed, a missing value was assigned to the daily maximum 8-h average. The summary statistics were computed without regard to data capture. Summary statistics (aside from the total number of observations) should be regarded as representative if at least 75% of the possible data values were valid. Statistics on central tendency and correlation were tabulated for all of the sites in each MSA for both the hourly and

8-hour running averages. The statistics were analyzed by year, season, day of week, and hour of the day.

The Kendall tau correlation statistic was used to evaluate the relations in the daily maximum 8-h averages among the different sites in the four MSAs chosen above. Kendall tau is a nonparametric measure of correlation between two ranked time series. The Kendall tau measures the similarity in rankings within two time series. It is plus one (+1) if the corresponding values in the two time series are ranked exactly the same way, and minus one (−1) if the corresponding values in the two time series are ranked exactly in reverse order.

3A.3 RESULTS AND DISCUSSION

3A.3.1 Denver

The locations of the eight monitors that had valid hourly average CO data for 1986 to1996 are shown in Figure 3A-1. The CO monitors in the Denver MSA are located in predominantly urban or suburban locations and represent six of the seven counties in the Denver MSA. The average hourly CO concentration among all the sites ranged from 0.32 to 1.52 ppm in 1996. The CO time series at each of these monitors show nuances unique to each site, but there are also similarities common to all of the sites. These similarities will be the focus for discussion; consequently, the downtown Denver monitoring site for CO will be used as the illustrative example of the trends in ambient CO concentrations in Denver over the last decade. This site is designated as *Broadway* (AIRS identification number 080310002).

Figure 3A-2 is a three-dimensional plot of the average diurnal CO concentration time series for weekdays for the winter seasons (November through February, as defined above) from 1986/87 through 1995/96. It is important to note that this graph shows the average concentrations during a 24-h period for each years' winter season and, as such, is not indicative of the CO time series of concentrations for any given day.

The most notable features in the CO concentration trends for Denver, as seen in Figure 3A-2, are the double peaks: (1) one maximum starting at approximately 6 a.m. and peaking at about 9 a.m. and (2) the second maximum occurring at approximately 6 p.m., after beginning at about 3 p.m. These peaks correspond to rush hour traffic and result almost entirely

from emissions from motor vehicles. For the 10-year period in this figure, 1986 through 1996, the average CO concentrations were higher during the afternoon peak. Also, the CO concentrations fall off much less rapidly following the afternoon peak than they do following the morning peak. Indeed, the average concentrations seen after midnight are still higher than those measured at noon, just 3 h after the morning peak. The nighttime behavior of CO may reflect the presence of additional sources, such as wood burning, and the influence of atmospheric dynamics, such as reduced vertical mixing in the atmospheric surface layer at night. However, wood burning has been restricted in the Denver area in recent years and so the reduction in atmospheric boundary layer height during the night may more than compensate for the decline in motor vehicle emissions. There is also a very noticeable downward trend in CO concentrations from 1986 to 1996 that was observed at all sites. At the Broadway site, for example, weekday hourly average CO concentrations during the winter season fell 60% from 1986 to 1996, whereas weekend values dropped by 47% over the same period.

Figures 3A-3 and 3A-4 show average monthly CO concentration data for the periods from May 1986 through May 1987 and May 1995 through May 1996, respectively. The dominant feature in Figure 3A-3 is the large peak occurring between 5 p.m. and 6 p.m. in December of 1986. A similar peak, although reduced in magnitude, for December 1995 is seen in Figure 3A-4. Overall, the concentrations observed in Figure 3A-4 are reduced substantially in relation to their counterparts in Figure 3A-3. However, the general shape of the CO time series shows little change from 1986/87 (Figure 3A-3) to 1995/96 (Figure 3A-4). The morning and early evening peaks are evident in both figures. These peaks, primarily because of motor vehicle emissions, occur throughout the entire year. However, the concentrations are elevated from about November though March compared with the rest of the year. In addition to being higher than those in 1995/96, the concentrations in 1986/87 also show greater variability. This is especially true for the concentrations observed during the off-peak hours (again, the peak hours are centered on 9 a.m. and 6 p.m.). The diurnal CO concentrations for May 1995 through May 1996 (Figure 3A-4) show less variability, particularly during the off-peak hours, than do those in the May 1986 through May 1987 period (Figure 3A-3).

Figure 3A-5 shows two graphs of the central tendency of the wintertime daily maximum 8-h average for weekdays at the Broadway monitoring site. The top graph shows a box plot for the entire range of data. The bottom graph focuses on the interquartile range of the same data

shown in the top graph. The horizontal line across the center of the top graph shows the current NAAQS 8-h standard for CO. The *P75*, *P50*, and *P25* in the legend for the lower graph refer to the 75-, 50-, and 25-percentiles, respectively. Figure 3A-5 shows the reduction in CO concentrations observed for the winter months of 1986/87 through 1995/96. Also apparent from this figure is the reduction in the "spread" or variability of the 8-h average CO concentrations for wintertime from 1986/87 through 1995/96. Each circle or diamond in the top graph represents an individual 8-h "observation". The designation of outliers (circles) or extremes (diamonds) relates to whether the observation is three or four standard deviations from the mean, respectively. It is clear from the top graph that the number of wintertime "exceedances" (the occurrence of an 8-h average concentration that is greater than 9 ppm) at the Broadway site has been reduced drastically in the period from 1986/87 to 1995/96.

Table 3A-1 shows the Kendall tau correlation coefficients for the daily maximum 8-h CO concentration at the sites in the Denver MSA. The correlation is strongest among the downtown sites, which also are located the closest together. A number of factors contribute to the generally low values that are seen. These factors include the influence of local sources, differences in meteorological conditions across the MSA, nonoverlapping averaging periods, and measurement error. The correlation coefficients for the site pairs generally increased from the 1986/87 to 1995/96 winter seasons (Table 3A-1). It is believed that, as the populated area of the Denver MSA spreads out and there is more motor vehicle traffic from increasingly distant suburbs, the ambient CO profiles for these distant communities become more homogeneous. Littleton, CO, provides a good example of the increase in correlation with several of the other CO sites in the Denver area. Littleton (1990 population of approximately 33,700 people) is a city located approximately 20 km south of downtown Denver. Its correlation coefficient has shown large increases, along with the Broadway and Julian Denver CO sites, as well as with the Arvada and Greeley, CO, sites. These increased correlations were for the weekday data and were all of at least one order of magnitude (Table 3A-1). One order of magnitude increases also were seen for the weekend data between Littleton and the Arvada and Greeley sites. Arvada and Greeley are approximately 25 km and 95 km, respectively, from Littleton. Therefore, it appears that the increase in correlation coefficients is related to the population spreading out from downtown Denver, resulting in the surrounding suburbs becoming more similar relative to traffic patterns and, hence, to the distribution of the ambient CO.

TABLE 3A-1. KENDALL TAU SPATIAL CORRELATIONS FOR THE DAILY MAXIMUM 8-HOUR AVERAGE CARBON MONOXIDE DATA IN THE DENVER METROPOLITAN STATISTICAL AREA

1986/87 Winter Season

	Welby	Littleton	Boulder-Marine	Denver-Broadway	Denver-Albion	Denver-Julian	Arvada	Greeley
				WEEKDAY				
Welby		0.06	0.42	0.55	0.61	0.66	0.60	0.59
Littleton	0.16		0.18	0.10	0.18	0.06	0.03	0.03
Boulder-Marine	0.13	0.16		0.46	0.42	0.41	0.37	0.38
Denver-Broadway	0.50	0.26	0.22		0.66	0.60	0.48	0.45
Denver-Albion	0.58	0.23	0.22	0.55		0.57	0.50	0.53
Denver-Julian	0.69	0.35	0.14	0.60	0.62		0.51	0.49
Arvada	0.49	0.05	0.26	0.37	0.41	0.67		0.54
Greeley	0.51	0.04	0.18	0.39	0.52	0.55	0.58	
				WEEKEND				

1995/96 Winter Season

	Welby	Littleton	Boulder-Marine	Denver-Broadway	Denver-Albion	Denver-Julian	Arvada	Greeley
				WEEKDAY				
Welby		0.25	0.29	0.64	0.57	0.72	0.63	0.50
Littleton	0.45		0.28	0.31	0.27	0.25	0.23	0.19
Boulder-Marine	0.41	0.66		0.42	0.28	0.33	0.38	0.32
Denver-Broadway	0.54	0.44	0.28		0.69	0.66	0.56	0.48
Denver-Albion	0.64	0.49	0.38	0.63		0.57	0.51	0.47
Denver-Julian	0.66	0.47	0.35	0.72	0.64		0.62	0.53
Arvada	0.63	0.60	0.53	0.49	0.60	0.61		0.48
Greeley	0.45	0.34	0.27	0.45	0.47	0.47	0.42	
				WEEKEND				

3A.3.2 Los Angeles

The Los Angeles CMSA (Consolidated Metropolitan Statistical Area) consists of five counties surrounding and including metropolitan Los Angeles (Los Angeles, Orange, Riverside, San Bernardino, and Ventura counties). Forty-two monitors had at least one year's worth of hourly average CO data in the years from 1986 through 1996, with 12 sites (Figure 3A-6) having CO time-series data that completely covered the entire 10-year period.

The monitoring data reflect pronounced variation in CO between sites throughout the Los Angeles CMSA. There are substantial differences in CO levels between sites. Hourly average CO concentrations ranged from 0.38 to 3.16 ppm in 1996. At the Lynwood site (Figure 3A-7), there are violations of the daily maximum 8-h average in every year of the monitoring period analyzed here. In contrast, the Barstow site (not shown), located about 190 km from downtown Los Angeles, shows no violations over the same 10 years of monitoring. Lynwood is located approximately 15 km south-southeast of downtown Los Angeles, about halfway between downtown Los Angeles and Long Beach. It is a densely populated area intersected by several major interstate highways.

Trends determined from the time-series graphs range from weak downward trends (usually found at those sites with the highest levels of CO, as shown in Figure 3A-8 for the Hawthorne site) to no discernable change in CO levels over the 10-year period (usually the case when CO levels are already low; as in the case of Barstow, shown in Figure 3A-9). However, the trend in CO levels is not uniformly downward at any given site. The CO time-series for the wintertime, weekday data for the 1989/90 winter season showed generally elevated CO levels at all sites, whereas the 1994/95 winter season had the lowest CO levels at most sites. This leads to a perceived upswing in CO levels for the 1995/96 winter season. However, the year-to-year fluctuations in CO do not mean necessarily that the CO concentrations were on the rise following the 1995/96 winter season. In general, there has been a decrease in the number of violations over time at most of the sites.

Wintertime diurnal CO patterns are also quite diverse. Many sites in the Los Angeles CMSA, such as the Hawthorne site (Figure 3A-10), show the afternoon peak beginning to rise rather late in the day (after 6 p.m.), with the CO levels rising gradually at some locations and more abruptly at others, and finally peaking around midnight with elevated levels of CO persisting until the morning rush hour. Other sites, like that at El Toro, approximately 65 km

southeast of downtown Los Angeles, show a more "classic" CO pattern (see Figure 3A-11), one where the afternoon CO begins to rise between 4 p.m. and 5 p.m., peaks at about 6 p.m., and gradually but steadily declines until about 1 a.m. the following morning. The CO concentration then maintains an average daily minimum value, usually around 1 or 2 ppm, until the next day's morning rush hour.

Each of the twelve sites in this analysis exhibited a wintertime maximum in CO concentrations. This wintertime peak in ambient CO is illustrated by Figure 3A-12, the monthly diurnal plots for Anaheim. The plots for 1986/87 and 1989/90 illustrate two points quite well: (1) the pronounced rush hour peaks and (2) the distinct peak in CO during the wintertime (peaking in the month of December). In these two respects, Los Angeles shows remarkable similarity to Denver.

Table 3A-2 shows the correlations for the daily maximum 8-h average CO concentration between sites for the Los Angeles CMSA. The upper table shows the correlations for the 1986/87 winter season, whereas the table at the bottom shows the correlations for the 1995/96 winter season. With some exceptions, the between-site correlations generally increased for each site-pair in 1995/96 compared with those in 1986/87. This was analogous to the Denver site correlations. The city-pair that had the highest correlation in the 1986/87 analysis remained unchanged for the 1995/96 analysis in 8 out of the 11 city-pairs in the weekday data, and in 7 out of the 11 city-pairs in the weekend data. This is indicative of the Los Angeles CMSA having several distinct airsheds. The monitoring sites that "reside" within a particular air shed likely will exhibit similar characteristics in ambient CO. For example, the Burbank, Hawthorne, Lynwood, and Reseda monitors show a history of violations of the daily maximum 8-h average over the last 5 years of monitoring data. These sites are located in heavily urbanized areas of Los Angeles County, with numerous major freeways nearby. The spatial correlations among these four sites are weak to moderate (range: 0.3 to 0.7, for the 1995/96 weekday data). Peripheral to the area containing the urbanized monitors, are the monitoring sites in La Habra, Long Beach, Anaheim, and Riverside. These sites had violations before 1991, but have not had any violations of the daily maximum 8-h average since 1991. The last group of sites, consisting of Asuza, Barstow, El Toro, and West Los Angeles, did not have any violations over the 10-year period.

TABLE 3A-2. KENDALL TAU SPATIAL CORRELATIONS FOR THE DAILY MAXIMUM 8-HOUR AVERAGE CARBON MONOXIDE DATA IN THE LOS ANGELES CONSOLIDATED METROPOLITAN STATISTICAL AREA

1986/87 Winter Season

	Azusa	West LA	Burbank	Reseda	Lynwood	Long Beach	Hawthorne	Anaheim	El Toro	La Habra	Riverside	Barstow
WEEKDAY												
Azusa		0.35	0.32	0.33	0.23	0.28	0.27	0.22	0.34	0.26	0.34	0.18
West LA	0.18		0.65	0.59	0.48	0.49	0.51	0.39	0.38	0.42	0.50	0.37
Burbank	0.20	0.38		0.66	0.52	0.55	0.60	0.51	0.45	0.54	0.52	0.45
Reseda	0.22	0.48	0.41		0.48	0.53	0.49	0.47	0.42	0.51	0.57	0.41
Lynwood	-0.01	0.31	0.47	0.28		0.71	0.65	0.52	0.48	0.63	0.43	0.40
Long Beach	0.05	0.51	0.46	0.41	0.63		0.70	0.54	0.44	0.57	0.45	0.44
Hawthorne	0.08	0.49	0.58	0.40	0.63	0.67		0.46	0.40	0.54	0.35	0.43
Anaheim	-0.08	0.31	0.31	0.25	0.56	0.65	0.50		0.56	0.61	0.44	0.47
El Toro	0.10	0.17	0.19	-0.004	0.26	0.17	0.20	0.22		0.58	0.44	0.39
La Habra	0.01	0.33	0.50	0.27	0.59	0.58	0.61	0.56	0.33		0.51	0.42
Riverside	0.30	0.50	0.45	0.64	0.26	0.51	0.41	0.32	0.06	0.34		0.31
Barstow	-0.07	0.20	0.31	0.17	0.24	0.25	0.28	0.12	0.07	0.14	0.27	
WEEKEND												

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TABLE 3A-2 (cont'd). KENDALL TAU SPATIAL CORRELATIONS FOR THE DAILY MAXIMUM 8-HOUR AVERAGE CARBON MONOXIDE DATA IN THE LOS ANGELES CONSOLIDATED METROPOLITAN STATISTICAL AREA

1995/96 Winter Season

	Azusa	West LA	Burbank	Reseda	Lynwood	Long Beach	Hawthorne	Anaheim	El Toro	La Habra	Riverside	Barstow
WEEKDAY												
Azusa		0.46	0.27	0.26	0.12	0.18	0.13	0.28	0.27	0.23	0.45	0.16
West LA	0.39		0.60	0.53	0.45	0.51	0.49	0.51	0.49	0.53	0.56	0.18
Burbank	0.38	0.56		0.54	0.51	0.55	0.54	0.56	0.57	0.61	0.50	0.26
Reseda	0.50	0.42	0.58		0.28	0.35	0.25	0.37	0.43	0.47	0.57	0.29
Lynwood	0.16	0.47	0.38	0.34		0.72	0.69	0.58	0.49	0.58	0.32	0.22
Long Beach	0.31	0.55	0.50	0.47	0.74		0.69	0.51	0.57	0.63	0.39	0.21
Hawthorne	0.01	0.48	0.38	0.25	0.62	0.61		0.51	0.45	0.55	0.30	0.18
Anaheim	0.36	0.56	0.57	0.53	0.54	0.55	0.43		0.60	0.60	0.44	0.18
El Toro	0.28	0.46	0.45	0.41	0.46	0.41	0.35	0.58		0.63	0.50	0.20
La Habra	0.35	0.50	0.63	0.49	0.58	0.59	0.40	0.73	0.53		0.48	0.21
Riverside	0.58	0.52	0.60	0.52	0.36	0.48	0.24	0.57	0.50	0.60		0.20
Barstow	0.28	0.33	0.40	0.35	0.24	0.33	0.25	0.35	0.20	0.31	0.32	
WEEKEND												

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A notable exception to the general increase in the between-site correlations was seen in the correlations between Barstow and each of the other sites for the weekday data, where the correlations were uniformly lower in 1995/96 compared to the correlations in 1986/87. However, this site is outside the Los Angeles Basin (lying across the San Bernardino Mountains from Los Angeles), and hence there is probably very little relationship between ambient CO in Barstow and the other Los Angeles CO sites.

3A.3.3 New York City

The CO monitors in the New York City CMSA are located in 10 of the 30 counties spanning the three states (New York, New Jersey, and Connecticut) that comprise that CMSA (Figure 3A-13). Thirteen of the 29 monitors had time series that cover the time period from 1986 to1996 and therefore were used in both the annual and seasonal data descriptions. Hourly average CO concentrations in the New York CMSA ranged from 0.63 to 3.65 ppm in 1996. The CO monitors were all in areas categorized as either urban or suburban. Despite this, the wintertime, daily maximum 8-h average CO did not reach the levels seen in Denver or Los Angeles (see above descriptions of these cities). One of the sites with the highest CO values was that located on Flatbush Avenue in downtown Brooklyn (AIRS identification number 360470071, Figure 3A-14). Yet, this site exceeded the NAAQS only twice since 1990, once in November 1991 (daily maximum 8-h average = 10.9 ppm) and once in February 1995 (daily maximum 8-h average = 9.8 ppm).

An interesting feature of the Flatbush Avenue site is the persistence of elevated CO levels after the morning rush hour, thereby making it difficult to discern between the morning and evening rush hours (Figure 3A-14). This feature also occurred at a site in downtown Manhattan (Figures 3A-15 and 16). The elevated CO levels between the rush hour peaks remained a feature at these sites despite a steady decline in the CO concentrations with passing years at both sites, and the elevated levels of CO between rush hours occurs throughout the year and are not limited to a particular season or time of year. Two possible explanations for this phenomenon are (1) that the sources of CO do not diminish after the “typical” rush hour has come to an end, and (2) that meteorological processes that normally dilute CO concentrations in surface air during midday (increased surface winds and mixing layer height) are not effective at these sites, perhaps because of microenvironmental conditions such as the “urban canyon” effect. Both of these sites

are located close to the approaches to major bridges spanning the East River, with heavy traffic throughout the day. In stark contrast to this finding is the observation that the CO concentrations fall off rapidly after midnight and reach minimal levels (1 to 2 ppm or less) at all of the sites investigated, even those in heavily urbanized areas.

Another interesting feature of the New York CMSA data was the lack of the seasonality in CO concentrations that was seen in the Denver and Los Angeles data. Many of the sites, particularly the urban sites, did not exhibit the pronounced wintertime peak in mean CO. This can be seen in the seasonal graphs for the two urban New York sites discussed above (Figures 3A-14 and 16) and for the suburban site at Morristown, NJ (Figure 3A-17). The reasons for these differences are not clear without data to characterize seasonal variations in mixing layer heights and other meteorological variables and emissions.

Table 3A-3 shows the Kendall tau correlation coefficients calculated for the daily maximum 8-h average CO concentration for the New York CMSA monitoring sites for the earliest year and the most recent year in these analyses. The correlation coefficients exhibit a wide range (from a correlation coefficient of zero [i.e., no correlation at all] to a correlation coefficient of 0.8) of values indicating heterogeneity in the 8-h maximum CO concentrations among the monitoring sites. Although the correlation coefficients generally rose from the 1986/87 winter season to the 1995/96 winter season, the increase was not as pronounced as those in either Denver or Los Angeles, and there were numerous exceptions where the correlations decreased during the same time period.

Care should be taken in attempting to draw any conclusions based on correlation coefficients involving any two sites. For example, the site that has the highest correlation coefficient (0.622) for the weekday data with the Flatbush Avenue site (the site in Brooklyn that had some of the highest measured CO values in the New York CMSA analysis) for the 1986/87 winter season was located in Morristown, a suburban, mostly residential community with seemingly little in common with Brooklyn. Interestingly, Morristown also had the highest correlation (0.615) with Brooklyn for the weekend data. Then, for weekdays in the 1995/96 winter season, Brooklyn had the highest correlation (0.60) with Elizabeth, NJ, whereas, for weekends, Brooklyn again had the highest correlation (0.54) with the Elizabeth site. The population density in downtown Brooklyn is more like that of Elizabeth than Morristown; however, they are still quite far apart. Apparently, characteristics shared by the New Jersey sites

TABLE 3A-3. KENDALL TAU SPATIAL CORRELATIONS FOR THE DAILY MAXIMUM 8-HOUR AVERAGE CARBON MONOXIDE DATA IN THE NEW YORK CITY CONSOLIDATED METROPOLITAN STATISTICAL AREA

1986/87 Winter Season

	Bridgeport	Stamford	Fort Lee	Hackensack	Newark	Jersey City	Perth Amboy	Freehold	Morristown	Elizabeth	Flatbush	7th Avenue	Manhattan
WEEKDAY													
Bridgeport		0.28	0.44	0.59	0.45	0.47	0.51	0.33	0.45	0.50	0.35	0.37	0.32
Stamford	0.31		0.39	0.31	0.25	0.23	0.17	0.38	0.01	0.04	-0.12	-0.01	0.41
Fort Lee	0.52	0.35		0.58	0.54	0.57	0.40	0.40	0.31	0.40	0.13	0.28	0.63
Hackensack	0.42	0.14	0.50		0.65	0.60	0.47	0.40	0.35	0.53	0.27	0.42	0.38
Newark	0.36	0.02	0.34	0.61		0.65	0.45	0.39	0.34	0.47	0.23	0.38	0.41
Jersey City	0.27	0.04	0.39	0.45	0.46		0.42	0.31	0.30	0.53	0.22	0.30	0.43
Perth Amboy	0.48	0.32	0.71	0.34	0.31	0.42		0.41	0.57	0.64	0.42	0.51	0.34
Freehold	0.26	0.14	0.30	0.23	0.36	0.16	0.41		0.30	0.29	0.21	0.22	0.33
Morristown	0.36	0.21	0.53	0.37	0.29	0.12	0.58	0.41		0.59	0.62	0.47	0.21
Elizabeth	0.41	0.06	0.59	0.48	0.42	0.48	0.75	0.33	0.51		0.54	0.48	0.25
Flatbush	0.25	0.05	0.38	0.30	0.15	0.13	0.48	0.32	0.62	0.47		0.43	0.06
7th Avenue	0.21	-0.13	0.28	0.46	0.43	0.27	0.29	0.25	0.44	0.51	0.40		0.21
Manhattan	0.20	0.23	0.28	0.11	0.13	0.21	0.38	0.30	0.18	0.29	0.14	0.12	
WEEKEND													

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TABLE 3A-3 (cont'd). KENDALL TAU SPATIAL CORRELATIONS FOR THE DAILY MAXIMUM 8-HOUR AVERAGE CARBON MONOXIDE DATA IN THE NEW YORK CITY CONSOLIDATED METROPOLITAN STATISTICAL AREA

1995/96 Winter Season

	Bridgeport	Stamford	Fort Lee	Hackensack	Newark	Jersey City	Perth Amboy	Freehold	Morristown	Elizabeth	Flatbush	7th Avenue	Manhattan
						WEEKDAY							
Bridgeport		0.16	0.57	0.62	0.55	0.51	0.55	0.32	0.48	0.55	0.45	0.51	0.24
Stamford	0.12		0.27	0.12	0.15	0.04	0.09	0.32	0.11	0.03	0.04	0.11	0.24
Fort Lee	0.48	0.39		0.57	0.62	0.51	0.55	0.32	0.55	0.59	0.43	0.50	0.40
Hackensack	0.60	0.16	0.51		0.68	0.60	0.54	0.22	0.47	0.58	0.38	0.49	0.34
Newark	0.52	0.18	0.54	0.81		0.59	0.51	0.26	0.46	0.55	0.36	0.48	0.39
Jersey City	0.48	0.17	0.41	0.59	0.57		0.44	0.16	0.32	0.50	0.31	0.30	0.35
Perth Amboy	0.39	0.33	0.56	0.59	0.60	0.50		0.32	0.63	0.66	0.55	0.63	0.37
Freehold	0.37	0.36	0.54	0.51	0.45	0.32	0.56		0.33	0.27	0.41	0.42	0.24
Morristown	0.36	0.34	0.51	0.50	0.53	0.34	0.67	0.57		0.70	0.59	0.59	0.28
Elizabeth	0.42	0.22	0.52	0.49	0.52	0.40	0.67	0.45	0.67		0.60	0.59	0.35
Flatbush	0.45	0.21	0.49	0.53	0.52	0.32	0.48	0.51	0.50	0.54		0.56	0.27
7th Avenue	0.40	0.14	0.49	0.44	0.39	0.37	0.49	0.64	0.45	0.33	0.38		0.25
Manhattan	0.33	0.18	0.38	0.23	0.33	0.21	0.25	0.19	0.32	0.37	0.31	-0.05	
						WEEKEND							

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with the Flatbush Avenue site, rather than proximity, are influencing the correlations between them.

3A.3.4 Phoenix

The Phoenix MSA consists of Maricopa and Pinal counties (Figure 3A-18). These two counties include all of metropolitan Phoenix. A total of 12 CO monitors (all were located in Maricopa county) were in the MSA during the study period; however, only five had complete time-series for the entire 10-year period. The analysis here will focus on these five sites. Hourly average CO concentrations ranged from 0.72 to 3.39 ppm at these sites in 1996.

There was a small decrease in average ambient CO levels at the five Phoenix sites from 1986 to 1996. At most of the sites, the morning rush hour peak showed a greater reduction than did the evening peak. In fact, only small improvement was seen in the evening rush hour peak levels at any of the sites. This is illustrated by the seasonal, diurnal pattern for Central Phoenix (Figure 3A-19). The evening rush hour peak showed little improvement, if any, from the 1987/88 to the 1995/96 time period. Although the sites did not exhibit a strong downward trend in concentrations, they experienced a trend toward decreased variance in the distribution of their CO values, as illustrated by the box plots for the East Butler Drive site (Figure 3A-20). Therefore, although the median CO values at these sites have shown either no improvement or only modest decreases, the highest values have decreased substantially in the 10-year period.

Much like the Denver and Los Angeles data, the CO patterns in Phoenix exhibited seasonal variations, with the wintertime concentrations being higher than those at other times of the year. However, note that although this statement is true for the morning and evening rush hour peaks, it is less true for the period of very low CO levels observed between noon and about 5 p.m. Take, for example, the site in West Phoenix (Figure 3A-21). There are pronounced morning and evening rush hour peaks at this site for all four time periods in this figure. Yet, during the interim period, approximately between noon and 5 p.m., the CO levels are almost negligible, even for the earliest period in the figure (i.e., May 1987 to May 1988). The obvious rationale is that the dynamic process of turbulent mixing in the lower troposphere is diluting rapidly and carrying away the ambient CO produced during the morning rush hour. Coinciding with the effects of atmospheric dynamics on the midday CO levels is the likely scenario that the source of the morning CO peak (almost certainly motor vehicle emissions) is effectively “turned off” after

about 8 a.m. at this site, resulting in a drastic reduction in the measured CO levels. This minimum of CO during midday was seen at four of the five sites, the one exception being the South Phoenix site (Figure 3A-22). And, in fact, as can be seen in Figure 3A-22, it was only the earliest time period (May 1987 to May 1988) where the CO levels remained elevated between the rush hour peaks. Subsequent to that 1-year period, the midday CO levels were quite low, as described above for the West Phoenix site.

The West Phoenix site (Figure 3A-21) illustrates another interesting feature of the seasonal, diurnal pattern for CO. Similar to the pattern seen in many of the Los Angeles sites, the Phoenix sites display a wintertime, evening peak whose elevated CO levels persist throughout the night, often not returning to their preevening peak levels before they begin to rise again for the morning peak. Obviously, the higher the evening peak, the higher the CO levels will be as they persist throughout the night, but, even for evening peak CO levels of around 5 ppm, the CO generally persisted through the night, remaining above preevening peak levels. The reason that the evening peak is much broader and persists much longer than does the morning peak is largely because the factors affecting the dispersion of the CO in the atmosphere (primarily the wind speed and the height of the mixed layer) are reduced greatly after sunset.

Table 3A-4 contains the Kendall tau correlation coefficients for the Phoenix MSA monitoring sites for the earliest year and the most recent year in these analyses. For the 10 pairs of sites for the weekday data, six pairs had correlations that rose between the 1986/87 winter season and the 1995/96 winter season, and four pairs remained about the same. For the 10 pairs of sites for the weekend data, only three pairs of correlations increased, five pairs decreased, and two pairs remained about the same. No discernable pattern is evident in the matrix of correlations in Table 3A-4. Indications are that the Phoenix airshed is more well mixed than are the others investigated here.

3A.4 SUMMARY

An analysis of ambient CO data obtained in the four geographically diverse metropolitan statistical areas of Denver, Los Angeles, New York, and Phoenix has shown that urban CO levels have decreased over the past 10 years. However, there have been instances where the downward trend has reversed itself on a year-to-year basis. Although the number of violation days has

TABLE 3A-4. KENDALL TAU SPATIAL CORRELATIONS FOR THE DAILY MAXIMUM 8-HOUR AVERAGE CARBON MONOXIDE DATA IN THE PHOENIX METROPOLITAN STATISTICAL AREA

	1986/87 Winter Season				
	South Phoenix	West Phoenix	East Butler Drive	Central Phoenix	North Miller Road
			WEEKDAY		
South Phoenix		0.47	0.45	0.58	0.50
West Phoenix	0.37		0.50	0.52	0.47
East Butler Drive	0.48	0.34		0.43	0.49
Central Phoenix	0.60	0.56	0.55		0.68
North Miller Road	0.59	0.41	0.59	0.57	
			WEEKEND		

	1995/96 Winter Season				
	South Phoenix	West Phoenix	East Butler Drive	Central Phoenix	North Miller Road
			WEEKDAY		
South Phoenix		0.63	0.49	0.57	0.53
West Phoenix	0.51		0.57	0.65	0.70
East Butler Drive	0.36	0.51		0.43	0.55
Central Phoenix	0.62	0.48	0.34		0.66
North Miller Road	0.52	0.62	0.49	0.56	
			WEEKEND		

declined for these cities, and the seasonally averaged peak concentrations generally do not exceed 8 ppm, at least one exceedance of 9 ppm for the maximum daily 8-h average for CO has occurred in 1995/1996 (the final year in this analysis) in all four of these cities.

Data obtained from different monitoring sites within a given MSA show a large degree of variability. During 1996, for example, annual mean CO concentrations ranged f rom 0.4 to 1.5 ppm in the Denver MSA, 0.4 to 3.2 ppm in the Los Angeles CMSA, 0.6 to 3.7 in the New

York CMSA, and 0.7 to 3.4 in the Phoenix MSA. Carbon monoxide concentrations during the cold season (November through February) range from 5 to 20% higher than the annual average in each MSA. However, it should be noted that, despite decreasing CO concentrations, the nature of the diurnal and seasonal variation observed at each monitoring site has remained remarkably constant over the 10-year period covered in this analysis. At all the sites investigated here, it is clear that the diurnal and seasonal variations in CO observed in these MSAs result largely from the interaction between motor vehicle emissions and meteorological parameters that, at times, can be conducive to the buildup of CO near the surface. The diurnal concentration profiles in most cases show a very distinctive two-peaked structure for weekdays. The peaks correspond to both the morning and evening rush hour commutes. Frequently, the morning peak is higher than the evening peak at any given site because the height of the mixed layer is much lower during the morning, thus inhibiting vertical mixing that would have diluted CO. In the late afternoon and into early evening, increased atmospheric turbulence resulting from solar heating raises the height of the mixed layer, resulting in generally lower CO concentrations compared with those of the morning.

Regional differences in atmospheric processes also may play a role in producing the nighttime behavior of CO observed at numerous sites in the Los Angeles and Phoenix MSAs compared with either the nationwide composite average diurnal cycle of CO shown in Figure 3A-6 or other locations, such as the Denver or New York MSAs. In the Los Angeles and Phoenix metropolitan areas CO concentrations often remain until midnight at levels reached during the evening rush hour. Then, although these concentrations gradually diminish throughout the night, they do not drop to the low afternoon levels (typically no more than 1 to 2 ppm, often less than this amount) before they begin to increase again because of the morning rush hour. This pattern is shown quite well in Figure 3A-19, which depicts the seasonal, diurnal concentration profile for the Central Phoenix site.

In general, the highest values of ambient CO were found during the wintertime (defined as the months of November through February, inclusive) in all of the MSAs included here. There were a few sites in the New York Metropolitan Area where a wintertime peak in CO was not discernable; the site on Flatbush Avenue in Brooklyn (Figure 3A-14) is an excellent example of this. It is not clear without further analysis, what combination of seasonal variations in emissions and meteorological parameters gave rise to this result.

There were large variations in the Kendall tau correlation coefficients calculated for the daily maximum 8-h average CO concentrations between individual sites in a given MSA during the winters of 1986/87 and 1995/96, suggesting a high degree of heterogeneity in the daily maximum 8-h average ambient CO levels in the MSAs that were characterized, likely indicating that daily maximum 8-h average CO levels observed at particular monitoring sites may not be related to CO levels occurring some distance away from the monitoring site. Further analyses will determine whether the correlation coefficients will increase significantly with an increase in averaging time to 24 h. Based on the above results, caution should be exercised in using the daily maximum 8-h average data to characterize the exposure of the general population within a given MSA (e.g., for studies relating health outcomes to ambient CO levels or in health studies in which CO may be viewed as a confounding variable).

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Shadwick, D.; Glen, G.; King, J.; Chen, X. (1998a) Analysis of carbon monoxide for the Los Angeles, California CMSA. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory; contract no. 68-D5-0049; June.

Shadwick, D.; Glen, G.; King, J.; Chen, X. (1998b) Analysis of carbon monoxide for the New York, New York CMSA. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory; contract no. 68-D5-0049; June.

Shadwick, D.; Glen, G.; King, J.; Chen, X. (1998c) Analysis of carbon monoxide for the Phoenix, Arizona MSA. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory; contract no. 68-D5-0049; June.

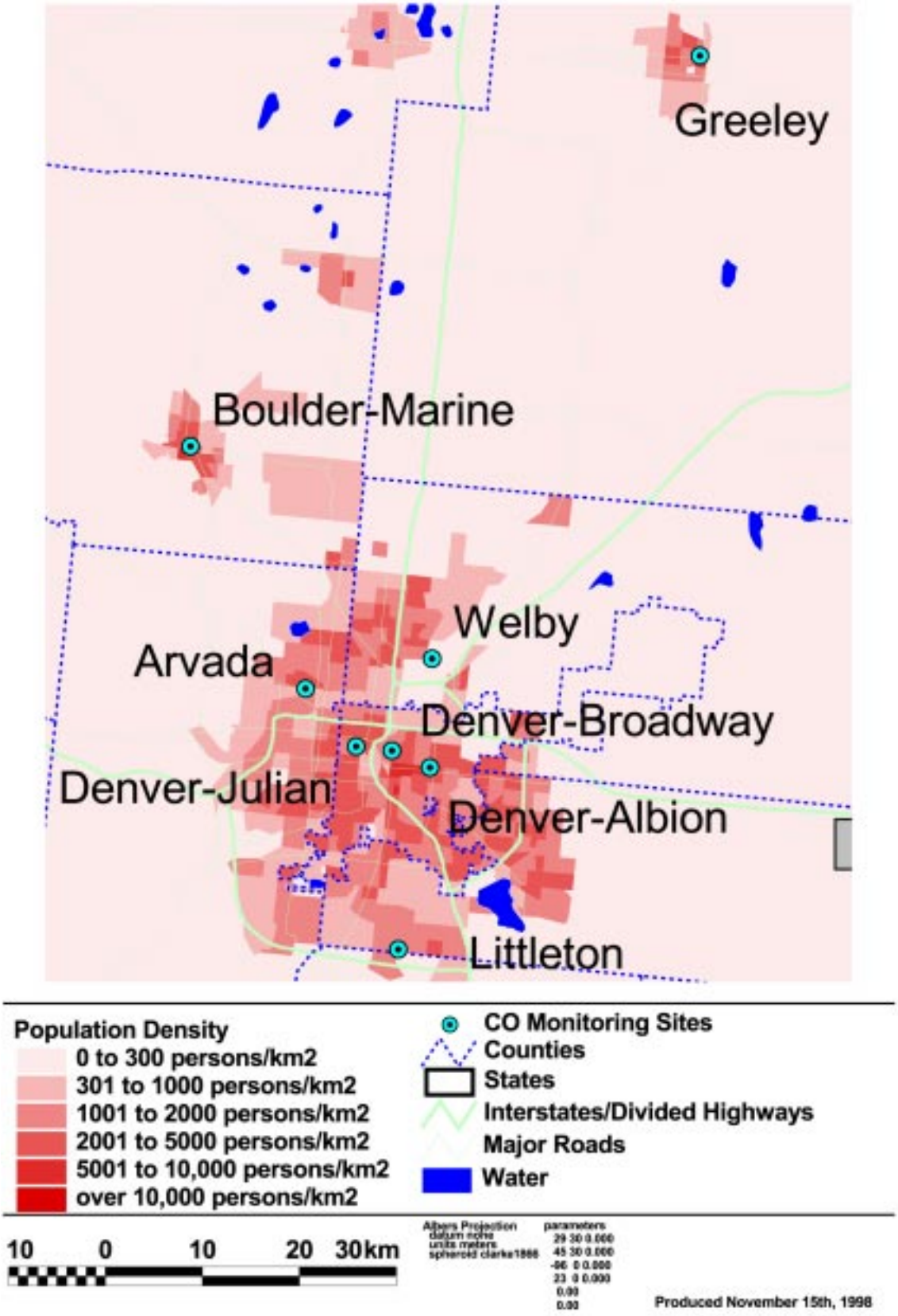


Figure 3A-1. Map of Denver showing locations of CO monitoring sites.

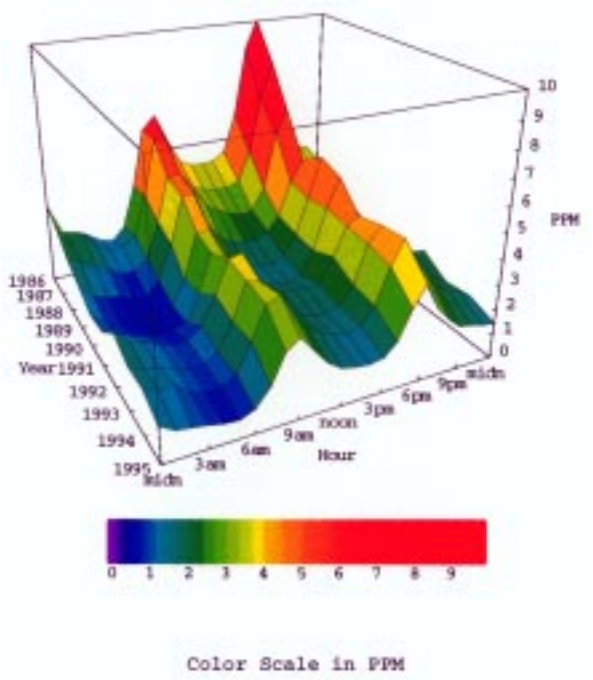


Figure 3A-2. Average diurnal variation in CO at the Denver-Broadway site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986/87 through 1995/96, and the z-axis shows CO mixing ratios in ppm.

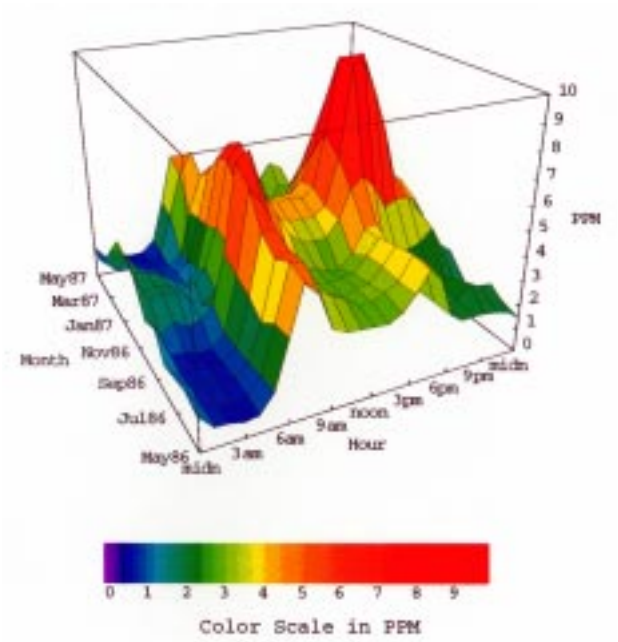


Figure 3A-3. Monthly average diurnal variation in CO at the Denver-Broadway site for weekdays from May 1986 through May 1987. The abscissa shows the time of day, the ordinate shows the month of the year, and the z-axis shows CO mixing ratios in ppm.

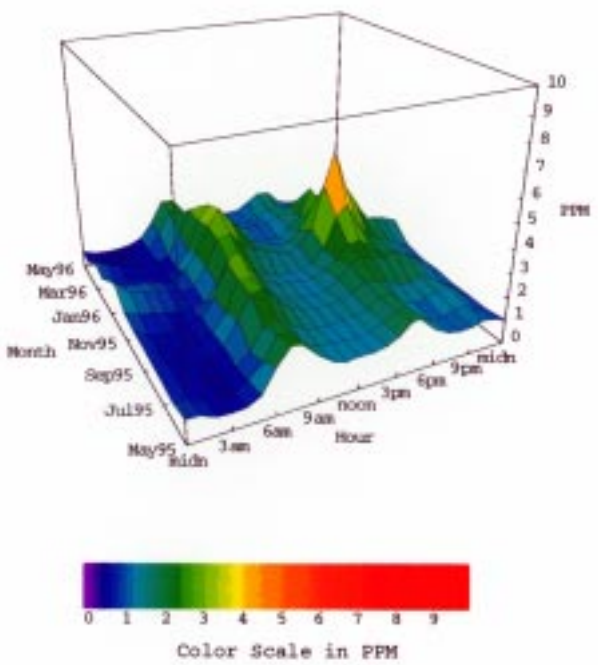


Figure 3A-4. Monthly average diurnal variation in CO at the Denver-Broadway site for weekdays from May 1995 through May 1996. The abscissa shows the time of day, the ordinate shows the month of the year, and the z-axis shows CO mixing ratios in ppm.

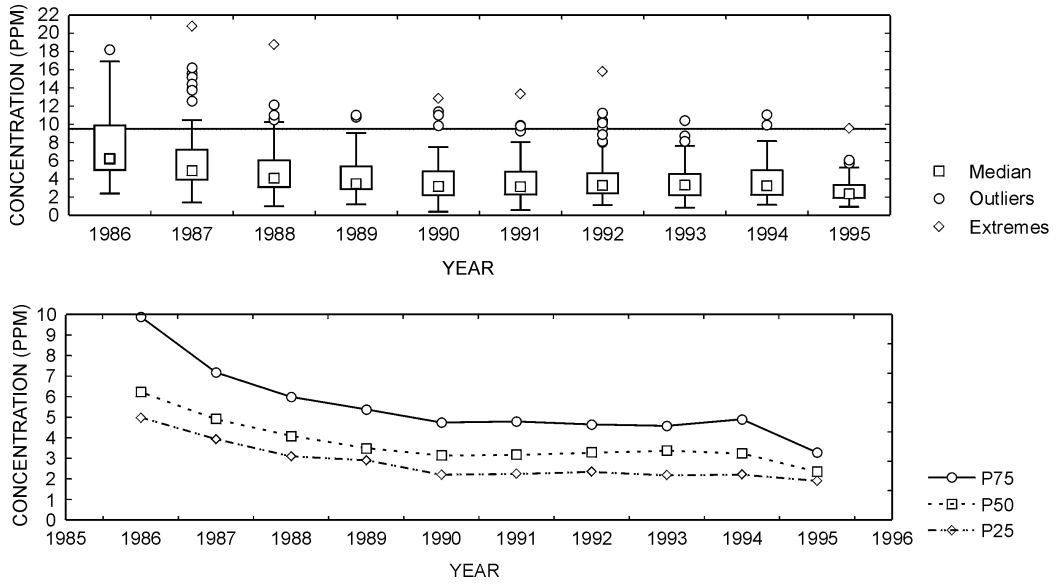


Figure 3A-5. Central tendency statistics for the daily 8-h max CO concentration at the Denver-Broadway site during the winter season from 1986 to 1995. The top graph shows box plots (with 10, 25, 50, 75, and 90 percentile values) for the entire time series. Each circle (outlier) or diamond (extreme) refers to an individual observation that is either three or four standard deviations (SDs) from the mean, and the horizontal line shows the current 8-h NAAQS for CO. The lower graph again shows the 25, 50, and 75 percentile values (P25, P50, and P75) from the upper graph.

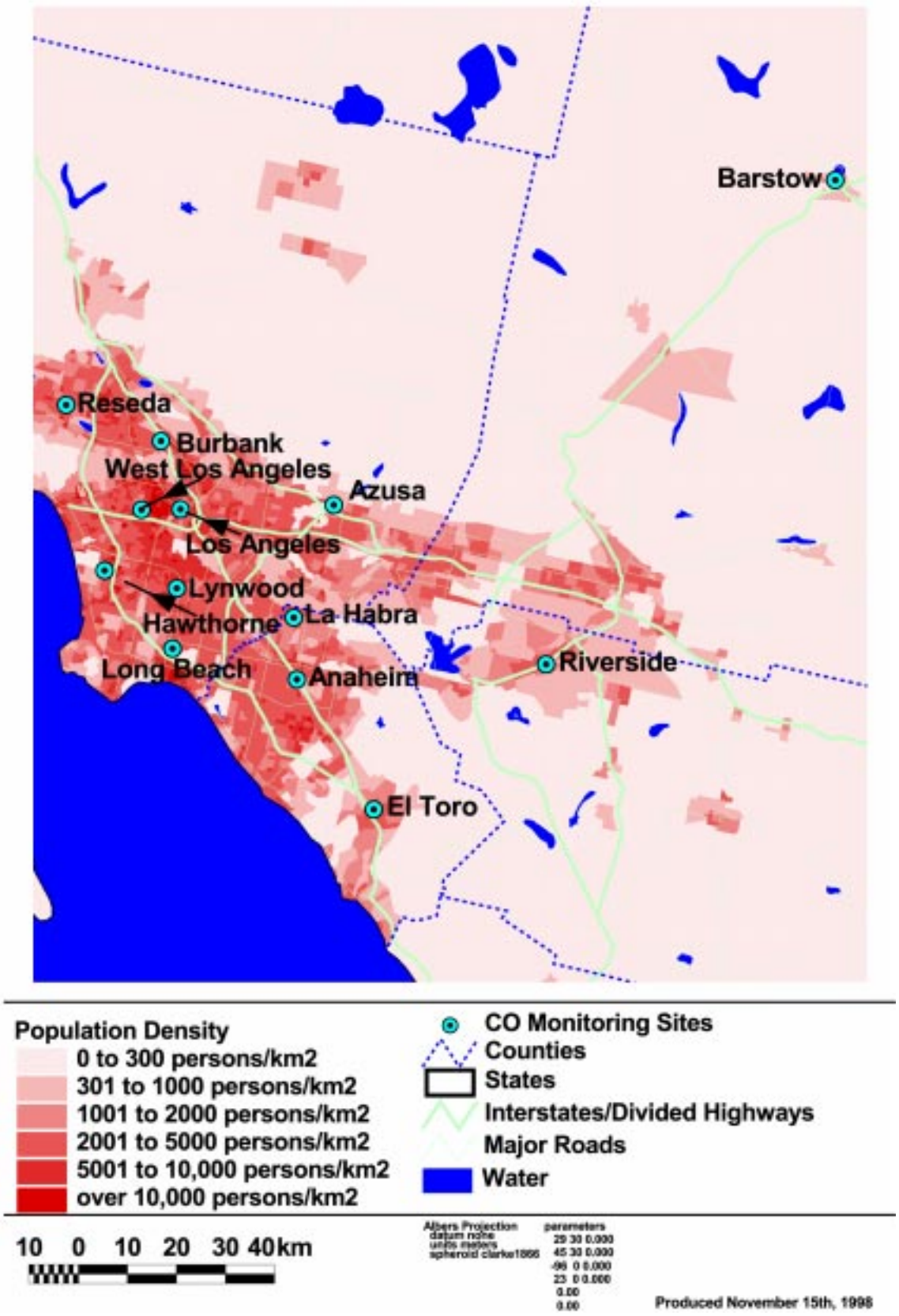


Figure 3A-6. Map of Los Angeles showing locations of CO Monitoring sites.

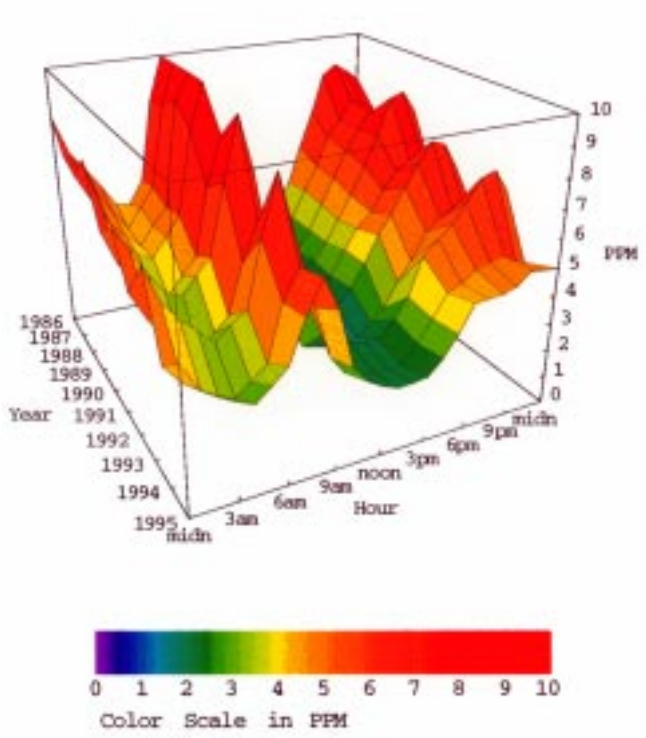


Figure 3A-7. Average diurnal variation in CO at the Los Angeles-Lynwood site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986/87 through 1995/96, and the z-axis shows CO concentrations in ppm.

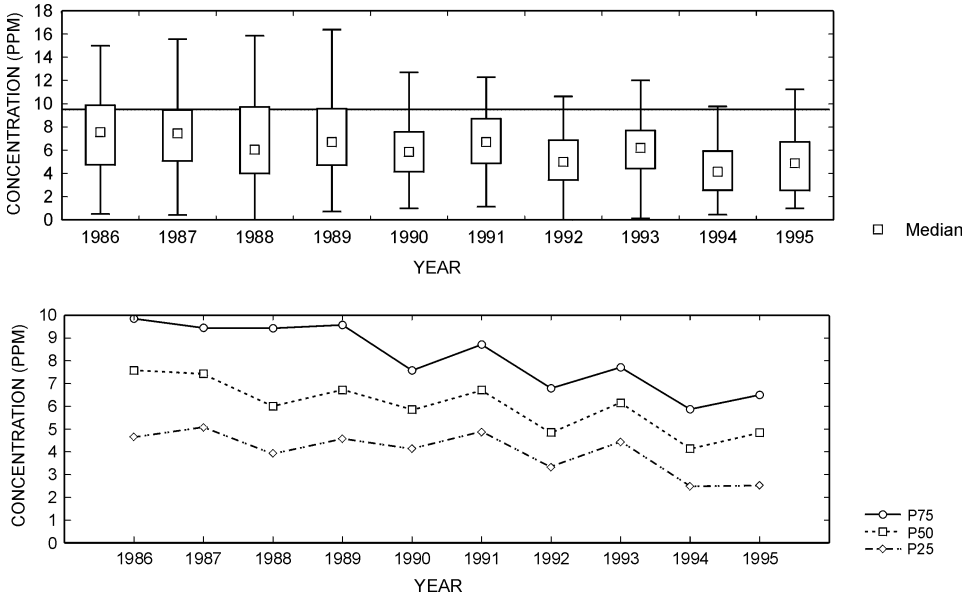


Figure 3A-8. Central tendency statistics for the daily 8-h max CO concentration at the Los Angeles-Hawthorne site during the winter season from 1986 to 1995. The top graph shows box plots (with 10, 25, 50, 75, and 90 percentile values) for the entire time series. The horizontal line shows the current 8-h NAAQS for CO. The lower graph again shows the 25, 50, and 75 percentile values (P25, P50, and P75) from the upper graph.

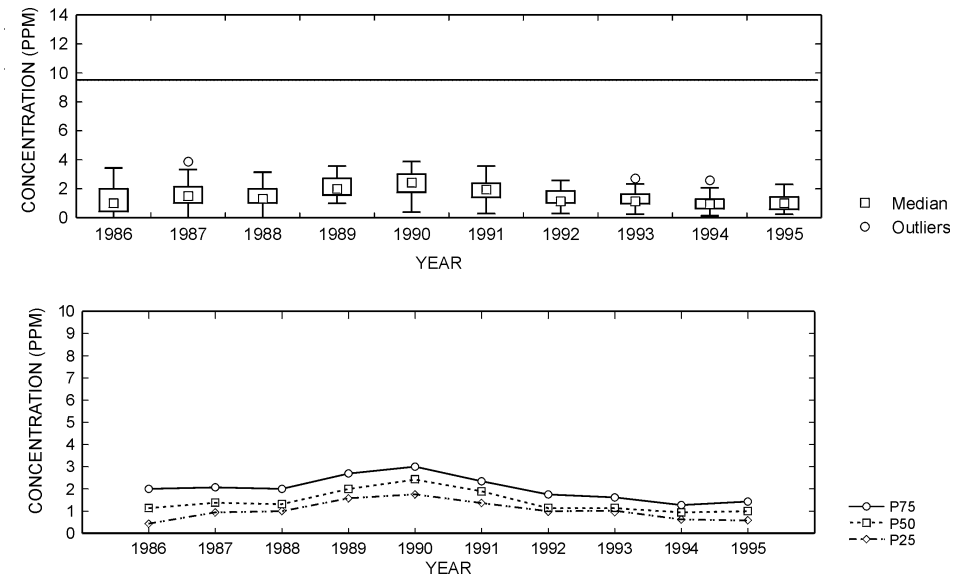


Figure 3A-9. Central tendency statistics for the daily 8-h max CO concentration at the Los Angeles-Barstow site during the winter season from 1986 to 1995. The top graph shows box plots (with 10, 25, 50, 75, and 90 percentile values) for the entire time series. Each circle (outlier) refers to an individual observation that is three SDs from the mean, and the horizontal line shows the current 8-h NAAQS for CO. The lower graph again shows the 25, 50, and 75 percentile values (P25, P50, and P75) from the upper graph.

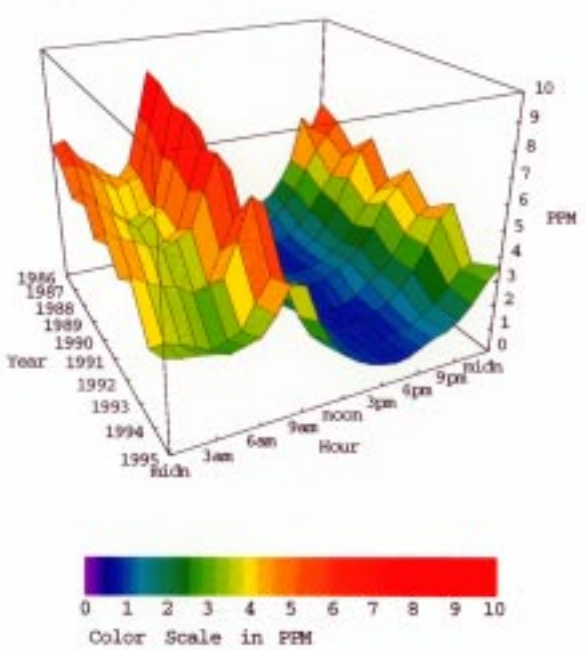


Figure 3A-10. Average diurnal variation in CO at the Los Angeles-Hawthorne site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986/87 through 1995/96, and the z-axis shows CO concentrations in ppm.

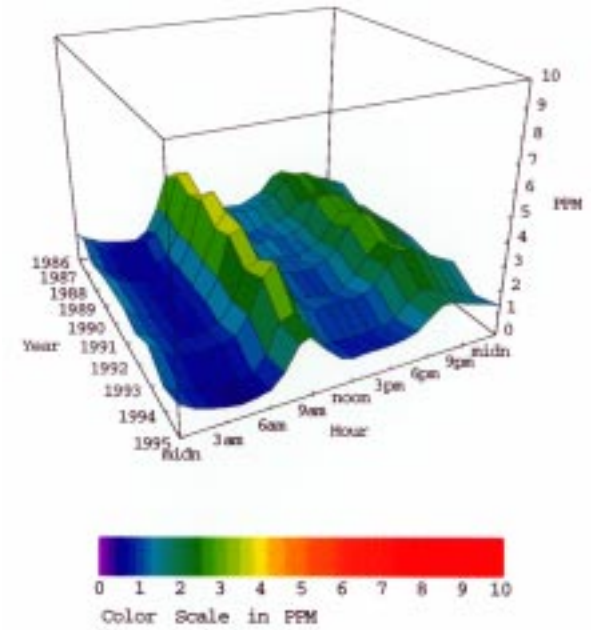


Figure 3A-11. Average diurnal variation in CO at the Los Angeles-El Toro site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986/87 through 1995/96, and the z-axis shows CO concentrations in ppm.

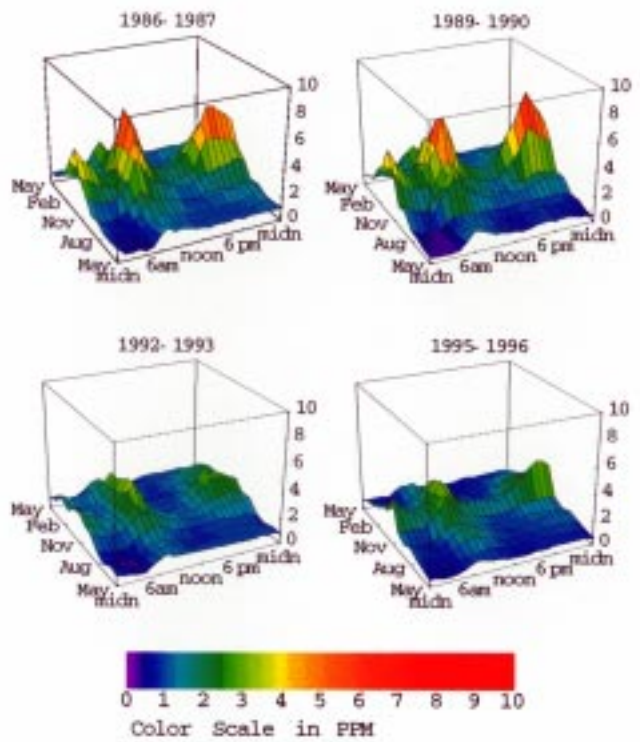


Figure 3A-12. Monthly average diurnal variation in CO at the Los Angeles-Anaheim site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis shows CO concentration in ppm.

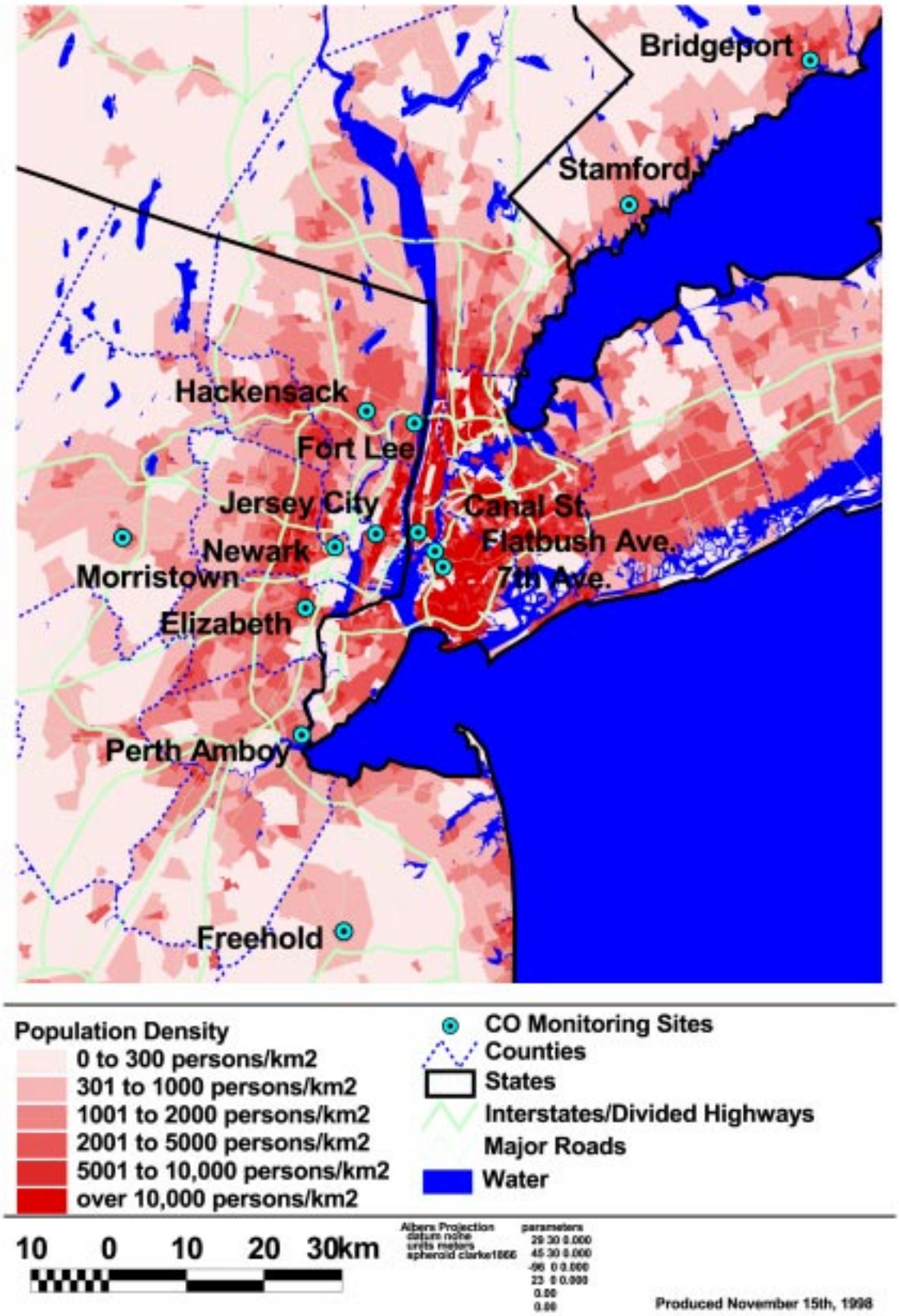


Figure 3A-13. Map of New York showing locations of CO monitoring sites.

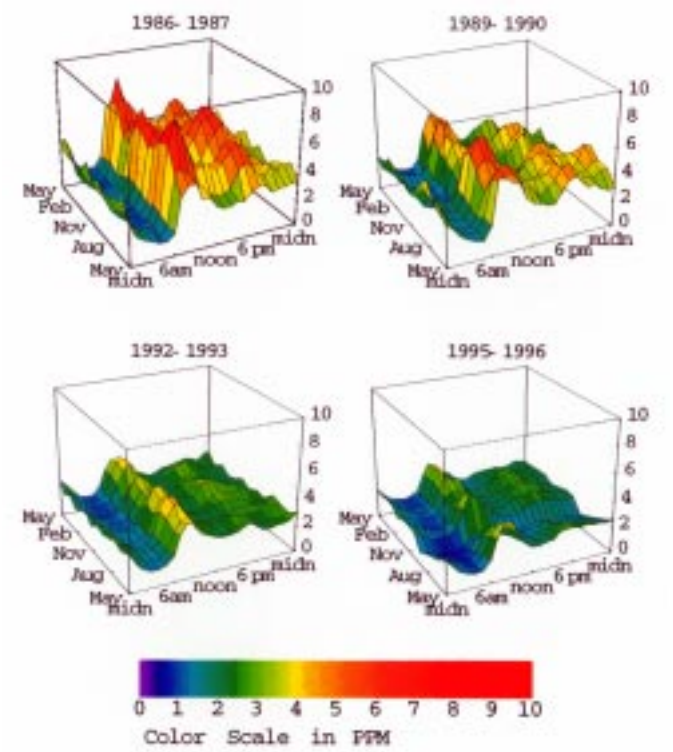


Figure 3A-14. Monthly average diurnal variation in CO at the New York-Flatbush site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis shows CO concentration in ppm.

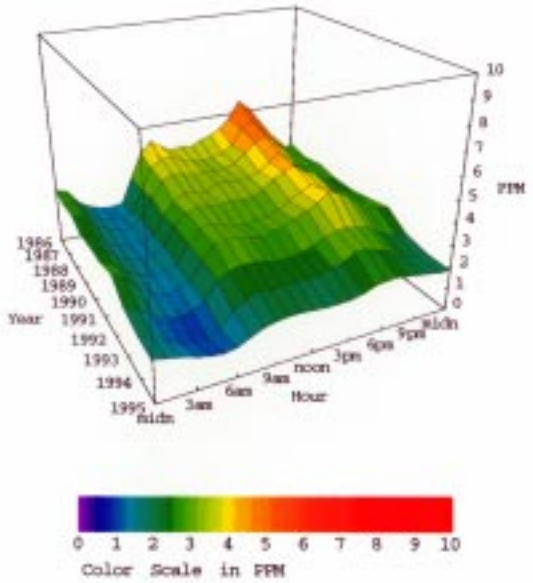


Figure 3A-15. Average diurnal variation in CO at the New York-Manhattan site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986/87 through 1995/96, and the z-axis shows CO concentrations in ppm.

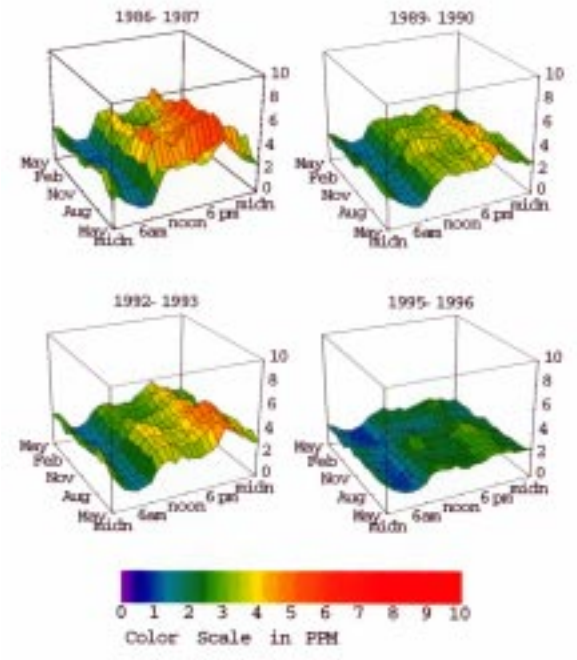


Figure 3A-16. Monthly average diurnal variation in CO at the New York-Manhattan site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis shows CO concentration in ppm.

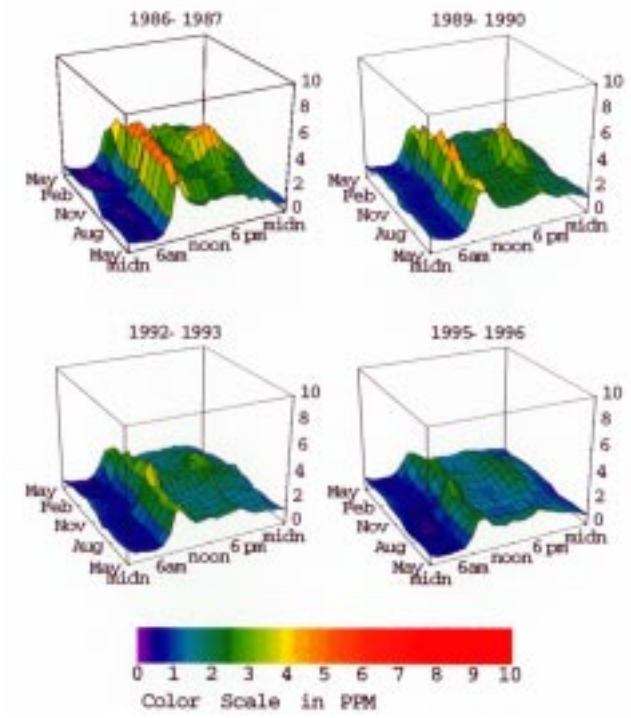


Figure 3A-17. Monthly average diurnal variation in CO at the New York-Morristown, NJ, site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis on each graph shows CO concentration in ppm.

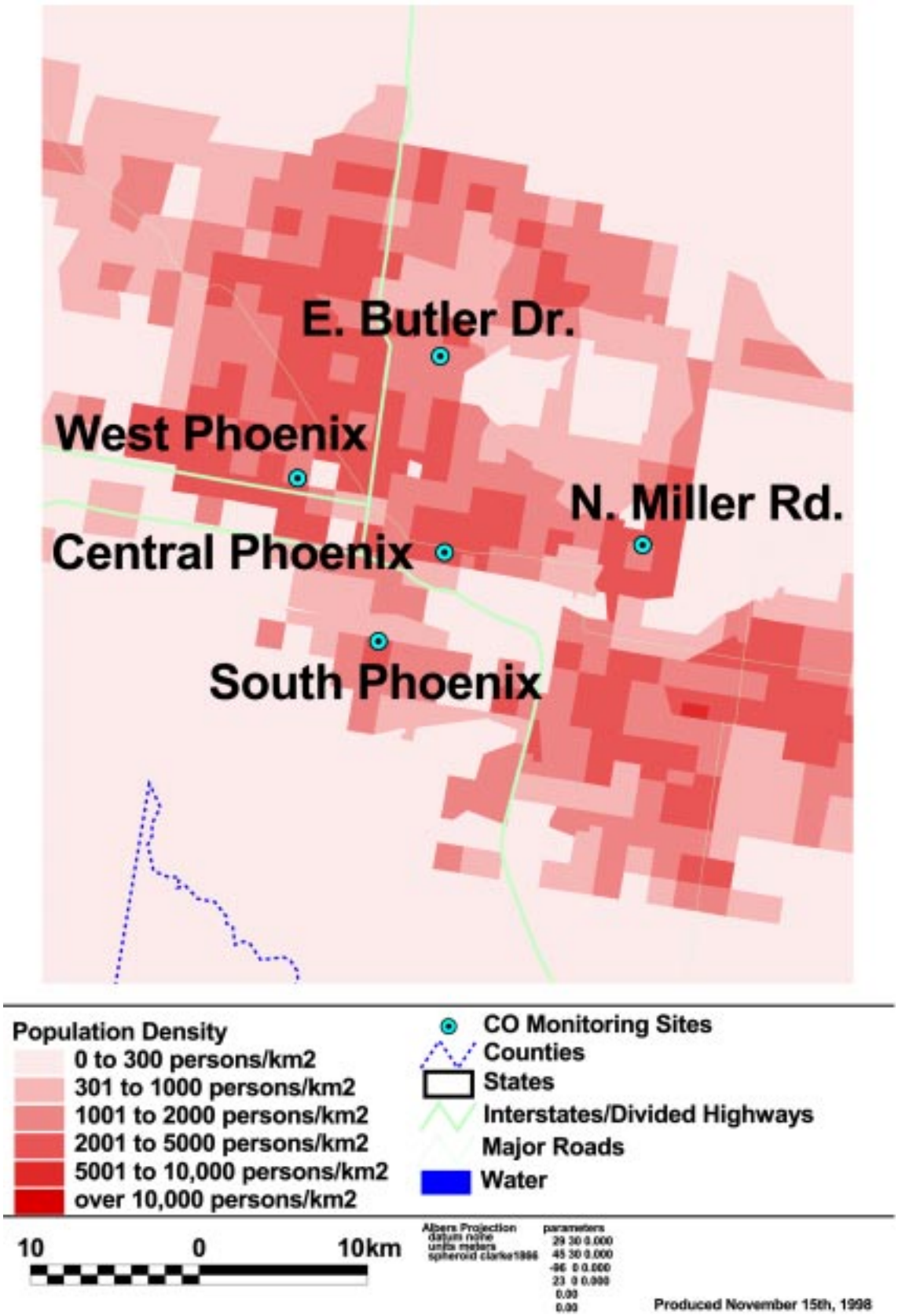


Figure 3A-18. Map of Phoenix showing locations of CO monitoring sites.

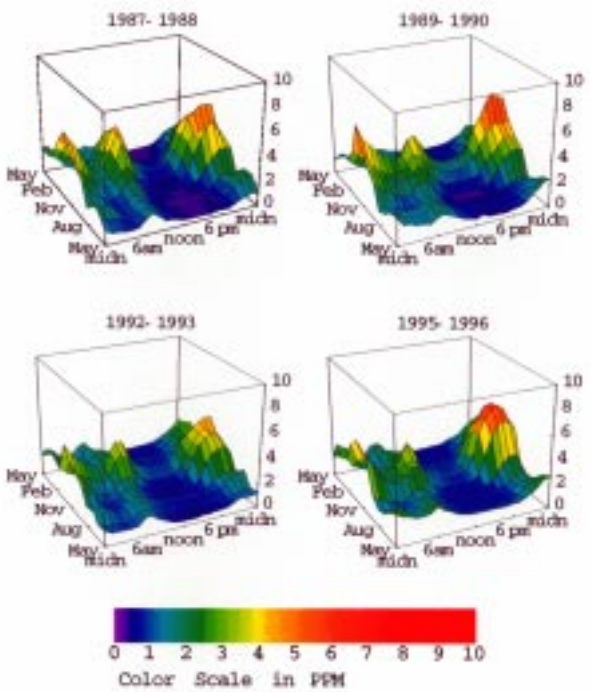


Figure 3A-19. Monthly average diurnal variation in CO at the Phoenix-Central site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis shows CO concentration in ppm.

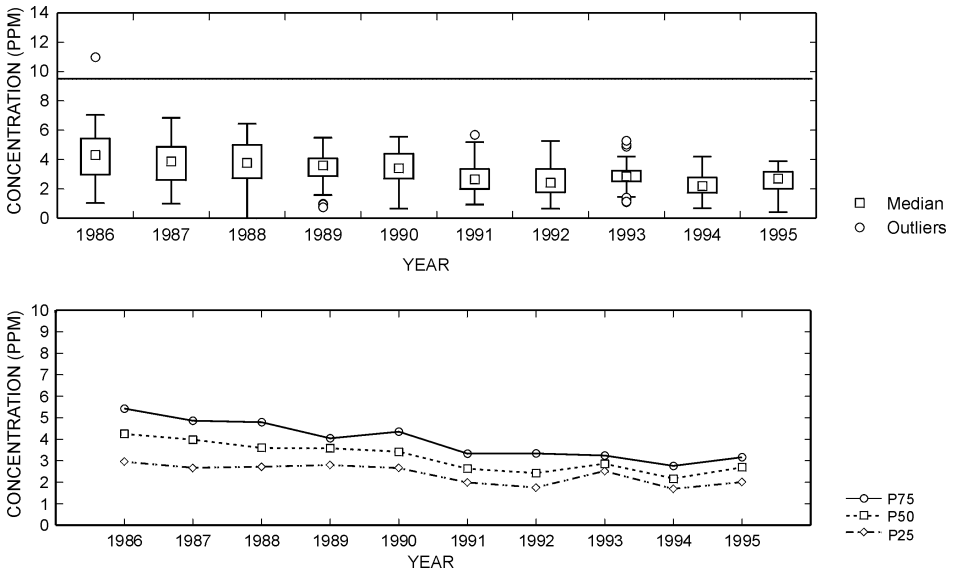


Figure 3A-20. Central tendency statistics for the daily 8-h max CO concentration at the Phoenix-East Butler site during the winter season from 1986 to 1995. The top graph shows box plots (with 10, 25, 50, 75, and 90 percentile values) for the entire time series. Each circle (outlier) refers to an individual observation that is three SDs from the mean, and the horizontal line shows the current 8-h NAAQS for CO. The lower graph again shows the 25, 50, and 75 percentile values (P25, P50, and P75) from the upper graph.

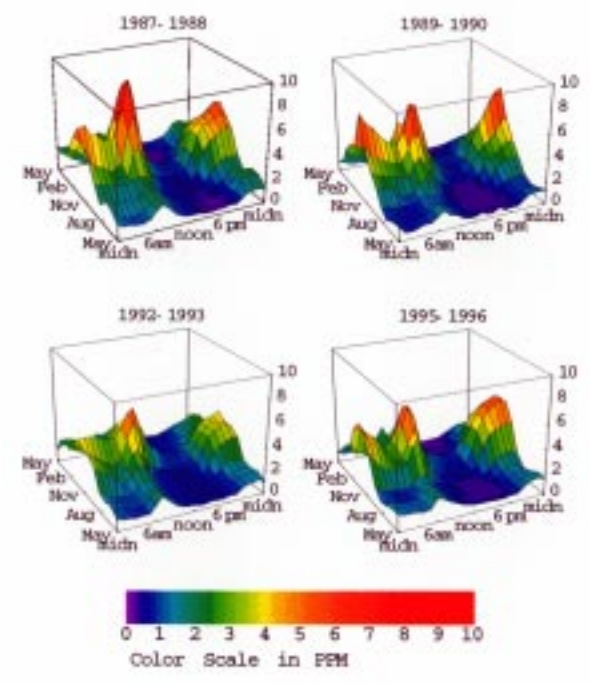


Figure 3A-21. Monthly average diurnal variation in CO at the Phoenix-West site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis shows CO concentration in ppm.

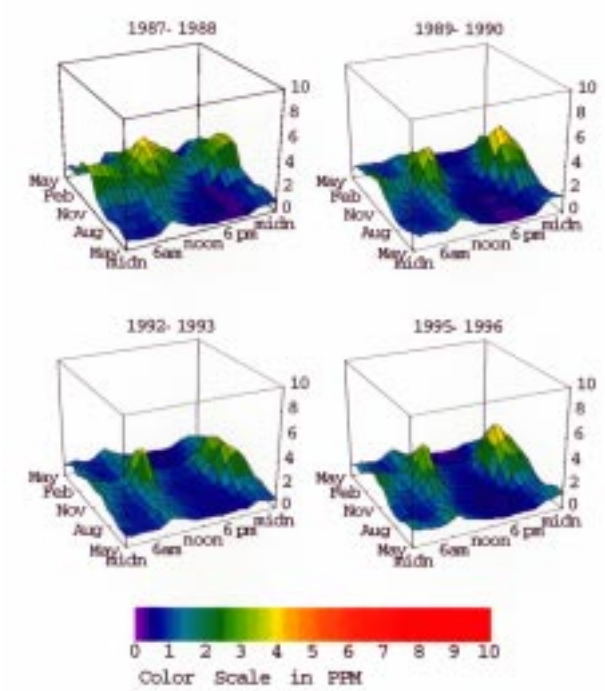


Figure 3A-22. Monthly average diurnal variation in CO at the Phoenix-South site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis shows CO concentration in ppm.

4. POPULATION EXPOSURE TO CARBON MONOXIDE

4.1 INTRODUCTION

National Ambient Air Quality Standards (NAAQS) have been set to protect public health and welfare. The NAAQS for carbon monoxide (CO), which are not to be exceeded more than once per year, are 9 ppm for an 8-h average and 35 ppm for a 1-h average. These standards include a margin of safety to protect the population from adverse effects of CO exposure. Accordingly, this chapter reviews studies of population exposure to CO concentrations from different sources and explains why CO exposure studies are necessary and how they are done. It also discusses how population exposures are estimated, describes typical levels and durations of CO exposure in various microenvironments, and examines how CO exposures have changed over time in the United States.

Because Americans spend substantial amounts of time indoors, it is important to determine the total population exposure to CO from both indoor and outdoor CO sources. In this chapter, "outdoor" concentrations are those measured in air that immediately surrounds an indoor microenvironment. Because of air exchange, "outdoor" CO concentrations have a direct effect on CO concentrations measured indoors. "Ambient" concentrations are those measured at fixed-site, air quality monitoring stations that are used to determine compliance with the NAAQS.

As discussed in Chapter 3, one cannot assume that "outdoor" and "ambient" concentrations are similar because of the ubiquitous presence of local motor vehicle traffic emissions that do not impact directly the monitoring station (e.g., downwind of it). However, one generally can assume that indoor and "outdoor" CO concentrations are approximately the same, except for situations when CO is emitted by indoor sources (e.g., gas appliances inside a home), or when CO emissions from an immediate outdoor source directly contaminate indoor microenvironments (e.g., when a vehicle's undiluted exhaust infiltrates the passenger cabin of that vehicle or a following vehicle).

After inhalation, CO binds with hemoglobin (Hb) in the blood to form carboxyhemoglobin (COHb). Besides endogenous CO production developed within the body from Hb catabolism,

everyone is exposed to a global background level of CO in the ambient air on the order of 0.1 ppm (see Section 3.2). These combined sources constitute a reference or baseline exposure as reflected in an endogenous COHb level on the order of 0.5% that varies individually, based on physiological differences. These differences reflect variation in basal metabolisms and other metabolic sources, as discussed in detail in Sections 5.3 and 5.4. This chapter discusses the exposure of nonsmokers to CO. Smokers are excluded, because they represent a potential source of CO, because of their higher baseline levels of COHb and adaptive response to elevated COHb.

The study of population exposure is multidisciplinary, and the definition of personal exposure has evolved over time (Ott, 1982; Duan, 1982; Lioy, 1990; Federal Register, 1992; Last et al., 1995; Zartarian et al., 1997). A recent definition offered by Zartarian et al. (1997) states that exposure is the contact between an agent and a target at a specified contact boundary, defined as a surface in space containing at least one exposure point (a point at which contact occurs). Under this definition, exposure can occur instantaneously at a single point in space, or it can occur over time or space. For purposes of reviewing the literature in this chapter, the target is the human, the agent is CO, and the contact boundary is assumed to be the lining of the lung where CO exchange takes place between the air and the blood.

This chapter is concerned only with CO exposures that occur at concentrations capable of increasing COHb levels above a reference baseline level. Besides exposure to CO concentrations above the background level, human COHb levels can be elevated because of metabolic degradation of many drugs, solvents (e.g., methylene chloride), and other compounds to CO. For details see Section 5.3. The maximum COHb level resulting from an exposure to methylene chloride has twice the half-life of the identical maximum COHb level produced by direct exposure to a CO molecule (Wilcosky and Simonsen, 1991). Therefore, people exposed to methylene chloride will be more susceptible to reaching any given COHb concentration resulting from CO exposure. Hence, the literature on exposure to methylene chloride also is discussed in this chapter.

The chapter is organized as follows. The first section summarizes the state of knowledge on population exposure to CO as of 1991, when the U.S. Environmental Protection Agency (EPA) published the last CO air quality criteria document (AQCD). This is followed by a discussion of more recently published studies of population exposure to all sources of CO, except those related to active inhalation of tobacco smoke. This discussion describes typical levels of

exposure as people engage in daily activities, including those related to an occupation. Next is a description of factors affecting trends in population exposure to carbon monoxide. These factors include public policies affecting motor vehicle emissions, travel behavior, and smoking and societal changes in human activity patterns. The conclusion summarizes findings of this review and discusses their implications for CO exposure models such as the probabilistic NAAQS Exposure Model.

4.2 BRIEF SUMMARY OF POPULATION EXPOSURE STUDIES PRIOR TO 1991

This section briefly reviews key population exposure studies that were completed by 1991. It identifies populations who are sensitive to CO exposure, discusses studies of population exposure based on fixed-site and personal monitors, and relevant population exposure models.

4.2.1 Sensitive Populations

The NAAQS are intended to protect certain sensitive and probable risk groups of the general population. These groups differ from one air pollutant to another. In the case of CO, these groups include anemics; the elderly; pregnant women; fetuses; young infants; and those suffering from certain blood, cardiovascular, or respiratory diseases. People currently thought to be at greatest risk from exposure to ambient CO levels are those with ischemic heart disease who have stable exercise-induced angina pectoris (cardiac chest pain). Individuals with this disease represented about 3% of the U.S. population in 1994. Studies show that earlier time to onset of cardiac chest pain occurred in these people while they exercised during exposures to CO concentrations that produced levels of COHb in the bloodstream in the range of 2 to 3% (U.S. Environmental Protection Agency, 1991). The National Health and Nutrition Examination Survey (NHANES) II study reported that 6.4% of the U.S. population who never smoked had COHb levels above 2.1%, based on a national random sample of people (n = 3,141) ranging in age from 12 to 74 years (Radford and Drizd, 1982). The NHANES II study was done in the late 1970s when ambient CO concentrations were much higher (see Figure 3-3).

4.2.2 Estimates of Population Exposure Based on Fixed-Site Monitors

In the United States, attainment of the NAAQS is based on ambient air quality measurements recorded at a nationwide network of fixed-site monitors. Based on this network, the Office of Air Quality Planning and Standards of EPA estimated that 12.7 million people lived in seven counties where CO levels exceeded the NAAQS in 1996 (U.S. Environmental Protection Agency, 1998a). The estimate was made by combining census data on county populations with data on violations of the CO NAAQS recorded by stationary monitors. Previous studies have shown that such estimates are insufficient for estimating population exposure to CO for the two reasons discussed below:

(1) Ambient CO concentrations are not spatially homogeneous within the area monitored. For example, Ott and Eliassen (1973) reported average CO levels ranging from 5.2 to 14.2 ppm for sidewalks along congested streets of downtown San Jose, CA. Corresponding CO averages at fixed-site monitors were only 2.4 to 6.2 ppm. A decade later, Ott and Flachsbart (1982) found a narrower gap between simultaneous CO measurements from fixed-site and personal exposure monitors deployed at indoor and outdoor commercial settings in five California cities.

(2) In the absence of indoor CO sources and immediate outdoor sources (i.e., idling motor vehicles), indoor CO concentrations tend to equal outdoor concentrations over the long term. In buildings with mechanical ventilation systems, the timing and scheduling of outdoor "make-up" air into the building affects ratios of indoor-outdoor concentrations both in the short and long term (Yocom, 1982). For example, when make-up air was introduced into an air-conditioned building during morning rush hours (when outdoor CO levels were high), indoor CO concentrations exceeded outdoor levels for the remainder of the day (Yocom et al., 1971). In the presence of indoor sources such as gas appliances, indoor CO concentrations often exceed the outdoor levels (U.S. Environmental Protection Agency, 1991). Many American homes use gas (natural gas and liquid propane) for space heating, cooking, heating water, and drying clothes. In a 1985 Texas study of a low-socioeconomic population, CO concentrations were greater than or equal to 9 ppm in 12% of surveyed homes. Residential CO concentrations were high where unvented gas space heaters were used as the primary heat source (Koontz and Nagda, 1988).

These facts take on added significance given that many Americans spend most of their time indoors (Szalai, 1972; Chapin, 1974; Meyer, 1983; Johnson, 1987; Schwab et al., 1990). Hence, studies of actual personal exposure to CO, rather than crude estimates of population exposure to ambient CO, are necessary to determine what risk CO poses to public health (Sexton and Ryan, 1988).

4.2.3 Surveys of Population Exposure Using Personal Monitors

With the development of personal exposure monitors (PEMs) in the 1970s, researchers began to measure either the total human exposure of a population or the exposures of subpopulations in microenvironments that posed higher risks of CO exposure, such as inside a motor vehicle moving slowly in congested traffic. In theory, a microenvironment exists if the CO concentration at a particular location and time is sufficiently homogeneous yet significantly different from the concentrations at other locations (Duan, 1982).

Human exposure studies of target populations typically use either a direct or an indirect approach. In the direct approach, PEMs are distributed either to a representative or "convenience" (nonrandom) sample of a human population. Population exposure parameters cannot be estimated from a convenience sample, because it does not represent the population from which it was drawn. Using PEMs, people record exposures to selected air pollutants as they engage in their regular daily activities. In the indirect approach, trained technicians use PEMs to measure pollutant concentrations in specific microenvironments or populations. This information then must be combined with additional data on human activity patterns to estimate the time spent in those microenvironments.

Sexton and Ryan (1988) discuss types of personal monitors and research methods used by the direct and indirect approaches. Although small passive monitors may be placed near a person's oral/nasal cavity where exposure actually occurs, larger monitors must be carried by a person or placed nearby. Using data from PEMs, one can construct exposure-time profiles for a particular activity such as commuting or the integrated exposure between two points in time. From this information, one can determine the average concentration to which a person has been exposed for a given time period. Based on the superposition principle, one also can determine a net microenvironmental concentration by subtracting the outdoor concentration, as measured by an appropriate fixed-site monitor, from a microenvironmental concentration measured by a

personal monitor. Because ambient CO concentrations are not spatially homogeneous at any given moment, the net microenvironmental concentration can be either positive or negative in value. A negative net value can occur, for example, in homes with no CO sources during morning periods when ambient CO concentrations from rising traffic emissions on highways have not yet diffused into residential areas. A negative net value simply indicates that the microenvironment has a lower positive CO concentration than the outdoor environment at a given moment.

In an early pilot study in Los Angeles, using the direct approach, subjects recorded their exposures and corresponding activities in diaries (Ziskind et al., 1982). Because this was cumbersome and potentially distorted the activity, later studies used data loggers to store concentrations electronically, as done by major studies of the urban populations of Denver, CO, and Washington, DC (Akland et al., 1985). In these studies, subjects still used diaries to record pertinent information about their activities in specified microenvironments while monitoring personal exposures. Data were then transferred electronically from data loggers and manually from diaries to computer files for analysis.

The direct approach, which uses the total exposure assessment methodology, provides a frequency distribution of air pollutant concentrations for a sample of people, selected randomly from either a general or a specific population (defined by demographic, occupational and health-risk factors) for a particular time period of interest (e.g., a day). Studies using the direct approach enable researchers to assess what percentage of a large population is exposed to pollutant concentrations in excess of ambient air quality standards (Akland et al., 1985). Studies using the indirect approach may focus on situations that bring large numbers of people in contact with high concentrations in specific microenvironments. For example, Flachsbart and Brown (1989) determined what percentage of employees were exposed to CO concentrations in excess of national and state ambient air quality standards at a large shopping center attached to a parking garage in Honolulu, HI.

Direct studies of general populations are rare because of their expense and the logistical problems of monitor distribution. Two examples for CO were those done in Denver and Washington during the winter of 1982-1983 (Akland et al., 1985). In both studies, the target population included noninstitutionalized, nonsmoking residents, 18 to 70 years of age, who lived in the city's metropolitan area. This was estimated to be about 1.2 million adults in Washington

and 500,000 in Denver. In both cities, the composite network of fixed-site monitors overestimated the 8-h exposures of people with low-level personal exposures and underestimated the 8-h exposures of people with high-level personal exposures. With respect to the underestimates, over 10% of the daily maximum 8-h personal exposures in Denver exceeded the NAAQS of 9 ppm, and about 4% of maximum 8-h personal exposures in Washington exceeded 9 ppm. The end-expired breath CO levels were in excess of 10 ppm, which is roughly equivalent to about 2% COHb in about 12.5% of the Denver participants and about 10% (after corrections were made for instrumental measurement drift) of the Washington participants. Simultaneous CO measurements at fixed-site monitors exceeded 9 ppm only 3% of the time in Denver and never exceeded 9 ppm in Washington (Akland et al., 1985).

The Denver and Washington studies identified certain activities associated with higher CO exposures. The two highest average CO concentrations occurred when subjects were inside a parking garage and when traveling by car. Those who commuted 6 h or more per week had higher average exposures than those who commuted less than 6 h per week. Higher mean CO concentrations occurred for travel by motor vehicle (car, bus, truck, etc.) than by walking. High exposures also were traced to indoor and occupational sources involving use of or proximity to gas appliances and gasoline engines. High indoor concentrations above the 8-h NAAQS of 9 ppm occurred in public garages, service stations, and motor vehicle repair facilities. Denver had higher average CO concentrations than Washington for all microenvironments because of Denver's higher altitude and colder winter climate (Ott et al., 1992).

4.2.4 Population Exposure Models

Many studies developed models to predict exposure in both general and special populations (U.S. Environmental Protection Agency, 1991). These models are important because it is impossible and impractical to know the hourly and daily exposure of every person in a population on a real-time basis. Models of human exposure are empirically derived mathematical relationships, theoretical algorithms, or hybrids of these two. To support policy decisions related to the setting of ambient and emission standards, EPA supported development of two general population exposure models: (1) the NAAQS Exposure Model (NEM) and (2) the Simulation of Human Activity and Pollutant Exposure (SHAPE) model. These models assume that an individual's total CO exposure over a specified time interval can be estimated as the sum

of the average concentration within a microenvironment, multiplied by the amount of time spent in that microenvironment (Duan, 1982).

The SHAPE model used a stochastic approach to simulate the exposure of an individual over a 24-h period (Ott, 1984). The model replicates a person's daily activity pattern by sampling from probability distributions representing the chance of entry, time of entry, and time spent in 22 different microenvironments. Transition probabilities determine a person's movement from one microenvironment to another. The model assumes that microenvironmental concentrations reflect the contribution of an ambient concentration and a component representing CO sources within each microenvironment. Because SHAPE relies on field surveys of representative populations, the data requirements of the model are fairly extensive.

The SHAPE model can estimate the frequency distribution of maximum standardized exposures to CO for an urban population and the cumulative frequency distribution of maximum exposures for both 1-h and 8-h periods, thereby allowing estimates of the proportion of the population that is exposed to CO concentrations above the NAAQS. An evaluation of SHAPE by Ott et al. (1988), using survey data from the aforementioned Denver study, showed that the observed and predicted arithmetic means of the 1-h and 8-h maximum average CO exposures were in close agreement. However, SHAPE overpredicted low-level exposures and underpredicted high-level exposures.

Compared to SHAPE, which focuses on an individual's exposure, NEM has a higher level of aggregation based on cohorts of people. The NEM model has evolved over time from deterministic to probabilistic versions. As described elsewhere (Johnson and Paul, 1983; Paul and Johnson, 1985), the deterministic version of NEM simulates movements of selected groups (cohorts) of an urban population through a set of exposure districts or neighborhoods and through different microenvironments. Cohorts are identified by district of residence and, if applicable, district of employment, as well as by age-occupation group and activity pattern subgroup. The NEM uses empirical adjustment factors for indoor and in-transit microenvironments, and accumulates exposure over 1 year. Although deterministic NEM was able to estimate central tendencies in total exposure accurately, it did less well estimating the associated uncertainty caused by variation in time spent in various microenvironments (Quackenboss et al., 1986) or to variation in microenvironmental concentrations (Akland et al., 1985). Paul et al. (1988) discussed advancements in the deterministic version of NEM.

In recent years, EPA developed the probabilistic NEM for CO (pNEM/CO); see Johnson et al. (1992) for a description of the assumptions and algorithms of pNEM/CO, as those details are beyond the scope of this chapter. Figure 4-1 shows the conceptual overview of the logic and data flow of the pNEM/CO model. It shows how any alternative CO NAAQS can be evaluated by establishing the distributions of personal exposures to CO when that alternative CO standard is met. The inputs to the model (e.g., activity patterns, ambient monitoring data, air exchange rates) are in the round-cornered boxes, and the model calculations are shown in the other boxes.

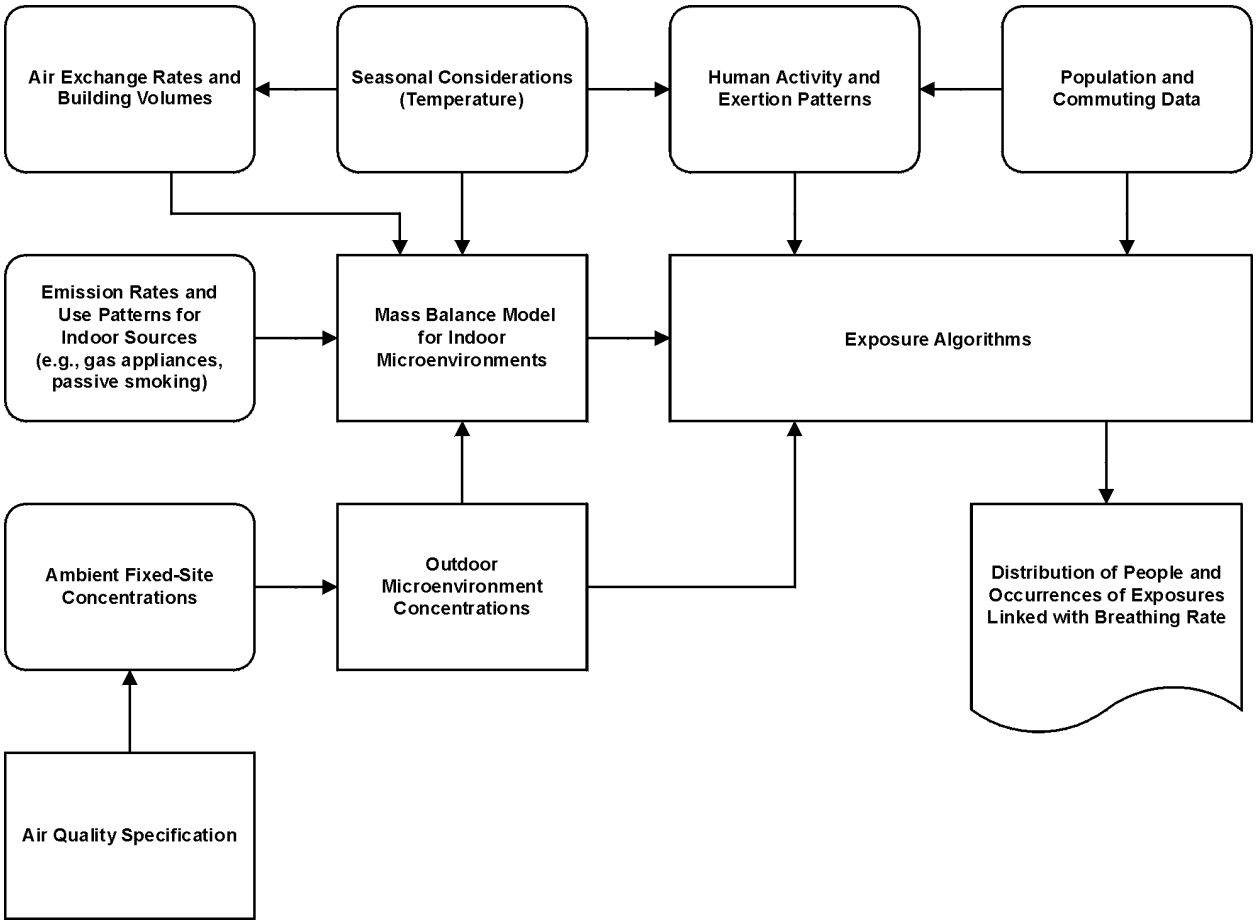


Figure 4-1. Conceptual overview of pNEM.

Source: Johnson et al. (1999).

McCurdy (1995) examined the history of both the NEM and pNEM models and the role they have played in reviews of criteria air pollutants such as CO. The EPA used pNEM/CO in its previous review of the CO NAAQS (U.S. Environmental Protection Agency, 1992). At the request of the Clean Air Science Advisory Committee, EPA evaluated the predictions of pNEM/CO against observed data for subjects of the Denver CO study. Based on this evaluation, Law et al. (1997) reported the predicted and observed population exposure cumulative frequency distributions (CFD), with and without gas stove use. Figures 4-2 and 4-3 show that, regardless of gas stove use, pNEM/CO overpredicted the CFD at low exposures and underpredicted the CFD at high exposures for 8-h daily maximum exposures. Similar results were reported for the 1-h daily maximum exposures, with and without gas stove use. Relatively close agreement between simulated and observed PEM data occurred for CO concentrations near the average exposure, within the range of 6 to 13 ppm for the 1-h case and within 5.5 to 7.0 ppm for the 8-h case.

In summary, there is a need to improve the abilities of both SHAPE and pNEM to predict high-end exposures. This perhaps could be achieved by introducing autocorrelation of inputs for time and concentration for nonindependent microenvironments (e.g., the commuting time and CO exposure from home to work is not independent of the commuting time and CO exposure from work to home). Also, both SHAPE and pNEM could consider CO emission sources, microenvironments and activity patterns that may have been excluded from the models.

4.3 SURVEY OF RECENT EXPOSURE STUDIES OF NONSMOKERS

This section discusses some population exposure studies that were excluded from the 1991 CO AQCD and studies that were published or accepted for publication in the scientific, peer-reviewed literature since then. The section is divided into nonoccupational and occupational subsections.

4.3.1 Nonoccupational Exposures

This subsection focuses on nonoccupational CO exposures that occur because of a variety of human activities that require contact with sources of CO emissions such as motor vehicles and fuel-burning tools and appliances. Section 3.5 discusses studies where CO has been measured by

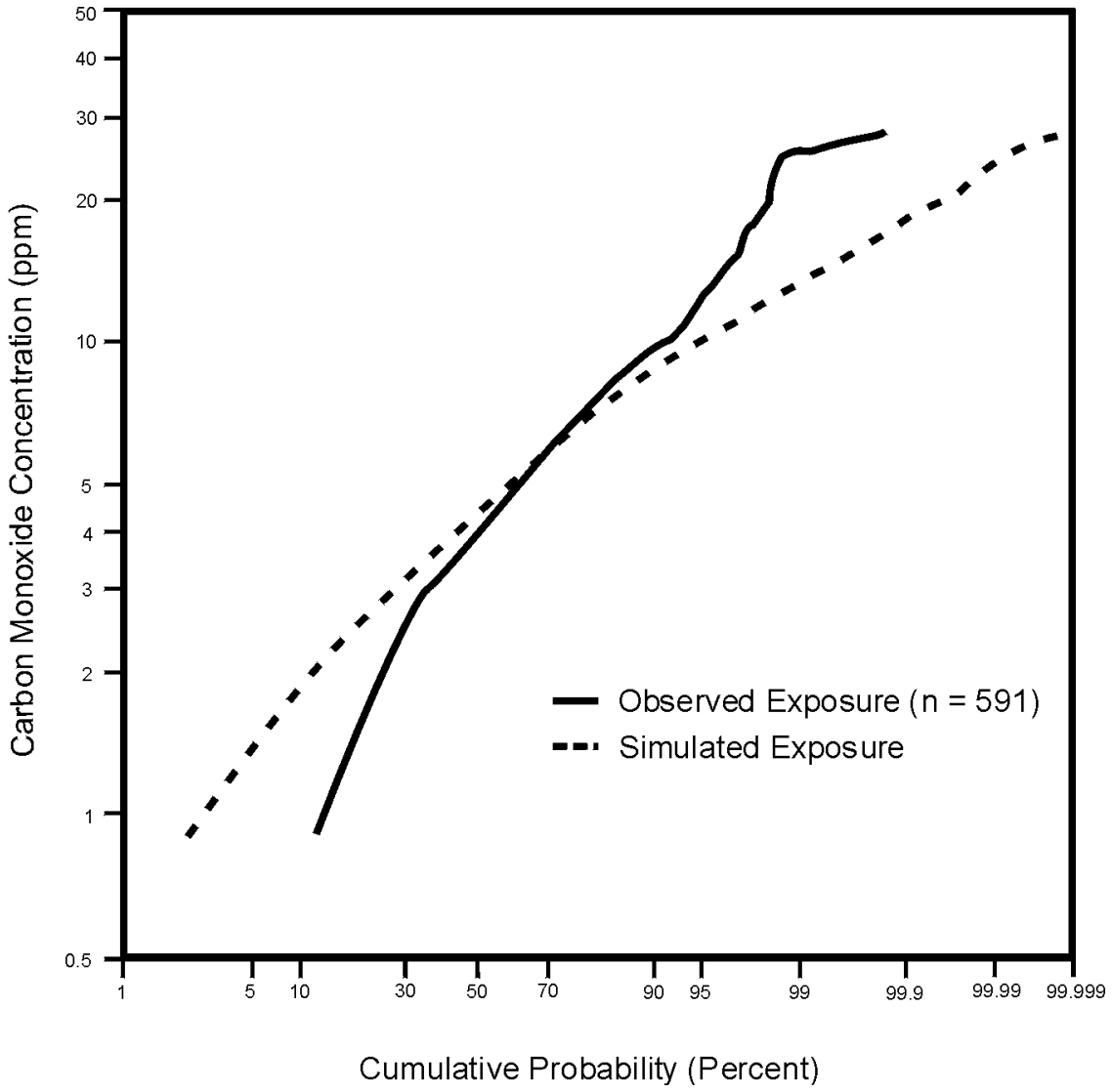


Figure 4-2. Observed versus simulated 8-h daily maximum exposure for persons residing in homes with gas stoves in Denver, CO.

Source: Law et al. (1997).

area monitors in indoor microenvironments because such measurements constitute an indirect exposure estimate. In addition, this section discusses studies of breath CO in populations and studies of exposure to methylene chloride because it increases COHb levels.

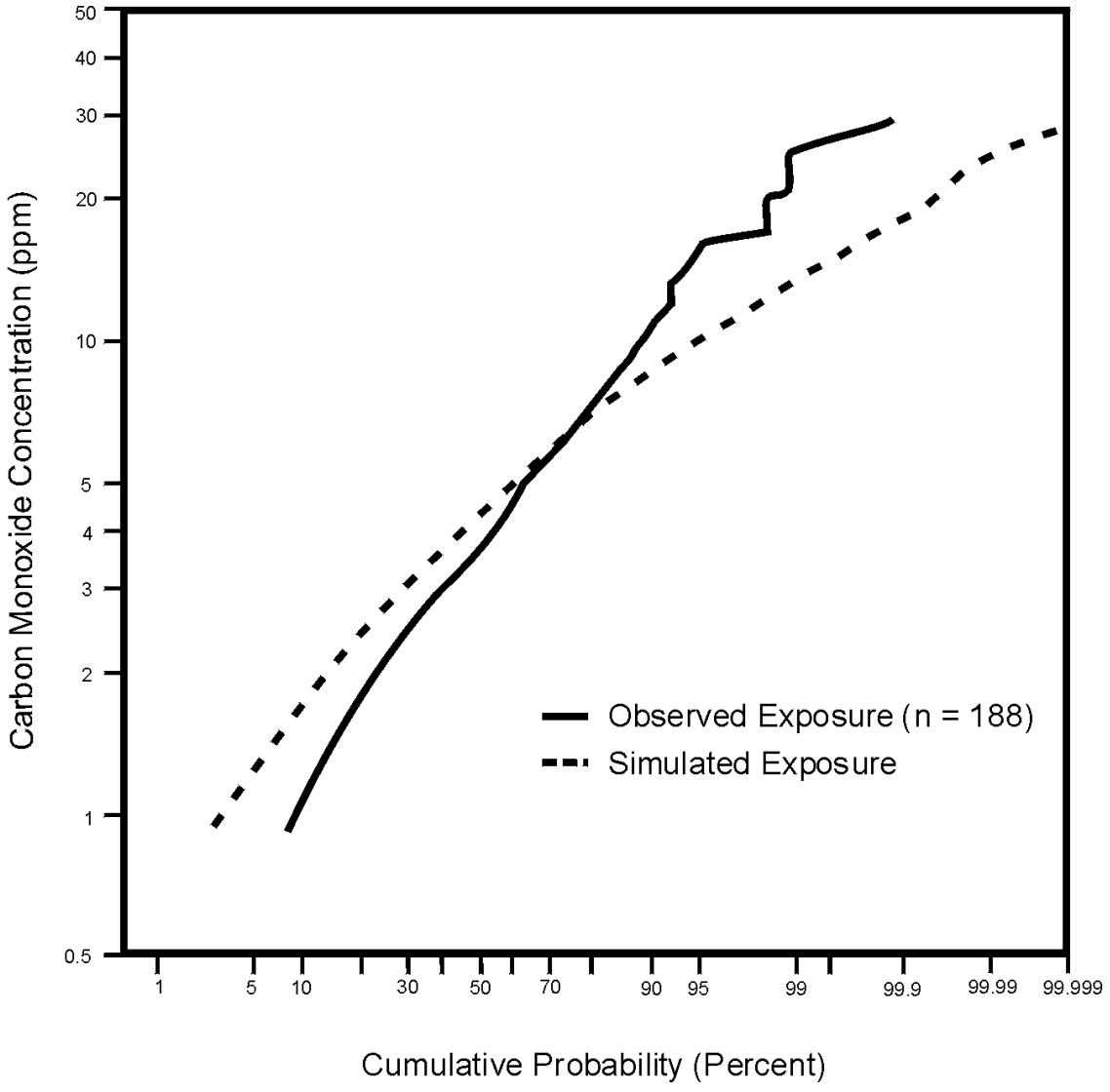


Figure 4-3. Observed versus simulated 8-h daily maximum exposure for persons residing in homes without gas stoves in Denver.

Source: Law et al. (1997).

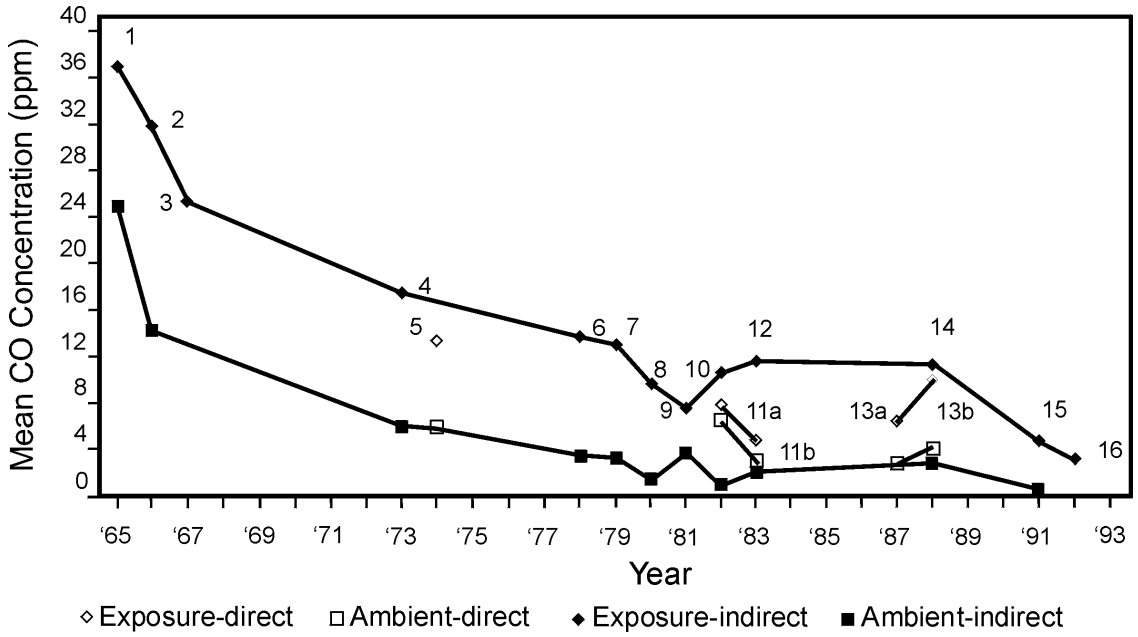
4.3.1.1 Exposure to Carbon Monoxide from Motor Vehicles

This subsection presents nonoccupational studies of exposure to CO concentrations from motor vehicles. Because these studies date to the mid-1960s, many of them were reviewed in the 1991 CO AQCD, and, therefore, they are not reviewed here. The studies in this section

examined the CO exposure of motorists and bicyclists. The first study examined passenger exposure to CO from air bags.

Air bags that use explosives for rapid deployment are a required safety feature on cars sold in the United States. Based on deployment of four different air bags, Wheatley et al. (1997) reported that the time-weighted-average (TWA) CO concentration ranged from 174 to 370 ppm. Peak CO concentrations occurred 2 min after deployment. Several studies done prior to 1991 reported passenger exposure to engine or tailpipe emissions of CO (Amiro, 1969; Clements, 1978; Ziskind et al., 1981). More recently, Hampson and Norkool (1992) reported that 20 of 68 children were treated for accidental CO poisoning after they rode in the back of pickup trucks in Seattle, WA. All trucks had exhaust systems with previously known leaks or tailpipes that exited at the rear rather than the side of the truck. In 17 trucks, children rode under a rigid closed canopy attached to the bed, and in the other three trucks they rode beneath a tarpaulin. Average COHb levels measured in an emergency room were 18.2% ± 2.4% (mean, plus or minus the standard error of the mean) and ranged from 1.6 to 37.0%.

Studies done both before and after 1991 continue to show that fixed-site monitors underestimate in-vehicle CO exposures. Flachsbart (1995) reported that 14 of 16 in-vehicle exposure studies performed in the United States between 1965 and 1992 simultaneously measured both ambient and passenger cabin concentrations. Regardless of the study, Figure 4-4 shows that the mean CO concentrations inside vehicles always exceeded the mean ambient CO concentrations measured at fixed-site monitors. The lines connecting points on the upper and lower lines of Figure 4-4 do not imply relationships between results for different cities. The lines are shown to make a clear distinction between exposure data from indirect studies, represented by the upper line, and the ambient data from indirect studies, represented by the lower line. The ratio between a study's mean in-vehicle CO concentration and its mean ambient CO concentration generally fell between 2 and 5 for most studies, regardless of when the study was done, but exceeded 5 for two studies done during the early 1980s. Of the more recent studies, Chan et al. (1991) found that median CO concentrations were 11 ppm inside test vehicles driven on hypothetical routes in Raleigh, NC, during August and September 1988, but median ambient concentrations were only 2.8 ppm at fixed-site monitors. Fixed-site samples were collected about 100 to 300 ft away from the midpoint of each route.



1 Los Angeles, CA
2 Chicago, IL; Cincinnati, OH; Denver, CO; St. Louis, MO; Washington, DC
3 14 cities
4 Los Angeles, CA
5 Boston, MA
6 Washington, DC
7 Los Angeles, CA
8 Menlo Park, Palo Alto, and Los Altos, CA
9 Denver, CO; Los Angeles, CA; Phoenix, AZ; Stamford, CT
10 Honolulu, HI
11a Denver, CO
11b Washington, DC
12 Washington, DC
13a Los Angeles, CA (summer)
13b Los Angeles, CA (winter)
14 Raleigh, NC
15 Menlo Park, Palo Alto, and Los Altos, CA
16 New Jersey Turnpike and Route 18, NJ

Figure 4-4. Trends in ambient CO concentrations and in-vehicle CO exposures, 1965 to 1992. (The upper and lower lines are provided to make a clear distinction between exposure and ambient CO data reported for each city; these lines do not imply that results for cities are related.)

Source: Flachsbart (1995).

Flachsbart (1995) proposed that the results of the 16 studies could be explained partly by different study approaches (direct versus indirect) and by other aspects of study design, including choice of city, season of the year, the surveyed road's functional type and location, travel mode, and vehicular ventilation. For example, by pairing three direct studies with three indirect studies (as shown in Figure 4-4) that were done at the same time, Flachsbart showed that the mean

in-vehicle exposure measured by the direct approach was always lower than that measured by the indirect approach. Although direct studies sampled real populations engaged in a variety of trips in all types of traffic, most indirect studies focused on hypothetical commuters with higher exposures in rush hour traffic. In another example, a comparison of Studies 8 through 10 in Figure 4-4 shows the effect of roadway type. Study 9 had a sizeable component of residential driving, which may explain why the mean in-vehicle CO exposure of 7.7 ppm for Study 9 was lower than the mean exposures for Studies 8 and 10. When the data of Study 9 were disaggregated by roadway location, the mean CO concentrations were 10 ppm for major commuting routes and 5.5 ppm for drives in residential areas. The mean concentration of 10 ppm for major commuting routes in Study 9 is similar to the mean CO concentrations reported for arterial highways by other studies (i.e., 9.8 ppm for Study 8 and 10.6 ppm for Study 10), which also were done during the early 1980s.

Like earlier studies, recent ones also have looked at the effect of different routes and travel modes on CO exposure. Chan et al. (1991) reported significantly different in-vehicle exposures to CO for standardized drives on three routes that varied in traffic volume and speed. The median in-vehicle CO concentration was 13 ppm for 30 samples in the downtown area of Raleigh, which had heavy traffic volumes, slow speeds, and frequent stops. The next highest concentrations (median = 11 ppm, n = 34) occurred on an interstate beltway that had moderate traffic volumes and high speeds, and the lowest concentrations (median = 4 ppm, n = 6) occurred on rural highways that had low traffic volumes and moderate speeds. Similarly, Dor et al. (1995) reported CO exposures of 12 ppm for 19 trips lasting an average of 82 min on a route through central Paris, France, which was 2 to 3 ppm higher than the mean exposure for 30 trips split between two suburban routes. In terms of travel modes, both Joumard (1991) and Dor et al. (1995) found differences in CO exposures for public and private modes of travel in French cities and towns. Their findings confirmed those made earlier in the United States by Flachsbart et al. (1987).

The CO exposure of cycling as a travel mode has been studied and compared to the exposure of motorists. In England, Bevan et al. (1991) reported that the mean CO exposure of cyclists in Southhampton was 10.5 ppm, based on 16 runs over two 6-mi routes that took an average of 35 min to complete. Keep in mind that the CO exposures of European cyclists may not be comparable to the exposures of cyclists in the United States because the installation of

catalytic converters on new cars in Europe occurred in 1988, about 13 years after their introduction in the United States (Faiz et al., 1996). In The Netherlands, Van Wijnen et al. (1995) compared exposures of volunteers serving as both car drivers and cyclists on several routes in Amsterdam during winter and spring. For a given route, the mean personal 1-h concentrations were always higher for car drivers than for cyclists regardless of when sampling occurred during the year. However, a volunteer breathed 2.3 times more air per minute on average as a cyclist than as a car driver. When adjusted for variation in breathing rate, the range in 1-h median CO concentrations of car drivers (1.4 to 1.9 ppm) was only slightly higher than that for cyclists (1.2 to 1.7 ppm).

Studies have quantified the effect of traffic volume and speed on in-vehicle CO exposure. Flachsbart et al. (1987) reported that in-vehicle CO exposures fell by 35% when test vehicle speeds increased from 10 to 60 mph on eight commuter routes in Washington. In a similar study of typical commuter routes in central Riyadh, Saudi Arabia, Koushki et al. (1992) found that in-vehicle CO exposures fell by 36% when vehicle speeds increased from 14 to 55 km/h (8.7 to 34.2 mph). They also found that mean in-vehicle CO concentrations increased by 71.5% when traffic volumes increased from 1,000 to 5,000 vehicles per hour. Mean CO levels ranged from 30 to 40 ppm averaged over trips of 25 to 43 min during peak hours, and ranged from 10 to 25 ppm for trips of 15 to 20 min during off-peak hours.

The effects of diurnal and seasonal variation on in-vehicle CO exposure were not completely discussed in the 1991 CO AQCD. Studies of diurnal effects on in-vehicle exposure during peak travel periods have been inconclusive because studies were unable to control for covariation in traffic volumes and speeds, ambient CO concentrations, or meteorological conditions (e.g., temperatures, wind speeds) during different periods of the day. In Los Angeles, CA, Haagen-Smit (1966) found evidence that CO exposures during afternoon commutes were greater than those during morning commutes. Similar results were later found by Cortese and Spengler (1976) in Boston, MA, by Wallace (1979) in Washington, and by Dor et al. (1995) in Paris. However, Holland (1983) found contrary evidence in four U.S. cities. In all of these studies, differences in exposures by time of day were not statistically significant. Recently, Alm et al. (1998) reported that the geometric mean CO concentration of 11 morning trips (3.1 ppm) exceeded that of 12 afternoon trips (2.0 ppm) on a standard route in Kuopio, Finland. This result was attributed to weather and traffic variables.

Studies in different parts of the world have shown that seasonal variation in ambient temperatures, wind conditions, and traffic volumes affect passenger cabin exposure to CO. Studies by Ott et al. (1994) in northern California and by Dor et al. (1995) in France both measured exposures for an entire year. Both studies reported that passenger cabin exposures were generally higher in fall and winter than they were in spring and summer. Such results usually are attributed to colder temperatures in temperate climates, which increase CO emissions per vehicle-mile during winter months. In a year-long study, Alm et al. (1998) reported that the highest CO concentrations for motorists in Kuopio occurred during morning rush hour periods in winter. In Hawaii, where temperatures are never cold enough to have a substantial effect on motor vehicle emissions, Flachsbart (1998a) reported that light traffic flows on an arterial highway in Honolulu and strong winds worked together to lower passenger cabin CO exposures during late fall, whereas heavy traffic flows and calmer winds elevated cabin exposures during winter and spring months.

4.3.1.2 Exposure to Carbon Monoxide in Recreational Vehicles

Two studies examined personal exposure to CO in the exhaust of recreational vehicles. In the first study, Simeone (1991) collected CO concentrations in the passenger areas of large power boats with side-mounted exhausts during routine cruises offshore of Boston and Annapolis, MD. In Boston Harbor, CO concentrations averaged 56 ppm during a 60-min cruise and 28 ppm after a 30-min cruise. For the Chesapeake Bay cruises near Annapolis, average stabilized CO concentrations at the helm ranged from 93 to 170 ppm over 20- to 30-min periods and 272 ppm over 30 min on the rear deck near the transom of the boat. In both studies, exhaust gas was affected significantly by airflow about the boat under certain head winds. At head-wind speeds of 10 to 30 knots, turbulent mixing occurred in closer proximity to the rear of the boats, enabling exhaust gases to migrate freely into each boat.

In the second study, researchers studied the CO exposure of a snowmobiler while traveling in the wake of a lead snowmobiler on a 2- to 3-mi straight trail over level terrain in Grand Teton National Park, WY (Snook, 1996). The CO exposure of the follower was collected under stable atmospheric conditions in Tedlar bags. The distance between the two snowmobiles ranged from 25 to 125 ft and speeds ranged from 10 to 40 mph. The follower's maximum average centerline exposure was 23.1 ppm, which occurred at 10 mph and 25 ft behind the lead snowmobile.

Although Snook (1996) reported no averaging times for exposures, one can estimate that these times ranged from 3 to 18 min from the data given on the snowmobiler's travel distance and vehicle speed. At distances greater than 25 ft, centerline exposures tended to increase with greater speeds. At 15 ft off centerline, average concentrations fell sharply to levels of 0 to 7.5 ppm. When the snowmobiler drove alone, the average concentration minus the background concentration was 1.3 to 3.0 ppm. Background concentrations ranged from 0.2 to 0.5 ppm.

Snowmobile tourism has become a booming business across the nation and in several national parks. Over 87,000 tourists traveled by snowmobile in Yellowstone National Park (Wilkinson, 1995) during the winter of 1993-1994. A snowmobile may emit from 10 to 20 g CO/mi, whereas a modern U.S. automobile emits far less (0.01 to 0.04 g/mi). There are no federal laws regulating the exhaust from snowmobile engines, and states are preempted from implementing snowmobile emission standards. The typical snowmobile utilizes a two-stroke engine, because it is less expensive than a four-stroke engine and provides a high power/weight ratio. However, a two-stroke engine produces relatively high emissions of CO (Snook and Davis, 1997).

4.3.1.3 Residential Exposure to Carbon Monoxide

Residential sources of CO concentrations include motor vehicle operation inside a home garage and the use of unventilated or poorly ventilated kerosene space heaters, gas appliances, and charcoal grills and hibachis in the living area of the home. Studies of exposures to nonfatal concentrations are discussed first, followed by studies of unintentional deaths caused by high indoor concentrations.

According to the Barbecue Industry Association, 44 million American households owned a charcoal grill in 1989, and an estimated 600 million charcoal-barbecuing events take place annually (Hampson et al., 1994). An early study showed that the air stream from charcoal grills contains 20 to 2,000 ppm of CO, with 75% of grills emitting 200 ppm and above (Yates, 1967). Gasman et al. (1990) reported COHb levels ranging from 6.9 to 17.4% in a family of four people in northern California who had been exposed to smoke from cooking indoors on a barbecue grill, which was found by fire fighters in the middle of the living room.

Mumford et al. (1991) and Williams et al. (1992) assessed CO exposure to emissions from unvented portable kerosene heaters in eight small mobile homes with no gas appliances and low

air exchange rates. Each home was monitored for an average of 6.5 h per day for 3 days per week for 4 weeks. For 2 weeks, the heater was on, and, for 2 weeks, it was off. When the heater was turned on, it was in use for an average of 4.5 h. When the heater was in use, study participants (all nonsmokers) spent most of their time in the family room or kitchen. Sampling took place in the living area about 1.5 to 3 m from the heater. The mean 8-h CO concentrations were 7.4 ppm (1-h peak = 11.5 ppm) when the heater was on and 1.4 ppm (1-h peak = 1.5 ppm) when it was off. Peaks usually were observed at the end of the combustion period. The ambient CO level measured 0.5 h prior to heater use ranged from 0 to 8 ppm. When the heater was on, three of the eight homes had 8-h average CO levels that exceeded the NAAQS, and one home routinely had levels of 30 to 50 ppm.

In joint studies, Wilson et al. (1993a,b) and Colome et al. (1994) reported CO exposures for a random sample of California homes that used gas appliances during a 48-h period from December 1991 to April 1992. For periods of 48 h, the median CO concentration was 1.2 ppm (indoors) and 0.8 ppm (outdoors), and the median of the maximum 8-h average CO concentrations was 2.0 ppm (indoors) and 1.4 ppm (outdoors). Of 277 surveyed homes, 13 (4.3%) had indoor CO concentrations and 8 (2.9%) had outdoor CO concentrations above the NAAQS of 9 ppm for 8 h. The study did not translate these percentages to statewide estimates. Using univariate regression analysis, outdoor CO concentrations explained approximately 55% of the variation found in indoor CO concentrations. Higher net indoor CO levels (indoor minus outdoor CO concentrations) were traced to several factors: space heating with a gas range and gas-fired wall furnaces, use of gas ranges with continuous gas pilot lights, small home volumes, and smoking cigarettes. The study reported that several factors may have contributed to higher indoor net CO levels: malfunctioning gas furnaces, automobile exhausts leaking into the home from attached garages and carports, improper use of gas appliances (e.g., gas fireplaces), and improper installation of gas appliances (e.g., forced air unit ducts).

In an area monitoring study, Kern et al. (1990) measured CO concentrations in a poorly sealed, detached garage from operation of an emissions controlled (catalytic reactor, oxygen sensor) and an emissions uncontrolled vehicle (carbureted, no catalytic reactor). Two tests were conducted: Test 1 involved a poorly sealed garage door with a 3-in opening, and Test 2 sealed the garage door with rags. The CO concentrations in the poorly sealed garage reached 4,700 ppm for the car without emission controls versus 2,000 ppm for the car with controls. When the

garage was better sealed, CO concentrations reached 8,400 ppm for the uncontrolled vehicle versus 3,600 ppm for the controlled vehicle.

Unintentional deaths caused by CO poisonings have been studied in California, New Mexico, and Washington. Two California studies collected data for the period from 1979 to 1988. In the first study, Liu et al. (1993) reported that 13.3% of 444 deaths were caused by improper use of charcoal grills and hibachies, of which 54% occurred inside motor vehicles (e.g., a van or recreational camper), and 46% occurred in residential structures (e.g., homes, apartments, shacks, or tents). Relative to their share of the state population, higher death rates occurred among Asians, blacks, males, and people aged 20 to 39. In the second study, Girman et al. (1998) identified specific factors that caused or contributed to unintentional deaths caused by CO from several combustion sources, including charcoal grills and hibachis, other heating and cooking appliances, motor vehicles, small engines, and camping equipment. There was a strong association between alcohol use and CO poisoning from motor vehicles. Faulty heating equipment used during winter months was implicated in about 50% of all unintentional deaths in studies by both Girman et al. (1998) in California and Yoon et al. (1998) in New Mexico.

Based on data for 10 counties in Washington, Hampson et al. (1994) reported characteristics of unintentional CO poisoning cases that occurred between 1982 and 1993. Most cases occurred when electrical power was interrupted during fall and winter months. Service was either interrupted because of regional storms or discontinued because of unpaid utility bills. Of 509 patients treated with hyperbaric oxygen, 79 (16%) were exposed when charcoal briquets were burned for either heating or cooking in 32 separate incidents. Non-English speaking Hispanic whites and Asians were disproportionately represented among the cases. The COHb levels averaged 21.6% and ranged from 3.0 to 45.8%.

The National Center for Health Statistics and the U.S. Consumer Product Safety Commission (CPSC) estimated that 212 deaths in 1992 were caused by fuel-burning appliances used in the home. Of these deaths, 13 involved use of gasoline-powered appliances (National Center for Health Statistics and U.S. Consumer Product Safety Commission, 1992). The CPSC also estimated that 3,900 CO injury accidents occurred in 1994, of which about 400 were associated with the use of gasoline-powered engines or tools (National Institute for Occupational Safety and Health, 1996). In response to the problem, several federal government agencies issued a joint alert concerning exposure to CO emitted by these sources (National Institute for

Occupational Safety and Health, 1996). These sources involved use of pressure washers, air compressors, concrete-cutting saws, electric generators, floor buffers, power trowels, water pumps, and welding equipment. Unintentional CO poisonings frequently happened indoors even when people took precautions to ventilate the building.

4.3.1.4 Exposure to Carbon Monoxide at Commercial Facilities

Increasingly, people pump their own fuel at service stations. This practice potentially puts people at greater risk of exposure to CO emissions from motor vehicles if nearby engines are idling. Wilson et al. (1991) randomly sampled 100 self-service filling stations and, for comparison, took convenience samples at 10 parking garages and 10 nearby office buildings in Los Angeles, Orange, Riverside, and San Bernardino counties of Southern California. They took 5-min samples of 13 motor vehicle air pollutants including CO in each microenvironment and in the ambient environment. Microenvironmental and ambient concentrations were measured on the same day but not simultaneously. The highest median CO concentration occurred in parking garages (11.0 ppm), followed by service stations (4.3 ppm), and office buildings (4.0 ppm). The median ambient CO concentration was 2.0 ppm.

Ice skating, motocross, and tractor pulls are sporting events in which significant quantities of CO may be emitted in short periods of time by machines in poorly ventilated indoor arenas. The CO is emitted by several sources, including ice resurfacing machines and ice edgers during skating events; motor vehicles at tractor-pull, monster-truck, and motocross competitions; and gas-powered radiant heaters used to heat viewing stands. At these events, a “tractor” is a truck or other vehicle modified to look like a farm tractor that is powered with aircraft turbines or supercharged automobile engines. These competitions usually involve many motor vehicles with no emission controls.

Several studies were not cited in the 1991 CO AQCD. First, Kwok (1981) reported episodes of CO poisoning among skaters inside four arenas in Ontario, Canada. Mean CO levels ranged from 4 to 81 ppm for periods of about 80 min. The CO levels in the spectator areas ranged from 90 to 100% of levels on the rink. The ice resurfacing machines lacked catalytic emission controls. Second, both Sorensen (1986) and Miller et al. (1989) reported CO concentrations greater than 100 ppm in ice rinks from the use of gas resurfacing machines. High concentrations were attributed to poorly maintained machines and to an ice rink without

sufficient ventilation. Third, based on data collected in the Quebec city area, Lévesque et al. (1990) developed a linear relationship between CO exposure and the CO concentration in exhaled breath (see Section 4.3.1.5 for discussion of CO exposure and breath CO relationships) but could not eliminate other factors affecting the relationship. In a later study, Lévesque et al. (1991) measured the alveolar CO of 14 male adult nonsmokers who played ice hockey, but who were not exposed in occupational settings. Rink CO concentrations ranged from 0 to 76.2 ppm. The study again found a linear relationship between exposure and absorbed CO such that, for each 10 ppm of CO in the indoor air, the players absorbed enough CO to raise alveolar CO by 4.1 ppm or about 0.76% COHb.

In the United States, surveys of CO exposure were done at ice arenas in the northern states of Vermont, Massachusetts, Wisconsin, and Washington. For a rink in Massachusetts, Lee et al. (1993) showed that excessive CO concentrations can occur even with well-maintained equipment and fewer resurfacing operations if ventilation is inadequate. Average CO levels were less than 20 ppm over 14 h. There was no significant source of outdoor CO. Ventilation systems could not disperse pollutants emitted and trapped by temperature inversions and low air circulation at ice level. In another study, Lee et al. (1994) reported that CO concentrations measured inside six enclosed rinks in the Boston area during a 2-h hockey game ranged from 4 to 117 ppm, whereas outdoor concentrations were about 2 to 3 ppm, and the alveolar CO of hockey players increased by an average of 0.53 ppm per 1 ppm CO exposure over 2 h. Fifteen years earlier, Spengler et al. (1978) found CO levels ranging from 23 to 100 ppm in eight enclosed rinks in the Boston area. This suggests that CO exposure levels in ice arenas have not improved.

In a letter, Paulozzi et al. (1991) reported that 25 people, exposed to CO during a high-school ice hockey game in Vermont, had mean COHb levels of 8.9%, but did not report whether any of them were smokers. Although Paulozzi et al. (1991) was unable to measure CO concentrations at the game, Smith et al. (1992) reported CO levels of 150 ppm (no averaging time was given) at an indoor ice-hockey rink in Wisconsin. To document the extent of the problem in Vermont, Paulozzi et al. (1993) took CO measurements during eight high-school games played in the state, and reported that average CO levels for the entire game ranged from <5 to 101 ppm, with a mean of 35 ppm. Hampson (1996) reported a maximum CO level of 354 ppm inside an ice arena in Seattle in March 1996. Based on data for 17 persons whose tobacco use was not reported, the average COHb level was 8.6%, with a range of 3.3 to 13.9%.

The source of the CO was a malfunction in a 20-year-old ice resurfacing machine. Hampson also reported that CO may have diffused to an adjacent bingo hall through an open door. In view of all these studies, the State of Minnesota declared in Regulation No. 4635 that CO measurements taken 20 min after ice resurfacing must be less than 30 ppm.

Studies also have been done in sports arenas that allow motor vehicles. Boudreau et al. (1994) reported CO levels for three indoor sporting events (i.e., monster-truck competitions and tractor pulls) in Cincinnati, OH. The CO measurements were taken before and during each event at different elevations in the public seating area of each arena with most readings obtained at the midpoint elevation where most people were seated. Average CO concentrations over 1 to 2 h ranged from 13 to 23 ppm before the event to 79 to 140 ppm during the event. Measured CO levels were lower at higher seating levels. Attendance was approximately 40% of the arena's capacity for each event. The ventilation system was operated maximally, and ground-level entrances were completely open.

High CO concentrations also have been reported at motor vehicle competitions in Canada. In an important study not cited in the 1991 CO AQCD, Luckurst and Solkoski (1990) recorded CO concentrations at two tractor-pull events in Winnipeg, Manitoba. The mean of instantaneous concentrations at 25 locations in the arena ranged from 68 ppm at the start of the first event to 262 ppm by the end. At the second event, the range was 78 to 436 ppm. Lévesque et al. (1997) reported CO levels at an indoor motocross competition that was held in a skating rink in the Quebec city region. The event lasted from roughly 8 p.m. to midnight in May 1994. The average CO concentrations were determined at five stations located at different points in the arena. The TWA concentrations ranged from 19.1 to 38.0 ppm, with concentrations higher during the second half of the show. High CO concentrations forced a health official to interrupt the event seven times to help clear the air. Covariance analysis showed that CO levels were related to the initial CO concentration, the event duration, motor size, and especially the number of motorcycles on the track.

4.3.1.5 Studies of Breath Carbon Monoxide in Populations: The Effects of Exposure to Carbon Monoxide

The EPA reviewed the pre-1990 literature reports of breath CO measurements in various populations (U.S. Environmental Protection Agency, 1991; Section 8.5.2.2). These data and the

more recent data on breath CO in the following part of this section often are collected with different breathhold-time, often are uncorrected for the CO content of the inhaled air (Smith, 1977; Wallace, 1983), and also may be subject to a positive hydrogen-interference if the breath CO is analyzed electrochemically (Vreman et al., 1993) (see Section 2.6.2 of this document). Consequently, this should be taken as a caveat by the reader that a portion of the variance between the results of different studies may be related to different breath collection methods and different breath CO measurement techniques.

Lando et al. (1991) collected breath samples of 4,647 workers using MiniCO breath kits (Model 1000, Catalyst Research Corporation, Owings Mills, MD). The latter part of a breath was collected in a balloon following a 15-s breathhold but the method of analysis was not described. Although the authors cite Jarvis et al. (1980) for this method, Jarvis et al. (1980) used the Jones et al. (1958) method that requires a 20-s breathhold. Furthermore, these data are uncorrected for the amount of CO in the maximal inhalation prior to the breathhold step (Smith, 1977; Wallace, 1983). Consequently, these data are not compatible with other studies using 20-s for the breathhold time and corrected data. Mean CO levels (Table 4-1) ranged from 4.2 (±1.66 standard deviation [SD]) ppm for never-smokers to 33.3 (±11.22 SD) ppm for heavy smokers (25 cigarettes/day or more). Based on cutoffs of 3 and 6 ppm above ambient, a larger number of ex-smokers (1.7 to 3.3%) than never-smokers (0.4 to 1.9%) appeared to be falsely reporting their smoking status.

Chung et al. (1994) employed the Lee and Yanagisawa (1992, 1995) sampler to measure personal exposure to CO of 15 Korean housewives using charcoal briquettes for cooking. The COHb levels also were measured using a CO-Oximeter (CO-Ox). Although the personal sampler had somewhat high imprecision based on four duplicate samples (average of 2.1 ppm difference), the investigators were able to document a higher level of both exposure to CO and blood COHb when the charcoal briquettes were used. Levels of COHb were generally high, even without use of the briquettes, leading the experimenters to hypothesize that the high prevalence of smoking (all 15 subjects had smokers in their homes) had elevated the level above the levels found in the U.S. among nonsmokers.

Seufert and Kiser (1996) measured CO levels in the end-tidal breath after a 10-s breathhold of 126 crew members of a nuclear submarine just before and just after a 62-h submerged period. The CO level in the submarine (called “ambient” by the authors) increased from 2.6 ppm to

TABLE 4-1. MEAN (M) BREATH CARBON MONOXIDE LEVELS AND SAMPLE SIZES ACROSS SMOKING CATEGORIES AND JOB TYPES[a]

			Job Type		
Smoking Category		Total	Blue Collar	Clerical	White Collar
Never-smokers	M	4.2	4.5	4.1	4.1
	SD	1.66	1.89	1.69	1.55
	n	2,328	294	958	1,076
Quitters	M	4.6	5.1	4.4	4.5
	SD	3.10	5.03	2.19	2.63
	n	1,148	217	427	504
Occasional smokers	M	7.6	7.6	8.0	7.1
	SD	6.12	3.98	7.05	5.34
	n	178	22	90	66
Light smokers	M	14.3	15.6	14.0	13.79
(1 to 15 cigarettes/day)	SD	8.40	8.94	8.70	7.21
	n	238	48	131	59
Moderate smokers	M	24.7	24.6	25.4	23.4
(16 to 24 cigarettes/day)	SD	10.47	11.72	10.06	9.67
	n	351	97	180	74
Heavy smokers	M	33.3	32.6	34.1	33.0
(25 cigarettes/day or more)	SD	11.22	9.61	12.73	10.50
	n	273	95	117	61

[a]Sample size refers to those with CO measurements; CO measurements were taken on 97.2% of those interviewed. The CO levels are in ppm. Data are for end-tidal breath collected after a 15-s breathhold without the required correction for the CO in the inhaled air (Smith, 1977; Wallace, 1983)

Source: Lando et al. (1991).

9.2 ppm in the fan room and in two other spaces. The authors state that the increase was caused primarily by cigarette smoke from the 40 smokers aboard because diesel engines were not used during the submersion period. The nonsmokers' breath CO increased from 9 to 21 ppm. Although the authors did not comment on the considerable difference between the nonsmokers' breath CO of 21 ppm and the measured "ambient" concentration of only 9.2 ppm, it may have been because of higher smoking rates in nonmonitored duty sections than in the monitored sections, the absence of a correction for higher CO concentrations in the air inhaled for the 10-s breathhold than in the end-tidal breath CO, and the end-tidal breath CO and "ambient" CO measurements were made with two different instrumental systems. The operation of an

atmospheric revitalization system that removed CO also may have contributed to a lower monitored "ambient" CO than the CO nonsmokers were exposed to in the nonmonitored duty sections.

Zayasu et al. (1997) present the first study showing that asthmatics untreated by corticosteroids have higher 20-s breathhold end-tidal breath CO than either healthy controls or treated asthmatics, as determined by subtracting the background level from the observed reading (Figure 4-5). This is not the required correction for CO in the inhaled air reported by Smith (1977) and Wallace (1983), so these data are not consistent with those studies where this correction was made. They attribute the higher levels to lung inflammation, leading to a possible increase in heme oxygenase, which creates endogenous CO. (For more information on endogenous CO production, see Section 5.3.)

Shenoi et al. (1998) tested 470 youths in hospital admissions (aged 5 to 20 years) for CO in breath using the electrochemical Vitalograph Breath CO monitor (Vitalograph, Inc., Lenexa, KS). The results, showing that 1.9% (9 out of 470) had end-tidal breath CO levels greater than 9 ppm after a 20-s breathhold, were confirmed by CO-Ox testing of blood. Five of the 9 patients with the higher breath CO were believed to be cigarette smokers, one may have been exposed to fumes from a faulty furnace, and three were believed to be exposed to environmental tobacco smoke or traffic exhaust. No corrections were made for the parts per million of CO in the air inhaled for the breathhold.

4.3.1.6 Nonoccupational Exposure to Methylene Chloride

Nonoccupational exposure to methylene chloride, which can be metabolized to CO in the body, potentially occurs when the chemical is found in contaminated ambient air and groundwater used as drinking water and in consumer products that contain the chemical as a solvent, flame-retardant additive, or propellant. Exposure to methylene chloride in the home primarily occurs through use of paint and varnish removers. Exposure also may occur through use of aerosol propellants such as those found in hair sprays, antiperspirants, air fresheners, and spray paints. The Agency for Toxic Substances and Disease Registry of the U.S. Public Health Service reported that some aerosol products may contain up to 50% methylene chloride (Agency for Toxic Substances and Disease Registry, 1993). However, the current extent of methylene

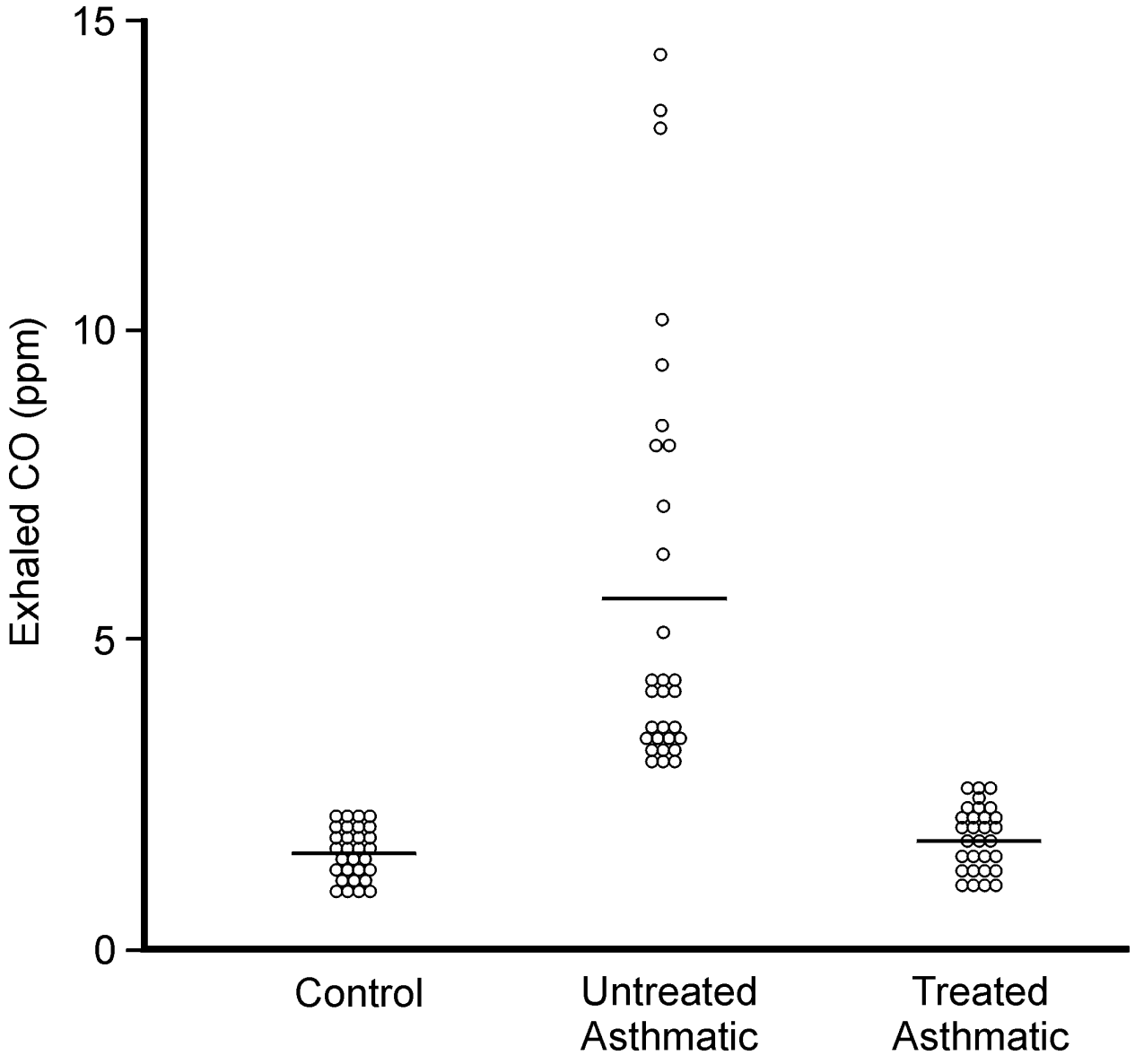


Figure 4-5. Excess CO concentrations in the exhaled air of nonsmoking control subjects (n = 30), untreated asthmatics (n = 30), and treated asthmatics (n = 30). The values shown were determined by subtracting the background level from the observed reading. "Untreated" means no inhaled corticosteroids, "Treated" refers to regularly inhaled corticosteroids, and the horizontal bar indicates the mean value.

Source: Zayasu et al. (1997).

chloride in aerosol products apparently has not been studied recently. Also unknown are typical population exposures to methylene chloride from consumer products.

Ambient exposure may occur near production and use facilities or near hazardous waste sites that store methylene chloride. Ambient concentrations of methylene chloride near organic solvent cleaning and paint and varnish removal operations range from 7.1 to 14.3 ppb, averaged over 1 year (Systems Applications Inc., 1983), and ambient levels at other locations were reported by the U.S. Environmental Protection Agency (1985). Although methylene chloride readily disperses when released into the air, it may remain in groundwater for years and be ingested in drinking water or inhaled when it volatilizes during showering and laundering (Agency for Toxic Substances and Disease Registry, 1993).

Exposure to about 500 ppm of methylene chloride for several hours can elevate COHb levels to 15%. Increases in COHb levels can be detected in the blood of nonsmokers about 30 min after exposure to methylene chloride. Stewart et al. (1972) demonstrated that elevated COHb levels were proportional to a series of controlled exposures to methylene chloride. In a controlled experiment, Stewart and Hake (1976) observed postexposure levels of COHb ranging from 5 to 10% after 3 h of use of a liquid-gel paint remover containing 80% methylene chloride and 20% methanol by weight. Concurrent exposure to methylene chloride and methanol prolongs the period of elevated COHb in the body (Stewart and Hake, 1976; Buie et al., 1986; Wilcosky and Simonsen, 1991). Peterson (1978) reported COHb levels of up to about 10% saturation after inhalation of methylene chloride concentrations ranging from 50 to 500 ppm over 5 days for 7.5 h per day.

4.3.2 Occupational Exposures

This subsection discusses occupational exposures to CO and methylene chloride.

4.3.2.1 Exposures to Carbon Monoxide in the Workplace

A survey by the National Institute for Occupational Safety and Health found that 3.5 million workers in the private sector potentially are exposed to CO primarily from motor exhaust. The number of persons potentially exposed to CO in the work environment is greater than that for any other physical or chemical agent (Pedersen and Sieber, 1988). In 1992, there were 900 work-related CO poisonings resulting in death or illness in private industry as reported

by the U.S. Bureau of Labor Statistics (as cited in National Institute for Occupational Safety and Health, 1996). Three risk factors affect industrial occupational exposure: (1) the work environment is located in a densely populated area that has high background CO concentrations; (2) the work environment produces CO as a product or by-product of an industrial process, or the work environment tends to accumulate CO concentrations that may result in occupational exposures; and (3) the work environment involves exposure to methylene chloride, which is metabolized to CO in the body. Proximity to fuel combustion of all types elevates CO exposure for certain occupations: airport employees; auto mechanics; small gasoline-powered tool operators (e.g., users of chainsaws); charcoal meat grillers; construction workers; crane deck operators; firefighters; forklift operators; parking garage or gas station attendants; policemen; taxi, bus, and truck drivers; toll booth and roadside workers; and warehouse workers (U.S. Environmental Protection Agency, 1991).

Studies of firefighters are discussed briefly below because these studies were not discussed in the 1991 CO AQCD. Other occupational studies of CO exposure are not discussed here, but are summarized in Table 4-2, which shows CO concentrations for each study (typical values or ranges), averaging periods, and the measured or estimated percent COHb levels for nonsmokers, if reported.

Lees (1995) reviewed studies of firefighter exposures to combustion products including CO. During severe fires, firefighters were exposed to CO concentrations in excess of 500 ppm in approximately 29% of 1,329 minutes sampled by Burgess et al. (1977) and in 48% of measurements taken by Barnard and Weber (1979). Gold et al. (1978) reported a geometric mean concentration of 110 ppm for a log-normal distribution of 65 samples with average duration of less than 10 min. The short-term exposure limit, designed to prevent acute effects of CO exposure, is 400 ppm averaged over 15 min. In three studies, the STEL was exceeded in 15 to 33% of measurements (Treitman et al., 1980; Brandt-Rauf et al., 1988; Jankovic et al., 1991). Inside a self-contained breathing apparatus, CO measurements ranged from 1 to 105 ppm in six samples (Jankovic et al., 1991).

Firefighters are exposed to lower CO levels when they suppress bushfires, wildland fires, and forest fires. For bushfires, Brotherhood et al. (1990) estimated that Australian firefighters were exposed to CO levels averaging 17 ppm based on COHb measurements taken afterwards. In a study of wildland fires in California, Materna et al. (1992) reported an average CO

TABLE 4-2. STUDIES OF OCCUPATIONAL EXPOSURES AND DOSAGES[a]

Occupational Category	CO Concentration (ppm) and Averaging Period	Measured or Estimated Percent COHb	State/Country	References
Airport workers	5.0-13.6 (0.25 h)	NA	Massachusetts, U.S.	Bellin and Spengler (1980)
	5-300 (0.1-1.7 h) (INT)	NA	U.S.	McCammon et al. (1981)
Bus drivers	5.8-12.5 TWA (0.5-1.0 h)	NA	France	Limasset et al. (1993)
Chainsaw/gas tool operators	NA	9.2-75.6 in 5 farmers	U.S.	Kahler et al. (1993)
	>200 (<2 min)	NA	U.S.	National Institute for Occupational Safety and Health (1996)
	16.2-24.3 TWA (8 h)	>4 in 10 NS	Germany	Bünger et al. (1997)
Charcoal meat grillers	NA (3.0-5.6 h)	5.7-7.0 in 56 NS	Bahrain	Madani et al. (1992)
Firefighters	NA	2.45 in 207 NS	Maryland, U.S.	Radford and Levine (1976)
	14-20 (0.5-3.0 + h)	3-7 in 9 NS	Australia	Brotherhood et al. (1990)
	0-105 ppm (IM) (0-1.7 h)	NA	U.S.	Jankovic et al. (1991)
	14.4 TWA (3.5 h)	NA	California, U.S.	Materna et al. (1992, 1993)
	1.2-24.2 (9 h)	NA	California, U.S.	National Institute for Occupational Safety and Health (1994)
Forklift operators and workers in facilities with forklifts	250-300 (5 h)	5-22 for 4 NS	North Carolina, U.S.	Baucom et al. (1987)
	NA (4.4 h)	4.2-28.7 for 7 NS	North Carolina, U.S.	Fawcett et al. (1992)
	370-386 (NA)	21.1 ± 0.7	North Carolina, U.S.	Ely et al. (1995)
	25-47 TWA (8-12 h)	6.3-13.3 for 4 NS	Colorado, U.S.	McCammon et al. (1996)
	3-34 (8 h)	NA	California, U.S.	Apte (1997)
Garage mechanics	42.6% > 35 (1 h)	>5 in 45% of NS	Ontario, Canada	Gourdeau et al. (1995)
Manufacturing jobs	0-83 TWA (4 h)	>3.5 in 71.4% of NS	Seven European countries	Gardiner et al. (1992)
Traffic/roadway workers	2-7 (8 h)	NA	Four states, U.S.	Boeniger (1995)
	1-4.3 (8 h)	NA	Denmark	Raaschou-Nielsen et al. (1995)
	5-42 (2 s)	<5	Massachusetts, U.S.	Kamei and Yanagisawa (1997)

[a]NA = not available, INT = interior of vehicle, NS = nonsmokers, and IM = inside mask.

Source: Adapted from Apte (1997) and updated.

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concentration of 14.4 ppm over a 3.5-h period (range 1.4 to 38 ppm) during fireline mop-up and a prescribed burn. Concentrations were higher during evening hours, when inversions occurred, and could range up to 300 ppm near gasoline-powered pumping engines. Materna et al. (1993) found comparable results using different methods. For forest fires, the National Institute for Occupational Safety and Health (1994) reported an average CO concentration of 11.5 ppm for a 9-h period.

4.3.2.2 Exposures to Methylene Chloride in the Workplace

Certain occupations expose workers to organic solvents such as methylene chloride. The solvent is widely used as a degreaser, paint remover, aerosol propellant, and blowing agent for polyurethane foams. It is used as an extractant for foods and spices, a grain fumigant, and a low-pressure refrigerant. It also is used in the manufacturing of synthetic fibers, photographic film, polycarbonate plastics, pharmaceuticals, printed circuit boards, and inks. More than one million workers have significant potential for exposure to methylene chloride (Agency for Toxic Substances and Disease Registry, 1993). Moreover, the highest levels of exposure to methylene chloride often occur in the workplace. To protect worker health, the 8-h TWA threshold limit value for methylene chloride was set at 50 ppm by the American Conference of Governmental Industrial Hygienists. Exposure at this concentration leads to COHb levels of about 1.9% in experimental subjects. Exposure to 500 ppm for several hours may elevate COHb levels as high as 15%. An 8-h exposure to about 500 mg/m^3 (3.5 mg/m^3 = 1 ppm) of methylene chloride vapor is equivalent to an 8-h exposure to 35 ppm of CO (U.S. Environmental Protection Agency, 1985).

Methylene chloride stored in tissue may continue to metabolize to CO after several hours of acute exposure. In such cases, COHb levels will continue to rise and peak as high as 25% about 5 to 6 h after exposure (Agency for Toxic Substances and Disease Registry, 1993). Shusterman et al. (1990) reported an apparent linear elevation of COHb as a function of hours worked by a furniture refinisher who used paint stripper containing methylene chloride. Ghittori et al. (1993) reported a significant linear correlation (correlation coefficient [r] = 0.87) between methylene chloride concentration in air and CO in alveolar air of nonsmoking and sedentary factory workers in Italy. Exposure to 600 mg/m^3 of methylene chloride for 7.5 h was associated with a COHb level of 6.8% in eight volunteers. Exposure to methylene chloride also can be fatal. Leikin et al.

(1990) reported fatalities of two people who were exposed to unknown concentrations of methylene chloride while they removed paint in an enclosed space. Death was caused not by CO poisoning, but by solvent-induced narcosis. Before they died, their COHb levels continued to rise following cessation of exposure despite treatment by high levels of oxygen.

4.3.3 Activity Pattern Studies

In assessing population exposure, studies of human activity patterns over a fixed time period (e.g., 24 h) are necessary to determine how many people potentially are exposed to sources of an air pollutant, and how long people spend in activities that involve use of these sources. Accordingly, this section reviews studies of human activity patterns that pertain to population exposure to CO and methylene chloride. Previous studies reported that many Americans spent most of their time indoors at home, school, or work, etc. (Szalai, 1972; Chapin, 1974; Meyer, 1983; Johnson, 1987; Schwab et al., 1990). Although more recent activity pattern studies largely confirm this finding, their sampling and questionnaire designs provide new insights. This section reviews, in chronological order, these newer studies that include two surveys of activity patterns in California, a similar survey of preadolescents in six states, a comparative study between California and the nation, a study in southwest England, a Boston study, and a recent survey at the national level. As a body, these studies were not discussed in the 1991 CO AQCD.

4.3.3.1 Activity Patterns of California Residents

The California Air Resources Board (CARB) conducted two surveys to determine the activity patterns of California residents. In each case, projectable probability samples were drawn from English-speaking households who had telephones. The first surveyed 1,762 adults and adolescents over 11 years of age from fall 1987 through summer 1988 (Wiley et al., 1991a; Jenkins et al., 1992), and the second surveyed 1,200 children under age 11 from April 1989 through February 1990 (Wiley et al., 1991b; Phillips et al., 1991). Using telephone interviews, both surveys asked participants to complete a 24-h diary for the preceding day. People ages 9 and over responded directly to the interview, and the primary adult careprovider responded for young children. The diaries enabled estimates of time spent in various activities and locations,

and determinations of whether respondents used or were near sources of pollutants, including consumer products, combustion appliances, and motor vehicles.

Similar to previous studies, the results showed that all age groups spent most of their time indoors. Adults and adolescents spent, on average, 87% of their time indoors (62% at home and 25% elsewhere), and only 6% of their time outdoors. They also spent 7% of their time in transit mostly in a car, van, or pickup truck. Compared to adults and adolescents, children spent a similar amount of time indoors (86%), but more time at home (76%) and outdoors (10%), and less time indoors elsewhere (10%) and in transit by car, van or pickup truck (4%). About 46% of nonsmoking adults/adolescents reported being near others' tobacco smoke at some time during the day.

Table 4-3 summarizes results of the two California surveys for various microenvironments pertinent to CO exposure. For each microenvironment, the table shows the mean and range in time spent per day by both the entire sample and by those who actually did an activity in the microenvironment (i.e., “doers”). The results show the disparity in mean time spent by the population and by doers of an activity, which has implications for calculating population exposure in risk assessment. Table 4-4 gives the percentage of each sampled population who reported use of or proximity to potential sources of either CO or methylene chloride on a given day. The study did not measure CO or methylene chloride concentrations from these sources in microenvironments. Also, the surveys did not indicate whether respondents lived in a home where combustion appliances were vented.

4.3.3.2 Activity Patterns of Children in Six States

In 1990-91, Silvers et al. (1994) surveyed the activities of preadolescent children (ages 5 to 12 years) from a projectable probability sample of 1,000 households in six states. These states included three on the East Coast (New Jersey, New York, and Pennsylvania) and three on the West Coast (California, Oregon, and Washington). Comparisons between this study known as the Children’s Activity Survey (CAS) and the CARB children's study are possible because both were done over an entire year at about the same time, and both used a retrospective time diary for a 24-h day. Both studies reported very similar results in terms of the mean hours per day spent by preadolescent children for locations designated “indoors” (21.5 h for CARB versus 21.7 h for CAS) and “at home” (18.0 h for CARB versus 17.8 h for CAS). For each study, these results

TABLE 4-3. TIME SPENT IN DIFFERENT MICROENVIRONMENTS BY CALIFORNIANS, 1987 TO 1990 (minutes per day; weighted)

	Adults/Adolescents				Children			
Microenvironment	Population Mean	Percent Doers	Doer Mean	Doer Range	Population Mean	Percent Doers	Doer Mean	Doer Range
Motor Vehicle								
Inside a garage	9	9.4	97	1-845	2	4.1	40	2-300
Inside an auto repair shop, parking garage, or gas station	11	11.6	91	1-685	<1	1	11	3-47
Inside a vehicle:								
Car	73	74.2	99	1-585	43	67.1	65	1-630
Van or pickup truck	18	17.5	102	2-785	13	10.4	129	1-985
Bus	4	3.4	114	5-1,320	3	7.4	39	1-134
Potential Gas Appliance								
Kitchen	74	75.3	98	1-930	47	70.0	66	1-320
Utility/laundry room	3	5.0	53	3-380	<1	0.6	34	5-180
Basement	<1	0.5	79	5-180	<1	<0.1	75	75-75
Industrial plant/factory	35	8.9	393	4-750	<1	<0.2	34	15-45
Restaurant	28	34.5	81	1-885	6	12.7	49	3-255
Bar/nightclub	8	4.6	174	5-825	NA	NA	NA	NA
Outdoor Transit								
Walking	10	26.4	38	1-360	6	24.7	24	1-195
Bicycle/skates	1	3.1	41	5-160	1	4.4	22	2-155
Motorcycle, scooter	1	1.9	62	5-430				
Bus/train/ride stop	NA	NA	NA	NA	<1	2.6	15	3-40
Stroller/carried					<1	2.0	40	1-195
Other	1	1.3	38	5-270	<1	0.4	72	10-110

NA = not available.

Source: Adapted from Jenkins et al. (1992); Phillips et al. (1991).

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TABLE 4-4. PERCENTAGE OF CALIFORNIANS WHO USE OR WHO ARE IN PROXIMITY TO POTENTIAL SOURCES OF EITHER CARBON MONOXIDE OR METHYLENE CHLORIDE ON A GIVEN DAY, 1987 TO 1990 (WEIGHTED)

Potential Pollutant Source	Adults/Adolescents 1987-88	Children 1989-90
Consumer Products[a]		
Personal care aerosols	40	36
Scented room fresheners	31[b]	37
Solvents	12	3
Oil-based paints	5	2
Activities/Places		
Went to a gas station, parking garage, or auto repair shop	26	11
Pumped gasoline	15	1
Have attached garage[b]	62	63
Had vehicle in attached garage[b]	37	36
Took a hot shower[a]	77	26
Near Combustion Appliances		
Had gas heat on[b]	26	24
Had gas oven/range on	35	29
Environmental Tobacco Smoke (ETS)		
Nonsmokers near ETS at any time during the day:		
Adults (18 years or older)	43	
Youths (12 to 17 years)	64	
Adults and youths (12 years and older)	46	
Youths (0 to 11 years)		38

[a]Potential methylene chloride exposure.
[b]Data presented for adult respondents (age 18 years or older) only.

Source: Adapted from Jenkins et al. (1992); Phillips et al. (1991).

varied by ±1 h for different seasons of the year. There was variation in specific activities (e.g., the CAS study reported that preadolescents spent less time per day "riding in a vehicle" in California [0.52 h] than they did in the five other states [0.82 h], when the five were combined as a group). The CAS study did not report time spent near other CO sources.

4.3.3.3 A Comparative Study Between California and the Nation

Robinson and Thomas (1991) compared results of activity pattern studies, one conducted by CARB in California in 1987-1988 (Wiley et al., 1991a; Jenkins et al., 1992), and the other

done at the national level in 1985 (Cutler, 1990; Cornish et al., 1991). Although the two surveys used different methods of gathering and coding data, the data were recoded to enable comparisons. The comparison showed that Californians averaged more time at work and in commuting to work than was the case nationally, but averaged less time doing housework and caring for children. California men also spent more time traveling. The national study appeared to show greater time spent at home and in the yard. However, these results could be explained by differences in location codes between the two studies, rather than by actual differences in participant activity patterns between them. For example, the national study did not ask participants to identify whether they worked indoors or outdoors. Because the national study was not designed for exposure assessment, the authors proposed that the CARB study become a model for a future national study oriented to exposure assessment. Such a study is discussed in Section 4.3.3.6.

4.3.3.4 An English Study

Farrow et al. (1997) determined how much time was spent inside the home from a sample of 170 households living in Avon, England, from November 1990 through June 1993. A pregnant woman lived in each household at the start of the study. Households completed a weekly diary for 1 year that covered roughly the last 6 mo of the woman's pregnancy and the first 6 mo of the new infant's life. The results indicated that the average amount of time spent inside the home per day varied by family member as follows: mothers, 18.4 h (76.7%); fathers, 14.7 h (61.3%); and infants, 19.3 h (80.4%). Infants spent more time at home during winter than summer. Although fathers spent more time at home on weekends, mothers and infants spent less time. The applicability of the study results for U.S. households was not determined, and it is hard to judge without comparative information about the two countries.

4.3.3.5 A Boston Study of Household Activities, Life Cycle, and Role Allocation

Using activity diary data from 150 households that participated in a 1991 Boston survey, Vadarevu and Stopher (1996) tested several hypotheses about household travel. One study hypothesis was that there are significant differences in mean time allocations of activities among different life-cycle groups based on age, working status, and household size. They tested the theory that life-cycle stage affects which activities fall into mandatory, flexible, and optional

categories; how much time can be allocated to different activities; and which household member does each activity. They found that time allocated by households to specific activities varied according to whether the household consisted of a single working adult, multiple adults, a young family, an older family, or a nonworking adult. However, they found no significant differences among the life-cycle groups or between any life-cycle group and the population mean in terms of the total time spent in mandatory activities (work, work-related, school, and certain at-home activities), which required on average 21 h per day. The amount of time spent in all flexible, optional, and travel activities was about 3 h per day.

4.3.3.6 The National Human Activity Pattern Survey

The National Human Activity Pattern Survey collected 24-h diary data of activities and locations provided by 9,386 respondents interviewed nationwide in the United States between October 1992 and September 1994 (Klepeis et al., 1996). To enable projections to a larger population, the sample was weighted by the 1990 U.S. Census data to account for disproportionate sampling of certain population groups defined by age and gender. Results were analyzed across a dozen subgroups: gender, age, race, Hispanic, education, employment, census region, day-of-week, season, asthma, angina, and bronchitis/emphysema. The weighted results showed that, on average, 86.9% of a person's day was spent indoors (68.7% at residential locations), 7.2% of the day was spent in or near vehicles, and 5.9% of the day was spent in outdoor locations.

The study also reported unweighted descriptive statistics and percentiles for both the full population and various subpopulations (i.e., people who actually did certain activities or who spent time in certain microenvironments) (Tsang and Klepeis, 1996). Of all 9,386 respondents, 38.3% reported having a gas range or oven at home, and another 23.7% said that the range/oven had a burning pilot light. In terms of motor vehicle use, 10% of 6,560 people (7.0% of total sample) spent more than 175 min per day inside a car, and 10% of 1,172 people (1.2% of total sample) spent more than 180 min inside a truck, pickup, or van. Of those who were inside a car and knew they had angina (n = 154 respondents), 10% of them spent more than 162 min per day inside a car. The survey also asked about sources of household pollutants. Of 4,723 respondents, 10.5% were exposed to solvents, 10.4% to open flames, and 8.4% to gas-diesel powered equipment; 6.3% of these respondents were in a garage or indoor parking lot;

and 5.7% reported that someone smoked cigarettes at home. Only 1.8% of 4,663 respondents reported having a kerosene space heater at home.

4.4 MAJOR FACTORS AFFECTING POPULATION EXPOSURE

This section discusses major factors that have and may continue to affect population exposure to CO. These factors include public policies affecting urban transportation planning and air quality, motor vehicle emissions, and smoking in public places and social changes affecting human activity patterns.

4.4.1 Federal Policies Affecting Transportation and Air Quality in Urban Areas

In the United States, the national effort to improve air quality can be traced to the Clean Air Act (CAA) amendments of 1970, 1977, and 1990. As discussed in Chapter 3, the effect of these CAA amendments on ambient CO concentrations has been substantial. Moreover, emissions from on-road vehicles have declined since 1970, even as other socioeconomic indicators of growth have increased. Between 1970 and 1995, nationwide emissions of CO from on-road vehicles fell 33.4% (U.S. Environmental Protection Agency, 1996), despite compound annual growth rates of 1.0% in the nation's population and 3.2% in vehicle miles of travel (VMT) during the same period (U.S. Department of Transportation, 1996). The faster growth rate of VMT can be attributed to many factors that have decentralized housing and jobs within urban regions since World War II.

Since the mid-1960s, major construction projects intended to expand highway capacities have been opposed in some metropolitan areas. Opponents claimed that these projects promoted urban sprawl and induced motor vehicle travel that raised regional air pollutant emissions. To address these concerns, the 1990 CAA amendments state that transportation actions (plans, programs, and projects) cannot create new NAAQS violations, increase the frequency or severity of existing NAAQS violations, nor delay attainment of the NAAQS (U.S. Code, 1990). Pursuant thereto, the U.S. Environmental Protection Agency promulgated its Transportation Conformity Rule. Complementary provisions of the 1991 Intermodal Surface Transportation Efficiency Act offered financial incentives under the Congestion Management and Air Quality (CMAQ)

improvement program. Under CMAQ, metropolitan planning organizations were offered federal funds to improve air quality by implementing transportation control measures (TCMs). Examples of TCMs include programs to promote car and van pooling, flextime, special lanes for high occupancy vehicles, and parking restrictions.

The U.S. Environmental Protection Agency (1994) examined how TCMs have changed travel activity, including number of trips, vehicle miles of travel, vehicle speed, travel time, and the extent to which commuters have shifted travel from peak to off-peak periods. Using an emission factors model (i.e., MOBILE5 [for a description of MOBILE5, see U.S. Environmental Protection Agency, 1998b]), the study inferred how much TCMs would change average speeds of motor vehicles and CO emissions therefrom. The direct effect of TCMs on commuter exposure to CO has received only limited study. Flachsbart (1989) found that priority (with-flow and contra-flow) lanes were effective in reducing exposure to motor vehicle exhaust on a coastal artery in Honolulu. Compared to commuter CO exposure in adjacent but congested lanes, exposure in priority lanes was about 18% less for those in carpools, 28% less for those in high-occupancy vehicles (e.g., vanpools), and 61% less for those in express buses. These differences occurred possibly because commuters in priority lanes traveled faster than those in the congested lanes. Faster vehicles created more air turbulence, which may have helped to disperse pollutants surrounding vehicles in priority lanes. Furthermore, these differences existed even though the priority lanes were often downwind of the congested lanes. Although higher speeds were related to lower exposures in priority lanes, differences in exposure also could have been caused by differences in vehicle type and ventilation, both of which were not controlled.

Models to estimate the direct effects of TCMs on commuter CO exposure are not apparent in the literature. However, Flachsbart (1998a) developed a series of statistical models to predict passenger cabin exposure to CO based on trip variables for a 3.85-mi, Honolulu artery divided into three links. Based on data for 80 trips, the most practical models of third-link exposure (adjusted correlation coefficient [R^2] = 0.69) combined three variables: (1) the ambient CO concentration; (2) the second-link travel time; and (3) either the travel time, vehicle speed, or CO emission factor for the third link. The models showed that the vehicle's travel time and average speed and the CO emission factor for a given link of the roadway had equal ability to predict passenger cabin exposure to CO on the third link because of mathematical relationships among these three predictor variables.

4.4.2 Federal and State Policies Affecting Temporal Trends in Exposure

Studies show significant temporal trends in population exposure to CO concentrations from motor vehicle emissions based on different indicators. One indicator is unintentional death rates from CO poisoning, and another is based on direct measurements of passenger cabin exposure to CO concentrations from traffic emissions. Table 4-5 summarizes data on these indicators from several U.S. studies and shows the federal and California tailpipe CO emission standards by model year for comparison. In Table 4-5, the net mean CO concentration value represents the microenvironmental component of total exposure. This value equals the mean in-vehicle CO concentration, minus the mean ambient CO concentration as recorded simultaneously at a fixed-site monitor.

4.4.2.1 Effects of Motor Vehicle Emission Standards on Unintentional Death Rates

Based on death certificate reports compiled by the National Center for Health Statistics, Cobb and Etzel (1991) reported statistics on the annual rate of unintentional deaths from CO poisoning in the United States. As shown in Table 4-5, the annual death rate per 100,000 population declined from 0.67 in 1979 to 0.39 in 1988. Motor vehicle exhaust gas accounted for 6,552 deaths or 56.7% of the total 11,547 unintentional deaths occurring during the 10-year period. The highest death rates per 100,000 persons occurred among males, blacks, the elderly, and those residing in northern states. Monthly variation in death rates indicated a seasonal pattern, with January fatalities routinely about two to five times higher than those occurring in July.

Cobb and Etzel (1991) speculated that declining death rates could be attributed in part to reductions in population CO exposure brought about by automaker compliance with the motor vehicle CO emission standards of the CAA. They argued that tighter CO emission standards may enable cars to emit exhaust into an enclosed space for a longer period of time before CO builds up to toxic levels. To test this hypothesis, Pearson's correlation coefficient (r) was computed using the federal emission standard data and annual death rate data shown in Table 4-5. The value of the correlation coefficient $r = 0.54$, probability $[p] < 0.05$ for a one-tailed test of the hypothesis) supports their argument.

TABLE 4-5. MOTOR VEHICLE CARBON MONOXIDE EMISSION STANDARDS, TYPICAL IN-VEHICLE CARBON MONOXIDE EXPOSURES, AND UNINTENTIONAL CARBON MONOXIDE-RELATED DEATH RATES IN THE UNITED STATES

Year	New Passenger Car CO Emission Standard: Federal (g/mi)	New Passenger Car CO Emission Standard: California (g/mi)	Net Mean In-Vehicle CO Concentration[a] (ppm)	CO Exposure Study Location	U.S. Unintentional CO-Related Annual Death Rate per 100,000 Population
Pre-control	84.0	84.0			
≈1965	84.0	84.0	12.0	Los Angeles	
1966	84.0	51.0	17.5	Five U.S. cities	
1968	51.0	51.0			
1970	34.0	34.0			
1972	28.0	34.0			
1973	28.0	34.0	11.5	Los Angeles	
1974	28.0	34.0			
1974-75	15.0	9.0	7.4	Boston	
1975	15.0	9.0			
1976	15.0	9.0			
1977	15.0	9.0			
1978	15.0	9.0	10.3	Washington	
1979	15.0	9.0	9.7	Los Angeles	0.67
1980	7.0	9.0	8.3	Santa Clara Co., CA	0.55
1981	3.4	7.0	5.2	Denver	0.58
1981	3.4	7.0	4.3	Los Angeles	0.58
1981	3.4	7.0	2.9	Phoenix	0.58
1981	3.4	7.0	2.9	Stamford	0.58
1981-82	3.4	7.0	9.5	Honolulu	
1982	3.4	7.0			0.56
1982-83	3.4	7.0	1.4	Denver	
1982-83	3.4	7.0	1.8	Washington	
1983	3.4	7.0	9.4	Washington	0.53
1984	3.4	7.0			0.49
1985	3.4	7.0			0.49
1986	3.4	7.0			0.44
1987	3.4	7.0			0.39
1987-88	3.4	7.0	4.9	Los Angeles	
1988	3.4	7.0	8.4	Raleigh	0.39
1989	3.4	7.0			
1990	3.4	7.0			
1991-92	3.4	7.0	~ 3.6	Santa Clara Co., CA	
1992	3.4	7.0	< 3.0	New Jersey suburbs of New York City, NY	

[a]Mean in-vehicle CO concentration, minus mean ambient CO concentration.

Source: Johnson (1988); Cobb and Etzel (1991); Flachsbart (1995); and Faiz et al. (1996).

4.4.2.2 Effects of Motor Vehicle Emission Standards on Passenger Cabin Exposure

Based on a review of 16 U.S. studies that occurred between 1965 and 1992, Flachsbart (1995) reported a long-term, downward trend in commuter exposure levels. Studies reported typical (mean or median) CO concentrations for trips, most of which lasted an hour or less. Mean CO concentrations fell from 37 ppm in 1965, as reported by Haagen-Smit (1966) for a study in Los Angeles to 3 ppm in 1992 for a study by Lawryk et al. (1995) in the New Jersey suburbs of New York City. If one assumes that these results are representative of commuter CO exposures in cities during these time periods, then exposures fell 92% over this 27-year period. This reduction implies that CO exposure levels reported in the past for a particular place and time in the United States may not be indicative of current exposures.

In the United States, the effect of progressively tighter CO emission standards on in-vehicle CO exposures over time is readily apparent in Table 4-5. Prior to 1968, each new passenger car emitted 84 g/mi of CO, but by the 1981 model year and thereafter, each new car sold outside of California emitted only 3.4 g/mi of CO, a reduction of 96% (Johnson, 1988). This reduction in certified CO emissions for new passenger cars is roughly equal to the 92% reduction in commuter exposure reported above for the same period. Further analysis reveals that net mean exposure data and the applicable emission standard data in Table 4-5 are highly correlated $r = 0.74$, $p < 0.0005$ for a one-tailed test of the hypothesis). In this analysis, the applicable emission standard (federal or California) was determined by the location of the exposure study. Because the exposure studies did not adhere to a standard protocol, Flachsbart (1995) recommended that future in-vehicle CO exposure studies should use standard protocols to facilitate comparisons and to document the effect on exposure of future measures taken under motor vehicle emission control programs.

Two of the 16 studies did follow a standard protocol. Ott et al. (1994) measured in-vehicle CO concentrations on 88 standardized trips over a 1-year period in 1980-1981 on a suburban highway near San Jose. They reported a mean CO concentration of 9.8 ppm for trips of 35 to 45 min. In 1991-1992, Ott et al. (1993) resurveyed this highway using a methodology similar to their previous study to determine in-vehicle exposure trends. They reported that the mean in-vehicle CO concentration had dropped to 4.6 ppm or 46.9% of the mean value estimated 11 years earlier. They attributed the exposure reduction to replacement of older vehicles with newer ones that have lower CO emission factors. This reduction is particularly significant, as

daily traffic volumes on this highway grew by 19.1% during the intervening period, according to estimates by Yu et al. (1996).

For this highway, Yu et al. (1996) developed a mathematical model known as the STREET model to predict trends in CO emissions and exposures. Based on fleet turnover and no changes in the 1990 California motor vehicle CO emission standards, the model predicted that the median CO concentrations would drop from 3.9 ppm in 1991-1992 to 1.6 to 1.8 ppm in 2002-2003. At the 99% percentile, the model predicted that the CO concentrations would drop from 10 ppm in 1991-1992 to 4.0 to 4.6 ppm in 2002-2003. This prediction was based on an additional expected reduction of up to 60% in tailpipe emissions of CO primarily because of continued replacement of older cars with newer, low-emission vehicles. This prediction suggests that CO exposure levels inside passenger cars will virtually disappear with vehicle fleet turnover in the next few years.

Similar studies of commuter CO exposure were done by Flachsbart et al. (1987) in the United States, Koushki et al. (1992) in Saudi Arabia, Fernández-Bremauntz and Ashmore (1995a,b) in Mexico, and Dor et al. (1995) in France. These studies used similar methods of data collection and analysis, with one exception. Smoking was allowed for some trips in the Saudi study, but was not allowed in the other studies. Table 4-6 shows typical values of the net mean CO concentration by travel mode for three of the studies. The net mean CO concentration for the Saudi study could not be determined. The net CO concentrations for each travel mode in Mexico City were much higher than for comparable modes in both Washington and Paris, where net CO concentrations were similar. The similarity between the U.S. and French studies occurred even though catalytic converters existed on 62% of American cars in 1982 (U.S. Department of Commerce, 1983) but were not yet common on French cars in 1992 (Dor et al., 1995).

The reasons for the similarity in results between the U.S. and French studies are not readily apparent. However, passenger cabin exposure levels in North and Central America can be explained partly by comparing the history of automotive emission standards in the United States and Mexico. The United States initiated nationwide emission standards on new passenger cars in 1968 and adopted progressively tighter controls throughout the 1970s (Johnson, 1988). By the 1975 model year, catalytic converters became standard equipment on new passenger cars. Mexico adopted a tailpipe CO emission standard of 47.0 g/mi for the 1975 model year, and, by the 1993 model year, Mexico finally reached parity with the 1981 U.S. standard of 3.4 g/mi.

TABLE 4-6. TYPICAL NET MEAN CARBON MONOXIDE CONCENTRATION RANGES BY TRAVEL MODE FOR CITIES IN THREE COUNTRIES[a,b]

	Washington, DC, USA (1983)		Mexico City, Mexico (1991)		Paris, France (1991-92)	
Travel Mode	Net Mean CO Concentrations (ppm)	Averaging Times (min)	Net Mean CO Concentrations (ppm)	Averaging Times (min)	Net Mean CO Concentrations (ppm)	Averaging Times (min)
Automobile	7-12	34-69	37-47	35-63	7-10	82-106
Diesel bus	2-6	82-115	14-27	40-99	2-3	NA
Rail transit	0-3	27-48	9-13	39-59	1	NA

[a]"Typical" means do not include outlier values that can be attributed to unusual circumstances.
[b]Net mean CO concentration = mean in-vehicle CO concentration, minus mean ambient CO concentration.
NA = not available.

Source: Adapted from Flachsbart (1998b).

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4.4.3 California's No-Smoking Policy

A California law prohibiting smoking in bars, lounges, nightclubs, and restaurants with bars took effect on January 1, 1998. The law is the first statewide ban of its kind in the nation. An assessment of the reduction in CO exposure from smoking because of the ban could not be found in the literature. However, several surveys were made in California to assess public support and proprietor compliance with the ban amidst media reports of noncompliance. The surveys did not assess whether total CO exposure from tobacco smoking in California has declined because of the ban, nor did they determine the extent to which smoking has shifted to or increased in locations not regulated by the ban. The results of the surveys have not yet been published in the scientific literature.

Shortly after the law took effect, several nonprofit organizations opposed to smoking did field surveys in the San Francisco Bay Area to verify proprietor compliance with the law. The first survey, which occurred in mid-January 1998, in San Mateo County, showed that 36 of 42 bars (85.7%) were in compliance (Licavoli, 1998). The second survey focused on bars located in areas with tourist attractions. It reported that 96% of 36 bars in San Francisco's Fisherman's Wharf district were in compliance, as were all 11 of those surveyed in Oakland's Jack London Square (Gordon, 1998).

A statewide survey of 1,001 adults (age 21 years and older) was conducted in February and March 1998 to determine public opinion and behavior regarding smoking in bars and similar establishments. The poll showed that a majority (64%) of respondents visited some kind of bar in the past year. Only 11% of them claimed to visit bars at least once or more per week. Patrons spent an average of 1.5 h per visit, although regular users spent more time than that. The survey found that 75% of bar patrons did not smoke in bars, and that 65% said that a law intended to prohibit smoking in bars would not affect their patronage (California Department of Health Services, 1998).

In February 1998, Communication Sciences Group (1998) reported results of a telephone survey in Los Angeles using a random-digit dialing method. The survey included English-speaking adults (ages 21 and over) who had visited a nightclub, bar, lounge, or restaurant/bar combination in California since the law took effect. Of 455 respondents, 102 (22%) said they were smokers. The survey found that 98% of the respondents were aware of the new law; 85% reported that they would either be more likely to visit a smoke-free

establishment, or that it made no difference; 78% of frequent patrons (one or more visits to a bar per week) reported either an increased intention or no effect on intention to visit smoke-free bars; 61% either strongly or somewhat approved the smoking ban; and 70% reported that it was important to have a smoke-free environment inside these places.

4.4.4 Social Changes Affecting Human Activity Patterns

Between 1965 and 1985, the Americans' Use of Time Project at the University of Maryland reported that average time spent in travel for all kinds of trips increased from 2.7 to 3.1 h per week (Cornish et al., 1991). Despite this trend, there is evidence that average commuting times between home and work have remained stable. The decennial census collected travel time data for the first time in 1980. By 1990, the census showed that the nation's average commuting time of 21.7 min in 1980 increased only 40 s to 22.4 min in 1990. Although the number of workers who traveled 45 min or more increased from 10.9 million in 1980 to 13.9 million in 1990, their mean travel time actually decreased from 59.6 min in 1980 to 58.5 min in 1990. One reason for this is that more people were taking their morning commute from home to work during the "shoulder hours" from 6 to 7 a.m. or from 8 to 9 a.m. than during the "peak hour" from 7 to 8 a.m. In 1990, the shoulder hours accounted for about 37% of worker trip starts, whereas the "peak hour" accounted for only 32% of all trip starts (Pisarski, 1992).

Typically, average commuting times in large cities are greater than those nationwide. Even so, some cities still show a stable trend in commuting times. For example, the average commuting time for the Washington metropolitan region was 33.5 min in 1957. By 1968, the average commuting time stood at 32.5 min, and it remained at 32.5 min for 1987-1988 when the city was resurveyed. This stability in travel times occurred despite an increase in average commuting distance between 1968 and 1988. In Washington, the average distance of those who commuted alone by automobile from home to work increased from 6.9 miles in 1968 to 7.8 miles in 1987-1988, but their average trip speeds also increased by more than 10.7% to offset the increase in distance (Levinson and Kumar, 1994). Such higher average trip speeds should contribute to lower commuter exposures, because passenger cabin exposure in the Washington area was shown to be inversely related to travel speed by passenger car (Flachsbart et al., 1987).

In another study of the Washington area based on the same data and time period, Levinson and Kumar (1995) observed an 85% overall increase in the number of jobs and a decline in average household size from 3.34 to 2.67 people. During the 20-year period from 1968 to 1988, vehicle registrations increased 118%, but road capacity increased only 13%, which led to more traffic congestion. The average number of autos per household increased from 1.6 to 2.0. However, the most important change was a higher percentage of women in the work force, which forced readjustments and reallocations of time spent in household activities. Specifically, workers had more per capita income but spent less time at home and engaged in more travel for nonwork trips during peak travel periods. Compared to 1968, working men spent 20 min less time at home in 1988, and working women spent about 40 min less. Commuters made multiple stops (i.e., trip chaining) on their way home from work (e.g., visiting health clubs, picking up children at day-care, shopping, eating at restaurants). In 1968, such errands and activities usually were done after the primary worker returned home with the household car. By 1988, these trips often were made in separate vehicles by each household member on their way home from work. By 1988, average time spent daily in travel per person in the Washington area had increased by 14 min for workers and by 11 min for nonworkers over 1968. Levinson and Kumar (1995) said that these results do not support the hypothesis "that individuals spend a fixed amount of time per day (just over 1 h) in transportation, and make all budget allocation adjustment on non-travel times." Instead, they suggested that some urban households have been spending more time in travel and less time at home, and have been buying more household services outside the home.

On the other hand, Levinson and Kumar (1995) anticipate that some people will spend more time at home in the future. They noted: "Several factors suggest that work at home, telecommuting, and teleshopping may be on the verge of wide-spread adoption. The technology is coming into place with the long-awaited advent of videophones, and of the 'information superhighway', that is, broad-band two-way communications facilitated by the recent consolidations in the telecommunications and entertainment industries." The percentage of people working at home increased from 2.3% in 1980 to 3% in 1990 (Pisarski, 1992). Currently, an estimated 52 million Americans are self-employed to some extent, working either in home offices for themselves or for companies as telecommuters. In 1975, only 2.5 million

Americans worked at home. The U.S. General Services Administration expects to see 60,000 telecommuters working for the federal government by the end of 1998. In 1994, there were fewer than 4,000 such workers (Webster, 1998). This employment shift could have tremendous implications for population exposure.

4.5 CONCLUSIONS

Several conclusions emerge from this review of new studies of population exposure to carbon monoxide. First, fixed-site ambient CO monitors do not necessarily represent the outdoor CO concentrations in a given urban location because of spatial and temporal variations in traffic patterns. Study has shown that fixed-site CO monitors often underestimate outdoor CO concentrations at the locations nearer traffic sources and overestimate the CO concentrations at the locations further from traffic sources than the fixed-site location. If the average ambient CO concentration measured at a fixed monitoring station adequately represents the average outdoor CO concentration in the surrounding community (e.g, within ±1 or 2 ppm), the station may provide a reasonable estimate of the community's mean exposure to CO of ambient origin. The station will not adequately represent the exposures to CO of the people residing in the community while they are exposed to tobacco smoke; motor vehicle exhaust during commutes to and from work, school, etc.; and occupational and residential sources of fuel combustion. The mean COHb level of people exposed to these sources will be greater than their mean COHb level predicted solely from exposure to CO of ambient origin.

Second, implementation of motor vehicle emission standards, catalytic converters, inspection/maintenance programs, and cleaner burning fuels over the past three decades has reduced the CO exposures of motorists, pedestrians, and bicyclists on streets and highways. This suggests that estimates of current population exposure based on pre-1990 exposure studies may no longer apply. Presently, there is no good estimate of the CO exposure distribution for the current population. Moreover, average CO concentrations in passenger cabins of motor vehicles are expected to drop further in the near future, based on mathematical projections for a standardized trip on an arterial highway (Yu et al., 1996). Further changes in exposure may occur because of certain trends in travel behavior caused by growth rates in vehicle miles of travel, growth in travel during the shoulder hours of peak traffic periods, and greater use of

computers to telecommute and teleshop from home. The effects of these trends on population exposure have not been studied fully. Also, the effect of transportation control measures on commuter exposure has received only limited study.

Third, personal CO exposures that exceed the NAAQS still occur among nonsmokers in certain locations and atypical situations. These include occasions when people (usually children) ride in the back of vehicles with leaky rear doors (e.g., school bus, covered pickup truck, ambulance) or ride certain recreational vehicles (i.e., snowmobiles, power boats). It also includes a growing number of events where people gather to barbecue food or watch sporting events held at indoor arenas used for ice skating, motocross and monster-truck competitions, and tractor-pulls, because the vehicles in these events lack emission controls. In some cases, ventilation has not lowered CO concentrations sufficiently. High CO exposures also still occur in small homes with malfunctioning and poorly ventilated gas and kerosene appliances. Moreover, unintentional poisonings and fatalities are still reported when people use gasoline-powered appliances, engines, and tools (e.g., chainsaws), even under ventilated conditions.

Fourth, CO exposures are still high in certain occupations such as charcoal meat grillers, garage mechanics, firefighters, forklift operators, and those who work in facilities adjacent to forklift operations. Also, more than one million people have high exposure to methylene chloride in the workplace, where it is used as a degreaser, paint remover, aerosol propellant, and blowing agent. Another concern is concurrent exposure to methylene chloride and methanol, which prolongs the period of elevated COHb in the body.

Fifth, the California and national activity pattern studies indicate that Americans spend, on average, between 87 and 89% of their day indoors and about 7% of time in or near vehicles. However, U.S. Census and metropolitan travel behavior surveys indicate that, although average commuting times from home to work have fallen, some Americans in large cities are spending a growing amount of time in surface travel compared with the past and less time at home. As a result, they have been buying more household services outside the home. This suggests that individuals do not have fixed daily travel-time budgets in the long term.

Finally, there are implications of this literature review for activity pattern studies and exposure models. The California and national activity pattern studies described time spent by conventional social categories (e.g., gender, age, race, etc.) These studies were not guided by

any theoretical framework as was the Boston study, which was able to explain activity patterns more convincingly. Hence, although the Boston study did not focus on exposure assessment, it still has profound implications for any study that analyzes activity pattern data. The lesson for simulation models is that they need to sample from distributions that more accurately represent current microenvironmental pollutant concentrations and time budgets, which have been affected by public policies affecting motor vehicle emissions, travel behavior in cities, and smoking in public places. Moreover, exposure models should not assume that time distributions in different microenvironments are independent of each other. Modern households appear to be making continuous tradeoffs in their activity patterns and role allocations, in terms of who gets to do what and when, to better adapt to ongoing technological and social changes affecting society.

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5. PHARMACOKINETICS AND MECHANISMS OF ACTION OF CARBON MONOXIDE

5.1 INTRODUCTION

Basic research on the physiology, pharmacodynamics, and toxicology of carbon monoxide (CO) that ended in late seventies was followed by studies focused primarily on the cardiopulmonary effects of CO as an ambient air pollutant. Although research in this area continues, more recent studies have refocused on the mechanisms of action and pathophysiological effects of CO at a cellular level and on its role as a cytotoxic agent and neural messenger. In this chapter, the sections discussing basic pharmacodynamics draw heavily from Chapter 9 of the previous CO criteria document (U.S. Environmental Protection Agency, 1991). However, all sections were revised and consolidated, many were expanded, and several new sections were added. In particular, sections on tissue production and metabolism of CO and intracellular effects of CO have been revised extensively and expanded. The new section on conditions affecting uptake and elimination of CO discusses the influence of physical activity, altitude, physical characteristics, and health status on carboxyhemoglobin (COHb) formation. Also, new sections on the mechanisms of CO and a review of the developing concepts have been added.

5.2 ABSORPTION, DISTRIBUTION, AND PULMONARY ELIMINATION

5.2.1 Pulmonary Uptake

Although CO is not one of the respiratory gases, the similarity of physico-chemical properties of CO and oxygen (O_2) permits an extension of the findings of studies on the kinetics of transport of O_2 to those of CO. The rate of formation and elimination of COHb, its concentration in blood, and its catabolism is controlled by numerous physical factors and physiological mechanisms. The relative contribution of these mechanisms to the overall COHb kinetics will depend on the environmental conditions, the physical activity of an individual, and

many other physiological processes, some of which are complex and still poorly understood (see Section 5.4 for details). All of the pulmonary uptake occurs at the respiratory bronchioles, alveolar ducts, and sacs. The rate of CO uptake depends on the rate of COHb formation. At the low concentration of CO in inhaled air, the rate of uptake and the rate of COHb formation could, for all practical purposes, be considered to be qualitatively the same.

5.2.1.1 Mass Transfer of Carbon Monoxide

The mass transport of CO between the airway opening (mouth and nose) and the red blood cell (RBC) hemoglobin (Hb) 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 the air-blood interface, including the RBC. In the gas phase, the key mechanisms of transport are convective flow, by the mechanical action of the respiratory system, and diffusion in the acinar zone of the lung (Engel et al., 1973). Subsequent molecular diffusion of CO across the alveolo-capillary membrane, plasma, and RBC is the virtual mechanism of the liquid phase. The principal transport pathways and body stores of CO are shown in Figure 5-1 (Coburn, 1967).

5.2.1.2 Effects of Dead Space and Ventilation/Perfusion Ratio

The effectiveness of alveolar gas exchange depends on effective gas mixing and matching of ventilation and perfusion. During normal tidal breathing, the inhaled gas is not distributed uniformly across the tracheobronchial tree. With increased inspiratory flow, as during exercise, intrapulmonary gas distribution becomes more uniform, but gas concentration inhomogeneity still will persist. Considering that almost 90% of gas is contained within the acinar zone of the lung, any increase in gas inhomogeneity in this terminal region will have about the same negative effect as an additional increase in the alveolar dead space or a decrease in the alveolo-capillary diffusion capacity (Engel et al., 1973).

The inefficiency of gas mixing and a consequent decrease in the effectiveness of alveolar gas exchange is aggravated by ventilation/perfusion ($\dot{V}_A/\dot{Q}$) mismatch. Because of the gravity-dependence of ventilation and even more of perfusion, regional $\dot{V}_A/\dot{Q}$ ratios will range from 0.6 (at the base of the lung) to 3.0 (at the apex), the overall value being 0.85. Because the $\dot{V}_A/\dot{Q}$

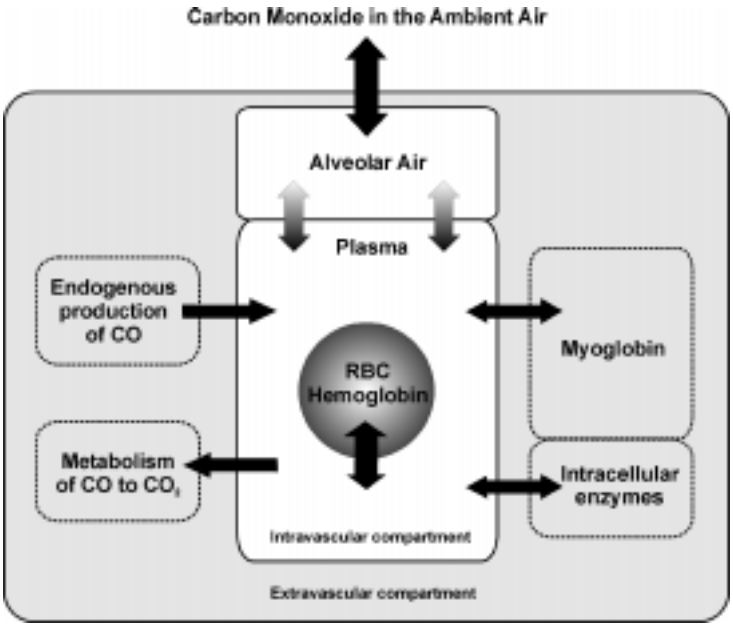

Figure 5-1. Diagrammatic presentation of CO uptake and elimination pathways and CO body stores.

Source: Adapted from Coburn (1967).

ratio is the principal variable controlling gas exchange, any inequalities not only will impair transfer of gases to the blood but also will interfere with unloading of gases from the blood into the alveolar air. In humans, a change in posture to recumbent or horizontal, or exercise will increase the uniformity of $\dot{V}_A/\dot{Q}$ ratios and promote more efficient gas exchange, whereas increased resting lung volume, increased airway resistance, decreased lung compliance, and, generally, any lung abnormality will aggravate $\dot{V}_A/\dot{Q}$ ratio inequality.

The simplest indicator of the $\dot{V}_A/\dot{Q}$ ratio inequalities is the volume of physiological dead space (V_D), which comprises both the anatomical and alveolar dead space. The alveolar dead space results from reduced perfusion of alveoli, relative to their ventilation (Singleton et al., 1972). An increase in tidal volume or respiratory frequency, or both, will increase moderately to substantially the V_D in healthy subjects and in individuals with lung function impairment, respectively (Lifshay et al., 1971).

5.2.1.3 Lung Diffusion of Carbon Monoxide

Although the above mechanisms controlling the rate of formation of blood COHb are predominantly active processes, the second key mechanism, diffusion of gases across the alveolar air-Hb barrier, is an entirely passive process. In order to reach the Hb-binding sites, CO and other gas molecules have to pass across the alveolo-capillary membrane, diffuse through the plasma, pass across the RBC membrane, and finally enter 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 physico-chemical laws, particularly by 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 a high level of CO rapidly increases blood COHb by immediate and tight binding of CO to Hb. The rapidity of CO binding to Hb keeps a low partial pressure of CO within the RBC, thus maintaining a high pressure differential between air and blood and consequent diffusion of CO into blood. Subsequent inhalation of CO-free air reverses the gradient (higher CO pressure on the blood side than alveolar air), and CO is released into alveolar air. The air-blood pressure gradient for CO is usually much higher than the blood-air gradient; therefore, the CO uptake will be a proportionately faster process than CO elimination. The rate of CO release will be further affected by tissue metabolism and endogenous production of CO.

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 oxyhemoglobin (O_2Hb), COHb, partial pressure of alveolar CO_2, ventilatory pattern, O_2 consumption, blood flow, functional residual capacity, etc. (Forster, 1987). In a supine position at rest, CO diffusion has been shown to be significantly higher than that at rest in a sitting position (McClean et al., 1981). Carbon monoxide diffusion increases with exercise, and, at maximum work rates, diffusion will be maximal regardless of body position. This increase is attained by increases in both the diffusing capacity of the alveolar-capillary membrane 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, diffusion is higher, whereas, at residual volume, it is lower than the average (McClean et al., 1981). Under

pathologic conditions, where one of several components of the air-blood interface might be affected severely, as in emphysema, fibrosis, or edema, both the uptake and elimination of CO will be affected (Barie et al., 1994).

5.2.2 Tissue Uptake

5.2.2.1 The Lung

Although the lung in its function as a transport system for gases is exposed continuously to CO, very little CO actually diffuses into the lung tissue itself (as dissolved CO), except for the alveolar region. The epithelium of the conductive zone (nasopharynx and large airways) presents a significant barrier to diffusion of CO. Therefore, diffusion and gas uptake by the tissue, even at high CO concentration, will be 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 on the concentration of CO and duration of exposure. Experimental exposures of the oronasal cavity in monkeys to very high concentrations of CO for a very short period of time (5 s) increased the blood COHb level to <3.5%. 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 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 the lung interstitium will be complete.

5.2.2.2 The Blood

The rate of CO binding with Hb is about 20% slower, and the rate of dissociation from Hb is an order of magnitude slower than are these rates for O_2. However, the CO chemical affinity (represented by the Haldane coefficient, M) for Hb is about 218 (210 to 250)-times greater than that of O_2 (Roughton, 1970; Rodkey et al., 1969). Under steady-state conditions (gas exchange between blood and atmosphere remain constant), one part of CO and 218 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 650 ppm CO. Moreover, the ratio of COHb to O_2Hb is proportional to the ratio of their respective partial pressures, PCO and PO_2. The relationship between the

affinity constant M and PO_2 and PCO, first expressed by Haldane (1897-1898), has the following form:

$$COHb / O_2Hb = M \times (PCO / PO_2). \quad (5\text{-}1)$$

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, CO_2, temperature, and 2,3-diphosphoglycerate that bind to the deoxygenated form of Hb and so lower its O_2 affinity over a wide range of PCO/PO_2 ratios (Wyman et al., 1982; Gronlund and Garby, 1984).

Under dynamic conditions, competitive binding of O_2 and CO to Hb is complex; simply said, the greater the number of heme molecules 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 the characteristic relationship between O_2Hb and PO_2, which in normal blood is S-shaped (v) (Figure 5-2). With increasing concentration of COHb in blood, the dissociation curve is shifted gradually to the left, and its shape is transformed into a near rectangular hyperbola. 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 caused by anemia. Thus, in an acute anemia patient (50% of Hb) at a tissue PO_2 of 26 torr (v_1'), 5 vol % of O_2 (50% desaturation) might be extracted from blood, an amount sufficient to sustain tissue metabolism. In contrast, in a person poisoned with CO (50% COHb), the tissue PO_2 will have to drop to 16 torr (v_2'; severe hypoxia) to release the same, 5 vol % O_2. Any higher demand on O_2 under these conditions (e.g., by exercise) might result in brain oxygen depletion and loss of consciousness of the CO-poisoned individual.

Because so many cardiopulmonary factors determine COHb formation, the association between COHb concentration in blood and duration of exposure is not linear but S-shaped. With progression of exposure, the initial slower COHb formation gradually accelerates, but, as COHb approaches equilibrium, the build-up slows down again. The S-shape form becomes more pronounced with higher CO levels or with exercise (Benignus et al., 1994; Tikuisis et al., 1992).

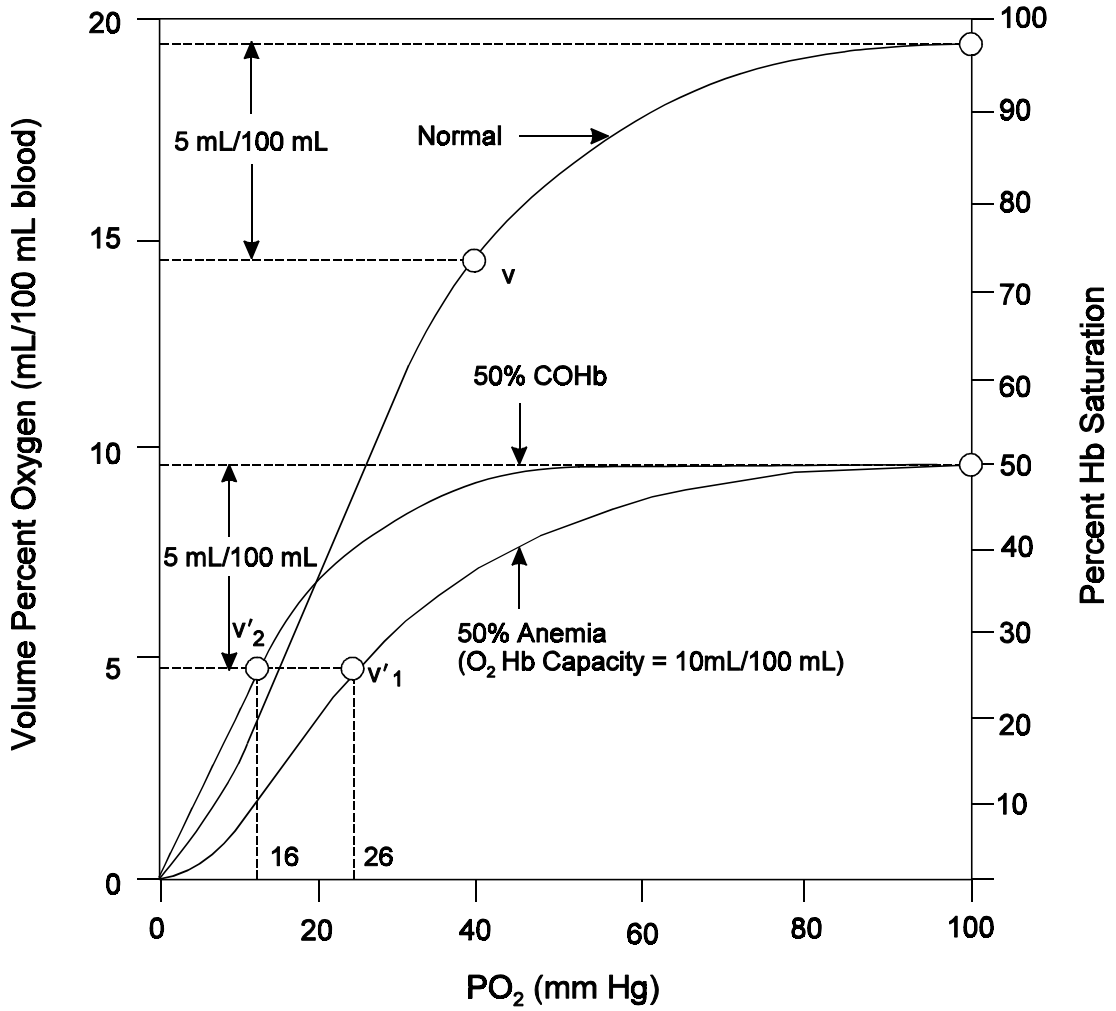

Figure 5-2. Oxyhemoglobin dissociation curve of normal human blood, of blood containing 50% COHb, and of blood with only 50% Hb because of anemia.

Source: U.S. Environmental Protection Agency (1991).

5.2.2.3 Heart and Skeletal Muscle

Myoglobin (Mb), as a respiratory hemoprotein of muscular tissue, will undergo a reversible reaction with CO in a manner similar to O_2. Greater affinity of O_2 for Mb than Hb (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 O_2Mb. The main function of Mb is thought to be a temporary store of O_2 and to act as a diffusion facilitator between hemoglobin and the tissues (Peters et al., 1994).

Myoglobin has a CO affinity constant approximately eight-times lower than hemoglobin (M = 20 to 40 versus 218, respectively) (Haab and Durand-Arczynska, 1991; Coburn and Mayers, 1971). As with Hb, the combination velocity constant between CO and Mb is only slightly lower than that for O_2, but the dissociation velocity constant is much lower than that 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 binding of CO to Mb (COMb) in heart and skeletal muscle in vivo has been demonstrated at levels of COHb below 2% in heart and 1% in skeletal muscle (Coburn, 1973; Coburn and Mayers, 1971). At rest, the COMb/COHb ratio (0.4 to 1.2) does not increase with an increase in COHb up to 50% saturation and appears to be independent of the duration of exposure (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 and Mayers, 1971). Consequent reduction in O_2-carrying capacity of Mb may have a profound effect on the supply of O_2 to the tissue. Apart from Hb and Mb, other hemoproteins will react with CO. However, the exact role of such compounds on O_2-CO kinetics still needs to be ascertained. For more discussion on this topic, see Section 5.6.1.

5.2.2.4 The Brain and Other Tissues

The 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). However, the energy requirement of brain tissue is very high and varies greatly with local metabolism. Because oxygen demand also is coupled to local functional activity, which at times may be very high, and because the brain's oxygen storage is minimal, any degree of hypoxia will have a detrimental effect on brain function. The primary effects of CO on other organs (e.g., liver, kidney) is via hypoxic mechanisms.

5.2.3 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. 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, may not be constant when the steady-state conditions have not yet been reached. 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). The reported divergence of the COHb decline rate in blood and in exhaled air suggests that the CO elimination rates from extravascular pools are slower than those 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 same factors that govern CO uptake will affect CO elimination. This suggests that the Coburn-Forster-Kane (CFK) model (see Section 5.5.1) may be suitable to predict CO elimination as well. Surprisingly, few studies tested this application. When breathing air, the CFK model predicted very well the COHb decline. However, at a higher partial pressure of O_2 in humidified inspired air (P_IO_2) or under hyperbaric O_2 conditions, the key CFK equation parameters, particularly the diffusing capacity for CO (D_LCO) value, must be adjusted for hyperoxic conditions so that CFK will predict more accurately the elimination of CO (Tikuisis, 1996; Tikuisis et al., 1992; Tyuma et al., 1981). The half-time of CO disappearance from blood under normal recovery (air) showed a considerable between-individual variance. For COHb concentrations 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 (Peterson and Stewart, 1970). The CO elimination half-time in nonsmokers is considerably longer in men (4.5 h) than in women (3.2 h). During sleep, the elimination rate slowed in both sexes, but, in men, it became almost twice as slow (8.0 h) as during waking hours. Although no ventilation variables were obtained during the study, the day-to-night differences have been attributed to lower ventilation rates at sleep. The authors speculate that the sex differences in elimination half-time are related to the skeletal muscle mass and intrinsically to the amount of stored Mb

(Deller et al., 1992). The half-time elimination rate appears to be independent of the CO exposure source (e.g., fire, CO intoxication). Normobaric O_2 administered to fire victims and CO-poisoned individuals resulted in about the same CO elimination half-time, 91 and 87 min, respectively (Levasseur et al., 1996).

Increased inhaled concentrations of O_2 accelerated elimination of CO; by breathing 100% O_2, the half-time was shortened by almost 75% (Peterson and Stewart, 1970). The average half-life of COHb in individuals with very low COHb level (1.16%) breathing hyperbaric O_2 was 26 min, compared with 71 min when breathing normobaric O_2 (Jay and McKindly, 1997). The elevation of PO_2 to 3 atm 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% carbon dioxide (CO_2) in O_2, hyperbaric O_2 treatment is more effective in facilitating displacement of CO. Therefore, hyperbaric oxygen is used as a treatment of choice in CO poisoning. A mathematical model of COHb elimination that takes into account P_IO_2 has been developed but not yet validated (Singh et al., 1991).

5.3 TISSUE PRODUCTION AND METABOLISM OF CARBON MONOXIDE

In the process of natural degradation of RBC hemoglobin to bile pigments, a carbon atom (a-bridge C) is separated from the porphyrin nucleus and, subsequently, is catabolized by microsomal heme oxygenase (HO_x) 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 have been used with mixed success as quantitative indices of the rate of heme catabolism (Landaw et al., 1970; Solanki et al., 1988). Diurnal variations in endogenous CO production are significant, reaching a maximum around noon and a minimum around midnight (Levitt et al., 1994; Mercke et al., 1975a). Week-to-week variations of CO production are greater than day-to-day or within-day variations for both males and females.

Any disturbance leading to accelerated destruction of RBCs and accelerated breakdown of other hemoproteins would lead to increased production of CO. Hematomas, intravascular hemolysis of RBCs, blood transfusion, and ineffective erythropoiesis all will elevate COHb concentration in blood. In females, COHb levels fluctuate with the menstrual cycle; the mean rate of CO production in the premenstrual, progesterone phase is almost doubled (Delivoria-Papadopoulos et al., 1974; Mercke and Lundh, 1976). Neonates and pregnant women also showed a significant increase in endogenous CO production related to increased breakdown of RBCs. Degradation of RBCs under pathologic conditions such as anemia (hemolytic, sideroblastic, and 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 was 2- to 3-times higher than in healthy individuals (Coburn et al., 1966). Anemias also may develop under many pathophysiologic conditions characterized by chronic inflammation, such as malignant tumors or chronic infections (Cavallin-Ståhl et al., 1976) (see also Section 5.4.3).

Not all endogenous CO comes from RBC degradation. Other hemoproteins, such as Mb, cytochromes, peroxidases, and catalase, contribute approximately 20 to 25% to the total amount of CO (Berk et al., 1976). Approximately 0.4 mL/h of CO is formed by Hb catabolism, and about 0.1 mL/h originates from nonhemoglobin sources (Coburn et al., 1964).

A large variety of drugs will affect endogenous CO production. Generally, any drug that will increase bilirubin production, primarily from the catabolism of Hb, will promote endogenous production of CO. Nicotinic acid (Lundh et al., 1975), allyl-containing compounds (acetamids and barbiturates) (Mercke et al., 1975b), diphenylhydantoin (Coburn, 1970a), progesterone (Delivoria-Papadopoulos et al., 1974), contraceptives (Mercke et al., 1975c) will all elevate tissue bilirubin and, subsequently, CO production.

Another mechanism that will increase CO production is a stimulation of HO_x and subsequent degradation of cytochrome P-450-dependent, mixed-function oxidases. Several types of compounds such as a carbon disulfide and sulfur-containing chemicals (parathion and phenylthiourea) will act on different moieties of the P-450 system leading to an increase in endogenous CO (Landaw et al., 1970). Other sources of CO involving HO_x activity include auto-oxidation of phenols, photooxidation of organic compounds and lipid peroxidation of cell

membrane lipids (Rodgers et al., 1994). The P-450 system also is involved in oxidative dehalogenation of dihalomethanes, widely used solvents in homes and industry (Kim and Kim, 1996). Metabolic degradation of these solvents and other xenobiotics results in the formation of CO that can lead to very high (>10%) COHb levels (Manno et al., 1992; Pankow, 1996).

Ascent to high elevations will increase the endogenous level of COHb in both humans and animals (McGrath, 1992; McGrath et al., 1993). The basal CO level has been shown to be positively dependent on altitude (McGrath, 1992). Assuming the same endogenous production of CO at altitude as at sea level, the increase in COHb most likely is consequent to a decrease in PO_2 (McGrath et al., 1993). Whether other variables, such as an accelerated metabolism or a greater pool of hemoglobin, transient shifts in body stores, or a change in the elimination rate of CO are contributing factors, remains to be explored. Animal studies suggest that the elevated basal COHb production is not a transient phenomenon but persists through a long-term adaptation period (McGrath, 1992).

In recent years, new discoveries in molecular biology identified the CO molecule as being involved in many physiological responses, such as smooth muscle relaxation, inhibition of platelet aggregation, and as a neural messenger in the brain (for details, see Sections 5.6 and 5.7). Most recently, several studies reported yet another function of CO, that of a possible marker of inflammation in individuals with upper respiratory tract infection (Yamaya et al., 1998) and in asthmatics (Zayasu et al., 1997). In the latter study, the investigators found that exhaled concentrations of CO in asthmatics taking corticosteroids were about the same as in healthy individuals (1.7 and 1.5 ppm, respectively), whereas, in asthmatics who did not use corticosteroids, the average CO concentration was 5.7 ppm. The authors speculate that one of the anti-inflammatory effects of corticosteroids is the down-regulation of HO_x. Whether asthmatics have an increased COHb level was not measured in this study or reported in other studies. Critical illness also seems to be associated with elevated production of CO (Meyer et al., 1998). When compared with controls, ill patients (not characterized) had higher COHb in both arterial and central venous blood not attributable to an elevated inspired concentration of O_2 used to treat patients. Moreover, the higher COHb in arterial blood than in central venous blood measured in both ill and control individuals has lead the authors to speculate that a positive arterio-venous COHb difference results from the up-regulation of the inducible isoform of heme oxygenase (HO-1) in the lung and subsequent production of CO (see Section 5.6.3).

5.4 CONDITIONS AFFECTING CARBON MONOXIDE UPTAKE AND ELIMINATION

5.4.1 Environment and Activity

During exercise, increased demand for O_2 requires adjustment of the cardiopulmonary system, so that an increased demand for O_2 is met with an adequate supply of O_2. Depending on the intensity of exercise, the physiologic changes may range from minimal, involving primarily the respiratory system, to substantial, involving extensively the respiratory, cardiovascular, and other organ systems, inducing local as well as systemic changes. Exercise will improve the $\dot{V}_A/\dot{Q}$ ratio in the lung, increase the respiratory exchange ratio (RER), increase cardiac output, increase D_LCO, mobilize RBC reserves from the spleen and induce other compensatory changes. Heavy exercise will cause a decrease in plasma volume leading to hemoconcentration and a subsequent decrease in blood volume. Of the many mechanisms operating during exercise, the two most important physiologic variables are (1) the alveolar ventilation ($\dot{V}_A$) and (2) cardiac output. Although some physiologic changes during exercise may impair CO loading into blood (e.g., relative decrease in D_LCO during severe exercise), the majority of the changes will facilitate CO transport. Thus, by increasing gas exchange efficiency, exercise also will promote CO uptake. Consequently, the rate of CO uptake and of COHb formation will be proportional to the intensity of exercise. During a transition period from rest to exercise while exposed to CO (500 ppm), the diffusing capacity and CO uptake were reported to rise faster than O_2 consumption for each exercise intensity (Kinker et al., 1992). Carbon monoxide hypoxemia (15% COHb), at a constant exercise intensity above the lactic acid threshold, was found to accelerate muscle deoxygenation compared with normoxic conditions (Maehara et al., 1997).

Apart from physiological factors, the concentration of CO, as well as the rate of change of CO concentration in an individual's immediate environment, can have a significant impact on COHb. For example, at intersections with idling and accelerating cars, pedestrians will be exposed for a short period of time to higher CO concentrations than those present at other places on the same street. Around home, an individual working with a chain saw, lawnmower, or other gasoline-powered tools will be exposed transiently to higher, and occasionally to much higher (e.g., breathing near the exhaust of a chain saw), concentrations of CO (up to 400 ppm) (Bünger et al., 1997). In indoor environments, exposure to elevated CO from unventilated gas appliances

or from environmental tobacco smoke may increase transiently the COHb level of a previously unexposed individual. Occupationally, there are many instances and conditions under which workers may be exposed briefly to moderate-to-high levels of CO from operating equipment or other sources. Despite the shortness of each exposure episode, such transients may result in a relatively high COHb concentration. As an example, exposure for 5 min or less of a resting individual to 7,600 ppm CO in inhaled air will result in almost 20% COHb (Benignus et al., 1994). On repeated brief exposures to high CO, the COHb will increase further until the concentrations in inhaled CO and in blood reach equilibrium. Once the distribution of CO within body stores is complete, the COHb will remain constant, unless the ambient CO concentration changes (either up or down) again. As is the CO uptake, so is the elimination of CO from blood governed by the gas concentration gradient between blood and alveolar air. However, the elimination CO from blood is a much slower process (see Section 5.2.3) and, therefore, will take many hours of breathing clean air before the baseline COHb value is reached.

Both hypoxic hypoxia and CO-induced hypoxia lowered the core temperature and metabolic rate of rats. The effects were more pronounced as ambient temperature decreased. Both types of hypoxia elicited compensatory hyperventilation, but, only during hypoxic hypoxia, was the minute ventilation progressively increased as ambient PO_2 decreased (Gautier and Bonora, 1994).

Recently, a unique source of CO exposure was identified. It has been found repeatedly that the use of volatile anesthetics (fluranes) in closed-circuit anesthetic machines, when CO_2 absorbent (soda lime) is dry, can result in a significant production of CO caused by a degradation of the anesthetic and subsequent exposure of a patient to CO (up to 7.0% COHb) (Woehlck et al., 1997a,b).

5.4.2 Altitude

Altitude may have a significant influence on the COHb kinetics (U.S. Environmental Protection Agency, 1978). These changes are consequent to compensatory and adaptive physiologic mechanisms. At sea level, at a barometric pressure (P_B) of 760 torr, the P_IO_2 (body temperature and pressure, saturated with water vapor at 37 °C [BTPS] conditions) is 149 torr. At an altitude of 3,000 m (9,840 ft; P_B = 526 torr), the P_IO_2 is only 100 torr, resulting in an acute hypoxic hypoxia. Direct measurements of blood gases on over 1,000 nonacclimatized

individuals at this altitude found the partial pressure of O_2 in alveolar air to be only 61 torr (Boothby et al., 1954). The hypoxic drive will trigger a complement of physiological compensatory mechanisms (to maintain O_2 transport and supply), the extent of which will depend on elevation, exercise intensity, and the length of a stay at the altitude. During the first several days, the pulmonary ventilation at a given O_2 uptake (work level) will increase progressively until a new quasi-steady-state level is achieved (Bender et al., 1987; Burki, 1984). The D_LCO will not change substantially at elevations below 2,200 m but was reported to increase above that altitude, and the spirometric lung function will be reduced as well (Ge et al., 1997). The maximal aerobic capacity and total work performance will decrease, and the RER will increase (Horvath et al., 1988). Redistribution of blood from skin to organs and within organs from blood into extravascular compartments, as well as an increase in cardiac output, will promote CO loading (Luomanmäki and Coburn, 1969). Because of a decrease in plasma volume (hemoconcentration), the Hb concentration will be higher than at sea level (Messmer, 1982). The blood electrolytes and acid-base equilibrium will be readjusted, facilitating transport of O_2. Thus, for the same CO concentration as at sea level, these compensatory changes will favor CO uptake and COHb formation (Burki, 1984). By the same token, the adaptive changes will affect not only CO uptake but CO elimination as well. Carboxyhemoglobin levels at altitude has been shown to be increased in both laboratory animals and humans (McGrath, 1992; McGrath et al., 1993). Breathing CO (9 ppm) at rest at altitude has produced higher COHb levels than those at sea level (McGrath et al., 1993). Surprisingly, exercise in a CO atmosphere (50 to 150 ppm) at altitude appeared either to suppress COHb formation or to shift the CO storage, or both. The measured COHb levels were lower than those found under similar conditions of exercise and exposure at sea level (Horvath et al., 1988).

The short-term acclimatization (within a week or two) will stabilize the compensatory changes. During a prolonged stay at high altitude (over a few months), most of the early adaptive changes gradually will revert to the sea level values, and long-term adaptive changes, such as an increase in tissue capillarity and myoglobin content in the skeletal muscle, begin to take place. Smokers appear to tolerate short-term hypoxic hypoxia caused by high altitude (7,620 m [25,000 ft]) much better than nonsmokers, who experience more severe subjective symptoms and a greater decline in task performance (Yoneda and Watanabe, 1997). Perhaps smokers, because of chronic hypoxemia (because of chronically elevated COHb), develop partial tolerance to

hypoxic hypoxia. Although the mechanisms of COHb formation in hypoxic hypoxia and CO hypoxia are different, the resultant decrease in O_2 saturation and activation of compensatory mechanisms (e.g., an increased cerebral blood flow) appear to be at least additive (McGrath, 1988). Psychophysiological studies, in particular, seem to support the possibility of physiological equivalency of hypoxic effects, whether induced by altitude at equlibrium or ambient CO concentration. However, it must be remembered that, although some of the mechanisms of action of hypoxic hypoxia and CO hypoxia are the same, CO elicits other toxic effects not necessarily related to O_2 transport mechanisms (Ludbrook et al., 1992; Zhu and Weiss, 1994). Recently, Kleinman et al. (1998) demonstrated that the effects of CO and simulated altitude were not synergistic but additive.

5.4.3 Physical Characteristics

Physical characteristics (e.g., sex, age, race, pregnancy) are not known to directly modify the basic mechanisms of CO uptake and COHb formation and elimination. However, the baseline values of many cardiopulmonary variables that may influence COHb kinetics are known to change with physical characteristics.

The CO uptake and elimination rates either at rest or exercise decrease with age. During the growing years (2 to 16 years of age), the COHb elimination half-time increases rapidly with age in both sexes and is relatively shorter for boys than for girls. Beyond teenage years, the half-time for CO elimination continues to grow longer but at a lower rate. In contrast to the adolescent period, the COHb half-life during the adult years was found to be persistently shorter (≈6%) in females than that in males (Joumard et al., 1981). Furthermore, it has been well established that, with age, the D_LCO, one of the key determinants, decreases (Guénard and Marthan, 1996). The rate of D_LCO decline is lower in middle-aged women than it is in men, however, at older ages, the rates evened and are about the same for both sexes (Neas and Schwartz, 1996). The decrease in D_LCO, combined with an increase in $\dot{V}_A/\dot{Q}$ mismatch, which increases with age, means that it will take longer to both load and eliminate CO from blood.

In pregnancy, increased requirement for iron may lead to iron deficiency and anemia (for further details see Section 5.4.3). Pregnant women who smoked showed a more pronounced shift of the O_2 dissociation curve to the left (≈5% COHb) than one would expect from the same

COHb concentration in nonpregnant women. Thus, increased O_2 affinity, combined with decreased O_2-carrying capacity of blood of CO-exposed women, may promote fetal hypoxia (Grote et al., 1994). Animal studies found that protein deficiency in pregnant mice had no modulating effect on maternal COHb but resulted in a greater concentration of placental COHb (Singh et al., 1993; Singh and Moore-Cheatum, 1993; Singh et al., 1992).

Young women were found to be more resistant to altitude hypoxia than were men, but the physiological factors for this difference remain unexplored (Horvath et al., 1988). Carboxyhemoglobin levels, although elevated at altitude, were found to be about the same for both males and females (McGrath et al., 1993).

Whether the dynamics of COHb formation and elimination or the absolute COHb levels for the same exposure conditions are different in any way between races have not been studied. Blacks have lower diffusion capacity than whites (Neas and Schwartz, 1996), which transiently will slow CO loading and unloading. It also is well documented that the black population has a higher incidence of sickle cell anemia, which may be a risk factor for CO hypoxia (see Section 5.4.3 below).

5.4.4 Health Status

An individual with any pathophysiologic condition that reduces the blood O_2 content will be at a greater risk from CO exposure because additional reduction in the O_2-carrying capacity of blood resulting from COHb formation will increase hypoxemia. Depending on the severity of initial hypoxia, exposure to CO may lower the O_2 content to the point where O_2 delivery to the tissues becomes insufficient.

One group of disorders that encompasses a range of etiologically varied diseases characterized by a decreased O_2-carrying capacity of blood are the anemias. In most general terms, anemia is any condition that will lead to a reduction in the concentration of RBCs in blood. Anemia is a result of either impaired formation of RBCs or increased loss or destruction of RBCs. The former category includes disorders of altered O_2 affinity, methemoglobinemias, and diseases with functionally abnormal and unstable hemoglobins. By far, the most prevalent disorder in this group is a single-point mutation of Hb (Hb S), causing sickle cell diseases, the most typical of which is a sickle cell anemia. The O_2-carrying capacity of individuals afflicted with sickle cell anemia is reduced not only because of a smaller amount of Hb, but also the

O_2 dissociation curve is shifted to the right, reducing the O_2 affinity as well. Initial compensation involves primarily the cardiovascular system. The cardiac output will increase as both heart rate and stroke volume increase.

The opposite condition of anemia is polycythemia, an increased number of RBCs in blood. Although in polycythemia the total amount of hemoglobin generally is elevated, under certain conditions the arterial O_2 saturation may be decreased, leading to a higher risk of additional hypoxia when exposed to CO.

One of the characteristic symptoms of chronic obstructive pulmonary disease (COPD) is increased V_D and $\dot{V}_A/\dot{Q}$ inequality (Marthan et al., 1985). Subsequently, impaired gas mixing because of poorly ventilated lung zones will result in decreased arterial O_2 saturation and hypoxemia. These pathophysiologic conditions will slow both CO uptake and elimination. Any COHb formation will further lower the O_2 content of blood and increase hypoxemia. Because COPD patients very often operate at the limit of their O_2 transport capability, exposure to CO may compromise severely tissue oxygenation.

Because O_2 extraction by the myocardium is high, a greater O_2 demand by the myocardium of healthy individuals is met by an increased coronary blood flow. Patients with coronary artery disease (CAD) have a limited ability to increase coronary blood flow in response to increased O_2 demand during physical activity. If this compensatory mechanism is further compromised by decreased O_2 saturation from CO inhalation, the physical activity of patients with CAD may be restricted severely consequent to more rapid development of myocardial ischemia.

Individuals with congestive heart failure, right-to-left shunt in congenital heart disease, or cerebrovascular disease also may be at a greater risk from CO exposure because of already compromised O_2 delivery.

5.5 MODELING CARBOXYHEMOGLOBIN FORMATION

5.5.1 The Coburn-Forster-Kane and Other Regression Models

5.5.1.1 Empirical Regression Models

The most direct approach to establishing a prediction equation for COHb is to regress observed COHb values against the concentration and duration of exogenous CO exposure.

Inclusion of other predictors such as initial COHb level and $\dot{V}_A$ 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 more or less exact conditions that were used to collect the data on which they are based.

Peterson and Stewart (1970) developed a regression equation for estimating percent COHb following a 15-min to 8-h exposure of resting nonsmokers to moderate levels of CO (25 to 523 ppm):

$$\text{Log \% COHb} = 0.858 \text{ Log CO} + 0.630 \text{ Log t} - 2.295 - 0.00094\, t', \qquad (5\text{-}2)$$

where CO refers to the concentration of CO in inhaled ambient air in parts per million, t is the exposure duration in minutes, and t′ is the postexposure time in minutes. Data from a subsequent study were used to derive a new empirical formula for much higher concentrations of CO (1,000 to 35,600 ppm) but much shorter exposure times (45 s to 10 min) (Stewart et al., 1973). These equations still are used occasionally in field conditions to quickly estimate COHb concentration.

Several mathematical models have been developed to predict COHb as a function of exposure time (Singh et al., 1991) or altitude (Selvakumar et al., 1992). The physiological variables used by Peterson and Stewart (Peterson and Stewart, 1970) were employed to test the models and compare the results to the CFK predictions (Coburn et al., 1965). The agreement between predicted COHb values by these models and the CFK model was very good; however, the models have not been validated by experimental studies.

To predict changes in COHb as a function of ambient CO concentration in an urban setting, Ott and Mage (1978) developed a linear differential equation where only ambient CO concentration varied with time. All other parameters were empirically derived constants. With this simple model, they were able to show that the presence of CO spikes in data averaged over hourly intervals may lead to underestimating the COHb concentration by as much as 21% of the true value. Consequently, they recommended that monitored CO be averaged over 10 to 15 min periods. Based on a similar approach, other empirical models have been developed but not validated (Chung, 1988; Forbes et al., 1945). Comparison of predicted COHb values by these

models revealed a progressive divergence of the COHb curves as exposure progressed, with differences approaching almost 7% COHb. Such wide variations in predicted COHb best demonstrate the inaccuracy of these types of models when applied outside of a narrowly defined range and question their utility in practical applications (Tikuisis et al., 1992).

5.5.1.2 Linear and Nonlinear Coburn-Forster-Kane Differential Equations

In 1965, Coburn, Forster, and Kane developed a differential equation to describe the major physical and physiological variables that determine the concentration of COHb in blood for the examination of the endogenous production of CO. The equation, referred to as the CFK model, either in its original form or adapted to special conditions is still much in use today for the prediction of COHb consequent to inhalation of CO. Equation 5-3 represents the linear CFK model that assumes O_2Hb is constant:

$$V_b \frac{d[COHb]_t}{dt} = \dot{V}_{CO} - \frac{[COHb]_0 P_{\bar{c}}O_2}{[O_2Hb]M}\left(\frac{1}{\frac{1}{D_L}+\frac{1}{\dot{V}_A}}\right)+\left(\frac{P_ICO}{\frac{1}{D_L}+\frac{1}{\dot{V}_A}}\right), \qquad (5\text{-}3)$$

where V_b is blood volume in milliliters; $[COHb]_t$ is the COHb concentration at time t in milliliters CO per milliliter blood, standard temperature and pressure, dry (STPD); $\dot{V}_{CO}$ is the endogenous CO production rate in milliliters per minute, STPD; $[COHb]_0$ is the COHb concentration at time zero in milliliters CO per milliliter blood, STPD; $[O_2Hb]$ is the oxyhemoglobin concentration in milliliters O_2 per milliliter blood, STPD; $P_{\bar{c}}O_2$ is the average partial pressure of O_2 in lung capillaries in millimeters of mercury; and P_ICO is the CO partial pressure in inhaled air in millimeters of mercury. The model also assumes an instant equilibration of gases in the lung, COHb concentration between venous and arterial blood, and COHb concentrations between blood and extravascular tissues. Because 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 $[O_2Hb]$, where Hb refers to the number of grams of Hb per milliliter of blood (Tikuisis et al., 1987a). The CFK differential equation (Equation 5-3) then becomes nonlinear:

$$\frac{d[COHb]_t}{dt} = \frac{\dot{V}_{CO}}{V_b} + \frac{1}{V_b\beta}\left(P_ICO - \frac{[COHb]_0 P_{\bar{c}}O_2}{[O_2Hb]M}\right), \quad (5\text{-}4)$$

where β is $(1/D_L) + (P_B - 47)/\dot{V}_A$, and P_B is the barometric pressure in millimeters of mercury. The nonlinear CFK model is more accurate physiologically but has no explicit solution. Therefore, interactive or numerical integration methods must be used to solve the equation (Muller and Barton, 1987; Johnson et al., 1992). One of the requirements of the method is that the volumes of all gases be adjusted to the same conditions (e.g., STPD) (Muller and Barton, 1987; Tikuisis et al., 1987a,b).

In general, the linear CFK equation is a better approximation to the nonlinear equation during the uptake of CO than during the elimination of CO. As long as the linear CFK equation is used to predict COHb levels at or below 6% COHb, the solution to the nonlinear CFK model will deviate no more than ±0.5% COHb (Smith, 1990). Over the years, it has been empirically determined that minute ventilation and the lung diffusion capacity for CO have the greatest influence on the CO uptake and elimination. The relative importance of other physiologic variables will vary with exposure conditions and health status. A comprehensive evaluation of fractional sensitivities of physiologic variables for both the linear and nonlinear CFK equation shows that each variable will exert its maximal influence at different times of exposure (McCartney, 1990). The analysis found that only the fractional concentration of CO in inhaled air, in parts per million (F_ICO) and V_{CO} will not affect the rate at which equilibrium is reached. Figure 5-3 illustrates the temporal changes in fractional sensitivities of the principal determinants of CO uptake for the linear form of the CFK equation. The fractional sensitivity of unity means that, for example, a 5% error in the selected variable induces a 5% error in predicted COHb equilibrium value by the nonlinear model.

5.5.1.3 Confirmation Studies of Coburn-Forster-Kane Models

Since the publication of the original paper (Coburn et al., 1965), several investigators have tested the fit of both the linear and nonlinear CFK model to experimental data using different CO exposure profiles, a variety of experimental conditions and different approaches to evaluating the parameters of the model. In all of these studies, almost all of the physiologic coefficients either

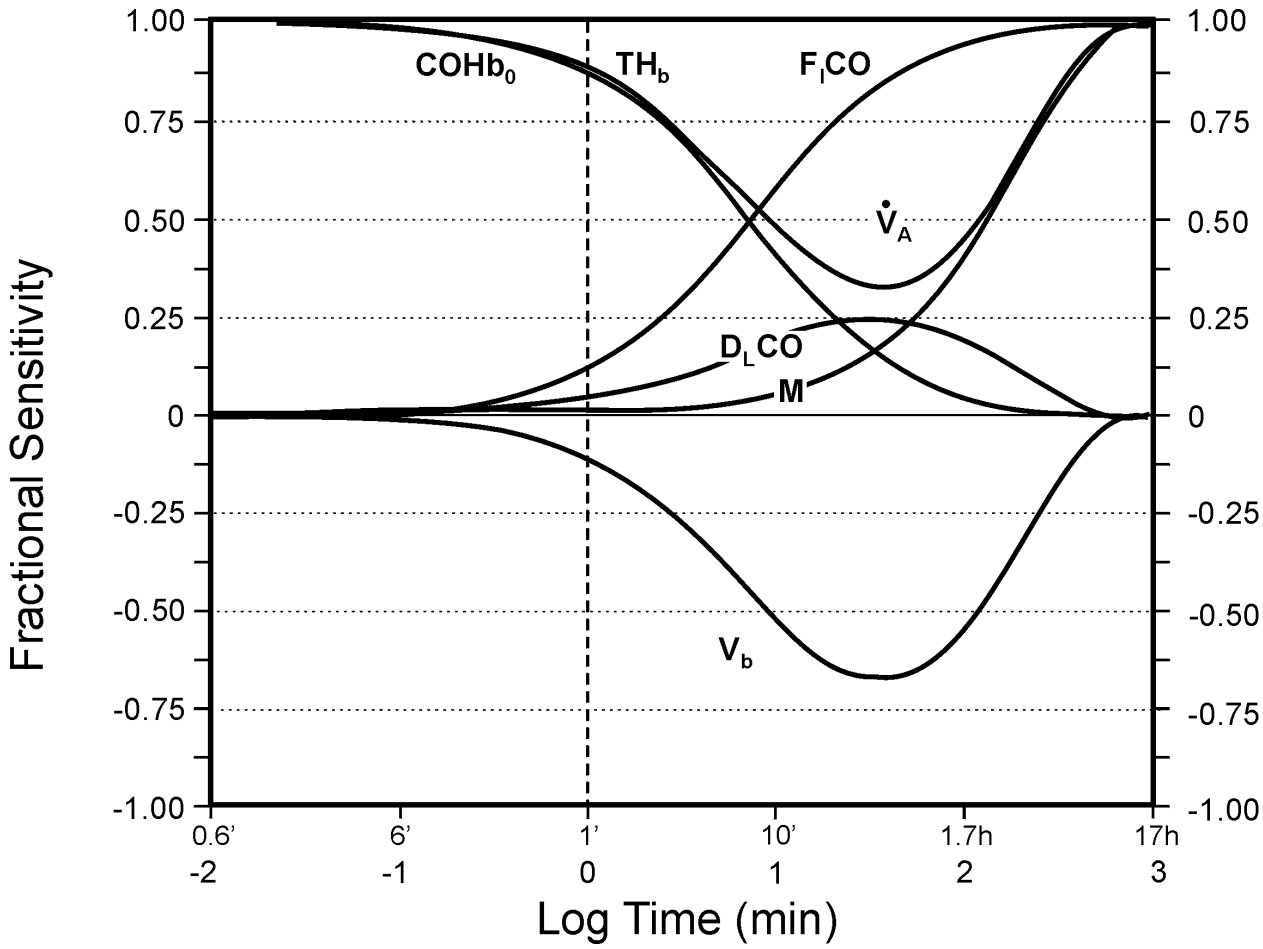

Figure 5-3. Plot of fractional sensitivities of selected variables versus time of exposure (see text for details).

Source: Modified from McCartney (1990).

were assumed or estimated based on each individual's physical characteristics; the COHb values were both measured directly and calculated for each individual.

Stewart et al. (1970) and Peterson and Stewart (1972) tested the CFK linear differential equation on 18 resting subjects exposed to 25 different CO exposure profiles for periods of 0.5 to 24 h and to CO concentrations ranging from 1 to 1,000 ppm. In a later study, they tested the nonlinear CFK equation on 22 subjects at various levels of exercise while being exposed to up to 200 ppm CO for up to 5.5 h (Peterson and Stewart, 1975). From the obtained values, they

concluded that either at rest or exercise the agreement between the predicted and measured COHb values was good (correlation coefficient [r] > 0.74).

The first study to test both the linear and nonlinear CFK models for CO uptake and elimination in pedestrians and car passengers exposed to ambient CO levels in a city was conducted by Joumard et al. (1981). The two cohorts exposed for 2 h to street and traffic concentrations of CO, respectively, comprised 73 nonsmokers (18 to 60 years of age). Blood COHb samples were taken only at the beginning and the end of each journey, where the COHb value reached 2.7%, on average. Both equations performed well in estimating accurately COHb levels, although the value for males was underestimated slightly.

The predictive strength of the CFK model under variable CO concentrations was tested by Hauck and Neuberger (1984). A series of experiments was performed on four subjects exposed to a total of 10 different CO exposure profiles at several exercise levels, so that each exposure was a unique combination of CO concentration and exercise pattern. The ventilation and COHb values (measured and calculated) were obtained at 1-min intervals. The agreement between measured and predicted COHb under these varied conditions was very good; the mean difference was only 7.4% of the nominal (maximal predicted) value.

A series of studies has tested the accuracy of the CFK equation under transient exposure conditions that would violate several assumptions of the CFK model, specifically the assumption of a single, well-mixed vascular compartment. These studies were designed to simulate everyday conditions (e.g., environmental, occupational, military) that may involve frequent but brief (75 s to 5 min) exposures to high (667 to 7,500 ppm) CO concentrations at rest and exercise. Moreover, the experiments were designed to test the accuracy of the CFK equation under transient exposure conditions during the CO uptake and early elimination phase from arterial and venous blood. Attempts were made to measure directly some of the key physiologic parameters of the CFK equation for each subject (Tikuisis et al., 1987a,b; Benignus et al., 1994). The studies have shown that during and immediately following exposure, the arterial COHb was considerably higher (1.5 to 6.1%), and the venous COHb was considerably lower (0.8 to 6%) than the predicted COHb. The observed individual COHb differences between arterial and venous blood ranged from 2.3 to 12.1% COHb among individuals (Benignus et al., 1994). The overprediction of venous COHb increased during exercise (≈10% of the true value). Provided that the total CO dose (concentration × time) is the same and within the time constant for the

CO uptake and elimination, the COHb value was found to be the same, regardless of the pattern of exposure. Because the CFK model appeared to be most sensitive to $\dot{V}_A$, inconsistencies in the estimates or conversion of gas volumes (ATPS and BTPS to STPD) will affect the predicted values. The interindividual and intraindividual disparities between measured and predicted COHb values were attributed primarily to delays in mixing of arterial and venous blood and differences in cardiac output; but, other factors such as lung wash-in also contribute to this phenomenon. Modification of the CFK equation by adjusting for regional differences in blood flow produced a model that predicted with much greater accuracy both the arterial (<0.7% COHb difference) and venous (<1% COHb difference) COHb during transient uptake and elimination of CO from blood (Smith et al., 1994).

Although the CO concentrations used in these studies are several orders of magnitude higher than the usual CO concentrations found in ambient air, under certain conditions (see Section 5.4.1) people can be exposed briefly (<10 min) to such (or even higher) levels of CO in their immediate environment. Because the physiologic mechanisms (but not the kinetics) of COHb formation are independent of CO concentration, high COHb transients, particularly in at-risk individuals, could be of clinical importance. Even briefly, higher arterial COHb may lead to functional impairment of the hypoxia-sensitive brain and heart (see Sections 5.2.2.3 and 5.2.2.4). In these situations, the predicted arterial COHb level will be seriously underestimated.

5.5.1.4 Application of Coburn-Forster-Kane Models

To obviate measurements of CFK equation parameters, many of which are complex techniques, attempts were made to simplify the CFK equation, because it may be difficult or even impossible to measure directly some of these parameters, particularly during physical activity. In one study, by relating physiological parameters to the O_2 uptake by the body, which was in turn related to an activity level, a simplified linear form of the CFK model was developed (Bernard and Duker, 1981). The model was used subsequently to draw simple nomograms of predictive relationship between pairs of variables, but the accuracy of the nomograms was not experimentally tested.

The need for more accurate COHb prediction under more complex physiologic or exposure conditions requires either modification or expansion of the CFK model. Benignus (1995) combined a physiological model of respiratory gas exchange, MACPUF (Ingram et al., 1987),

with the CFK model. The new model allows for continuous output and input of 60 cardiopulmonary variables, including F_ICO. The usefulness of the model is particularly in its ability to continuously update COHb concentration in response to dynamically changing physiologic parameters. The model also allows COHb prediction under hypothetical conditions that otherwise would be very difficult to duplicate in the laboratory.

A fundamental modification of the CFK model was made by Hill et al. (1977) to study the effects of CO inspired by the mother on the level of fetal COHb. The Hill equation combines the CFK equation (for maternal COHb), with a term denoting COHb transfer from a placenta into the fetus. Comparative evaluation of predicted and measured fetal COHb concentrations under time-varying and steady-state conditions in both women and animals showed acceptable agreement only under steady-state conditions (Hill et al., 1977; Longo and Hill, 1977).

As mentioned in Section 5.5.1.4, Smith et al. (1994) expanded the CFK model to allow for prediction of arterial and venous COHb during a transient CO uptake and early elimination phase. The model incorporated regional differences in blood flow, particularly in the forearm, because the forearm is used most frequently for blood sampling. This more elaborate model performed extremely well in predicting blood COHb. Although the model was validated on a small number of subjects using the same experimental setting, the validation was not performed under more demanding conditions of physical activity and varying CO concentrations.

To accurately predict COHb in individuals exposed to dihalomethanes, which are a source of endogenous CO (see Section 5.3), the CFK model was extended to account for the CO production caused by oxidation of a parent chemical (Andersen et al., 1991). The model developed and validated on rats employed a variety of exposure scenarios to dichloromethane. It subsequently was tested on six volunteers exposed to dichloromethane, where, after adjustment of a few parameters, the COHb level was predicted remarkably well. After further validation, this model has potential use in predicting accurately COHb caused by exogenous and endogenous CO originating from different sources.

Reexpression of the solution of the CFK model from units of percent COHb to parts per million of CO allows the examination of a variety of CO concentration profiles, while keeping a simple preselected target COHb as a constant. Application of the transformed model to urban hourly averaged CO concentrations that just attained alternative 1-h and 8-h CO NAAQS showed that, depending on the air quality pattern used, between 0.01 to 10% of the population may

exceed a target 2.1% COHb level in blood without CO ever exceeding the standard. By including transients, the models predicted COHb more accurately, particularly when built into the 8-h running averages (Venkatram and Louch, 1979; Biller and Richmond, 1982, 1992). Actually, the ambient CO concentrations could be averaged over any time period less than or equal to the half-life of COHb (Saltzman and Fox, 1986).

5.6 INTRACELLULAR EFFECTS OF CARBON MONOXIDE

5.6.1 Inhibition of Hemoprotein Function

Traditional concepts for CO pathophysiology have been based on the high affinity of CO for deoxyhemoglobin and consequent reduction of O_2 delivery. Carbon monoxide also can inhibit a number of hemoproteins found in cells, such as myoglobin, cytochrome c oxidase, cytochrome P-450, dopamine β hydroxylase, and tryptophan oxygenase (Coburn and Forman, 1987). Inhibition of these enzymes could have adverse effects on cell function.

Carbon monoxide acts as a competitive inhibitor, hence biological effects depend on the partial pressures of both CO and O_2. The cellular hemoprotein with the highest Warburg partition coefficient for CO is myoglobin. Carbon monoxide will inhibit myoglobin-facilitated oxygen diffusion, but physiological compromise is seen only with high concentrations of COMb. Wittenberg and Wittenberg (1993) found that high-energy phosphate production was inhibited in isolated cardiac myocytes, maintained at a physiologically relevant oxygen concentration, when COMb exceeded 40%. The authors estimated that formation of sufficient COMb to impair oxidative phosphorylation in vivo would require a COHb level of 20 to 40%.

Warburg partition coefficients for cytochrome P-450-like proteins vary between 0.1 and approximately 12, and there have been recent discussions suggesting that CO-mediated inhibition of these proteins could cause smooth muscle relaxation in vivo (Coburn and Forman, 1987; Wang et al., 1997a; Wang, 1998). The issue relates to inhibition of cytochrome P-450-dependent synthesis of several potent vasoconstricting agents (Wang, 1998). Vasodilation has been shown via this mechanism with high concentrations of CO (ca. 90,000 ppm) (Coceani et al., 1988). It is unclear, however, whether this could arise under physiological conditions and CO concentrations produced endogenously. The competition between CO and O_2 for cytochrome c oxidase was

well outlined in the previous review (U.S. Environmental Protection Agency, 1991), but some additional information has been published. Based on its Warburg partition coefficient of between 5 and 15, CO binding is favored only in situations where oxygen tension is extremely low (Coburn and Forman, 1987). Carbon monoxide binding to cytochrome c oxidase in vivo will occur when COHb is high (ca. 50%), a level that causes both systemic hypotension as well as impaired oxygen delivery (Brown and Piantadosi, 1992). Mitochondrial dysfunction, possibly linked to cytochrome inhibition, has been shown to inhibit energy production, and it also may be related to enhanced free radical production (Piantadosi et al., 1995; 1997a). There has been no new information published since the last air quality criteria document that pertains to the effects of CO on dopamine β hydroxylase or tryptophan oxygenase.

5.6.2 Free Radical Production

Laboratory animal studies indicate that nitrogen- and oxygen-based free radicals are generated in vivo during CO exposures. Exposure to CO at concentrations of 20 ppm or more for 1 h will cause platelets to become a source of the nitric oxide free radical (•NO) in the systemic circulation of rats (Thom et al., 1994, Thom and Ischiropoulos, 1997). Studies with cultured bovine pulmonary endothelial cells have demonstrated that exposures to CO at concentrations as low as 20 ppm cause cells to release •NO, and the exposure will cause death by a •NO process that is manifested 18 to 24 h after the CO exposure (Thom et al., 1997; Thom and Ischiropoulos, 1997). The mechanism is based on elevations in steady-state •NO concentration and production of peroxynitrite (Thom et al., 1994; Thom et al., 1997). Peroxynitrite is a relatively long-lived, strong oxidant that is produced by the near diffusion-limited reaction between •NO and superoxide radical (Huie and Padjama, 1993).

The mechanism by which CO concentrations of 20 ppm or more cause an elevation of steady-state •NO concentrations appears to be based on altered intracellular "routing" of •NO in endothelial cells and platelets. It is well established that the association and dissociation rate constants of •NO with hemoproteins exceed the rate constants for O_2 or CO (Gibson et al., 1986). However, Moore and Gibson (1976) found that when CO was incubated with nitrosyl (•NO)-myoglobin or •NO-hemoglobin, CO slowly displaced the •NO. Carbon monoxide replacement occurred even when there was excess •NO-heme protein, and replacement rates were enhanced by increasing the CO concentration or by carrying out the reaction in the presence of agents such as

thiols, which will react with the liberated •NO. These conditions, including the presence of thiols, exist in cells exposed to environmentally relevant concentrations of CO. Exposures to up to 1,000 ppm CO do not alter the rate of production of •NO by platelets and endothelial cells, yet liberation of •NO was enhanced by CO (Thom and Ischiropoulos, 1997; Thom et al., 1994; Thom et al., 1997).

Carbon monoxide will increase the concentration of •NO available to react with in vivo targets in both lung and brain, based on electron paramagnetic resonance studies of experimental animals (Ischiropoulos et al., 1996; Thom et al., 1999a). The concentrations of nitric oxide synthase isoforms in lung were not altered because of CO, and the mechanism for elevation in •NO was thought to be the same as that found in isolated cells (Thom et al., 1994; 1997). Exposure to 50 to 100 ppm CO also will increase hydrogen peroxide (H_2O_2) production in lungs of rats (Thom et al., 1999a). The phenomenon depended on •NO production, as it was inhibited in rats pretreated with N^{ω}nitro-L-arginine methyl ester (L-NAME), a nitric oxide synthase inhibitor. Production of •NO-derived oxidants also is increased in CO-exposed rats, based on measurements of nitrotyrosine, a major product of the reaction of peroxynitrite with proteins (Ischiropoulos et al., 1996; Thom et al., 1998, 1999a,b).

The mechanism for enhanced H_2O_2 production in lungs of CO-exposed rats is not clear. It is possible that •NO or peroxynitrite may perturb mitochondrial function. Peroxynitrite inhibits electron transport at complexes I through III, and •NO targets cytochrome oxidase (Cassina and Radi, 1996; Lizasoain et al., 1996; Poderoso et al., 1996). It is important to note, however, that alterations in mitochondrial function and an increase of cellular H_2O_2 were not found in studies where cultured endothelial cells were exposed to similar CO concentrations (Thom et al., 1997). An alternative possible mechanism to mitochondrial dysfunction is that exposure to CO may inhibit antioxidant defenses. Mechanisms linked to elevations in •NO could be responsible for inhibiting one or more enzymes. Nitric oxide-derived oxidants can inhibit manganese superoxide dismutase and glyceraldehyde-3-phosphate dehydrogenase and deplete cellular stores of reduced glutathione (Ischiropoulos et al., 1992; Luperchio et al., 1996).

Exposure to high CO concentrations (2,500 to 10,000 ppm) cause mitochondria in brain cells to generate hydroxyl-like radicals (Piantadosi et al., 1995; 1997a). An additional source of partially reduced O_2 species found in animals exposed to CO is xanthine oxidase. Conversion of xanthine dehydrogenase, the enzyme normally involved with uric acid metabolism, to xanthine

oxidase, the radical-producing form of the enzyme, occurred in the brains of rats exposed to approximately 3,000 ppm CO (Thom, 1992). Lower CO concentrations did not trigger this change. Therefore, xanthine oxidase is unlikely to be a free radical source following exposures to CO at concentrations found in ambient air. Moreover, enzyme conversion was not a primary effect of CO. Rather, it only occurred following sequestration and activation of circulating leukocytes (Thom, 1993).

5.6.3 Stimulation of Guanylate Cyclase

In recent years, CO has been demonstrated to play a physiological role in vasomotor control and neuronal signal transduction (Morita et al., 1995; Ingi et al., 1996). Carbon monoxide is produced endogenously by oxidation of organic molecules, but the predominant source is from the degradation of heme (Rogers et al., 1994). The rate-limiting enzyme for heme metabolism is heme oxygenase (HO), which converts heme to biliverdin, free iron, and CO. Three isoforms of HO have been characterized. The HO-1 is an inducible enzyme found in vascular endothelial cells, smooth muscle cells, bronchoalveolar epithelium, and pulmonary macrophages. The HO-1 is induced by its substrate, heme, as well as $^{\bullet}NO$, H_2O_2, several cytokines, and lipopolysaccharide (Arias-Díaz et al., 1995; Durante et al., 1997; Morita et al., 1995; Motterlini et al., 1996). The HO-2 is a constitutive enzyme found in certain neurons within the central nervous system, testicular cells, and vascular smooth muscle cells (Marks, 1994). Little is known about HO-3, which was recently identified in homogenates from a number of organs (McCoubrey et al., 1997).

A main physiological role for CO is thought to be regulation of soluble guanylate cyclase activity. Both CO and $^{\bullet}NO$ can activate guanylate cyclase, although activation by CO is approximately 30-fold lower (Stone and Marletta, 1994). In neuronal cells possessing both heme oxygenase and nitric oxide synthase, regulation of cyclic guanosine monophosphate (cGMP) synthesis is mediated in a reciprocal fashion by producing either CO or $^{\bullet}NO$ (Ingi et al., 1996; Maines et al., 1993). A compensatory interrelationship between nitric oxide synthase and heme oxygenase also has been found in endothelial cells and activated macrophages, although its functional significance is unknown (Kurata et al., 1996; Seki et al., 1997). In macrophages, cGMP synthesis promotes chemotaxis, and cGMP-mediated synthesis and secretion of tumor necrosis factor α has been linked to both CO and $^{\bullet}NO$ (Arias-Díaz et al., 1995; Belenky et al.,

1993). Carbon monoxide causes smooth muscle relaxation by stimulating soluble guanylate cyclase (Utz and Ullrich, 1991; Wang et al., 1997b). Smooth muscle relaxation also may occur because of activation of calcium dependent potassium channels, although this effect may be linked to guanylate cyclase activity (Trischmann et al., 1991; Wang et al., 1997a). Carbon monoxide-mediated smooth muscle relaxation is involved with control of microvascular hepatic portal blood flow (Goda et al., 1998; Pannen and Bauer, 1998) and suppressing contractions in the gravid uterus (Acevedo and Ahmed, 1998). It also may play a role in gastrointestinal motility (Farrugia et al., 1998).

5.7 MECHANISMS OF CARBON MONOXIDE TOXICITY

5.7.1 Alterations in Blood Flow

Carbon monoxide from environmental pollution may exert similar effects in vivo to those of endogenously produced CO, because the tissue concentrations resulting from inhalation of CO are comparable or greater than concentrations produced by cells possessing heme oxygenase. Environmental exposures to CO result in interstitial CO concentrations in the nanomolar range. Coburn demonstrated this relation to be true for COHb levels up to 50%. For example, at a COHb of 3.8%, the extravascular fluid CO concentration is approximately 11 nmol (Coburn, 1970b; Göthert et al., 1970). Liver parenchyma has been estimated to generate approximately 0.45 nmol CO/gram liver/min (Goda et al., 1998). Carbon monoxide synthesis by smooth muscle cells is approximately 8 pmol/mg protein/min for human aorta and 23 to 37 pmol/mg protein/min for rat aorta (Cook et al., 1995; Grundemar et al., 1995). Carbon monoxide production by unstimulated pulmonary macrophages is 3.6 pmol/mg protein/min, and, after stimulation with lipopolysaccharide, it increases to about 5.1 pmol/mg protein/min (Arias-Díaz et al., 1995). The rate of synthesis of CO varies widely for nerve cells. Cerebellar granule cells generate approximately 3 fmol/mg protein/min, olfactory nerve cells produce 4.7 pmol/mg protein/min, and rat cerebellar homogenates can generate as much as 56.6 pmol/mg protein/min (Ingi and Ronnett, 1995; Ingi et al., 1996; Maines, 1988; Nathanson et al., 1995).

Vasodilation is a well-established effect caused by exposure to environmental CO. At high CO concentrations, the mechanism is related to impairment of O_2 delivery (Kanten et al., 1983;

MacMillan, 1975). At low CO concentrations, the increases in cerebral blood flow exceed those predicted to be required to maintain adequate O_2 supply (Koehler et al., 1982). In a setting where cellular oxidative metabolism was not impaired by CO, elevations in cerebral blood flow appeared to be mediated by •NO (Meilin et al., 1996). Whether the mechanism was the same as that outlined in the section above, which causes oxidative stress, remains to be determined.

It is unclear whether disturbances in vascular tone by environmental CO is a generalized, systemic response, and the impact of variables such as the duration of exposure have not been adequately investigated. Although cerebral vasodilation mediated by •NO was reported with exposures to 1,000 ppm CO, 1,000 ppm CO did not alter pulmonary vasoconstriction in an isolated-perfused rat lung model (Cantrell and Tucker, 1996). Exposure to 150,000 ppm CO caused no changes in pulmonary artery pressure in isolated blood-perfused lungs, although CO did inhibit hypoxic pulmonary vasoconstriction (Tamayo et al., 1997). Humans exposed to CO for sufficient time to achieve COHb levels of approximately 8% were not found to have alterations in forearm blood flow, blood pressure, or heart rate (Hausberg and Somers, 1997).

Animals exposed to high CO concentrations (e.g., 3,000 to 10,000 ppm) have diminished organ blood flow, which contributes to CO-mediated tissue injury (Brown and Piantadosi, 1992; Ginsberg and Meyers, 1974; Okeda et al., 1981; Song et al., 1983; Thom, 1990). The mechanism is based on CO-mediated hypoxic stress and cardiac dysfunction; therefore, these effects do not arise at CO concentrations relevant to ambient air quality.

5.7.2 Mitochondrial Dysfunction and Altered Production of High-Energy Intermediates

When exposed to 10,000 ppm CO, rats exhibit impaired high-energy phosphate synthesis and production of hydroxyl free radicals because of mitochondrial dysfunction (Brown and Piantadosi, 1992; Piantadosi et al., 1995). Exposure to 2,500 ppm CO also will cause hydroxyl radicals to be produced, apparently by mitochondria, because of a process that could not be related to hypoxic stress (Piantadosi et al., 1997a). Evidence for mitochondrial dysfunction has not been observed in vivo at lower CO concentrations. However, under conditions of high metabolic demand, exposure to even 1,000 ppm CO in the absence of an overt hypoxic stress will result in impaired energy production in brain (Meilin et al., 1996).

Carbon monoxide binding to mitochondrial cytochromes of respiring cells in vitro has been documented only when either the CO concentration was extraordinarily high, or O_2 tension was extremely low, such that the CO/O_2 ratio exceeded 12:1 (Coburn and Forman, 1987). Following CO exposure and removal to fresh air, CO diffuses out from cells, and mitochondrial function is restored. This process is enhanced by inspiration of hyperbaric oxygen (Brown and Piantadosi, 1992). Studies in mice indicate that high CO concentrations inhibit synthesis of high-energy phosphates during exposure to 5,000 ppm CO for 15 min and these changes do not persist following removal to fresh air (Matsuoka et al., 1993). In summary, mitochondrial dysfunction and impaired high-energy phosphate synthesis have been shown by several independent laboratories to occur during exposures to high CO concentrations. Current information suggests that this alteration does not occur at CO concentrations relevant to ambient air quality, and that changes in energy production are not persistent for long periods of time following CO exposure.

5.7.3 Vascular Insults Associated with Exposure to Carbon Monoxide

There are two primary variables that impact on CO toxicity. One is the concentration of CO, the other is the duration of exposure. Traditionally, these two variables have been viewed as merely alternative ways of elevating COHb concentration in the body. The concentration of CO breathed dictates the duration of exposure required to achieve a particular blood level of COHb or tissue level of CO. This view is predicated on the notion that CO pathophysiology is determined by its binding to one or another hemoprotein and to inhibition of oxygen delivery or oxidative metabolism.

There is a substantial body of literature to suggest that, at least with regard to vascular effects, the duration of exposure has a greater impact on the magnitude of CO pathophysiology than what is predicted based on the concentration of CO that is inspired. For example, the lungs are the first site for potential action of environmental CO. Results from investigations have been conflicting regarding the risk for pulmonary injury from CO. Because of the lack of consensus and also the absence of a recognized biochemical mechanism, low concentrations of CO have been viewed as posing little risk to lung physiology (U.S. Environmental Protection Agency, 1992). When animals have been exposed to high CO concentrations sufficient to raise COHb levels to 56 to 90%, exposures have lasted for only minutes because of the hypoxic stress. In these studies, evidence of increased capillary permeability was inconsistent (Fein et al., 1980;

Niden and Schulz, 1965; Penney et al., 1988), and no other alterations in lung physiology were detected (Fisher et al., 1969; Robinson et al., 1985; Shimazu et al., 1990; Sugi et al., 1990). In contrast, when human beings or experimental animals have been exposed to relatively low CO concentrations for many hours at a time, capillary leakage of macromolecules from the lungs and systemic vasculature have been documented, but the presence of an hypoxic stress was questioned (Kjeldsen et al., 1972; Maurer, 1941; Parving et al., 1972; Siggaard-Andersen et al., 1968).

In light of the physiological role for CO in vasomotor control, protracted exposures may be prone to disturb vascular homeostasis, giving rise to pathophysiological responses. Intermittent exposures to CO for 1 day increased glomerular filtration rate by 50% (Pauli et al., 1968). Monkeys exposed to 250 ppm CO for 2 weeks exhibited coronary artery damage consisting of subendothelial edema, fatty streaking, and lipid-loaded cells (Thomsen, 1974). This study and others (Armitage et al., 1976; Davies et al., 1976; Turner et al., 1979; Webster et al., 1968) have suggested a link between atherosclerosis and chronic CO exposure. However, other studies have failed to find evidence for an association (Hugod et al., 1978; Penn et al., 1992).

Carbon monoxide may cause vascular insults, including leakage of albumin and leukocyte sequestration, because of a process mediated by $^{\bullet}$NO-derived oxidants (Ischiropoulos et al., 1996; Thom, 1993; Thom et al., 1998, 1999a,b). Brain oxidative stress associated with this mechanism has been shown with exposures of 1,000 to 3,000 ppm CO (Ischiropoulos et al., 1996; Thom, 1993). However, it is unclear whether the flux of $^{\bullet}$NO, resulting from exposures to lower CO concentrations contribute to oxidative or nitrosative stress in vivo. Important differences in the patterns of leakage from pulmonary and systemic vascular beds suggest that they may be caused by different mechanisms. For example, systemic vascular leakage was present for several hours after CO exposure, and the leakage resolved within 18 h, whereas pulmonary vascular leakage was not measurable until 18 h after CO exposure, and it resolved by 48 h. Both pulmonary and systemic vascular leakage occurred after hour-long exposures to CO, but not when exposures lasted for only 30 min, and vascular changes were not different whether rats were exposed to just 50 ppm or as much as 1,000 ppm CO. These are recent observations and further investigations are required before their relevance to environmental CO contamination can be assessed adequately. Moreover, it should be emphasized that the vascular leakage observed in lungs and systemic microvasculature following exposures to CO at concentrations as low as 50 ppm may

have no pathophysiological impact if regional lymphatics can sustain a higher flow so that edema does not occur (Thom et al., 1998, 1999a,b).

5.8 OTHER EFFECTS OF CARBON MONOXIDE

Among the most concerning pathophysiological effects of CO is its propensity for causing brain damage. There has been considerable effort focussed on potential mechanisms for this process. With regard to ambient air standards, however, it is important to note that recent studies were done with high CO concentrations. Carbon monoxide poisoning is not a "pure" pathological process, as injuries may be precipitated by a combination of cardiovascular effects linked to hypoperfusion or frank ischemia, COHb-mediated hypoxic stress, and intracellular effects, including free radical production and oxidative stress. For example, CO poisoning causes elevations of glutamate and dopamine in experimental models and human fatalities (Arranz et al., 1997; Ishimaru et al., 1991, 1992; Nabeshima et al., 1990, 1991; Newby et al., 1978; Piantadosi et al., 1997b). These elevations occur because of the CO-associated cardiovascular compromise and, possibly, other direct CO-mediated effects. Based on the effects of agents that block the N-methyl-D-aspartate (NMDA) receptor, elevations of glutamate in experimental CO poisoning have been linked to a delayed type (but not an acute type) of amnesia, to loss of CA1 neurons in the hippocampus of mice, and to loss of glutamate-dependent cells in the inner ear of rats (Ishimaru et al., 1991, 1992; Liu and Fechter, 1995; Nabeshima et al., 1990, 1991). Antioxidants can protect against CO-mediated cytotoxicity of glutamate-dependent nerve cells (Fechter et al., 1997). Mechanisms of glutamate neurotoxicity include excessive calcium influx, free radical-mediated injury that may include calcium-calmodulin-dependent activation of cytosolic NO synthase, and lipid peroxidation. Moderate stimulation by excitatory amino acids may cause mitochondrial dysfunction with impaired synthesis of adenosine triphosphate and production of reactive O_2 species (Beal, 1992). Cell death can be through necrosis or programmed cell death, depending on the intensity of the stimulus (Gwag et al., 1995). There also may be a synergistic injury with other forms of oxidative stress because reactive O_2 species can intensify excitotoxicity (Bridges et al., 1991; Pellegrini-Giampietro et al., 1990). Glutamate also can injure cells in the central nervous system that do not have NMDA

receptors by competing for cysteine uptake, which inhibits synthesis of glutathione (Lipton et al., 1997; Murphy et al., 1989; Oka et al., 1993).

5.9 SUMMARY

The most prominent pathophysiological effect of CO is hypoxemia caused by avid binding of CO to Hb. Formation of COHb reduces O_2-carrying capacity of blood and impairs release of O_2 from O_2Hb to tissues. In addition to tissue hypoxia, ultimate diffusion of CO to cells may affect adversely their function. The brain and heart tissues are particularly sensitive to CO-induced hypoxia and cytotoxicity. The rate of COHb formation and elimination depends on many physical and physiological factors. The same factors that govern CO uptake determine CO elimination as well. The flow of CO between blood and either alveolar air or the tissues, and vice versa, is governed by the CO concentration gradient between these compartments. Because of a small blood-to-air CO gradient, and tight binding of CO to Hb, the elimination half-time is quite long, varying from 2.0 to 6.5 h. Apart from the CO concentration in ambient air, the principal determinants of CO uptake are minute ventilation and lung diffusion capacity. Thus, any physiological conditions that affect these variables (e.g., exercise, age) also will affect the kinetics of COHb. Both the physical and physiological variables have been integrated into many empirical and mathematical models of COHb formation and elimination under static and dynamic conditions of ambient CO concentration and physiologic function. The nonlinear CFK equation is the most widely used predictive model of COHb formation, and it still is considered the best all-around model for COHb prediction. Altitude may have a significant influence on COHb kinetics. The effects of hypoxic hypoxia (altitude) and CO-induced hypoxia appear to be additive. Adaptation to altitude will moderate COHb formation. In addition to exogenous sources of CO, the gas also is produced endogenously through catabolism of Hb, metabolic processes of drugs, and degradation of inhaled solvents and other xenobiotics. This last source may lead to very high (up to 50%) COHb concentrations. Many disorders, particularly anemias of any etiology, will predispose affected individuals to CO hypoxia. Furthermore, patients with a variety of cardiopulmonary (e.g., COPD, CAD) and chronic inflammatory diseases may be at increased risk because of elevated COHb.

Apart from impaired O_2 delivery to the tissues because of COHb formation, recent studies of CO pathophysiology suggest cytotoxic effects independent of O_2. New investigations have expanded the understanding of CO in two areas. First, there is a growing recognition of the role that CO may play in normal neurophysiology and in microvascular vasomotor control. The impact of CO from ambient air on these processes has not been investigated adequately. Hence, there is insufficient information available to influence decisions on ambient air quality standards. The second area of investigation of CO is related to its propensity for causing free-radical-mediated changes in tissues. Mechanisms for these changes have been linked to both mitochondria and to a CO-mediated disturbance of intracellular "buffering" of endogenously generated free radicals (e.g., $^{\bullet}NO$). The role these mechanisms play in pathophysiology currently is being investigated. Where dose-response studies are available, the concentrations of CO that cause adverse effects in animals exceed current NAAQS.

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6. HEALTH EFFECTS OF EXPOSURE TO AMBIENT CARBON MONOXIDE

6.1 INTRODUCTION

Concerns about the potential health effects of exposure to carbon monoxide (CO) have been addressed in extensive controlled-exposure studies and more limited population-exposure studies. Under varied experimental protocols, considerable information has been obtained on the toxicity of CO, its direct effects on blood and tissues, and the manifestations of these effects in the form of changes in organ function. This chapter summarizes the current understanding of health effects that may occur in individuals breathing CO in ambient air. A more detailed discussion of studies reporting CO-associated health effects can be found in the previous document, *Air Quality Criteria for Carbon Monoxide* (U.S. Environmental Protection Agency, 1991) and in a number of excellent reviews (Kleinman, 1992; Bascom et al., 1996; Penney, 1996a).

Although evidence from laboratory animal studies indicates that CO can adversely affect the cardiovascular and nervous systems of both mature animals and developing offspring, the concentrations of CO used during exposure and consequent levels of carboxyhemoglobin (COHb) saturation are much higher than typically would be experienced by ambient exposures of humans. The laboratory animal studies, therefore, must be interpreted with caution. However, they can be useful for exploring the properties and possible mechanisms of an effect much more thoroughly and extensively than is possible in humans. An effort will be made in this chapter to compare the health effect levels for CO found in laboratory animal and human controlled-exposure studies.

A review of the health effects literature on CO since the last assessment was published in 1991 finds many published articles on CO poisoning, possibly reflecting more media attention to this topic. Many of these articles, however, reported effects at CO levels far higher than in ambient air. Severe effects from acute exposure to high levels of CO are not directly germane to the problems associated with exposure to current ambient levels of CO and, thus, are not discussed in detail in this chapter. They are, however, mentioned briefly in the summary of this

chapter and in the following chapter to present a complete understanding of what is known about CO toxicity and to provide public health information about potential effects of accidental exposure to CO, particularly those exposures occurring indoors.

The next section of this chapter (Section 6.2) addresses cardiovascular effects of CO. The section begins (Section 6.2.1) with a discussion of epidemiologic studies because of their potential importance in assessing health effects of low-level, ambient CO exposure. In available epidemiologic studies, associations of short-term ambient CO concentrations with frequency of cardiovascular hospital admissions, especially for congestive heart failure (CHF), have been observed quite consistently. An association of short-term CO levels with mortality also has been observed in several studies. This association does not appear to be as specific as that of CO with CHF admissions.

The remainder of Section 6.2 (Section 6.2.2) summarizes controlled-exposure studies of CO effects on maximal exercise performance and in subjects with reproducible exercise-induced angina. In 1991, these studies formed a major scientific basis for U.S. Environmental Protection Agency (EPA) review of the levels and adequacy of existing national ambient air quality standards (NAAQS) for CO. Although these areas have changed little since 1991, controlled-exposure studies continue to provide the most quantitative evidence on low-level CO effects in humans.

Next in importance to cardiovascular effects, but of questionable impact for the young and healthy population, are the studies on neurobehavioral effects that provided the scientific basis for the first CO NAAQS. Subsequent assessments of the neurobehavioral literature, however, have questioned both the methods and results of the early studies. Articles published since the last assessment in 1991 have been mostly reviews that attempted to understand the equivocal results found at low COHb levels and to provide a physiological basis for behavioral effects. This section (Section 6.3) discusses the difficulty in studying an organ system with exquisite compensatory responses to a reduced oxygen supply (hypoxia).

The rest of the chapter summarizes current knowledge about developmental toxicity (Section 6.4), acute pulmonary effects (Section 6.5), other systemic effects of CO (Section 6.6), physiologic responses to CO exposure (Section 6.7), and combined exposure of CO with other pollutants, drugs, and environmental factors (Section 6.8). Little new information has been published on these areas of CO toxicity, and their summaries remain essentially the same as

published in the previous criteria document (U.S. Environmental Protection Agency, 1991). Significant new studies have been added to the summaries, where applicable, if these studies provide confirmation of the conclusions. No new published studies are known to refute or draw into question the conclusions drawn from the previous literature review of these topics. Finally, a summary section (Section 6.9) provides a concise review of the key human health effects most clearly demonstrated to be associated with ambient exposure to CO.

6.2 CARDIOVASCULAR EFFECTS

Cardiovascular disease (CVD) is the leading cause of death in the United States (American Heart Association, 1997; U.S. Centers for Disease Control and Prevention, 1997). An estimated 58 million people in the United States (≈20% of the population) have one or more types of CVD (American Heart Association, 1997). For the major diseases within this category of total CVD, about 50 million Americans have high blood pressure, 14 million have ischemic (coronary) heart disease, 5 million have heart failure, 4 million have cerebrovascular disease (stroke), and 1.8 million have rheumatic fever or heart disease. In fact, more than one in five males and females have some form of CVD. Because the numbers of affected people are so high, any true relationship between CO exposure and increased cardiovascular mortality or morbidity in the population could have a large impact on both public health and health care costs. In the following discussion, the effects of CO on potentially susceptible population groups are explored through epidemiologic and controlled laboratory studies (for a more detailed discussion of subpopulations at risk, see Chapter 7).

6.2.1 Epidemiologic Studies

6.2.1.1 Introduction

In recent years, many epidemiologic studies have shown associations of ambient air pollution exposure with mortality, morbidity, and physiologic changes. These studies have increased concern that ambient air pollution can promote, and perhaps even produce, adverse health outcomes, even when concentrations of individual pollutants are at or below current U.S. air quality standards. At the same time, the relevant epidemiologic database is growing rapidly,

and its interpretation is changing over time. For example, as recently as the mid-1990s, numerous epidemiologic studies had reported associations of mortality and morbidity with exposure to ambient particulate matter (PM), but relatively few had investigated or reported such associations with gaseous pollutants such as CO. Since then, however, investigators have given more thorough and balanced consideration to PM and gaseous pollutants, and although statistically significant associations of harmful health outcomes with PM continue to be observed, the role of gaseous pollution exposure appears stronger than it did even a few years ago.

Recent epidemiologic studies of CO exemplify this point. To date, several well-conducted studies in the United States and Canada have reported an association of ambient CO exposure with hospital admissions for CHF. Current evidence suggests that this association is quite specific in two important ways. First, consistent and strong associations have been found between CHF admissions and CO, whereas associations with other criteria pollutants are less clear. Second, CO does not appear to be especially strongly associated with admissions for cardiovascular causes other than CHF or with respiratory disorders. Also, the association of CO with CHF has considerable biological plausibility, particularly because it appears to be strongest during cold weather, which may heighten underlying susceptibility to the worsening of CHF. On balance, the observed association of ambient CO exposure with CHF admissions is as biologically and epidemiologically credible as any other association of ambient air pollution with harmful health outcome yet observed in time series studies of ambient air pollution. An association of ambient CO exposure with mortality also has been reported in epidemiologic studies, although not as consistently or specifically as with CHF admissions.

At the same time, there remain important uncertainties in the current epidemiologic database for ambient CO and other air pollutants. For example, the health effects of long-term ambient CO exposures are not known. Also, there is increasing realization that health effects observed in association with any single pollutant may actually be mediated by multiple components of the complex ambient mix. Specific attribution of effects to CO or any other single pollutant thus may yield an oversimplistic picture of biological reality. Also, observed effects of CO and other pollutants appear to be subtle in relation to effects of other risk factors such as smoking, socioeconomic status, and demographic factors. This lends uncertainty to the

potential public health consequences of further reductions of ambient CO or any other single ambient air pollutant at present-day U.S. levels.

Individual epidemiologic studies of ambient CO exposure are discussed below, first for hospital admissions (largely CHF admissions) and then for daily mortality.

6.2.1.2 Carbon Monoxide and Hospital Admissions

Kurt et al. (1978) observed a relationship between ambient CO levels and emergency room visits for cardiovascular complaints in Denver, CO. However, correlations were relatively weak, and environmental factors other than CO were not evaluated. A number of recent studies in the United States (Morris et al., 1995; Schwartz and Morris, 1995; Schwartz, 1997; Morris and Naumova, 1998), Canada (Burnett et al., 1997), and Europe (Pantazopoulou et al., 1995; Poloniecki et al., 1997) have suggested that daily variation in ambient CO levels is related to daily hospital admissions for cardiovascular illness, especially for both CHF and people over 64 years of age.

As discussed above, the observed association of ambient CO exposure with CHF admissions has biological plausibility. However, full understanding of this observation will require resolution of several issues. Congestive heart failure is a major cause of hospital admissions. In 1996, there were an estimated 4,239,000 hospital admissions for heart disease in the United States, and 870,000 (20.5%) of these had a discharge diagnosis of CHF (Graves and Owings, 1998). In addition, CHF is one of the most common indications for hospitalization in adults over 64 years old (May et al., 1991; Croft et al., 1997; Haldeman et al., 1998). At the same time, readmission rates are substantial in elderly CHF patients, ranging from 29 to 47%. Behavioral factors (e.g., smoking, noncompliance with medications and dietary guidelines) and social factors (e.g., isolation) contribute to CHF readmissions, suggesting that a portion of such admissions could be prevented. Some admissions with a diagnosis of CHF actually may result from other causes such as noncardiogenic pulmonary edema and pneumonia. Although these factors would probably not seriously confound observed relationships of short-term ambient CO exposure and CHF admissions, they lend uncertainty as to the actual number of CHF patients potentially at risk. Additional characterization of individual subjects (e.g., smoking habits, personal CO exposure, specific clinical findings) would be highly desirable in future epidemiologic studies of ambient CO exposure. Also, as mentioned in Chapter 3, in most U.S.

metropolitan areas there is considerable spatial variation among simultaneous CO measurements made at different monitoring sites. In most epidemiologic studies to date, exposure metrics have consisted of CO measurements averaged across sites. The effects of such averaging on statistical health effects estimates are not yet well understood.

The average daily maximum CO concentrations measured by stationary monitors in the epidemiologic studies are generally very low (≤5 ppm). Any increase over endogenous COHb levels produced by a 1-h exposure to <10 ppm exogenous CO, for example, would be difficult to measure. Even 8 h of exposure to 10 ppm CO with light to moderate exercise ventilation (20 L/min) would produce only 1.5% COHb, assuming a baseline of 0.5% COHb. In addition, CO levels measured at stationary monitors usually are not highly correlated with personal CO exposures, especially for compromised persons (such as cardiac patients) who spend much of their time indoors.

Morris et al. (1995) performed a time-series analysis of ambient levels of gaseous air pollutants (CO, nitrogen dioxide [NO_2], sulfur dioxide [SO_2], and ozone [O_3]) and Medicare hospital admissions for CHF in seven U.S. cities (Chicago, IL; Detroit, MI; Houston, TX; Los Angeles, CA; Milwaukee, WI; New York City, NY; and Philadelphia, PA) during the 4-year period from 1986 through 1989. The average daily maximum 1-h CO levels (mean ± standard deviation [SD]) ranged from 1.8 (±1.0) ppm in Milwaukee to 5.6 (±1.7) ppm in New York City. The relative risk of admissions associated with a 10 ppm increase in CO ranged from 1.10 in New York City to 1.37 in Los Angeles. All seven cities showed similar patterns of increasing admissions with increasing ambient CO concentrations. The authors estimated that approximately 3,250 hospital admissions for congestive heart failure (5.7% of all such admissions) each year could be attributed to the observed association with CO levels.

Schwartz and Morris (1995) examined air pollution and cardiovascular hospital admissions for people aged 65 years or older in the Detroit metropolitan area during the years 1986 through 1989. Air quality data were available for PM ≤10 µm (PM_{10}) on 82% of possible days and for O_3 on 85% of possible days. Data were available for SO_2 and CO on all days during the study period. The mean PM_{10} was 48.0 $\mu g/m^3$, the mean O_3 was 41.0 ppb, the mean SO_2 was 25.4 ppb, and the mean CO was 2.4 ppm. A Poisson auto-regressive model was used to analyze the data, with independent variables for temperature, dew point, month, and linear and quadratic time trends. For each pollutant, the difference between the 25th and 75th percentiles of the

distribution of ambient concentrations during the study period (the "interquartile range") was calculated. Relative risks for the health outcomes assessed were reported per increment in ambient concentration equal to each pollutant's interquartile range. Daily admissions for ischemic heart disease were associated with interquartile range increases of 32 $\mu g/m^3$ for PM_{10} (relative risk [RR] = 1.018; 95% confidence interval [CI] 1.005 to 1.032), 18 ppb for SO_2 (RR = 1.014; 95% CI 1.003 to 1.026), and 1.28 ppm for CO (RR = 1.010; 95% CI 1.001 to 1.018); however, both SO_2 and CO became insignificant after controlling for PM_{10}, whereas PM_{10} remained significant after controlling for the other pollutants. Daily admissions for heart failure were associated independently with the interquartile range increases for both PM_{10} (RR = 1.024; 95% CI 1.004 to 1.044) and CO (RR = 1.022; 95% CI 1.010 to 1.034). Ozone was not a significant risk factor for cardiovascular admissions, and no pollutant was a significant risk factor for dysrhythmia admissions.

It is possible that CO could be a surrogate for general mobile-source pollution. In some locations, CO is highly correlated with particles during the winter months. Particles (PM_{10}) were found to be associated with CVD in the Schwartz and Morris (1995) study, but were not assessed in the Morris et al. (1995) analysis. Also, particles previously have been shown to be associated with hospital admissions for both heart failure and ischemic heart disease in Ontario (Burnett et al., 1995).

Schwartz (1997) examined relationships of short-term ambient air pollution levels with cardiovascular hospital admissions in people at least 65 years old in Tucson, AZ, from 1988 through 1990. The author assessed effects of CO, SO_2, O_3, NO_2, and PM_{10}, as measured at a single monitoring station, as well as of meteorologic variables. Poisson regression was conducted on temperature, humidity, day of week, and air pollution levels. Long-term temporal patterns were removed by nonparametric smoothing. It appears that exposure-to-admission lags of 0, 1, and 2 days were assessed in different models, and that effects estimates for levels on the same day as admission were reported. During the study, the median maximum hourly CO concentration and the median 24-h average PM_{10} concentration were 3.03 ppm and 39 $\mu g/m^3$, respectively. The correlation between PM_{10} and SO_2 was lower than in eastern U.S. cities. Relative risk estimates of CO and PM_{10} for cardiovascular admissions were of similar magnitude, independent, additive, and statistically significant at a 5% level of significance (p). In a model assessing both pollutants simultaneously, the estimated percentage increases in admissions across

the interquartile ranges of CO and PM_{10} levels were 2.33% and 2.37%, respectively. Relative risk estimates for both pollutants appeared to be quite stable across seasons, and to be unconfounded with the meteorologic parameters assessed. There was no appreciable association of SO_2, O_3, or NO_2 levels with cardiovascular admissions in the elderly.

Burnett et al. (1997) examined temporal relationships between ambient air pollutants and hospitalizations among the elderly (individuals >64 years of age) in 10 Canadian cities during the 11-year period from 1981 through 1991. Out of a study population of 12.6 million, an average of 39 elderly patients were admitted daily to 134 hospitals because of CHF. A time series analysis adjusted for long-term time trends, seasonal and subseasonal temporal variations, and day-of-week effects was used to explore the association between cardiopulmonary illness and the ambient air pollutants CO, NO_2, SO_2, and O_3 and coefficient of haze (COH). After stratifying by month of the year and adjusting for temperature, dew point, and other pollutants, the log of the daily 1-h maximum CO concentration recorded on the day of admission had the strongest and most consistent statistical association with hospitalization for CHF. The relative risk was 1.065 (95% CI = 1.028 to 1.104) for an increase from 1 to 3 ppm CO (the interquartile range of the exposure distribution). Associations of levels of other pollutants with admissions also were observed in single-pollutant models. However, risk estimates for these other pollutants were more sensitive to simultaneous adjustment for multiple pollutants or weather variables than were the estimates for CO. The authors noted that CO could possibly be acting as a marker for pollution from transportation sources in general, and that independent effects of non-CO pollutants could not be ruled out.

Pantazopoulou et al. (1995) studied the daily number of emergency outpatient visits and admissions for cardiac and respiratory causes to all major hospitals in the greater Athens, Greece, area during 1988. Air pollutant concentrations were obtained from the Greek Ministry of the Environment for smoke, CO, and NO_2. Mean levels of CO for all available monitoring stations were 4.5 ± 1.6 (SD) mg/m^3 (4.0 ± 1.4 ppm) in winter and 3.4 ± 1 (SD) mg/m^3 (3.0 ± 0.9 ppm) in summer. Multiple linear regression modeling was used, controlling, separately for winter and summer, for the potential effects of meteorological and chronological variables. A positive association was found between the daily number of emergency admissions for cardiac and respiratory causes and all measured pollutants during the winter, but not during the summer.

Poloniecki et al. (1997) studied emergency admissions to London, England, hospitals for circulatory diseases from 1987 through 1994. Time series relationships were assessed with daily measurements of O_3, NO_2, SO_2, CO, and black smoke on the day prior to admission. Long-term and day-of-week trends, temperature, humidity, an influenza epidemic in 1989, and cyclical covariations with periodicity >20 days in daily measures of pollution and admissions were accounted for in the analysis. No associations were found between O_3 and circulatory diseases; the remaining pollutants were associated with combined acute myocardial infarction (MI) and circulatory diseases. The associations with acute MI were significant only in the cool season; attributable cases (95% CIs) and p values were 2.5% (0.8 to 4.3%), $p = 0.003$ for black smoke; 2.7% (0.8 to 4.6%), $p = 0.002$ for NO_2; 2.1% (0.7 to 3.5%), $p = 0.001$ for CO; and 1.7% (0.7 to 2.6%), $p = 0.0006$ for SO_2. There were also associations between black smoke and angina ($p = 0.02$), NO_2 and arrhythmia ($p = 0.04$), and CO and other circulatory diseases ($p = 0.004$). However, unlike several U.S. studies (Morris et al., 1995; Schwartz and Morris, 1995; Morris and Naumova, 1998), the ambient CO level was not associated with admissions for heart failure or ischemic heart disease.

Morris and Naumova (1998) investigated joint effects of short-term ambient CO exposure and ambient temperature on daily hospital admissions for CHF in people >64 years of age, in Cook County (Chicago), IL, from 1986 through 1989. Ambient air pollution data were taken from EPA's Aerometric Information Retrieval System database. Data were analyzed with general linear models (GLM) and general additive models (GAM). Pollutant metrics assessed in analytical models were daily maximum hourly levels of CO, NO_2, SO_2, and O_3, as well as 24-h average PM_{10}. For each day of the study, gaseous pollutant measurements were averaged across Cook County's eight monitoring stations, six of which were in downtown Chicago. Only one station collected daily PM_{10} samples (on 80% of study days). In addition to these pollutant variables, models included variables for daily maximum hourly temperature, day of week, month of year, and year of study. In single-pollutant GLMs, the level of each measured pollutant except O_3 was associated positively and statistically significantly ($p = 0.05$) with admissions on the same day. In a GLM that included all pollutants, only CO was associated significantly with admissions. In this model, the RR for CHF admission at the 75th percentile of maximum hourly CO concentration was 1.08 (95% CI 1.03 to 1.12), compared with RR = 1 at CO concentration

of zero. Associations of CO and other pollutants with admissions were strongest with a lag time of 0 days and weakened rapidly with successively longer lag times.

Effects of ambient CO on CHF admissions at different temperatures were analyzed in three ways: (1) inclusion of a CO-temperature interaction term in GLM; (2) simultaneous inclusion of a CO term and a temperature term in GAM, generating an additive CO-temperature effects surface; and (3) analysis with stratification on daily maximum ambient temperature (<40, 40 to 75, and >75 °F). Effects of CO on CHF admissions consistently were associated inversely with temperature (stronger effects at lower temperatures). For example, in a multipollutant GLM, RRs for CHF admissions at the 75th percentile of maximum hourly CO concentration were 1.09 (1.01 to 1.18), 1.07 (1.01 to 1.13), and 1.01 (0.92 to 1.11) when maximum temperature was <40, 40 to 75, and >75 °F, respectively.

The authors pointed out that fixed-site CO measurements give inexact estimates of individual subjects' total CO exposures and could well underestimate them during cold weather. Thus, a given ambient CO level could reflect higher total CO exposure in cold weather than in warm weather. Also, a given day-to-day difference in ambient CO level could reflect a greater day-to-day difference in total CO exposure in cold weather than in warm weather. The authors also hypothesized, plausibly, that persons with CHF may be unusually susceptible to CO, and that cardiovascular and other stresses imposed by cold weather may heighten this susceptibility. In any event, this study adds to the epidemiologic database linking ambient CO exposure with aggravation of preexisting CHF. It also lends considerable weight to the hypothesis that CO-mediated aggravation of CHF is most likely to occur during cold weather.

6.2.1.3 Carbon Monoxide and Daily Mortality

Epidemiologic studies of the relationship between CO exposure and daily mortality are not yet conclusive. Early studies in Southern California (Goldsmith and Landaw, 1968; Cohen et al., 1969; Hexter and Goldsmith, 1971) suggested an association between atmospheric levels of CO and increased mortality from CVD, but potential confounders were not controlled thoroughly. In contrast, a study in Baltimore, MD (Kuller et al., 1975), showed no association between ambient CO levels and CVD or sudden death. More recent time series studies in North and South America and in Europe also have yielded mixed results in relating day-to-day variations in CO levels with daily mortality. For example, no relationship was found between CO and daily

mortality in Los Angeles, Chicago, or Philadelphia (Ito et al., 1995; Kinney et al., 1995; Ito and Thurston, 1996; Kelsall et al., 1997) after adjusting for particles (i.e., PM_{10}), time trends, and weather. Verhoeff et al. (1996) found no relationship between 24-h average CO concentrations and daily mortality in Amsterdam, with or without adjustment for PM_{10} and other pollutants. Saldiva et al. (1994, 1995) found no association between CO and daily mortality among children or the elderly in São Paulo, Brazil, after adjusting for nitrogen oxides and PM_{10}, though Pereira et al. (1998) did observe a limited relationship of ambient CO concentration with intrauterine mortality. Interestingly, in the latter study, COHb levels in cord blood were correlated with short-term ambient CO levels, even though intrauterine mortality was associated somewhat more strongly with other pollutants than with CO. At the same time, Pereira et al. (1998) is difficult to interpret because the investigators assessed fetal loss occurring only after 28 weeks of gestation, whereas the large majority of spontaneous abortions occur before that time.

Three other studies (Touloumi et al., 1994; Salinas and Vega, 1995; Wietlisbach et al., 1996) showed small, statistically significant relationships between CO and daily mortality. However, effects of other pollutants (e.g., total suspended particles [TSP], SO_2, NO_2, black smoke) and of meteorologic variables (e.g., temperature, relative humidity) were also significant. Further research will be needed to determine whether low-level CO exposure actually is increasing mortality, particularly in the elderly population, whether CO is a surrogate marker for some other mobile-source or combustion-related pollutant, or whether CO is a surrogate for the overall combustion-related or automotive pollution mix.

Touloumi et al. (1994) investigated air pollution and daily all-cause mortality in Athens from 1984 through 1988. Daily mean pollution indicators for SO_2, black smoke, and CO were averaged over all available monitoring stations. Autoregressive models with log-transformed daily mortality as the dependent variable were used to adjust for temperature, relative humidity, year, season, day of week, and for serial correlations in mortality. Separate models for log(SO_2), log(smoke), and log(CO) yielded statistically significant effects estimates ($p < 0.001$). Air pollution measurements lagged by 1 day were most strongly associated with daily mortality. A multipollutant model showed that SO_2 and smoke were independent predictors of mortality, though to a lesser extent than temperature and relative humidity. Addition of an independent variable for CO concentration did not improve this model's ability to predict daily mortality,

suggesting that CO may be a surrogate marker for other mobile-source or combustion-related pollutants.

In one of the European Air Pollution and Health—A European Approach studies in Athens, Touloumi et al. (1996) observed a distinct positive association of ambient CO levels with daily mortality. Ambient CO concentrations were compiled from three fixed outdoor monitoring stations. Median, mean, and maximum 8-h CO levels were 6.1 mg/m^3 (5.3 ppm), 6.6 mg/m^3 (5.8 ppm), and 24.9 mg/m^3 (21.7 ppm), respectively. The relative risk for daily mortality of a 10 mg/m^3 (9 ppm) increase in the daily ambient air CO concentration was 1.10 (95% CI = 1.05 to 1.15). This finding is of interest, but it has not yet been confirmed in other epidemiologic studies. It may be explained by yet unknown health effects of low levels of CO, by the presence of highly compromised susceptible groups in the population, or, again, by CO acting as a surrogate for other combustion-generated air pollutants.

Salinas and Vega (1995) examined the effect of urban air pollution on daily mortality in Metropolitan Santiago, Chile, from 1988 through 1991. Measurements of maximum 8-h average CO; maximum hourly O_3; daily mean SO_2, PM_{10}, and $PM_{2.5}$; and meteorologic variables were obtained from five monitoring stations. Total and respiratory disease-specific deaths were assessed, calculating the risk of death by municipality and month of the year using age-adjusted standardized mortality ratios and controlling for socioeconomic status. Daily death counts were regressed on pollutant levels, using Poisson regression and controlling for temperature and relative humidity. A clear pattern in the geographic distribution of risk of death was found, both for total mortality and disease-specific mortality (e.g., pneumonia, chronic obstructive pulmonary disease, asthma), regardless of socioeconomic and living conditions. The number of deaths was significantly associated with humidity, CO, and suspended particles and also was associated with temperature when the model included all days with available data during the 4-year period. The associations remained significant for those days with $PM_{2.5}$ levels below 150 $\mu g/m^3$.

Wietlisbach et al. (1996) assessed the association between daily mortality and air pollution in metropolitan Zurich, Basel, and Geneva, Switzerland, from 1984 through 1989. Daily counts were obtained for total mortality, mortality in people 65 years of age or older, and respiratory and cardiovascular disease mortality. Daily measurements of weather variables and TSP, SO_2, NO_2, CO, and O_3 were obtained in each city. Poisson models were used to regress daily death counts on pollutant levels, controlling for time trends, seasonal factors, and weather variables.

A positive, statistically significant association was found between daily mortality and TSP, SO_2, and NO_2. The strongest associations were observed with 3-day moving averages. Somewhat weaker associations were observed in each city between mortality in people 65 years of age or older and measured average daily CO concentrations (mean = 1 to 2 mg/m^3 [1 to 2 ppm], max = 5 to 8 mg/m^3 [4 to 7 ppm]). Associations with O_3 were weak and inconsistent. When all pollutants were modeled simultaneously, the regression coefficients were unstable and not statistically significant.

In two recent studies, Burnett and colleagues investigated associations of CO and other pollutants with daily nonaccidental mortality in Canada. In one study (Burnett et al., 1998a), the investigators assessed the roles of average daily concentrations of ambient CO, other gaseous pollutants, sulfates, TSP, COH, estimated $PM_{2.5}$ and PM_{10}, and meteorology in Toronto from 1980 through 1994. The time series was adjusted for long-term trends and temporal cycles. Effects of several different exposure-to-mortality lags were explored, and the final choice of lags was based on the Akaike Information Criterion. A two-day moving average was selected as the optimum lag for CO, but not for all pollutants. Final models included same-day dew point temperature. In single-pollutant models, ambient levels of all pollutants except O_3 were associated positively and statistically significantly with daily mortality, and this association was strongest for ambient CO. Two-pollutant models also were constructed, each including CO and one of the other pollutants. In these models, the magnitudes of relative risks for CO differed little from that in the single-pollutant model for CO. In contrast, the relative risks for other pollutants generally decreased appreciably. Also, the relative risks for CO remained statistically significant (at $p = 0.05$) in all two-pollutant models. Although the relative risk of CO was highest for deaths from cardiac causes, there was also a clear positive association of CO with deaths from other causes.

Burnett et al. (1998b) also examined associations of ambient levels of gaseous pollutants (CO, NO_2, O_3, and SO_2) with daily nonaccidental mortality in 11 Canadian cities from 1980 through 1991. In single-pollutant models, relative risks of CO for mortality were more consistent across cities than were relative risks of the other pollutants. However, in multipollutant models, CO-associated relative risks decreased substantially, and NO_2 and SO_2 appeared to explain much of the CO effect on mortality. The estimated percentage increase in mortality risk attributable to combined exposure to all four pollutants differed widely from city to

city, ranging from 3.6% in Edmonton and Windsor to 11.0% in Quebec. The authors reasoned that reductions in gaseous pollutant levels might be more effective than reductions in PM levels in lessening mortality rates. It is difficult to interpret this study quantitatively, because direct measurements of PM and PM constituents were not included in the analyses. At the same time, the results underscore the need for measurement and statistical treatment of a broad range of pollutants and for further systematic assessment and comparison of the public health importance of exposure to CO, other ambient gaseous pollutants, and PM.

6.2.2 Controlled Laboratory Studies

The most extensive human experimental studies on the cardiovascular effects of CO have been those conducted in predominantly young, healthy, nonsmoking subjects during exercise. Previous assessments of these effects (U.S. Environmental Protection Agency, 1979, 1984, 1991; Horvath, 1981; Shephard, 1983, 1984) have identified what appears to be a linear relationship between the level of COHb in the blood and decrements in human exercise performance, measured as maximal oxygen uptake. Short-term maximal exercise performance significantly decreases at COHb levels ranging from 5 to 20% (Pirnay et al., 1971; Vogel and Gleser, 1972; Ekblom and Huot, 1972; Weiser et al., 1978; Stewart et al., 1978; Klein et al., 1980; Koike and Wasserman, 1992). One study (Horvath et al., 1975) observed a marginal decrease in maximal exercise performance at a COHb level as low as 4.3% COHb. Short-term maximal exercise duration also has been shown to be significantly reduced at COHb levels ranging from 2.3 to 20% (Ekblom and Huot, 1972; Drinkwater et al., 1974; Raven et al., 1974a,b; Horvath et al., 1975; Weiser et al., 1978; Koike and Wasserman, 1992). The observed decreases in maximal exercise performance and duration, however, are so small that they are only of concern primarily for competing athletes, rather than for healthy people conducting everyday activities at less than maximal exercise levels. In fact, no significant effects on oxygen uptake or on exercise ventilation and heart rate were reported during submaximal exercise at COHb saturations as high as 15 to 20% (see Section 10.3.2 in U.S. Environmental Protection Agency, 1991), especially at work rates below the metabolic acidosis threshold (Koike et al., 1991). Cigarette smoking has a similar effect on cardiopulmonary response to exercise in nonathletic human subjects, indicating a reduced ability for sustained work.

Of greater concern at more typical ambient CO levels are certain cardiovascular effects during exercise that are likely to occur in a smaller, but sizeable, segment of the general population having a deficiency of blood supply (ischemia) to the heart muscle. This group of patients with coronary artery disease (CAD) and reproducible exercise-induced angina (chest pain) is regarded as the most sensitive risk group for CO-exposure effects. Several important studies (Anderson et al., 1973; Sheps et al., 1987; Adams et al., 1988; Kleinman et al., 1989; Allred et al., 1989a,b, 1991) have provided the cardiovascular database for CO in CAD patients. In these studies, discussed in detail in the previous document (see Section 10.3.2 in U.S. Environmental Protection Agency, 1991), 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 electrocardiogram. Adverse effects were found with postexposure COHb levels as low as 3 to 6% when compared on the basis of optical measurements (Figure 6-1). This represents incremental increases of 1.5 to 4.4% COHb from preexposure baseline levels. Effects on silent ischemia episodes (no chest pain), which represent the majority of episodes in these patients, have not been studied.

Only one new study has become available since publication of the 1991 document. As part of an investigation of CO exposure at high altitude, 17 men with documented CAD and stable angina performed exercise stress tests after random 2-h exposures to either clean air or 100 ppm CO at sea level (Kleinman et al., 1998; Leaf and Kleinman, 1996a; Kleinman and Leaf, 1991). The methods used were similar to those previously reported by Kleinman et al. (1989). Group mean COHb levels measured by CO-Oximetry (CO-Ox)were 0.6 ± 0.3 (SD)% and 3.9 ± 0.5 (SD)% for clean air and CO exposures, respectively. Repeated measures analysis of variance for a subgroup (number = 13) with angina on all test days demonstrated a statistically significant ($p < 0.05$) decrease of 9.1 ± 0.6% in the time to onset of angina (from 5.94 to 5.40 min) during exercise after exposure to CO. The results are in good agreement with those observed in the previously reported studies (see Figure 6-1). There was no statistically significant effect on ST segment change, on the duration of angina, or on hemodynamic factors such as blood pressure and heart rate.

Despite clearly demonstrable effects of low-level CO exposure in patients with ischemic heart disease, the adverse health consequences of these types of effects are very difficult to predict in the at-risk population of individuals with heart disease. There is a wide distribution of

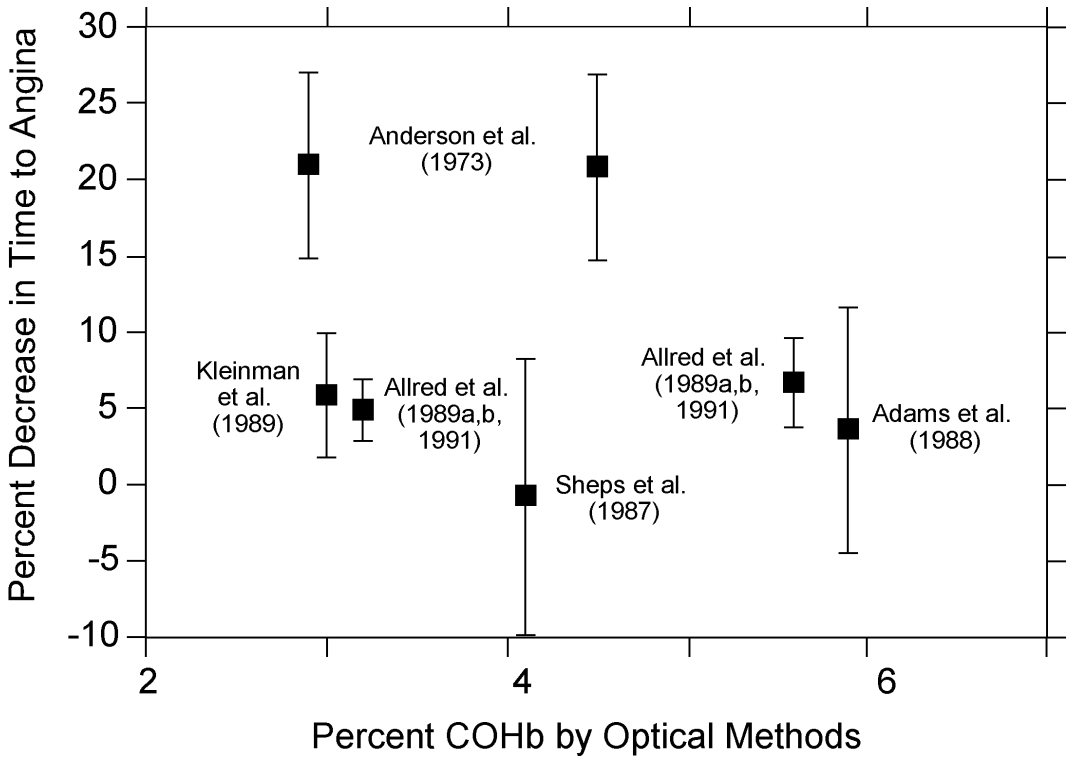

Figure 6-1. The effect of CO exposure on time to onset of angina. For comparison across studies, data are presented as mean percent differences between air- and CO-exposure days for individual subjects calculated from each study. Bars indicate calculated standard errors of the mean. The COHb levels were measured at the end of exposure; however, because of protocol differences among studies and lack of precision in optical measurements of COHb, comparisons must be interpreted with caution.

Source: Modified from U.S. Environmental Protection Agency (1991); Allred et al. (1989b,1991).

professional judgments on the clinical significance of small performance decrements occurring with the levels of exertion and CO exposure defined in the studies noted above. The decrements in performance that have been described at the lowest levels (≤3% COHb) are in the range of reproducibility of the test and may not be alarming to some physicians. On the other hand, the consistency of the responses in time to onset of angina across the studies and the dose-response relationship described by Allred et al. (1989a,b, 1991) between COHb and time to ST segment changes strengthen the argument in the minds of other physicians that, although small, the effects

could limit the activity of these individuals and affect their quality of life. In addition, it has been argued by Bassan (1990) that 58% of cardiologists believe recurrent episodes of exertional angina are associated with a substantial risk of precipitating a myocardial infarction (heart attack), a fatal arrhythmia (abnormal heart rhythm), or slight but cumulative myocardial damage.

Exposures to low levels of CO resulting in 5 to 20% COHb do not produce significant changes in cardiac rhythm or conduction during rest or exercise in healthy humans (Davies and Smith, 1980; Kizakevich et al., 1994). Effects of CO on resting and exercise-induced ventricular arrhythmia in patients with CAD are dependent on their clinical status. Hinderliter et al. (1989) reported no effects of 4 and 6% COHb in patients with ischemic heart disease who did not have chronic arrhythmia (ectopy) during baseline monitoring. In more severely compromised individuals with higher levels of baseline ectopy, exposures to CO that produce 6% COHb have been shown to significantly increase the number and complexity of arrhythmias (Sheps et al., 1990), but not at lower COHb levels (Sheps et al., 1990, 1991; Chaitman et al., 1992; Dahms et al., 1993). This finding, combined with epidemiologic evidence of CO-related morbidity and mortality noted above, and the morbidity and mortality studies of workers who are routinely exposed to combustion products (e.g., Stern et al., 1981, 1988; Edling and Axelson, 1984; Sardinas et al., 1986; Michaels and Zoloth, 1991; Koskela, 1994; Melius, 1995; Ström et al., 1995) suggest that CO exposure may provide an increased risk of hospitalization or death in patients with more severe heart disease.

There also is evidence from experimental studies with laboratory animals that CO can adversely affect the cardiovascular system. The lowest-observed-effect level (LOEL) varies, depending on the exposure regime used and species tested (see Table 6-1). Results from animal studies (reviewed in U.S. Environmental Protection Agency, 1979, 1991; Turino, 1981; McGrath, 1982; Penney, 1988, 1996a) suggest that inhaled CO can cause disturbances in cardiac rhythm and conduction in healthy and cardiac-impaired animals that are consistent with the human data. Results from animal studies (U.S. Environmental Protection Agency, 1991) also indicate that inhaled CO can increase hemoglobin concentration and hematocrit ratio, probably representing compensation for the reduction in oxygen transport caused by CO. At high CO concentrations, excessive increases in hemoglobin and hematocrit may impose an additional workload on the heart and compromise blood flow to the tissues.

TABLE 6-1. ESTIMATED LOWEST-OBSERVED-EFFECT LEVELS FOR EXPOSURE OF LABORATORY ANIMALS TO CARBON MONOXIDE

	LOEL				
Health Effect Category	CO (ppm)	COHb (%)	Duration	Species	Reference
Cardiovascular effects					
Cardiac rhythm	50	2.6	6 weeks	Dog	Preziosi et al. (1970)
Cardiomegaly	200	12.0	30 days	Rat	Penney et al. (1974)
Hemodynamics	150	7.5	30 min	Rat	Kanten et al. (1983)
Hematology	100	9.3	45 days	Rat	Penney et al. (1974)
Atherosclerosis and thrombosis	250	20.0	10 weeks	Rabbit	Davies et al. (1976)
Schedule-Controlled behavior	330	25.0	2 h	Rat	Merigan and McIntire (1976)
Developmental effects	60	6.0	21 days	Rat	Prigge and Hochrainer (1977)
Lung morphology and function	5,000	60.0	15 min	Rat	Niden and Schulz (1965)

There is conflicting evidence that CO exposure enhances development of atherosclerosis in laboratory animals, but most studies show no measurable effect when the animals are fed normal diets without added cholesterol, even at high (≈20%) COHb saturations (U.S. Environmental Protection Agency, 1979, 1991; Penn et al., 1992; Penn, 1993; Mennear, 1993; Smith and Steichen, 1993; Ström et al., 1995). Similarly, the possibility that CO promotes significant changes in lipid metabolism that may accelerate atherosclerosis is suggested in only a few laboratory animal studies (see Table 10-7 in U.S. Environmental Protection Agency, 1991) but not in humans (Leaf and Kleinman, 1996b); however, any such effect must be subtle at most. More recent in vitro studies utilizing cell culture techniques have explored the hypothesis that CO causes cellular oxidative stress and leads to injuries of the vascular endothelium that may precipitate atherosclerosis (Thom and Ischiropoulos, 1997; Thom et al., 1997). Unfortunately, the ability of environmentally relevant CO concentrations to mediate this activity in the intact organism has not been evaluated. Finally, CO probably inhibits rather than promotes platelet aggregation (U.S. Environmental Protection Agency, 1991; Min et al., 1992), lending support to forensic observations that thrombosis is not a prominent feature of CO-mediated injury.
In general, there are few data to indicate that an atherogenic effect of exposure is likely to occur in human populations at frequently encountered levels of ambient CO.

6.3 CENTRAL NERVOUS SYSTEM AND BEHAVIORAL EFFECTS

6.3.1 Brain Oxygen Metabolism

6.3.1.1 Whole Brain

It has been documented amply in the literature that, as COHb is formed, there is vasodilation in the brain (and increased blood supply) in such proportion as to keep the supply of oxygen (O_2) to the brain constant (Helfaer and Traystman, 1996; U.S. Environmental Protection Agency, 1991). The increased blood flow is sufficient to compensate not only for the oxygen supply decrease caused by reduced arterial O_2 content (CaO_2) but is also sufficient to compensate for the increased difficulty of extraction of O_2 because of the shifted oxyhemoglobin dissociation curve. This compensatory vasodilation appears to be effective from low levels to very high levels of COHb (at least up to 60%) and is similar in the fetus, neonate, and healthy adult.

Despite the compensatory regulation of O_2 supply to the brain, it appears that O_2 consumption, measured as the cerebral metabolic rate for O_2 ($CMRO_2$), is reduced as COHb rises. The reason for this is unclear, but the fact is well documented (Doblar et al., 1977; Jones and Traystman, 1984; U.S. Environmental Protection Agency, 1991; Langston et al., 1996). The amount of reduction in $CMRO_2$ as a function of COHb can be shown by combining the information of Doblar et al. (1977) from goats and Langston et al. (1996) from sheep into one graph (see Figure 6-2). Although information from Jones and Traystman (1984) and associated studies was expressed as a function of CaO_2, not COHb, and was difficult to incorporate into Figure 6-2 and the associated analysis, their data corroborate those of the other workers.

From Figure 6-2, it may be seen that the $CMRO_2$ does not decrease to 90% of baseline until ≈27% COHb (95% confidence limits were ≈21 to 32% COHb). The data from sheep and goats agreed with the results of Paulson et al. (1973), who reported that the mean human $CMRO_2$ did not decrease significantly, even for COHb up to 20%. Because Paulson et al. (1973) did not report the value of their means, it was not possible to include their results as data points on Figure 6-2.

6.3.1.2 Subregions of the Brain

There are a number of reports of the blood-flow response to COHb of subregions of the brain (U.S. Environmental Protection Agency, 1991). The results generally demonstrate that

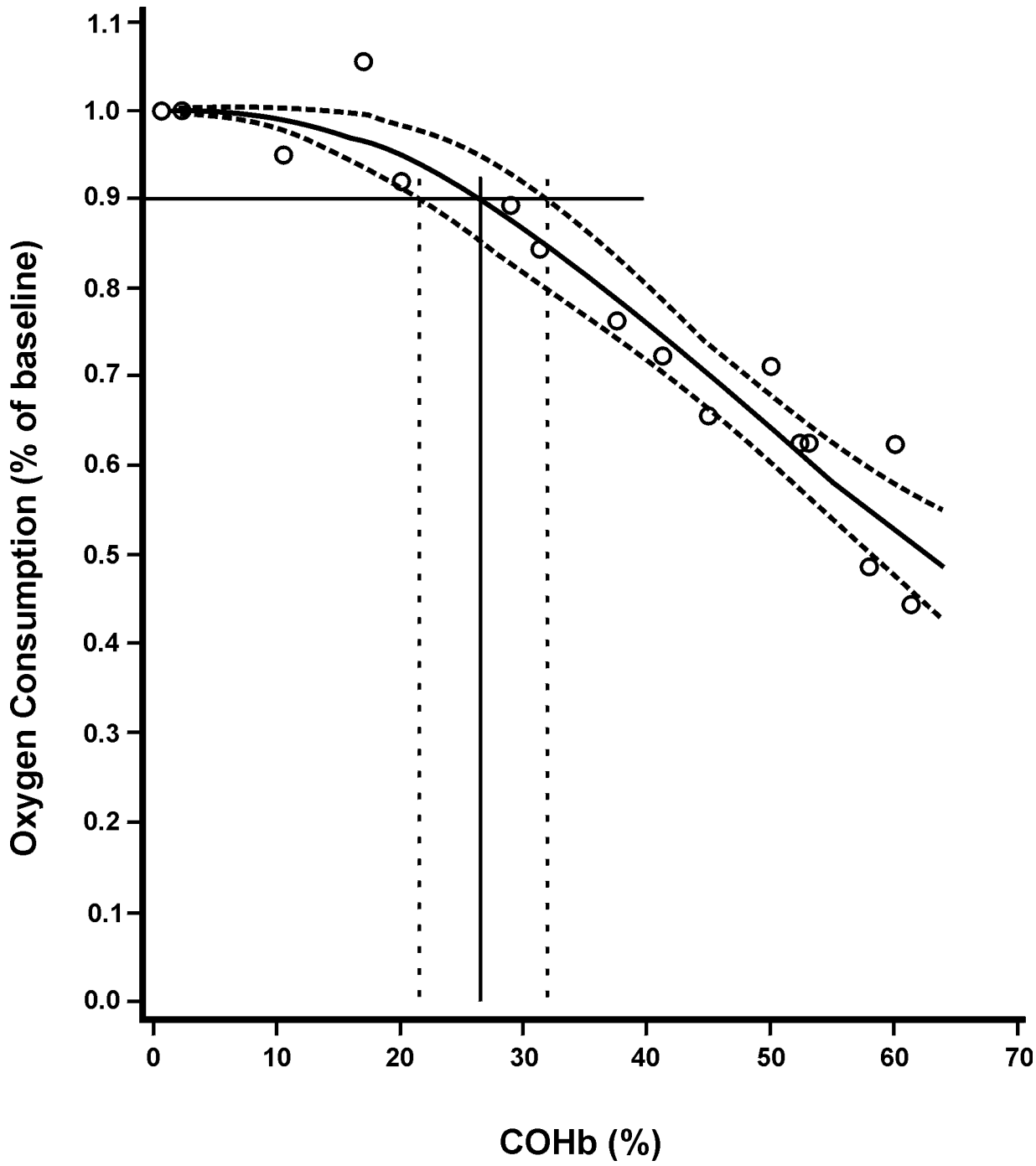

Figure 6-2. The relationship between COHb and $CMRO_2$. Means from Doblar et al. (1977) were taken from their Tables 1 and 3, and $CMRO_2$ values were transformed to percent of baseline. Figures 1 and 3 of Langston et al. (1996) were converted digitally (Summasketch III graphical to digital conversion) and also were transformed to percent of baseline. Data from both sources were merged into the same database and a logit function was fitted to the data using SAS, PROC NLIN (SAS Institute Inc., 1990). The solid line is the best fit, dashed lines are the 95% confidence limits, and the points plotted are means from the published studies.

some areas of the brain have less baseline blood flow than others, and that the COHb-compensatory increase in blood flow is not the same for all areas. Generally, however, the percent increases over baseline are nearly the same for all areas except the neurohypophysis (Hanley et al., 1986). It is important to note that the latter area serves homoeostatic and not ongoing behavioral functions. Thus, it would appear that the subregions of the brain have compensatory increased blood flow in the presence of COHb similar to the whole brain. To be sure, all possible regions of the brain have not been tested, but no evidence to indicate otherwise has been found.

Work by Sinha et al. (1991), measuring regional capillary perfusion and blood flow in the presence of COHb elevation, indicates that the problem of compensation for COHb-reduced CaO_2 is not as simple as indicated above. Blood flow was measured using radiolabeled dye and capillary morphology was measured by fluorescence microscopy. With these methods, there appeared to be an increase in the number of perfused capillaries and in the amount of blood flow as COHb increased. Thus, not only may more blood be delivered, but increased capillary perfusion would decrease the diffusion distance to the tissue.

Presumably the compensatory mechanisms in subareas of the brain would work in a manner similar to that of the whole brain and thus would show similar decreases in $CMRO_2$ as COHb increases. No corroborative studies, however, have been reported in the literature.

Better and more detailed documentation of regional $CMRO_2$ in humans as well as other species seems appropriate, but does not have high priority because not much evidence exists to suggest that the results would differ from whole-brain results. It appears that what is needed is not more descriptive work, but an effort should be made to understand the mechanism by which COHb elevation reduces $CMRO_2$. Furthermore, information is needed about brain conditions under which brain compensatory mechanisms might be impaired (e.g., injury, inflammation, ailments associated with aging and co-exposure to other pollutants). If such information were available, specific theoretical (biologically based) predictions could be made, and behavioral experiments designed to test them.

6.3.2 Behavioral Effects of Carbon Monoxide

The effects of CO on behavior, especially the ability to perform certain time discrimination tasks, provided the scientific basis for the first air quality standard in 1971 (see Section 1.2).

As further research data became available, however, the results on human behavior at low levels of CO exposure (<5% COHb) were called into question and subsequently dismissed as the basis for the standard (U.S. Environmental Protection Agency, 1979). After reviewing available studies, the previous criteria document (U.S. Environmental Protection Agency, 1991) concluded that effects on behavior were demonstrated unambiguously in both humans and laboratory animals at COHb elevations above 20%. Below this level, the results were less consistent. The document also concluded, however, that it seems unwise to ignore the historical evidence in favor of effects on human performance at COHb levels between 5 and 20% (e.g., Horvath et al., 1971; Fodor and Winneke, 1972; Putz et al., 1976, 1979; Benignus et al., 1987). Even if behavioral effects are small or occasional, they may be important to the performance of critical tasks.

Behavioral experiments with the effects of elevated COHb frequently have been marred by methodological problems. In particular, experiments employing single-blind designs were shown to be 2.5 times as likely to find significant results as similar studies employing double-blind methods (Benignus, 1993, 1996). This problem was noted previously, and reports of findings of behavioral effects of CO were summarized with respect to whether a double-blind procedure had been followed (see Table 10-25 of U.S. Environmental Protection Agency, 1991). From this summary, it was concluded that, at most, there was credible evidence for effects on only three (somewhat artificially defined) categories of behavior: (1) tracking, (2) vigilance, and (3) continuous performance. Even within these categories, considering only double-blind studies, it was noted that less than 50% of all studies found significant effects. Furthermore, most of the double-blind experiments reporting significant results were unreplicable.

Benignus (1994) performed extensive meta-analyses of the CO-behavioral literature. Because single-blind studies were likely to include many type I errors (results erroneously declared significant), only double-blind human CO studies were included. In this report, two dose-effect curves were estimated from the literature by converting all behavioral endpoints to percent of baseline. A dose-effect curve for COHb and behavior was estimated from experiments with rats and was corrected for the effects of hypothermia. Another dose-effect curve was estimated from the human literature on hypoxic hypoxia, which was converted to equivalent COHb via equal arterial oxygen contents and corrected for effects of hypocapnia. These two curves virtually overlapped each other. Human data points from CO-behavior

experiments then were plotted onto the curve fitted to the rat CO data (no curve was fitted to human data because of the small effect sizes and small COHb levels). The conclusion from this meta-analysis was that human behavioral impairments of 10% (ED-10) should not be expected until COHb exceeds 20%.

Data for the rat studies from Benignus (1994) were refitted for the present purposes using the same dose-effect model (a logit) as for the $CMRO_2$ data above (originally a different function was used). Data from all available double-blind human studies also were converted to percent of baseline and plotted on the same graph as the rat data and the logit curve fitted to the rat data (Figure 6-3). With the logit function, it is estimated that a 10% decrement should be produced in rats by ca. 25% COHb (95% confidence limits of ≈20 to 30%). The human data plotted in Figure 6-3 (asterisks) seem, as a group, not to have a dose-related trend of decrements, and it could be argued reasonably that effects in humans cannot be shown to differ from those in rats. Some of the human data, however, at low levels of COHb (4 to 10%) do appear below baseline and were declared statistically significant by the authors of the original reports.

The low-COHb significant results plotted in Figure 6-3 were invariably reported in studies in which only a few levels of COHb were evaluated. Studies in which more and higher COHb levels were tested invariably did not find statistically significant effects, even at much higher levels. Furthermore, for every study reporting low-COHb level impairments, other studies failed to replicate the findings, or highly similar studies failed to find effects.

In summary, no reliable evidence demonstrating decrements in neural or behavioral function in healthy young adult humans has been reported for COHb levels below 20%, and even these studies are untested by replications. The low-COHb behavioral effects that have sometimes been reported cannot be taken at face value because they are not reliably repeatable, and they do not fit into a wider range, dose-effect pattern reported in other studies. It is more reasonable to conclude that no statistically detectable behavioral impairments occur until COHb exceeds 20 to 30%. The conclusion, based on behavioral evidence alone, is bolstered by the findings that whole-brain $CMRO_2$ is not reduced by a similar amount until COHb rises to 21 to 32%. Because a dose-effect curve has been fitted, any level of effect may be considered (e.g., ED-5 or ED-20). The interpolation of a curve to an ED-5 point would imply that the COHb levels for such an effect size would be 15 to 26%. Such an interpolation is more speculative than an ED-10, however, because the experimental verification would be difficult, requiring large

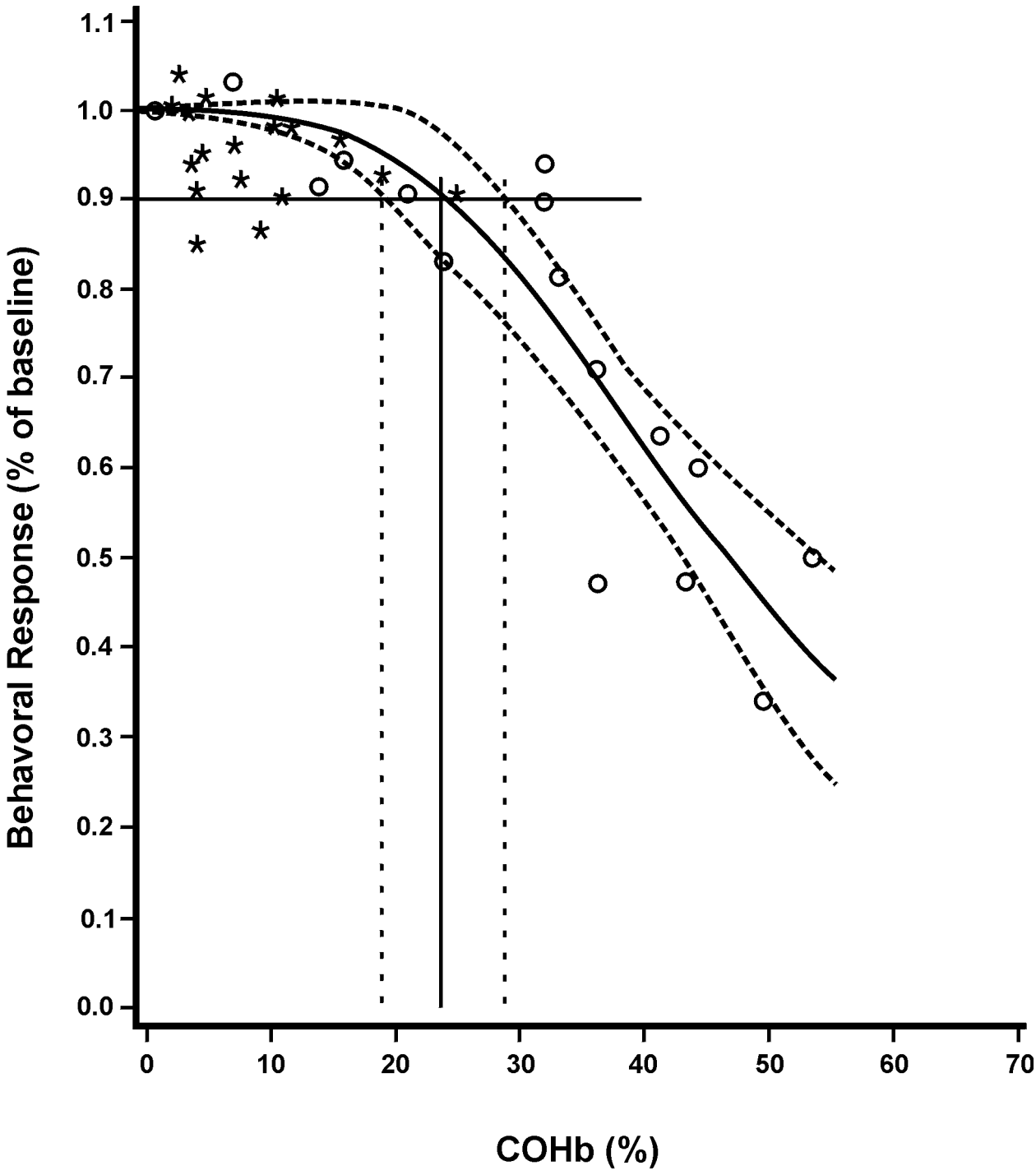

Figure 6-3. The relationship between COHb and behavior. Open circles are the hypothermia-corrected means from four studies of effects of COHb in rats (see Benignus, 1994). The solid line is a best-fit logit curve to the rat data. The dashed lines are 95% confidence limits. Asterisks are data from double-blind human studies (see Benignus, 1994) that were plotted in the figure but were not used to fit the logit function.

numbers of subjects and careful control of error variance. Additionally, as interpolation approaches small effect sizes, the error possibility because of statistical model selection (threshold versus continuous) increases dramatically.

Unless the effort is to find a behavioral paradigm that would yield replicable low-level COHb decrements in behavior that were part of a wider range, dose-effect curve, it would seem unfruitful to continue behavioral work. It is important, however, that any new behavioral experiments demonstrate a dose-effect curve that includes higher COHb levels. The lack of such dose-effect information within a study has contributed to the problems of interpreting published literature. Because of the difficulties in replication, it would seem desirable that behavioral experiments be designed to verify prediction from biologically based information (e.g., mechanistic theory about $CMRO_2$ and how it is affected by COHb elevation).

The behaviors implicated by the research findings involve such abilities as detection of infrequent events (vigilance), hand-eye coordination (compensatory tracking), and other forms of continuous performance (U.S. Environmental Protection Agency, 1991). Because of the unreliability of the findings, however, it is questionable whether these behaviors should be cited as effects. Until reliable behavioral effects are demonstrated in a dose-related manner, it seems premature to speculate about the kind of behavioral effects and thus lend credence to unreliable findings.

Because COHb elevates brain blood flow, it has the possibility of altering the delivery of other toxicants to the brain or altering the biotransformation or elimination of toxicants (e.g., Doi and Tanaka, 1984; Kim and Carlson, 1983; Roth and Rubin, 1976a,b). In combination with exercise or hypoxic hypoxia, the interactions would become even more complex. Disease and ailments associated with aging concomitant with all of the above could be important. Interactions such as these are understood from physiological theory and can be given quantitative estimates by the use of physiological simulation using whole-body physiological simulators.

6.4 DEVELOPMENTAL TOXICITY

An issue directly relevant to the protection of public health is the potential effect of CO on growth and function of the developing fetus, infant, and child. Results obtained from new research on this specific outcome of CO exposure (e.g., Carratù et al., 1993, 1996; Di Giovanni

et al., 1993; De Salvia et al., 1995; De Luca et al., 1996) have not changed the conclusions presented in Section 10.5 of the previous criteria document (U.S. Environmental Protection Agency, 1991). From all of the laboratory animal studies, it is clear that severe, acute CO poisoning 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. Available data (reviewed in U.S. Environmental Protection Agency, 1991; Annau and Fechter, 1994; Carratù et al., 1995; Penney, 1996b) provide strong evidence that maternal CO exposures of 150 to 200 ppm, leading to approximately 15 to 25% COHb, produce reductions in birth weight, cardiomegaly, delays in behavioral development, and disruption of cognitive function in laboratory animals of several species. Isolated experiments (Prigge and Hochrainer, 1977; Abbatiello and Mohrmann, 1979; Singh, 1986) suggest that some of these effects may be present at concentrations as low as 60 to 65 ppm (approximately 6 to 11% COHb) maintained throughout gestation (see Table 6-1). Studies relating human CO exposure from ambient sources or cigarette smoking to reduced birth weight (e.g., Martin and Bracken, 1986; Rubin et al., 1986; Alderman et al., 1987; Wouters et al., 1987; Brooke et al., 1989; Spitzer et al., 1990; Wen et al., 1990; Peacock et al., 1991a; Zarén et al., 1996; Jedrychowski and Flak, 1996; Secker-Walker et al., 1997) are of concern because of the risk for developmental disorders (Olds et al., 1994a,b; Olds, 1997); however, many of these studies have not considered all sources of CO exposure, other pollutants (Wang et al., 1997), or other risk factors during gestation (Peacock et al., 1991b; Luke, 1994; Robkin, 1997).

Results from laboratory animal studies indicate that CO, by itself, should not have much of an effect on the developing fetus until later in gestation when the embryo is much larger and more dependent on transport of oxygen by red blood cells. In addition, results from a multicenter, prospective study (Koren et al., 1991) of fetal outcome following mild to moderate accidental CO poisoning in pregnancy suggests that hypoxemia associated with measured COHb saturations of up to 18% (or even higher estimated levels) does not impair the growth potential of the fetus when pregnancy continues normally. Therefore, it is very unlikely that ambient levels of CO typically encountered by pregnant women would cause increased fetal risk. It is necessary, however, to consider the combined effects of CO with the other common risk factors

that may cause adverse fetal outcome (e.g., tobacco and alcohol consumption, genetic background, maternal general health and obstetric history).

One of the more important determinants of the course and outcome of pregnancy that was not previously discussed is maternal-fetal nutrition (Luke, 1994). Laboratory animal studies conducted to determine the combined effect of gestational CO exposure and nutritional deficiency suggest that CO has a greater effect on the fetus in protein-deficient mice (Singh and Moore-Cheatum, 1993; Singh et al., 1993). Reductions in the rate of pregnancy, lower fetal weights, and increased fetal malformations were reported at CO concentrations as low as 65 ppm maintained for 6 h per day during the first trimester of pregnancy. Previous evidence of the fetotoxic and teratogenic effects of CO in laboratory animals (U.S. Environmental Protection Agency, 1991) came largely from high levels of exposure (i.e., in the range of 500 ppm for rodents).

There are studies (e.g., Schoendorf and Kiely, 1992; Scragg et al., 1993; Mitchell et al., 1993; Klonoff-Cohen et al., 1995; Blair et al., 1996; Hutter and Blair, 1996; MacDorman et al., 1997) linking maternal cigarette smoking with sudden infant death syndrome (SIDS), but the role of CO is uncertain, especially in relation to other known risk factors for SIDS, such as developmental abnormalities (Schwartz et al., 1998), prone sleeping (Kahn et al., 1993; Franco et al., 1996), overheating (Douglas et al., 1996), and soft bedding (Ponsonby et al., 1993; Kemp et al., 1998). Data from human populations (Hoppenbrouwers et al., 1981) suggesting a link between ambient CO exposures and SIDS are weak, but further study should be encouraged. Children may experience neurological symptoms such as dizziness or fainting after an acute episode of CO poisoning (>15% COHb) or, in some cases, neurological impairment may develop days to weeks after very high exposures (Crocker and Walker, 1985). Human data from these cases of accidental high CO exposures are difficult to use in identifying a LOEL for CO because of the small number of cases reviewed and problems in documenting exposure levels. However, such data, if systematically gathered and reported, could be useful in identifying possible ages of special sensitivity to CO and co-factors or other risk factors that might identify sensitive subpopulations.

6.5 ACUTE PULMONARY EFFECTS

It is unlikely that CO has any direct effects on lung tissue, except for extremely high concentrations that can cause cell damage and edema (Niden and Schulz, 1965; Fein et al., 1980; Burns et al., 1986). No new information has been published in the literature to change this conclusion drawn from Section 10.2 of the previous criteria document (U.S. Environmental Protection Agency, 1991). Experimental studies on the effects of CO exposures producing COHb saturations up to 39% failed to find any consistent effects on pulmonary cells and tissue or on the vasculature of the lung (Fisher et al., 1969; Weissbecker et al., 1969; Hugod, 1980; Chen et al., 1982). 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. Decrements in lung function have been observed with increasing severity of CO poisoning (Kolarzyk, 1994a,b, 1995). For example, occupational or accidental exposure to the products of combustion and pyrolysis, particularly indoors, may lead to acute decrements in lung function if COHb levels are greater than 17% (Sheppard et al., 1986) but not at saturations less than 2% (Cooper and Alberti, 1984; Hagberg et al., 1985; Evans et al., 1988). It is difficult, however, to separate the potential effects of CO from the effects of other respiratory irritants in smoke and exhaust. Community population studies on CO in ambient air have not found strong relationships with pulmonary function, symptomatology, and disease (Lutz, 1983; Robertson and Lebowitz, 1984; Lebowitz et al., 1987).

6.6 OTHER SYSTEMIC EFFECTS OF CARBON MONOXIDE

Laboratory animal studies (reviewed in Section 10.6 of U.S. Environmental Protection Agency, 1991) suggest that enzyme metabolism and the P-450-mediated metabolism of xenobiotic compounds may be affected by CO exposure (e.g., Montgomery and Rubin, 1971; Pankow et al., 1974; Roth and Rubin, 1976a,b,c). Most of the authors of these studies have concluded, however, that effects on metabolism at low COHb levels ($\leq$15%) are attributable entirely to tissue hypoxia produced by increased levels of COHb because the effects are no greater than those produced by comparable levels of hypoxia produced by insufficient oxygen delivery. 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 may be important to individuals receiving drug treatment.

Inhalation of high levels of CO, leading to COHb concentrations greater than 10 to 15%, have been reported to cause a number of other systemic effects in laboratory animals and 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 of effects on liver (Katsumata et al., 1980), kidney (Kuska et al., 1980), bone (Zebro et al., 1983), and immune capacity in the lung and spleen (Snella and Rylander, 1979). It generally is agreed that these effects are caused by the severe tissue damage occurring during acute CO poisoning resulting from one or more of the following: ischemia resulting from the formation of COHb, inhibition of oxygen release from oxyhemoglobin, inhibition of cellular cytochrome function (e.g., cytochrome oxidases), and metabolic acidosis.

6.7 PHYSIOLOGIC RESPONSES TO CARBON MONOXIDE EXPOSURE

The only evidence for short- or long-term compensation to increased COHb levels in the blood is indirect. Experimental animal data (reviewed in Section 10.7 of U.S. Environmental Protection Agency, 1991) indicate that incremental increases in COHb produce physiological responses that tend to offset the deleterious effects of CO exposure on oxygen delivery to the tissues. Experimental human data (presented in a report by Kizakevich et al., 1994) indicate that compensatory cardiovascular responses to submaximal upper- and lower-body exercise (e.g., increased heart rate, cardiac contractility, cardiac output) occur after CO exposures. These changes were highly significant for exposures attaining 20% COHb. Other compensatory responses are increased coronary blood flow, cerebral blood flow, hemoglobin (through increased hemopoiesis), and oxygen consumption in muscle.

Short-term compensatory responses in blood flow or oxygen consumption may not be complete or may even be absent in certain persons. For example, from the 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 (6% or less). The implication is that, in some cases of cardiac impairment, the short-term compensatory mechanism is impaired.

From neurobehavorial studies (see Section 6.3.2 of the present document), it is apparent that decrements resulting from CO exposure have not been consistent in all subjects, even in the same studies, and have not demonstrated a dose-response relationship with increasing COHb levels. The implication from this data suggests there may be some threshold or time lag in a compensatory mechanism such as increased blood flow. Without direct physiological evidence in either laboratory animals or humans, this concept can be only hypothesized.

The mechanism by which long-term adaptation may occur, if it can be demonstrated in humans, is assumed to be increased hemoglobin concentration via an increase in hemopoiesis. This alteration in hemoglobin production has been demonstrated repeatedly in laboratory animal studies, but no recent studies have been conducted that indicate the occurrence of some adaptational benefit. Even if the hemoglobin increase is a signature of adaptation, it has not been demonstrated at low ambient concentrations of CO.

6.8 COMBINED EXPOSURE OF CARBON MONOXIDE WITH OTHER POLLUTANTS, DRUGS, AND ENVIRONMENTAL FACTORS

6.8.1 High-Altitude Effects

Although there are many studies comparing and contrasting the effects of inhaling CO with those produced by short-term, high-altitude exposure, there are relatively few reports on the combined effects of inhaling CO at high altitudes. There are data (reviewed in Section 11.1 of U.S. Environmental Protection Agency, 1991) to support the possibility that the effects of these two hypoxic factor episodes are at least additive. Most of these early data were obtained at CO concentrations too high to have much meaning for regulating the amount of CO in ambient air. More recent studies by Kleinman et al. (1998) evaluated the combined effects of lower levels of CO at high altitude. In general, the results confirm the additivity of hypoxic effects at a simulated altitude of 2.1 km and CO exposures resulting in 4% COHb.

There are even fewer studies of the long-term effects of CO at high altitude. These studies, identified in Table 11-2 of the previous criteria document (U.S. Environmental Protection Agency, 1991), indicate few changes at CO concentrations below 100 ppm and altitudes below 4,572 m (15,000 ft). The fetus may be particularly sensitive to the effects of CO at altitude, as is especially true with the high levels of CO associated with maternal smoking (Moore et al., 1982).

The potential effects on human health of inhaling CO at high altitudes are complex (see Section 5.4.1) Whenever CO binds to hemoglobin (Hb), it reduces the amount of Hb available to carry oxygen. People visiting high altitudes (where the partial pressure of oxygen in the atmosphere is lower) will experience reduced levels of oxygen in the blood (hypoxemia) because of a relative hypoventilation that occurs, particularly during sleep. Carbon monoxide, by binding to Hb, intensifies the hypoxemia existing at high altitudes by further reducing transport of oxygen to the tissues. In addition, COHb saturations are higher at altitude than at sea level because, in part, of changes in elimination of endogenous CO and of more rapid uptake of exogenous CO (McGrath, 1992; McGrath et al., 1991, 1993). However, within hours of arrival at high altitude, certain physiological adjustments begin to take place (Grover et al., 1986), and, over several days, these mechanisms will operate to lessen the initial impact of atmospheric hypoxia. Hemoconcentration occurs, and the increased Hb concentration offsets the decreased blood oxygen saturation and restores oxygen concentrations to former levels. Consequently, the simple additive model of COHb and altitude hypoxemia may be valid only during early altitude exposure. The new visitor to higher altitudes, especially the elderly and those with CAD (Kleinman et al., 1998; Leaf and Kleinman, 1996a), may be at greater risk from the added effects of ambient CO than the adapted resident. The period of increased risk probably is prolonged in the elderly because adaptation to high altitude proceeds more slowly with increasing age (Dill et al., 1985).

6.8.2 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 published data available on CO combinations

with drugs concern psychoactive drugs (Montgomery and Rubin, 1971, 1973; McMillan and Miller, 1974; Medical College of Wisconsin, 1974; Pankow et al., 1974; Rockwell and Weir, 1975; Roth and Rubin, 1976a,b,c; Mitchell et al., 1978; Topping et al., 1981; Kim and Carlson, 1983; Engen, 1986; Knisely et al., 1987, 1989). Descriptions of these studies were provided in Section 11.2 of the previous criteria document (U.S. Environmental Protection Agency, 1991). The following summary has been excerpted from the last review.

The use and abuse of psychoactive drugs and alcohol are widespread. Because of the effect of CO on brain function, interactions between CO and psychoactive drugs could be anticipated. However, 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 from 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. The greatest evidence for a potentially important interaction of CO comes from studies with alcohol in both laboratory animals and humans, where at least additive effects have been obtained (Mitchell et al., 1978; Knisely et al., 1987, 1989). The significance of these effects is augmented by the probable high incidence of combined alcohol use and CO exposure in the population.

Besides interaction with psychoactive drugs, there is growing concern that prescribed medications, especially nitric oxide blockers and calcium channel blockers, could interact with CO. There are no known published data available, however, on CO combinations with these drugs.

6.8.3 Interaction with Other Air Pollutants and Environmental Factors

Much of the data concerning the combined effects of CO and other pollutants found in ambient air are based on laboratory animal experiments that were discussed in Section 11.3 of the previous criteria document (U.S. Environmental Protection Agency, 1991). More recent studies published since then have confirmed the conclusions made at that time and are included here for completeness. Only a few controlled-exposure studies of humans are available, and the results were discussed in more detail in the previous document. These early studies in healthy human subjects (Drinkwater et al., 1974; Raven et al., 1974a,b; Gliner et al., 1975; Hackney

et al., 1975a,b; DeLucia et al., 1983) on common air pollutants such as CO, NO_2, O_3, and peroxyacetylnitrate failed to show any interaction from combined exposure. The more recent epidemiology studies (e.g., Morris et al., 1995; Schwartz and Morris, 1995; Schwartz, 1997; Burnett et al., 1997) suggest an association between hospital admissions for cardiovascular disease and ambient exposure to multiple pollutants, including CO and PM. In animal studies, no interaction was observed following combined exposure of CO and common air pollutants such as NO_2 and SO_2 (Busey, 1972; Murray et al., 1978; Hugod, 1979). However, an additive effect on learning behavior was observed following combined exposure of high levels of CO and NO (Groll-Knapp et al., 1988), and a synergistic dose effect (increased COHb) was observed after combined exposure to CO and O_3 (Murphy, 1964).

Toxicological interactions of combustion products, primarily CO, carbon dioxide, NO_2, and hydrogen cyanide (HCN), at levels typically produced by indoor and outdoor fires, have shown a synergistic effect on mortality following CO plus CO_2 exposure (Rodkey and Collison, 1979; Levin et al., 1987a) and CO plus NO_2 exposure (Levin, 1996), and an additive effect with HCN (Levin et al., 1987b). Additive effects on mortality also were observed when CO, HCN, and low oxygen were combined; adding CO_2 to this combination was synergistic (Levin et al., 1988).

Finally, laboratory animal studies (Young et al., 1987; Yang et al., 1988; Fechter et al., 1988, 1997; Fechter, 1995; Cary et al., 1997) suggest that combinations of environmental factors such as heat stress and noise may be important determinants of health effects occurring in combination with CO exposure. Of the effects described, one potentially most relevant to typical human exposures is a greater decrement in the 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).

6.8.4 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 (e.g., nicotine, NO_2, HCN, polyaromatic hydrocarbons [PAHs], aldehydes, ketones) that could interact with environmental CO. Available data suggest that some of these components can affect the cardiovascular system. For example, nicotine clearly aggravates the decrease in oxygen capacity induced by CO through an increase in the oxygen demand of the heart (Khosla et al., 1994; Benowitz, 1997), and PAHs have been implicated in

atherosclerosis (Glantz and Parmley, 1991). Little is known, however, about the relative importance of CO compared with the other components of tobacco smoke.

The association between active smoking and CVD is fully established (Surgeon General of the United States, 1983). 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 environmental tobacco smoke (ETS), compared with 100% in an active smoker (Wall et al., 1988; Jarvis, 1987). Therefore, exposure to ETS will be the closest to pure CO exposure, even if the resultant levels of COHb are low (about 1 to 2%) (Jarvis, 1987). The relationship between passive smoking and increased risk of CVD is controversial. Early studies on this relationship were reviewed in the 1986 report of the Surgeon General of the United States (1986) and by the National Research Council (1986). Since that time, the epidemiological evidence linking passive smoking exposure to heart disease has expanded rapidly. The available literature on the relationship between passive exposure to ETS in the home and the risk of cardiovascular-associated morbidity or mortality in the nonsmoking spouse of a smoker consists of numerous published reports (e.g., Glantz and Parmley, 1991; Steenland, 1992; Wells, 1994; Kritz et al., 1995; LeVois and Layard, 1995; Steenland et al., 1996; Kawachi et al., 1997; Howard et al., 1998). The data suggest an increase of approximately 1.3 in the relative risk of CVD (95% CI of 1.2 to 1.4) is associated with prolonged exposure to ETS that may be caused by any number of biochemical mechanisms, including greater platelet aggregation, endothelial cell damage, reduced oxygen supply, greater oxygen demand, and the direct effects of CO (Kalmaz et al., 1993; Zhu and Parmley, 1995; Weiss, 1996; Werner and Pearson, 1998).

6.9 SUMMARY

As noted at the beginning of this chapter, the lethality of CO that results from exposure to very high concentrations is well known to health professionals and the public. Symptoms of acute CO poisoning cover a wide range, depending on severity of exposure: headache, dizziness, weakness, nausea, vomiting, disorientation, confusion, collapse, and coma. Perhaps the most insidious effects of CO poisoning are the delayed development of neurological impairment that occur within 1 to 3 weeks after exposure and the neurobehavioral consequences, especially in

children. Carbon monoxide poisoning during pregnancy results in high risk for the mother by increasing the short-term complication rate and, for the fetus, by causing reduced birth weight, heart and brain disorders, and possibly death.

The effects of exposure to low concentrations, such as the levels found in ambient air, are far more subtle and considerably less threatening than those occurring in frank poisoning from high CO concentrations. Because the COHb level of the blood is the best indicator of potential health risk, symptoms of exposures to excessive ambient air levels of CO are described here in terms of associated COHb levels. The LOEL, however, depends on the method used for analysis of COHb. Gas chromatography (GC) is the method of choice for measuring COHb, particularly at saturation levels ≤5%, because of the large variability and potential high bias of the optical methods such as CO-Ox. The key human health effects most clearly demonstrated to be associated with exposure to ambient CO are summarized in Table 6-2.

Maximal exercise duration and performance in healthy individuals have been shown to be reduced at COHb levels of ≥2.3% and ≥4.3% (GC), respectively. The decrements in performance at these levels are small and likely to affect only competing athletes rather than people engaged in everyday activities. In fact, no effects were observed during submaximal exercise in healthy individuals at COHb levels as high as 15 to 20%.

Adverse effects have been observed in individuals with CAD at 3 to 6% COHb by optical methods of measurement. At these levels, individuals with reproducible exercise-induced angina (chest pain) are likely to experience a reduced capacity to exercise because of decreased time to onset of angina. The indicators of myocardial ischemia during exercise, which is detectable by electrocardiographic (ECG) changes (ST depression) and associated angina, were statistically significant in one study at ≥2.4% COHb (GC) and showed a dose-response relationship with increasing COHb. An increase in the number and complexity of exercise-related arrhythmias also has been observed at ≥6% COHb (CO-Ox) in some people with CAD and high levels of baseline ectopy (chronic arrhythmia) that may present an increased risk of sudden death.

Results from the controlled laboratory studies and reports of increased morbidity and mortality in workers routinely exposed to combustion products provide support for the recent epidemiology studies suggesting that day-to-day variations in ambient CO concentrations are related to cardiovascular hospital admissions and daily mortality, especially for individuals over

TABLE 6-2. KEY HEALTH EFFECTS OF EXPOSURE TO AMBIENT CARBON MONOXIDE

Target Organ	Health Effects[a,b]	Tested Population[c]	References
Lungs	Reduced maximal exercise duration with 1-h peak CO exposures resulting in ≥2.3% COHb (GC)	Healthy individuals	Drinkwater et al. (1974) Raven et al. (1974b) Horvath et al. (1975)
Heart	Reduced time to ST segment change of the ECG (earlier onset of myocardial ischemia) with peak CO exposures resulting in ≥2.4% COHb (GC)	Individuals with coronary artery disease	Allred et al. (1989a,b; 1991)
Heart	Reduced exercise duration because of increased chest pain (angina) with peak CO exposures resulting in ≥3% COHb (CO-Ox)	Individuals with coronary artery disease	Anderson et al. (1973) Sheps et al. (1987) Adams et al. (1988) Kleinman et al. (1989, 1998) Allred et al. (1989a,b; 1991)
Heart	Increased number and complexity of arrhythmias (abnormal heart rhythm) with peak CO exposures resulting in ≥6% COHb (CO-Ox)	Individuals with coronary artery disease and high baseline ectopy (chronic arrhythmia)	Sheps et al. (1990)
Heart	Increased hospital admissions associated with ambient pollutant exposures	Individuals >65 years old with cardiovascular disease	Schwartz and Morris (1995) Morris et al. (1995) Schwartz (1997) Burnett et al. (1997)
Brain	Central nervous system effects, such as decrements in hand-eye coordination (driving or tracking) and in attention or vigilance (detection of infrequent events), with 1-h peak CO exposures (≈5 to 20% COHb)	Healthy individuals	Horvath et al. (1971) Fodor and Winneke (1972) Putz et al. (1976, 1979) Benignus et al. (1987)

[a]The EPA has set significant harm levels of 50 ppm (8-h average), 75 ppm (4-h average), and 125 ppm (1-h average). Exposure under these conditions could result in COHb levels of 5 to 10% and cause significant health effects in sensitive individuals.
[b]Measured blood COHb level after CO exposure.
[c]Fetuses, infants, pregnant women, elderly people, and people with anemia or with a history of cardiac or respiratory disease may be particularly sensitive to CO.

65 years of age. The relative influences on these associations of ambient and nonambient CO have not been determined.

Central nervous system effects, including reductions in hand-eye coordination (driving or tracking) and in attention or vigilance, have been reported at peak COHb levels of 5% and

higher, but later work indicates that significant behavioral impairments in healthy individuals should not be expected until COHb levels exceed 20%. It must be emphasized, however, that even a 5% COHb level is associated with 1-h CO concentrations of 100 ppm or higher. Thus, at typical ambient air levels of CO, no observable central nervous system effects would be expected to occur in the healthy population.

The current ambient air quality standards for CO (9 ppm for 8 h and 35 ppm for 1 h) are intended to keep COHb levels below 2.1% to protect the most sensitive members of the general population (i.e., individuals with CAD). Individuals in motor vehicles are at the greatest risk from ambient CO exposure, followed by pedestrians, bicyclists, and joggers in the proximity of roadways and the rest of the general urban population exposed to vehicle exhaust. Several hours of exposure to peak ambient CO concentrations found occasionally at downtown urban sites during periods of heavy traffic would be required to produce COHb levels of concern in the most sensitive nonsmokers. Carbon monoxide levels occurring outside the downtown urban locations are expected to be lower and are probably representative of levels found in residential areas where most people live. Significant health effects from ambient CO exposure are not likely under these latter exposure conditions. Active cigarette smoking increases the risk for developing cardiovascular and pulmonary disease, and passive smoking also can elevate COHb levels in nonsmokers under conditions of poor ventilation, putting nonsmoking co-workers and family members at increased risk. Carbon monoxide poisoning from indoor exposures to higher than ambient CO levels occurs frequently, has more severe consequences, and often is overlooked. Efforts in prevention through public and medical education should be encouraged.

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7. INTEGRATIVE SUMMARY AND CONCLUSIONS

7.1 INTRODUCTION

Carbon monoxide (CO) is a colorless, tasteless, odorless, and nonirritating gas that is a product of incomplete combustion of carbon-containing fuels. It also is produced within living organisms by the natural degradation of hemoproteins (e.g., hemoglobin, myoglobin, cytochromes) or as a by-product of xenobiotic metabolism, especially the breakdown of inhaled organic solvents containing halomethanes (e.g., methylene bromide, iodide, or chloride). With external exposure to additional CO, subtle health effects can begin to occur, and exposure to very high levels can result in death.

The public health significance of CO in the air largely results from CO being absorbed readily from the lungs into the bloodstream, there forming a slowly reversible complex with hemoglobin (Hb), known as carboxyhemoglobin (COHb). The presence of significant levels of COHb in the blood causes hypoxia (i.e., reduced availability of oxygen to body tissues). The blood COHb level, therefore, represents a useful physiological marker to predict the potential health effects of CO exposure. The amount of COHb formed is dependent on the CO concentration and duration of exposure, exercise (which increases both the amount of air inhaled and exhaled per unit of time and the pulmonary diffusing capacity for CO), ambient pressure, health status, and the specific metabolism of the exposed individual. The formation of COHb is a reversible process, but, because of tight binding of CO to Hb, the elimination half-time is quite long, varying from 2 to 6.5 h depending on the initial COHb levels. This may lead to accumulation of COHb, and even relatively low inhaled concentrations of CO can produce substantial blood levels of COHb. Fortunately, mechanisms exist in normal, healthy individuals to compensate for the reduction in tissue oxygen caused by increasing levels of COHb. Cardiac output increases and blood vessels dilate to carry more blood so that the tissue can extract adequate amounts of oxygen from the blood. There are several medical conditions, however, that can make an individual more susceptible to the potential adverse effects of low levels of CO, especially during exercise. Occlusive vascular disease may restrict the increase in blood flow to the tissues, chronic obstructive lung disease causes gas-exchange abnormalities that limit the

amount of oxygen that diffuses into the blood, and anemia reduces the oxygen-carrying capacity of the blood. Under any of these conditions, exposure to CO could reduce further the amount of oxygen available to the affected tissues.

The prevailing national ambient air quality standards (NAAQS) for CO of 9 ppm for 8 h and 35 ppm for 1 h (Federal Register, 1994) have been established to prevent adverse health effects in the most sensitive population groups associated with the presence of CO in the ambient air. The term "ambient air" is interpreted to mean outdoor air at ground level where people live and breathe. A great majority of people, however, spend most of their time indoors. A realistic assessment of the health effects from exposure to ambient CO, therefore, must be set in the context of total exposure, a major component of which is indoor exposure.

This chapter provides an overall summary of the key factors presented in Chapters 2 through 6 of the present document that determine what risk ambient CO poses to public health. An effort also is made to qualitatively delineate key factors that contribute to anticipated health risks from ambient CO in special subpopulations that form a significant proportion of the population at large. Risk factors such as age, gender, and pregnancy are discussed, as well as preexisting heart, lung, vascular, and hematologic diseases. Subpopulations at risk because of exposure to ambient CO alone, or combined with other environmental factors are identified. This information will be used by the U.S. Environmental Protection Agency's Office of Air Quality Planning and Standards for development of their staff paper and associated assessments that will help to determine the adequacy of the existing CO NAAQS.

7.2 ENVIRONMENTAL SOURCES

Carbon monoxide comes from both natural and anthropogenic processes. About half of the atmospheric CO is released at the earths's surface from fossil fuel and biomass burning, and the rest is produced naturally in the atmosphere. About 80% of the CO emitted at the surface is from human activities, whereas natural processes account for the remaining 20%. The background concentration of CO in the troposphere influences the abundance of hydroxyl radicals (OH), thus affecting the global cycles of many natural and anthropogenic trace gases such as methane that are removed from the atmosphere by reacting with OH. During the 1980s, global CO concentrations increased at approximately 1% per year. More recent reports, however, show that

global CO concentrations declined rapidly between 1988 and 1993. Since 1993, the downward trend in global CO has leveled off, and it is not clear whether CO will continue to decline or will increase.

7.3 ENVIRONMENTAL CONCENTRATIONS

The annual average CO concentration is about 0.13 ppm at monitoring sites located in the marine boundary layer of the Pacific Ocean in the mid-latitudes of the Northern Hemisphere. These sites are remote from local pollutant sources, and the values obtained at these sites are meant to represent global background values for CO. Because of seasonal variations in the emissions and chemical loss of CO through reaction with OH radicals, mean global background CO levels vary between about 0.09 ppm in summer and about 0.16 ppm in winter. Annual 24-h average CO concentrations obtained at U.S. monitoring sites in rural areas away from metropolitan areas are typically about 0.20 ppm, compared with an annual 24-h average of 1.2 ppm across all monitoring sites in the Aerometric Information Retrieval System network in 1996.

In the United States, ambient air 8-h average CO concentrations monitored from fixed-site stations in metropolitan areas are generally below 9 ppm and have decreased significantly since 1990 when the last CO criteria document was completed (U.S. Environmental Protection Agency, 1991). In the latest year of record, 1997, the annual mean CO concentrations were all less than 9 ppm. However, in spite of the vehicle emission reductions responsible for the decrease in ambient CO, high short-term peak CO concentrations still can occur in certain outdoor locations and situations associated with motor vehicles, for example, riding behind high emitters or in a vehicle with a defective exhaust system. Also, air quality data from fixed-site monitoring stations underestimate the short-term peak CO levels in heavy traffic environments.

Indoor and in-transit concentrations of CO can be significantly different from the typically low ambient CO concentrations. The CO levels in homes without combustion sources are usually lower than 5 ppm. The highest residential concentrations of CO that have been reported in the scientific literature are associated with the use of unvented gas or kerosene space heaters where peak concentrations of CO as high as 50 ppm have been reported. Carbon monoxide concentrations also have exceeded 9 ppm for 8 h in several homes with gas stoves and, in one

case, 35 ppm for 1 h; however, these higher CO concentrations were in homes with older gas ranges that had pilot lights that burn continuously. Newer or remodeled homes have gas ranges with electronic pilot lights. Also, the availability of other cooking appliances (e.g., microwaves, heating plates) has decreased the use of gas ranges in meal preparation.

Average CO concentrations as high as 10 to 12 ppm have been reported in human exposure studies for in-vehicle compartments of moving automobiles. Carbon monoxide concentrations will depend, however, on the season and traffic pattern, and the findings of more recent studies imply that pre-1990 study results are no longer applicable. For example, commuter exposure to motor vehicle exhaust fell from a high of 37 ppm CO for a Los Angeles, CA, study in 1965 to a low of 3 ppm CO for a New Jersey Turnpike study in 1992, and for San Francisco, CA, using the same data collection protocol, typical commuter exposures fell about 50% in the 11-year period from 1980 to 1991, despite a 19% increase in average daily traffic. Carbon monoxide levels in other indoor environments affected by engine exhaust (e.g., parking garages, tunnels) follow similar trends but tend to be higher than in other indoor environments.

Because indoor and outdoor air quality differ substantially, and because people spend much of their time indoors, ambient air quality measurements alone do not provide accurate estimates of personal or population exposure to CO from ambient and nonambient sources. Whereas the ambient monitoring data reflect exposure to ambient sources of CO only, the measurement of CO from personal monitors reflects more accurately the actual total human population exposure to CO.

Occupational 8-h exposure levels are generally below 35 ppm, the recommended occupational exposure limit for CO (Federal Register, 1989; American Conference of Governmental Industrial Hygienists, 1994; Code of Federal Regulations, 1998). Workers exposed to exhaust gases, especially from older vehicles, may have peak exposures over 200 ppm in enclosed spaces.

7.4 CARBOXYHEMOGLOBIN LEVELS IN THE POPULATION

Carbon monoxide diffuses rapidly across the alveolar and capillary membranes and more slowly across the placental membrane. At equilibrium, approximately 95% of the absorbed CO binds with hemoglobin to form COHb that, when elevated above the endogenous level, is a

specific biomarker of CO exposure in blood. The remaining 5% is distributed extravascularly. During continuous exposure to a fixed ambient concentration of CO, the COHb concentration increases rapidly at the onset of exposure, starts to level off after 3 h, and approaches a steady state after 6 to 8 h of exposure. Therefore, an 8-h COHb value would be closely representative of any longer continuous exposures. In real-life situations, the prediction of individual COHb levels is difficult because of large spatial and temporal variations in both indoor and outdoor levels of CO and temporal variations of alveolar ventilation rates. Because COHb measurements are not readily available in the exposed population, mathematical models have been developed to predict COHb levels from known CO exposures under a variety of circumstances (see Figure 7-1).

Evaluation of human CO exposure situations indicates that occupational exposures in some workplaces or exposures in homes with faulty or unvented combustion appliances can exceed 100 ppm CO, often leading to COHb levels of 4 to 5% with 1-h exposure and 10% or more with continued exposure for 8 h or longer (see Table 7-1). Such high exposure levels are encountered much less frequently by the general public under ambient conditions. More frequently, short-term exposures to less than 25 to 50 ppm CO occur among the general population, and, at the low exercise levels usually engaged in under such circumstances, resulting COHb levels typically remain below 2 to 3% among nonsmokers. Those levels can be compared to the physiological baseline for nonsmokers, which is estimated to be in the range of 0.3 to 0.7% COHb. Unfortunately, no new data have become available on the distribution of COHb levels in the U.S. population since large-scale nationwide surveys (e.g., National Health and Nutrition Examination Survey II [Radford and Drizd, 1982]) and human exposure field studies (e.g., Denver, CO, and Washington, DC [Akland et al., 1985]) were conducted in the late 1970s and early 1980s.

The major source of total exposure to CO for smokers comes from active tobacco smoking. Baseline COHb concentrations in smokers average 4%, with a usual range of 3 to 8% for one- to two-packs-per-day smokers, reflecting absorption of CO from inhaled smoke. Carboxyhemoglobin levels as high as 15% have been reported for chain smokers. Exposure to tobacco smoke not only increases COHb concentrations in smokers, but, under some circumstances, it also can affect nonsmokers. In some of the studies cited in this document, neither the smoking habits of the subjects nor their exposure to passive smoking have been taken into account. In addition, as the result of their higher baseline COHb levels, smokers actually

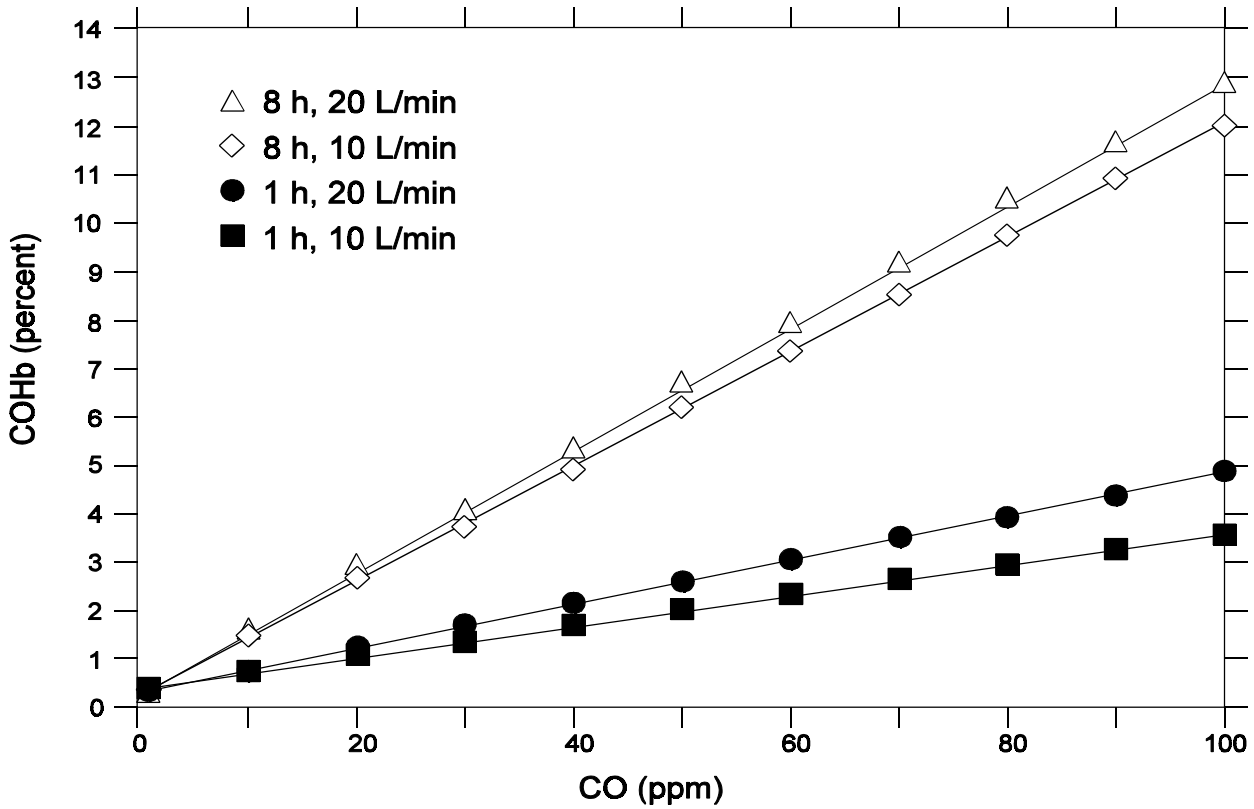

Figure 7-1. Relationship between CO exposure and COHb levels in the blood. Predicted COHb levels resulting from 1- and 8-h exposures to CO at rest (alveolar ventilation rate of 10 L/min) and with light exercise (20 L/min) are based on the Coburn-Forster-Kane equation, using the following assumed parameters for nonsmoking adults: altitude = 0 ft, initial COHb level = 0.5%, Haldane coefficient = 218, blood volume = 5.5 L, Hb level = 15 g/100 mL, lung diffusivity = 30 mL/torr/min, and endogenous rate of CO production = 0.007 mL/min.

may be exhaling more CO into the air than they are inhaling from the ambient environment when they are not smoking. Smokers may even show an adaptive response to the elevated COHb levels, as evidenced by increased red blood cell volumes or reduced plasma volumes. As a consequence, it is not clear if incremental increases in COHb caused by typical ambient exposures actually would be additive to the chronically elevated COHb levels resulting from tobacco smoke.

TABLE 7-1. PREDICTED CARBON MONOXIDE EXPOSURES IN THE POPULATION

	Predicted COHb Response[a,b]	
Exposure Conditions	1 h, Light Exercise	8 h, Light Exercise
Nonsmoking adults exposed to 25- to 50-ppm peak CO levels	2 to 3%	4 to 7%
Workplace or home with faulty combustion appliances at ≈100 ppm	4 to 5%	12 to 13%

[a] See Figure 7-1 for details on the Coburn-Forster-Kane equation (Coburn et al., 1965).
[b] Light exercise at 20 L/min.

7.5 MECHANISMS OF CARBON MONOXIDE TOXICITY

A clear mechanism of action underlying the potentially toxic effects of low-level CO exposure is the decreased oxygen-carrying capacity of blood and subsequent interference with oxygen release at the tissue level that is caused by the binding of CO with Hb, producing COHb. The resulting impaired delivery of oxygen can interfere with cellular respiration and cause tissue hypoxia. The critical tissues (e.g., brain, heart) of healthy subjects have intrinsic physiologic mechanisms (e.g., increased blood flow and oxygen extraction) to compensate for CO-induced hypoxia. In compromised subjects, or as CO levels increase, these compensatory mechanisms may be overwhelmed, and tissue hypoxia, combined with impaired tissue perfusion and hypotension induced by hypoxia, may cause identifiable health effects.

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. Hemoprotein binding to CO would be favored 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 hemoprotein to be inhibited functionally at relevant levels of COHb is Mb, found predominantly in heart and skeletal muscle. The physiological significance of CO uptake by Mb is uncertain, but sufficient concentrations of carboxymyoglobin potentially could limit maximal oxygen uptake of

exercising muscle. There is also some evidence that binding of CO to intracellular hemoprotein may secondarily precipitate oxidative stress. The health risks associated with this mechanism have not been clearly established.

7.6 HEALTH EFFECTS OF CARBON MONOXIDE

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 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 chapter, to unconsciousness and death following acute exposure to high concentrations of CO. 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 reported to be the cause of more than half of the fatal poisonings that are reported in many countries. Fatal cases also are grossly under-reported or misdiagnosed by medical professionals. Therefore, the precise number of individuals who have suffered from CO intoxication is not known. The symptoms, signs, and prognosis of acute CO poisoning correlate poorly with the level of COHb measured at the time of hospital admission; however, because CO poisoning is a diagnosis frequently overlooked, the importance of the early symptoms (headache, dizziness, weakness, nausea, confusion, disorientation, and visual disturbances) has to be emphasized, especially if they recur with a certain periodicity or in certain circumstances. Complications occur frequently in CO poisoning. Immediate death is most likely cardiac in origin because myocardial tissues are highly sensitive to the hypoxic effects of CO. Severe poisoning results in marked hypotension and lethal arrhythmias and other electrocardiographic changes. Pulmonary edema is a fairly common feature. Neurological manifestation of acute CO poisoning includes disorientation, confusion, and coma. Perhaps the most insidious effect of CO poisoning is the delayed development of neuropsychiatric impairment within 1 to 3 weeks and the neurobehavioural consequences, especially in children. Carbon monoxide poisoning during pregnancy results in high risk for the mother by increasing the short-term complication rate and, for the fetus, by causing fetal death, developmental disorders, and chronic cerebral lesions.

The health effects from exposure to low CO concentrations, such as the levels found in ambient air, are far more subtle and considerably less threatening than those occurring in frank poisoning from high CO concentrations. Effects of exposure to excessive ambient air levels of CO are described here in terms of COHb levels; however, the lowest-observed-effect level depends on the method used for analysis of COHb. Gas chromatography (GC) is the method of choice for measuring COHb at saturation levels ≤5% because of the large variability and potential high bias of optical methods such as CO-Oximetry (CO-Ox). Health effects are possible in sensitive nonsmoking individuals exposed to ambient CO if peak concentrations are high enough or of sufficient duration to raise the COHb saturation to critical levels above their physiological baseline of 0.3 to 0.7% (GC). At 2.3% COHb (GC) or higher, some (predominantly young and healthy) individuals may experience decreases in maximal exercise duration. At 2.4% COHb (GC) or higher, patients with coronary artery disease (CAD) experience reduced exercise time before the onset of acute myocardial ischemia, which is detectable either by symptoms (angina) or by electrocardiographic changes (ST depression). At 5% COHb (CO-Ox) or higher, some healthy individuals may experience impaired psychomotor performance; however, there is large variability in response across studies that tested the same concentrations of CO, and later work indicates that significant behavioral impairments in healthy individuals should not be expected until COHb levels exceed 20% (CO-Ox). At 6% COHb (CO-Ox) or higher, some people with CAD and high levels of baseline ectopy (chronic arrhythmia) may experience an increase in the number and complexity of exercise-related arrhythmias.

Epidemiologic studies have associated elevated ambient CO levels with increased incidence of cardiovascular illness in the population, but overall findings are inconclusive, possibly because personal exposures may not be represented adequately by the CO concentrations measured by fixed-site monitors. For example, exposure to cigarette smoke or to combustion exhaust gases from small engines and recreational vehicles typically raises COHb levels much higher than levels resulting from mean ambient CO exposures, and, for most people, exposures to indoor sources of CO will exceed controllable outdoor exposures.

Health effects are more likely to occur, therefore, in individuals who are physiologically stressed, either by exercise or by medical conditions that can make them more susceptible to low

levels of CO. The specific subpopulations potentially at risk from exposure to ambient CO are discussed next.

7.7 SUBPOPULATIONS POTENTIALLY AT RISK FROM EXPOSURE TO AMBIENT CARBON MONOXIDE

Most of the known quantifiable concentration-response relationships regarding the human health effects of CO come from two carefully defined population groups: (1) healthy, predominantly male, young adults and (2) patients with diagnosed CAD. On the basis of the 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 of experiencing the health effects (i.e., decreased exercise duration because of exacerbation of cardiovascular symptoms) of concern at ambient or near-ambient CO-exposure concentrations that result in COHb levels as low as 3%. 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, primarily would be a concern for athletes, rather than for people performing everyday activities.

It can be hypothesized, however, from both clinical and theoretical work and from experimental research in laboratory animals, that certain other groups in the population are at potential risk to exposure from CO. Probable risk groups that have not been studied adequately, but that could be expected to be susceptible to CO because of gender differences, aging, or preexisting disease or because of the use of medications or alterations in their environment include fetuses and young infants; pregnant women; the elderly, especially those with compromised cardiovascular function; individuals with partially obstructed coronary arteries, but not yet manifesting overt symptomatology of CAD; those with congestive heart failure (CHF); people with peripheral vascular or cerebrovascular disease; individuals with hematological diseases (e.g., anemia) that affect oxygen-carrying capacity or transport in the blood; individuals with genetically unusual forms of hemoglobin associated with reduced oxygen-carrying capacity; those with chronic obstructive pulmonary disease; people using medicinal or recreational drugs having central nervous system depressant properties; individuals exposed to other chemical

substances (e.g., methylene chloride) that increase endogenous formation of CO; and individuals who have not adapted to high altitude and are exposed to a combination of high altitude and CO. Little empirical evidence is available by which to specify health effects associated with ambient or near-ambient CO exposures in these probable risk groups.

7.7.1 Age, Gender, and Pregnancy 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 because of differences in uptake and elimination of CO from fetal Hb. Because the fetus normally has a lower oxygen tension in the blood than does the mother, a drop in fetal oxygen tension resulting from the presence of COHb could have potentially serious effects. The newborn infant, with a comparatively high rate of oxygen consumption and lower oxygen-transport capacity for Hb than those of most adults, also would be potentially susceptible to the hypoxic effects of increased COHb. Data from laboratory animal studies on the developmental toxicity of CO suggest that prolonged exposure to high levels (>60 ppm) of CO during gestation may produce a reduction in birth weight, cardiomegaly, and delayed behavioral development. Human data are scant and more difficult to evaluate, and further research is warranted. Additional studies are needed 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 well understood.

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 an expanded blood volume associated with hemodilution and thus are anemic because of the disproportionate increase in plasma volume compared with erythrocyte volume. This group may be at increased risk and, therefore, should be studied to evaluate the effects of ambient CO exposure and elevated COHb levels.

Changes in metabolism with age may make the aging population particularly susceptible to the effects of CO. Maximal oxygen uptake declines with age. The rate of decline varies widely

among individuals because of the many confounding factors such as heredity, changes in body mass and composition, and level of fitness.

7.7.2 Preexisting Disease as Risk Factors

7.7.2.1 Subjects with Coronary Heart Disease

Coronary heart disease (CHD) remains the major cause of death and disability in industrialized societies. In the United States, CHD is the single largest killer of males and females, causing a total of 481,000 deaths in 1995 (American Heart Association, 1997), two-thirds of all deaths from heart disease (U.S. Centers for Disease Control and Prevention, 1997) and about half of all deaths from cardiovascular disease (see Figure 7-2). Almost 14 million Americans have a history of this disease, with much greater prevalence in both males and females at increasing ages (see Figure 7-3). Individuals with CHD have myocardial ischemia, which occurs when the heart muscle receives insufficient oxygen delivered by the blood. For some, exercise-induced angina pectoris (chest pain) can occur. In all patients with diagnosed CAD, however, the predominant type of ischemia, as identified by ST segment depression, is asymptomatic (i.e., silent). In other words, patients who experience angina typically have additional ischemic episodes that are asymptomatic. Unfortunately, some individuals in the population have coronary artery disease but are totally asymptomatic and, therefore, do not know they are potentially at risk. It has been estimated that 5% of middle-aged men show signs of ischemia during an exercise stress test; a significant number of these men will have angiographic evidence of CAD. Persons with both asymptomatic and symptomatic CAD have a limited coronary flow reserve and, therefore, will be sensitive to a decrease in oxygen-carrying capacity induced by CO exposure. In addition, CO might exert a direct effect on vascular smooth muscle, particularly in those individuals with an already damaged vascular endothelium.

7.7.2.2 Subjects with Congestive Heart Failure

Congestive heart failure is a major and growing public health problem. Almost 5 million Americans have CHF, and about 400,000 new cases occur each year (American Heart Association, 1997). Because the prevalence of heart failure is known to increase with age,

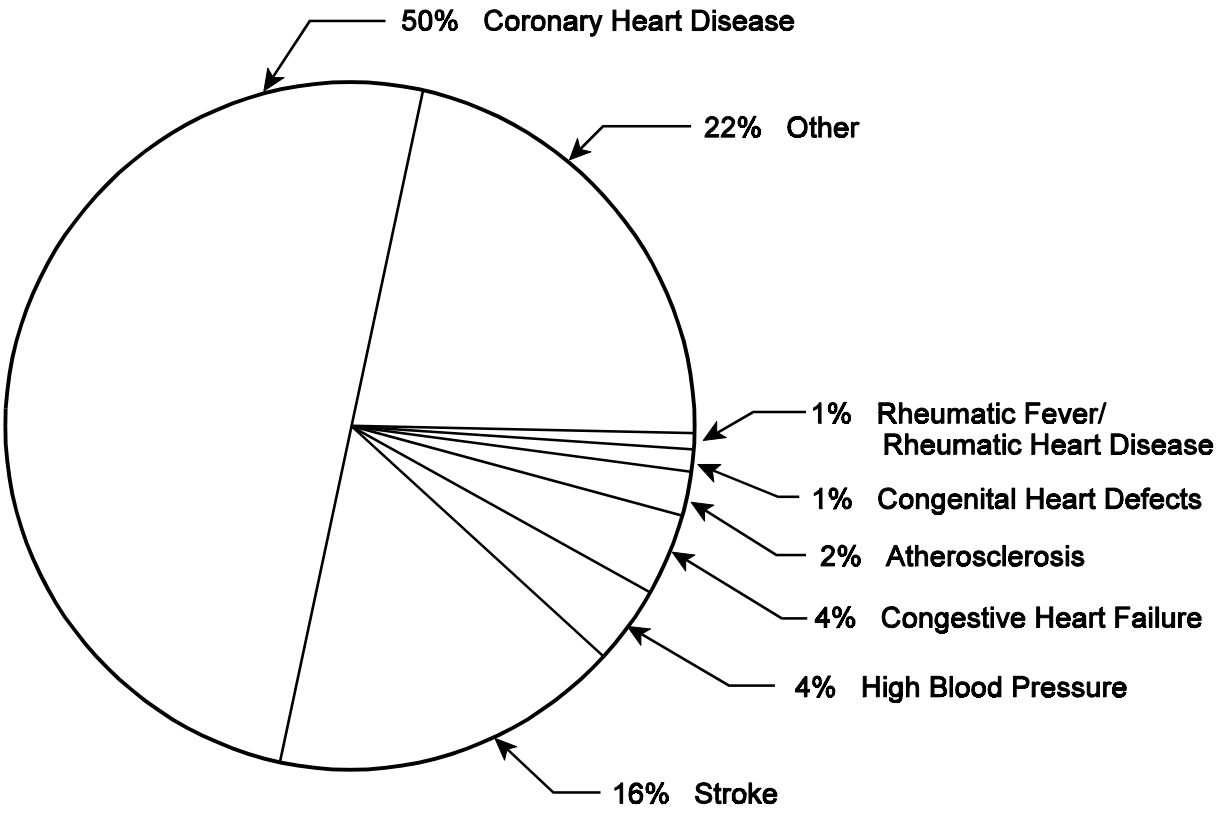

Figure 7-2. Percentage breakdown of deaths from cardiovascular diseases in the United States (1996 mortality statistics).

Source: American Heart Association (1997); National Center for Health Statistics (1995).

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.

Patients with CHF have a markedly reduced circulatory capacity and, therefore, may be very sensitive to limitations in oxygen-carrying capacity. Thus, exposure to CO will reduce their exercise capacity and, especially because of its arrhythmogenic activity, may have serious consequences. The etiology of heart failure is diverse, but the most common secondary conditions observed in hospitalized patients are coronary heart disease, hypertension, chronic obstructive pulmonary disease, diabetes, and cardiomyopathy (Croft et al., 1997). Many heart failure patients with CAD, therefore, might be even more sensitive to CO exposure.

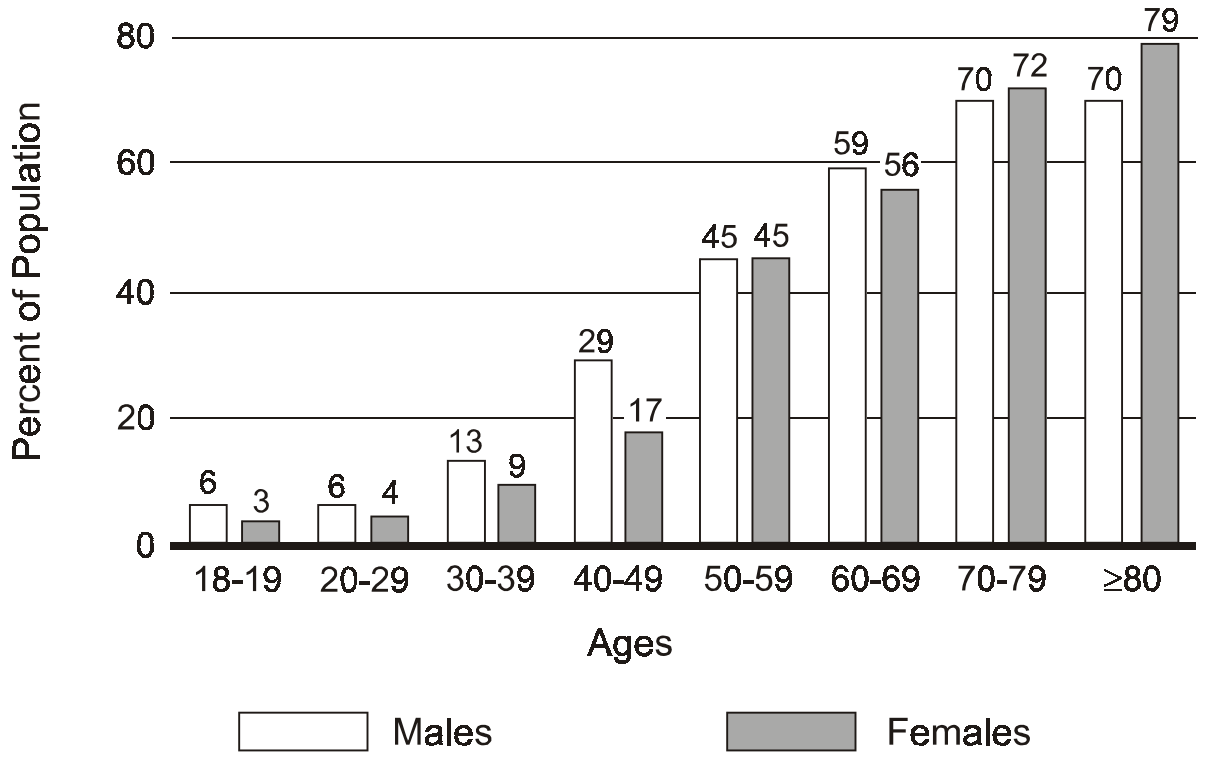

Figure 7-3. Estimated prevalence of cardiovascular disease by age and sex for the United States, 1988 to 1991.

Source: American Heart Association (1997); Collins (1997); Adams and Marano (1995).

7.7.2.3 Subjects with Other Vascular Diseases

Vascular disease, including cerebrovascular disease, is present in both the male and female population and is more prevalent above 65 years of age because of the increasing likelihood of adverse effects from atherosclerosis or thickening of the artery walls. Atherosclerosis is a leading cause of many deaths from heart attack and stroke (American Heart Association, 1997). In fact, when considered separately from other cardiovascular diseases, stroke ranks as the third leading cause of death behind heart disease and cancer (U.S. Centers for Disease Control and Prevention, 1997). Vascular diseases are associated with a limited blood flow capacity and, therefore, patients with these diseases should be sensitive to CO exposure. It is not clear, however, how low levels of exposure to CO will affect these individuals. For example, only one

study reviewed in the previous criteria document (U.S. Environmental Protection Agency, 1991), 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 individuals with vascular disease to CO.

7.7.2.4 Subjects with Anemia and Other Hematologic Disorders

Clinically diagnosed low values of Hb, characterized as anemia, are a relatively prevalent condition throughout the world. If the anemia is mild to moderate, an inactive person is often asymptomatic. However, because of the limitation in the oxygen-carrying capacity resulting from the low Hb values, an anemic person should be more sensitive to low-level CO exposure than would be a person with normal Hb levels. If anemia is combined with other prevalent diseases, such as CAD, the individual also will be at an increased risk to CO exposure. Anemia is more prevalent in women and in the elderly, two already potentially high-risk groups. An anemic person also will be more sensitive to the combination of CO exposure and high altitude.

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 Hb in the blood. For example, in sickle-cell disease, the average lifespan of red blood cells with abnormal hemoglobin S is 12 days compared to an average of 88 days in healthy individuals with normal Hb. As a result, baseline COHb levels can be as high as 4%. In subjects with Hb Zurich, where affinity for CO is 65 times that of normal Hb, COHb levels range from 4 to 7%. Presumably, exogenous exposure to CO, in conjunction with higher endogenous CO levels, could result in critical levels of COHb. However, it is not known how ambient or near-ambient levels of CO would affect individuals with these disorders.

7.7.2.5 Subjects with Obstructive Lung Disease

Chronic obstructive pulmonary disease (COPD) is a prevalent disease especially among smokers, and 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.

As a consequence, individuals with hypoxia resulting from COPD such as bronchitis and emphysema may be susceptible to CO during submaximal exercise typical of normal daily activity. In spite of their symptoms, many of them (≈30%) continue to smoke and already may have COHb levels of 4 to 8%. The COPD patients with hypoxia are also more likely to have a progression of the disease resulting in severe pulmonary insufficiency, pulmonary hypertension, and right heart failure.

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 experience hypoxia during attacks and be susceptible to CO. It is not known, however, how exposure to CO actually would affect these individuals.

7.7.3 Subpopulations at Risk from Combined Exposure to Carbon Monoxide and Other Chemical Substances

7.7.3.1 Interactions with Drugs

There is an almost complete absence of data on the possible toxic consequences of combined CO exposure and drug use. Because of the diverse classes of both cardiovascular and psychoactive drugs, and the many other classes of drugs that have not been examined at all, it must be concluded that this is an area of concern that is difficult to meaningfully address at the present time.

7.7.3.2 Interactions with Other Chemical Substances in the Environment

Besides direct exposure to ambient 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, and some of its derivatives that could result in potentially harmful levels of COHb in individuals at risk.

7.7.4 Subpopulations Exposed to Carbon Monoxide at High Altitudes

For patients with CAD, 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 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 may be unusually sensitive to the added effects of atmospheric CO.

It is important to distinguish between the long-term resident of high altitude and the newly arrived visitor from low altitude. Specifically, the visitor will be more hypoxemic than the fully adapted resident. The combination of high altitude with CO will pose the greatest risk to persons newly arrived at high altitude who have underlying cardiopulmonary disease, particularly because they are usually older individuals.

It is known that low birth weights occur both in infants born at altitudes above 6,000 ft and in infants born near sea level, whose mothers had elevated COHb levels because of cigarette smoking. It also has been shown that COHb levels in smokers at high altitude are higher than those in smokers at sea level. Although it is probable that the combination of hypoxic hypoxia and hypoxia resulting from ambient exposure to CO could reduce birth weight further at high altitude and possibly modify future development, no data are available to evaluate this hypothesis.

7.8 CONCLUSIONS

Ambient CO concentrations measured at central, fixed-site monitors in metropolitan areas of the United States have decreased significantly since the late 1980s, when air quality was reviewed in the previous criteria document (U.S. Environmental Protection Agency, 1991). The decline in ambient CO follows approximately the decline in motor vehicle emissions. Exposure to tobacco smoke, to CO indoors from unvented or partially vented combustion appliances, and to CO from uncontrolled outdoor sources (e.g, small combustion engines) may represent a significant portion of an individual's total CO exposure. Unfortunately, there is not a good estimate of CO exposure distribution for the current population.

Health assessment information provided in the present document supports and substantiates the conclusions drawn in the previous document. Young, healthy individuals are not at immediate risk from ambient CO exposure because only limitations at maximal exercise performance have been demonstrated at <5% COHb saturation levels. Effects have not been demonstrated on heathy individuals performing submaximal exercise that is more germane to typical daily human activity. The greater concern regarding the effect of ambient exposure has, therefore, focused on subpopulations who are particularly susceptible to CO. The air quality criteria used to support the existing CO NAAQS for the general population were primarily those data obtained from the exposure to CO of nonsmoking subjects with CAD while exercising. The principal cause of CO-induced effects at low levels of ambient exposure is still thought to be increased COHb formation and the subsequent impaired delivery of oxygen to critical tissues. Available health effects information on the subpopulation with CAD has identified adverse effects with CO exposures, leading to COHb levels of 2.4% (GC) or higher.

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APPENDIX A

Abbreviations and Acronyms

AC	Alternating current
AER	Air exchange rate
AIRS	Aerometric Information Retrieval System
AQCD	Air quality criteria document
BTPS	Body temperature and pressure, saturated with water vapor at 37 °C
C	Carbon
CAA	Clean Air Act
CAD	Coronary artery disease
CaO_2	Arterial oxygen content
CARB	California Air Resources Board
CAS	Children's Activity Survey
CASAC	Clean Air Scientific Advisory Committee
CFD	Cumulative frequency distribution
CFK	Coburn-Foster-Kane
cGMP	Cyclic guanosine monophosphate
CH_3	Methyl radical
CH_4	Methane
CH_3Br	Methyl bromide
CH_3CCl_3	Methyl chloroform
CH_3CHO	Acetaldehyde
CH_3Cl	Methyl chloride
CH_3CO	Acetyl radical
CH_2O	Formaldehyde
CH_3O_2	Methyl peroxy radical
CH_3OOH	Methyl hydroperoxide

1	CHD	Coronary heart disease
2	CHF	Congestive heart failure
3	CI	Confidence interval
4	CMAQ	Congestion Management and Air Quality
5	$CMRO_2$	Cerebral metabolic rate for oxygen
6	CMSA	Consolidated metropolitan statistical area
7	CO	Carbon monoxide
8	CO_2	Carbon dioxide
9	COH	Coefficient of haze
10	COHb	Carboxyhemoglobin
11	COMb	Carboxymyoglobin
12	CO-Ox	CO-Oximetry or CO-Oximeter
13	COPD	Chronic obstructive pulmonary disease
14	CPSC	Consumer Product Safety Commission
15	CRM	Certified Reference Material
16	CTM	Chemical Transport Model
17	CVD	Cardiovascular disease
18	D_LCO	Diffusing capacity for carbon monoxide
19	ECG	Electrocardiogram
20	ED	Effective dose for a specific decrement in function
21	EMFAC7	Emissions Factor 7
22	EPA	U.S. Environmental Protection Agency
23	ETS	Environmental tobacco smoke
24	FAF	Forced-air furnace
25	F_ICO	Fractional concentration of carbon monoxide in inhaled air
26	FDA	Food and Drug Administration
27	FID	Flame ionization detection or detector
28	GAM	General additive model

1	GC	Gas chromatography or gas chromatograph
2	GFC	Gas filter correlation
3	GLM	General linear model
4	hυ	Photon
5	H	Atomic hydrogen
6	H_2	Molecular hydrogen
7	Hb	Hemoglobin
8	HCN	Hydrogen cyanide
9	HCO	Formyl radical
10	HO	Heme oxygenase
11	HO_2	Hydroperoxy radical
12	HO_x	Microsomal heme oxygenase
13	H_2O_2	Hydrogen peroxide
14	HOCO	Carboxyl radical
15	IR	Infrared
16	LOEL	Lowest-observed-effect level
17	M	Haldane coefficient
18	M	Mediator
19	Mb	Myoglobin
20	MDL	Minimum detection limit
21	MI	Myocardial infarction
22	MSA	Metropolitan Statistical Area
23	n	Number
24	N	North
25	N_2	Molecular nitrogen
26	NAAQS	National Ambient Air Quality Standards
27	NAMS	National Air Monitoring Station
28	NASA	National Aeronautics and Space Administration

1	$Ni(CO)_4$	Nickel tetracarbonyl
2	NDIR	Nondispersive infrared
3	NEM	National Ambient Air Quality Standards Exposure Model
4	NHANES	National Health and Nutrition Examination Survey
5	NIST	National Institute of Standards and Technology
6	NMDA	N-methyl-D-aspartate
7	NMHC	Non-methane hydrocarbon
8	NMi	Nederland Meetinstitut (i.e., Dutch Bureau of Standards)
9	NMOC	Non-methane organic compounds
10	NO	Nitric oxide
11	$^{\bullet}NO$	Nitric oxide free radical
12	NO_2	Nitrogen dioxide
13	NO_x	Nitrogen oxides
14	NOAA/CMDL	National Oceanic and Atmospheric Administration Climate Monitoring Diagnostics Laboratory
15	NTRM	National Institute of Standards and Technology Traceable Reference Material
16	O	Atomic oxygen
17	O_2	Molecular oxygen
18	O_3	Ozone
19	OGI	Oregon Graduate Institute
20	OH	Hydroxyl radical
21	O_2Hb	Oxyhemoglobin
22	p	Probability
23	P_{atm}	Pressure in atmospheres
24	P_B	Barometric pressure
25	PAH	Polyaromatic hydrocarbon
26	PAN	Peroxyacetly nitrate
27	PCO	Partial pressure of carbon monoxide

1	PEM	Personal exposure monitor
2	PM	Particulate matter
3	$PM_{2.5}$	Particulate matter with an aerodynamic diameter ≤2.5 µm
4	PM_{10}	Particulate matter with an aerodynamic diameter ≤10 µm
5	pNEM	Probabilistic National Ambient Air Quality Standards Exposure Model
6	P_IO_2	Partial pressure of oxygen in humidified inspired air
7	PO_2	Partial pressure of oxygen
8	PRM	Primary Reference Material
9	$\dot{Q}$	Perfusion
10	r	Linear regression correlation coefficient
11	R^2	Multiple correlation coefficient
12	RBC	Red blood cell
13	RER	Respiratory exchange ratio
14	RR	Relative risk
15	S	South
16	SD	Standard deviation
17	SHAPE	Simulation of Human Activity and Pollutant Exposure
18	SIDS	Sudden infant death syndrome
19	SLAMS	State and Local Air Monitoring Station
20	SO_2	Sulfur dioxide
21	SRM	Standard Reference Materials
22	ST	Segment of the electrocardiogram
23	STPD	Standard temperature and pressure, dry
24	TCM	Transportation Control Measure
25	TDL	Tunable diode laser
26	TDLS	Tunable diode laser spectroscopy
27	Tg	Teragram
28	TSP	Total suspended particulate

TWA	Time-weighted average
UHC	Unburned hydrocarbon
UV	Ultraviolet
UVGSH	Unvented gas space heater
$\dot{V}_A$	Alveolar ventilation
V_D	Volume of physiological dead space
VMT	Vehicle miles of travel
W/F	Wall or floor furnace