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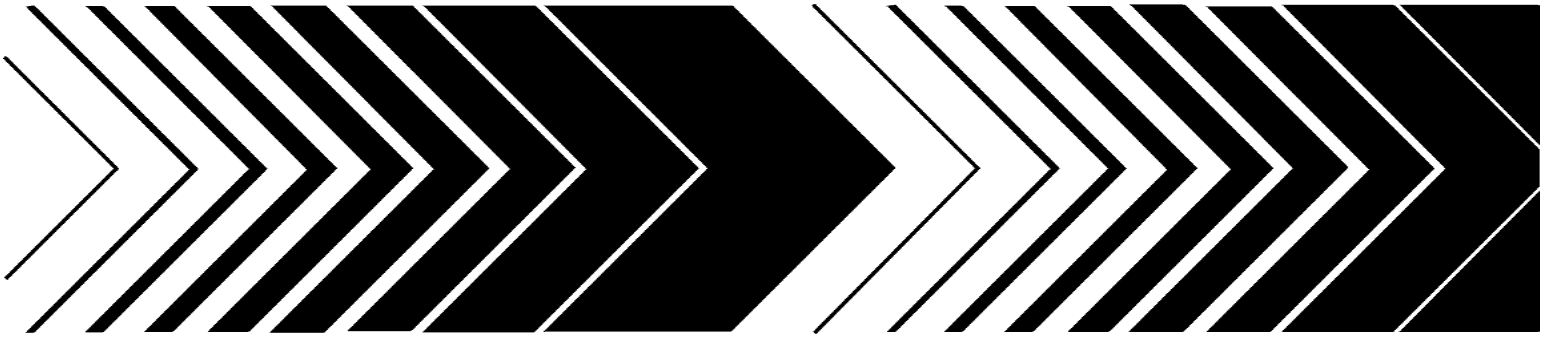
Air Quality Criteria for Carbon Monoxide



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Air Quality Criteria for Carbon Monoxide

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

Disclaimer

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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 1999.

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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AIR QUALITY CRITERIA FOR CARBON MONOXIDE

Executive Summary

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 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 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 exposure of human populations to ambient CO.

- 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 optical transmission technique, the technique on which the U.S. Environmental Protection Agency-designated analytical reference methods are based. One category of nondispersive infrared 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 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 not equivalent to compliance monitoring methods but are useful for personal exposure studies and for measuring CO concentrations in indoor, outdoor, and in-transit microenvironments.
- Blood carboxyhemoglobin (COHb) level and CO concentration in exhaled breath are biological indicators of exogenous CO exposure and endogenous CO production. 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 levels (<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 for error in the estimation of COHb than does the direct measurement of COHb.

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 participates in the formation of 20 to 40% of the ozone found 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 the CO budget is understood.
- Global background CO concentrations average about 120 and 40 ppb in remote marine 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 from 1993 through 1997.
- 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 is 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.

- 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 at least one urban air shed, CO was found to participate in the formation of 10 to 20% of the ozone found there.
- The nationwide average annual second-highest 8-h ambient CO concentration decreased from 10 ppm in 1978 to 4 ppm in 1997.
- On- and nonroad mobile sources account for approximately 80% of the 1997 nationwide emissions inventory for CO. Declines in ambient CO levels in the United States follow approximately the decline in motor vehicle emissions of CO. However, the relative importance of nonroad sources has increased over the past decade from 12.7% of total emissions in 1988 to 19.2% in 1997.
- There were 41 exceedances of the 8-h NAAQS for CO at 12 U.S. monitoring sites in 1997. These sites, in descending order, were located in Calexico and Los Angeles-Long Beach, CA; Fairbanks, AK; Steubenville, OH; El Paso, TX; and Phoenix, AZ.
- Median CO concentrations in the geographically diverse urban areas of Denver, CO; Los Angeles, New York, NY; Phoenix; and Fairbanks, 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 four of the five air sheds was highly heterogeneous. For instance, the average correlation between time series of weekday 8-h average maximum CO concentrations at different monitoring sites in the Denver, New York, Los Angeles, and Phoenix urban areas ranged from 0.4 to 0.5. The corresponding average between-site correlation was 0.8 in Fairbanks.

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 properly installed vented combustion appliances (e.g., gas and oil furnaces, gas water heaters and dryers) will not contaminate indoor air unless the units or venting systems are malfunctioning.
- The major sources of CO in residential microenvironments are tobacco smoke, vehicle start-up and idling in attached garages, and unvented or improperly installed or malfunctioning vented combustion appliances. Factors affecting emissions of CO in the home include the type of source (e.g., gas appliances, woodstoves and fireplaces, tobacco products), appliance design, 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 unvented space heaters as the primary source of heat.
- Woodstoves 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. For example, it is possible for cigar smokers to raise indoor CO concentrations to more than 9 ppm above ambient levels measured outside.

Population Exposure

The reduction in automotive emissions brought about by the Clean Air Act have reduced in-traffic CO exposures and traffic-related ambient CO concentrations well below those measured in the 1970s and 1980s. Chapter 4 describes the reduction over the past decade in human exposures to CO brought about by the reduction in automotive emissions of CO. However, people still are exposed to CO at concentration levels above the NAAQS in areas of high traffic density, and in indoor locations where tobacco is smoked and where combustion devices (e.g., stoves, heaters) are not adequately vented.

- Fixed-site monitors often are used in urban areas to estimate 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.
- Neighborhood scale, fixed-site ambient CO monitoring may provide a reasonable estimate of the average CO exposures for people who live nearby and 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 Clean Air Act 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 Clean Air Act (e.g., recreational vehicles, garages, 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).
- Current 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.

- A clear mechanism of action underlying the 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 hemoglobin, 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 systemic hypotension induced by hypoxia, may cause identifiable health effects.
- Carbon monoxide is produced endogenously through heme degradation; metabolism of drugs; and degradation of unsaturated fatty acids, inhaled solvents, and other xenobiotics. High altitude and many medical disorders, especially anemias and inflammatory lung diseases, also may increase endogenous levels of CO.
- The amount of COHb formed from exogenous exposure is dependent on the CO concentration and duration of exposure, minute ventilation, lung diffusion capacity, and ambient pressure, as well as on 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 hemoglobin, 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 still is considered the best all-around model for COHb prediction.
- Intracellular binding of CO to hemoproteins, particularly myoglobin 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 myoglobin is not well understood.
- New investigations have expanded knowledge of the physiological effects of CO in two areas. First, there is a growing recognition that CO may play a role in normal neurotransmission and 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 roles they may have in pathophysiology are not yet 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 known indicators 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 (<5%) COHb levels.

- 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 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 clinical 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 beat) has been observed at ≥6% COHb (CO-Ox) in some people with coronary artery disease and a high level of baseline ectopy (a chronic arrhythmia) that may present increased risk of sudden death.
- Some recent epidemiology studies are suggestive of community average ambient CO variations being positively associated with fluctuations of indicators (e.g., cardiac-related hospital admissions) of heart disease exacerbation. However, these findings are not considered conclusive because of questions regarding (a) internal inconsistencies and coherence of the reported results within and across studies, (b) the representativeness of the average ambient CO levels of spatially heterogenous ambient CO values derived from fixed monitoring sites or of personal exposures that often include nonambient CO, and (c) the biologic implausibility of any harmful effects occurring with the very small changes in COHb levels (from near 0 up to about 1.0%) over typical baseline levels (about 0.5%) that would be expected with the low average ambient CO levels (< 5.0 ppm, 1-h daily max) evaluated in the epidemiology studies.
- Some epidemiologic studies also suggest associations of short-term ambient CO exposure with 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, and the possibility that CO is acting as a marker for other combustion-related pollutants cannot be ruled out.
- Laboratory animal studies indicate that acute CO poisoning can affect the growth and function of the developing fetus. Epidemiologic studies show a limited association between subchronic ambient CO exposure and low birth weight; however, these studies are not conclusive.
- 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%.
- Ambient levels of CO are not known to have any direct effects on lung tissue. Observed epidemiologic associations of short-term ambient CO levels with daily respiratory illness frequency cannot yet be interpreted with confidence.
- Carbon monoxide has the potential to interact with other stressors. These include visitation to high altitudes, especially for patients with coronary artery disease; use of psychoactive drugs or alcohol; use of specific medications, especially nitric oxide and calcium channel blockers; prolonged exposure to heat; and 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 the 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.

CHAPTER 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 1999.

Carbon monoxide, a trace constituent of the troposphere, is produced both by 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, may 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 it 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 the NAAQS. Section 108 (U.S. Code, 1991) directs the Administrator of EPA to identify and issue air quality criteria for pollutants that reasonably may 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 18,1980, 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.

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).

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 CO NAAQS and rescinding the secondary CO NAAQS.

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 CAA requirements, EPA's National Center for Environmental Assessment again periodically reviewed and revised the criteria for CO, as presented in this document.

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

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., lawn equipment, woodstoves, 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 Standard

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 $\geq$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 (acute) 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 109(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 key scientific issues that are addressed in this 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 this 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. The term “transportation” includes both onroad and nonroad sources. Onroad sources consist of automobiles, trucks, and buses. Nonroad sources consist of categories such as trains; aircraft; boats and ships; and lawn, construction, recreational, logging, and agricultural equipment (see Section 3.3). 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.

There are a number of ways to express the amount of a substance in the atmosphere. Perhaps the most commonly used measure is concentration, which is the amount, or mass, of a substance in a given volume divided by that volume (e.g., moles per cubic meter in International System of Units [SI]). Often in the literature, however, quantities of gaseous substances are expressed as volume mixing ratios, such as parts per million or parts per billion. These terms are technically not "concentrations", but rather refer properly to the molar mixing ratio of a substance (equivalent to volumetric mixing ratio for an ideal gas), which is the ratio of the concentration of a substance to the concentration of all gaseous components in a given air volume (both in moles per cubic meter) (Seinfeld and Pandis, 1998). Thus, mixing ratio is a mole fraction that in SI units should be expressed as micromoles per mole for parts per million, and nanomoles per mole for parts per billion. Throughout this document, however, mixing ratio will be referred to as concentration of CO in parts per million or parts per billion because these terms have been extensively referred to in the human exposure, toxicological, and epidemiological literature and as the basis for CO compliance monitoring for the NAAQS.

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 CO exposures are generally higher than ambient CO concentrations and often do not have a significant positive correlation when compared to ambient CO concentrations measured 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. The reader should note, however, that such exposure estimates are affected by the time interval between peak CO exposure and blood sampling and by the use of any supplemental oxygen therapy. It also has been shown 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 (LOEL) for CO. Gas chromatography (GC) is regarded as more accurate than CO-Ox for measuring the lower COHb levels.

1.4.8 Mechanisms of Action

The principle cause of CO toxicity is tissue hypoxia caused by CO binding to hemoglobin (Hb) and failure of vasodilation to compensate for the reduced oxygen delivery. 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 Hb to be inhibited functionally at relevant levels of COHb is myoglobin, found in heart and skeletal muscle. The extent of effects caused by CO molecules in solution needs to be evaluated in relation to typical ambient CO exposures in the population. Other mechanisms of interest, which have not yet been demonstrated to occur at ambient CO levels, are cytotoxic effects (e.g., vasomotor control, free oxygen radicals) independent of impaired oxygen delivery.

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 duration is reduced in young, healthy, nonsmoking individuals at COHb levels as low as 2.3% (GC), but this effect is small and would be of concern primarily 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 2.4% (GC). 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. 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 high-level 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 LOEL for developmental effects. Studies relating human CO exposures from ambient sources or cigarette smoking to reduced birth weight are potentially relevant because of the risk for developmental disorders; however, many of these studies have not considered all sources of CO and may be confounded by other variables (e.g., smoke components, maternal behavior, nutrition, genetics). Nevertheless, some health professionals have considered this evidence sufficient to identify pregnant women, and the developing fetuses, 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 need to be considered.

1.4.10 Carbon Monoxide Interaction with Drugs

There remains little direct information on the possible enhancement of CO toxicity by concomitant illegal and prescription 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, heart disease 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 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.

Among early steps used in development of this revised document was the convening of symposia or workshops to identify key scientific issues and to focus on selection of material to 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.

First, 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. 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 published symposium papers presented are included by reference in this revised criteria document.

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

Next, EPA convened on September 17 and 18, 1998, a public peer-review workshop to define further key issues, to review early drafts of the criteria document chapters, and to ascertain and discuss any pertinent new literature. The 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 then were incorporated into the First External Review Draft of the document, which was released for public comment and was reviewed by CASAC on June 9, 1999. Necessary revisions were made in response to public comments and CASAC recommendations before a Second External Review Draft of the criteria document was released in October 1999 and closure was reached on the document with CASAC at a November 18, 1999, public meeting.

1.6 Organization and Content of the Document

This 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 1999 on those issues most relevant to review of the NAAQS for CO.

To aid in the development of this document, concise summaries of the relevant published literature and selective discussion of the literature have 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, primarily is 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 are potentially useful in deriving revised standards for CO. Generally, only published information that has undergone scientific peer review has been included in this revised criteria document. However, some newer studies not yet published in the open literature but meeting high standards of scientific reporting also have been included in 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) includes the measurement of CO in ambient (outdoor) and indoor air, as well as methods for measuring breath 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 final chapter (Chapter 7) provides an overall integrative summary of key findings and an evaluation of subpopulations potentially at risk from exposure to CO.

References

Beard, R. R.; Wertheim, G. A. (1967) Behavioral impairment associated with small doses of carbon monoxide. Am. J. Public Health 57: 2012-2022.

Federal Register. (1980) Carbon monoxide; proposed revisions to the national ambient air quality standards: proposed rule. F. R. (August 18) 45: 55,066-55,084.

Federal Register. (1985) Review of the national ambient air quality standards for carbon monoxide; final rule. F. R. (September 13) 50: 37,484-37,501.

Federal Register. (1990) Draft criteria document for carbon monoxide; notice of availability of external review draft. F. R. (April 19) 55: 14,858.

Federal Register. (1994) National ambient air quality standards for carbon monoxide—final decision. F. R. (August 1) 59: 38,906-38,917.

Horvath, S. M.; Ayres, S. M.; Sheps, D. S.; Ware, J. (1983) [Letter to Dr. Lester Grant, including the peer-review committee report on Dr. Aronow's studies]. Washington, DC: U.S. Environmental Protection Agency, Central Docket Section; Docket no. OAQPS-79-7 IV. H.58.

National Air Pollution Control Administration. (1970) Air quality criteria for carbon monoxide. Washington, DC: U.S. Department of Health, Education, and Welfare, Public Health Service; report no. NAPCA-PUB-AP-62.

Seinfeld, J. H.; Pandis, S. N. (1998) Atmospheric chemistry and physics: from air pollution to climate change. New York, NY: John Wiley & Sons, Inc.

U.S. Code. (1991) Clean Air Act, §108, air quality criteria and control techniques, §109, national ambient air quality standards. U. S. C. 42: §§7408-7409.

U.S. Environmental Protection Agency. (1979) Air quality criteria for carbon monoxide. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA-600/8-79-022.

U.S. Environmental Protection Agency. (1984) Revised evaluation of health effects associated with carbon monoxide exposure: an addendum to the 1979 EPA air quality criteria document for carbon monoxide. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA-600/8-83-033F.

U.S. Environmental Protection Agency. (1991) Air quality criteria for carbon monoxide. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/8-90/045F.

U.S. Environmental Protection Agency. (1992) Review of the national ambient air quality standards for carbon monoxide: 1992 reassessment of scientific and technical information. OAQPS staff paper. Research Triangle Park, NC: Office of Air Quality Planning and Standards; report no. EPA-452/R-92-004.

U.S. Environmental Protection Agency. (1996) National air quality and emissions trends report, 1995. Research Triangle Park, NC: Office of Air Quality Planning and Standards, Emissions Monitoring and Analysis Division; report no. EPA/454/R-96-005.

CHAPTER 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 an 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 11 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 improve 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 (GC) (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; Tesařík and Krejčí, 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 FIDs. (Section 2.4.4.3). These methods have no known interferences and can be used to measure levels from 0.02 to 45 ppm.

In some environments, new technologies allow CO measurements to be made where it is difficult to install reference instruments. Methods using electrochemistry, or integrated observations using absorbents, allow measurements for personal monitoring exposure studies, for in-transit measurements, and in areas where sites are being investigated and permanent installations are not yet planned or available. Focused studies of these developing methods should be encouraged to determine their precision, sensitivity and stability because an understanding of the impact that CO has on human health requires the ability to monitor under a wide variety of conditions.

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 concentration ratios in urban areas are typically 100s of ppb (Seinfeld and Pandis, 1998; Moy et al., 1994; Morales-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 having 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 mixtures: (1) pre-made blends and (2) 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

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).

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.

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/m^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

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).

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 within ±1% of 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 bar (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 have 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 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 and are not recommended. 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 since have 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 concentration 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 concentration 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, 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 from 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 concentration 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 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 and 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 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®) if several pollutants are to be monitored (Code of Federal Regulations, 1991b). 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 data processing, control sample, and water vapor interference checks, all of 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).

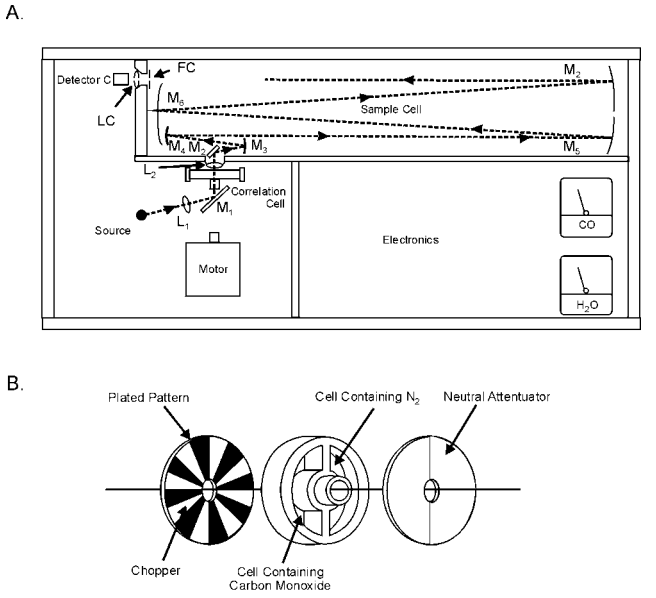

Figure 2-1. Schematic diagram of GFC monitor for CO. A = optical layout (M denotes mirror reflector, and L denotes lens); B = detail of correlation cell.
Source: Chaney and McClenny (1977).

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. 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 (GC-FID) (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 produce 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 (GC-ML) 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 ppb to more than 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. 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 alternating current signal. The background is measured by catalytic oxidation of CO to CO_2.

Instruments based on TDLS are the fastest and most sensitive extant, with a typical detection limit of a few parts per billion 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 ultraviolet 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:

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

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 photomultiplier 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, 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 oxygen and the signal from CO.

Recent improvements (Gerbig et al., 1999) have reduced the detection limit to 3 ppb for a response time as short as a few seconds. 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, loss in the span of a factor of two can be expected.

2.4.5 Intercomparisons of Methods

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

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 highly improved resolution and specificity (e.g., Langan, 1992; Lee et al., 1992a; Ott et al., 1995). Electrochemical sensors operate by measuring the current of a small fuel cell and, because of their reduced size and power requirements, have been used extensively in exposure and indoor research studies (see Section 2.5). Precision of 0.2 to 2 ppm has been reported. Further independent evaluation and intercomparison, followed by publication in the reviewed scientific literature, is called for to determine the sensitivity, stability, and selectivity of electrochemical methods to establish equivalency to the NDIR instrument by EPA for use in compliance monitoring.

2.5 Measurement Using Personal and Remote Monitors

2.5.1 Personal Monitors

Monitors at fixed locations provide useful information on ambient CO concentrations and their variability and trends, but such monitors cannot measure personal exposure. Information on personal exposure, including home, in-transit, and work-related concentrations is needed for epidemiologic 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., 1992b,c; 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 has an interference with ethylene, inconsequential in most microenvironments, 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 change in temperature, humidity, and interferences. These passive techniques lack the response speed and sensitivity for compliance ambient air monitoring or short time-scale personal monitoring, but they have been field tested and found adequate for occupational CO exposure studies where a longer 8-h average CO value is measured for comparison to an 8-h Occupational Safety and Health Administration standard (Apte et al., 1999).

Numerous field studies on personal exposure and microenvironmental sampling have been conducted with electrochemical sensors (Akland et al., 1985; Ott et al., 1986; Wallace et al., 1988; Langan, 1992; Ott et al., 1994; Klepeis et al., 1999; McBride et al., 1999); some are described in Chapters 3 and 4. Over the past 15 years, the electrochemical personal CO monitors have been much improved, and the latter studies show the increased versatility of the electrochemical sensor for field sampling. These studies documented the spatial and temporal variability of CO concentrations in an urban area at locations away from a central monitoring site and showed how the effects of sources of CO in microenvironments can add a major increment to a person's CO exposure, as estimated only from compliance measurements of CO at a central ambient monitoring station.

2.5.2 Remote Monitor

Carbon monoxide emissions from vehicles can be measured rapidly with a remote sensing IR technique (Bishop et al., 1989; Bishop and Stedman, 1996) in which CO is measured near 4.3 μm and CO_2 at 3.6 μm; a third wavelength is used as a reference for intensity. The instrument has been evaluated in a double blind intercomparison with on-board NDIR, and the two methods agreed well within experimental uncertainty (Lawson et al., 1990). Surveys conducted with this technique reveal that the majority of CO is emitted by a minority of vehicles. The method has been used to evaluate the efficacy of inspection and maintenance programs and oxygenated fuels (Beaton et al., 1995; Stedman et al., 1997, 1998). The sum

of measurements indicates a general decrease in fleet-averaged CO emissions over the past decade (Bradley et al., 1999).

2.6 Biological Monitoring

A unique feature of CO exposure is that there is a biological marker for the recent dose that an 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 usually is performed in the clinical or hospital setting through the use of a direct-reading spectrophotometer, such as a CO-Oximeter (CO-Ox). For clinical purposes, 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 the 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. Marshall et al. (1995) showed a wide range of threshold COHb values (measured in the blood by CO-Ox, not estimated from breath CO) 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 modern 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.

The performance of the various early versions of the CO-Ox instruments for measuring blood COHb was reviewed in Section 8.5 of the previous criteria document (U.S. Environmental Protection Agency, 1991). These and later instruments, of different design from different manufacturers, used several wavelengths of light for simultaneous measurement of hemoglobin (Hb), oxyhemoglobin (O_2Hb), COHb, and methemoglobin (Freeman and Steinke, 1993; Gong, 1995; Bailey et al., 1997). Vreman et al. (1993) and Mahoney et al. (1993) confirmed that considerable difficulties were encountered for COHb concentrations below 5% (a region with which most environmental studies of nonsmokers are concerned), and the authors concluded that the CO-Ox is unreliable for environmental studies. Some versions of the CO-Ox also were found to be influenced by bilirubin and by fetal hemoglobin (Hb), presenting difficulty in diagnosing newborn infants with jaundice (Vreman and Stevenson, 1994; Stevenson and Vreman, 1997). Shepherd and McMahan (1996) present a highly detailed analysis of the causes and effects of oximeter errors in blood gas analyses.

Recent CO-Ox developments have been a new six-wavelength instrument (Instrumentation Laboratory, 1999) used by Kimmel et al. (1999) and a 128-wavelength instrument (Krarup, 1998) both of which identify and correct for possible interferences. The latter instrument is still under formal independent evaluation, and, although peer-reviewed published results of comparison testing are expected to be forthcoming shortly, the only article currently in press is in German, in a non-peer-reviewed journal (Krarup, 1999). It is possible that comparison of the results on the same sample using the new multi-wavelength instruments and older instruments with fewer wavelengths may show that the new instruments measure lower COHb if they better correct for the positive interferences of various non-COHb species in the blood, such as varying fractions of fetal hemoglobin and sulfhemoglobin. This would be consistent with

the report that some laboratories, as cited above, accepted 5 to 6% COHb from oximeter readings as normal for nonsmokers.

For a research study to relate health effects or breath CO to COHb, the method of choice is GC analysis of the CO gas released from the blood when COHb is dissociated (U.S. Environmental Protection Agency, 1991; Van Dam and Daenens, 1994; Lloyd and Rowe, 1999). The reader, therefore, is alerted to the difference between end-tidal breath CO to blood COHb relationships when the COHb is determined by CO-Ox or GC. A calibration curve relating exhaled end-tidal breath CO to COHb should be based on a standard breath-hold maneuver for the CO collection and the GC method of COHb analysis. It is beyond the scope of this chapter to reanalyze the early COHb literature and estimate the effect of the possible positive interferences that were not accounted for by the early CO-Ox instruments because each instrument and its on-site calibration procedure would create a different bias that cannot be known with certainty. However, in general, the levels of COHb associated with low levels of ambient CO exposure in field studies may have been overestimated in the past.

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 the previous criteria document (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 parts per million of 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-, 15-, 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 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).

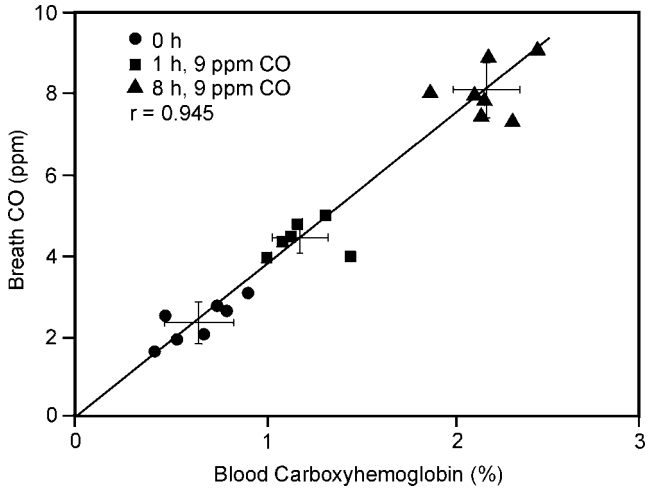

Figure 2-2. The correlation between an end-tidal breath CO concentration after a 10-s breathhold and blood COHb levels expressed as individual data points, as well as mean ± standard deviation. The breath concentration was not corrected for the concentration of CO in the inhaled air (Smith, 1977; Wallace, 1983).
Source: Lee et al. (1991, 1994).

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 (Allred et al., 1991).

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 in vitro static equilibrium, and the empirical end-tidal breath CO-blood COHb relationship is for an in vivo 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. Compressed air mixtures, traceable to NIST or NMi, provide reliable means of precise calibration.

The NDIR, GC-ML, GC-FID, and TDL techniques have undergone careful evaluation with synthetic air mixtures and ambient air, and are deemed reliable. The methods were intercompared in both open and blind studies with designated “disinterested, third-party” referees. Early problems were identified and corrected, and the most recent intercomparisons indicate general agreement on calibration standards and ambient air measurements over a broad range of concentrations. New techniques should undergo the same rigorous evaluation.

Several new electrochemical and passive sampling methods have become available. These techniques are not yet equivalent to the NDIR method for compliance monitoring or precise enough for CO measurements in background ambient air (<0.5 ppm CO) for inputs to CTM, but they are very useful for personal exposure and indoor research studies. Further work on the stability and specificity of the electrochemical methods to obtain EPA equivalency is warranted.

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 in vitro Haldane relationship between breath and blood still remains in question, especially at low environmental CO concentrations.

References

Akland, G. G.; Hartwell, T. D.; Johnson, T. R.; Whitmore, R. W. (1985) Measuring human exposure to carbon monoxide in Washington, D.C., and Denver, Colorado, during the winter of 1982-1983. Environ. Sci. Technol. 19: 911-918.

Allred, E. N.; Bleecker, E. R.; Chaitman, B. R.; Dahms, T. E.; Gottlieb, S. O.; Hackney, J. D.; Pagano, M.; Selvester, R. H.; Walden, S. M.; Warren, J. (1991) Effects of carbon monoxide on myocardial ischemia. Environ. Health Perspect. 91: 89-132.

Apte, M. G. (1997) A population-based exposure assessment methodology for carbon monoxide: development of a carbon monoxide passive sampler and occupational dosimeter [dissertation]. Berkeley, CA: U.S. Department of Energy, Lawrence Berkeley National Laboratory, Environmental Energy Technologies Division; LBNL-40838.

Apte, M. G.; Cox, D. D.; Hammond, S. K.; Gundel, L. A. (1999) A new carbon monoxide occupational dosimeter: results from a worker exposure assessment survey. J. Exposure Anal. Environ. Epidemiol. 9: 546-559.

Bailey, S. R.; Russell, E. L.; Martinez, A. (1997) Evaluation of the AVOXimeter: precision, long-term stability, linearity, and use without heparin. J. Clin. Monit. 13: 191-198.

Beaton, S. P.; Bishop, G. A.; Zhang, Y.; Ashbaugh, L. L.; Lawson, D. R.; Stedman, D. H. (1995) On-road vehicle emissions: regulations, costs, and benefits. Science (Washington, DC) 268: 991-993.

Beckman, A. O.; McCullough, J. D.; Crane, R. A. (1948) Microdetermination of carbon monoxide in air: a portable instrument. Anal. Chem. 20: 674-677.

Bergman, I.; Coleman, J. E.; Evans, D. (1975) A simple gas chromatograph with an electrochemical detector for the measurement of hydrogen and carbon monoxide in the parts per million range, applied to exhaled air. Chromatographia 8: 581-583.

Bishop, G. A.; Stedman, D. H. (1996) Measuring the emissions of passing cars. Acc. Chem. Res. 29: 489-495.

Bishop, G. A.; Starkey, J. R.; Ihlenfeldt, A.; Williams, W. J.; Stedman, D. H. (1989) IR long-path photometry: a remote sensing tool for automobile emissions. Anal. Chem. 61: 671A-677A.

Bradley, K. S.; Stedman, D. H.; Bishop, G. A. (1999) A global inventory of carbon monoxide emissions from motor vehicles. In: Khalil, M. A. K.; Pinto, J. P.; Shearer, M. J., eds. Carbon monoxide [special issue of papers from an international conference; December 1997; Portland, OR]. Chemosphere Global Change Sci. 1: 65-72.

Bruner, F.; Ciccioli, P.; Rastelli, R. (1973) The determination of carbon monoxide in air in the parts per billion range by means of a helium detector. J. Chromatogr. 77: 125-129.

Brunke, E.-G.; Scheel, H. E.; Seiler, W. (1990) Trends of tropospheric CO, N_2O, and CH_4 as observed at Cape Point, South Africa. Atmos. Environ. 24A: 585-595.

Burch, D. E.; Gates, F. J.; Pembrook, J. D. (1976) Ambient carbon monoxide monitor. Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Sciences Research Laboratory; report no. EPA-600/2-76-210.

Carter, W. P. L. (1991) Development of ozone reactivity scales for volatile organic compounds. Research Triangle Park, NC: U.S. Environmental Protection Agency, Atmospheric Research and Exposure Assessment Laboratory; report no. EPA/600/3-91/050.

Chaney, L. W.; McClenny, W. A. (1977) Unique ambient carbon monoxide monitor based on gas filter correlation: performance and application. Environ. Sci. Technol. 11: 1186-1190.

Chaney, L. W.; Rickel, D. G.; Russwurm, G. M.; McClenny, W. A. (1979) Long-path laser monitor of carbon monoxide: system improvements. Appl. Opt. 18: 3004-3009.

Code of Federal Regulations. (1991a) Ambient air monitoring reference and equivalent methods. C. F. R. 40: §53.

Code of Federal Regulations. (1991b) National primary and secondary ambient air quality standards. C. F. R. 40: §50.

Commins, B. T.; Berlin, A.; Langevin, M.; Peal, J. A. (1977) Intercomparison of measurement of carboxyhaemoglobin in different European laboratories and establishment of the methodology for the assessment of COHb levels in exposed populations. Luxembourg, Sweden: Commission of the European Communities, Health and Safety Directorate; doc. no. V/F/1315/77e.

Dagnall, R. M.; Johnson, D. J.; West, T. S. (1973) A method for the determination of carbon monoxide, carbon dioxide, nitrous oxide and sulphur dioxide in air by gas chromatography using an emissive helium plasma detector. Spectrosc. Lett. 6: 87-95.

Dickerson, R. R.; Delany, A. C. (1988) Modification of a commercial gas filter correlation CO detector for enhanced sensitivity. J. Atmos. Oceanic Technol. 5: 424-431.

Elwood, J. H. (1976) A calibration procedural system and facility for gas turbine engine exhaust emission analysis. In: Calibration in air monitoring: a symposium; August 1975; Boulder, CO. Philadelphia, PA: American Society for Testing and Materials; pp. 255-272; ASTM special technical publication no. 598.

Federal Register. (1978) Air quality surveillance and data reporting: proposed regulatory revisions. F. R. (August 7) 43: 34892-34934.
Feldstein, M. (1967) Methods for the determination of carbon monoxide. Prog. Chem. Toxicol. 3: 99-119.
Fishman, J.; Seiler, W.; Haagenson, P. (1980) Simultaneous presence of O_3 and CO bands in the troposphere. Tellus 32: 456-463.
Freeman, G. L.; Steinke, J. M. (1993) Evaluation of two oximeters for use in cardiac catheterization laboratories. Catheterization Cardiovasc. Diagn. 30: 51-57.
Fried, A.; Henry, B.; Parrish, D. D.; Carpenter, J. R.; Buhr, M. P. (1991) Intercomparison of tunable diode laser and gas filter correlation measurements of ambient carbon monoxide. Atmos. Environ. 25A: 2277-2284.
Garbarz, J.-J.; Sperling, R. B.; Peache, M. A. (1977) Time-integrated urban carbon monoxide measurements. San Francisco, CA: Environmental Measurements, Inc.
Gerbig, C.; Kley, D.; Volz-Thomas, A.; Kent, J.; Dewey, K.; McKenna, D. S. (1996) Fast response resonance fluorescence CO measurements aboard the C-130: instrument characterization and measurements made during North Atlantic Regional Experiment 1993. J. Geophys. Res. [Atmos.] 101: 29,229-29,238.
Gerbig, C.; Schmitgen, S.; Kley, D.; Volz-Thomas, A.; Dewey, K.; Haaks, D. (1999) An improved fast-response vacuum-UV resonance fluorescence CO instrument. J. Geophys. Res. [Atmos.] 104: 1699-1704.
Goldstein, G. M. (1977) COHb measurements, results of discussion between Drs. A. Berlin, CEC and G. Goldstein, EPA on ECE doc V/F/1315/77e [letter to Mr. Jack Thompson]. Research Triangle Park, NC: U.S. Environmental Protection Agency; September 23.
Gong, A. K. (1995) Near-patient measurements of methemoglobin, oxygen saturation, and total hemoglobin: evaluation of a new instrument for adult and neonatal intensive care. Crit. Care Med. 23: 193-201.
Greenberg, J. P.; Zimmerman, P. R.; Heidt, L.; Pollock, W. (1984) Hydrocarbon and carbon monoxide emissions from biomass burning in Brazil. J. Geophys. Res. [Atmos.] 89: 1350-1354.
Guenther, F. R.; Dorko, W. D.; Miller, W. R.; Rhoderick, G. C. (1996) The NIST traceable reference material program for gas standards. Washington, DC: U.S. Department of Commerce, National Institute of Standards and Technology; NIST special publication 260-126.
Haldane, J. (1897-1898) Some improved methods of gas analysis. J. Physiol. (London) 22: 465-480.
Heidt, L. E. (1978) Whole air collection and analysis. Atmos. Technol. (9): 3-8.
Hoell, J. M.; Gregory, G. L.; Carroll, M. A.; McFarland, M.; Ridley, B. A.; Davis, D. D.; Bradshaw, J.; Rodgers, M. O.; Torres, A. L.; Sachse, G. W.; Hill, G. F.; Condon, E. P.; Rasmussen, R. A.; Campbell, M. C.; Farmer, J. C.; Sheppard, J. C.; Wang, C. C.; Davis, L. I. (1984) An intercomparison of carbon monoxide, nitric oxide, and hydroxyl measurement techniques: overview of results. J. Geophys. Res. [Atmos.] 89: 11,819-11,825.
Hoell, J. M., Jr.; Gregory, G. L.; McDougal, D. S.; Sachse, G. W.; Hill, G. F.; Condon, E. P.; Rasmussen, R. A. (1985) An intercomparison of carbon monoxide measurement techniques. J. Geophys. Res. [Atmos.] 90: 12,881-12,889.
Hoell, J. M., Jr.; Gregory, G. L.; McDougal, D. S.; Sachse, G. W.; Hill, G. F.; Condon, E. P.; Rasmussen, R. A. (1987) Airborne intercomparison of carbon monoxide measurement techniques. J. Geophys. Res. [Atmos.] 92: 2009-2019.
Hughes, E. E.; Dorko, W. D.; Scheide, E. P.; Hall, L. C.; Beilby, A. L.; Taylor, J. K. (1973) Gas generation systems for the evaluation of gas detecting devices. Washington, DC: U.S. Department of Commerce, National Bureau of Standards; report no. NBSIR 73-292.
Hughes, E. E.; Davenport, A. J.; Woods, P. T.; Zielinski, W. L., Jr. (1991) Intercomparison of a range of primary gas standards of carbon monoxide in nitrogen and carbon dioxide in nitrogen prepared by the National Institute of Standards and Technology and the National Physical Laboratory. Environ. Sci. Technol. 25: 671-676.
Hunt, W. F., Jr. (1972) The precision associated with the sampling frequency of log-normally distributed air pollutant measurements. J. Air Pollut. Control Assoc. 22: 687-691.
Instrumentation Laboratory. (1999) IL 682 CO-Oximeter: ready when you are. Lexington, MA: Instrumentation Laboratory, Critical Care Technical Support Group.
Jones, R. H.; Ellicott, M. F.; Cadigan, J. B.; Gaensler, E. A. (1958) The relationship between alveolar and blood carbon monoxide concentrations during breathholding. J. Lab. Clin. Med. 51: 553-564.
Kimmel, E. C.; Carpenter, R. L.; Reboulet, J. E.; Still, K. R. (1999) A physiological model for predicting carboxyhemoglobin formation from exposure to carbon monoxide in rats. J. Appl. Physiol. 86: 1977-1983.
Klepeis, N. E.; Ott, W. R.; Repace, J. L. (1999) The effect of cigar smoking on indoor levels of carbon monoxide and particles. J. Exposure Anal. Environ. Epidemiol. 9: 622-635.
Krarup, T. (1998) The ABL™700 Oximeter: new standards in interference detection. Copenhagen, Denmark: Radiometer Medical; bulletin no. 3.
Krarup, T. (1999) ABL 700 series [email to D. Mage]. Denmark, Copenhagen: Radiometer Medical; September 2.
Langan, L. (1992) Portability in measuring exposure to carbon monoxide. In: Measuring, understanding, and predicting exposures in the 21st century: proceedings of the conference; November 1991; Atlanta, GA. J. Exposure Anal. Environ. Epidemiol. 1(suppl. 1): 223-239.

Larsen, R. I. (1971) A mathematical model for relating air quality measurements to air quality standards. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Programs; report no. AP-89.

Lawson, D. R.; Groblicki, P. J.; Stedman, D. H.; Bishop, G. A.; Guenther, P. L. (1990) Emissions from in-use motor vehicles in Los Angeles: a pilot study of remote sensing and the inspection and maintainence program. J. Air Waste Manage. Assoc. 40: 1096-1105.

Lee, K.; Yanagisawa, Y. (1992) Development of a sampler for carbon monoxide in expired air. Presented at: 85th annual meeting and exhibition of the Air & Waste Management Association; June; Kansas City, MO. Pittsburgh, PA: Air & Waste Management Association; paper no. 92-145.03.

Lee, K.; Yanagisawa, Y. (1995) Sampler for measurement of alveolar carbon monoxide. Environ. Sci. Technol. 29:104-107.

Lee, P. S.; Majkowski, R. F.; Perry, T. A. (1991) Tunable diode laser spectroscopy for isotope analysis - detection of isotopic carbon monoxide in exhaled breath. IEEE Trans. Biomed. Eng. 38: 966-973.

Lee, K.; Yanagisawa, Y.; Spengler, J. D. (1992a) Comparison of carbon monoxide measurement methods. Presented at: 85th annual meeting & exhibition of the Air & Waste Management Association; June; Kansas City, MO; paper no. 92-80.04.

Lee, K.; Yanagisawa, Y.; Hishinuma, M.; Spengler, J. D.; Billick, I. H. (1992b) A passive sampler for measurement of carbon monoxide using a solid adsorbent. Environ. Sci. Technol. 26: 697-702.

Lee, K.; Yanagisawa, Y.; Spengler, J. D.; Billick, I. H. (1992c) Measurement of personal carbon monoxide exposures by mailed passive sampler. J. Air Waste Manage. Assoc. 42: 1212-1213.

Lee, P. S.; Schreck, R. M.; Hare, B. A.; McGrath, J. J. (1994) Biomedical applications of tunable diode laser spectrometry: correlation between breath carbon monoxide and low level blood carboxyhemoglobin saturation. Ann. Biomed. Eng. 22: 120-125.

Lloyd, W. G.; Rowe, D. R. (1999) Estimation of carboxyhemoglobin. Environ. Sci. Technol. 33: 782-785.

Mahoney, J. J.; Vreman, H. J.; Stevenson, D. K.; Van Kessel, A. L. (1993) Measurement of carboxyhemoglobin and total hemoglobin by five specialized spectrophotometers (CO-oximeters) in comparison with reference methods. Clin. Chem. (Washington, DC) 39: 1693-1700.

Marshall, M. D.; Kales, S. N.; Christiani, D. C.; Goldman, R. H. (1995) Are reference intervals for carboxyhemoglobin appropriate? A survey of Boston area laboratories. Clin. Chem. (Washington, DC) 41: 1434-1438.

McBride, S. J.; Ferro, A. R.; Ott, W. R; Switzer, P.; Hildemann, L. M. (1999) Investigations of the proximity effect for pollutants in the indoor environment. J. Exposure Anal. Environ. Epidemiol. 9: 602-621.

McCullough, J. D.; Crane, R. A.; Beckman, A. O. (1947) Determination of carbon monoxide in air by use of red mercuric oxide. Anal. Chem. 19: 999-1002.

Morales-Morales, R. (1998) Carbon monoxide, ozone, and hydrocarbons in the Baltimore metropolitan area [dissertation]. College Park, MD: University of Maryland. Available from: University Microfilms International, Ann Arbor, MI; publication no. 9908993.

Moser, L.; Schmid, O. (1914) Die Bestimmung des Kohlenoxyds durch gelbes quecksilberoxyd [The determination of carbon monoxide through yellow mercury oxide]. Z. Anal. Chem. 53: 217-233.

Moy, L. A.; Dickerson, R. R.; Ryan, W. F. (1994) Relationship between back trajectories and tropospheric trace gas concentrations in rural Virginia. Atmos. Environ. 28: 2789-2800.

Mueller, R. H. (1954) A supersensitive gas detector permits accurate detection of toxic or combustible gases in extremely low concentrations. Anal. Chem. 26: 39A-42A.

National Bureau of Standards. (1975) Catalog of NBS standard reference materials, 1975-76 edition. Washington, DC: U.S. Department of Commerce, National Bureau of Standards; NBS special publication no. 260.

Novelli, P. C.; Elkins, J. W.; Steele, L. P. (1991) The development and evaluation of a gravimetric reference scale for measurements of atmospheric carbon monoxide. J. Geophys. Res. [Atmos.] 96: 13,109-13,121.

Novelli, P. C.; Collins, J. E., Jr.; Myers, R. C.; Sachse, G. W.; Scheel, H. E. (1994) Reevaluation of the NOAA/CMDL carbon monoxide reference scale and comparisons with CO reference gases at NASA-Langley and the Fraunhofer Institut. J. Geophys. Res. [Atmos.] 99: 12,833-12,839.

Novelli, P. C.; Connors, V. S.; Reichle, H. G., Jr.; Anderson, B. E.; Brenninkmeijer, C. A. M.; Brunke, E. G.; Doddridge, B. G.; Kirchhoff, V. W. J. H.; Lam, K. S.; Masarie, K. A.; Matsuo, T.; Parrish, D. D.; Scheel, H. E.; Steele, L. P. (1998) An internally consistent set of globally distributed atmospheric carbon monoxide mixing ratios developed using results from an intercomparison of measurements. J. Geophys. Res. [Atmos.] 103: 19,285-19,293.

O'Keeffe, A. E.; Ortman, G. C. (1966) Primary standards for trace gas analysis. Anal. Chem. 38: 760-763.

Ott, W. R.; Mage, D. T. (1975) Random sampling as an inexpensive means for measuring average annual air pollutant concentrations in urban areas. Presented at: 68th annual meeting of the Air Pollution Control Association; June; Boston, MA. Pittsburgh, PA: Air Pollution Control Association; paper no. 75-14.3.

Ott, W. R.; Rodes, C. E.; Drago, R. J.; Williams, C.; Burmann, F. J. (1986) Automated data-logging personal exposure monitors for carbon monoxide. J. Air Pollut. Control Assoc. 36: 883-887.

Ott, W.; Switzer, P.; Willits, N. (1994) Carbon monoxide exposures inside an automobile traveling on an urban arterial highway. J. Air Waste Manage. Assoc. 44: 1010-1018.

Ott, W. R.; Vreman, H. J.; Switzer, P.; Stevenson, D. K. (1995) Evaluation of electrochemical monitors for measuring carbon monoxide concentrations in indoor, in-transit, and outdoor microenvironments. In: Measurement of toxic and related air pollutants: proceedings of an international symposium; May; Research Triangle Park, NC. Pittsburgh, PA: Air & Waste Management Association; pp. 172-177. (A&WMA publication VIP-50).

Palanos, P. N. (1972) A practical design for an ambient carbon monoxide mercury replacement analyzer. Anal. Instrum. 10: 117-125.

Parrish, D. D.; Holloway, J. S.; Fehsenfeld, F. C. (1994) Routine, continuous measurement of carbon monoxide with parts per billion precision. Environ. Sci. Technol. 28: 1615-1618.

Paulsell, C. D. (1976) Use of the National Bureau of Standards standard reference gases in mobile source emissions testing. In: Calibration in air monitoring: a symposium; August 1975; Boulder, CO. Philadelphia, PA: American Society for Testing and Materials; pp. 232-245. (ASTM special technical publication 598).

Phinney, D. E.; Newman, J. E. (1972) The precision associated with the sampling frequencies of total particulate at Indianapolis, Indiana. J. Air Pollut. Control Assoc. 22: 692-695.

Porter, K.; Volman, D. H. (1962) Flame ionization detection of carbon monoxide for gas chromatographic analysis. Anal. Chem. 34: 748-749.

Poulida, O.; Dickerson, R. R.; Doddridge, B. G.; Holland, J. Z.; Wardell, R. G.; Watkins, J. G. (1991) Trace gas concentrations and meteorology in rural Virginia. 1. Ozone and carbon monoxide. J. Geophys. Res. [Atmos.] 96: 22,461-22,475.

Rhodes, R. C.; Evans, E. G. (1987) Precision and accuracy assessments for state and local air monitoring networks 1985. Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory; report no. EPA-600/4-87-003.

Robbins, R. C.; Borg, K. M.; Robinson, E. (1968) Carbon monoxide in the atmosphere. J. Air Pollut. Control Assoc. 18: 106-110.

Rodgers, P. A.; Vreman, H. J.; Dennery, P. A.; Stevenson, D. K. (1994) Sources of carbon monoxide (CO) in biological systems and applications of CO detection technologies. Semin. Perinatol. 18: 2-10.

Roths, J.; Zenker, T.; Parchatka, U.; Wienhold, F. G.; Harris, G. W. (1996) Four-laser airborne infrared spectrometer for atmospheric trace gas measurements. Appl. Opt. 35: 7075-7084.

Ryan, W. F.; Doddridge, B. G.; Dickerson, R. R.; Morales, R. M.; Hallock, K. A.; Roberts, P. T.; Blumenthal, D. L.; Anderson, J. A.; Civerolo, K. (1998) Pollutant transport during a regional O_3 episode in the mid-Atlantic states. J. Air Waste Manage. Assoc. 48: 786-797.

Sachse, G. W.; Hill, G. F.; Wade, L. O.; Perry, M. G. (1987) Fast-response, high-precision carbon monoxide sensor using a tunable diode laser absorption technique. J. Geophys. Res. [Atmos.] 92: 2071-2081.

Scaringelli, F. P.; Rosenberg, E.; Rehme, K. A. (1970) Comparison of permeation devices and nitrite ion as standards for the colorimetric determination of nitrogen dioxide. Environ. Sci. Technol. 4: 924-929.

Seiler, W.; Giehl, H.; Roggendorf, P. (1980) Detection of carbon monoxide and hydrogen by conversion of mercury oxide to mercury vapor. Atmos. Technol. (12): 40-45.

Seinfeld, J. H.; Pandis, S. N. (1998) Atmospheric chemistry and physics: from air pollution to climate change. New York, NY: John Wiley & Sons, Inc.

Shepherd, A. P.; McMahan, C. A. (1996) Role of oximeter error in the diagnosis of shunts. Catheterization Cardiovasc. Diagn. 37: 435-446.

Smith, N. J. (1977) End-expired air technic for determining occupational carbon monoxide exposure. J. Occup. Med. 19: 766-769.

Smith, F.; Nelson, A. C., Jr. (1973) Guidelines for development of a quality assurance program: reference method for the continuous measurement of carbon monoxide in the atmosphere. Research Triangle Park, NC: U.S. Environmental Protection Agency, Quality Assurance and Environmental Monitoring Laboratory; report no. EPA-R4-73-028a.

Smith, R. G.; Bryan, R. J.; Feldstein, M.; Locke, D. C.; Warner, P. O. (1975) Tentative method for constant pressure volumetric gas analysis for O_2, CO_2, CO, N_2, hydrocarbons (ORSAT). Health Lab. Sci. 12: 177-181.

Stedman, D. H.; Kok, G.; Delumyea, R.; Alvord, H. H. (1976) Redundant calibration of nitric oxide, carbon monoxide, nitrogen dioxide, and ozone air pollution monitors by chemical and gravimetric techniques. In: Calibration in air monitoring: a symposium; August 1975; Boulder, CO. Philadelphia, PA: American Society for Testing and Materials; pp. 337-344. (ASTM special technical publication 598).

Stedman, D. H.; Bishop, G. A.; Aldrete, P.; Slott, R. S. (1997) On-road evaluation of an automobile emission test program. Environ. Sci. Technol. 31: 927-931.

Stedman, D. H.; Bishop, G. A.; Slott, R. S. (1998) Repair avoidance and evaluating inspection and maintenance programs. Environ. Sci. Technol. 32: 1544-1545.

Stevenson, D. K.; Vreman, H. J. (1997) Carbon monoxide and bilirubin production in neonates. Pediatrics 100: 252-254.

Swinnerton, J. W.; Linnenbom, V. J.; Cheek, C. H. (1968) A sensitive gas chromatographic method for determining carbon monoxide in seawater. Limnol. Oceanogr. 13: 193-195.

Tesařík, K.; Krejčí, M. (1974) Chromatographic determination of carbon monoxide below the 1 ppm level. J. Chromatogr. 91: 539-544.

U.S. Code. (1991) Clean Air Act, §108, air quality criteria and control techniques, §109, national ambient air quality standards. U. S. C. 42: §§7408-7409.

U.S. Environmental Protection Agency. (1991) Air quality criteria for carbon monoxide. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/8-90/045F.

U.S. Environmental Protection Agency. (1997) EPA traceability protocol for assay and certification of gaseous calibration standards. Washington, DC: National Center for Environmental Research and Quality Assurance; report no. EPA/600/R-97/121.

Van Dam, J.; Daenens, P. (1994) Microanalysis of carbon monoxide in blood by head-space capillary gas chromatography. J. Forensic Sci. 39: 473-478.

Volz, A.; Kley, D. (1985) A resonance-fluorescence instrument for the in-situ measurement of atmospheric carbon monoxide. J. Atmos. Chem. 2: 345-357.

Vreman, H. J.; Stevenson, D. K. (1994) Carboxyhemoglobin determined in neonatal blood with a CO-oximeter unaffected by fetal oxyhemoglobin. Clin. Chem. (Washington, DC) 40: 1522-1527.

Vreman, H. J.; Mahoney, J. J.; Stevenson, D. K. (1993) Electrochemical measurement of carbon monoxide in breath: interference by hydrogen. Atmos. Environ. Part A 27: 2193-2198.

Vreman, H. J.; Mahoney, J. J.; Stevenson, D. K. (1995) Carbon monoxide and carboxyhemoglobin. Adv. Pediatr. 42: 303-334.

Wallace, L. A. (1983) Carbon monoxide in air and breath of employees in an underground office. J. Air Pollut. Control Assoc. 33: 678-682.

Wallace, L.; Thomas, J.; Mage, D.; Ott, W. (1988) Comparison of breath CO, CO exposure, and Coburn model predictions in the U.S. EPA Washington-Denver (CO) study. Atmos. Environ. 22: 2183-2193.

Weeks, I. A.; Galbally, I. E.; Fraser, P. J.; Matthews, G. (1989) Comparison of the carbon monoxide standards used at Cape Grim and Aspendale. In: Forgan, B. W.; Ayres, G. P., eds. Baseline Atmosheric Program (Australia) 1987. Canberra, New South Wales: Department of Administrative Services, Bureau of Meteorology; pp. 21-25.

Weinheimer, A. J.; Ridley, B. A. (1990) A cautionary note on the use of some mass flow controllers. J. Geophys. Res. [Atmos.] 95: 9817-9821.

Wohlers, H. C.; Newstein, H.; Daunis, D. (1967) Carbon monoxide and sulfur dioxide adsorption on- and desorption from glass, plastic, and metal tubings. J. Air Pollut. Control Assoc. 17: 753-756.

CHAPTER 3

Sources, Emissions, and Concentrations of Carbon Monoxide in Ambient and Indoor Air

3.1 Introduction

This chapter summarizes 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. Carbon monoxide is studied in these widely varied environments for different reasons. Sources such as unvented, malfunctioning, or misused combustion appliances, combustion engines in garages or basements, and tobacco combustion can cause high concentrations of CO to exist in the indoor environment. Sources such as motor vehicles, nonroad combustion engines or vehicles, and biomass burning can cause high concentrations of CO in the outdoor environment. In both of these environments, CO is of direct concern because of the health effects that can result from human exposure to these high concentrations. Human exposures to CO are discussed in Chapter 4, and possible health effects are discussed in Chapter 6.

Carbon monoxide in less polluted air 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 that affect the abundance of stratospheric O_3 and the energy budget of the atmosphere. Changes in CO concentrations, 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 spatial 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 concentrations 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 by-product.

Carbon monoxide is formed as an intermediate product during the photochemical oxidation of methane and non-methane hydrocarbons (NMHCs) to carbon dioxide (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,

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]
Methane (CH_4) oxidation	Wetlands,[a] agriculture (rice cultivation, animal husbandry, and biomass burning), landfills, coal mining, and natural gas and petroleum industry
Non-methane hydrocarbon (NMHC) oxidation	Transportation (alkanes, alkenes, and aromatic 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 cataloged.

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

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.

Carbon monoxide concentrations and trends in the background atmosphere are discussed in Section 3.2.1. 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. 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 concentrations" refers to concentrations observed in remote areas relatively unaffected by local pollution sources. However, several definitions of background concentrations 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 concentrations in the United States. The first definition is the concentration resulting from anthropogenic and natural emissions outside North America, and natural sources within North America. The second definition is the concentration resulting from global natural sources. Because of long-range transport from anthropogenic source regions in North America, it is impossible to obtain background concentrations defined above solely on the basis of direct measurement in remote areas in North America. However, some inferences about what these concentrations 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 concentrations are summarized in the three-dimensional diagram shown in Figure 3-1 (National Oceanic and Atmospheric Administration, 1999a). Annual average CO concentrations are about 120 ppb in the Northern Hemisphere and about 40 ppb in the Southern Hemisphere. Seasonal maxima in CO concentrations 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 concentrations exists between about 30° north (N) latitude and about 10° south (S) latitude. Carbon monoxide concentrations range from a minimum of about 30 ppb during summer in the Southern Hemisphere to about 200 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).

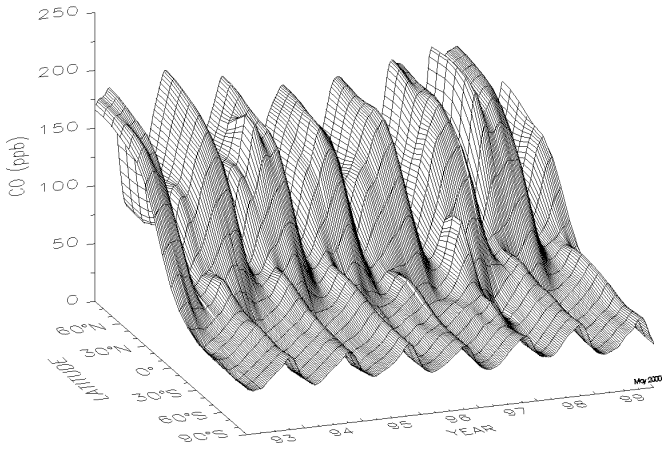

Figure 3-1. Latitudinal and seasonal variability in CO concentrations obtained by the NOAA/CMDL monitoring network.
Source: National Oceanic and Atmosphere Administration (1999a).

There were sufficient data on tropospheric air quality trends to suggest that CO concentrations measured at global background sites were increasing at 1.2 ± 0.6% per year from 1981 to 1986, based on data collected by the Oregon Graduate Institute (Khalil and Rasmussen, 1988a). From 1987 until 1992, global background concentrations of CO declined at a rate of about −2.6 ± 0.8% per year (Khalil and Rasmussen, 1994), whereas Novelli et al. (1994) determined a rate of decrease in CO of −6.5 ± 0.8% per year from 1990 to 1993, and later results reported by NOAA/CMDL indicate that background concentrations of CO continued to decline, although at a lower rate of −2.6 ± 0.2% per year from 1990 to 1995 (Novelli et al., 1998). Hypotheses to explain these observations include reductions in fossil fuel combustion (Bakwin et al., 1994; Novelli et al., 1994; Khalil and Rasmussen, 1994) and tropical biomass burning (Yung et al., 1999). Possible increases in tropospheric OH concentrations resulting from enhanced transmission of solar ultraviolet radiation caused by stratospheric O_3 depletion may have been an additional factor (Fuglestvedt et al., 1994; Bekki et al., 1994). More recent data for changes in global background CO concentrations are shown in Figure 3-2. The data from 1993 to 1997 do not show clearly any stable upward or downward trend.

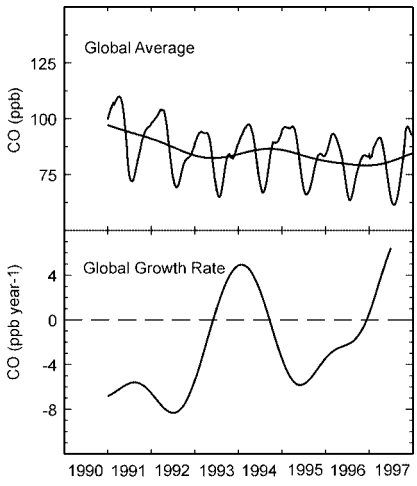

Figure 3-2. Global background average CO concentrations (upper) and growth rates for global background average CO (lower).
Source: National Oceanic and Atmospheric Administration (1999b).

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 concentrations 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. Column CO abundances obtained over Zvenigorod, Russia, from 1974 through 1997 have increased by about 1% per year (Yurganov et al., 1999), whereas measurements obtained with a similar technique over the Alps have indicated decreases in CO of $-0.18 \pm 0.16\%$ per year from 1984 to 1995 compared with a change of $-0.95 \pm 0.32\%$ per year from 1984 to 1993 (Mahieu et al., 1997). The difference arises mainly from a pronounced minimum during the second half of 1992 and 1993, depending on the fitting function. Thus, there is still considerable uncertainty in defining global trends for CO based on differences in trends found in specific regions.

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 about 50 ppb for the high-latitude Southern Hemisphere. 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. 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 concentrations of about 50 ppb (Thompson and Cicerone, 1986; Pinto and Khalil, 1991; Thompson et al., 1993).

3.2.2 Sources and Global Emissions Estimates of Carbon Monoxide

Global CO emission estimates are summarized in Table 3-2. Motor vehicles contribute most of the emissions from fossil fuel combustion on the global scale according to the entries by Logan et al. (1981) and Dignon et al. (1998). Bradley et al. (1999) estimated global emissions from motor vehicles of 213 Tg/year in 1991 based on roadside remote sensing measurements around the world. They also calculated a decrease of 17% in global motor vehicle emissions from 1991 to 1995. Their estimated uncertainty in both figures is about 20%. 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 CO_2. Carbon monoxide is produced primarily during conditions of incomplete combustion. The estimates for fossil fuel emissions by stationary sources, shown in the footnotes to 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. These latter sources are of significance only in eastern Europe and in developing countries of Africa and Asia (especially China). However, it also should be noted that the importance of these sources has been declining as energy needs are met increasingly by centralized power plants.

Biomass burning consists of wildfires and the burning of vegetation to clear new land for agriculture and population resettlement; to control the growth of unwanted plants on pasture land; to manage forest resources (prescribed burning); to dispose of agricultural and domestic waste; and as fuel for cooking, heating, and water sterilization. Most wildfires may be ignited directly as the result of human activities with

Table 3-2. Annual Global Carbon Monoxide Emissions Estimates (in teragrams 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.

only a fraction (10 to 30%) initiated by lightning (Andreae, 1991). However, because of fire management practices in which natural wildfires are suppressed, the buildup of fire fuels increases the susceptibility of forests to more severe but less frequent fires in the future. Thus, there is considerable uncertainty in attributing the fraction of wildfire emissions to human activities because the emissions from naturally occurring fires that would have been present in the absence of fire suppression practices would have to be known. For these reasons, values given above for the average contribution from human activities given above are likely to be upper limits. 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 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, where most wildfires also occur (Andreae, 1991).

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 (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 found in most soils favor CO uptake, whereas hot and dry conditions as found in deserts and some savannas favor the release of CO (King, 1999). 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). Moxley and Cape (1997) hypothesized that from 20 to 80% of CO in the stable nocturnal boundary layer (calculated heights between 40 and 220 m) could have been depleted by soil microorganisms during transport inland 100 km from the Scottish coast.

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. By using a mean value of 80% for biomass burning resulting from human activity and a value of two-thirds for the fraction of CH_4 produced by human activity (Tegart and Sheldon, 1993), it can be seen that approximately two-thirds of CO is produced globally as the result of human activities.

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 (Tegart and Sheldon, 1993). Methane oxidation can be summarized by the following sequence of reactions:

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

where M is a mediator (e.g., nitrogen, molecular oxygen [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 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.

Although 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 the methyl radical (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 peroxyacetyl 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 require 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 concentrations. For higher NO_x concentrations, 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.

The major pathway for removal of CO from the atmosphere is the reaction of CO 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 concentrations 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 values) 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. Models of the atmospheric distribution of methyl chloroform (CH_3CCl_3) have been used to derive diurnal and global average OH concentrations for calculating the atmospheric lifetimes of long-lived species by Prinn et al. (1992). Average OH values they 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 $0.46 \pm 0.6\%$ $year^{-1}$. Krol et al. (1998) also used a three dimensional model of atmospheric chemistry to examine the sensitivity of the OH trend to stratospheric ozone depletion, decreases in CO emissions, increases in tropical water vapor, and NO_x and CH_4 emissions, and they derived an overall change of 6% in OH concentrations from 1978 to 1993. However, it should be noted that many of the changes used as input to the model calculations are highly uncertain and thus, the results should be viewed only as a sensitivity study (Law, 1999). It also should be noted that Prinn et al. (1995) found little or no trend in OH based on CH_3CCl_3 data.

The resulting globally averaged atmospheric lifetime of CO is then approximately 2 mo. Shorter lifetimes are found in the tropics, whereas longer lifetimes are found at higher latitudes. During winter at high latitudes, CO is essentially inert. The CO lifetime is 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. However, the lifetime of CO is much longer than typical residence times of CO in urban areas (assuming a diurnally averaged OH concentration of 3×10^6 OH/cm^3 in urban areas) and in indoor environments, where OH concentrations are expected to be orders of magnitude lower.

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 concentrations, interest has focused on the possible effects of increases in anthropogenic CO emissions on the concentrations of gases such as those listed above (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 (1999) have examined the consequences of decreases in CO concentrations 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 ($\approx$25%) in the growth rate of CH_4 and even to a decrease in CH_4 concentrations in the case where CH_4 emissions remain constant. 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

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

Atmospheric Reactions Leading to O_3 Destruction

$$\begin{aligned} & CO + OH \rightarrow CO_2 + H \\ & H + O_2 (+M) \rightarrow HO_2 (+M) \\ & HO_2 + O_3 \rightarrow OH + 2O_2 \\ \text{Net} \quad & CO + O_3 \rightarrow CO_2 + O_2 \end{aligned}$$

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 concentrations are greater than about 10 ppt, the oxidation of CO leads to O_3 formation, whereas, in areas where NO concentrations are less than about 10 ppt, the oxidation of CO leads to O_3 destruction. Nitric oxide concentrations 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 (1995), can give the amount of O_3 formed because of the reaction of CO. However, only a few such analyses have been performed. Jeffries (1995), presented the results of a numerical simulation of an O_3 episode in Atlanta, GA, on June 6, 1988, and found that reaction with CO constituted 33% of the loss of OH radicals. It was found, by tracking sources of various radicals produced by the oxidation of volatile organic compounds (VOCs) and that oxidize NO to NO_2, that CO accounted for about 17.5% of the O_3 formed in this example (compared to about 82.5% for VOCs). 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 concentrations on O_3 production rates in the case studies cited above.

3.3 Nationwide Carbon Monoxide Emissions Estimates

Total estimated primary CO emissions in the United States for the period of 1988 through 1997, summarized from the National Emissions Inventory Trends database, are shown in Table 3-3 (U.S. Environmental Protection Agency, 1998). These emissions are shown in the original units used in their calculation (i.e., thousands of short tons per year) and with the same number of significant figures. 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 24.7% from 1988 to 1997; however, the fractional contribution of transportation (the major source of CO both then and now) remained relatively constant at 77%. The term "transportation" includes both onroad and nonroad sources. Onroad sources consist of automobiles, trucks, and buses. Nonroad sources consist of categories such as trains; aircraft; boats; ships; and lawn, recreational, construction, logging, and agricultural equipment. From 1988 to 1997, the contribution of onroad sources decreased from 61 to 57%, whereas the contribution of nonroad sources increased from 13 to 19%. In addition, there are several categories, such as fuel consumption by electric utilities and industry, 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 CO air quality criteria document. It can be seen from inspection of Table 3-3 that the values for 1990 have been revised upward in the interim to 95,794 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, 1994) replaced the earlier MOBILE4.1 version (U.S. Environmental Protection Agency, 1991a). The most significant change was in using IM240 data to replace FTP testing of recruited in-use vehicles. This change yielded significantly higher exhaust emissions, especially for older, higher mileage vehicles. In addition, changes were made in methods for calculating inputs to the model (e.g., temperatures, operating mode) and in the method for calculating vehicle miles traveled. Additional differences relate to the use of county-level

Table 3-3. U.S. Carbon Monoxide Emissions (thousands of short tons)

Source Category	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Fuel Combustion Electrical Utility[a]	**314**	**321**	**363**	**349**	**350**	**363**	**370**	**372**	**394**	**406**
Fuel Combustion Industrial[b]	**669**	**672**	**879**	**920**	**955**	**1,043**	**1,041**	**1,056**	**1,072**	**1,110**
Fuel Combustion Residential, Commercial, Institutional[c]	**6,390**	**6,450**	**4,269**	**4,587**	**4,849**	**4,181**	**4,108**	**4,506**	**4,513**	**3,301**
Commercial/Institutional Coal	15	15	14	14	15	15	15	15	15	16
Commercial/Institutional Oil	18	17	18	17	18	18	18	19	19	19
Commercial/Institutional Gas	47	49	44	44	51	53	54	54	54	56
Miscellaneous Fuel Combustion (except residential)	55	55	149	141	141	143	147	145	163	168
Residential Wood (fireplaces and woodstoves)	6,086	6,161	3,781	4,090	4,332	3,679	3,607	3,999	3,993	2,278
Residential Other	168	153	262	281	292	274	268	273	269	264
Chemical and Allied Product Manufacturing[d]	**1,917**	**1,925**	**1,183**	**1,127**	**1,112**	**1,093**	**1,171**	**1,223**	**1,223**	**1,287**
Ferrous and Nonferrous Metal Processing[e]	**2,101**	**2,132**	**2,640**	**2,571**	**2,496**	**2,536**	**2,475**	**2,380**	**2,378**	**2,465**
Petroleum and Related Industries[f]	**441**	**436**	**333**	**345**	**371**	**371**	**338**	**348**	**348**	**364**
Other Industrial Processes[g]	**711**	**716**	**537**	**548**	**544**	**594**	**600**	**624**	**635**	**663**
Solvent Utilization	**2**	**2**	**5**	**5**	**5**	**5**	**5**	**6**	**6**	**6**
Storage and Transport	**56**	**55**	**76**	**28**	**17**	**51**	**24**	**25**	**25**	**26**
Waste Disposal and Recycling	**1,806**	**1,747**	**1,079**	**1,116**	**1,138**	**1,248**	**1,225**	**1,185**	**1,203**	**1,242**
Incineration	903	876	372	392	404	497	467	432	443	467
Conical wood burner	19	19	6	7	6	6	6	6	6	6
Municipal incinerator	35	35	16	17	15	14	14	15	15	16
Industrial	10	9	9	10	10	87	48	10	10	11
Commercial/institutional	38	39	19	20	21	21	21	21	22	23

Table 3-3 (cont'd). U.S. Carbon Monoxide Emissions (thousands of short tons)

Source Category	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Waste Disposal and Recycling (cont'd)										
Residential	800	773	294	312	324	340	347	351	360	380
Other	2	2	27	26	28	29	30	29	30	31
Open Burning	903	870	706	722	731	749	755	750	757	772
Industrial	21	21	14	14	15	15	15	15	16	16
Commercial/institutional	4	5	46	18	50	52	54	52	53	55
Residential	877	845	509	516	523	529	533	536	539	545
Other	NA	NA	137	144	144	153	153	147	149	156
Onroad Vehicles	**71,081**	**66,050**	**57,848**	**62,074**	**59,859**	**60,202**	**61,833**	**54,106**	**53,262**	**50,257**
Light-Duty Gas Vehicles and Motorcycles	45,553	42,234	37,407	40,267	39,370	39,163	37,507	33,701	28,732	27,036
Light-duty gas vehicles	45,367	42,047	37,198	40,089	39,190	38,973	37,312	33,500	28,543	26,847
Motorcycles	186	187	209	177	180	190	195	200	189	189
Light-Duty Gas Trucks	17,133	15,940	13,816	15,014	14,567	15,196	17,350	14,829	19,271	18,364
Heavy-Duty Gas Vehicles	7,072	6,506	5,360	5,459	4,569	4,476	5,525	4,123	3,766	3,349
Diesels	1,322	1,369	1,265	1,334	1,352	1,367	1,451	1,453	1,493	1,508
Heavy-duty diesel vehicles	1,290	1,336	1,229	1,298	1,315	1,328	1,411	1,412	1,453	1,468
Light-duty diesel vehicles	32	34	36	36	37	38	38	39	35	35
Nonroad Engines and Vehicles	**14,698**	**14,820**	**15,376**	**15,368**	**15,652**	**15,828**	**16,050**	**16,271**	**16,409**	**16,755**
Nonroad Gasoline	12,464	12,537	13,088	13,065	13,305	13,454	13,638	13,805	13,935	14,242
Recreational	318	321	359	365	370	374	378	382	386	389
Construction	401	398	355	329	334	348	382	393	400	423

Table 3-3 (cont'd). U.S. Carbon Monoxide Emissions (thousands of short tons)

Source Category	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Nonroad Engines and Vehicles (cont'd)										
Industrial	1,207	1,227	1,387	1,350	1,374	1,371	1,404	1,436	1,446	1,510
Lawn and garden	5,866	5,929	6,501	6,599	6,684	6,770	6,823	6,895	6,949	7,009
Farm	92	63	213	170	199	209	175	145	150	152
Light commercial	3,219	3,223	2,428	2,385	2,453	2,472	2,551	2,621	2,658	2,787
Logging	31	33	32	33	34	34	36	40	41	44
Airport service	144	147	116	114	118	119	121	129	131	141
Recreational marine vessels	1,185	1,195	1,698	1,720	1,739	1,757	1,769	1,763	1,775	1,788
Nonroad Diesel	1,129	1,149	1,180	1,207	1,236	1,268	1,300	1,329	1,330	1,301
Recreational	3	3	3	3	3	3	3	4	3	3
Construction	634	655	677	699	721	744	766	788	789	768
Industrial	150	148	146	146	147	149	152	155	156	154
Lawn and garden	23	25	27	30	32	35	38	41	44	47
Farm	176	177	178	179	180	181	183	184	182	176
Light commercial	44	45	46	48	49	51	53	54	56	56
Logging	58	58	58	58	57	57	56	56	52	45
Airport service	35	31	38	38	38	40	41	39	40	43
Railway maintenance	2	2	2	2	2	3	3	3	3	3
Recreational marine vessels	4	4	4	4	5	5	5	5	5	5
Aircraft	931	955	904	888	901	905	915	942	949	1,012
Marine Vessels	56	59	83	87	85	81	82	82	82	85
Railroads	118	121	121	120	125	120	114	114	112	115

Table 3-3 (cont'd). U.S. Carbon Monoxide Emissions (thousands of short tons)

Source Category	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Miscellaneous	**15,895**	**8,153**	**11,208**	**8,751**	**7,052**	**7,013**	**9,614**	**7,050**	**9,463**	**9,568**
Other Combustion	15,895	8,153	11,207	8,751	7,052	7,013	9,613	7,049	9,462	9,568
Structural fires	242	242	164	166	168	169	170	171	142	143
Agricultural fires	612	571	415	413	421	415	441	465	475	501
Slash/prescribed burning	4,332	4,332	4,668	4,713	4,760	4,810	4,860	4,916	4,955	5,033
Forest wildfires	10,709	3,009	5,928	3,430	1,674	1,586	4,114	1,469	3,863	3,863
Other	NA	NA	32	28	30	34	28	28	27	28
Total All Sources	**116,081**	**103,480**	**95,794**	**97,790**	**94,400**	**94,526**	**98,854**	**89,151**	**90,929**	**87,451**

Major Subcategories:
[a]Coal burning
[b]Natural gas burning
[c]Residential wood burning
[d]Carbon black manufacturing
[e]Ferrous metal production
[f]Refineries
[g]Wood, paper, and pulp

Notes:
NA = not available. For several source categories, emissions either prior to or beginning with 1985 are not available at the more detailed level but are contained in the more aggregate estimate. "Other" categories may contain emissions that could not be allocated accurately to specific source categories. To convert emissions to gigagrams (thousands of metric tons), multiply the above values by 0.9072.

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

statistics for vehicle registration, as well as the use of temperature data from individual counties. The value of 6.2×10^7 short tons (56 Tg) shown in Table 3-3 for emissions from onroad vehicles for 1991 may be compared to a value of 4.0×10^7 short tons (36 Tg) derived from remote sensing of vehicle exhausts for 1991 (Bradley et al., 1999).

In addition, it should be noted that Table 3-3 does not include formation of secondary CO, such as from the oxidation of isoprene. Annual emissions of isoprene in the contiguous United States are about 17.2 Tg/year (Pierce and Dudek, 1996). A source of CO of 7.1 Tg/year can be calculated using the conversion factor of 0.20 for carbon in isoprene to carbon in CO estimated by Jacob and Wofsy (1990). This value would add about 9% to the estimated U.S. emissions for CO in 1995, 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 sampling in tunnels 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 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 had been systematically underestimated by as much as a factor of two in emissions factor models. As a result of these studies, a number of revisions have been made to emissions inventories.

Roadside remote sensing data indicate that over 50% of CO and NMHC emissions are produced by less than 10% of the vehicles (Lawson et al., 1990; Stephens and Cadle, 1991). These "superemitters" are typically older, poorly maintained vehicles. Bishop and Stedman (1996) also found that the most important variables governing CO emissions are fleet age and owner maintenance. 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 and the failure of that 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 usually is done. For example, rapid accelerations have been shown to increase emissions relative to less stressful driving modes.

Roadside remote sensing of motor vehicle emissions has been used to evaluate the effectiveness of inspection and maintenance programs in a number of locations (Zhang et al., 1996; Stedman et al., 1997, 1998). These studies generally have yielded disappointing results, indicating undetectable or smaller than expected effects of inspection on vehicle emissions. Detailed analyses implicate behavioral responses, such as shopping for a passing inspection (Bishop and Stedman, 1996) and reregistering nonconforming vehicles in neighboring counties (Stedman et al., 1997, 1998). Roadside emissions data also have been used to evaluate the effects of reformulated fuels on emissions. Remote sensing (Bishop and Stedman, 1990) and tunnel measurements (Gertler et al., 1999) both indicate fleet CO reductions in the 15 to 20% range.

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). However, in a reinterpretation of the Van Nuys tunnel data using more recent versions of these models, Pollack et al. (1998) found that emissions factors calculated using MOBILE5a were a few percent greater 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) indicated that both versions of the MOBILE model gave predictions within ±50% of observations most of the time (Pierson et al., 1996). However, it should be noted that emissions in tunnels

arise from vehicles in warmed-up or hot-stabilized operation. Cold and hot start emissions, which are important components of the emissions inventory, generally are not present in tunnels and, thus, are not evaluated in these studies.

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 the 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 the effects of atmospheric processing and transport, emerged 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_x 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 to NO_x ratio for Los Angeles and the San Joaquin Valley show better agreement than in the previous studies mentioned above (Croes et al., 1996; Ipps and Popejoy, 1998; Haste et al., 1998). These improvements have arisen largely through the process of model development, evaluation, and further refinement.

Stationary sources account for approximately 23% of nationwide CO emissions shown in Table 3-3. Indoor sources represented in Table 3-3 by residential combustion of wood and other fuels account for only about 3% of annually averaged, nationwide CO emissions. However, on a local basis where wood burning is widespread, these sources can account for significant fractions of the CO present in ambient air. Khalil and Rasmussen (1988b, 1989) have shown that during the winter in Medford, OR, and in Olympia, WA, the contribution of wood burning to CO concentrations was of comparable importance to automobiles. Khalil and Rasmussen (1999) have found that biomass burning, which takes the form of agricultural burning during the fall and residential wood burning during the winter, accounts for 20 to 40% of excess over nonurban background CO concentrations.

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 or equal to 35 ppm (40 mg/m^3), and the second-highest, nonoverlapping 8-h value is less than or equal to 9 ppm (10 mg/m^3). Nationwide trends in ambient CO concentrations are presented in Section 3.4.1, diurnal variations in ambient CO concentrations 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 is presented in Section 3.4.3. The analyses in Section 3.4.3 were performed for the Denver, CO (Shadwick et al., 1997); Los Angeles; New York City, NY; and Phoenix, AZ, Metropolitan Statistical Areas (MSAs) (Shadwick et al., 1997, 1998a,b,c) and for Fairbanks, AK.

Figure 3-3. Locations of sites in the nationwide ambient CO monitoring network, 1997.
Source: U.S. Environmental Protection Agency (1998).

3.4.1 Nationwide Trends in Ambient Carbon Monoxide Concentrations

In 1997, 538 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 3-3 displays the geographic locations of the monitoring sites reporting CO data to AIRS for 1997. 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 specific monitoring needs. These NAMS and SLAMS sites conform to uniform criteria for monitorsiting, 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).

Twenty-seven sites in 15 areas failed to meet the 8-h CO NAAQS in at least 1 year of the 5-year period, 1993 to 1997. In 1996, only six of the sites shown in Figure 3-3 failed to meet the 8-h standard of 9 ppm, and none of the 538 monitoring sites exceeded the 1-h standard of 35 ppm. The locations of these 27 sites and the second-highest 8-h CO concentrations and the number of exceedances by year are given in Table 3-4.

Figure 3-4 shows the consistent, downward trend in the nationwide composite average of the annual second-highest 8-h CO concentration during the 20-year period, 1978 through 1997. 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 3-4 tracks the trend in the composite mean of the annual second-highest 8-h average concentration for 184 monitoring sites that reported ambient air quality data in at least 17 of the 20 year period, 1978 to 1997. 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 90 cities in 39 states. Each year, site leases are lost, or sites are discontinued, and new sites come online; therefore, the 184 long-term-trend sites compose only one-third of the currently active CO monitors. The solid line in Figure 3-4 shows the trend in the composite mean for a larger database of 368 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 1988. Specific computational details are described elsewhere (U.S. Environmental Protection Agency, 1998). This larger data set permits the examination of the intersite variability in peak CO concentrations. Figure 3-5 presents the 10th, 50th, and 90th percentile concentrations and the composite mean concentrations across these 368 sites. The 10th, 50th, and 90th CO

Table 3-4. Sites Not Meeting the 8-Hour Carbon Monoxide National Ambient Air Quality Standard, 1993 to 1997

		1993		1994		1995		1996		1997	
Location	Airs Site ID	2nd Max[a]	No. Exc.[b]	2nd Max	No. Exc.	2nd Max	No. Exc.	2nd Max	No. Exc.	2nd Max	No. Exc.
Anchorage, AK	020200017	7.7	0	8.3	0	7.6	0	9.6	3	6.8	0
	020200018	9.7	2	8.6	0	7.4	0	8.7	0	7.1	0
	020200037	9.9	2	11	2	8.4	0	10.5	3	7	0
Denver, CO	080310002	10.4	2	8.2	1	9.5	2	7.3	0	5.5	0
Detroit, MI	261630014	5.6	0	10.3	2	5.6	0	4.5	0	n/d[c]	n/d
El Paso, TX	481410027	7.4	0	7.1	1	7.9	0	10.3	2	7.9	1
	481410044	10.6	2	7.6	0	7.5	0	9.1	1	7.2	1
Fairbanks, AK	020900002	10.1	5	10.2	3	11.8	9	8.6	1	12.1	3
	020900013	9.6	2	8.5	1	10.6	3	8.4	0	10.8	2
	020900020	9	1	9.8	3	11.6	7	8.6	0	10.6	4
Flathead Co., MT	300290045	n/d	n/d	n/d	n/d	6.5	0	11.1	2	4.9	0
Calexico, CA	060250005	n/d	n/d	12.9	10	19.7	15	14.1	9	16.7	12
	060250006	n/d	n/d	n/d	n/d	n/d	n/d	7.8	0	9.6	2
Jersey City, NJ	340175001	7.6	0	10.7	3	8.1	1	6.7	0	6.7	0
Las Vegas, NV/AZ	320030557	9.9	3	10.6	5	9.2	1	10.1	3	6.3	0
Los Angeles-Long Beach, CA	060371002	8.1	0	10.2	5	11	5	8.5	0	7.2	0
	060371201	8	0	9.9	3	9.4	1	6.7	0	7.7	1
	060371301	13.8	20	15.3	24	11.6	14	14.5	22	15	12

Table 3-4 (cont'd). Sites Not Meeting the 8-Hour Carbon Monoxide National Ambient Air Quality Standard, 1993 to 1997

		1993		1994		1995		1996		1997	
Location	Airs Site ID	2nd Max[a]	No. Exc.[b]	2nd Max	No. Exc.	2nd Max	No. Exc.	2nd Max	No. Exc.	2nd Max	No. Exc.
	060375001	9.6	2	11.3	6	8.7	0	10.5	5	7.9	1
Newark, NJ	340390003	6	0	11.3	2	7.7	0	6	0	5.1	0
Phoenix-Mesa, AZ	040130019	8	0	9.6	2	8.4	0	8.2	0	7	0
	040130022	n/d	n/d	n/d	n/d	9.9	3	10	2	7.8	1
Provo-Orem, UT	490490004	9.6	2	9.3	1	7.1	0	9.1	1	n/d	n/d
Spokane, WA	530630040	9.8	2	8.1	0	8.4	0	9	1	6.3	0
	530630044	11.8	4	8.8	0	11.2	4	8.4	1	n/d	n/d
Steubenville-Weirton, OH-WV	540290009	8.3	1	9.6	2	6	0	6.2	0	8.8	1
	540290011	9.4	1	17.1	5	6.7	1	3.6	0	2.5	0

[a] Annual second-highest nonoverlapping 8-h average CO concentration.
[b] Number of exceedances of the 8-h CO NAAQS.
[c] n/d = no data.

Source: U.S. Environmental Protection Agency's Aerometric Information Retrieval System (AIRS).

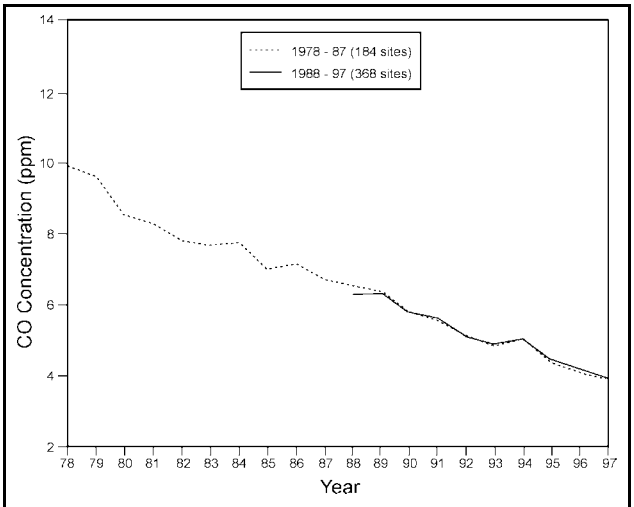

Figure 3-4. Nationwide composite average of the annual second-highest 8-h CO concentrations, 1978 to 1997.
Source: U.S. Environmental Protection Agency (1998).

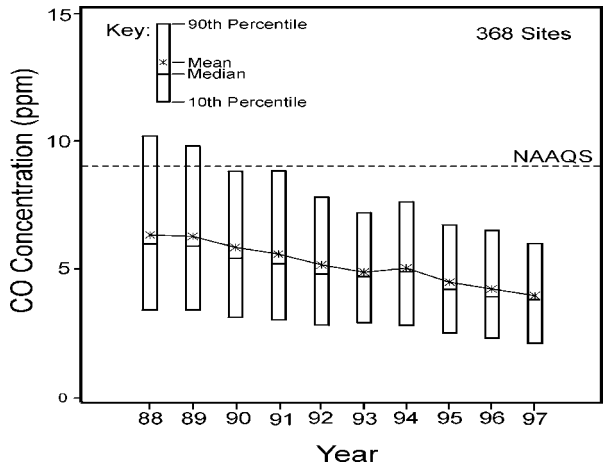

Figure 3-5. Variability in the annual second-highest 8-h CO concentrations across all sites in the United States reporting at least 8 years of data, 1988 to 1997.
Source: U.S. Environmental Protection Agency (1998).

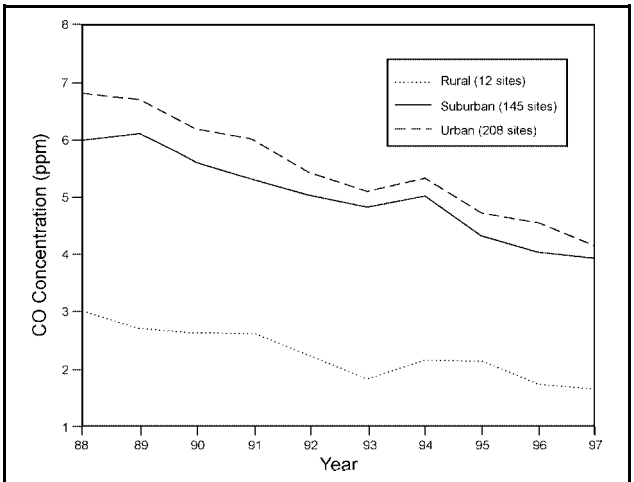

Figure 3-6. Composite average of the annual second-highest 8-h CO concentrations for rural, suburban, and urban sites, 1988 to 1997.
Source: U.S. Environmental Protection Agency (1998).

concentrations for each year are indicated, respectively, by the bottom, middle, and top lines of each box. For example, 10% of the 368 trends sites reported 1988 second-highest 8-h CO concentrations lower than the bottom of the first bar in Figure 3-5. The yearly composite mean across all 368 sites is indicated by the"×" in each bar. Figure 3-6 shows trends in CO concentrations in each of the different sampling environments (urban, suburban, and rural sites). As can be seen from Figure 3-6, the downward trend in ambient CO concentrations occurred at monitoring sites in urban, suburban, and rural environments. An interesting feature of the data shown in Figures 3-4 to 3-6 is the increase in CO concentrations from 1993 to 1994, which is the only year over year increase except for 1985 to 1986. The increase corresponds to an increase in mobile source and wildfire emissions presented in Table 3-3. The decrease in ambient CO concentrations measured in populated areas over the past decade also is reflected at least at one continental background site at Shenandoah National Park, VA (Hallock-Waters et al., 1999).

3.4.2 Circadian Patterns in Carbon Monoxide Concentrations

The circadian variation in winter time, composite, hourly CO concentrations from 1987 through 1996 is shown in Figure 3-7 (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 primarily from CO emitted into the relatively shallow morning boundary layer by motor vehicles (e.g., Fujita et al., 1992). The CO concentrations decline towards mid-afternoon, as the height of the atmospheric mixing layer increases and then increase again with the onset of the evening rush hour. Carbon monoxide concentrations fall off less rapidly after the afternoon peak because the mixing layer height decreases during evening and

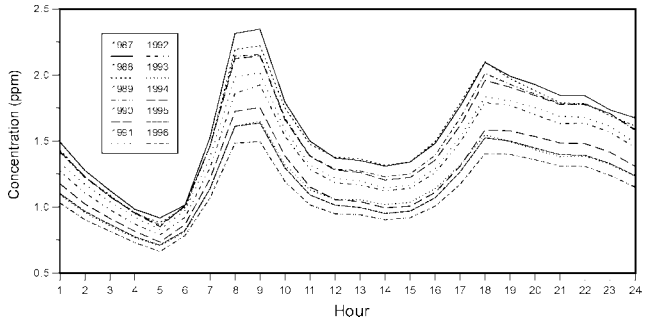

Figure 3-7. Diurnal variation of nationwide composite hourly average CO concentrations for winter (December to February), 1987 to 1996.
Source: Cohen and Iwamiya (1998).

nighttime. There is a general decrease in CO concentrations 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.

The circadian pattern of 8-h average CO concentrations that exceed 9.5 ppm is somewhat different from the hourly average concentration pattern shown in Figure 3-7. One way to estimate the time of day when 8-h average CO concentrations are likely to exceed 9.5 ppm is to total 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 CO criteria document (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 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.

Table 3-5. Running-Average Exceedances of the 9-ppm 8-Hour Carbon Monoxide Standard, 1988, 1996, and 1997

Location	AIRS Site ID	1988	1996	1997	1997 Data Completeness
Lynwood, CA	060371301	392	110	62	Jan.-Dec. 1997
Hawthorne, CA	060375001	163	19	2	Jan.-Dec. 1997
Las Vegas, NV	320030557	102	3	0	Jan.-Mar. 1997
New York City, NY	360610081	123	NA[a]	0	Jan.-June, Oct.-Dec. 1997
Steubenville, OH	390811012	152	0	0	Jan.-Sep. 1997
Spokane, WA	530630040	169	1	0	Jan.-Dec. 1997

[a] NA = not available

Note: As of June 14, 1999, the 1997 data for the Las Vegas, New York City, and Steubenville stations were incomplete. Based on 1996 data, Steubenville probably is not a problem; the New York City station is missing summer months, and the "zero" is probably warranted; and the Las Vegas station is missing the fall 1997 months; hence, the conclusion is indeterminate.

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

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.

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 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 concentrations 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.

3.4.3 Characterization of the Spatial and Temporal Variability in Carbon Monoxide Concentrations in Selected U.S. Cities

The spatial and temporal variability of ambient carbon monoxide was characterized in four MSAs in the continental United States (New York, Denver, Phoenix, and Los Angeles) and for Fairbanks. These five urban areas were chosen to characterize the spatial and temporal variability in CO in widely different geographic regions. New York City is characterized by urban canyons. Denver is a rapidly growing, high-altitude city. Phoenix is a rapidly growing city in an arid environment. Los Angeles is characterized by emissions which are confined to a mountain basin. Fairbanks is located in a mountain valley with a much higher potential for air stagnation than the continental U.S. cities. Each of these cities has been in nonattainment of the 8-h NAAQS for CO at some time within the past 5 years. In addition, the four cities in the continental Unites States have been the locations of studies either characterizing personal exposure to CO or relating health outcomes to air pollution concentrations.

Hourly average CO data obtained from EPA's AIRS 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 urban area for both the hourly and 8-h running averages. The statistics were analyzed by year, season, day of week, and hour of the day.

Figures 3-8 through 3-12 graphically represent air quality data from the Denver area CO monitoring sites, then similar data are presented for CO monitoring sites in Los Angeles (Figures 3-13 through 3-19), New York (Figures 3-20 through 3-24), and Phoenix (Figures 3-25 through 3-29) metropolitan areas. Analysis of ambient CO data obtained in these four geographically diverse MSAs has shown that urban CO concentrations 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 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 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 from 0.4 to 1.5 ppm in the Denver MSA, 0.4 to 3.2 ppm in the Los Angeles Consolidated Metropolitan Statistical Area (CMSA), 0.6 to 3.7 in the New York CMSA, and 0.7 to 3.4 in the Phoenix MSA. A more detailed analysis of the spatial variability in CO concentrations in these four MSAs in the continental United States and in Fairbanks is given in Appendix 3A. 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 metropolitan areas 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 3-7 or other locations, such as the Denver or New York MSAs. Colucci and Begeman (1969) suggested that the higher concentrations found in Los Angeles than in Detroit, MI, or New York were caused, at least in part, by more frequent temperature inversions and lower wind speeds in Los Angeles. 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 concentrations (typically no more than 1 to 2 ppm and often less than that amount) before they

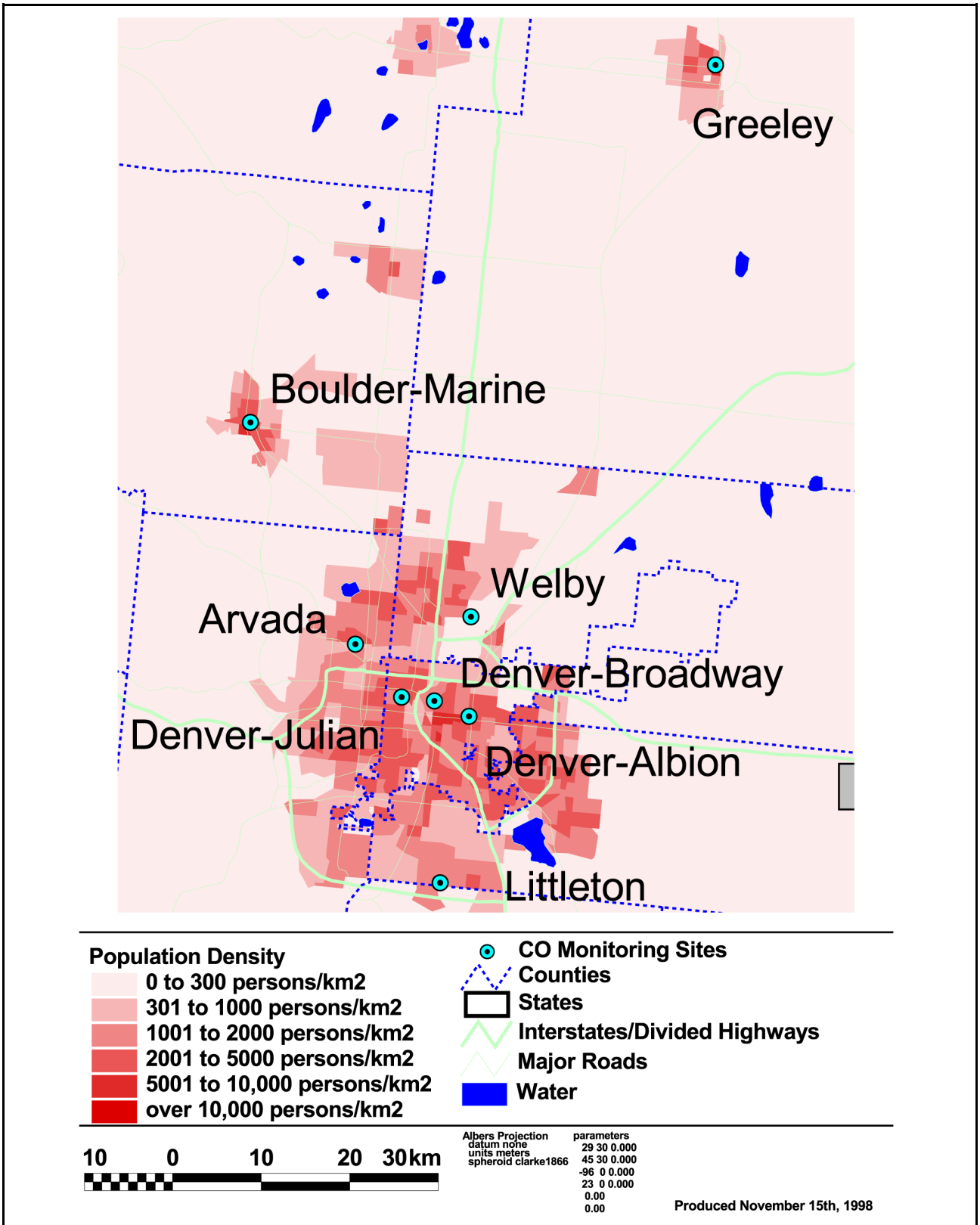

Figure 3-8. Map of Denver showing locations of CO monitoring sites.

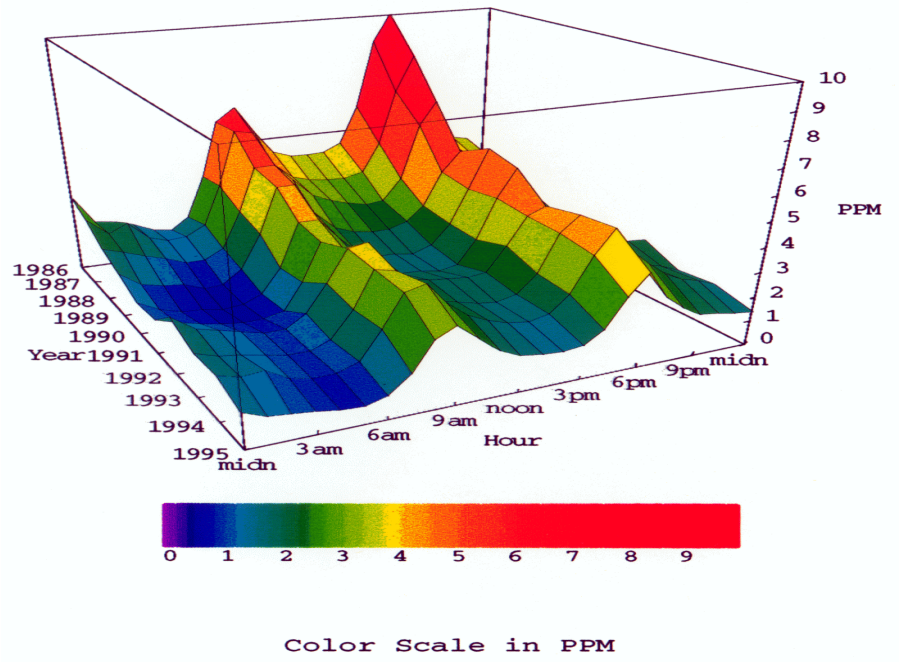

Figure 3-9. Average diurnal variation in CO at the Denver-Broadway site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986-87 through 1995-96, and the z-axis shows CO concentration in parts per million.

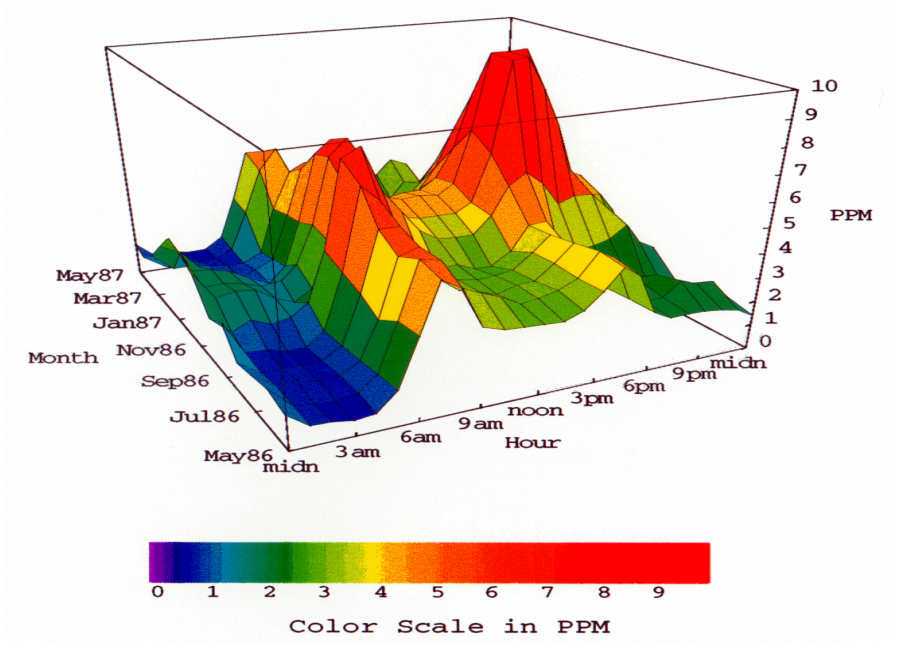

Figure 3-10. Monthly average diurnal variation in CO at the Denver-Broadway site for weekdays from May 1986 through May 1987. The abscissa shows the time of day, the ordinate shows the month of the year, and the z-axis shows CO concentration in parts per million.

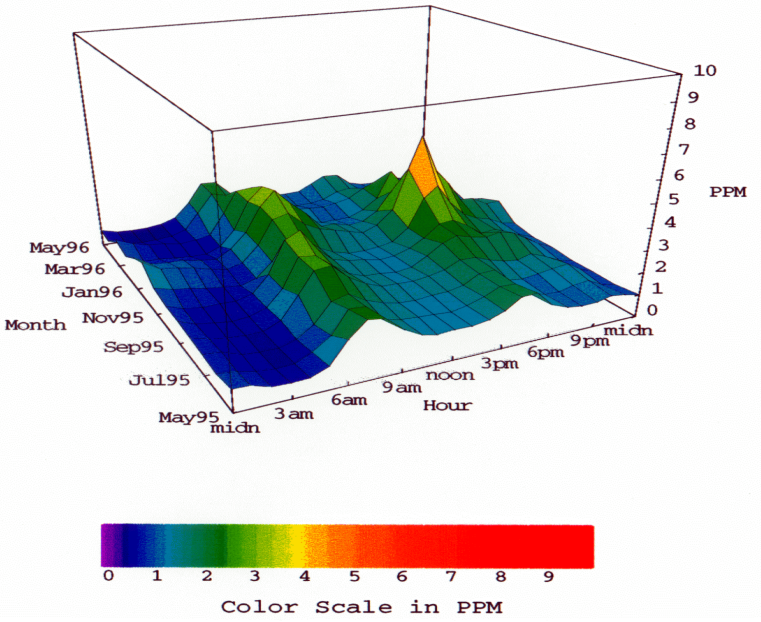

Figure 3-11. Monthly average diurnal variation in CO at the Denver-Broadway site for weekdays from May 1995 through May 1996. The abscissa shows the time of day, the ordinate shows the month of the year, and the z-axis shows CO concentration in parts per million.

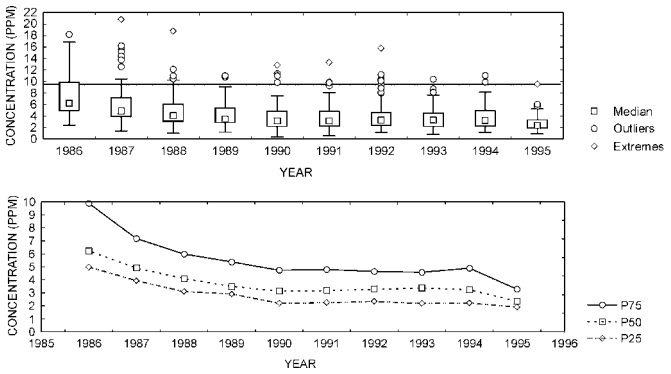

Figure 3-12. Central tendency statistics for the daily 8-h max CO concentration at the Denver-Broadway site during the winter season from 1986 to 1995. The top graph shows box plots (with 10, 25, 50, 75, and 90 percentile values) for the entire time series. Each circle (outlier) or diamond (extreme) 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, respectively) from the upper graph.

begin to increase again because of the morning rush hour. This pattern is shown quite well in Figure 3-26, which depicts the seasonal diurnal concentration profile for the Central Phoenix site. Comrie and Diem (1999) found that the timing and strength of the nocturnal low-level thermal inversion is the dominant meteorological factor affecting CO concentrations in Phoenix.

In general, the highest values of ambient CO were found during the wintertime (defined as the months of November through February) in all of the MSAs included here. During colder seasons, there is a higher incidence of enhanced stability in the atmospheric boundary layer, inhibiting vertical mixing (dilution) of emissions from the surface. 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 3-21) 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.

A map of Fairbanks showing the locations of the CO monitoring sites is shown in Figure 3-30. Fairbanks is located in the Tanana Valley, in the interior of Alaska and exhibits a number of significant differences in climatology from the four MSAs described previously. Although the areas in the continental

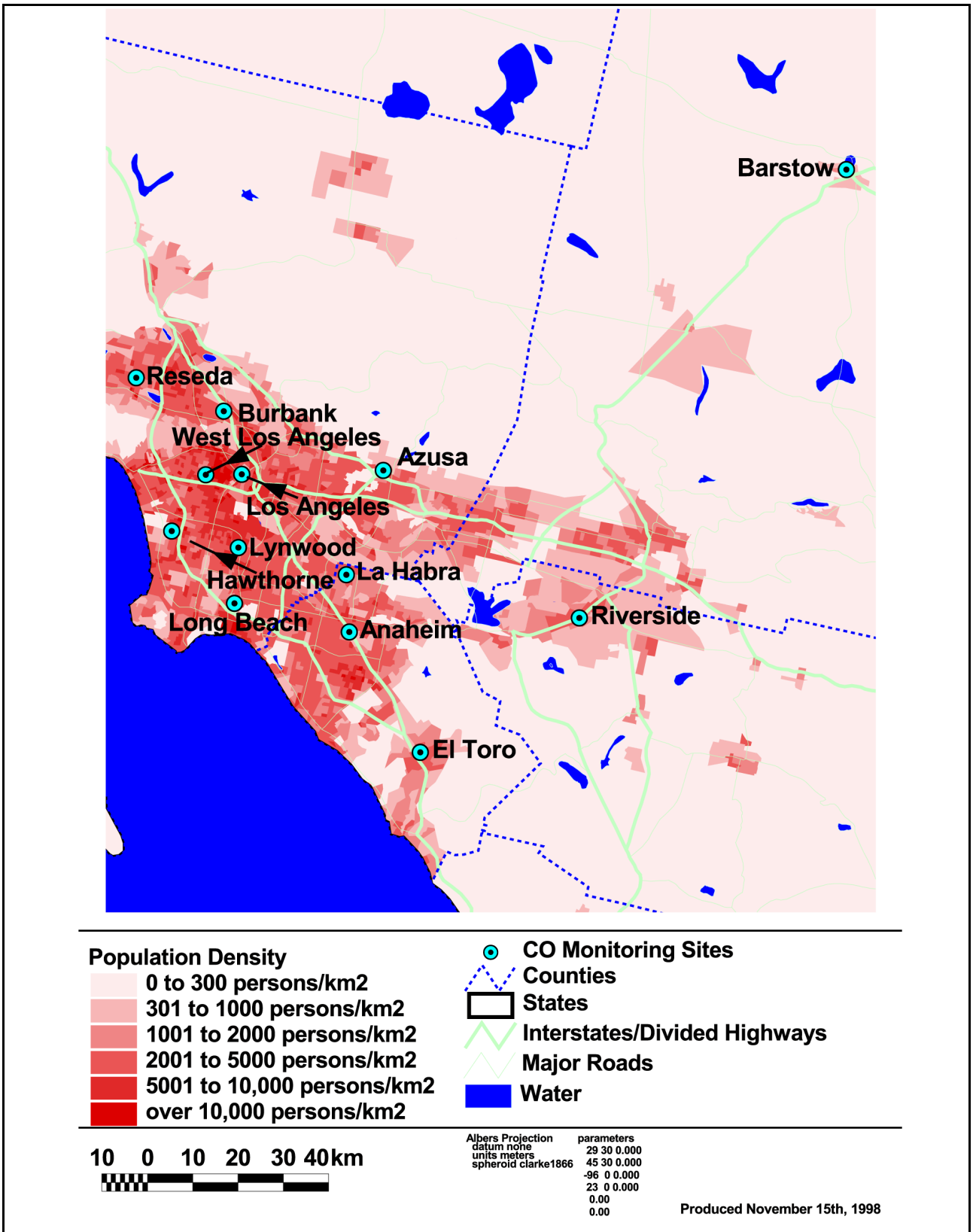

Figure 3-13. Map of Los Angeles showing locations of CO monitoring sites.

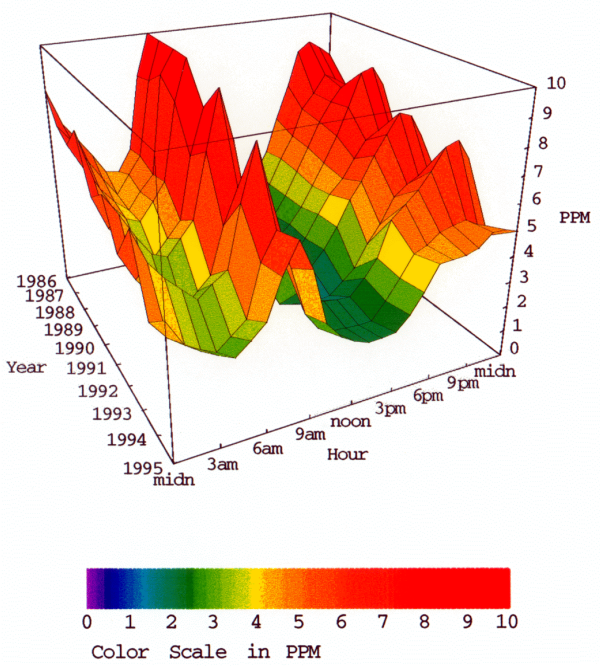

Figure 3-14. Average diurnal variation in CO at the Los Angeles-Lynwood site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986-87 through 1995-96, and the z-axis shows CO concentration in parts per million.

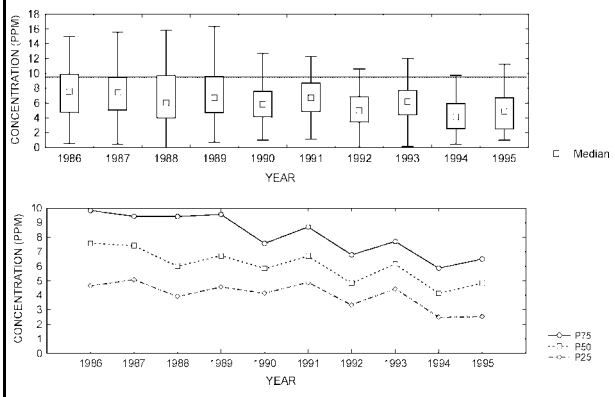

Figure 3-15. Central tendency statistics for the daily 8-h max CO concentration at the Los Angeles-Hawthorne site during the winter season from 1986 to 1995. The top graph shows box plots (with 10, 25, 50, 75, and 90 percentile values) for the entire time series. The horizontal line shows the current 8-h NAAQS for CO. The lower graph again shows the 25, 50, and 75 percentile values (P25, P50, and P75, respectively) from the upper graph.

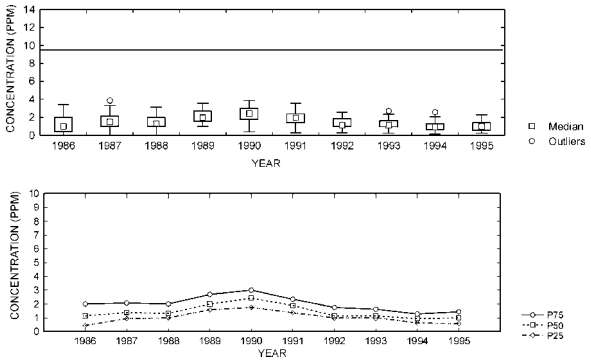

Figure 3-16. Central tendency statistics for the daily 8-h max CO concentration at the Los Angeles-Barstow site during the winter season from 1986 to 1995. The top graph shows box plots (with 10, 25, 50, 75, and 90 percentile values) for the entire time series. Each circle (outlier) refers to an individual 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, respectively) from the upper graph.

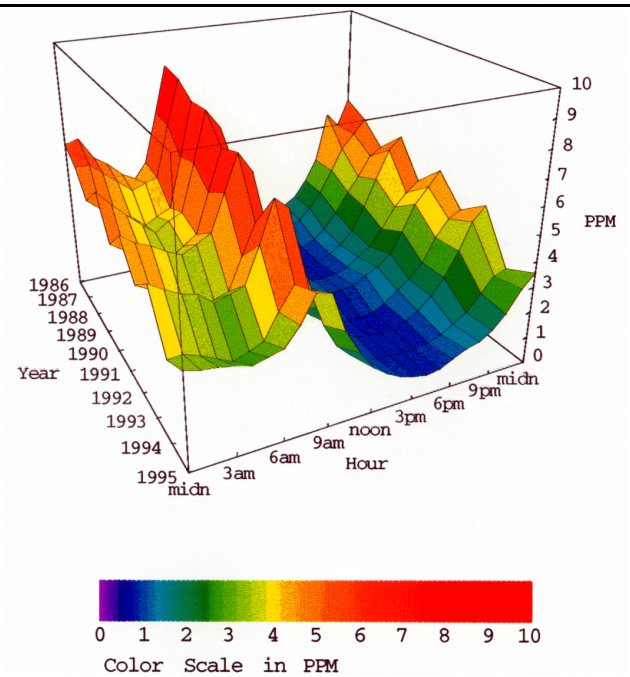

Figure 3-17. Average diurnal variation in CO at the Los Angeles-Hawthorne site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986-87 through 1995-96, and the z-axis shows CO concentration in parts per million.

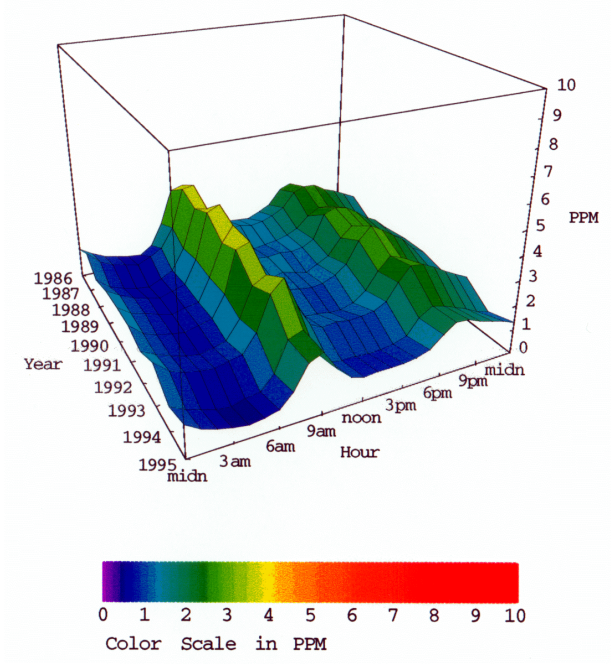

Figure 3-18. Average diurnal variation in CO at the Los Angeles-El Toro site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986-87 through 1995-96, and the z-axis shows CO concentration in parts per million.

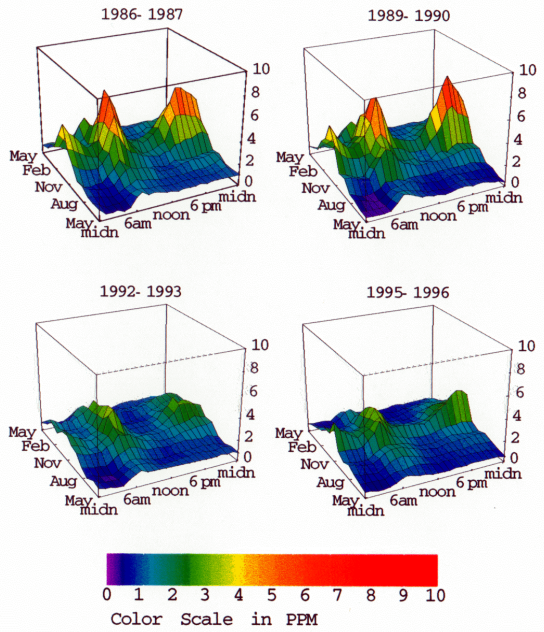

Figure 3-19. Monthly average diurnal variation in CO at the Los Angeles-Anaheim site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and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

United States are subject to nocturnal inversions that are more pronounced during the winter season, the low solar elevation, even at midday, particularly in December and January, result in nocturnal inversion conditions that can persist 24 h/day in Fairbanks. The median midwinter inversion duration varied from 2 to 4 days in a study of the climatology of surface-based inversions at several sites in Alaska (Point Barrow, Barter Island, and Kotzebue) and Northern Canada (Alert, Eureka, Mould Bay, Resolute, Sachs Harbour, and Inuvik) (Bradley et al., 1992). Hence, intense inversions may continue during the hours of maximum CO emissions (typically rush hour traffic). Downtown mixing heights as low as 10 m and wind speeds less than 0.5 m/s have been measured simultaneously in Fairbanks. The result is that even nonindustrial areas of moderate size such as Fairbanks are subject to high CO levels (Bowling, 1986).

A unique meteorological feature of extreme cold weather climates like that at Fairbanks is the formation of ice fog (Robinson and Bell, 1956). Ice fogs are typically present at temperatures below −30 °C. Ice fogs in Fairbanks vary from 10 m to over 100 m in depth, which tends to deepen the mixing layer. This increases dilution, resulting in lower CO concentrations. One study suggests that ice fog days have only 40 to 50% of the CO concentrations seen on otherwise similar non-ice-fog days (Bowling, 1986).

The average hourly diurnal CO concentration patterns during the winter months for the period from 1986 through 1995 are shown in Figure 3-31 for the Federal Building site. A downward trend in the hourly average values is seen over the 10-year period. It is particularly interesting to note the shape of the diurnal pattern in Figure 3-31. The daily CO concentration minimum occurs at approximately 6:00 a.m. This is followed by a very rapid increase in CO levels that coincides with morning commuting activity. Then, at approximately 9:00 a.m., the *rate* of change in CO concentrations remains positive but decreases in magnitude (i.e., the concentrations are still increasing, but at a lower rate). At about 4:00 p.m., the rate of change in CO concentrations noticeably increases again. The increase usually culminates with the daily 1-h average maximum CO value occurring approximately between 5:00 and 6:00 p.m. After the occurrence of the daily CO maximum at approximately 6 p.m., the concentrations rapidly decrease. The decrease in

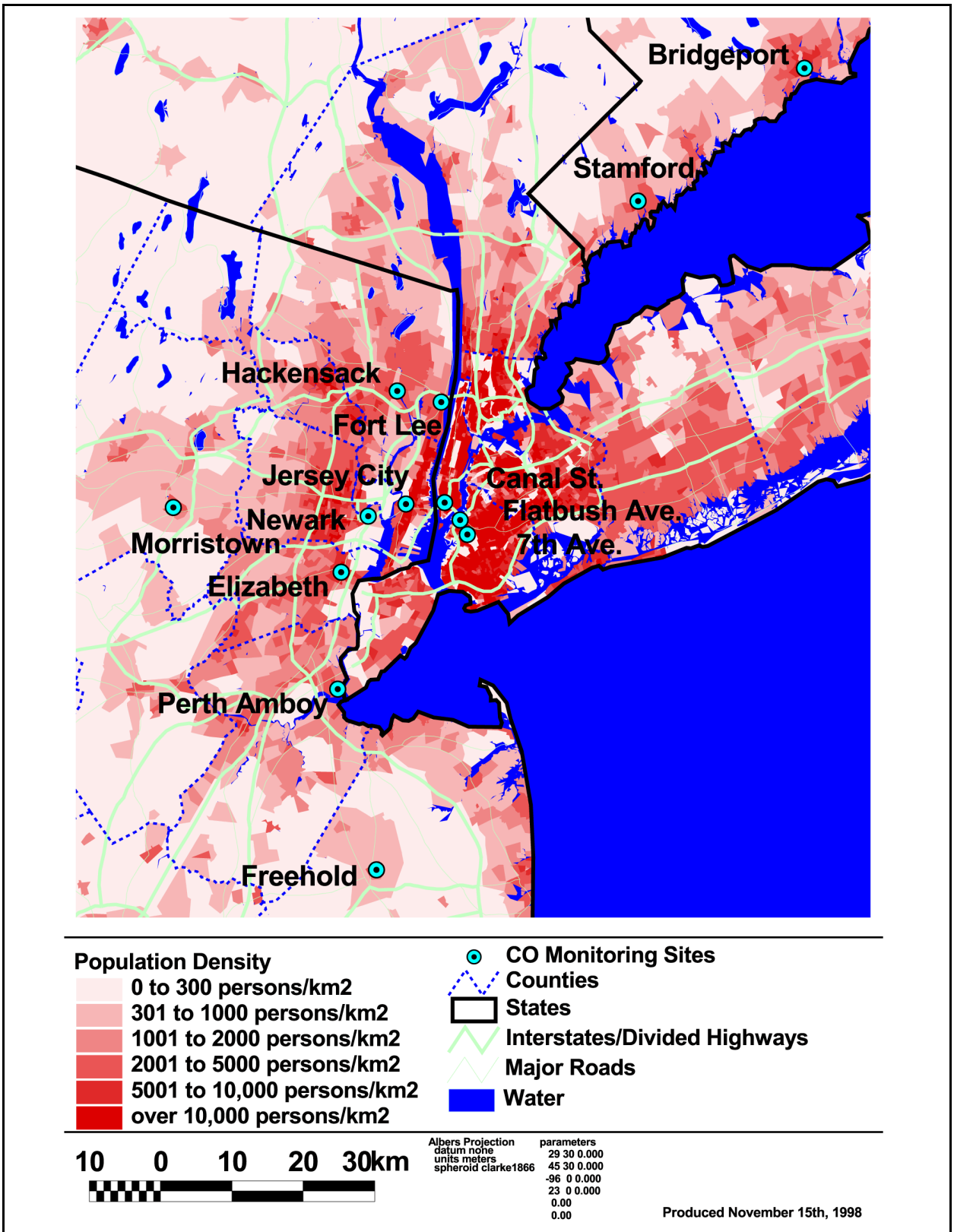

Figure 3-20. Map of New York showing locations of CO monitoring sites.

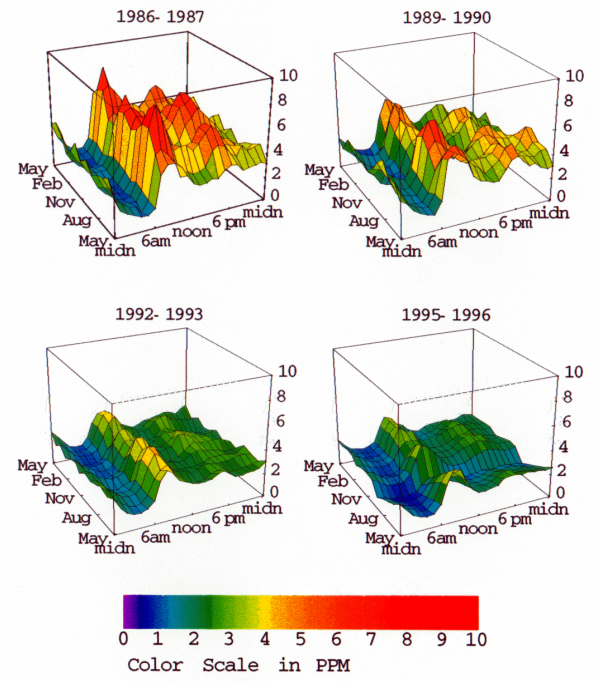

Figure 3-21. Monthly average diurnal variation in CO at the New York-Flatbush site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the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

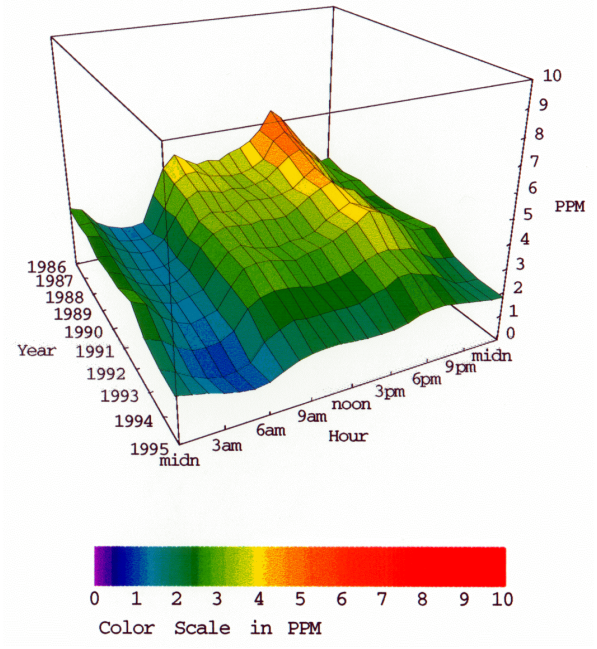

Figure 3-22. Average diurnal variation in CO at the New York-Manhattan site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986-87 through 1995-96, and the z-axis shows CO concentration in parts per million.

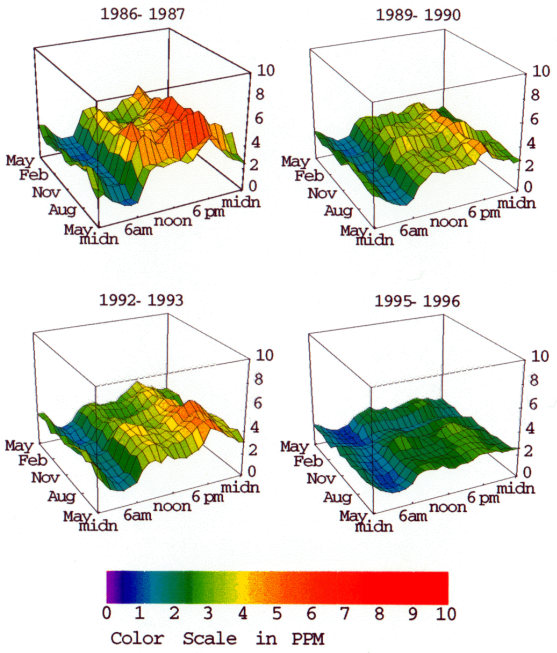

Figure 3-23. Monthly average diurnal variation in CO at the New York-Manhattan site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis shows CO concentration in parts per million.

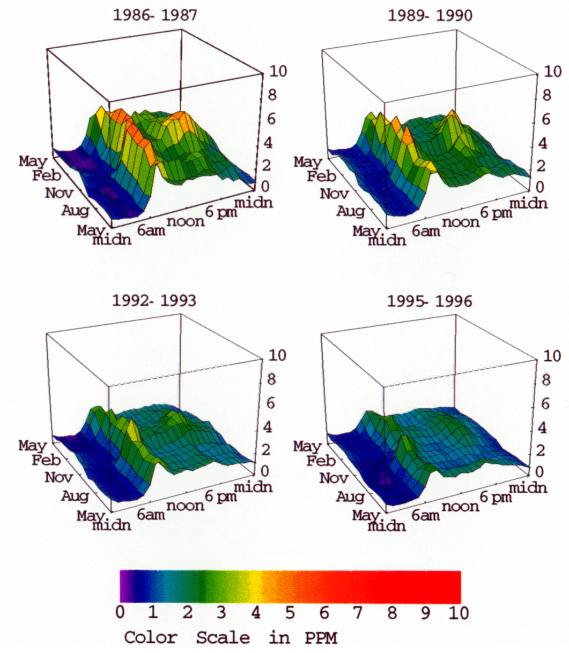

Figure 3-24. Monthly average diurnal variation in CO at the New York-Morristown, NJ, site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis on each graph shows CO concentration in parts per million.

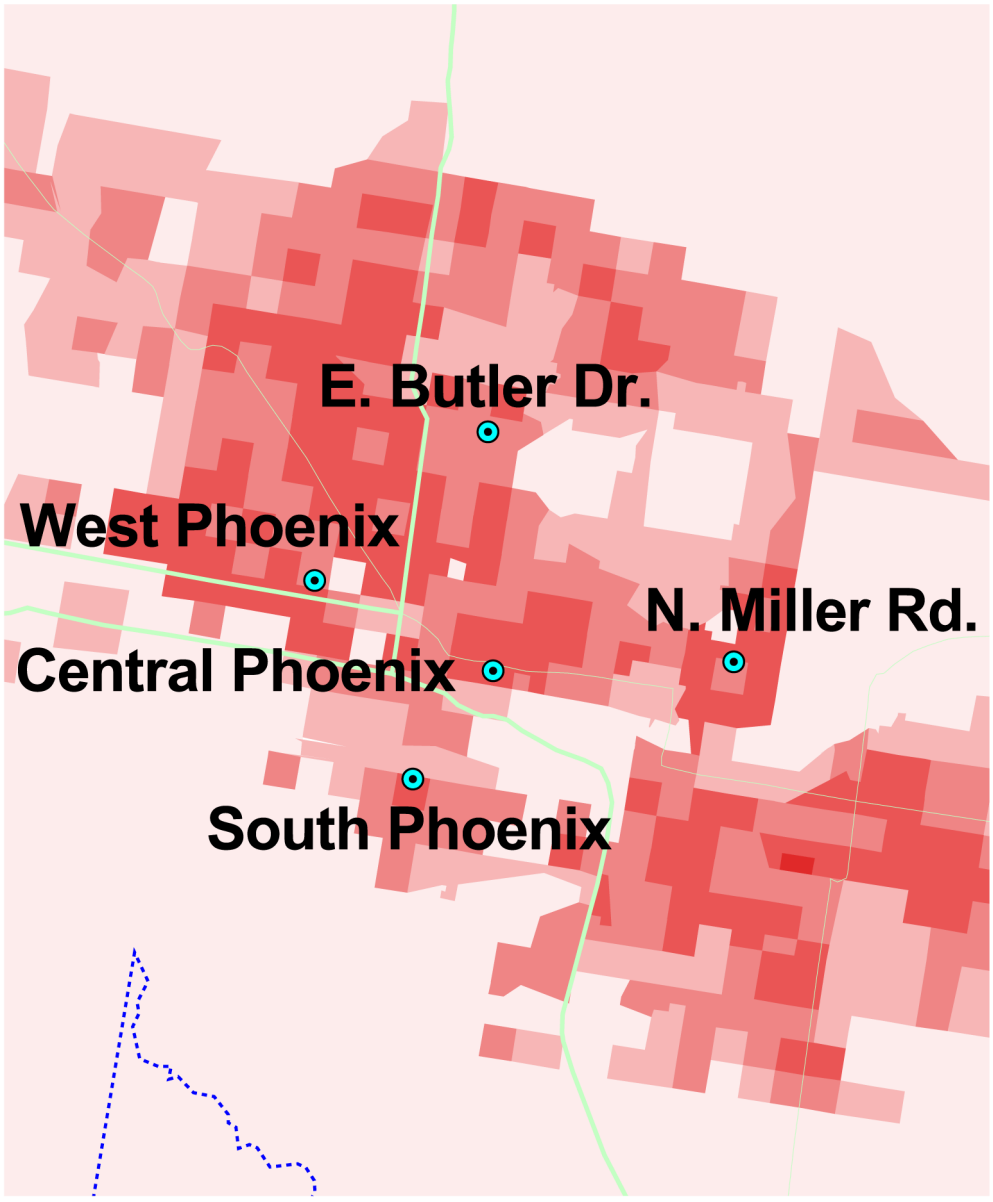

Figure 3-25. Map of Phoenix showing locations of CO monitoring sites.

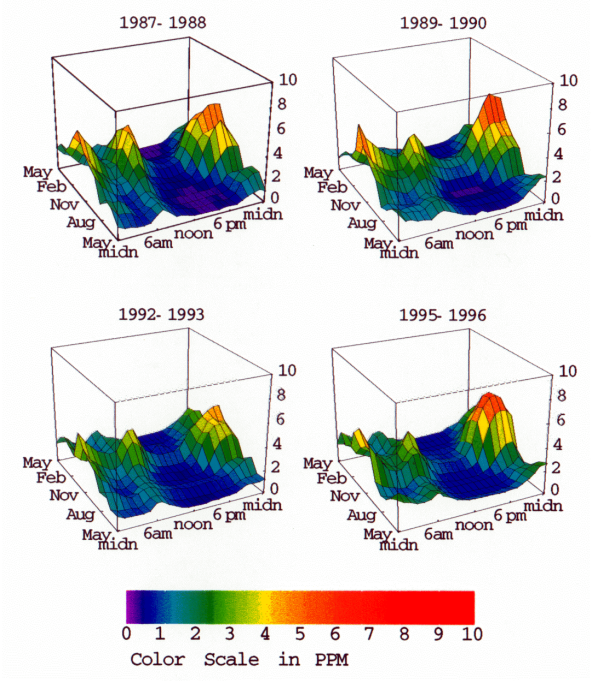

Figure 3-26. Monthly average diurnal variation in CO at the Phoenix-Central site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis shows CO concentration in parts per million.

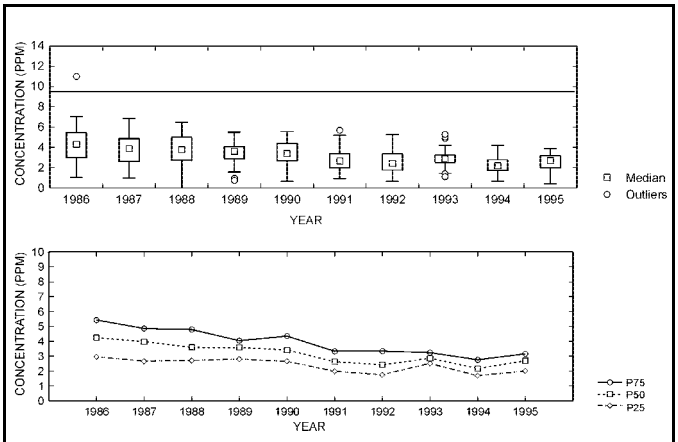

Figure 3-27. Central tendency statistics for the daily 8-h max CO concentration at the Phoenix-East Butler site during the winter season from 1986 to 1995. The top graph shows box plots (with 10, 25, 50, 75, and 90 percentile values) for the entire time series. Each circle (outlier) refers to an individual 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, respectively) from the upper graph.

CO concentrations continues until the concentration minimum occurs at approximately 6:00 a.m., when, on weekdays, the cycle repeats. This diurnal CO pattern indicates a situation where there are bimodal peaks in concentration but inadequate dilution between peaks to reduce the CO concentration from one maxima to the other. This diurnal pattern contrasts with those found in the continental U.S. cities described earlier (cf. Figures 3-9, 3-14, 3-17, and 3-18) and, indeed, from the nationwide diurnal pattern shown in Figure 3-7.

The central tendency statistics for the daily maximum 8-h average CO concentrations for the winter season from 1986 to 1995 for the Fairbanks Federal Building site are shown in Figure 3-32. The median and interquartile range have remained relatively unchanged from about 1989 to 1995, the last complete winter season in this analysis. Of particular interest is the apparent upward trend in the wintertime daily maximum 8-h average CO concentrations after a brief period of lower values from about 1990 to 1992. Since then, however, the number and magnitude of daily maximum 8-h average CO concentrations over 9 ppm (the 8-h average NAAQS for CO) have increased. This pattern again contrasts with that for the four

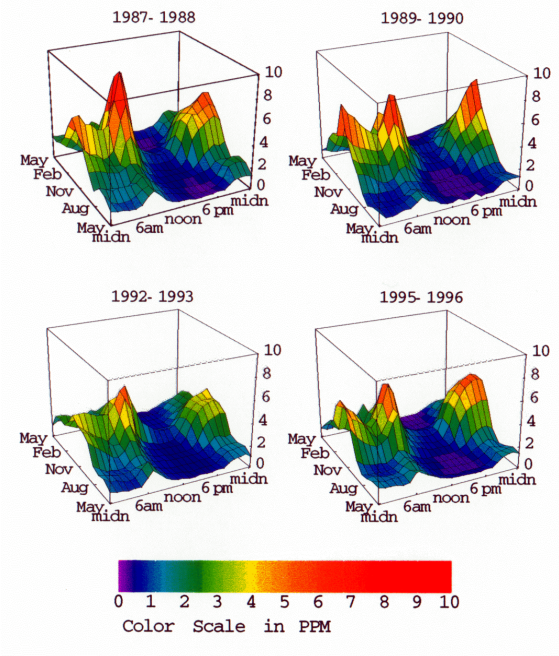

Figure 3-28. Monthly average diurnal variation in CO at the Phoenix-West site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis shows CO concentration in parts per million.

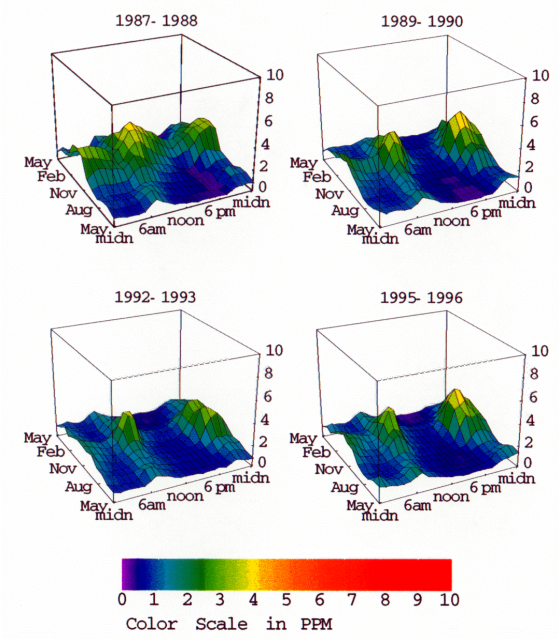

Figure 3-29. Monthly average diurnal variation in CO at the Phoenix-South site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis shows CO concentration in parts per million.

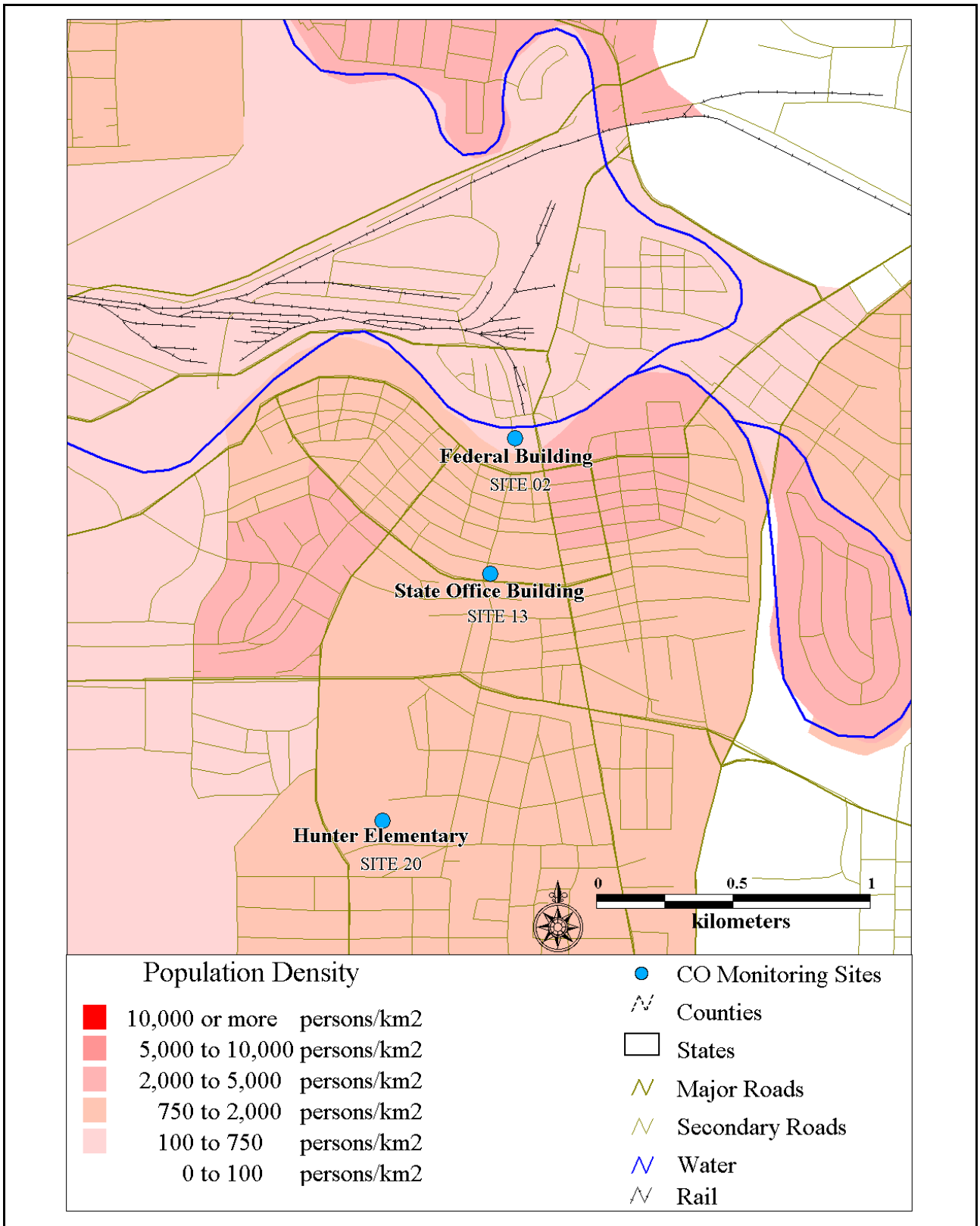

Figure 3-30. Map of Fairbanks showing locations of CO monitoring sites.

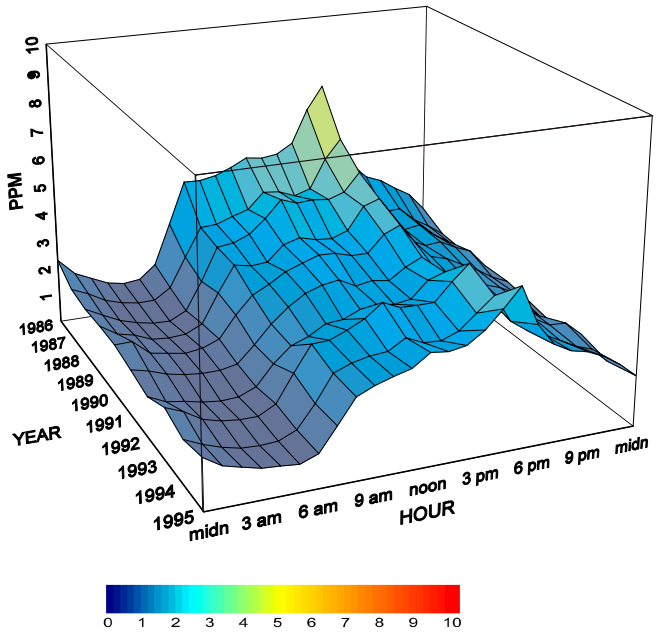

Figure 3-31. Average diurnal variation in CO at the Fairbanks-Federal Building site for weekdays during the winter season (October through March). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986-87 through 1995-96, and the z-axis shows CO concentration in parts per million.

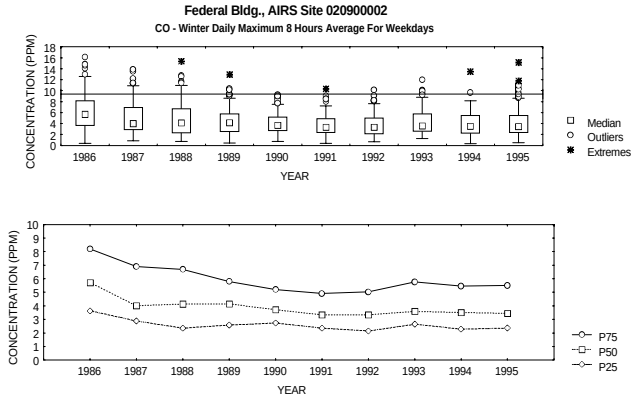

Figure 3-32. Central tendency statistics for the daily 8-h max CO concentration at the Fairbanks-Federal Building site during the winter season from 1986 to 1995. The top graph shows box plots (with 10, 25, 50, 75, and 90 percentile values) for the entire time series. Each circle (outlier) or diamond (extreme) refers to an individual observation that is either three or four 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, respectively) from the upper graph.

MSAs in the continental United States considered earlier. At these MSAs, the maximum values have tended to track variations in the median and the interquartile range.

The monthly average diurnal pattern for CO at the Federal Building site for weekdays from October 1986 through March 1987 is shown in Figure 3-33. This figure shows the 5:00 to 6:00 p.m. maximum in average CO concentrations. It also shows the continual increase in CO concentrations throughout the day, starting with the morning rush hour and continuing unabated until the evening rush hour. Similarity in the shape of the average monthly diurnal CO patterns for the three sites in Fairbanks is to be expected, considering the relatively high correlation coefficients between each site combination. However, these patterns are quite different from those found at the four MSAs in the continental United States, which tend to have more similarities among themselves.

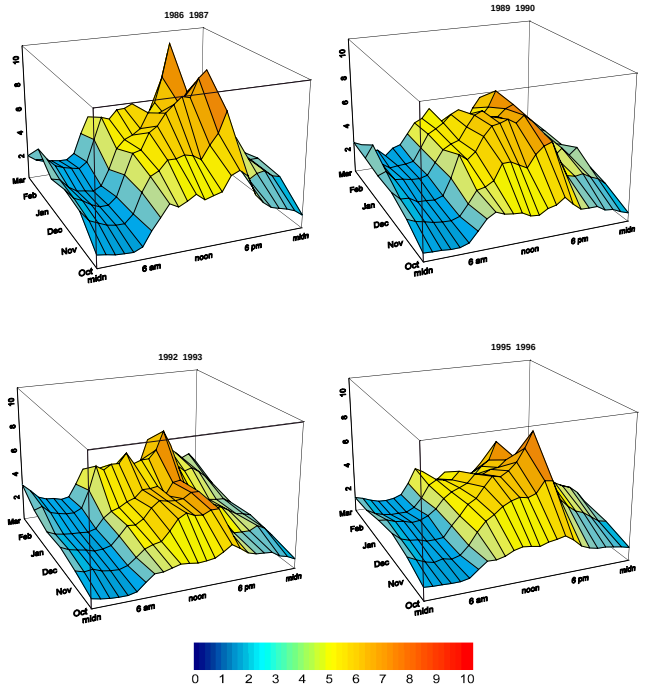

Figure 3-33. Monthly average diurnal variation in CO at the Fairbanks-Federal Building site for weekdays from October through March 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis shows CO concentration in parts per million.

3.5 Sources, Emissions, and Concentrations of Carbon Monoxide in Indoor Environments

The general United States population spends a significant portion of 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 following sections include a discussion of sources, emissions, and concentrations of CO in occupied enclosed environments. The discussion will primarily focus on residential environments; however, a brief discussion of CO concentrations in other enclosed environments is also included. Emphasis is placed on the evaluation of manufacturer-recommended uses of combustion appliances and consumer products and the resulting CO emissions and concentrations. Accidental sources and concentrations and improper uses of combustion appliances will be mentioned only briefly. This section will discuss the results of recently available studies but will only summarize those studies discussed in the previous criteria document (U.S. Environmental Protection Agency, 1991b).

3.5.1 Sources and Emissions of Carbon Monoxide in Indoor Environments Prior to 1991

Gas cooking stoves, unvented space heaters, tobacco combustion, wood-burning stoves, and combustion engines represent sources of CO in indoor environments. Approximately 45% of the homes in the United States used gas for cooking, drying clothes, and heating water in 1981. Emissions from burners on gas cooking stoves were highly variable on the same cooking range and between gas ranges. Improperly adjusted gas stoves (improper air-fuel ratio, often characterized by a yellow-tipping flame) could result in a greater than fivefold increase in emissions over that of properly adjusted stoves (blue-flame). However,

on the average, emissions were comparable for top burners, ovens, and pilot lights. Vented gas dryers and furnaces contributed a negligible amount of CO to the indoor environment (U.S. Environmental Protection Agency, 1991b).

Carbon monoxide emissions from unvented gas and kerosene space heaters were variable from heater to heater. Carbon monoxide emissions from unvented gas space heaters were higher for maltuned units and varied with the method of emission testing. Among the types of unvented space heaters, emissions were higher for the infrared gas space heaters than those for convective and catalytic unvented gas units. For unvented kerosene space heaters, emissions were higher for the radiant heaters (U.S. Environmental Protection Agency, 1991b).

Limited information was available on CO emissions from wood-burning stoves. However, nonairtight wood-burning stoves could contribute substantial amounts of CO into the indoor environment. Carbon monoxide from cigarette combustion showed little variability among the brands but could be substantial. In 1987, 29% of the United States population smoked. Carbon monoxide emissions from two cigarettes smoked over an hour approached that of one range top burner operating under blue-flame conditions. Ranges in average emissions for CO sources in the indoor environment are listed in Table 3-7 (U.S. Environmental Protection Agency, 1991b).

3.5.2 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. In the absence of an indoor source, CO concentrations will equal that of the ambient air. Nearby ambient sources of CO can result in higher levels of CO indoors. Unvented, such as gas stoves and gas and kerosene space heaters; vented, including furnaces, hot water heaters, fireplaces, and woodstoves; and improperly vented combustion appliances and consumer products represent the primary sources of CO emissions in the indoor environment. Table 3-8 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., gas cooking stoves, unvented space heaters, woodstoves, fireplaces), appliance design, type of fuel used, fuel consumption rate, use pattern, and operating condition. Vented combustion appliances usually vent the combustion by-products directly to the outside. However, if a flue, chimney, or vent leaks or is blocked, the combustion by-products will be spilled into the indoor environment. Spillage of combustion by-products also may occur during conditions of depressurization. Negative pressure exists when the outdoor air pressure exceeds that in the indoor environment. Depressurization may develop during operation of kitchen or bathroom exhaust fans, combustion appliances, and forced-air distribution systems and during fire start-up.

Two different approaches are used to evaluate CO emissions for combustion appliances: (1) the direct or sampling-hood approach and (2) the mass-balance/chamber approach. For details on these two approaches, see U.S. Environmental Protection Agency (1991b).

3.5.2.1 Gas Cooking Ranges, Ovens, and Furnaces

Emissions of CO from gas top ranges will depend on the use pattern, operating condition, fuel consumption rate, and air infiltration into the microenvironment. A discussion on the use of gas appliances in food preparation and air infiltration appears in Section 3.5.4 on indoor CO concentrations. 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

Table 3-7. 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	15-215	Himmel and DeWerth (1974) Traynor et al. (1982) Borrazzo et al. (1987) Cote et al. (1974) Moschandreas et al. (1985) Fortman et al. (1984)
		—	Yellow-tipping	92-197	Himmel and DeWerth (1974) Cote et al. (1974) Moschandreas et al. (1985)
Ovens	NG	—	Blue	12-257	Himmel and DeWerth (1974) Traynor et al. (1982) Borrazzo et al. (1987) Fortman et al. (1984)
		—	Yellow-tipping	53-62	Himmel and DeWerth (1974)
Burner pilots	NG	—	Blue	28-56	Himmel and DeWerth (1974)
Oven pilots	NG	—	Blue	209-322	Himmel and DeWerth (1974)
			Yellow-tipping	40	Moschandreas et al. (1985)
Gas Space Heaters					
Convective	NG	131-784	Blue	3-33	Traynor et al. (1984, 1985) Moschandreas et al. (1985) Thrasher and DeWerth (1979) Zawacki et al. (1984)
	P	353-660	Blue	16	Traynor et al. (1984, 1985)
Infrared	NG	260-368	Infrared	45-69	Traynor et al. (1984, 1985) Moschandreas et al. (1985)
	P	258	Infrared	45	Traynor et al. (1984, 1985)
Catalytic	NG	207	Blue	9-14	Moschandreas et al. (1985)
Kerosene Heaters					
Convective		37-202	—	4-60	Leaderer (1982) Traynor et al. (1983) Moschandreas et al. (1985)
Radiant		85-168	—	27-173	Leaderer (1982) Traynor et al. (1983) Moschandreas et al. (1985)
Two-stage		132-182	—	9-54	Traynor et al. (1983)

Table 3-7 (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
Gas Dryer	NG	—	—	40-69	Moschandreas et al. (1985)
Water Heater	NG	—	—	25-77 ppm	Belles et al. (1979)
Woodstoves and Fireplaces	—	—	—	0.08-2.18 g/h	Traynor et al. (1987)
Tobacco Smoke					
Cigarette		—	—	40-67 mg/cigarette[d]	National Research Council (1986) Rickert et al. (1984)

[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]Mainstream and sidestream smoke.

Table 3-8. 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.

more frequently for preparing meals than did young adults), the amount of time spent at home, and the presence of a standing pilot, and such consumption showed a seasonal trend. A recent study by Spicer and Billick (1996) evaluated CO emissions from a gas stove-top burner, both with and without a load. An indoor monitoring study of 293 homes conducted by the Gas Research Institute, Pacific Gas and Electric, and Southern California Gas showed increased CO emissions from the use of gas ranges with standing pilot lights (Billick et al., 1984, 1996). Study details are included in the section on indoor concentrations.

Carbon monoxide emissions from vented gas furnaces and hot water heaters are generally negligible (Borrazzo et al., 1987); however, emissions may vary based on the working condition and efficiency of the unit. Dangerous levels of CO have been noted in cases where units malfunctioned or the venting system leaked or was improperly installed. Ryan and McCrillis (1994) evaluated CO emissions from two gas furnaces; one furnace 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. No recent studies were found on the emission of CO from gas hot water heaters. However, Ault (1999) reported that approximately 3% of the CO-related mortality and up to 3% of the nonfatal CO poisonings between 1992 and 1996 were caused by malfunctioning water heaters.

3.5.2.2 Emissions from Unvented Space Heaters

Higher CO emissions have been reported for infrared gas space heaters than for convective or catalytic units. Other factors that may affect emissions from unvented space heaters include air circulation near the heater, primary aeration, and air infiltration and exchange.

Hedrick and Krug (1995) determined the emissions of CO from four different gas space heaters in operation and the emissions from the pilot lights. The study was conducted in a 2,300 ft^2, 1-story, 3-bedroom single-family dwelling with a full basement. Eight burner experiments and three pilot light experiments were conducted. The heaters were of four types: (1) 10,000 BTU-h, blue-flame convective; (2) 15,000 BTU-h (maximum) radiant-tile (infrared); (3) 14,000 BTU-h (maximum), fan-forced, blue-flame convective; and (4) 16,000 BTU-h, perforated-tube convective. The heaters were operated for 8-h, followed by a 15-h decay period. The pilot studies were conducted over a 48-h period. The emission rates for CO varied from 8.7 μg/kJ for fan-forced models to 63.7 μg/kJ for the infrared unit and to 200.31 μg/kJ for the perforated-tube type (CO emissions enhanced by leaky gas pressure regulating valve). Carbon monoxide concentrations in the test house are discussed in Section 3.5.4 on CO concentrations. Spicer and Billick (1996) reported CO emissions indexes of 19.1 and 28.7 μg/kJ for a convective, blue-flame space heater. An emission index of 44.1 μg/kJ was noted for a radiant unit.

Fan et al. (1997) reported the average pollutant emission rates for a new portable gas stove, a used kerosene radiant space heater, a kerosene lamp, an oil lamp, and several candles. Both 1-K-grade kerosene and citronella patio torch fuel were used for the oil lamp test. The lamp wick was tested at the normal height (1 in.) and at high flame (2 in.). Four 7.6-cm diameter candles were burned together in each candle test. Both the lamp tests and the candle tests were conducted in a 0.15 m^3 chamber. Butane was used for the portable gas stove and 1-K-grade kerosene was used in the kerosene space heater; both tests were conducted in a room with a volume of 19 m^3. The tests were run for 30 min to 2 h, with a 30-min decay period. Estimates of the emission rates were done using a single-compartment mass balance model. The CO emission rates for the portable gas stove and kerosene heater were 33.6 ± 15.0 and 226.7 ± 100 mg/h, respectively. Carbon monoxide emission rates of 8.2 ± 1.1, 7.1 ± 0.8, and 4.7 ± 3.0 mg/h were established for the kerosene lamp, oil lamp, and candles, respectively. The height of the wick did not affect the emission of CO from either the kerosene lamp or the oil lamp.

Miller and Hannigan (1999) reported the potential for high indoor concentrations of CO from the use of unvented gas fireplaces. A series of tests were conducted in two homes in Denver with professionally

installed, according to the manufacturer's specifications, unvented gas fireplaces. Fireplace A was equipped with an oxygen sensing system that switches off the gas supply if the oxygen level falls below the manufacturer-defined safe level. Fireplace B was equipped with a thermoelectric safety gas control valve that automatically shuts off all gas supply to the heater if enough fresh air is not available. The unvented gas fireplaces were operated for 2 to 9 h at the low, medium, and high settings for fireplace A and the low and high settings for fireplace B. Carbon monoxide emissions for fireplace A ranged from 250 to 9,000 mg/h. Emissions from fireplace B ranged from 2,600 to 5,000 mg/h. The highest emissions were noted when fireplace A was operated at the medium setting and fireplace B at the high setting. The high emissions were attributed to the high elevation of Denver, resulting in a lower ambient air pressure and a higher fuel-to-air ratio.

3.5.2.3 Woodstoves and Fireplaces

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. Mueller Associates (1985) reported CO emission ranges of 0.07 to 0.375 g/h for wood heaters (stoves). 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, forced-air distribution systems, and combustion appliances and because of outdoor conditions. 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 concentrations represented leaking glass doors). Carbon monoxide emissions on the order of 70 g/h were noted for glass-door-opened tests under negative pressure.

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. Carbon monoxide leakage into the indoor environment was noted from nonairtight woodstoves during conditions of negative pressure.

3.5.2.4 Environmental Tobacco Smoke

Carbon monoxide emissions from the combustion of tobacco occurs in the indoor environment when smokers exhale the previously inhaled or mainstream smoke and from the emission of sidestream smoke from smoldering tobacco products. The amount of CO emitted will vary based on the type (e.g., cigarette, cigar) and brand of tobacco product, 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 majority of the CO emissions are from sidestream smoke. Ott et al. (1992) reported a sidestream-to-mainstream ratio of ≈ 3.

The Federal Trade Commission compiled data on 933 varieties of cigarettes 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 (mainstream and sidestream) 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 (mainstream and sidestream) was reported by Ott et al. (1992). Löfroth et al.

(1989) estimated a CO emission rate of 67 mg per cigarette (sidestream) 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 82 to 200 mg CO/g (mass smoked; mainstream and sidestream) were reported by Klepeis et al. (1999) (smoked by machine and by a person). Cigar mass ranged from 5.9 to 16.7 g, and the smoking time was 7 to 40 min for the machine-smoked test and 78 and 90 min for the test measuring emissions from a cigar being smoked by a person.

3.5.3 Source-Related Concentrations of Carbon Monoxide in Indoor Environments Prior to 1991

Microenvironments associated with motor vehicles usually result in the highest concentrations of CO. Carbon monoxide concentrations of up to 28 ppm were reported in indoor parking garages and indoor environments associated with attached garages (Akland et al., 1985; Johnson et al., 1984; Wallace, 1983; Flachsbart and Ott, 1984). Carbon monoxide concentrations inside moving vehicles can exceed the 8-h, 9 ppm and 1-h, 35 ppm NAAQS for CO (Flachsbart et al., 1987; Chaney, 1978; Ziskind et al., 1981) and are generally higher in personal vehicles than in public transportation vehicles (Flachsbart et al., 1987; Cortese and Spengler, 1976).

Based on the intermittent use of gas cooking stoves, average long-term concentrations of CO are not expected to be significant (Research Triangle Institute, 1990; Koontz and Nagda, 1987). However, short-term peak concentrations of CO of 1.8 to 120 ppm have been reported from the use of gas cooking stoves (Research Triangle Institute, 1990; Koontz and Nagda, 1987; Leaderer et al., 1984; Moschandreas and Zabransky, 1982; Sterling and Sterling, 1979).

The use of unvented gas space heaters as primary heat sources is expected to result in higher long-term concentrations of CO ranging from 0.26 to 9.49 ppm (mean) (McCarthy et al., 1987; Koontz and Nagda, 1988). Peak CO concentrations from the use of unvented gas heaters are also generally higher than unvented kerosene heaters and gas cooking stoves (Koontz and Nagda, 1987; Leaderer et al., 1984; Davidson et al., 1987).

Indoor concentrations of CO from the use of nonairtight wood-burning stoves can contribute as much as 9 ppm to the average indoor CO concentration (Traynor et al., 1984). Airtight stoves have been shown to contribute from 0.1 to 2.0 ppm CO to the average CO background level (Humphreys et al., 1986; Traynor et al., 1984)

Concentrations of CO in environments with smoking is highly variable, depending on the type of environment, number of cigarettes smoked, and the type and amount of ventilation. Peak CO concentrations of 32 ppm (mechanical ventilation) and 41 ppm (natural ventilation) have been measured in automobiles (Harke and Peters, 1974). However, although cigarettes are expected to contribute to the indoor CO concentrations, the additions are not expected to be substantial except when heavy smoking occurs in small spaces.

3.5.4 Indoor Concentrations of Carbon Monoxide

3.5.4.1 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, and air mixing within the indoor compartments.

The major sources of CO in residential environments are unvented gas or kerosene appliances. Carbon monoxide in the indoor environment from vented combustion appliances (furnaces, hot water heaters, and gas clothes dryers) are generally negligible unless the unit is malfunctioning. Dangerous levels of CO have been noted in cases where the venting system leaked or was improperly installed. Because gas cooking ranges are used intermittently for cooking purposes, it is not likely that the use of gas ranges would result in substantial increases in CO over long periods of time, except possibly in households where gas

cooking stoves have continuously burning pilots or are used improperly as a primary or secondary source of heat. Of 83.2 million adults surveyed that used gas stoves or ovens for cooking during the years 1988 to 1994, 7.7 million had used the stoves for supplemental heating at least one time during the previous year (Slack and Heumann, 1997). Koontz et al. (1992) reported the results of a survey conducted in 1985 and 1991 designed to determine the prevalence of kitchen fans and the factors affecting their use and the impact of other cooking appliances (e.g., microwave ovens, toaster ovens, hot plates) on the use of gas ranges for cooking. The authors reported a 27% increase in the use of gas ranges without standing pilot lights between 1985 and 1991 and a 20% reduction in the use of both electric and gas 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. The use of gas for cooking varies by location (Johnson, 1984; Hartwell et al., 1984; U.S. Census Bureau, 1998, 1999; Wilson et al., 1993). However, an estimated 40% of the households in the United States used gas for cooking between 1985 and 1995 (Koontz et al., 1992; U.S. Census Bureau, 1998, 1999).

The use of unvented space heaters represent a significant source of CO in indoor environments. 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 3-34) (Slack and Heumann, 1997). The U.S. Census Bureau estimated that 1,055,000 and 1,159,000 households used kerosene or another liquid fuel as primary and secondary heating fuels, respectively, in 1995 (U.S. Census Bureau, 1999). The U.S. Environmental Protection Agency (1990) estimated that kerosene heaters are used 16.7 h/day in southern states as primary sources of heat, and, in regions where the heaters are used as secondary heat sources, estimated use ranges from 2.6 to 10.7 h/day. Information on the number of households using combustion appliances in the United States in 1995 appear in Table 3-9.

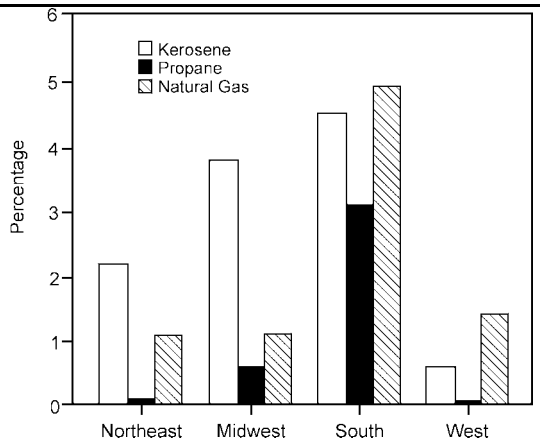

Figure 3-34. Percentage of U.S. households using unvented combustion heaters, by type of fuel, stratified by region (Third National Health and Nutrition Examination Survey, 1988 to 1994).
Source: Slack and Heumann (1997).

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 seasonral (Koontz and Rector, 1995). 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). Air exchange rates are generally higher during the summer and lower during the winter months (Wilson et al., 1996; Murray and Burmaster, 1995; Colome et al., 1994; Research Triangle Institute, 1990). Air exchange rates were about 1.5 h^{-1} during

Table 3-9. Combustible Fuels in Homes in the United States in 1995

	Combustible Fuel Type				
	Piped Gas	Bottled Gas	Fuel Oil	Kerosene/Other Liquid Fuel	Wood
Heating[a]	49,203,000 (848,000)	4,251,000 (558,000)	10,974,000 (451,000)	1,055,000 (1,159,000)	3,533,000 (7,949,000)
Cooking[b]	35,001,000	4,217,000	—	301,000	33,000
Central Air Conditioning[c]	2,971,000	—	—	—	—
Clothes Dryer[d]	15,998,000				
Water Heater[e]	50,558,000	3,239,000	5,808,000	331,000	44,000

[a]Based on 96,650,000 occupied housing units with heating fuel. Values in parenthesis represent use of fuel type as secondary heating fuel.
[b]Based on 97,406,000 occupied housing units with cooking fuel.
[c]Based on 46,577,000 occupied housing units with central air-conditioning.
[d]Based on 70,756,000 occupied housing units with central air-conditioning.
[e]Based on 97,522,000 occupied housing with hot piped water.

Source: U.S. Census Bureau (1999).

warm weather and from 0.41 to 0.59 h^{-1} (arithmetic) during cold weather months. The one study that reported AER for all seasons, reported an AER of 0.76 h^{-1} (arithmetic) (Murray and Burmaster, 1995). Homes with gas cooking stoves with standing pilots and gas wall furnaces had the highest AER. Homes with gas stoves without pilots had higher AER than electric stoves. Also, homes with forced air furnaces had higher AER than electric homes.

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 were 2.45 (2.24), 1.35 (1.09), and 2.22 (1.79) h^{-1} for schools, offices, and retail establishments, respectively. Air infiltration rates for 40 of the 49 buildings were 0.32, 0.31, and 1.12 h^{-1} 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^{-1} (mean [median = 1.3 h^{-1}]). The geometric mean of the AERs for six garages was 1.6 h^{-1} (Marr et al., 1998). 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^{-1} for windows closed and fan off, 13.3 to 23.5 h^{-1} for window opened and fan off, 1.8 to 3.7 h^{-1} for window closed and fan on recirculation (two cars tested), and 36.2 to 47.5 h^{-1} for windows closed and fan on fresh air (one car tested). An average AER of 13.1 h^{-1} was reported by Ott et al. (1992) for a station wagon moving at 20 mph with the windows closed.

3.5.4.2 Models for Carbon Monoxide Concentrations

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 and no air cleaner:

$$\frac{dC_{IN}}{dt} = vC_{OUT} + \frac{S}{V} - vC_{IN}, \qquad (3\text{-}1)$$

where dC_{IN} is the indoor pollutant concentration (mass/volume), t is time in hours, v is the air exchange rate, C_{OUT} is the outdoor pollutant concentration (mass/volume), V is the volume of the microenvironment, and S is the indoor source emission rate. 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 model 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 model 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. 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 3-35). The findings illustrated in Figure 3-35 are for only a limited number of model runs, sources, and building conditions.

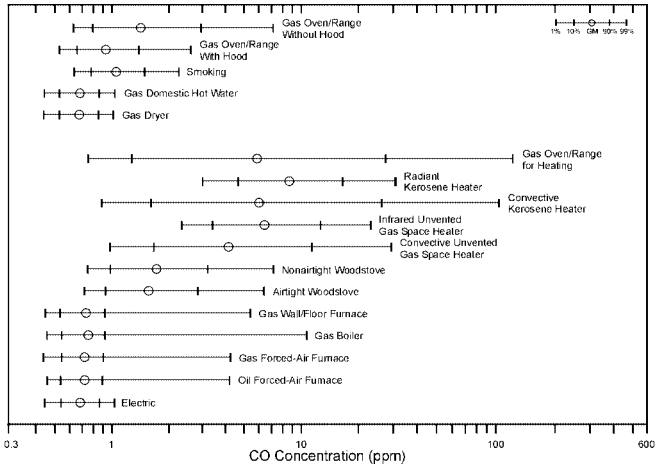

Figure 3-35. Modeled indoor CO concentration distributions in houses with only one indoor combustion pollutant source.
Source: Traynor et al. (1989).

3.5.4.3 Microenvironmental Monitoring Studies

Residential Carbon Monoxide Concentrations Related to Indoor Sources

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 in California. Monitoring was for a single 48-h period. Carbon monoxide concentrations indoors were reported to be closely associated with concentrations 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 rank homes. Using that criterion, 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 multifamily homes had higher CO than larger single-family homes), and more than one CO source. The average AER varied by type of heating system (wall furnaces > forced-air > electric) and building type (multifamily units > single-family units) (Billick et al., 1984, 1996; Colome et al., 1994). The CO descriptive statistics for homes in this study are given in Table 3-10.

Research Triangle Institute (1990) monitored CO concentrations in 400 homes for 3 days in Suffolk and Onondaga Counties, NY. Homes in Suffolk County were monitored in January and February. The selected homes in Onondaga County were monitored in February, March, and April. The average room

Table 3-10. Carbon Monoxide Descriptive Statistics for All Homes (number = 277; in parts per million)

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).

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 3-36). An explanation for the finding of higher CO in homes without wood stoves and fireplaces was not provided. Lower CO concentrations may have been associated with an increased air exchange rate. Also, CO emissions for the use of wood stoves and fireplaces are intermittent and will generally only occur during fire start-up and tending or through leaks in the stove or venting system.

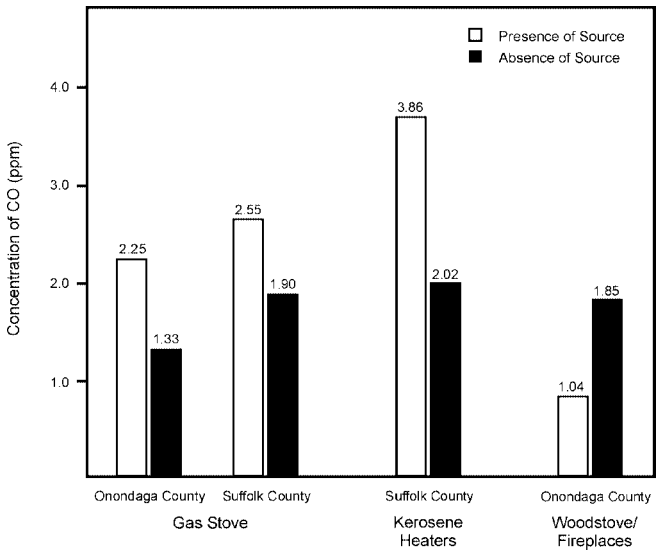

Figure 3-36. Arithmetic mean CO concentrations by presence or absence of combustion source. Homes in Suffolk County were monitored in January and February and in Onondaga County in February, March, and April.
Source: Research Triangle Institute (1990).

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 rates for the units are discussed in Section 3.5.2.2. The house was a 2,300 ft^2, single-family, 3-bedroom dwelling with a full basement. 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 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.

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 radiant and convective unvented kerosene space heaters. 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. Measured CO in homes 0.5 h prior to kerosene heater use 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 multi-stage units had higher CO than homes with convective heaters. Average 1-h concentrations of CO for convective units ranged from 1.3 to 5.3 ppm, and from 1.1 to 28.3 ppm and 16.0 to 50.0 ppm for radiant and multi-stage units, respectively.

A series of tests were conducted in two homes with professionally installed, according to the manufacturer's specifications, unvented gas fireplaces in Denver. Details on how the tests were conducted and the CO emission rates are discussed in Section 3.5.2.2. The highest concentration of CO, given as the time-weighted average, was at the medium setting for one of the unvented gas fireplaces and at the high setting for the other. Carbon monoxide concentrations ranged from 1.6 to 78 ppm for the first fireplace and 5.7 to 30 ppm for the second. The high concentrations were attributed to the high elevation of Denver, resulting in a lower ambient air pressure and a higher fuel-to-air ratio (Miller and Hannigan, 1999).

Carbon Monoxide Concentrations Related to Environmental Tobacco Smoke

Carbon monoxide concentrations in environments where smoking occurs exceed background CO concentrations. The indoor 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). The U.S. Centers for Disease Control and Prevention reported an estimated 61 million smokers in the United States in 1995, representing 29% of the population. The percentage of smokers between 1994 and 1995 was unchanged. In 1994, an estimated 1.5 million American became daily smokers. The estimated number of new smokers per year has not changed since 1980 (Tobacco Information and Prevention Source, 1996). The United States Department of Agricultural estimated that 487 billion cigarettes were sold in 1995 (Federal Trade Commission, 1997). An estimated 4.4 billion cigars were sold in the United States in 1997, compared to 3.8 billion in 1996 (Federal Trade Commission, 1999). 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 sampling periods 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 identified 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 3-11. Löfroth et al. (1989) reported CO concentrations in a chamber tests for cigarettes smoked every 150 or 30 min for 4 h. The chamber volume

Table 3-11. Carbon Monoxide Concentrations in Smoking and Nonsmoking Areas in Real-Life Situations (in parts per million)

			Smoking			Nonsmoking		Diff. in Means
Category	No. of Studies	Sample Size	Mean	Range	Sample Size	Mean	Range	Smoking Minus Nonsmoking
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).

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.

Carbon monoxide concentrations approaching 20 ppm were reported by Ott et al. (1992) in the compartment of a moving vehicle after three cigarettes were smoked over a 60-min period. The vehicle traveled at 20 mi/h with the windows closed, and the air conditioned set at recirculation. Carbon monoxide concentrations reached almost 17 ppm after the first cigarette had been smoked. An averaged CO concentration of 9 ppm, over a 200-min period, was reported by Klepeis et al. (1999) during a cigar banquet. More than 100 cigars were smoked by approximately 30 people. Concentrations were reported to range from 3 to 19 ppm under various smoking conditions.

Carbon Monoxide Concentrations Associated with Motor Vehicles

In the United States, motor vehicles dominate total anthropogenic emissions of CO. Older vehicles are likely to emit more CO than newer models. However, when the newer models with catalytic converters are started, CO emissions are higher because of the rich fuel-air mixture to facilitate ignition and to improve cold engine operation. Also, the catalytic convertor is not warm enough to function efficiently (Marr et al., 1998). Concentrations of CO inside a moving motor vehicle also can be affected by the CO being emitted from other vehicles. Emission rates for combustion vehicles are discussed in Section 3.3 of this chapter.

Several studies have monitored the CO concentrations inside a moving vehicle under various operating conditions. Chan et al. (1989, 1991) evaluated CO, NO_x, O_3, and VOCs inside two moving vehicles (1983 and 1987 models). Tailpipe emissions were higher for the older model. Driving routes were selected to represent three distinct traffic patterns: (1) urban traffic, (2) heavy traffic, and (3) rural traffic. Inside ventilation was windows and vents closed and air-conditioning on, windows and vents closed and fan on, or front windows half opened and vent and fan on. Average CO concentrations for 70 samples, including both cars and all driving routes, were 11.3 ppm. The in-vehicle concentrations were almost four times higher than ambient CO (3.0 ppm). Carbon monoxide concentrations in the rural traffic pattern were significantly less than either the urban or heavy traffic patterns. Carbon monoxide in urban and heavy traffic

patterns was not significantly different. The lowest CO concentrations were measured when the windows were open; however, the concentration difference between the different ventilation modes was only 1.0 ppm. Ott et al. (1994) reported an average CO concentration of 10.2 ppm inside a moving vehicle for 93 trips under urban highway conditions at varying times of the day. A more detailed discussion of this study appears in the chapter on human exposure. Higher CO concentrations were reported both inside and outside of moving vehicles in Sacramento and Los Angeles than those measured at roadside and ambient monitoring stations. Carbon monoxide concentrations inside vehicles ranged from nondetectable to 6 ppm (Rodes et al., 1998).

Carbon monoxide emissions from the use of combustion engines in enclosed areas may produce significant increases in CO in the environments where the engines are being operated. Reports from various municipalities on activated CO alarms have identified a car idling in the garage as the source of CO in the living compartment. Also, in a study of unintentional deaths in California, of a reported 128 accidental poisonings resulting from CO from combustion engine exhaust, 80 incidents were found to have occurred in a garage or house, 38 in a vehicle parked outside, and 4 in vehicles while driving (Marr et al., 1998). Kern et al. (1990) measured CO concentrations in a 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: the first with the garage door poorly sealed (3-in. crack) and the second with the 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, respectively; 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 70% of the CO produced globally is the result of human activities. Carbon monoxide in the atmosphere is of both primary and secondary origin. Secondary sources such as the photochemical oxidation of CH_4 and NMHCs account 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 that of 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 concentrations 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. Since then, there has been no clear trend in CO concentrations.

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 concentrations and allow the concentrations of these trace gases contributing to global-scale environmental problems to increase, even

if their 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 participates in the formation of 20 to 40% of O_3 in the background or "clean" troposphere and may be involved in urban O_3 formation. One study suggests that CO participated in the formation of 10 to 20% of the O_3 formed during a smog episode in Atlanta on June 6, 1988. Obviously, the photochemistry must be examined in more cities before any more general statements about the importance of CO in urban air chemistry can be made.

Emissions from transportation dominate other sources of CO within the United States. Residential wood burning may be an important source of CO in a number of urban areas. The uncertainties in the magnitudes of individual sources 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-highest 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 concentrations during times of day when CO concentrations result primarily 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 the indoor environment directly as a result of the emissions from various indoor combustion sources or indirectly as a result of infiltration or ventilation from outdoor sources. Sources of CO in the indoor environment include vented (furnaces, hot water heaters, gas cooking stoves, fireplaces and woodstoves) and unvented (kerosene and gas space heaters) combustion appliances, tobacco smoke, and combustion engines.

Carbon monoxide emissions and indoor concentrations from the use of combustion appliances are highly variable. Emissions from combustion appliances are a function of the appliance design, combustion efficiency and operating condition, length and frequency of use, and the fuel type and consumption rate. Concentrations of CO in the indoor environment will depend on the CO emission rate and use pattern of the combustion appliance, ambient air concentrations and infiltration through the building envelope, air exchange rate, building volume, and air mixing with the indoor environment. In the absence of an indoor source, CO concentrations generally will equal that of the surrounding ambient environment. Higher concentrations are likely to occur in environments with multiple combustion sources.

Unvented gas and kerosene space heaters generate the highest CO emissions and concentrations in the indoor environment. The highest CO concentrations likely will be found in homes where unvented space heaters are the primary heat source rather than in homes where unvented space heaters are used to supplement another heat source. However, with the decreasing usage of unvented space heaters, CO emissions from this source likely will decrease.

The use of well-maintained, energy-efficient gas stoves will result in only intermittent, small increases in CO emissions and concentrations. Gas ranges with standing pilots emit more CO than do units

with electronic pilots; however, a steady decrease in the emission of CO from pilot lights likely will occur with the replacement of gas cooking stoves with standing lights with models with electronic 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. High indoor CO emissions and concentrations can occur when gas cooking stoves are used improperly for heating.

Carbon monoxide emissions and concentrations in the indoor environment from vented combustion appliances (furnaces, hot water heaters, and gas clothes dryers) are generally negligible unless the unit is malfunctioning. Less efficient vented appliances will emit more CO than the more efficient appliances. Dangerous levels of CO have been noted in cases where the unit was malfunctioning or the venting system leaked or was improperly installed.

Carbon monoxide generally is not emitted by airtight woodstoves and fireplaces, except during fire start-up and maintenance, leaks in the venting system, and through backdrafting when the natural ventilation is disrupted by depressurization. Depressurization generally occurs during fire start-up but also can occur during operation of other equipment such as kitchen and bathroom exhaust fans, combustion appliances, and forced-air distribution systems and because of outdoor conditions. Non-airtight stoves can emit a significantly higher amount of CO in the indoor environment.

Concentrations of CO in environments where smoking occurs can exceed CO background concentrations. Like combustion appliances, CO emissions and concentrations will depend on the CO emission rate of the tobacco product, smoking rate, size of the indoor compartment, and air exchange rate. The Center for Disease Control estimated that 29% of the United States population smoked in 1995.

Carbon monoxide emissions from the use of combustion engines in enclosed areas may produce significant increases in CO in the environments where the engines are being operated. Reports from various municipalities on activated CO alarms identified a car idling in the garage as the source of CO in the living compartment. Also, in a study of unintentional deaths in California, of a reported 128 accidental poisonings resulting from CO from combustion engine exhaust, 80 incidents were found to have occurred in a garage or house, 38 in a vehicle parked outside, and 4 in vehicles while driving.

References

Akbar-Khanzadeh, F.; Greco, T. M. (1996) Health and social concerns of restaurant/bar workers exposed to environmental tobacco smoke. Med. Lav. 87: 122-132.

Akland, G. G.; Hartwell, T. D.; Johnson, T. R.; Whitmore, R. W. (1985) Measuring human exposure to carbon monoxide in Washington, D.C., and Denver, Colorado, during the winter of 1982-1983. Environ. Sci. Technol. 19: 911-918.

Allen, D. J.; Kasibhatla, P.; Thompson, A. M.; Rood, R. B.; Doddridge, B. G.; Pickering, K. E.; Hudson, R. D.; Lin, S.-J. (1996) Transport-induced interannual variability of carbon monoxide determined using a chemistry and transport model. J. Geophys. Res. [Atmos.] 101: 28,655-28,669.

Amendola, A. A.; Hanes, N. B. (1984) Characterization of indoor carbon monoxide levels produced by the automobile. In: Berglund, B.; Lindvall, T.; Sundell, J., eds. Indoor air. Volume 4: chemical characterization and personal exposure. Proceedings of the 3rd international conference on indoor air quality and climate; August; Stockholm, Sweden. Stockholm, Sweden: Swedish Council for Building Research; pp. 97-102.

Andreae, M. O. (1991) Biomass burning: its history, use, and distribution and its impact on environmental quality and global climate. In: Levine, J. S., ed. Global biomass burning: atmospheric, climatic, and biospheric implications. Cambridge, MA: MIT Press; pp. 1-21.

Ault, K. (1999) Non-fire carbon monoxide deaths and injuries associated with the use of consumer products: annual estimates. Bethesda, MD: U.S. Consumer Product Safety Commission; June.

Bakwin, P. S.; Tans, P. P.; Novelli, P. C. (1994) Carbon monoxide budget in the Northern Hemisphere. Geophys. Res. Lett. 21: 433-436.

Bekki, S.; Law, K. S.; Pyle, J. A. (1994) Effect of ozone depletion on atmospheric CH_4 and CO concentrations. Nature 371: 595-597.

Belles, F. E.; DeWerth, D. W.; Himmel, R. L. (1979) NOx emissions of furnaces and water heaters predominant in the California market. Presented at: 72nd annual meeting of the Air Pollution Control Association; June; Cincinnati, OH. Pittsburgh, PA: Air Pollution Control Association; paper no. 79-60.1.

Billick, I.; Johnson, D.; Moschandreas, D.; Relwani, S. (1984) An investigation of operational factors that influence emission rates from gas appliances. In: Berglund, B.; Lindvall, T.; Sundell, J., eds. Indoor air. Volume 4: chemical characterization and personal exposure. Proceedings of the 3rd international conference on indoor air quality and climate; August; Stockholm, Sweden. Stockholm, Sweden: Swedish Council for Building Research; pp. 181-187.

Billick, I. H.; Behrens, D. W.; Becker, E. W.; Garrison, C. A.; Wilson, A. L.; Colome, S. D.; Tian, Y. (1996) California residential indoor air quality study: an overview. In: Proceedings of the 1995 international gas research conference; November 1995; Cannes, France. Rockville, MD: Government Institutes, Inc.; pp. 1707-1716.

Bishop, G. A.; Stedman, D. H. (1990) On-road carbon monoxide emission measurement comparisons for the 1988-1989 Colorado oxy-fuels program. Environ. Sci. Technol. 24: 843-847.

Bishop, G. A.; Stedman, D. H. (1996) Measuring the emissions of passing cars. Acc. Chem. Res. 29: 489-495.

Borrazzo, J. E.; Davidson, C. I.; Hendrickson, C. T. (1987) A statistical analysis of published gas stove emission factors for CO, NO, and NO_2. In: Seifert, B.; Esdorn, H.; Fischer, M.; Rüden, H.; Wegner, J., eds. Indoor air '87: proceedings of the 4th international conference on indoor air quality and climate. Volume 1: volatile organic compounds, combustion gases, particles and fibres, microbiological agents; August; Berlin, Federal Republic of Germany. Berlin, Federal Republic of Germany: Institute for Water, Soil and Air Hygiene; pp. 316-320.

Bowling, S. A. (1986) Climatology of high-latitude air pollution as illustrated by Fairbanks and Anchorage, Alaska. J. Clim. Appl. Meteorol. 25: 22-34.

Bradley, R. S.; Keimig, F. T.; Diaz, H. F. (1992) Climatology of surface-based inversions in the North American Arctic. J. Geophys. Res. [Atmos.] 97: 15,699-15,712.

Bradley, K. S.; Stedman, D. H.; Bishop, G. A. (1999) A global inventory of carbon monoxide emissions from motor vehicles. In: Khalil, M. A. K.; Pinto, J. P.; Shearer, M. J., eds. Carbon monoxide [special issue of papers from an international conference; December 1997; Portland, OR]. Chemosphere Global Change Sci. 1: 65-72.

Brühl, C.; Crutzen, P. J. (1999) Reductions in the anthropogenic emissions of CO and their effect on CH_4. In: Khalil, M. A. K.; Pinto, J. P.; Shearer, M. J., eds. Carbon monoxide [special issue of papers from an international conference; December 1997; Portland, OR]. Chemosphere Global Change Sci. 1: 249-254.

Burton, R. M.; Seila, R. A.; Wilson, W. E.; Pahl, D. A.; Mumford, J. L.; Koutrakis, P. (1990) Characterization of kerosene heater emissions inside two mobile homes. In: Indoor air '90: precedings of the 5th international conference on indoor air quality and climate, volume 2, characteristics of indoor air; July-August; Toronto, ON, Canada. Ottawa, ON, Canada: International Conference on Indoor Air Quality and Climate, Inc.; pp. 337-342.

Carroll, M. A.; Hastie, D. R.; Ridley, B. A.; Rodgers, M. O.; Torres, A. L.; Davis, D. D.; Bradshaw, J. D.; Sandholm, S. T.; Schiff, H. I.; Karecki, D. R.; Harris, G. W.; Mackay, G. I.; Gregory, G. L.; Condon, E. P.; Trainer, M.; Hubler, G.; Montzka, D. D.; Madronich, S.; Albritton, D. L.; Singh, H. B.; Beck, S. M.; Shipham, M. C.; Bachmeier, A. S. (1990) Aircraft measurement of NO_x over the eastern Pacific and continental United States and implications for ozone production. J. Geophys. Res. [Atmos.] 95: 10,205-10,233.

Chameides, W. L.; Liu, S. C.; Cicerone, R. J. (1977) Possible variations in atmospheric methane. J. Geophys. Res. 82: 1795-1798.

Chan, C.-C.; Ozkaynak, H.; Spengler, J. D.; Sheldon, L.; Nelson, W.; Wallace, L. (1989) Commuter's exposure to volatile organic compounds, ozone, carbon monoxide, and nitrogen dioxide. Presented at: 82nd annual meeting of the Air and Waste Management Association; June; Anaheim, CA. Pittsburgh, PA: Air and Waste Management Association; paper no. 89-34A.4.

Chan, C.-C.; Özkaynak, H.; Spengler, J. D.; Sheldon, L. (1991) Driver exposure to volatile organic compounds, CO, ozone and NO_2 under different driving conditions. Environ. Sci. Technol. 25: 964-972.

Chaney, L. W. (1978) Carbon monoxide automobile emissions measured from the interior of a traveling automobile. Science (Washington, DC) 199: 1203-1204.

Cicerone, R. J. (1988) How has the atmospheric concentration of CO changed? In: Rowland, F. S.; Isaksen, I. S. A., eds. The changing atmosphere: report of the Dahlem workshop on the changing atmosphere; November 1987; Berlin, Federal Republic of Germany. Chichester, United Kingdom: John Wiley & Sons, Ltd.; pp. 49-61. (Physical, chemical, and earth sciences research report no. 7).

Cohen, J.; Iwamiya, R. (1998) Analyses of diurnal patterns in hourly and eight-hourly average ambient carbon monoxide concentrations. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards; contract no. EPA 68-D7-0066.

Collins, W. J.; Stevenson, D. S.; Johnson, C. E.; Derwent, R. G. (1997) Tropospheric ozone in a global-scale three-dimensional Lagrangian model and its response to NO_x emission controls. J. Atmos. Chem. 26: 223-274.

Colome, S. D.; Wilson, A. L.; Tian, Y. (1994) California residential indoor air quality study. Volume 2. Carbon monoxide and air exchange rate: an univariate and multivariate analysis. Chicago, IL: Gas Research Institute; report no. GRI-93/0224.3.

Colucci, J. M.; Begeman, C. R. (1969) Carbon monoxide in Detroit, New York, and Los Angeles air. Environ. Sci. Technol. 3: 41-47.

Comrie, A. C.; Diem, J. E. (1999) Climatology and forecast modeling of ambient carbon monoxide in Phoenix, Arizona. Atmos. Environ. 33: 5023-5036.

Conrad, R. (1996) Soil microorganisms as controllers of atmospheric trace gases (H_2, CO, CH_4, OCS, N_2O and NO). Microbiol. Rev. 60: 609-640.

Conrad, R.; Seiler, W. (1985) Influence of temperature, moisture, and organic carbon on the flux of H_2 and CO between soil and atmosphere: field studies in subtropical regions. J. Geophys. Res. [Atmos.] 90: 5699-5709.

Cortese, A. D.; Spengler, J. D. (1976) Ability of fixed monitoring stations to represent personal carbon monoxide exposure. J. Air Pollut. Control Assoc. 26: 1144-1150.

Cote, W. A.; Wade, W. A., III; Yocom, J. E. (1974) A study of indoor air quality. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development; report no. EPA-650/4-74-042.

Croes, B. E.; Effa, R. C.; Pasek, R. J. (1996) A comparison of the California emission inventory with 1995 ambient concentration data in Los Angeles. Presented at: 6th CRC on-road vehicle emissions workshop; March; San Diego, CA. Sacramento, CA: California Air Resources Board.

Davidson, C. I.; Borrazzo, J. E.; Hendrickson, C. T. (1987) Pollutant emission factors for gas stoves: a literature survey. Research Triangle Park, NC: U.S. Environmental Protection Agency, Air and Energy Engineering Research Laboratory; report no. EPA-600/9-87-005.

Dignon, J.; Ando, T.; Brenninkmeijer, C.; Conny, J.; Granier, C.; Khalil, A.; King, G.; King, S.; Law, K.; Levine, J. S.; Röckmann, T.; Stedman, D.; Yung, Y.; Zafiriou, O. (1998) Carbon monoxide sources and sinks: working group summary report. In: Khalil, M. A. K.; Pinto, J. P.; Shearer, M. J., eds. Atmospheric carbon monoxide and its environmental effects [proceedings of an international conference]; December 1997; Portland, Oregon. Washington, DC: U.S. Environmental Protection Agency; report no. EPA/600/R-98/047; pp. 359-374.

Fan, C.; Zhang, J.; Cheung, J. P. (1997) Air pollutants emitted from household combustion sources. In: Measurement of toxic and related air pollutants. Volume 2: proceedings of an A&WMA/EPA specialty conference; April-May; Research Triangle Park, NC. Pittsburgh, PA: Air & Waste Management Association; pp. 837-846. (A&WMA publication VIP-74).

Federal Trade Commission. (1994) Tar, nicotine, and carbon monoxide of the smoke of 933 varieties of domestic cigarettes. Washington, DC: Federal Trade Commission.

Federal Trade Commission. (1997) Federal Trade Commission report to Congress for 1995, pursuant to the Federal Cigarette Labeling and Advertising Act. Washington, DC: Federal trade Commission. Available: www.ftc.gov/os/1997/9708/cigrep97.htm [2000, February 14].

Federal Trade Commission. (1999) Cigar sales and advertising and promotional expenditures for calendar years 1996 and 1997. Washington, DC: Federal Trade Commission. Available: www.ftc.gov/os/1999/9907/cigarreport1999.htm [2000, February 14].

Flachsbart, P. G.; Ott, W. R. (1984) Field surveys of carbon monoxide in commercial settings using personal exposure monitors. Washington, DC: U.S. Environmental Protection Agency, Office of Monitoring Systems and Quality Assurance; EPA report no. EPA-600/4-84-019.

Flachsbart, P. G.; Mack, G. A.; Howes, J. E.; Rodes, C. E. (1987) Carbon monoxide exposures of Washington commuters. JAPCA 37: 135-142.

Fortmann, R. C.; Borrazzo, J. E.; Davidson, C. I. (1984) Characterization of parameters influencing indoor pollutant concentrations. In: Berglund, B.; Lindvall, T.; Sundell, J., eds. Indoor air: proceedings of the 3rd international conference on indoor air quality and climate, v. 4, chemical characterization and personal exposure; August; Stockholm, Sweden. Stockholm, Sweden: Swedish Council for Building Research; pp. 259-264.

Fuglestvedt, J. S.; Jonson, J. E.; Isaksen, I. S. A. (1994) Effects of reductions in stratospheric ozone on tropospheric chemistry through changes in photolysis rates. Tellus Ser. B 46: 172-192.

Fujita, E. M.; Croes, B. E.; Bennett, C. L.; Lawson, D. R.; Lurmann, F. W.; Main, H. H. (1992) Comparison of emission inventory and ambient concentration ratios of CO, NMOG, and NO_x in California's south coast air basin. J. Air Waste Manage. Assoc. 42: 264-276.

Gertler, A. W.; Sagebiel, J. C.; Dippel, W. A.; O'Connor, C. M. (1999) The impact of California phase 2 reformulated gasoline on real-world vehicle emissions. J. Air Waste Manage. Assoc. 49: 1339-1346.

Grosjean, D.; Fung, K. (1984) Hydrocarbons and carbonyls in Los Angeles air. J. Air Pollut. Control Assoc. 34: 537-543.

Haan, D.; Martinerie, P.; Raynaud, D. (1996) Ice core data of atmospheric carbon monoxide over Antarctica and Greenland during the last 200 years. Geophys. Res. Lett. 23: 2235-2238.

Hallock-Waters, K. A.; Doddridge, B. G.; Dickerson, R. R.; Spitzer, S.; Ray, J. D. (1999) Carbon monoxide in the U.S. mid-Atlantic troposphere: evidence for a decreasing trend. Geophys. Res. Lett. 26: 2861-2864.

Hameed, S.; Pinto, J. P.; Stewart, R. W. (1979) Sensitivity of the predicted CO-OH-CH_4 perturbation to tropospheric NO_x concentrations. J. Geophys. Res. C: Oceans Atmos. 84: 763-768.

Hard, T. M.; Mehrabzadeh, A. A.; Chan, C. Y.; O'Brien, R. J. (1992) FAGE measurements of tropospheric HO with measurements and model of interferences. J. Geophys. Res. [Atmos.] 97: 9795-9817.

Harke, H.-P.; Peters, H. (1974) Zum Problem des Passivrauchens. III. Über den Einfluß des Rauchens auf die CO-Konzentration im Kraftfahrzeug bei Fahrten im Stadtgebiet [The problem of passive smoking. III. The influence of smoking on the CO concentration in driving automobiles]. Int. Arch. Arbeitsmed. 33: 221-229.

Hartwell, T. D.; Clayton, C. A.; Ritchie, R. M.; Whitmore, R. W.; Zelon, H. S.; Jones, S. M.; Whitehurst, D. A. (1984) Study of carbon monoxide exposure of residents of Washington, DC and Denver, Colorado. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Environmental Monitoring Systems Laboratory; report no. EPA-600/4-84-031.

Haste, T. L.; Chinkin, L. R.; Kumar, N.; Lurmann, F. W.; Hurwitt, S. B. (1998) Use of ambient data to evaluate a regional emission inventory for the San Joaquin Valley in California. In: Chow, J.; Koutrakis, P., eds. $PM_{2.5}$: a fine particle standard. Volume I: proceedings of an international specialty conference; January; Long Beach, CA. Pittsburgh, PA: Air & Waste Management Association; pp. 451-462. (A&WMA publication VIP-81).

Hedrick, R. L.; Krug, E. K. (1995) Conventional Research House measurements of emissions from unvented gas space heaters. Chicago, IL: Gas Research Institute; report no. GRI-95/0205.

Himmel, R. L.; DeWerth, D. W. (1974) Evaluation of the pollutant emissions from gas-fired ranges. Project EP-1-23: analysis of flue products from gas-fired appliances. Cleveland, OH: American Gas Association Laboratories; report no. 1492.

Hofmann, D. J.; Peterson, J. T.; Rosson, R. M., eds. (1996) Climate monitoring and diagnostics laboratory no. 23. Summary report 1994-95. Boulder, CO: U.S. Department of Commerce, National Oceanic and Atmospheric Administration, Environmental Research Laboratories.

Holcomb, L. C. (1993) Indoor air quality and environmental tobacco smoke: concentration and exposure. Environ. Int. 19: 9-40.

Humphreys, M. P.; Knight, C. V.; Pinnix, J. C. (1986) Residential wood combustion impacts on indoor carbon monoxide and suspended particulates In: Proceedings of the 1986 EPA/APCA symposium on measurement of toxic air pollutants; April; Raleigh, NC. Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory; pp. 736-747; report no. EPA-600/9-86-013.

Ingalls, M. N.; Smith, L. R.; Kirksey, R. E. (1989) Measurement of on-road vehicle emission factors in the California South Coast Air Basin: volume I, regulated emissions. Atlanta, GA: Coordinating Research Council, Inc.; report no. CRC-APRAC-AP-4-SCAQS-1.

Inman, R. E.; Ingersoll, R. B.; Levy, E. A. (1971) Soil: a natural sink for carbon monoxide. Science (Washington, DC) 172: 1229-1231.

Ipps, D. T.; Popejoy, D. (1998) An updated verification of the on-road vehicle emission inventory for the Los Angeles basin using ambient air quality data. Presented at: 8th CRC on-road vehicle emissions workshop; April; San Diego, CA. Sacramento, CA: California Air Resources Board.

Jaasma, D. R.; Stern, C. H.; Honeycutt, D. J.; Fugler, D. (1995) Effect of glass doors on carbon monoxide spillage from masonry fireplaces. Presented at: 88th annual meeting and exhibition of the Air & Waste Management Association; June; San Antonio, TX. Pittsburgh, PA: Air & Waste Management Association; paper no. 95-RP137.01.

Jacob, D. J.; Wofsy, S. C. (1990) Budgets of reactive nitrogen, hydrocarbons, and ozone over the Amazon forest during the wet season. J. Geophys. Res. [Atmos.] 95: 16,737-16,754.

Jeffries, H. E. (1995) Photochemical air pollution. In: Singh, H. B., ed. Composition, chemistry, and climate of the atmosphere. New York, NY: Van Nostrand Reinhold; p. 337.

Johnson, T. (1984) A study of personal exposure to carbon monoxide in Denver, Colorado. Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory; report no. EPA-600/4-84-014.

Johnson, D.; Billick, I.; Moschandreas, D.; Relwani, S. (1984) Emission rates from unvented gas appliances. In: Berglund, B.; Lindvall, T.; Sundell, J., eds. Indoor air: proceedings of the 3rd international conference on indoor air quality and climate, v. 4, chemical characterization and personal exposure; August; Stockholm, Sweden. Stockholm, Sweden: Swedish Council for Building Research; pp. 367-373.

Johnson, T.; Capel, J.; Paul, R.; Wijnberg, L. (1992) Estimation of carbon monoxide exposures and associated carboxyhemoglobin levels in Denver residents using a probabilistic version of NEM. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards; contract no. 68-D0-0062.

Kanakidou, M.; Crutzen, P. J. (1993) Scale problems in global tropospheric chemistry modeling: comparison of results obtained with a three-dimensional model, adopting longitudinally uniform and varying emissions of NO_x and NMHC. Chemosphere 26: 787-801.

Kanakidou, M.; Singh, H. B.; Valentin, K. M.; Crutzen, P. J. (1991) A two-dimensional study of ethane and propane oxidation in the troposphere. J. Geophys. Res. [Atmos.] 96: 15,395-15,413.

Kern, R. A.; Knoedler, J. A.; Trester, R. J. (1990) Automotive carbon monoxide emissions in a closed garage. Presented at: International congress and exposition; February-March; Detroit, MI. Warrendale, PA: Society of Automotive Engineers; pp. 33-38. (SAE technical paper series no. 900499).

Khalil, M. A. K.; Rasmussen, R. A. (1988a) Carbon monoxide in the earth's atmosphere: indications of a global increase. Nature (London) 332: 242-245.

Khalil, M. A. K.; Rasmussen, R. A. (1988b) Carbon monoxide in an urban environment: application of a receptor model for source apportionment. JAPCA 38: 901-906.

Khalil, M. A. K.; Rasmussen, R. A. (1989) Urban carbon monoxide: contributions of automobiles and wood burning. Chemosphere 19: 1383-1386.

Khalil, M. A. K.; Rasmussen, R. A. (1994) Global decrease in atmospheric carbon monoxide concentration. Nature (London) 370: 639-641.

Khalil, M. A. K.; Rasmussen, R. A. (1999) Non-automotive sources of carbon monoxide in urban areas. In: Khalil, M. A. K.; Pinto, J. P.; Shearer, M. J., eds. Carbon monoxide [special issue of papers from an international conference; December 1997; Portland, OR]. Chemosphere Global Change Sci. 1: 111-114.

King, G. M. (1999) Characteristics and significance of atmospheric carbon monoxide consumption by soils. In: Khalil, M. A. K.; Pinto, J. P.; Shearer, M. J., eds. Carbon monoxide [special issue of papers from an international conference; December 1997; Portland, OR]. Chemosphere Global Change Sci. 1: 53-63.

Klepeis, N. E.; Ott, W. R.; Switzer, P. (1995) Modeling the time series of respirable suspended particles and carbon monoxide from multiple smokers: validation in two public smoking lounges. Presented at: 88th annual meeting and exhibition of the Air & Waste Management Association; June; San Antonio, TX. Pittsburgh, PA: Air & Waste Management Association; paper no. 95-MPH.03.

Klepeis, N. E.; Ott, W. R.; Switzer, P. (1996) A multiple-smoker model for predicting indoor air quality in public lounges. Environ. Sci. Technol. 30: 2813-2820.

Klepeis, N. E.; Ott, W. R.; Repace, J. L. (1999) The effect of cigar smoking on indoor levels of carbon monoxide and particles. J. Exposure Anal. Environ. Epidemiol. 9: 622-635.

Koontz, M. D.; Nagda, N. L. (1987) Survey of factors affecting NO_2 concentrations. In: Seifert, B.; Esdorn, H.; Fischer, M.; Rüden, H.; Wegner, J., eds. Indoor air '87: proceedings of the 4th international conference on indoor air quality and climate, v. 1, volatile organic compounds, combustion gases, particles and fibres, microbiological agents; August; Berlin, Federal Republic of Germany. Berlin, Federal Republic of Germany: Institute for Water, Soil and Air Hygiene; pp. 430-434.

Koontz, M. D.; Nagda, N. L. (1988) A topical report on a field monitoring study of homes with unvented gas space heaters. Volume III—methodology and results. Chicago, IL: Gas Research Institute; report no. GRI-87/0044.2.

Koontz, M. D.; Rector, H. E. (1995) Estimation of distributions for residential air exchange rates: final report. Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics; contract nos. 68-D9-0166 and 68-D3-0013.

Koontz, M. D.; Mehegan, L. L.; Nagda, N. L. (1992) Distribution and use of cooking appliances that can affect indoor air quality: topical report (November 1985—December 1991). Chicago, IL: Gas Research Institute; report no. GRI-93/0013.

Korc, M. E.; Roberts, P. T.; Chinkin, L. R.; Main, H. H. (1993) Comparison of emission inventory and ambient concentration ratios of NMOC, NO_x, and CO in the Lake Michigan air quality region. Santa Rosa, CA: Sonoma Technology, Inc.; report no. STI-90218-1357-FR.

Krol, M.; Van Leeuwen, P. J.; Lelieveld, J. (1998) Global OH trend inferred from methylchloroform measurements. J. Geophys. Res. [Atmos.] 103: 10,697-10,711.

Lagus Applied Technology, Inc. (1995) Air change rates in non-residential buildings in California. Sacramento, CA: California Energy Commission; contract no. 400-91-034; July.

Law, K. S. (1999) Theoretical studies of carbon monoxide distributions, budgets and trends. In: Khalil, M. A. K.; Pinto, J. P.; Shearer, M. J., eds. Carbon monoxide [special issue of papers from an international conference; December 1997; Portland, OR]. Chemosphere Global Change Sci. 1: 19-31.

Lawson, D. R.; Groblicki, P. J.; Stedman, D. H.; Bishop, G. A.; Guenther, P. L. (1990) Emissions from in-use motor vehicles in Los Angeles: a pilot study of remote sensing and the inspection and maintainence program. J. Air Waste Manage. Assoc. 40: 1096-1105.

Leaderer, B. P. (1982) Air pollutant emissions from kerosene space heaters. Science (Washington, DC) 218: 1113-1115.

Leaderer, B. P.; Stolwijk, J. A. J.; Zagraniski, R. T.; Qing-Shan, M. (1984) A field study of indoor air contaminant levels associated with unvented combustion sources. Presented at: 77th annual meeting of the Air Pollution Control Association; June; San Francisco, CA. Pittsburgh, PA: Air Pollution Control Association; paper no. 84-33.3.

Lobert, J. M.; Scharffe, D. H.; Hao, W.-M.; Kuhlbusch, T. A.; Seuwen, R.; Warneck, P.; Crutzen, P. J. (1991) Experimental evaluation of biomass burning emissions: nitrogen and carbon containing compounds. In: Levine, J. S., ed. Global biomass burning: atmospheric, climatic, and biospheric implications. Cambridge, MA: MIT Press; pp. 289-304.

Löfroth, G.; Burton, R. M.; Forehand, L.; Hammond, S. K.; Seila, R. L.; Zweidinger, R. B.; Lewtas, J. (1989) Characterization of environmental tobacco smoke. Environ. Sci. Technol. 23: 610-614.

Logan, J. A.; Prather, M. J.; Wofsy, S. C.; McElroy, M. B. (1981) Tropospheric chemistry: a global perspective. J. Geophys. Res. C: Oceans Atmos. 86: 7210-7254.

Magliano, K. L.; Lurmann, F. W.; Watson, J. G. (1993) Reconciliation of emissions inventory and ambient data in the San Joaquin Valley and the San Francisco Bay area. Presented at: 86th annual meeting & exhibition of the Air & Waste Management Association; June; Denver, CO. Pittsburgh, PA: Air & Waste Management Association; paper no. 93-WP-100.8.

Mahieu, E,; Zander, R.; Delbouille, L.; Demoulin, P.; Roland, G.; Servais, C. (1997) Observed trends in total vertical column abundances of atomspheric gases from IR solar spectra recorded at the Jungfraujoch. J. Atmos. Chem. 28: 227-243.

Marr, L. C.; Morrison, G. C.; Nazaroff, W. W.; Harley, R. A. (1998) Reducing the risk of accidental death due to vehicle-related carbon monoxide poisoning. J. Air Waste Manage. Assoc. 48: 899-906.

McCarthy, S. M.; Yarmac, R. F.; Yocom, J. E. (1987) Indoor nitrogen dioxide exposure: the contribution from unvented gas space heaters. In: Seifert, B.; Esdorn, H.; Fischer, M.; Rüden, H.; Wegner, J., eds. Indoor air '87: proceedings of the 4th international conference on indoor air quality and climate, v. 1, volatile organic compounds, combustion gases, particles and fibres, microbiological agents; August; Berlin, Federal Republic of Germany. Berlin, Federal Republic of Germany: Institute for Water, Soil and Air Hygiene; pp. 478-482.

Menkedick, J.; Niemuth, N.; Hartford, P.; Landstrom, D. K. (1993) Metered ranges, cooktops and ovens in the northern Illinois gas residential load study data base: topical report. Chicago, IL: Gas Research Institute; report no. GRI-93/0204; July.

Miller, S. L.; Hannigan, M. (1999) Indoor carbon monoxide levels from the use of unvented natural gas fireplaces in Boulder, CO. Presented at: The first National Science Foundation international conference on indoor air health; May; Denver, CO.

Moschandreas, D. J.; Zabransky, J., Jr. (1982) Spatial variation of carbon monoxide and oxides of nitrogen concentrations inside residences. Environ. Int. 8: 177-183.

Moschandreas, D. J.; Relwani, S. M.; O'Neill, H. J.; Cole, J. T.; Elkins, R. H.; Macriss, R. A. (1985) Characterization of emission rates from indoor combustion sources. Chicago, IL: Gas Research Institute; report no. GRI 85/0075.

Mount, G. H.; Williams, E. J. (1997) An overview of the tropospheric OH photochemistry experiment, Fritz Peak/Idaho Hill, Colorado, fall 1993. J. Geophys. Res. [Atmos.] 102: 6171-6186.

Moxley, J. M.; Cape, J. N. (1997) Depletion of carbon monoxide from the nocturnal boundary layer. Atmos. Environ. 31: 1147-1155.

Mueller Associates. (1985) Indoor air quality environmental information handbook: combustion sources. Washington, DC: U.S. Department of Energy, Office of Environmental Analysis; report no. DOE/EV/10450-1.

Mumford, J. L.; Lewtas, J.; Burton, R. M.; Svendsgaard, D. B.; Houk, V. S.; Williams, R. W.; Walsh, D. B.; Chuang, J. C. (1990) Unvented kerosene heater emissions in mobile homes: studies on indoor air particles, semivolatile organics, carbon monoxide, and mutagenicity. In: Indoor air '90: precedings of the 5th international conference on indoor air quality and climate, volume 2, characteristics of indoor air; July-August; Toronto, ON, Canada. Ottawa, ON, Canada: International Conference on Indoor Air Quality and Climate, Inc.; pp. 257-262.

Mumford, J. L.; Williams, R. W.; Walsh, D. B.; Burton, R. M.; Svendsgaard, D. J.; Chuang, J. C.; Houk, V. S.; Lewtas, J. (1991) Indoor air pollutants from unvented kerosene heater emissions in mobile homes: studies on particles, semivolatile organics, carbon monoxide, and mutagenicity. Environ. Sci. Technol. 25: 1732-1738.

Murray, D. M.; Burmaster, D. E. (1995) Residential air exchange rates in the United States: empirical and estimated parametric distributions by season and climatic region. Risk Anal. 15: 459-465.

Nagda, N. L.; Koontz, M. D.; Fortmann, R. C.; Billick, I. H. (1987) Detailed evaluation of range-exhaust fans. In: Seifert, B.; Esdorn, H.; Fischer, M.; Rüden, H.; Wegner, J., eds. Indoor air '87: proceedings of the 4th international conference on indoor air quality and climate. Volume 3: developing countries, guaranteeing adequate indoor air quality, control measures, ventilation effectiveness, thermal climate and comfort, policy and strategies; August; Berlin, Federal Republic of Germany. Berlin, Federal Republic of Germany: Institute for Water, Soil and Air Hygiene; pp. 324-328.

Nagda, N. L.; Koontz, M. D.; Billick, I. H.; Leslie, N. P.; Behrens, D. W. (1996) Causes and consequences of backdrafting of vented gas appliances. J. Air Waste Manage. Assoc. 46: 838-846.

National Aeronautics and Space Administration, Panel for Data Evaluation. (1997) Chemical kinetics and photochemical data for use in stratospheric modeling: evaluation number 12. Pasadena, CA: National Aeronautics and Space Administration, Jet Propulsion Laboratory; JPL publication 97-4.

National Oceanic and Atmospheric Administration. (1999a) Global distribution of atmospheric carbon monoxide. Boulder, CO: Climate Monitoring & Diagnostics Laboratory, Carbon Cycle Group. Available: www.cmdl.noaa.gov/ccgg/figures/corug.gif [2000, February 14].

National Oceanic and Atmospheric Administration. (1999b) CO trends and growth rates. Boulder, CO: Climate Monitoring & Diagnostics Laboratory, Carbon Cycle Group. Available: www.cmdl.noaa.gov/ccgg/figures/cotrend_global.gif [2000, February 14].

National Research Council. (1986) Environmental tobacco smoke: measuring exposures and assessing health effects. Washington, DC: National Academy Press.

Novelli, P. C.; Masarie, K. A.; Tans, P. P.; Lang, P. M. (1994) Recent changes in atmospheric carbon monoxide. Science (Washington, DC) 263: 1587-1590.

Novelli, P. C.; Connors, V. S.; Reichle, H. G., Jr.; Anderson, B. E.; Brenninkmeijer, C. A. M.; Brunke, E. G.; Doddridge, B. G.; Kirchhoff, V. W. J. H.; Lam, K. S.; Masarie, K. A.; Matsuo, T.; Parrish, D. D.; Scheel, H. E.; Steele, L. P. (1998) An internally consistent set of globally distributed atmospheric carbon monoxide mixing ratios developed using results from an intercomparison of measurements. J. Geophys. Res. [Atmos.] 103: 19,285-19,293.

Ott, W.; Langan, L.; Switzer, P. (1992) A time series model for cigarette smoking activity patterns: model validation for carbon monoxide and respirable particles in a chamber and an automobile. In: Measuring, understanding, and predicting exposures in the 21st century: proceedings of the conference; November 1991; Atlanta, GA. J. Exposure Anal. Environ. Epidemiol. 2(suppl. 2): 175-200.

Ott, W.; Switzer, P.; Willits, N. (1994) Carbon monoxide exposures inside an automobile traveling on an urban arterial highway. J. Air Waste Manage. Assoc. 44: 1010-1018.

Ott, W. R.; Klepeis, N. E.; Switzer, P. (1995) Modeling environmental tobacco smoke in the home using transfer functions. Presented at: 88th annual meeting and exhibition of the Air & Waste Management Association; June; San Antonio, TX. Pittsburgh, PA: Air & Waste Management Association; paper no. 95-WP84B.03.

Pacyna, J. M.; Graedel, T. E. (1995) Atmospheric emissions inventories: status and prospects. Annu. Rev. Energy Environ. 20: 265-300.

Park, J.-H.; Spengler, J. D.; Yoon, D.-W.; Dumyahn, T.; Lee, K.; Ozkaynak, H. (1998) Measurement of air exchange rate of stationary vehicles and estimation of in-vehicle exposure. J. Exposure Anal. Environ. Epidemiol. 8: 65-78.

Pierce, T. E.; Dudek, M. P. (1996) Biogenic emission estimates for 1995. In: The emission inventory: key to planning, permits, compliance, and reporting; proceedings of a specialty conference; September; New Orleans, LA. Pittsburgh, PA: Air & Waste Management Association; pp. 309-326. (AWMA publication VIP-65).

Pierson, W. R.; Gertler, A. W.; Bradow, R. L. (1990) Comparison of the SCAQS tunnel study with other on-road vehicle emission data. J. Air Waste Manage. Assoc. 40: 1495-1504.

Pierson, W. R.; Gertler, A. W.; Robinson, N. F.; Sagebiel, J. C.; Zielinska, B.; Bishop, G. A.; Stedman, D. H.; Zweidinger, R. B.; Ray, W. D. (1996) Real-world automotive emissions—summary of studies in the Fort McHenry and Tuscarora mountain tunnels. In: Parrish, D.; Trainer, M.; Rao. S. T.; Solomon, P. A., eds. A&WMA international specialty conference on regional photochemical measurements and modeling, part 2; November 1993; San Diego, CA. Atmos. Environ. 30: 2233-2256.

Pinto, J. P.; Khalil, M. A. K. (1991) The stability of tropospheric OH during ice ages, inter-glacial epochs and modern times. Tellus 43B: 347-352.

Pollack, A. K.; Dunker, A. M.; Fieber, J. K.; Heiken, J. G.; Cohen, J. P.; Shepard, S. B.; Schleyer, C. H.; Yarwood, G. (1998) Revision of light-duty vehicle emission inventories using real-world measurements-Auto/Oil Program, phase II. J. Air Waste Manage. Assoc. 48: 291-305.

Poppe, D.; Zimmermann, J.; Bauer, R.; Brauers, T.; Brüning, D.; Callies, J.; Dorn, H.-P.; Hofzumahaus, A.; Johnen, F.-J.; Khedim, A.; Koch, H.; Koppmann, R.; London, H.; Müller, K.-P.; Neuroth, R.; Plass-Dülmer, C.; Platt, U.; Rohrer, F.; Röth, E.-P.; Rudolph, J.; Schmidt, U.; Wallasch, M.; Ehhalt, D. H. (1994) Comparison of measured OH concentrations with model calculations. J. Geophys. Res. [Atmos.] 99: 16,633-16,642.

Prinn, R.; Cunnold, D.; Simmonds, P.; Alyea, F.; Boldi, R.; Crawford, A.; Fraser, P.; Gutzler, D.; Hartley, D.; Rosen, R.; Rasmussen, R. (1992) Global average concentration and trend for hydroxyl radicals deduced from ALE/GAGE trichloroethane (methyl chloroform) data for 1978-1990. J. Geophys. Res. [Atmos.] 97: 2445-2461.

Prinn, R. G.; Weiss, R. F.; Miller, B. R.; Huang, J.; Alyea, F. N.; Cunnold, D. M.; Fraser, P. J.; Hartley, D. E.; Simmonds, P. G. (1995) Atmospheric trends and lifetime of CH_3CCl_3 and global OH concentrations. Science (Washington, DC) 269: 187-192.

Research Triangle Institute. (1990) An investigation of infiltration and indoor air quality. Albany, NY: New York State Energy Research and Development Authority; report no. NYERDA 90-11.

Rickert, W. S.; Robinson, J. C.; Collishaw, N. (1984) Yields of tar, nicotine, and carbon monoxide in the sidestream smoke from 15 brands of Canadian cigarettes. Am. J. Public Health 74: 228-231.

Rinsland, C. P.; Levine, J. S. (1985) Free tropospheric carbon monoxide concentrations in 1950 and 1951 deduced from infrared total column amount measurements. Nature (London) 318: 250-254.

Ritter, J. A.; Barrick, J. D. W.; Watson, C. E.; Sachse, G. W.; Gregory, G. L.; Anderson, B. E.; Woerner, M. A.; Collins, J. E., Jr. (1994) Airborne boundary layer flux measurements of trace species over Canadian boreal forest and northern wetland regions. J. Geophys. Res. [Atmos.] 99: 1671-1685.

Robinson, E.; Bell, G. B., Jr. (1956) Low-level temperature structure under Alaskan ice fog conditions. Bull. Am. Meteorol. Soc. 37: 506-513.

Rodes, C.; Sheldon, L.; Whitaker, D.; Clayton, A.; Fitzgerald, K.; Flanagan, J.; DiGenova, F.; Hering, S.; Frazier, C. (1998) Measuring concentrations of selected air pollutants inside California vehicles [final report]. Sacramento, CA: California Environmental Protection Agency, Air Resources Board; contract no. 95-339.

Rogers, J. D. (1990) Ultraviolet absorption cross sections and atmospheric photodissociation rate constants of formaldehyde. J. Phys. Chem. 94: 4011-4015.

Ryan, J. V.; McCrillis, R. C. (1994) Analysis of emissions from residential natural gas furnaces. Presented at: 87th annual meeting and exhibition of the Air & Waste Management Association; June; Cincinnati, OH. Pittsburgh, PA: Air & Waste Management Association; paper no. 94-WA75A.04.

Seila, R. L.; Lonneman, W. A.; Meeks, S. A. (1989) Determination of C_2 to C_{12} ambient air hydrocarbons in 39 U.S. cities from 1984 through 1986. Research Triangle Park, NC: U.S. Environmental Protection Agency, Atmospheric Research and Exposure Assessment Laboratory; report no. EPA/600/3-89/058.

Seiler, W.; Conrad, R. (1987) Contribution of tropical ecosystems to the global budget of trace gases especially CH_4, H_2, CO and N_2O. In: Dickinson, R. E., ed. The geophysiology of Amazonia: vegetation and climate interactions. New York, NY: John Wiley; pp. 133-162. (Glantz, H. H., ed. Wiley series in climate and biosphere).

Shadwick, D.; Glen, G.; Lakkadi, Y.; Lansari, A.; del Valle-Torres, M. (1997) Analysis of carbon monoxide for the Denver, Colorado MSA. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory; contract no. 68-D5-0049; December.

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.

Slack, H. H.; Heumann, M. A. (1997) Use of unvented residential heating appliances—United States, 1988-1994. Morb. Mortal. Wkly. Rep. 46: 1221-1224.

Spicer, C. W.; Billick, I. H. (1996) Persistence and fate of natural gas appliance emissions. In: Proceedings of the 1995 international gas research conference; November 1995; Cannes, France. Rockville, MD: Government Institutes, Inc.; pp. 1752-1761.

Stedman, D. H.; Bishop, G. A.; Aldrete, P.; Slott, R. S. (1997) On-road evaluation of an automobile emission test program. Environ. Sci. Technol. 31: 927-931.

Stedman, D. H.; Bishop, G. A.; Slott, R. S. (1998) Repair avoidance and evaluating inspection and maintenance programs. Environ. Sci. Technol. 32: 1544-1545.

Stephens, R. D.; Cadle, S. H. (1991) Remote sensing measurements of carbon monoxide emissions from on-road vehicles. J. Air Waste Manage. Assoc. 41: 39-46.

Sterling, T. D.; Sterling, E. (1979) Carbon monoxide levels in kitchens and homes with gas cookers. J. Air Pollut. Control Assoc. 29: 238-241.

Sze, N. D. (1977) Anthropogenic CO emissions: implications for the atmospheric CO-OH-CH_4 cycle. Science (Washington, DC) 195: 673-675.

Tegart, W. J. McG.; Sheldon, G. W., eds. (1993) Climate change 1992: the supplementary report to the IPCC impacts assessment. Canberra, Australia: Australian Government Publishing Service.

Thompson, A. M.; Cicerone, R. J. (1986) Possible perturbations to atmospheric CO, CH_4, and OH. J. Geophys. Res. [Atmos.] 91: 10,853-10,864.

Thompson, A. M.; Chappellaz, J. A.; Fung, I. Y.; Kucsera, T. L. (1993) The atmospheric CH_4 increase since the last glacial maximum. (2). Interactions with oxidants. Tellus 45B: 242-257.

Thrasher, W. H.; DeWerth, D. W. (1979) Evaluation of the pollutant emissions from gas-fired room heaters. Cleveland, OH: American Gas Association, Cleveland Laboratories; research report no. 1515.

Tiegs, P.; Bighouse, R. (1994) Spillage of combustion byproducts from woodstoves operated in negative pressure environments. Presented at: 87th annual meeting and exhibition of the Air & Waste Management Association; June; Cincinnati, OH. Pittsburgh, PA: Air & Waste Management Association; paper no. 94-FA150.04.

Tobacco Information and Prevention Source. (1996) 1995 national household survey on drug abuse, tobacco related statistics, SAMHSA, August 1996. Atlanta, GA: U.S. Centers for Disease Control and Prevention. Available: www.cdc.gov/tobacco/samhsa.htm [2000, February 14].

Traynor, G. W.; Anthon, D. W.; Hollowell, C. D. (1982) Technique for determining pollutant emissions from a gas-fired range. Atmos. Environ. 16: 2979-2987.

Traynor, G. W.; Allen, J. R.; Apte, M. G.; Girman, J. R.; Hollowell, C. D. (1983) Pollutant emissions from portable kerosene-fired space heaters. Environ. Sci. Technol. 17: 369-371.

Traynor, G. W.; Apte, M. G.; Carruthers, A. R.; Dillworth, J. F.; Grimsrud, D. T. (1984) Pollutant emission rates from unvented infrared and convective gas-fired space heaters. Berkeley, CA: U.S. Department of Energy, Lawrence Berkeley Laboratory; report no. LBL-18258.

Traynor, G. W.; Girman, J. R.; Apte, M. G.; Dillworth, J. F.; White, P. D. (1985) Indoor air pollution due to emissions from unvented gas-fired space heaters. J. Air Pollut. Control Assoc. 35: 231-237.

Traynor, G. W.; Apte, M. G.; Carruthers, A. R.; Dillworth, J. F.; Grimsrud, D. T.; Gundel, L. A. (1987) Indoor air pollution due to emissions from wood-burning stoves. Environ. Sci. Technol. 21: 691-697.

Traynor, G. W.; Aceti, J. C.; Apte, M. G.; Smith, B. V.; Green, L. L.; Smith-Reiser, A.; Novak, K. M.; Moses, D. O. (1989) Macromodel for assessing residential concentrations of combustion-generated pollutants: model development and preliminary predictions for CO, NO_2, and respirable suspended particles. Berkeley, CA: U.S. Department of Energy, Lawrence Berkeley Laboratory; report no. LBL-25211.

Turk, B. H.; Grimsrud, D. T.; Brown, J. T.; Geisling-Sobotka, K. L.; Harrison, J.; Prill, R. J. (1989) Commercial building ventilation rates and particle concentrations. ASHRAE Trans. 95(part 1): 422-433.

Turner, S.; Cyr, L.; Gross, A. J. (1992) The measurement of environmental tobacco smoke in 585 office environments. Environ. Int. 18: 19-28.

U.S. Census Bureau. (1998) American housing survey: detailed tables from the 1993 AHS-N data chart. How do you fuel your home? - Table 2-5. Washington, DC: U.S. Department of Commerce.

U.S. Census Bureau. (1999) USA Statistics in brief—law, education, communications, transportation, housing. Washington, DC: U.S. Department of Commerce. Available: www.census.gov/statab/www/part2.html [2000, February 14].

U.S. Environmental Protection Agency. (1981) U.S. Environmental Protection Agency Intra-Agency Task Force on Air Quality Indicators. Research Triangle Park, NC: Office of Air Quality Planning and Standards; report no. EPA-450/4-81-015.

U.S. Environmental Protection Agency. (1990) National air quality and emissions trends report, 1988. Research Triangle Park, NC: Office of Air Quality Planning and Standards; report no. EPA/450/4-90/002.

U.S. Environmental Protection Agency. (1991a) User's guide to MOBILE4.1 (mobile source emission factor model). Ann Arbor, MI: Office of Mobile Sources; report no. EPA-AA-TEB-91-01.

U.S. Environmental Protection Agency. (1991b) Air quality criteria for carbon monoxide. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/8-90/045F.

U.S. Environmental Protection Agency. (1994) User's guide to MOBILE5 (Mobile Source Emission Factor Model). Ann Arbor, MI: Office of Air and Radiation, Office of Mobile Sources; report no. EPA-AA-TEB-94-01. Available: www.epa.gov/oms/models/mobile5/mob5ug.pdf [2000, March 3].

U.S. Environmental Protection Agency. (1996) Air quality criteria for particulate matter. Research Triangle Park, NC: National Center for Environmental Assessment-RTP Office; report nos. EPA/600/P-95/001aF-cF. 3v.

U.S. Environmental Protection Agency. (1998) National air quality and emissions trends report, 1997. Research Triangle Park, NC: Office of Air Quality Planning and Standards; report no. EPA 454/R-98-016. Available: www.epa.gov/oar/aqtrnd97/ [2000, February 14].

Wallace, L. A. (1983) Carbon monoxide in air and breath of employees in an underground office. J. Air Pollut. Control Assoc. 33: 678-682.

Williams, R.; Walsh, D.; White, J.; Jackson, M.; Mumford, J. (1992) Effect on carbon monoxide levels in mobile homes using unvented kerosene heaters for residential heating. Indoor Environ. 1: 272-278.

Wilson, A. L.; Colome, S. D.; Tian, Y. (1993) California residential indoor air quality study. Volume 1: methodology and descriptive statistics. Appendices. Chicago, IL: Gas Research Institute; report no. GRI-93/0224.2.

Wilson, A. L.; Colome, S. D.; Tian, Y.; Becker, E. W.; Baker, P. E.; Behrens, D. W.; Billick, I. H.; Garrison, C. A. (1996) California residential air exchange rates and residence volumes. J. Exposure Anal. Environ. Epidemiol. 6: 311-326.

Yung, Y. L.; Shia, C.; Herman, R. L. (1999) Is the biomass burning source of CO decreasing? In: Khalil, M. A. K.; Pinto, J. P.; Shearer, M. J., eds. Carbon monoxide [special issue of papers from an international conference; December 1997; Portland, OR]. Chemosphere Global Change Sci. 1: 83-90.

Yurganov, L. N.; Grechko, E. I.; Dzhola, A. V. (1999) Zvenigorod carbon monoxide total column time series: 27 yr of measurements. In: Khalil, M. A. K.; Pinto, J. P.; Shearer, M. J., eds. Carbon monoxide [special issue of papers from an international conference; December 1997; Portland, OR]. Chemosphere Global Change Sci. 1: 127-136.

Zawacki, T. S.; Cole, J. T.; Huang, V. M. S.; Banasiuk, H.; Macriss, R. A. (1984) Efficiency and emissions improvement of gas-fired space heaters. Task 2. Unvented space heater emission reduction [final report]. Chicago, IL: Gas Research Institute; report no. GRI-84/0021.

Zhang, Y.; Stedman, D. H.; Bishop, G. A.; Beaton, S. P.; Guenther, P. L. (1996) On-road evaluation of inspection/maintenance effectiveness. Environ. Sci. Technol. 30: 1445-1450.

Ziskind, R. A.; Rogozen, M. B.; Carlin, T.; Drago, R. (1981) Carbon monoxide intrusion into sustained-use vehicles. Environ. Int. 5: 109-123.

APPENDIX 3A

Spatial Correlation Coefficients for Carbon Monoxide

This appendix contains information about the spatial variability of carbon monoxide (CO) that was not presented in Section 3.4.3. Spatial correlation coefficients have been calculated in ambient monitoring studies to provide insight into the geographical distribution of sources of particulate matter (Suh et al., 1995) or into pollutants' spatio-temporal exposure characterization errors (Ito et al., 1998; Peters et al., 1999).

Two types of spatial correlations, the Pearson correlation coefficient and the Kendall tau statistic, were used to evaluate the relationship of daily CO maximum 8-h averages among the different monitoring sites in the five geographically diverse urban areas of Denver, CO; Los Angeles, CA; New York, NY; Phoenix, AZ; and Fairbanks, AK (Shadwick et al., 1997, 1998a,b,c). Both types of nonparametric correlation coefficients are intended to measure the "strength of relationship"; however, each does so in different ways. The Pearson correlation coefficient stresses numerical levels, and the Kendall tau statistic emphasizes differences between ranked sets of values. The Kendall tau correlation coefficients are presented in this section because they allow for a more simplistic interpretation of the resulting statistic than do Pearson coefficients (Hollander and Wolfe, 1973). For example, in any two time series, a given pair of (bivariate) observations can exhibit a simultaneous increase (or decrease) in ranks (i.e., a concordant pair) or a change of ranks in opposing directions (i.e., a discordant pair). Kendall tau estimates the probability that two pairs of observations are concordant. As the sample statistic approaches +1, a high probability of concordance between two randomly selected pairs is implied, and as it approaches −1, a low probability of concordance (high probability of discordance) is implied.

Table 3A-1 shows the Kendall tau correlation coefficients for the daily maximum 8-h CO concentration at the sites in the Denver Metropolitan Statistical Area (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). 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							

Table 3A-2 shows the correlations for the daily maximum 8-h average CO concentration between sites for the Los Angeles Consolidated Metropolitan Statistical Area (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 air sheds. 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, CA, 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, CA. These sites had violations before 1991, but have not had any violations of the daily maximum 8-h average since then. The last group of sites, consisting of Asuza, Barstow, El Toro, and West Los Angeles, CA did not have any violations over the 10-year period.

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.

Table 3A-3 shows the Kendall tau correlation coefficients calculated for the daily maximum 8-h average CO concentration for the New York, NY, 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, NY, 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, NJ, 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, and, 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 with the Flatbush Avenue site, other than proximity, are influencing the correlations between them.

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 air shed is more well mixed than are the others investigated here.

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												

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												

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													

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													

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				

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.

Table 3A-5 shows Kendall spatial tau correlation coefficients for the daily maximum 8-h CO concentration at the three sites in the Fairbanks, AK, MSA. As can be seen from the table, there are uniformly high correlation coefficients among each of the site pairs with much smaller variation among them than among those given in Tables 3A-1 through 3A-4. There is very little change in values over the 10-year period of interest. In addition, for each winter season in Table 3A-5, there is no substantial difference between the weekday correlations and those for the weekend. No other discernable pattern or trend is revealed by the correlation analysis.

Table 3A-5. Kendall Tau Spatial Correlations for the Daily Maximum 8-Hour Average Carbon Monoxide Data in the Fairbanks Metropolitan Statistical Area

	1986/87 Winter Season		
	Federal Building	State Building	Hunter Elementary
	WEEKDAY		
Federal Building		0.83	0.77
State Building	0.75		0.79
Hunter Elementary	0.70	0.80	
	WEEKEND		
	1995/96 Winter Season		
	Federal Building	State Building	Hunter Elementary
	WEEKDAY		
Federal Building		0.79	0.76
State Building	0.79		0.80
Hunter Elementary	0.77	0.77	
	WEEKEND		

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).

References

Hollander, M.; Wolfe, D. A. (1973) Nonparametric statistical methods. New York: John Wiley & Sons.

Ito, K.; Thurston, G. D.; Nadas, A.; Lippmann, M. (1998) Multiple pollutants' spatio-temporal exposure characterization errors. In: Measurement of toxic and related air pollutants: proceedings of a specialty conference, volume I; September; Cary, NC; pp. 53-63. (A&WMA publication VIP-85).

Peters, A.; Kotesovec, F.; Skorkovsky, J.; Brynda, J.; Heinrich, J. (1999) Akute Auswirkung der Schwebstaubkonzentrationen in der Außenluft auf die Mortalität - Vergleichsstudie Nordost-Bayern / Nordböhmen. Abschlußbericht [Acute effects of suspended particle concentrations in the atmosphere on mortality - a study comparing northeast Bavaria and north Bohemia. Final report]. Bavaria, Federal Republic of Germany: Institut für Epidemiologie; report no. GSF-EP S 1/99.

Shadwick, D.; Glen, G.; Lakkadi, Y.; Lansari, A.; del Valle-Torres, M. (1997) Analysis of carbon monoxide for the Denver, Colorado MSA. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory; contract no. 68-D5-0049; December.

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.

Suh, H. H.; Allen, G. A.; Koutrakis, P.; Burton, R. M. (1995) Spatial variation in acidic sulfate and ammonia concentrations within metropolitan Philadelphia. J. Air Waste Manage. Assoc. 45: 442-452.

CHAPTER 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 always the same because sometimes outdoor sources (e.g., highway emissions) are downwind of an ambient monitoring station." 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., unvented combustion 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 source of CO, and 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; U.S. Environmental Protection Agency, 1992a; 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). Using this definition, this chapter assumes that an inhaled CO molecule (the agent) reaches a human (the target) at the lining of the lung (the contact boundary) where CO exchange takes place between air and blood. In actual field studies,

the air in the immediate vicinity of the target often is assumed to be well mixed, such that a measured CO concentration in the air can be assumed to represent a nonsmoking person's actual exposure from CO inhalation.

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). Because the endogenous production of CO from drugs and solvents may continue for several hours, it can prolong any cardiovascular stress from COHb. Moreover, the maximum COHb level from endogenous CO production can last up to twice as long as comparable COHb levels caused by comparable exposures to exogenous CO (Wilcosky and Simonsen, 1991; Agency for Toxic Substances and Disease Registry, 1993). Hence, the literature on exposure to methylene chloride also is discussed in this chapter.

Descriptive studies of exposure typically report average and peak concentrations to which people are exposed, the temporal aspects of exposure (i.e., averaging times), where exposures occurred (i.e., outdoor and indoor microenvironments), and the sources of microenvironmental exposures (e.g., motor vehicles, combustion appliances). Explanatory studies of microenvironmental concentrations when sources are operating try to identify factors that affect or contribute to exposure, because that information may enable mitigation of high-level exposures. Unlike epidemiologic or clinical studies of health effects, exposure studies rarely identify the health outcomes (e.g., headache, dizziness, nausea, etc.) associated with measured exposures.

For completeness, this chapter also briefly discusses high-level nonambient CO exposures that can lead to CO poisoning and death (e.g., accidental exposure to undiluted motor vehicle exhaust). Although such effects are not health outcomes presently used in setting the NAAQS for CO, they may be affected by reduced emissions from sources regulated by the U.S. Environmental Protection Agency (EPA) to meet the CO NAAQS. Chapter 6 discusses relevant health effects resulting from exposure to ambient CO concentrations.

This chapter is organized as follows: the first section summarizes the state of knowledge on population exposure to CO as of 1991, when EPA published the previous CO air quality criteria document. Next follows a discussion of more recently published studies of population exposure to all sources of CO (except the active inhalation of tobacco smoke), which delineates typical and peak levels of exposure as people engage in daily activities, including those related to an occupation. Factors affecting trends in population exposure are then described, including factors such as public policies affecting motor vehicle emissions, travel behavior, and societal changes in human activity patterns, particularly those related to motor vehicles (which are a major source of CO emissions, as shown in Chapter 3). The conclusion section summarizes findings of this assessment and discusses their implications for CO exposure models, such as the probabilistic NAAQS Exposure Model (NEM) used for evaluating CO exposures under different air quality indicators for the NAAQS. The conclusion also examines the extent to which CO exposures have changed since the previous criteria document.

4.2 Brief Summary of Population Exposure Studies Prior to 1991

This section briefly reviews key population exposure studies that were completed by 1990. It identifies populations sensitive to CO exposure and discusses studies of population exposure based on fixed-site and personal monitors, as well as relevant population exposure models. This section does not discuss many pre-1990 exposure studies for two reasons: (1) the pre-1990 studies are reviewed in the previous criteria document, and the primary purpose of the present criteria document is to focus on more recent studies; and (2) the results of older studies no longer may be indicative of current population exposures, given the major reductions in CO emissions per motor vehicle, social changes affecting

commuting patterns and growth in vehicle miles of travel, and other factors. Factors affecting changes in population exposure are discussed in Section 4.4.

4.2.1 Sensitive Populations

The NAAQS are intended to protect the general public, including probable high-risk groups of the general population. These groups differ from one air pollutant to another. In the case of CO, these groups include the elderly; pregnant women; fetuses; young infants; and those suffering from anemia or certain other blood, cardiovascular, or respiratory diseases. People 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 3-4).

4.2.2 Estimates of Population Exposure Based on Fixed-Site Monitors

In the United States, NAAQS attainment is based on ambient air quality measurements recorded at a nationwide network of fixed-site monitors. Based on this network, EPA's Office of Air Quality Planning and Standards estimated that 9.1 million people lived in three counties where ambient CO levels exceeded the NAAQS in 1997 and, thus, were at increased risk of exposure to CO levels above the NAAQS (U.S. Environmental Protection Agency, 1998). 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 why such estimates should not be interpreted as assessments of 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 (e.g., idling motor vehicles), indoor CO concentrations tend to equal outdoor concentrations over 24 h. 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 incompletely vented indoor combustion sources such as gas stoves used for supplementary space heating, kerosene heaters, etc., indoor CO concentrations often exceed the outdoor levels (U.S. Environmental Protection Agency, 1991). 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, 1989; Schwab et al., 1990). Hence, studies of actual personal

exposure to CO are preferred over crude estimates of population exposure to ambient CO in determining what risk CO poses to public health from a total exposure perspective (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 (Duan, 1982; Sexton and Ryan, 1988). For further discussion of these topics, see Section 8.2 of the previous CO criteria document (U.S. Environmental Protection Agency, 1991) and Mage (1991).

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 (Duan, 1982). 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 indoor 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 then were 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 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, DC, during the winter of 1982 and 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, an estimated 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% did so in Washington. The end-expired breath CO levels were in excess of 10 ppm, which is roughly equivalent to 2% COHb in about 12.5% of the Denver participants and about 10% of the Washington participants (after correcting the measured breath concentrations for the influence of room air CO concentrations). 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 (1) inside a parking garage and (2) traveling by car. Those who commuted 6 h or more per week had higher average exposures than those who commuted fewer hours per week. Table 4-1 shows that higher mean CO concentrations occurred for travel by motor vehicle (motorcycle, bus, car, and truck) than that by walking or bicycle, and that high indoor concentrations (above the 8-h NAAQS of 9 ppm) occurred in public garages, service stations, or motor vehicle repair facilities. Denver had higher average CO concentrations than did Washington for all microenvironments because of Denver's higher altitude and colder winter climate (Ott et al., 1992a).

4.3 Population Exposure Models

Many studies developed computer 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 logistically impractical to measure 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 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

Table 4-1. Carbon Monoxide Concentrations in Selected Microenvironments of Denver, CO, 1982 and 1983 (listed in descending order of mean CO concentration)

Microenvironment	Number of Observations[a]	Mean (ppm)	Standard Error (ppm)
In-Transit			
Motorcycle	22	9.79	1.74
Bus	76	8.52	0.81
Car	3,632	8.10	0.16
Truck	405	7.03	0.49
Walking	619	3.88	0.27
Bicycling	9	1.34	1.20
Outdoor			
Public garages	29	8.20	0.99
Residential garages or carports	22	7.53	1.90
Service stations or vehicle repair facilities	12	3.68	1.10
Parking lots	61	3.45	0.54
Other locations	126	3.17	0.49
School grounds	16	1.99	0.85
Residential grounds	74	1.36	0.26
Sports arenas, amphitheaters	29	0.97	0.52
Parks, golf courses	21	0.69	0.24
Indoor			
Public garages	116	13.46	1.68
Service stations or vehicle repair facilities	125	9.17	0.83
Other locations	427	7.40	0.87
Other repair shops	55	5.64	1.03
Shopping malls	58	4.90	0.85
Residential garages	66	4.35	0.87
Restaurants	524	3.71	0.19
Offices	2,287	3.59	0.002
Auditoriums, sports arenas, concert halls	100	3.37	0.48
Stores	734	3.23	0.21
Health care facilities	351	2.22	0.23
Other public buildings	115	2.15	0.30
Manufacturing facilities	42	2.04	0.39
Homes	21,543	2.04	0.02
Schools	426	1.64	0.13
Churches	179	1.56	0.25

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

Sources: Johnson (1984) and Akland et al. (1985), as reported in U.S. Environmental Protection Agency (1991).

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.

Unlike SHAPE, which uses diary data from each person in a population, the NEM model aggregates people into cohorts. 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 the 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 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.

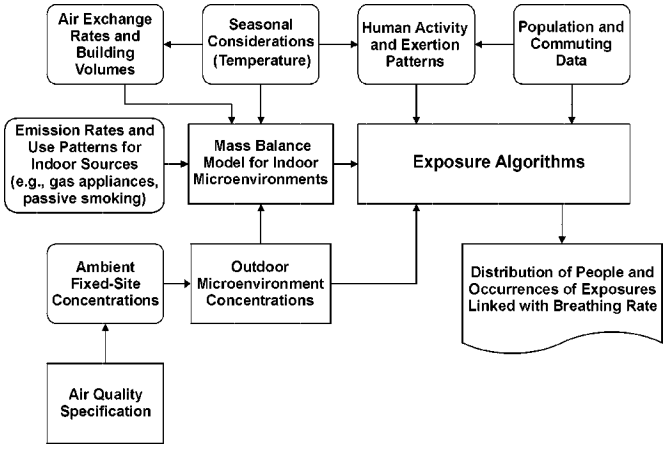

Figure 4-1. Conceptual overview of pNEM. Model inputs (e.g., activity patterns, ambient monitoring data, air exchange rates) are in round-cornered boxes, and model calculations are shown in rectangles.
Source: Johnson et al. (1999).

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, rather than the SHAPE model, in its previous review of the CO NAAQS (U.S. Environmental Protection Agency, 1992b). At the request of the Clean Air Scientific Advisory Committee, as part of that review, EPA performed a limited evaluation of the predictions of pNEM/CO against observed data for subjects of the Denver study (Johnson et al., 1992). That evaluation concluded that there was generally good agreement between the distributions of observed and predicted 1-h daily maximum exposures, but that the model tended to underpredict the highest 8-h daily maximum exposures (i.e., >12 ppm) and overpredict the lowest 8-h daily maximum exposures (i.e., <5 ppm). Extending the earlier evaluation of the pNEM/CO model, Law et al. (1997) performed 20 simulated runs, the average values of which were used for evaluation purposes. 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. The proportion of the Denver population exposed at or above

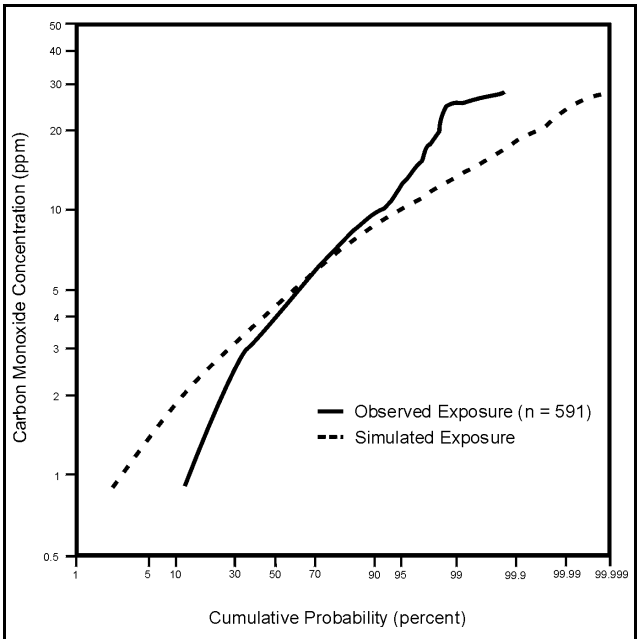

Figure 4-2. Observed versus simulated 8-h daily maximum exposure for persons residing in homes with gas stoves in Denver, CO.
Source: Law et al. (1997).

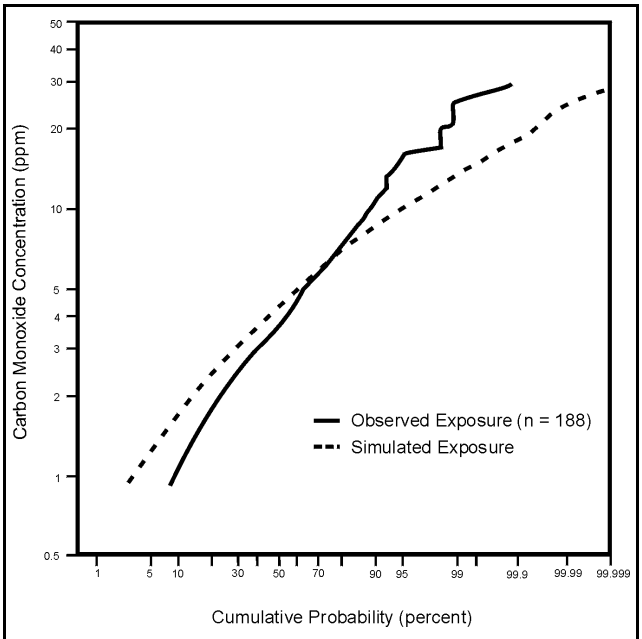

Figure 4-3. Observed versus simulated 8-h daily maximum exposure for persons residing in homes without gas stoves in Denver.
Source: Law et al. (1997).

9 ppm (the 8-h NAAQS) was 12.7% (observed) versus 9.9% (highest predicted) for those with gas stoves and 13.3% (observed) versus 8.8% (highest predicted) for those without gas stoves. Similar results were reported for the 1-h daily maximum exposures, with and without gas stove use. The proportion of the Denver population exposed at or above 35 ppm (the 1-h NAAQS) was 3.2% (observed) versus 1.2% (highest predicted) for those with gas stoves and 2.1% (observed) versus 1.1% (highest predicted) for those without gas stoves. 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.

Law et al. (1997) proposed four factors that may explain why pNEM/CO underpredicted the observed CFD of people with high-level exposures ($\geq$90th percentile).

(1) The pNEM/CO modeled only two indoor CO sources (passive smoking and gas stoves) and omitted other home combustion sources (e.g., attached garages, fireplaces, kerosene heaters, woodstoves, etc.) that may have impacted observed levels using personal monitors.
(2) Although people with high-level exposures were observed for two consecutive days, the model randomly sampled each day separately, thereby diluting the chances of sampling that person on both days.
(3) The model used activity pattern data from three cities (Cincinnati, OH; Denver; and Washington) to predict exposures of Denver residents. In reality, activity patterns of Cincinnati or Washington residents may not reflect those residing in Denver.
(4) The model used a constant vehicular air-exchange rate and a constant secondary-smoke CO value that are known to vary in reality.

The EPA's Office of Air Quality Planning and Standards is in the process of revising the pNEM/CO model. Given the Law et al. (1997) study and EPA's mandate under the Clean Air Act (CAA) to protect public health, research is needed to improve the abilities of both SHAPE and pNEM to predict high-end exposures. One possible improvement is to consider addressing autocorrelation of inputs for time and concentration, particularly inputs of possibly nonindependent microenvironments. For example, the

commuting time and CO exposure of someone going from home to work may not be independent of their commuting time and exposure from work to home. Also, both SHAPE and pNEM may need to consider CO emission sources, microenvironments, and activity patterns excluded from previous versions of the models to improve characterization of high-end exposures. Model refinements should recognize that high-end exposures may come from either regulated or unregulated CO emissions under the CAA.

4.4 Survey of Recent Exposure Studies of Nonsmokers

This section focuses primarily on population exposure studies published or accepted for publication in the scientific, peer-reviewed literature since the previous CO criteria document was published in 1991, and includes some earlier studies that were omitted. It compares results from both old and new studies wherever possible. However, the scope is limited to the exposure of nonsmokers. Studies involving smokers were excluded because it is impossible to determine whether CO concentrations inhaled by smokers originated from smoking or other sources (e.g., motor vehicles, gas appliances, etc.)." As such, smokers have higher baseline levels of COHb than nonsmokers and an adaptive response to elevated COHb.

The section is subdivided into three parts. The first part discusses nonoccupational exposure studies because the NAAQS are intended to protect the general public. The second part reviews occupational studies because urban population exposure models (e.g., pNEM/CO) must account for that portion of total exposure that occurs in occupational settings. The third part describes recent activity pattern studies because they focus on the important temporal component of exposure.

4.4.1 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 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 can indirectly increase COHb levels. Also discussed are studies of the passive exposure of nonsmokers to CO concentrations in cigarette and cigar smoke because the pNEM/CO model accounts for this type of exposure.

4.4.1.1 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 previous CO criteria document and, therefore, are not reviewed again here. Subsection 4.4.2.2 examines the effects of progressively tighter CO emission standards on passenger cabin exposure; this subsection, on the other hand, focuses on other factors that affect the CO exposure of motorists and bicyclists.

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 children were treated for accidental CO poisoning after riding in the back of eight closed pickup trucks in Seattle, WA, between 1986 and 1991. Forty-eight children riding with them in the backs of these same pickup trucks did not require treatment. Seventeen of the 20 children rode under a rigid closed canopy attached to the bed of the truck, and the other three rode beneath a tarpulin. Six pickup trucks had known exhaust system leaks; three had rear-end tailpipes, and three had side-mounted tailpipes. For the 20 children, average COHb levels measured in an emergency room were 18.2% (mean) ±2.4% (standard error), and levels ranged from 1.6 to 37.0% COHb.

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, Table 4-2 shows that the mean CO concentrations inside vehicles always exceeded the mean ambient CO concentrations measured at fixed-site monitors. The ratio between a study's mean in-vehicle CO concentration and its mean ambient CO concentration 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 30 to 100 m from the midpoint of each route.

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 (studies 5, 11 and 13 in Table 4-2) with three indirect studies (studies 4, 12 and 14, respectively, in Table 4-2) 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 Table 4-2 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 study 9 data were disaggregated by roadway location, 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 effects 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 with 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, confirming findings made earlier in the United States by Flachsbart et al. (1987).

Ott et al. (1994) developed statistical models of passenger cabin exposure to CO concentrations from highway emissions, based on 88 trips taken during a 13.5-mo period in 1980 and 1981. All trips occurred in one vehicle with windows set in a "standard position" as it traveled an arterial highway (El Camino Real) in the San Francisco Bay area of California. The models are noteworthy because they examined the explanatory power of nine variables. The best model predicted the average CO exposure per trip as a function of just two variables: (1) traffic conditions, as measured by the proportion of travel time stopped, and (2) a seasonal trend term expressed as a cosine function of the day of the year on which the trip was taken (adjusted multiple correlation coefficient [R^2] = 0.67). A model that included ambient CO concentrations from a fixed-site monitor slightly improved the explanatory power of the model (adjusted R^2 = 0.71).

Flachsbart (1999a) developed a set of statistical models of passenger exposure to CO concentrations inside a motor vehicle as it traveled a coastal artery (the Kalanianaole Highway) in Honolulu, HI. All trips

Table 4-2. Summary of Studies of In-Vehicle Exposure and Ambient Carbon Monoxide Concentrations, 1965 to 1992

Study Sites	Study Period	Mean In-Vehicle CO Concentration (ppm)	Variation of In-Vehicle CO Concentration (ppm)[a]	Typical Ambient CO (ppm)
1	≈1965	37.0	23-58	20-30
2	≈1966	31.8[b]	7-77	14.3
3	April 1966 - June 1967	25.4[c]	18-36	No data
4	≈Summer 1973	17.5	15-20	6.0
5	October 1974 - February 1975	13.4	±5.5	6.0
6	July - August 1978	13.8	±7.2	3.5
7	October 1979	13.1	10.9-15.3	3.4
8	January 1980 - February 1981	9.8	±5.8	<1.5
9	January - March 1981	7.7[d]	±3.6 - ±7.7	2.5-8.4[e]
10	November 1981 - May 1982	10.6	5-30	1.1
11	November 1982 - February 1983	6.5[f]	0.14-0.32[g]	3.2-6.6[e]
12	January - March 1983	11.7	±2.2 - ±9.0	2.3
13	May 1987 - March 1988	8.6	±4.95	3.7
14	August - September 1988	11.3	±5.1	2.9
15	January 1991 - March 1992	4.6	±2.1	<1.0
16	November 1991 - December 1992	3.0	±2.9	No data

Study Sites:

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
11. Denver, CO; Washington, DC
12. Washington, DC
13. Los Angeles, CA
14. Raleigh, NC
15. Menlo Park, Palo Alto, and Los Altos, CA
16. New Jersey Turnpike and Route 18, NJ

Note: Numbers shown below in parentheses are mean in-vehicle CO concentrations in ppm.
[a]Range or one standard deviation except as noted.
[b]Chicago (37), Cincinnati (21), Denver (40), St. Louis (36), Washington (25).
[c]Atlanta (29), Baltimore (21), Chicago (24), Cincinnati (23), Denver (29), Detroit (25), Houston (23), Los Angeles (36), Louisville (20), Minneapolis-St. Paul (28), New York (34), Phoenix (29), St. Louis (18), Washington (19).
[d]Denver (10.3), Los Angeles (8.5), Phoenix (6.7), Stamford (5.2), commuting and residential driving microenvironments weighted by sample size.
[e]Range across all cities studied.
[f]Denver (8.0), Washington (5.0).
[g]Range in standard error for all cities studied.

Source: Flachsbart (1995).

occurred during morning periods over a 6-mo period in 1981 and 1982. The 6.2-km study site was divided into three links. The models predicted the average CO concentration inside the vehicle's passenger cabin on the third link as a function of several variables. Based on data for 80 trips, the three most powerful models (adjusted $R^2 = 0.69$) were nonlinear combinations of several variables: the average CO concentration inside the cabin for the second link; wind speed and direction; and either travel time, vehicle speed, or the estimated motor vehicle CO emission factor for the third link. Several nonlinear models were based on data for 62 trips for which nonzero, ambient CO concentrations were available. For this smaller database, the most practical models (adjusted $R^2 = 0.67$) 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 cabin exposure was strongly affected by travel time and average vehicle speed, both of which were affected by the time that the test vehicle entered each link of the highway. This implied that stochastic simulations of exposure (e.g., the SHAPE model by Ott [1984] and Ott et al. [1988]) should not assume that trip times and commuter exposures are independent of trip-starting times.

The most recent U.S. study of in-vehicle CO exposure reported results for hypothetical commutes on standardized routes in Los Angeles and Sacramento, CA, during early fall, 1997 (Rodes et al., 1998). Continuous CO concentrations were measured over 2-h periods at different times of day for 29 trips by two test vehicles (one vehicle following the other). The CO levels were measured both inside and outside (at the base of the windshield) of the vehicles, and outdoors along surveyed routes and at nearby fixed monitoring stations. Since the minimum quantification limit (MQL) of the portable monitor was 2 ppm, all data below the MQL were treated as zero concentrations. The research design employed a balanced factorial design to determine the range of CO concentrations encountered in each city under different scenarios. The scenarios represented combinations of different test vehicle types and ventilation settings, roadway types, level of roadway congestion, and time of day. The study is unique in that the lead test vehicle, equipped with a video camera, followed vehicles with detectable emissions (by eye or nose) whenever possible. Although the lead vehicle frequently trailed city buses and heavy duty diesel trucks, it also targeted visibly gross-emitting, gasoline-powered vehicles.

Because the California study design purposely emphasized scenarios likely to result in high in-vehicle emissions, the study results cannot easily be compared to results of the 16 studies in Table 4-2. Mean CO concentrations inside both test vehicles were reported for each scenario based on only two to four commutes in each city. These concentrations ranged from less than MQL to 2.6 ppm, based on a total of 13 trips in Sacramento, and from 3.0 to 6.0 ppm, based on a total of 16 trips in Los Angeles. As in similar studies, the means of ambient CO concentrations measured at fixed-site monitors fell below the means of in-vehicle CO levels in both cities, and typically were less than the MQL of the portable monitor. Because ambient CO levels vary from city to city, the study computed net microenvironmental concentrations of test vehicles by subtracting ambient from interior CO levels to estimate CO exposure resulting solely from roadway emissions. They found average net microenvironmental concentrations to be higher in Los Angeles (4.6 to 4.9 ppm) than in Sacramento (2.1 to 3.1 ppm) during rush hour trips on freeways; but, there was little difference in average net microenvironmental concentrations between freeway and arterial trips during rush hour trips in both cities. Based on preliminary analysis of five trips, the study reported that CO concentrations could reach short-term peaks, ranging from $\approx$15 to 70 ppm, when the vehicle trailed gasoline-powered delivery trucks and older sedans.

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. Note that the CO exposures of European cyclists may not be comparable to cyclists' exposures in the United States because 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 CO 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 median 1-h averaged uptakes of CO of cyclists (2.4 to 3.2 mg) approached that of car drivers (2.7 to 3.4 mg).

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 (9 to 34 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 discussed completely in the previous CO criteria document. Studies of diurnal effects on in-vehicle exposure during peak travel periods have been inconclusive because they did not 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, Haagen-Smit (1966) found evidence that CO exposures during afternoon commutes were greater than those during morning commutes. Similar results were found later by Cortese and Spengler (1976) in Boston, MA, by Wallace (1979) in Washington, and by Dor et al. (1995) in Paris. However, contrary evidence was reported by Holland (1983) for four U.S. cities and by Joumard (1991) in France. Recently, Rodes et al. (1998) compared commuter exposures for morning and evening rush hour periods for 12 freeway trips in two California cities. Ambient CO levels were subtracted from in-vehicle CO levels to estimate the vehicle's net microenvironmental concentration. In Los Angeles, net microenvironmental concentrations during evening commutes were about 25% lower than morning values because of higher wind speeds. In Sacramento, such net concentrations during evening trips were slightly higher than morning values because of higher traffic congestion levels. In another recent study, Alm et al. (1999) 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, but attributed this difference to weather and traffic variables.

Seasonal variations in ambient temperatures, wind conditions, and traffic volumes affect passenger cabin exposure to CO, as shown in studies by Shikiya et al. (1989) in southern California, Ott et al. (1994) in northern California, Dor et al. (1995) in France, and Flachsbart (1999a) in Hawaii. Ott et al. (1994) and Dor et al. (1995), who both measured exposures for an entire year, reported that exposures were generally higher in the fall and winter than in the 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 Hawaii, where temperatures are never cold enough to have a substantial effect on motor vehicle emissions, Flachsbart (1999a) found that traffic flows and wind speeds had reinforcing effects on passenger cabin exposures to CO concentrations on a coastal highway in Honolulu. During late fall, exposures were low because traffic flows were light and wind speeds were high. During winter and spring, exposures were relatively higher because traffic flows were greater and winds calmer than during the fall.

4.4.1.2 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 Annapolis, MD, and Boston. In Boston Harbor, CO concentrations averaged 56 ppm during a 60-min cruise and 28 ppm after a 30-min cruise. For

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, Snook (1996) 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. The CO exposure of the following snowmobiler was measured 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. In general, the centerline CO concentrations decreased with increasing distance between snowmobiles and increased with greater speeds, but only for distances greater than 25 ft between snowmobiles. At 15 ft off centerline, average concentrations fell sharply to levels of 0 to 7.5 ppm. When the snowmobiler drove alone (self-exposure), 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 including several national parks. For example, over 87,000 tourists traveled by snowmobile in Yellowstone National Park (Wilkinson, 1995) during the winter of 1993 and 1994. Under steady-state conditions, a snowmobile may emit from 10 to 20 g/mi of CO, while a modern U.S. automobile equipped with a catalytic converter emits far less (0.01 to 0.04 g/mi) at speeds of 10 to 40 mph. 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).

4.4.1.3 Residential Exposure to Carbon Monoxide

Residential sources of CO concentrations include motor vehicle operation inside an attached 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.

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 concentration was 2.0 ppm (indoors) and 1.4 ppm (outdoors). Of surveyed homes, 13 of 286 homes (4.5%) had indoor CO concentrations above the NAAQS of 9 ppm for 8 h, and 8 of 282 homes (2.8%) had outdoor CO concentrations above this standard. Although most of the exceedances occurred in the Los Angeles basin, these percentages could be low because the basin was underrepresented in the statewide sample. The study did not translate these percentages into statewide estimates.

Figures 4-4 and 4-5 show log-probability plots of the 1-h and 8-h maximum indoor minus outdoor CO concentrations, respectively, for a common sample of 277 homes. These figures show that 17 homes (6.1%) had 1-h maximum concentrations indoors that were at least 5 ppm higher than outdoor levels, and that 10 homes (3.6%) had 8-h maximum CO concentrations indoors that were at least 5 ppm higher than outdoor levels. They suggest that a small percentage of California homes would still have indoor CO problems even if outdoor CO levels at these homes complied with federal ambient standards. Using univariate regression analysis, outdoor CO concentrations explained approximately 55% of the variation found in indoor CO concentrations.

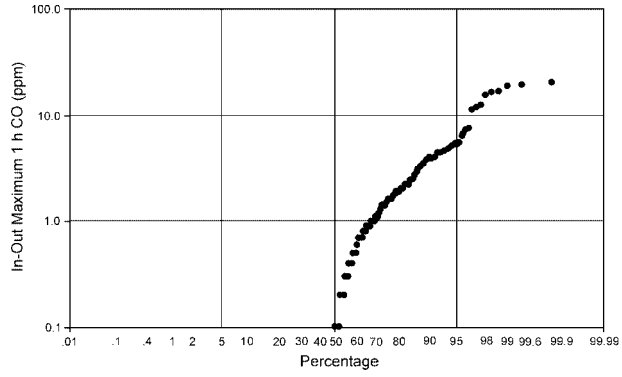

Figure 4-4. Log-probability plot of the maximum 1-h indoor minus outdoor CO concentrations based on a random sample of 277 homes that used gas appliances in California, 1991 and 1992. (Only those indoor minus outdoor values greater than or equal to 0.1 ppm are shown.)
Source: Wilson et al. (1993a).

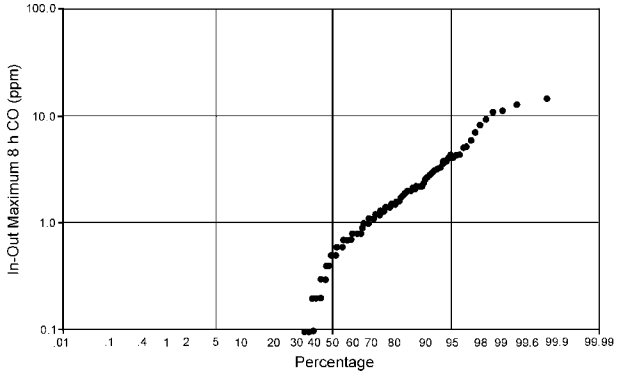

Figure 4-5. Log-probability plot of the maximum 8-h indoor minus outdoor CO concentrations based on a random sample of 277 homes that used gas appliances in California, 1991 and 1992. (Only those indoor minus outdoor values greater than or equal to 0.1 ppm are shown.)
Source: Wilson et al. (1993a).

Higher net indoor CO levels (indoor minus outdoor CO concentrations) were traced definitively to space heating with gas ranges and gas-fired wall furnaces, use of gas ranges with continuous gas pilot lights, small home volumes, and cigarette smoke; however, several other factors also may have contributed to the higher CO levels: malfunctioning gas furnaces, automobile exhausts leaking into homes 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).

Unintentional deaths caused by CO poisonings have been studied in California, New Mexico, and Washington. Two California studies collected data for the 1979 to 1988 period. In the first, 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., vans, campers) and 46% in residential structures (e.g., homes, apartments, shacks, 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 contributed to unintentional deaths caused by CO from several combustion sources (e.g., charcoal grills and hibachis, other heating and cooking appliances, motor vehicles, small engines, camping equipment). There was a strong association between alcohol use and CO poisoning from motor vehicles. Typically, motorists under the influence of alcohol would pull into their garages, leave the engine running while listening to cassette tapes, and then fall asleep. 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 features of unintentional CO poisoning cases that occurred between 1982 and 1993. Most cases occurred when electrical power was interrupted during fall and winter months, because of either regional storms or unpaid utility bills. Of 509 patients treated with hyperbaric oxygen, 79 (16%) were exposed when charcoal briquets were burned for 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 accidental CO injuries 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.

4.4.1.4 Exposure to Carbon Monoxide at Commercial Facilities

Although motorists typically turn off their engines during refueling, people still may be exposed to CO concentrations from idling cars and other cars entering and leaving the fueling area of the station. 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; gas-powered radiant heaters used to heat viewing stands; and motor vehicles at motocross, monster-truck, and tractor-pull competitions. These competitions usually involve many motor vehicles with no emission controls.

Several studies of CO exposure in commercial facilities were not cited in the previous CO criteria document. 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 ice rinks. 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 rinks from the use of gasoline-powered resurfacing machines. High concentrations were attributed to poorly maintained machines and insufficient ventilation in one rink. 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 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, with 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 levels 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, which 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 Vermont high-school ice hockey game 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) measured CO during eight high-school games 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% (range 3.3 to 13.9%). The source of CO was a malfunction in a 20-year-old ice resurfacing machine. Hampson also reported that CO may have diffused into an adjacent bingo hall through an open door. In view of 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, tractor pulls) in Cincinnati. 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. The ventilation system was operated maximally, and ground-level entrances were completely open.

High CO levels also have been found at motor vehicle competitions in Canada. In a study not cited in the previous CO criteria document, Luckurst and Solkoski (1990) recorded CO concentrations at two tractor-pull events in Winnipeg, Manitoba. The mean instantaneous concentration 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 held in a skating rink in the Quebec city region. The May 1994 event lasted from roughly 8 p.m. to

midnight. Average CO concentrations determined at five stations located at different points in the arena ranged from 19.1 to 38.0 ppm, with the higher levels measured 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, engine size, and especially the number of motorcycles on the track.

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

The concentration of CO in the end-tidal breath of a nonsmoker, after a standardized breathholding maneuver, can be related to an exponentially time-weighted average of the previous CO exposures (U.S. Environmental Protection Agency, 1991). As described in Chapter 2, the breath concentration of CO also can be related to percentage of blood COHb by constructing a calibration curve from simultaneous blood and end-tidal breath sampling. These end-tidal breath CO measurements can demonstrate whether nonsmoking subjects recently have exceeded a protective level of 2.1% COHb (U.S. Environmental Protection Agency, 1992b). Such measurements are more informative than an 8-h personal CO exposure measurement because a nominal 8-h average of 9 ppm can attain different COHb concentrations. For example, a subject starting with 0.5% COHb will reach a higher COHb level after a 4-h exposure to 3 ppm CO followed by a 4-h exposure to 15 ppm CO than the reverse combination (i.e., exposed to 4-h at 15 ppm CO followed by 4-h at 3 ppm CO).

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 found 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 among 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 4-3) 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

Table 4-3. Mean (M) Breath Carbon Monoxide Levels and Sample Sizes Across Smoking Categories and Job Types[a]

Smoking Category		Total	Job Type		
			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 per 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 per 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 per day or more)	SD	11.22	9.61	12.73	10.50
	n	273	95	117	61

[a]Sample size (n) refers to those with CO measurements; CO measurements were taken on 97.2% of those interviewed. The CO levels are in parts per million. 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).

in the submarine (called "ambient" by the authors) increased from 2.6 ppm to 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 auxiliary 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 monitored sections, the absence of a correction for higher CO concentrations in air inhaled for the 10-s breathhold than in the end-tidal breath CO, and the end-tidal breath CO and "ambient" CO measurements being made with two different instrument systems. Operation of a 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 4-6). 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

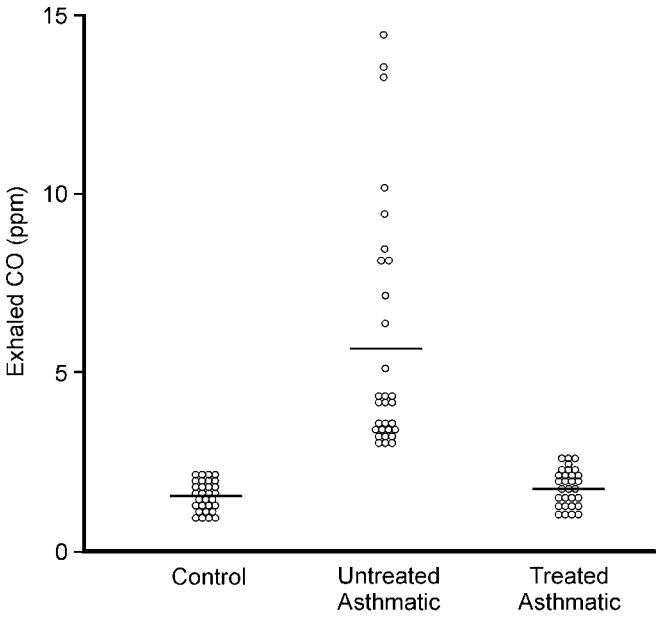

Figure 4-6. Excess CO concentrations in the exhaled air of nonsmoking control subjects (n = 30), untreated asthmatics (n = 30), and treated asthmatics (n = 30). The values shown were determined by subtracting the background level from the observed reading. "Untreated" means no inhaled corticosteroids, "Treated" refers to regularly inhaled corticosteroids, and the horizontal bar indicates the mean value.
Source: Zayasu et al. (1997).

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 (aged 5 to 20 years) in hospital admissions for CO in breath, using the electrochemical Vitalograph Breath CO monitor (Vitalograph, Inc., Lenexa, KS). The results, showing that 1.9% (9 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 nine 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.

4.4.1.6 Nonoccupational Exposure to Methylene Chloride

Nonoccupational exposure to halogenated hydrocarbons like methylene chloride (see Sections 5.3 and 6.8.3), which can be metabolized to CO in the body, potentially occurs when the chemicals are 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, for example, 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 (1993) reported that some aerosol products may contain up to 50% methylene chloride. However, the current extent of methylene chloride in aerosol products apparently has not been studied recently; nor are typical population exposures to methylene chloride from consumer products known.

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.

4.4.1.7 Exposures to Carbon Monoxide from Passive Smoking

Given that the pNEM/CO exposure model accounts for the passive exposure of nonsmokers to CO concentrations from smoking, this section briefly reviews two studies of this type. In April 1992, Ott et al. (1992b) took continuous readings of CO concentrations inside a passenger car for an hour-long trip through a residential neighborhood of the San Francisco Bay Area. Measurements were taken in both the front and back seats of the vehicle as a passenger smoked cigarettes. The neighborhood had low ambient CO levels, because it had little traffic and few stop signs. During the trip, the air conditioning system was operated in the recirculation mode. Concentrations in the front and rear seats were similar indicating that CO concentrations were well mixed throughout the passenger compartment. CO concentrations reached a peak of 20 ppm after the third cigarette. Using the breath measurement technique of Jones et al. (1958), the breath CO level of the driver (a nonsmoker) increased from 2 ppm before the trip to 9.2 ppm at the end of the trip. Based on a mathematical model, the predicted mean CO exposures for three air exchange rates were 0.8 ppm for windows open (20 mph); 7.2 ppm for windows closed (20 mph); and 63.3 ppm for windows closed (0 mph).

Klepeis et al. (1999) reported CO concentrations for two social events that featured cigar smoking. At one event, about 50 people were exposed to CO concentrations that averaged 5.8 ppm (range 5 to 11 ppm) for nearly a 2 h period. After subtracting the ambient CO level (1.5 ppm), the event's net CO concentration (4.5 ppm) was comparable to the CO exposure from freeway traffic during the drive to the event. At the second event inside a restaurant in San Francisco, the CO concentration averaged over 200 min reached 10 ppm (net 9 ppm after subtracting the ambient CO level of 1 ppm). About 75% of 40 persons at the event were smoking cigars at any instant of time.

4.4.2 Occupational Exposures

This subsection discusses occupational exposures to CO and methylene chloride.

4.4.2.1 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. This 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 (i.e., ambient) 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 gasoline 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 previous CO criteria document. Other occupational studies of CO exposure are summarized in Table 4-4,

Table 4-4. 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) (interior of vehicle)	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/gasoline 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 (inside mask) (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)	>3.25 in 5% of NS	California, U.S.	Apte (1997); Apte et al. (1999)
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, NS = nonsmokers, TWA = time-weighed average.

Source: Adapted from Apte (1997) and updated.

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 min 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 (STEL), 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 level 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.

4.4.2.2 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 (1996). 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.

4.4.3 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. Studies reviewed in the previous CO criteria document reported that many Americans spent most of their time indoors at home, school, or work, etc. (Szalai, 1972; Chapin, 1974; Meyer, 1983; Johnson, 1989; 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, 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. Most of the available data from activity pattern studies have been combined into one comprehensive database called the Consolidated Human Activity Database (CHAD) and containing over 20,000 person-days of 24-h activity (Glen et al., 1997). The information in CHAD will be accessible for constructing population cohorts of people with diverse characteristics that are useful for analysis and modeling (McCurdy, 2000).

4.4.3.1 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 years 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 years 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 in California 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 (4%). About 46% of nonsmoking adults and adolescents reported being near others' tobacco smoke at some time during the day.

Table 4-5 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 4-6 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.

4.4.3.2 Activity Patterns of Children in Six States

In 1990 and 1991, 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

Table 4-5. Time Spent in Different Microenvironments by Californians, 1987 to 1990 (minutes per day; weighted)[a]

Microenvironment	Adults/Adolescents				Children			
	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 gasoline 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 or 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 or 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 or skates	1	3.1	41	5-160	1	4.4	22	2-155
Motorcycle or scooter	1	1.9	62	5-430				
Bus, train, or ride stop	NA	NA	NA	NA	<1	2.6	15	3-40
In stroller or carried					<1	2.0	40	1-195
Other	1	1.3	38	5-270	<1	0.4	72	10-110

NA = not available.

[a]To generalize the results of the survey sample to the entire state population, the data were weighted to correct for nonuniform probabilities of including certain individuals in the sample.

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

Table 4-6. 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)[a]

Potential Pollutant Source	Adults/Adolescents 1987 to 88	Children 1989 to 90
Consumer Products[b]		
Personal care aerosols	40	36
Scented room fresheners	31[c]	37
Solvents	12	3
Oil-based paints	5	2
Activities/Places		
Went to a gasoline station, parking garage, or auto repair shop	26	11
Pumped gasoline	15	1
Have attached garage[c]	62	63
Had vehicle in attached garage[c]	37	36
Took a hot shower[b]	77	26
Near Combustion Appliances		
Had gas heat on[c]	26	24
Had gas oven/range on	35	29
Nonsmokers Near Environmental Tobacco Smoke 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]To generalize the results of the survey sample to the entire state population, the data were weighted to correct for nonuniform probabilities of including certain individuals in the sample.
[b]Potential methylene chloride exposure.
[c]Data presented for adult respondents (age 18 years or older) only.

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

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 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.

4.4.3.3 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 and 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, but, these results might be explained by differences in location codes between the two studies, rather than by actual differences in participant activity patterns. 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.

4.4.3.4 An English Study

Farrow et al. (1997) studied time spent inside the home from a sample of 170 households 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. However, the study in England indicates that exposure may be a function of a parent's gender or household role, supporting a similar conclusion based on a nationwide study of U.S. activity patterns (see Section 4.3.3.6).

4.4.3.5 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.

4.4.3.6 The National Human Activity Pattern Survey

The EPA's National Human Activity Pattern Survey (NHAPS) 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 respondents, 38.3% reported having a gas range or oven at home, and 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 the total sample) spent more than 175 min per day inside a car, and 10% of 1,172 people (1.2% of the total sample) spent more than 180 min inside a truck 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 "gasoline-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.

4.5 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 social and technological changes affecting human activity patterns.

4.5.1 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 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 EPA 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.

Austin et al. (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, 1999a]), 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 CO concentrations in motor

vehicle exhaust on a coastal artery in Honolulu. Compared to commuter CO exposure in adjacent, 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.

More recently, Rodes et al. (1998) compared the CO concentrations of two test vehicles driven on standardized routes that included a freeway carpool lane in Los Angeles. One vehicle used the carpool lane and the other the unrestricted lanes. Each vehicle repeatedly drove its route for both the morning and evening rush hour periods of one day, and CO measurements were taken continuously both inside and outside of each vehicle. Because the vehicles had different air exchange rates, comparisons of external CO levels (measured at the base of the windshield) are appropriate. Based on these measurements, the average CO concentration of the vehicle in the noncarpool lane (5.6 ppm) was twice as high as that of the vehicle in the carpool lane (2.8 ppm). For a hypothetical 48-km commute, exposure in the noncarpool lane (measured in parts per million-minutes) was estimated to be 187% greater than exposure in the carpool lane. The study suggests that carpoolers may have lower total CO exposure for their entire commute, because they are exposed to lower CO concentrations and spend less time commuting in heavy traffic. However, the study did not account for the extra time to collect nonfamily members of a carpool.

Models to estimate the direct effects of TCMs on commuter CO exposure are not apparent in the literature. However, Flachsbart (1999a) developed a series of statistical models to predict passenger cabin exposure to CO based on trip variables for a 6.2-km Honolulu artery divided into three links. Based on data for 80 trips, the most practical models of third-link exposure (adjusted $R^2 = 0.69$) 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.

4.5.2 Federal and State Policies Affecting Temporal Trends in Exposure

Studies show significant decreasing 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 4-7 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 4-7, 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.

4.5.2.1 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 4-7, 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 residents of northern states. Monthly variation in death

Table 4-7. 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[a] Federal (g/mi)	New Passenger Car CO Emission Standard[a] California (g/mi)	Net Mean In-Vehicle CO Concentration[b] (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, CA	
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, CA	
1974	28.0	34.0			
1974-75	15.0	9.0	7.4	Boston, MA	
1975	15.0	9.0			
1976	15.0	9.0			
1977	15.0	9.0			
1978	15.0	9.0	10.3	Washington, DC	
1979	15.0	9.0	9.7	Los Angeles, CA	0.67
1980	7.0	9.0	8.3	Santa Clara Co., CA	0.55
1981	3.4	7.0	5.2	Denver, CO	0.58
1981	3.4	7.0	4.3	Los Angeles, CA	0.58
1981	3.4	7.0	2.9	Phoenix, AZ	0.58
1981	3.4	7.0	2.9	Stamford, CT	0.58
1981-82	3.4	7.0	9.5	Honolulu, HI	
1982	3.4	7.0			0.56
1982-83	3.4	7.0	1.4	Denver, CO	
1982-83	3.4	7.0	1.8	Washington, DC	
1983	3.4	7.0	9.4	Washington, DC	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, CA	
1988	3.4	7.0	8.4	Raleigh, NC	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	
1995	3.4	3.4			

[a]Standards apply at a useful life of 5 years/50,000 miles.
[b]Mean in-vehicle CO concentration minus mean ambient CO concentration.

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

rates indicated a seasonal pattern, with January fatalities routinely about two to five times higher than in July.

Although mortality is not a health effect used in setting the NAAQS for CO, the Cobb and Etzel (1991) study still has value in its revelations about cofactors of personal exposure to high CO levels. Moreover, the study speculated that declining death rates could be attributed in part to automaker compliance with the motor vehicle CO emission standards of the CAA. The investigators 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.

4.5.2.2 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 (Table 4-2). Evidence of this downward trend appears in Figure 4-7, which shows the ambient (lower line) and mean CO concentrations inside vehicles (top line) for these studies. These lines do not imply that CO concentrations can be inferred from points on the lines themselves, or that relationships exist between results for different cities. 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 typical commuter CO exposures in other large cities during the same time periods, then exposures fell approximately 90% 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.

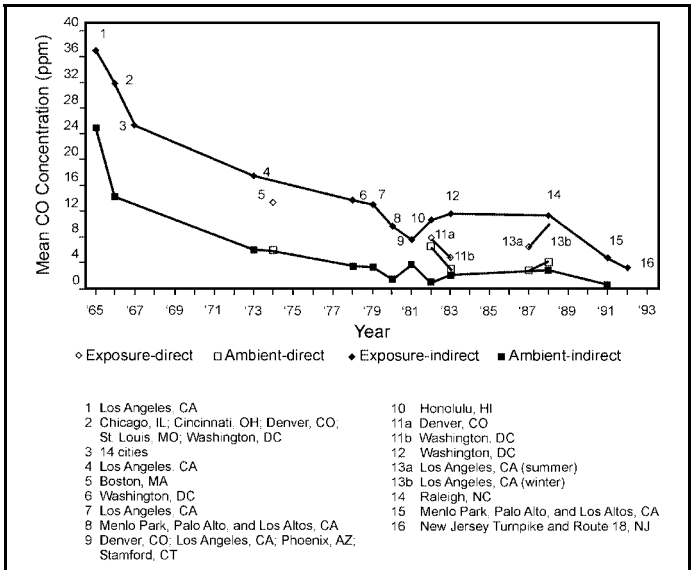

Figure 4-7. Trends in ambient CO concentrations and in-vehicle CO exposures, 1965 to 1992. (The upper and lower lines are provided to make a clear distinction between exposure and ambient CO data reported for each city; these lines do not imply that results for cities are related.)
Source: Flachsbart (1995).

In the United States, the effect of progressively tighter CO emission standards on in-vehicle CO exposures over time is readily apparent in Table 4-7. 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 the same magnitude as the 90% 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 4-7 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 and 1981 on a suburban highway nearSan Jose. They reported a mean CO concentration of 9.8 ppm for trips of 35 to 45 min. In 1991 and

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 47% 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 and 1992 to 1.6 to 1.8 ppm in 2002 and 2003. At the 99% percentile, the model predicted that the CO concentrations would drop from 10 ppm in 1991 and 1992 to 4.0 to 4.6 ppm in 2002 and 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. However, these predictions could be too low because the study did not anticipate the phenomenal growth in sport utility vehicle (SUV) use in California during the 1990s. The certified CO emissions of SUVs exceed that of standard passenger cars.

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 4-8 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).

Table 4-8. 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 to 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 (1999b).

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 (Faiz et al., 1996).

4.5.3 Social Changes Affecting Human Activity Patterns

Between 1965 and 1985, the Americans' Use of Time Project at the University of Maryland reported that the average time spent in travel for leisure trips increased from 2.7 to 3.1 h per week (Cornish et al., 1991). In contrast, 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 commuted 45 min or more increased from 10.9 million in 1980 to 13.9 million in 1990, the mean travel time of this commuter cohort actually decreased slightly 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 metropolitan regions are greater than those nationwide. In the Washington metropolitan region, for example, the average daily commuting time for all modes of travel between home and work was 62 min per day in 1957 (Bello, 1958). This value increased to 69 min per day by 1968 and fell slightly to 68.3 min in 1987 and 1988 when the region was resurveyed. The stability in daily commuting times between the 1968 and the 1987 and 1988 surveys was achieved by an increase in travel speed. This increase in travel speed offset greater travel distances between home and work that occurred during that 20-year period. For those who commuted alone by automobile in Washington, the average euclidean, round-trip travel distance from home to work increased from 13.8 miles in 1968 to 16.1 miles in 1987 and 1988. However, the average trip speeds of solo commuters in Washington also increased (by 10.7% for home-to-work trips and by 20.3% for work-to-home trips) to offset increased commuting distance (Levinson and Kumar, 1994). This increase in trip speeds is significant because passenger cabin exposure to CO concentrations has been shown in a separate study to be inversely related to travel speed in the Washington area (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%. 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, the investigators 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. In 1994, there were fewer than 4,000 telecommuters working for the federal government and Webster (1998) reported that the U.S. General Services Administration expected to see 60,000 such workers by the end of 1998. This employment shift could have beneficial implications for reduction in population CO exposure.

4.6 Conclusions

This chapter has reviewed studies of population exposure to carbon monoxide, including some key studies from the previous CO criteria document and studies that have been published in the peer-reviewed scientific literature since 1991. This section draws several conclusions from this review, and identifies both the extent to which CO exposures have changed since the previous criteria document and some current gaps in knowledge about population exposure to CO. The previous CO criteria document concluded that, on an individual basis, personal exposure is poorly correlated with ambient CO concentrations as measured at fixed-site monitors, because of personal mobility relative to the monitor's fixed location, and the spatial and temporal variability of CO concentrations (U.S. Environmental Protection Agency, 1991). Like earlier studies, more recent ones indicate that the extent and magnitude of observed personal CO exposures may be greater than those predicted from fixed-site monitors used to determine compliance with the NAAQS (Wilson et al., 1993a,b; Colome et al., 1994). Yet, when ambient CO levels are either high or low on a given day, fixed-site monitors still reflect the corresponding high or low aggregates of personal exposures on those days. Otherwise, the stations do not adequately represent the CO exposures of community residents while they are exposed to motor vehicle exhaust during commuting, to occupational and residential sources of unvented fuel combustion, or to tobacco smoke. The mean COHb level of people exposed to CO from these sources will be greater than their mean COHb level predicted solely from exposure to CO of ambient origin.

Implementation of motor vehicle emission standards, catalytic converters, motor vehicle inspection and maintenance programs, and cleaner burning fuels during the past three decades has reduced the CO exposures of urban commuters (Flachsbart, 1995, 1999b). This conclusion has important implications, because it suggests that modeled estimates of current commuter exposure, based on data inputs from pre-1990 exposure studies, may be too high. Moreover, the Yu et al. (1996) study indicates that the average CO concentrations in passenger cabins of motor vehicles are expected to drop further in the near future. However, those projections could be too low because the study did not anticipate or account for the phenomenal growth in SUV use during the 1990s. The certified CO emissions of SUVs presently exceed those of standard passenger cars, and EPA did not propose tighter emission standards for SUVs until 1999. As compared to the federal (Tier 1) 3.4 g/mi emission standards shown in Table 4-7,

the corresponding emission standards for SUVs (3,750 to 5,750 lbs) are 4.4 g/mi (Federal Register, 2000; U.S. Environmental Protection Agency, 1999b). Hence, new studies using standard protocols of in-vehicle CO exposure would appear to be needed, not only to assess current commuter exposure, but also to enable comparisons with past studies and projections of future exposure.

Likewise, there are uncertainties over the extent to which population exposure to CO has changed in other ways since the previous criteria document. First, there are no published trend studies of CO exposure in other important microenvironments (e.g., indoor parking garages, pedestrian sidewalks on commercial streets, or home environments affected by greater use of microwaves for cooking in lieu of gas ranges). Second, the net effect of various travel behavior trends on commuter CO exposure is uncertain. Trends noted in this chapter include disproportionately high growth rates in vehicle miles of travel, growth in travel during shoulder hours of peak-traffic periods, and growing use of personal computers for telecommuting and teleshopping from home in lieu of trips by motor vehicles. These trends and their implications for exposure suggest that the results of earlier personal CO monitoring studies, such as those of Akland et al. (1985) summarized in Table 4-1, are probably no longer indicative of present CO levels and population exposures. These types of personal exposure studies would need to be redone to determine current CO exposure levels of similar urban populations.

The previous CO criteria document reported that people are exposed to elevated CO levels in certain indoor microenvironments (e.g., unventilated parking garages, motor vehicles with leaky exhaust systems, small homes with unvented gas stoves and space heaters). More recent studies in California homes indicate that elevated CO concentrations (>9 ppm) still exist and can be caused by several factors, such as attached garages and carports; ranges with continuous gas pilot lights; and improper use and installation of gas appliances, especially in small homes (Wilson et al., 1993a,b; Colome et al., 1994). Also, recent studies have found elevated CO concentrations (>9 ppm) when people ride certain types of recreational vehicles (i.e., snowmobiles, power boats), gather indoors to barbecue food (sometimes to cope with electrical power outages), and watch sporting events held at indoor arenas. High-level exposures (>25 ppm) may occur inside arenas when they are used for ice skating or motocross, monster-truck, and tractor pull competitions. Vehicles used in these competitions often lack any type of emission controls. In some cases, ventilation alone has not lowered CO sufficiently to safe levels (<9 ppm) at these events. Moreover, recent studies report that high-level CO exposures can occur when people use unregulated gasoline-powered appliances, engines, and tools (e.g., chainsaws), even under ventilated conditions.

The previous CO criteria document reported that many Americans spend most of their time indoors. This finding still appears to be true, according to more recent studies of activity patterns in California and nationwide (e.g., the NHAPS study). These studies indicate that Americans now spend, on average, between 87 and 89% of their day indoors and about 7% of their time in or near vehicles. However, activity patterns have shifted since the pioneering studies of the early 1970s. Recent study of travel behavior in Washington indicates that some people are spending relatively more time in travel and less time at home, compared with the past, because of growth in the service sector of the nation's economy. This growth has enabled a growing number of people to buy services outside the home that once were provided by household members. Buyers often visit one or more retailers (i.e., trip chaining) as part of the daily commute to and from work (Levinson and Kumar, 1995), which extends their trip times.

In analyzing activity patterns, the California and national studies both analyzed activities by conventional social categories (e.g., gender, age, race, etc.). In a travel behavior study, Vadarevu and Stopher (1996) used a different social construct that revealed significant differences in activity patterns among different life cycle groups defined by age, working status, and household size. Hence, although their study did not focus on CO exposure assessment per se, it still has useful lessons for the design and analysis of activity pattern studies. Their study also revealed that people who are part of a household make continuous tradeoffs in their activity patterns and household role allocations (in terms of who does

what and when) in response to ongoing social and technological changes. However, the effects of these activity and role adjustments by householders on personal CO exposure still needs to be documented by empirical study.

In light of the above, population exposure models (e.g., pNEM/CO, SHAPE) may need to sample from distributions that more accurately represent current microenvironmental CO concentrations and time budgets and add certain high-exposure level microenvironments (e.g., tobacco smoke exposure while in a vehicle, sporting events involving motor vehicles at indoor arenas) to their current list. In the future, simulation models of exposure should consider that trip times and commuter exposures are not independent of trip-starting times, and that the distribution of CO exposure is not homogeneous for all types of commuters. As evidence of the former, Flachsbart (1999a) showed that a commuter's travel time and CO exposure inside a passenger car for a trip from home to work was related to trip departure time. Not surprisingly, travel during off-peak hours (i.e., shoulder periods) to avoid congested traffic resulted in both shorter travel time and less CO exposure. As evidence of the latter, carpoolers can reduce their CO exposure if they use high-occupancy vehicle lanes on highways, as shown by both Flachsbart (1989) in Hawaii and by Rodes et al. (1998) in Southern California.

References

Agency for Toxic Substances and Disease Registry. (1993) Methylene chloride toxicity. Am. Fam. Phy. 47: 1159-1166.

Akland, G. G.; Hartwell, T. D.; Johnson, T. R.; Whitmore, R. W. (1985) Measuring human exposure to carbon monoxide in Washington, D.C., and Denver, Colorado, during the winter of 1982-1983. Environ. Sci. Technol. 19: 911-918.

Alm, S.; Jantunen, M. J.; Vartiainen, M. (1999) Urban commuter exposure to particle matter and carbon monoxide inside an automobile. J. Exposure Anal. Environ. Epidemiol. 9: 237-244.

American Conference of Governmental Industrial Hygienists. (1996) Threshold limit values for chemical substances and physical agents: biological exposure indices. Cincinnati, OH: American Conference of Governmental and Industrial Hygienists.

Amiro, A. G. (1969) Carbon monoxide presents public health problem. Presented at: 33rd annual educational conference, National Association of Sanitarians; June; Houston, TX. J. Environ. Health 32: 83-88.

Apte, M. G. (1997) A population-based exposure assessment methodology for carbon monoxide: development of a carbon monoxide passive sampler and occupational dosimeter [dissertation]. Berkeley, CA: U.S. Department of Energy, Lawrence Berkeley National Laboratory, Environmental Energy Technologies Division; LBNL-40838.

Apte, M. G.; Cox, D. D.; Hammond, S. K.; Gundel, L. A. (1999) A new carbon monoxide occupational dosimeter: results from a worker exposure assessment survey. J. Exposure Anal. Environ. Epidemiol. 9: 546-559.

Austin, B. S.; Heiken, J. G.; Shepard, S. B.; Duvall, L. L. (1994) Methodologies for estimating emission and travel activity effects of TCMs. Washington, DC: U.S. Environmental Protection Agency, Office of Mobile Sources; report no. EPA-420-R-94-002.

Barnard, R. J.; Weber, J. S. (1979) Carbon monoxide: a hazard to firefighters. Arch. Environ. Health 34: 255-257.

Baucom, C. D.; Freeman, J. I.; MacCormack, J. M. (1987) Carbon monoxide poisoning in a garment-manufacturing plant - North Carolina. Morb. Mortal. Wkly. Rep. 36: 543-545.

Bellin, P.; Spengler, J. D. (1980) Indoor and outdoor carbon monoxide measurements at an airport. J. Air Pollut. Control Assoc. 30: 392-394.

Bello, F. (1958) The city and the car. In: The exploding metropolis. Garden City, NY: Doubleday Anchor Books; pp. 32-61.

Bevan, M. A. J.; Proctor, C. J.; Baker-Rogers, J.; Warren, N. D. (1991) Exposure to carbon monoxide, respirable suspended particulates, and volatile organic compounds while commuting by bicycle. Environ. Sci. Technol. 25: 788-791.

Boeniger, M. F. (1995) Description of facilities and employee exposure to carbon monoxide at four different bridge and tunnel toll authorities in the United States. Cincinnati, OH: National Institute for Occupational Safety and Health, Division of Surveillance, Field Studies, Hazard Evaluations; report no. IWS-45-02.

Boudreau, D. R.; Spadafora, M. P.; Wolf, L. R.; Siegel, E. (1994) Carbon monoxide levels during indoor sporting events—Cincinnati, 1992-1993 [reprint from MMWR 43: 21-23]. JAMA J. Am. Med. Assoc. 271: 419.

Brandt-Rauf, P. W.; Fallon, L. F., Jr.; Tarantini, T.; Idema, C.; Andrews, L. (1988) Health hazards of fire fighters: exposure assessment. Br. J. Ind. Med. 45: 605-612.

Brotherhood, J. R.; Budd, G. M.; Jeffery, S. E.; Hendrie, A. L.; Beasley, F. A.; Costin, B. P.; Wu, Z. (1990) Fire fighters' exposure to carbon monoxide during Australian bushfires. Am. Ind. Hyg. Assoc. J. 51: 234-240.

Buie, S. E.; Pratt, D. S.; May, J. J. (1986) Diffuse pulmonary injury following paint remover exposure. Am. J. Med. 81: 702-704.

Bünger, J.; Bombosch, F.; Mesecke, U.; Hallier, E. (1997) Monitoring and analysis of occupational exposure to chain saw exhausts. Am. Ind. Hyg. Assoc. J. 58: 747-751.

Burgess, W. A.; Sidor, R.; Lynch, J. J.; Buchanan, P.; Clougherty, E. (1977) Minimum protection factors for respiratory protective devices for firefighters. Am. Ind. Hyg. Assoc. J. 38: 18-23.

Chan, C.-C.; Özkaynak, H.; Spengler, J. D.; Sheldon, L. (1991) Driver exposure to volatile organic compounds, CO, ozone and NO_2 under different driving conditions. Environ. Sci. Technol. 25: 964-972.

Chapin, F. S., Jr. (1974) Human activity patterns in the city: things people do in time and in space. New York, NY: John Wiley & Sons.

Chung, Y.; Park, S. E.; Lee, K.; Yanagisawa, Y.; Spengler, J. D. (1994) Determinations of personal carbon monoxide exposure and blood carboxyhemoglobin levels in Korea. Yonsei Med. J. 35: 420-428.

Clements, J. S. (1978) School bus carbon monoxide intrusion. Washington, DC: U.S. Department of Transportation, National Highway Traffic Safety Administration; report no. DOT-HS-803 705.

Cobb, N.; Etzel, R. A. (1991) Unintentional carbon monoxide-related deaths in the United States, 1979 through 1988. JAMA J. Am. Med. Assoc. 266: 659-663.

Colome, S. D.; Wilson, A. L.; Tian, Y. (1994) California residential indoor air quality study. Volume 2. Carbon monoxide and air exchange rate: an univariate and multivariate analysis. Chicago, IL: Gas Research Institute; report no. GRI-93/0224.3.

Cornish, E.; Willard, T.; Fields, D. (1991) How Americans use time: an interview with sociologist John P. Robinson. Futurist Sept./Oct.: 23-27.

Cortese, A. D.; Spengler, J. D. (1976) Ability of fixed monitoring stations to represent personal carbon monoxide exposure. J. Air Pollut. Control Assoc. 26: 1144-1150.

Cutler, B. (1990) Where does the free time go? Am. Demograph. (November): 36-39.

Dor, F.; Le Moullec, Y.; Festy, B. (1995) Exposure of city residents to carbon monoxide and monocyclic aromatic hydrocarbons during commuting trips in the Paris metropolitan area. J. Air Waste Manage. Assoc. 45: 103-110.

Duan, N. (1982) Models for human exposure to air pollution. Environ. Int. 8: 305-309.

Ely, E. W.; Moorehead, B.; Haponik, E. F. (1995) Warehouse workers' headache: emergency evaluation and management of 30 patients with carbon monoxide poisoning. Am. J. Med. 98: 145-155.

Faiz, A.; Weaver, C. S.; Walsh, M. P.; Gautam, S. P.; Chan, L.-M. (1996) Emission standards and regulations. In: Air pollution from motor vehicles: standards and technologies for controlling emissions. Washington, DC: World Bank; pp. 1-24.

Farrow, A.; Taylor, H.; Golding, J. (1997) Time spent in the home by different family members. Environ. Technol. 18: 605-613.

Fawcett, T. A.; Moon, R. E.; Fracica, P. J.; Mebane, G. Y.; Theil, D. R.; Piantadosi, C. A. (1992) Warehouse workers' headache: carbon monoxide poisoning from propane-fueled forklifts. J. Occup. Med. 34: 12-15.

Federal Register. (2000) Control of air pollution from new motor vehicles: tier 2 motor vehicle emissions standards and gasoline sulfur control requirements; final rule. F. R. 65 (February 10): 6697-6870.

Fernández-Bremauntz, A. A.; Ashmore, M. R. (1995a) Exposure of commuters to carbon monoxide in Mexico City—I. Measurement of in-vehicle concentrations. Atmos. Environ. 29: 525-532.

Fernández-Bremauntz, A. A.; Ashmore, M. R. (1995b) Exposure of commuters to carbon monoxide in Mexico City II. Comparison of in-vehicle and fixed-site concentrations. J. Exposure Anal. Environ. Epidemiol. 5: 497-510.

Flachsbart, P. G. (1989) Effectiveness of priority lanes in reducing travel time and carbon monoxide exposure. Inst. Transport. Eng. J. 59: 41-45.

Flachsbart, P. G. (1995) Long-term trends in United States highway emissions, ambient concentrations, and in-vehicle exposure to carbon monoxide in traffic. J. Exposure Anal. Environ. Epidemiol. 5: 473-495.

Flachsbart, P. G. (1999a) Models of exposure to carbon monoxide inside a vehicle on a Honolulu highway. J. Exposure Anal. Environ. Epidemiol. 9: 245-260.

Flachsbart, P. G. (1999b) Human exposure to carbon monoxide from mobile sources. In: Khalil, M. A. K.; Pinto, J. P.; Shearer, M. J., eds. Carbon monoxide [special issue of papers from an international conference; December 1997; Portland, OR]. Chemosphere Global Sci. Change 1: 301-329.

Flachsbart, P. G.; Brown, D. E. (1989) Employee exposure to motor vehicle exhaust at a Honolulu shopping center. J. Architect. Plan. Res. 6: 19-33.

Flachsbart, P. G.; Mack, G. A.; Howes, J. E.; Rodes, C. E. (1987) Carbon monoxide exposures of Washington commuters. JAPCA 37: 135-142.

Gardiner, K.; Trethowan, W. N.; Harrington, J. M.; Calvert, I. A.; Glass, D. C. (1992) Occupational exposure to carbon monoxide and sulphur dioxide during the manufacture of carbon black. Ann. Occup. Hyg. 36: 363-372.

Gasman, J. D.; Varon, J.; Gardner, J. P. (1990) Revenge of the barbecue grill: carbon monoxide poisoning. West. J. Med. 153: 656-657.

Ghittori, S.; Marraccini, P.; Franco, G.; Imbriani, M. (1993) Methylene chloride exposure in industrial workers. Am. Ind. Hyg. Assoc. J. 54: 27-31.

Girman, J. R.; Chang, Y.-L.; Hayward, S. B.; Liu, K.-S. (1998) Causes of unintentional deaths from carbon monoxide poisonings in California. West. J. Med. 168: 158-165.

Glen, G.; Lakkadi, Y.; Tippett, J. A.; del Valle-Torres, M. (1997) Development of NERL/CHAD: the National Exposure Research Laboratory consolidated human activity database. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development; contract no. 68-D5-0049.

Gold, A.; Burgess, W. A.; Clougherty, E. V. (1978) Exposure of firefighters to toxic air contaminants. Am. Ind. Hyg. Assoc. J. 39: 534-539.

Gourdeau, P.; Parent, M.; Soulard, A. (1995) Exposition à l'oxyde de carbone dans les garages d'automobiles: évaluation chez les mécaniciens [Exposure of carbon monoxide in car repair shops: evaluation of mechanics]. Can. J. Public Health 86: 414-417.

Haagen-Smit, A. J. (1966) Carbon monoxide levels in city driving. Arch. Environ. Health 12: 548-551.

Hampson, N. B. (1996) Carbon monoxide poisoning at an indoor ice arena and bingo hall—Seattle, 1996 [reprint of MMWR 1996; 45: 265-267]. JAMA J. Am. Med. Assoc. 275: 1468-1469.

Hampson, N. B.; Norkool, D. M. (1992) Carbon monoxide poisoning in children riding in the back of pickup trucks. JAMA J. Am. Med. Assoc. 267: 538-540.

Hampson, N. B.; Kramer, C. C.; Dunford, R. G.; Norkool, D. M. (1994) Carbon monoxide poisoning from indoor burning of charcoal briquets. JAMA J. Am. Med. Assoc. 271: 52-53.

Holland, D. M. (1983) Carbon monoxide levels in microenvironment types of four U.S. cities. Environ. Int. 9: 369-377.

Jankovic, J.; Jones, W.; Burkhart, J.; Noonan, G. (1991) Environmental study of firefighters. Ann. Occup. Hyg. 35: 581-602.

Jarvis, M. J.; Russell, M. A. H.; Saloojee, Y. (1980) Expired air carbon monoxide: a simple breath test of tobacco smoke intake. Br. Med. J. 281: 484-485.

Jenkins, P. L.; Phillips, T. J.; Mulberg, E. J.; Hui, S. P. (1992) Activity patterns of Californians: use of and proximity to indoor pollutant sources. Atmos. Environ. Part A 26: 2141-2148.

Johnson, T. (1984) A study of personal exposure to carbon monoxide in Denver, Colorado. Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory; report no. EPA-600/4-84-014.

Johnson, J. H. (1988) Automotive emissions. In: Watson, A. Y.; Bates, R. R.; Kennedy, D., eds. Air pollution, the automobile, and public health. Washington, DC: National Academy Press; pp. 39-75.

Johnson, T. (1989) Human activity patterns in Cincinnati, Ohio [final report]. Palo Alto, CA: Electric Power Research Institute; project no. RP940-06; report no. EN-6204.

Johnson, T.; Paul, R. A. (1983) The NAAQS Exposure Model (NEM) applied to carbon monoxide. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards; report no. EPA-450/5-83-003.

Johnson, T.; Capel, J.; Paul, R.; Wijnberg, L. (1992) Estimation of carbon monoxide exposures and associated carboxyhemoglobin levels in Denver residents using a probabilistic version of NEM. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards; contract no. 68-D0-0062.

Johnson, T.; Mihlan, G.; LaPointe, J.; Fletcher, K.; Capel, J. (1999) Estimation of carbon monoxide exposures and associated carboxyhemoglobin levels in Denver residents using pNEM/CO (version 2.0) [draft]. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards; March 15.

Jones, R. H.; Ellicott, M. F.; Cadigan, J. B.; Gaensler, E. A. (1958) The relationship between alveolar and blood carbon monoxide concentrations during breathholding. J. Lab. Clin. Med. 51: 553-564.

Joumard, R. (1991) Pollution de l'air dans les transports [Air pollution from transportation]. Pollut. Atmos. 33: 20-24.

Kahler, M.; Kuhse, W.; Wintermeyer, L. A. (1993) Unintentional carbon monoxide poisoning from indoor use of pressure washers—Iowa, January 1992-January 1993. Morb. Mortal. Wkly. Rep. 42: 777-779, 785.

Kamei, M.; Yanagisawa, Y. (1997) Estimation of CO exposure of road construction workers in tunnel. Ind. Health 35: 119-125.

Klepeis, N. E.; Tsang, A. M.; Behar, J. V. (1996) Analysis of the national human activity pattern survey (NHAPS) respondents from a standpoint of exposure assessment. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development; report no. EPA/600/R-96/074.

Klepeis, N. E.; Ott, W. R.; Repace, J. L. (1999) The effect of cigar smoking on indoor levels of carbon monoxide and particles. J. Exposure Anal. Environ. Epidemiol. 9: 622-635.

Koontz, M. D.; Nagda, N. L. (1988) A topical report on a field monitoring study of homes with unvented gas space heaters. Volume III—methodology and results. Chicago, IL: Gas Research Institute; report no. GRI-87/0044.2.

Koushki, P. A.; Al-Dhowalia, K. H.; Niaizi, S. A. (1992) Vehicle occupant exposure to carbon monoxide. J. Air Waste Manage. Assoc. 42: 1603-1608.

Kwok, P. W. (1981) Reduction of carbon monoxide in indoor skating arenas. Environ. Health Rev. 25: 60-63.

Lando, H. A.; McGovern, P. G.; Kelder, S. H.; Jeffery, R. W.; Forster, J. L. (1991) Use of carbon monoxide breath validation in assessing exposure to cigarette smoke in a worksite population. Health Psychol. 10: 296-301.

Last, J. M.; Abramson, J. H.; Friedman, G. D.; Porta, M.; Spasoff, R. A.; Thuriaux, M. (1995) A dictionary of epidemiology. 3rd ed. New York, NY: Oxford University Press; pp. 5, 60.

Law, P. L.; Lioy, P. J.; Zelenka, M. P.; Huber, A. H.; McCurdy, T. R. (1997) Evaluation of a probabilistic exposure model applied to carbon monoxide (pNEM/CO) using Denver personal exposure monitoring data. J. Air Waste Manage. Assoc. 47: 491-500.

Lawryk, N. J.; Lioy, P. J.; Weisel, C. P. (1995) Exposure to volatile organic compounds in the passenger compartment of automobiles during periods of normal and malfunctioning operation. J. Exposure Anal. Environ. Epidemiol. 5: 511-531.

Lee, K.; Yanagisawa, Y. (1992) Development of a sampler for carbon monoxide in expired air. Presented at: 85th annual meeting and exhibition of the Air & Waste Management Association; June; Kansas City, MO. Pittsburgh, PA: Air & Waste Management Association; paper no. 92-145.03.

Lee, K.; Yanagisawa, Y. (1995) Sampler for measurement of alveolar carbon monoxide. Environ. Sci. Technol. 29: 104-107.

Lee, K.; Yanagisawa, Y.; Spengler, J. D. (1993) Carbon monoxide and nitrogen dioxide levels in an indoor ice skating rink with mitigation methods. Air Waste 43: 769-771.

Lee, K.; Yanagisawa, Y.; Spengler, J. D.; Nakai, S. (1994) Carbon monoxide and nitrogen dioxide exposures in indoor ice skating rinks. J. Sports Sci. 12: 279-283.

Lees, P. S. J. (1995) Combustion products and other firefighter exposures. Occup. Med.: State of the Art Rev. 10: 691-706.

Leikin, J. B.; Kaufman, D.; Lipscomb, J. W.; Burda, A. M.; Hryhorczuk, D. O. (1990) Methylene chloride: report of five exposures and two deaths. Am. J. Emerg. Med. 8: 534-537.

Lévesque, B.; Dewailly, E.; Lavoie, R.; Prud'Homme, D.; Allaire, S. (1990) Carbon monoxide in indoor ice skating rinks: evaluation of absorption by adult hockey players. Am. J. Public Health 80: 594-598.

Lévesque, B.; Lavoie, R.; Dewailly, E.; Prud'Homme, D.; Allaire, S. (1991) An experiment to evaluate carbon monoxide absorption by hockey players in ice skating rinks. Vet. Hum. Toxicol. 33: 5-8.

Lévesque, B.; Allaire, S.; Prud'homme, H.; Rhainds, M.; Lebel, G.; Bellemarre, D.; Dupuis, K. (1997) Indoor motocross competitions: air quality evaluation. Am. Ind. Hyg. Assoc. J. 58: 286-290.

Levinson, D. M.; Kumar, A. (1994) The rational locator: why travel times have remained stable. J. Am. Plan. Assoc. 60: 319-332.

Levinson, D.; Kumar, A. (1995) Activity, travel, and the allocation of time. J. Am. Plan. Assoc. 61: 458-470.

Limasset, J.-C.; Diebold, F.; Hubert, G. (1993) Exposition des conducteurs de bus urbains aux polluants de la circulation automobile [Assessment of bus drivers' exposure to the pollutants of urban traffic]. Sci. Total Environ. 134: 39-49.

Lioy, P. J. (1990) Assessing total human exposure to contaminants: a multidisciplinary approach. Environ. Sci. Technol. 24: 938-945.

Liu, K.-S.; Girman, J. R.; Hayward, S. B.; Shusterman, D.; Chang, Y.-L. (1993) Unintentional carbon monoxide deaths in California from charcoal grills and hibachis. J. Exposure Anal. Environ. Epidemiol. 3(suppl. 1): 143-151.

Luckhurst, D. G.; Solkoski, G. (1990) Carbon monoxide levels in indoor "tractor-pull" events—Manitoba. Can. Dis. Wkly. Rep. 16-17: 79-81.

Madani, I. M.; Khalfan, S.; Khalfan, H.; Jidah, J.; Aladin, M. N. (1992) Occupational exposure to carbon monoxide during charcoal meat grilling. Sci. Total Environ. 114: 141-147.

Mage, D. T. (1991) A comparison of the direct and indirect methods of human exposure. In: Gledhill, B. L.; Mauro, F., eds. New horizons in biological dosimetry: proceedings of the international symposium on trends in biological dosimetry; October 1990; Lerici, Italy. New York, NY: Wiley-Liss, Inc.; pp. 443-454. (Progress in clinical and biological research: v. 372).

Materna, B. L.; Jones, J. R.; Sutton, P. M.; Rothman, N.; Harrison, R. J. (1992) Occupational exposures in California wildland fire fighting. Am. Ind. Hyg. Assoc. J. 53: 69-76.

Materna, B. L.; Koshland, C. P.; Harrison, R. J. (1993) Carbon monoxide exposure in wildland firefighting: a comparison of monitoring methods. Appl. Occup. Environ. Hyg. 8: 479-487.

McCammon, C. S., Jr.; Halperin, W. F.; Lemen, R. A. (1981) Carbon monoxide exposure from aircraft fueling vehicles. Arch. Environ. Health 36: 136-138.

McCammon, J. B.; McKenzie, L. E.; Heinzman, M. (1996) Carbon monoxide poisoning related to the indoor use of propane-fueled forklifts in Colorado workplaces. Appl. Occup. Environ. Hyg. 11: 192-198.

McCurdy, T. (1995) Estimating human exposure to selected motor vehicle pollutants using the NEM series of models: lessons to be learned. J. Exposure Anal. Environ. Epidemiol. 5: 533-550.

McCurdy, T. (2000) Conceptual basis for multi-route intake dose modeling using an energy expenditure approach. J. Expos. Anal. Environ. Epidemiol. 10: 86-97.

Meyer, B. (1983) Indoor air quality. Reading, MA: Addison-Wesley Publishing Company, Inc.

Miller, R. K.; Ryan, M. C.; Bilowus, P. (1989) Carbon monoxide poisoning in indoor ice skating arenas. Va. Med. 116: 74-76.

Mumford, J. L.; Williams, R. W.; Walsh, D. B.; Burton, R. M.; Svendsgaard, D. J.; Chuang, J. C.; Houk, V. S.; Lewtas, J. (1991) Indoor air pollutants from unvented kerosene heater emissions in mobile homes: studies on particles, semivolatile organics, carbon monoxide, and mutagenicity. Environ. Sci. Technol. 25: 1732-1738.

National Center for Health Statistics and U.S. Consumer Product Safety Commission. (1992) Death certificate file. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention.

National Institute for Occupational Safety and Health. (1994) Health hazard evaluation report HETA 90-0365-2415, U.S. Department of the Interior, National Park Service, Yosemite National Park, California. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention.

National Institute for Occupational Safety and Health. (1996) Preventing carbon monoxide poisoning from small gasoline-powered engines and tools [NIOSH alert]. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service; report no. DHHS (NIOSH) publication no. 96-118.

Ott, W. R. (1982) Concepts of human exposure to air pollution. Environ. Int. 7: 179-196.

Ott, W. R. (1984) Exposure estimates based on computer generated activity patterns. J. Toxicol. Clin. Toxicol. 21: 97-128.

Ott, W.; Eliassen, R. (1973) A survey technique for determining the representativeness of urban air monitoring stations with respect to carbon monoxide. J. Air Pollut. Control Assoc. 23: 685-690.

Ott, W.; Flachsbart, P. (1982) Measurement of carbon monoxide concentrations in indoor and outdoor locations using personal exposure monitors. Environ. Int. 8: 295-304.

Ott, W.; Thomas, J.; Mage, D.; Wallace, L. (1988) Validation of the simulation of human activity and pollutant exposure (SHAPE) model using paired days from the Denver, CO, carbon monoxide field study. Atmos. Environ. 22: 2101-2113.

Ott, W. R.; Mage, D. T.; Thomas, J. (1992a) Comparison of microenvironmental CO concentrations in two cities for human exposure modeling. J. Exposure Anal. Environ. Epidemiol. 2: 249-267.

Ott, W.; Langan, L.; Switzer, P. (1992b) A time series model for cigarette smoking activity patterns: model validation for carbon monoxide and respirable particles in a chamber and an automobile. In: Measuring, understanding, and predicting exposures in the 21st century: proceedings of the conference; November 1991; Atlanta, GA. J. Exposure Anal. Environ. Epidemiol. 2(suppl. 2): 175-200.

Ott, W.; Switzer, P.; Willits, N.; Hildemann, L.; Yu, L. (1993) Trends of in-vehicle CO exposures on a California arterial highway over one decade. Research Triangle Park, NC: U.S. Environmental Protection Agency, Atmospheric Research and Exposure Assessment Laboratory; report no. EPA/600/A-93/220.

Ott, W.; Switzer, P.; Willits, N. (1994) Carbon monoxide exposures inside an automobile traveling on an urban arterial highway. J. Air Waste Manage. Assoc. 44: 1010-1018.

Paul, R. A.; Johnson, T. (1985) The NAAQS exposure model (NEM) applied to carbon monoxide: addendum. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards; report no. EPA 450/5-85-004.

Paul, R. A.; Johnson, T.; McCurdy, T. (1988) Advancements in estimating urban population exposure. Presented at: 81st annual meeting of the Air Pollution Control Association; June; Dallas, TX. Pittsburgh, PA: Air Pollution Control Association; paper no. 88-127.1.

Paulozzi, L. J.; Satink, F.; Spengler, R. F. (1991) A carbon monoxide mass poisoning in an ice arena in Vermont [letter]. Am. J. Public Health 81: 222.

Paulozzi, L. J.; Spengler, R. F.; Vogt, R. L.; Carney, J. K. (1993) A survey of carbon monoxide and nitrogen dioxide in indoor ice arenas in Vermont. J. Environ. Health 56(5): 23-25.

Pedersen, D. H.; Sieber, W. K. (1988) National occupational exposure survey. Volume III: analysis of management interview responses. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health; DHHS (NIOSH) publication no. 89-103.

Peterson, J. E. (1978) Modeling the uptake, metabolism and excretion of dichloromethane by man. Am. Ind. Hyg. Assoc. J. 39: 41-47.

Phillips, T. J.; Jenkins, P. L.; Mulberg, E. J. (1991) Children in California: activity patterns and presence of pollutant sources. In: Health risk and risk communication: papers from the 84th annual meeting & exhibition of the Air & Waste Management Association; June; Vancouver, BC, Canada. Pittsburgh, PA: Air & Waste Management Association; paper no. 91-172.5.

Pisarski, A. E. (1992) New perspectives in commuting: based on early data from the 1990 decennial census and the 1990 Nationwide Personal Transportation Study. Washington, DC: U.S. Department of Transportation, Federal Highway Administration; report no. FHWA-PL/92-026.

Quackenboss, J. J.; Spengler, J. D.; Kanarek, M. S.; Letz, R.; Duffy, C. P. (1986) Personal exposure to nitrogen dioxide: relationship to indoor/outdoor air quality and activity patterns. Environ. Sci. Technol. 20: 775-783.

Raaschou-Nielsen, O.; Nielsen, M. L.; Gehl, J. (1995) Traffic-related air pollution: exposure and health effects in Copenhagen street cleaners and cemetery workers. Arch. Environ. Health 50: 207-213.

Radford, E. P.; Drizd, T. A. (1982) Blood carbon monoxide levels in persons 3-74 years of age: United States, 1976-80. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics; publication no. (PHS) 82-1250. (Advance data from vital and health statistics: no. 76).

Radford, E. P.; Levine, M. S. (1976) Occupational exposures to carbon monoxide in Baltimore firefighters. J. Occup. Med. 18: 628-632.

Robinson, J. P.; Thomas, J. (1991) Time spent in activities, locations, and microenvironments: a California-national comparison. Las Vegas, NV: U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory; report no. EPA/600/4-91/006.

Rodes, C.; Sheldon, L.; Whitaker, D.; Clayton, A.; Fitzgerald, K.; Flanagan, J.; DiGenova, F.; Hering, S.; Frazier, C. (1998) Measuring concentrations of selected air pollutants inside California vehicles [final report]. Sacramento, CA: California Environmental Protection Agency, Air Resources Board; contract no. 95-339.

Schwab, M.; Colome, S. D.; Spengler, J. D.; Ryan, P. B.; Billick, I. H. (1990) Activity patterns applied to pollutant exposure assessment: data from a personal monitoring study in Los Angeles. Toxicol. Ind. Health 6: 517-532.

Seufert, K. T.; Kiser, W. R. (1996) End-expiratory carbon monoxide levels as an estimate of passive smoking exposure aboard a nuclear-powered submarine. South. Med. J. 89: 1181-1183.

Sexton, K.; Ryan, P. B. (1988) Assessment of human exposure to air pollution: methods, measurements, and models. In: Watson, A. Y.; Bates, R. R.; Kennedy, D., eds. Air pollution, the automobile, and public health. Washington, DC: National Academy Press; pp. 207-238.

Shenoi, R.; Stewart, G.; Rosenberg, N. (1998) Screening for carbon monoxide in children. Pediatr. Emerg. Care 14: 399-402.

Shikiya, D. C.; Liu, C. S.; Kahn, M. I.; Juarros, J.; Barcikowski, W. (1989) In-vehicle air toxics characterization study in the South Coast Air Basin [draft]. El Monte, CA: South Coast Air Quality Management District, Office of Planning and Rules; May.

Shusterman, D.; Quinlan, P.; Lowengart, R.; Cone, J. (1990) Methylene chloride intoxication in a furniture refinisher: a comparison of exposure estimates utilizing workplace air sampling and blood carboxyhemoglobin measurements. J. Occup. Med. 32: 451-454.

Silvers, A.; Florence, B. T.; Rourke, D. L.; Lorimor, R. J. (1994) How children spend their time: a sample survey for use in exposure and risk assessments. Risk Anal. 14: 931-944.

Simeone, L. F. (1991) The intrusion of engine exhaust into the passenger areas of recreational power boats. Washington, DC: U.S. Coast Guard, Office of Navigation Safety and Waterway Services; report no. DOT-VNTSC-CG-91-1.

Smith, N. J. (1977) End-expired air technic for determining occupational carbon monoxide exposure. J. Occup. Med. 19: 766-769.

Smith, W.; Anderson, T.; Anderson, H. A.; Remington, P. L. (1992) Nitrogen dioxide and carbon monoxide intoxication in an indoor ice arena - Wisconsin, 1992. Morb. Mortal. Wkly. Rep. 41: 383-385.

Snook, L. M. (1996) An investigation of driver exposure to carbon monoxide while traveling in the wake of a snowmobile [dissertation]. Knoxville, TN: University of Tennessee. Available from: University Microfilms International, Ann Arbor MI; publication no. AAG9709060.

Snook, L. M.; Davis, W. T. (1997) An investigation of driver exposure to carbon monoxide while traveling in the wake of a snowmobile. Presented at: 90th annual meeting & exhibition of the Air & Waste Management Association; Toronto, ON, Canada. Pittsburgh, PA: Air & Waste Management Association; paper no. 97-RP143.02.

Sorensen, A. J. (1986) The importance of monitoring carbon monoxide levels in indoor ice skating rinks. J. Am. Coll. Health 34: 185-186.

Spengler, J. D.; Stone, K. R.; Lilley, F. W. (1978) High carbon monoxide levels measured in enclosed skating rinks. J. Air Pollut. Control Assoc. 28: 776-779.

Stewart, R. D.; Hake, C. L. (1976) Paint-remover hazard. JAMA J. Am. Med. Assoc. 235: 398-401.

Stewart, R. D.; Fisher, T. N; Hosko, M. J.; Peterson, J. E.; Baretta, E. D.; Dodd, H. C. (1972) Experimental human exposure to methylene chloride. Arch. Environ. Health 25: 342-348.

Systems Applications, Inc. (1983) Human exposure to atmospheric concentrations of selected chemicals. Volume II. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards; EPA contract no. 68-02-3066.

Szalai, A., ed. (1972) The use of time: daily activities of urban and suburban populations in twelve countries. The Hague, The Netherlands: Mouton & Co.

Treitman, R. D.; Burgess, W. A.; Gold, A. (1980) Air contaminants encountered by firefighters. Am. Ind. Hyg. Assoc. J. 41: 796-802.

Tsang, A. M.; Klepeis, N. E. (1996) Descriptive statistics tables from a detailed analysis of the national human activity pattern survey (NHAPS) data. Las Vegas, NV: U.S. Environmental Protection Agency, Office of Research and Development; report no. EPA/600/R-96/148.

U.S. Code. (1990) Clean Air Act, as amended by PL 101-549, November 15, 1990. U. S. C. 42: §§7401-7671q.

U.S. Department of Commerce. (1983) Statistical abstract of the United States: 1982-83. National data book and guide to sources. 103rd ed. Washington, DC: Bureau of the Census; p. 618.

U.S. Department of Transportation. (1996) Transportation and air quality: selected facts and figures. Washington, DC: Federal Highway Administration; FHWA/PD/96-006; p. 6.

U.S. Environmental Protection Agency. (1985) Health assessment document for dichloromethane (methylene chloride). Final report. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA-600/8-82/004F.

U.S. Environmental Protection Agency. (1991) Air quality criteria for carbon monoxide. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/8-90/045F.

U.S. Environmental Protection Agency. (1992a) Guidelines for exposure assessment. Washington, DC: Risk Assessment Forum; report no. EPA/600/Z-92/001.

U.S. Environmental Protection Agency. (1992b) Review of the national ambient air quality standards for carbon monoxide: 1992 reassessment of scientific and technical information. OAQPS staff paper. Research Triangle Park, NC: Office of Air Quality Planning and Standards; report no. EPA-452/R-92-004.

U.S. Environmental Protection Agency. (1996) National air pollutant emission trends, 1900-1995. Research Triangle Park, NC: Office of Air Quality Planning and Standards; report no. EPA 454/R-96-007.

U.S. Environmental Protection Agency. (1998) National air quality and emissions trends report, 1997. Research Triangle Park, NC: Office of Air Quality Planning and Standards; report no. EPA 454/R-98-016. Available: www.epa.gov/oar/aqtrnd97/ [1999, November 24].

U.S. Environmental Protection Agency. (1999a) AP-42: compilation of air pollutant emission factors. Volume II: mobile sources (AP-42), pending 5th edition. Ann Arbor, MI: Office of Mobile Sources. Available: www.epa.gov/oms/ap42.htm [2000, February, 24].

U.S. Environmental Protection Agency. (1999b) Federal and California light-duty exhaust emission standards. Washington, DC: Office of Transporation and Air Quality; report no. EPA420-B-98-001. Available: www.epa.gov/oms/stds-ld.htm [2000, February 4].

Vadarevu, R. V.; Stopher, P. R. (1996) Household activities, life cycle, and role allocation. Trans. Res. Rec. 1556: 77-85.

Van Wijnen, J. H.; Verhoeff, A. P.; Jans, H. W. A.; van Bruggen, M. (1995) The exposure of cyclists, car drivers and pedestrians to traffic-related air pollutants. Int. Arch. Occup. Environ. Health 67: 187-193.

Vreman, H. J.; Mahoney, J. J.; Stevenson, D. K. (1993) Electrochemical measurement of carbon monoxide in breath: interference by hydrogen. Atmos. Environ. Part A 27: 2193-2198.

Wallace, L. (1979) Use of personal monitor to measure commuter exposure to carbon monoxide in vehicle passenger compartments. Presented at: 72nd annual meeting of the Air Pollution Control Association; June; Cincinnati, OH. Pittsburgh, PA: Air Pollution Control Association; paper no. 79-59.2.

Wallace, L. A. (1983) Carbon monoxide in air and breath of employees in an underground office. J. Air Pollut. Control Assoc. 33: 678-682.

Webster, H. (1998) Would you like to work at home? Read. Dig. 152: 128-134.

Wilcosky, T. C.; Simonsen, N. R. (1991) Solvent exposure and cardiovascular disease. Am. J. Ind. Med. 19: 569-586.

Wiley, J. A.; Robinson, J. P.; Piazza, T.; Garrett, K.; Cirksena, K.; Cheng, Y.-T.; Martin G. (1991a) Activity patterns of California residents. Final report. Sacramento, CA: California Air Resources Board; report no. ARB/R93/487.

Wiley, J. A.; Robinson, J. P.; Cheng, Y.-T.; Piazza, T.; Stork, L.; Pladsen, K. (1991b) Study of children's activity patterns: final report. Sacramento, CA: California Air Resources Board; report no. ARB-R-93/489.

Wilkinson, T. (1995) Snowed under. Natl. Parks 69: 32-37.

Williams, R.; Walsh, D.; White, J.; Jackson, M.; Mumford, J. (1992) Effect on carbon monoxide levels in mobile homes using unvented kerosene heaters for residential heating. Indoor Environ. 1: 272-278.

Wilson, A. L.; Colome, S. D.; Tian, Y. (1991) Air toxics microenvironment exposure and monitoring study. Final report. El Monte, CA: South Coast Air Quality Management District; February.

Wilson, A. L.; Colome, S. D.; Tian, Y. (1993a) California residential indoor air quality study. Volume 1: methodology and descriptive statistics. Chicago, IL: Gas Research Institute; report no. GRI-93/0224.1.

Wilson, A. L.; Colome, S. D.; Tian, Y. (1993b) California residential indoor air quality study. Volume 1: methodology and descriptive statistics. Appendices. Chicago, IL: Gas Research Institute; report no. GRI-93/0224.2.

Yates, M. W. (1967) A preliminary study of carbon monoxide gas in the home. J. Environ. Health 29: 413-420.

Yocom, J. E. (1982) Indoor-outdoor air quality relationships: a critical review. J. Air Pollut. Control Assoc. 32: 500-520.

Yocom, J. E.; Clink, W. L.; Cote, W. A. (1971) Indoor/outdoor air quality relationships. J. Air Pollut. Control Assoc. 21: 251-259.

Yoon, S. S.; Macdonald, S. C.; Parrish, R. G. (1998) Deaths from unintentional carbon monoxide poisoning and potential for prevention with carbon monoxide detectors. JAMA J. Am. Med. Assoc. 279: 685-687.

Yu, L. E.; Hildemann, L. M.; Ott, W. R. (1996) A mathematical model for predicting trends in carbon monoxide emissions and exposures on urban arterial highways. J. Air Waste Manage. Assoc. 46: 430-440.

Zartarian, V. G.; Ott, W. R.; Duan, N. (1997) A quantitative definition of exposure and related concepts. J. Exposure Anal. Environ. Epidemiol. 7: 411-437.

Zayasu, K.; Sekizawa, K.; Okinaga, S.; Yamaya, M.; Ohrui, T.; Sasaki, H. (1997) Increased carbon monoxide in exhaled air of asthmatic patients. Am. J. Respir. Crit. Care Med. 156: 1140-1143.

Ziskind, R. A.; Rogozen, M. B.; Carlin, T.; Drago, R. (1981) Carbon monoxide intrusion into sustained-use vehicles. Environ. Int. 5: 109-123.

Ziskind, R. A.; Fite, K.; Mage, D. T. (1982) Pilot field study: carbon monoxide exposure monitoring in the general population. Environ. Int. 8: 283-293.

CHAPTER 5

Pharmacokinetics and Mechanisms of Action of Carbon Monoxide

5.1 Introduction

Basic research on the physiology, pharmacokinetics, and toxicology of carbon monoxide (CO) that ended in the 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 pharmacokinetics 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.

Although the focus of this document is on the effects of ambient and near ambient levels of CO leading to low COHb levels ($\leq$5%), this chapter discusses, where appropriate, findings of a selected number of human studies carried out at moderate COHb levels ($\leq$20%). Also discussed are observations from a limited number of relevant animal studies at even higher COHb levels. The purpose for the inclusion of such observations from human studies at higher CO concentrations, and animal studies in general, is to facilitate the understanding of CO kinetics, related pathophysiologic processes, and mechanisms of cytotoxicity. Despite much higher CO uptake and elimination rates in animal species than in humans, primarily because of substantially higher ventilation rates, the laboratory animal data still fill, although only partially, the knowledge gaps for which no human data are available in these areas of research. Over the range of CO concentrations that are most relevant experimentally to typical environmental CO exposures (e.g., 50 to 500 ppm), the rate of both CO uptake and elimination in mammals is inversely proportional to body mass (i.e., the smaller the animal, the faster the rate [Klimisch et al., 1975; Tyuma et al., 1981]). Over this same range of CO concentrations, the most widely used predictive model of COHb formation, the Coburn-Forster-Kane (CFK) equation, accurately predicts the resulting COHb levels not only in human subjects, but also in laboratory rats and mice (Tyuma et al., 1981; Benignus and Annau, 1994; Kimmel et al., 1999). Thus, despite many well identified interspecies differences in the toxicokinetics of CO, the basic mechanisms of CO toxicity between laboratory animals and humans are similar and, in many respects, close to identical. Although a more detailed discussion of interspecies differences as they relate to humans may aid in interpretation of data and elucidation of mechanisms, it is not essential for understanding the material presented in this chapter and is well beyond the scope of this document (see Chapter 1). Despite interspecies differences, especially in the uptake and elimination kinetics of CO, extrapolation of observations from animals to man as applied in this chapter, even with its many assumptions, may be useful

in identifying potential pathophysiologic and histotoxic processes associated with ambient or near ambient CO exposure.

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 and 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 along the CO pressure gradient, 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).

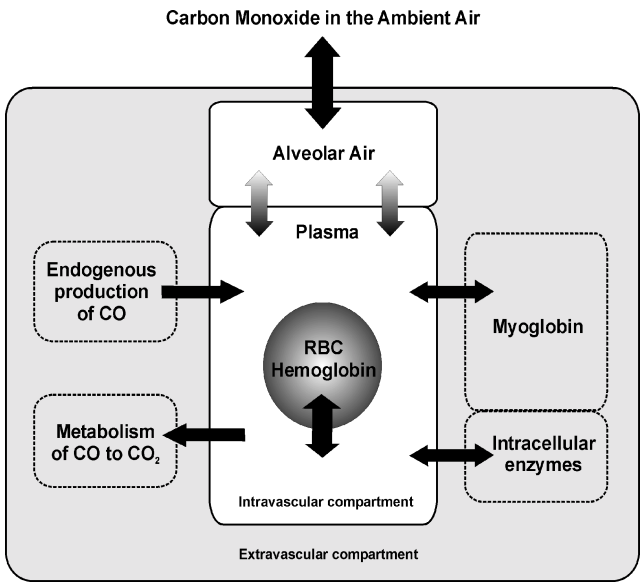

Figure 5-1. Diagrammatic presentation of CO uptake and elimination pathways and CO body stores.
Source: Adapted from Coburn (1967).

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 in an upright posture, 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. As a result, the $\dot{V}_A/\dot{Q}$ ratio is the principal variable controlling gas exchange, and 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 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). Both right-to-left and physiological shunts under normal conditions contribute little to $\dot{V}_A/\dot{Q}$ inequality (West, 1990a). 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

The next step in the transfer of gases across the alveolar air-Hb barrier is accomplished by gas diffusion, which is an entirely passive process. To reach the Hb-binding sites, CO and other gas molecules have to diffuse across the alveolo-capillary membrane, through the plasma, across the RBC membrane, and, finally, into 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 (West, 1990b). 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 levels of CO above blood baseline rapidly increases blood COHb. 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 gradient for CO pressure is usually much higher than the blood-air gradient; therefore, CO uptake will be a proportionately faster process than CO elimination. The rate of CO release also will be affected by back pressure from endogenous production of CO.

Diurnal variations in CO diffusion capacity of the lung (D_LCO) related to variations in Hb concentration 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 carbon dioxide (CO_2), ventilatory pattern, O_2 consumption, blood flow, functional residual capacity, etc. (Forster, 1987). Diffusion capacity seems to be relatively independent of lung volume within the mid-range 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). In a supine position at rest, D_LCO has been shown to be significantly higher than that at rest in a sitting position (McClean et al., 1981). Carbon monoxide diffusion capacity increases with exercise, and, at maximum work rates, diffusion will be maximal regardless of body position. This increase is attained not only by increases in both the diffusing capacity of the alveolar-capillary membrane and the pulmonary capillary blood flow (Stokes et al., 1981) but also by increased $\dot{V}_A/\dot{Q}$ uniformity (Harf et al., 1978). Under pathologic conditions, where several components of the air-blood interface may be affected severely, and the $\dot{V}_A/\dot{Q}$ ratio inequality also may increase (as in emphysema, and 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 where it diffuses across the lung tissue and into blood. 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 and duration of CO exposure and on the relative surface area. Experimental exposures of the oronasal cavity in monkeys to very high concentrations of CO (>400 ppm) 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.

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, 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 (Wyman et al., 1982; Grønlund 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. 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. Figure 5-2 illustrates the basic mechanisms of CO toxicity operating at any CO concentration. The a and a′ points represent the arterial values of PO_2. The v represents the venous PO_2 of healthy individuals after extraction of 5 vol % of O_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

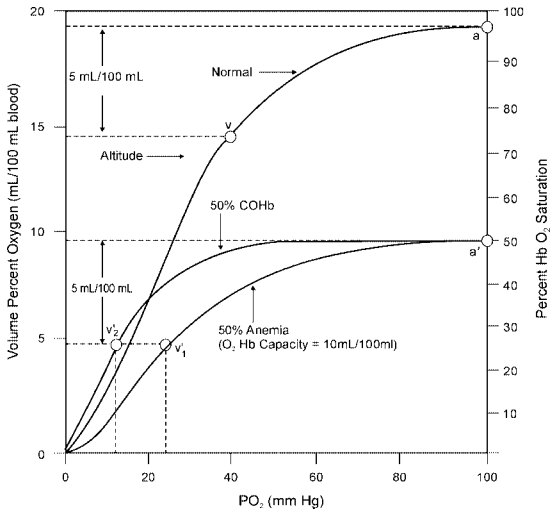

Figure 5-2. Oxyhemoglobin dissociation curve of normal human blood, of blood containing 50% COHb, and of blood with only 50% Hb because of anemia. See the text for additional details.
Source: U.S. Environmental Protection Agency (1991).

over a critical saturation range for release of O_2 to tissues, a reduction in O_2Hb by CO binding 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 venous PO_2 of 26 torr (v_1'), 5 vol % of O_2 (50% desaturation) was extracted from blood, an amount sufficient to sustain tissue metabolism. In contrast, in a person poisoned with CO (50% COHb), the venous 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).

As Figure 5-1 shows, CO not only is exchanged between alveolar air and blood but also is distributed by blood to other tissues. Studies on dogs (Coburn, 1967; Luomanmäki and Coburn, 1969) found that, over the range of 2 to 35% COHb, an average of 77% of total body CO remains in the vascular compartment. The rest of CO diffused to extravascular tissues, primarily skeletal muscle where it is bound to myoglobin (Mb). Compared to dogs, the extravascular CO stores in men are smaller and account for 10 to 15% of total body CO, and less than 1% of the body CO stores appears to be physically dissolved in body fluids (Coburn, 1970a). Similar to animals, no shift between blood and extravascular compartments in men was found at low (<4%) COHb.

5.2.2.3 Heart and Skeletal Muscle

Myoglobin, 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 oxymyoglobin. The main function of Mb is thought to be a temporary store of O_2 and to act as a diffusion facilitator between Hb and the tissues (Peters et al., 1994).

Myoglobin has a CO affinity constant approximately eight-times lower than Hb (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 (Luomanmäki and Coburn, 1969). The binding of CO to Mb (carboxymyoglobin [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 myocyte 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 storage 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 the 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 if uncompensated will have a detrimental effect on brain function. The primary effects of low ambient concentrations of CO on other organs (e.g., liver, kidney) is via hypoxic mechanisms (see Section 6.6).

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. Although almost all of the studies investigating CO elimination pattern and processes were done at moderate COHb levels ($\leq$20%), the physiologic mechanisms involved in CO elimination kinetics also are effected at lower blood COHb, including levels resulting from ambient exposures ($\leq$5%). 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 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 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 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% 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; Selvakumar et al., 1993).

5.3 Tissue Production and Metabolism of Carbon Monoxide

In the process of natural degradation of RBC Hb to bile pigments, a carbon atom is separated from the porphyrin nucleus and, subsequently, is catabolized by heme oxygenase (HO) 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 (Lynch and Moede, 1972; Mercke et al., 1975b).

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 non-Hb sources (Coburn et al., 1963, 1964). This will result in a blood COHb concentration between 0.4 and 0.7% (Coburn et al., 1965).

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., 1975c), diphenylhydantoin (Coburn, 1970b), progesterone (Delivoria-Papadopoulos et al., 1974), and contraceptives (Mercke et al., 1975b) all will elevate tissue bilirubin and, subsequently, CO production.

Another mechanism that will increase CO production is a stimulation of HO 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 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 baseline COHb 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 Hb, 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 bronchiectasis (Horvath et al., 1998a) and in asthmatics (Zayasu et al., 1997; Horvath et al., 1998b). In the Zayasu et al. (1997) 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. Whether asthmatics have an increased COHb level was not measured in this study or reported in other studies. Patients with chronic inflammatory lung disease, such as bronchiectasis may produce a substantial amount of CO (e.g., 11.8 ppm). As with asthma, induction of heme oxygenase appears to be the primary mechanism involved in the production of CO (Horvath et al., 1998a,b). 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 5.6.4).

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 rates

of CO uptake and COHb formation will be proportional to the intensity of exercise. During a transition period from rest to exercise while exposed to CO (500 ppm/10 min), the diffusing capacity and CO uptake were reported to rise faster than O_2 consumption for each exercise intensity (Kinker et al., 1992).

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 of 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.

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% 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 body temperature of 37 °C, barometric pressure (P_B) of 760 torr, and air (gas) saturated with water vapor (BTPS conditions) the P_IO_2 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 have 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 Mb 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 with 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 the D_LCO decreases with age (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 and hemodilution may lead to iron deficiency and anemia (for further details see Sections 6.4 and 7.7.1). 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., 1992, 1993; Singh and Moore-Cheatum, 1993).

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 5.4.4 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 reduction in total blood Hb and subsequent insufficiency to meet O_2 demands are the anemias. 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 Hb. By far, the most prevalent disorder in this group is a single-point mutation of Hb, 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 Hb 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 (Foster et al., 1978; Stork et al., 1988).

A distinctive characteristic 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 severely compromise 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. Most of the CO 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):

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

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 (set to 0 until the end of exposure). 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.

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 two models revealed a progressive divergence of the estimated COHb curves between models as exposure (100 ppm) progressed, with absolute 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 make their utility in practical applications questionable (Tikuisis, 1996).

Several more sophisticated mathematical models have been developed to predict COHb as a function of exposure time (Singh et al., 1991; Sharan et al., 1990) or altitude (Selvakumar et al., 1992). The physiological variables used by Peterson and Stewart (1970) were employed to test these models and compare the results to the CFK predictions. The agreement between predicted COHb values by these models and the CFK model was very good; however, these theoretical models have not been validated by experimental studies.

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:

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

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; $\dot{V}_A$ is the alveolar ventilation in milliliters per minute, STPD; $D_L CO$ is the lung diffusing capacity of CO in milliliters per minute per millimeter of mercury, STPD; and $P_I CO$ 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:

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

where β is $(1/D_L CO) + (P_B - 47)/\dot{V}_A$, 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 $D_L CO$ 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 equations 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 ($F_I CO$), 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; THb is the total blood concentration of Hb. The fractional sensitivity of unity means that, for example, a 5% error in the selected variable induces a 5% error in predicted COHb 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

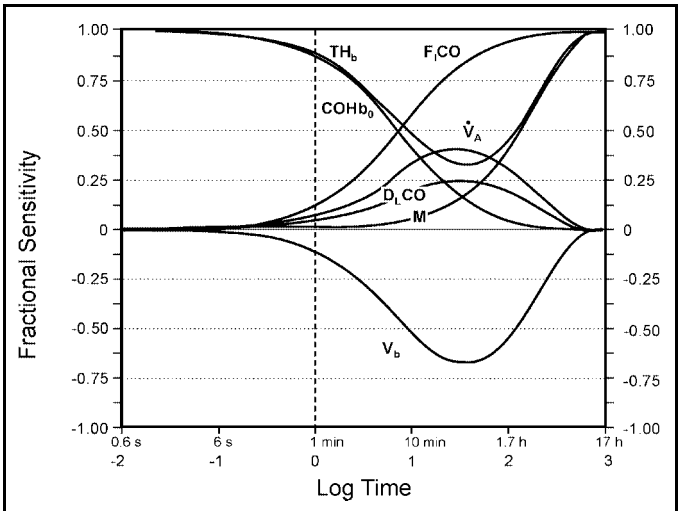

Figure 5-3. Plot of fractional sensitivities of selected variables versus time of exposure (see text for details).
Source: Modified from McCartney (1990).

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

Stewart et al. (1970) tested the CFK linear differential equation on 18 resting, healthy 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 5.25 h (Peterson and Stewart, 1975). From the obtained values, they concluded that, either at rest or with 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 with 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 phases 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 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 $\dot{V}_A$ affects both the equilibrium and the rate at which

it is achieved, 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 heart and brain (see Sections 5.2.2.3 and 5.2.2.4). In these situations, the predicted instantaneous arterial COHb level will be substantially 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 relationships between pairs of variables, but the accuracy of the nomograms was not tested experimentally.

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 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 5.5.1.3, Smith et al. (1994) expanded the CFK model to allow for prediction of arterial and venous COHb during transient CO uptake and early elimination phases. 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, and, 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 (e.g., Hb degradation, metabolism of dihalomethanes, inhaled CO).

Reexpression of the solution of the CFK model from 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 National Ambient Air Quality Standards (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 ambient CO concentrations 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 Introduction

Traditional concepts for CO pathophysiology have been based on the high affinity of CO for deoxyhemoglobin and consequent reduction of O_2 delivery. This mechanism is relevant for high CO concentrations, but it is less likely to be relevant to the concentrations of CO currently found in the ambient environment. This section will summarize recently published information on biochemical mechanisms that is not related to an impairment of oxygen delivery from elevations in COHb. Some of the studies outlined in this section were done with cells in culture and others with laboratory rats. To be relevant to human exposures from environmental contamination, it is important to note what concentrations of CO are likely to occur in vivo. Lung parenchyma represents a special situation where cells may be exposed to ambient CO without the reduction in concentration associated with Hb-bound CO. Elsewhere in the body, only a fraction of COHb will dissociate to elevate extravascular CO concentrations. This elevation is in the range of approximately 2 to 10 nmol when the COHb concentration is from 0.8 to 3.8% (Coburn, 1970a; Göthert et al., 1970). The COHb values near steady-state conditions in laboratory rats are close to values for humans (Kimmell et al., 1999). This strengthens the potential for human relevance in recent animal studies that show that newly identified biochemical mechanisms do have adverse physiological effects. However, caution still is warranted because direct evidence for the occurrence of these mechanisms in humans has not been shown.

5.6.2 Inhibition of Hemoprotein Function

Carbon monoxide can inhibit a number of hemoproteins found in cells, such as Mb, 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 relative affinity for CO over that for O_2 is Mb. Carbon monoxide will inhibit Mb-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%.

Coefficients for binding CO versus O_2 among 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 since then. 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.

5.6.3 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, 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 Padmaja, 1993).

The mechanism by which CO concentrations of 11 nmol 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)-Mb or •NO-Hb, 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 1,070 nmol 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 with rats exposed to 50 ppm CO or more (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, 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 bovine 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 occurred only following sequestration and activation of circulating leukocytes (Thom, 1993).

5.6.4 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 (Rodgers 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 •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 recently was 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 •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 •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 •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 nanomolar tissue concentrations resulting from inhalation of CO are comparable or greater than concentrations produced by cells possessing heme oxygenase. 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, on the order of 500 to 2,000 ppm, the mechanism is related to impairment of O_2 delivery (Kanten et al., 1983; MacMillan, 1975). However, a portion of the observed increases in cerebral blood flow are independent of perturbations in 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 $^{\bullet}NO$ (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 $^{\bullet}NO$ was reported with exposures to 1,000 ppm CO, that level of exposure 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, 1991, 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 were exposed to CO for many hours at a time, capillary leakage of macromolecules from the lungs and systemic vasculature has been documented, but the presence of 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. 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. Leakage of albumin and leukocyte sequestration have been shown following exposures of rats to 50 ppm or more for 1 h, and the process is 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 rats exposed to 1,000 to 3,000 ppm CO for 1 h (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 focused 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. Failure of vasodilation to compensate causes tissue hypoxia. 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 and becomes the rate-determining step in the mass transfer of CO for COHb formation and elimination. 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 diseases (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 both to mitochondria and to a CO-mediated disturbance of intracellular "buffering" of endogenously generated free radicals (e.g., ·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.

References

Acevedo, C. H.; Ahmed, A. (1998) Hemeoxygenase-1 inhibits human myometrial contractility via carbon monoxide and is upregulated by progesterone during pregnancy. J. Clin. Invest. 101: 949-955.

Andersen, M. E.; Clewell, H. M., III; Gargas, M. L.; MacNaughton, M. G.; Reitz, R. H.; Nolan, R. J.; McKenna, M. J. (1991) Physiologically based pharmacokinetic modeling with dichloromethane, its metabolite, carbon monoxide, and blood carboxyhemoglobin in rats and humans. Toxicol. Appl. Pharmacol. 108: 14-27.

Arias-Díaz, J.; Vara, E.; García, C.; Villa, N.; Balibrea, J. L. (1995) Evidence for a cyclic guanosine monophosphate-dependent, carbon monoxide-mediated, signaling system in the regulation of TNF-α production by human pulmonary macrophages. Arch. Surg. (Chicago) 130: 1287-1293.

Armitage, A. K.; Davies, R. F.; Turner, D. M. (1976) The effects of carbon monoxide on the development of atherosclerosis in the White Carneau pigeon. Atherosclerosis 23: 333-344.

Arranz, B.; Blennow, K.; Eriksson, A.; Månsson, J.-E.; Marcusson, J. (1997) Serotonergic, noradrenergic, and dopaminergic measures in suicide brains. Biol. Psychiatry 41: 1000-1009.

Barie, P. S.; Wu, W.; Hariri, R. J.; Halebian, P. H.; Shires, G. T. (1994) Alterations of pulmonary gas exchange after superimposed carbon monoxide poisoning in acute lung injury. Surgery (St. Louis) 115: 678-686.

Beal, M. F. (1992) Does impairment of energy metabolism result in excitotoxic neuronal death in neurodegenerative illnesses? Ann. Neurol. 31: 119-130.

Belenky, S. N.; Robbins, R. A.; Rubinstein, I. (1993) Nitric oxide synthase inhibitors attenuate human monocyte chemotaxis in vitro. J. Leukocyte Biol. 53: 498-503.

Bender, P. R.; Weil, J. V.; Reeves, J. T.; Moore, L. G. (1987) Breathing pattern in hypoxic exposures of varying duration. J. Appl. Physiol. 62: 640-645.

Benignus, V. A. (1995) A model to predict carboxyhemoglobin and pulmonary parameters after exposure to O_2, CO_2, and CO. Aviat. Space Environ. Med. 66: 369-374.

Benignus, V. A.; Annau, Z. (1994) Carboxyhemoglobin formation due to carbon monoxide exposure in rats. Toxicol. Appl. Pharmacol. 128: 151-157.

Benignus, V. A.; Hazucha, M. J.; Smith, M. V.; Bromberg, P. A. (1994) Prediction of carboxyhemoglobin formation due to transient exposure to carbon monoxide. J. Appl. Physiol. 76: 1739-1745.

Berk, P. D.; Rodkey, F. L.; Blaschke, T. F.; Collison, H. A.; Waggoner, J. G. (1974) Comparison of plasma bilirubin turnover and carbon monoxide production in man. J. Lab. Clin. Med. 83: 29-37.

Berk, P. D.; Blaschke, T. F.; Scharschmidt, B. F.; Waggoner, J. G.; Berlin, N. I. (1976) A new approach to quantitation of the various sources of bilirubin in man. J. Lab. Clin. Med. 87: 767-780.

Bernard, T. E.; Duker, J. (1981) Modeling carbon monoxide uptake during work. Am. Ind. Hyg. Assoc. J. 42: 361-364.

Biller, W. F.; Richmond, H. M. (1982) Sensitivity analysis on Coburn model predictions of COHb levels associated with alternative CO standards. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards; EPA contract no. 68-02-3600.

Biller, W. F.; Richmond, H. M. (1992) COHb module for a probabilistic CO NEM. In: Johnson, T.; Capel, J.; Paul, R.; Wijnberg, L. Estimation of carbon monoxide exposures and associated carboxyhemoglobin levels in Denver residents using a probabilistic version of NEM. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards; contract no. 68-D0-0062; appendix C.

Boothby, W. M.; Lovelace, W. R., II; Benson, O. O., Jr.; Strehler, A. F. (1954) Volume and partial pressures of respiratory gases at altitude. In: Boothby, W. M., ed. Respiratory physiology in aviation. Randolph Field, TX: U.S. Air Force School of Aviation Medicine; pp. 39-49.

Bridges, R. J.; Koh, J.-Y.; Hatalski, C. G.; Cotman, C. W. (1991) Increased excitotoxic vulnerability of cortical cultures with reduced levels of glutathione. Eur. J. Pharmacol. 192: 199-200.

Britten, J. S.; Myers, R. A. M. (1985) Effects of hyperbaric treatment on carbon monoxide elimination in humans. Undersea Biomed. Res. 12: 431-438.

Brown, S. D.; Piantadosi, C. A. (1992) Recovery of energy metabolism in rat brain after carbon monoxide hypoxia. J. Clin. Invest. 89: 666-672.

Bünger, J.; Bombosch, F.; Mesecke, U.; Hallier, E. (1997) Monitoring and analysis of occupational exposure to chain saw exhausts. Am. Ind. Hyg. Assoc. J. 58: 747-751.

Burki, N. K. (1984) Effects of acute exposure to high altitude on ventilatory drive and respiratory pattern. J. Appl. Physiol. Respir. Environ. Exercise Physiol. 56: 1027-1031.

Cantrell, J. M.; Tucker, A. (1996) Low-dose carbon monoxide does not reduce vasoconstriction in isolated rat lungs. Exp. Lung Res. 22: 21-32.

Cassina, A.; Radi, R. (1996) Differential inhibitory action of nitric oxide and peroxynitrate on mitochondrial electron transport. Arch. Biochem Biophys. 328: 309-316.

Cavallin-Ståhl, E.; Mercke, C.; Lundh, B. (1976) Carbon monoxide production in patients with breast carcinoma. Br. J. Haematol. 32: 177-182.

Chung, S. J. (1988) Formulas predicting carboxyhemoglobin resulting from carbon monoxide exposure. Vet. Hum. Toxicol. 30: 528-532.

Coburn, R. F. (1967) Endogenous carbon monoxide production and body CO stores. Acta Med. Scand. Suppl. 472: 269-282.

Coburn, R. F. (1970a) The carbon monoxide body stores. In: Coburn, R. F., ed. Biological effects of carbon monoxide. Ann. N. Y. Acad. Sci. 174: 11-22.

Coburn, R. F. (1970b) Enhancement by phenobarbital and diphenylhydantoin of carbon monoxide production in normal man. N. Engl. J. Med. 283: 512-515.

Coburn, R. F. (1973) Mean myoglobin oxygen tension in skeletal and cardiac muscle. In: Bicher, H. I.; Bruley, D. F., eds. Oxygen transport to tissue: instrumentation, methods, and physiology. New York, NY: Plenum Press; pp. 571-577. (Advances in experimental medicine and biology: v. 37A-B).

Coburn, R. F.; Forman, H. J. (1987) Carbon monoxide toxicity. In: Fishman, A. P.; Farhi, L. E.; Tenney, S. M.; Geiger, S. R., eds. Handbook of physiology: a critical, comprehensive presentation of physiological knowledge and concepts. Section 3: the respiratory system. Volume IV. Gas exchange. Bethesda, MD: American Physiological Society; pp. 439-456.

Coburn, R. F.; Mayers, L. B. (1971) Myoglobin O_2 tension determined from measurements of carboxymyoglobin in skeletal muscle. Am. J. Physiol. 220: 66-74.

Coburn, R. F.; Blakemore, W. S.; Forster, R. E. (1963) Endogenous carbon monoxide production in man. J. Clin. Invest. 42: 1172-1178.

Coburn, R. F.; Williams, W. J.; Forster, R. E. (1964) Effect of erythrocyte destruction on carbon monoxide production in man. J. Clin. Invest. 43: 1098-1103.

Coburn, R. F.; Forster, R. E.; Kane, P. B. (1965) Considerations of the physiological variables that determine the blood carboxyhemoglobin concentration in man. J. Clin. Invest. 44: 1899-1910.

Coburn, R. F.; Williams, W. J.; Kahn, S. B. (1966) Endogenous carbon monoxide production in patients with hemolytic anemia. J. Clin. Invest. 45: 460-468.

Coceani, F.; Breen, C. A.; Lees, J. G.; Falck, J. R.; Olley, P. M. (1988) Further evidence implicating a cytochrome P-450-mediated reaction in the contractile tension of the lamb ductus arteriosus. Circ. Res. 62: 471-477.

Cook, M. N.; Nakatsu, K.; Marks, G. S.; McLaughlin, B. E.; Vreman, H. J.; Stevenson, D. K.; Brien, J. F. (1995) Heme oxygenase activity in the adult rat aorta and liver as measured by carbon monoxide formation. Can. J. Physiol. Pharmacol. 73: 515-518.

Davies, R. F.; Topping, D. L.; Turner, D. M. (1976) The effect of intermittent carbon monoxide exposure on experimental atherosclerosis in the rabbit. Atherosclerosis 24: 527-536.

Delivoria-Papadopoulos, M.; Coburn, R. F.; Forster, R. E. (1974) Cyclic variation of rate of carbon monoxide production in normal women. J. Appl. Physiol. 36: 49-51.

Deller, A.; Stenz, R.; Forstner, K.; Konrad, F. (1992) Die elimination von kohlenmonoxydhamoglobin - geschlechtsspezifische und zirkadiane einflusse [The elimination of carboxyhemoglobin COHB sex-specific and circadian influences in healthy volunteers]. Infusionstherapie 19: 121-126.

Durante, W.; Kroll, M. H.; Christodoulides, N.; Peyton, K. J.; Schafer, A. I. (1997) Nitric oxide induces heme oxygenase-1 gene expression and carbon monoxide production in vascular smooth muscle cells. Circ. Res. 80: 557-564.

Engel, L. A.; Wood, L. D. H.; Utz, G.; Macklem, P. T. (1973) Gas mixing during inspiration. J. Appl. Physiol. 35: 18-24.

Farrugia, G.; Miller, S. M.; Rich, A.; Liu, X.; Maines, M. D.; Rae, J. L.; Szurszewski, J. H. (1998) Distribution of heme oxygenase and effects of exogenous carbon monoxide in canine jejunum. Am. J. Physiol. 274: G350-G358.

Fechter, L. D.; Liu, Y.; Pearce, T. A. (1997) Cochlear protection from carbon monoxide exposure by free radical blockers in the guinea pig. Toxicol. Appl. Pharmacol. 142: 47-55.

Fein, A.; Grossman, R. F.; Jones, J. G.; Hoeffel, J.; McKay, D. (1980) Carbon monoxide effect on alveolar epithelial permeability. Chest 78: 726-731.

Fisher, A. B.; Hyde, R. W.; Baue, A. E.; Reif, J. S.; Kelly, D. F. (1969) Effect of carbon monoxide on function and structure of the lung. J. Appl. Physiol. 26: 4-12.

Forbes, W. H.; Sargent, F.; Roughton, F. J. W. (1945) The rate of carbon monoxide uptake by normal men. Am. J. Physiol. 143: 594-608.

Forster, R. E. (1987) Diffusion of gases across the alveolar membrane. In: Fishman, A. P.; Farhi, L. E.; Tenney, S. M.; Geiger, S. R., eds. Handbook of physiology: a critical, comprehensive presentation of physiological knowledge and concepts. Section 3: the respiratory system. Volume IV. Gas exchange. Bethesda, MD: American Physiological Society; pp. 71-88.

Foster, L. J.; Corrigan, K.; Goldman, A. L. (1978) Effectiveness of oxygen therapy in hypoxic polycythemic smokers. Chest 73: 572-576.

Frey, T. M.; Crapo, R. O.; Jensen, R. L.; Elliott, C. G. (1987) Diurnal variation of the diffusing capacity of the lung: is it real? Am. Rev. Respir. Dis. 136: 1381-1384.

Ge, R.-L.; Matsuzawa, Y.; Takeoka, M.; Kubo, K.; Sekiguchi, M.; Kobayashi, T. (1997) Low pulmonary diffusing capacity in subjects with acute mountain sickness. Chest 111: 58-64.

Gibson, Q. H.; Olson, J. S.; McKinnie, R. E.; Rohlfs, R. J. (1986) A kinetic description of ligand binding to sperm whale myoglobin. J. Biol. Chem. 261: 10,228-10,236.

Ginsberg, M. D.; Myers, R. E. (1974) Experimental carbon monoxide encephalopathy in the primate. I. Physiologic and metabolic aspects. Arch. Neurol. 30: 202-208.

Goda, N.; Suzuki, K.; Naito, M.; Takeoka, S.; Tsuchida, E.; Ishimura, Y.; Tamatani, T.; Suematsu, M. (1998) Distribution of heme oxygenase isoforms in rat liver: topographic basis for carbon monoxide-mediated microvascular relaxation. J. Clin. Invest. 101: 604-612.

Göthert, M.; Lutz, F.; Malorny, G. (1970) Carbon monoxide partial pressure in tissue of different animals. Environ. Res. 3: 303-309.

Grønlund, J.; Garby, L. (1984) Numerical values of the classical Haldane coefficient. J. Appl. Physiol. 57: 850-859.

Grote, J.; Dall, P.; Oltmanns, K.; Stolp, W. (1994) The effect of increased blood carbon monoxide levels on the hemoglobin oxygen affinity during pregnancy. In: Vaupel, P.; Zander R.; Bruley, D. F., eds. Oxygen transport to tissue XV. Proceedings of the twentieth annual meeting of the International Society on Oxygen Transport to Tissue; August 1992; Mainz, Germany. New York, NY: Plenum Press; pp. 145-150. (Advances in experimental medicine and biology: v. 345).

Grundemar, L.; Johansson, M.-B.; Ekelund, M.; Högestätt, E. D. (1995) Haem oxygenase activity in blood vessel homogenates as measured by carbon monoxide production. Acta Physiol. Scand. 153: 203-204.

Guénard, H.; Marthan, R. (1996) Pulmonary gas exchange in elderly subjects. Eur. Respir. J. 9: 2573-2577.

Gwag, B. J.; Lobner, D.; Koh, J. Y.; Wie, M. B.; Choi, D. W. (1995) Blockade of glutamate receptors unmasks neuronal apoptosis after oxygen-glucose deprivation *in vitro*. Neuroscience 68: 615-619.

Haab, P. E.; Durand-Arczynska, W. Y. (1991) Carbon monoxide effects on oxygen transport. In: Crystal, R. G.; West, J. B.; Barnes, P. J.; Cherniack, N. S.; Weibel, E. R., eds. The lung: scientific applications, v. 2. New York, NY: Raven Press; pp. 1267-1275.

Haldane, J. (1897-1898) Some improved methods of gas analysis. J. Physiol. (London) 22: 465-480.

Harf, A.; Pratt, T.; Hughes, J. M. B. (1978) Regional distribution of $\dot{V}_A/\dot{Q}$ in man at rest and with exercise measured with krypton-81m. J. Appl. Physiol.: Respir. Environ. Exercise Physiol. 44: 115-123.

Hauck, H.; Neuberger, M. (1984) Carbon monoxide uptake and the resulting carboxyhemoglobin in man. Eur. J. Appl. Physiol. 53: 186-190.

Hausberg, M.; Somers, V. K. (1997) Neural circulatory responses to carbon monoxide in healthy humans. Hypertension 29: 1114-1118.

Hill, E. P.; Hill, J. R.; Power, G. G.; Longo, L. D. (1977) Carbon monoxide exchanges between the human fetus and mother: a mathematical model. Am. J. Physiol. 232: H311-H323.

Horvath, S. M.; Agnew, J. W.; Wagner, J. A.; Bedi, J. F. (1988) Maximal aerobic capacity at several ambient concentrations of carbon monoxide at several altitudes. Cambridge, MA: Health Effects Institute; research report no. 21.

Horvath, I.; Loukides, S.; Wodehouse, T.; Kharitonov, S. A.; Cole, P. J.; Barnes, P. J. (1998a) Increased levels of exhaled carbon monoxide in bronchiectasis: a new marker of oxidative stress. Thorax 53: 867-870.

Horvath, I.; Donnelly, L. E.; Kiss, A.; Paredi, P.; Kharitonov, S. A.; Barnes, P. J. (1998b) Raised levels of exhaled carbon monoxide are associated with an increased expression of heme oxygenase-1 in airway macrophages in asthma: a new marker of oxidative stress. Thorax 53: 668-672.

Hugod, C.; Hawkins, L. H.; Kjeldsen, K.; Thomsen, H. K.; Astrup, P. (1978) Effect of carbon monoxide exposure on aortic and coronary intimal morphology in the rabbit. Atherosclerosis 30: 333-342.

Huie, R. E.; Padmaja, S. (1993) The reaction of NO with superoxide. Free Radical Res. Commun. 18: 195-199.

Ingi, T.; Ronnett, G. V. (1995) Direct demonstration of a physiological role for carbon monoxide in olfactory receptor neurons. J. Neurosci. 15: 8214-8222.

Ingi, T.; Cheng, J.; Ronnett, G. V. (1996) Carbon monoxide: an endogenous modulator of the nitric oxide-cyclic GMP signaling system. Neuron 16: 835-842.

Ingram, D.; Dickinson, C. J.; Ahmed, K. (1987) MACPUF software package. London, United Kingdom: Centre for Health Informatics and Multiprofessional Education (CHIME), University College London, Medical School and Health Sciences Centre, McMaster University. Available: www.chime.ucl.ac.uk/Models/macpuf.htm.

Ischiropoulos, H.; Zhu, L.; Chen, J.; Tsai, M.; Martin, J. C.; Smith, C. D.; Beckman, J. S. (1992) Peroxynitrate-mediated tyrosine nitration catalyzed by superoxide dismutase. Arch. Biochem. Biophys. 298: 431-437.

Ischiropoulos, H.; Beers, M. F.; Ohnishi, S. T.; Fisher, D.; Garner, S. E.; Thom, S. R. (1996) Nitric oxide production and perivascular tyrosine nitration in brain after carbon monoxide poisoning in the rat. J. Clin. Invest. 97: 2260-2267.

Ishimaru, H.; Nabeshima, T.; Katoh, A.; Suzuki, H.; Fukuta, T.; Kameyama, T. (1991) Effects of successive carbon monoxide exposures on delayed neuronal death in mice under the maintenance of normal body temperature. Biochem. Biophys. Res. Commun. 179: 836-840.

Ishimaru, H.; Katoh, A.; Suzuki, H.; Fukuta, T.; Kameyama, T.; Nabeshima, T. (1992) Effects of N-methyl-D-aspartate receptor antagonists on carbon monoxide-induced brain damage in mice. J. Pharmacol. Exp. Ther. 261: 349-352.

Jay, G. D.; McKindley, D. S. (1997) Alterations in pharmacokinetics of carboxyhemoglobin produced by oxygen under pressure. Undersea Hyperbaric Med. 24: 165-173.

Johnson, T.; Capel, J.; Paul, R.; Wijnberg, L. (1992) Estimation of carbon monoxide exposures and associated carboxyhemoglobin levels in Denver residents using a probabilistic version of NEM. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards; contract no. 68-D0-0062.

Joumard, R.; Chiron, M.; Vidon, R.; Maurin, M.; Rouzioux, J.-M. (1981) Mathematical models of the uptake of carbon monoxide on hemoglobin at low carbon monoxide levels. Environ. Health Perspect. 41: 277-289.

Kanten, W. E.; Penney, D. G.; Francisco, K.; Thill, J. E. (1983) Hemodynamic responses to acute carboxyhemoglobinemia in the rat. Am. J. Physiol. 244: H320-H327.

Kim, S. K.; Kim, Y. C. (1996) Effect of a single administration of benzene, toluene or *m*-xylene on carboxyhaemoglobin elevation and metabolism of dichloromethane in rats. J. Appl. Toxicol. 16: 437-444.

Kimmel, E. C.; Carpenter, R. L.; Reboulet, J. E.; Still, K. R. (1999) A physiological model for predicting carboxyhemoglobin formation from exposure to carbon monoxide in rats. J. Appl. Physiol. 86: 1977-1983.

Kinker, J. R.; Haffor, A.-S.; Stephan, M.; Clanton, T. L. (1992) Kinetics of CO uptake and diffusing capacity in transition from rest to steady-state exercise. J. Appl. Physiol. 72: 1764-1772.

Kjeldsen, K.; Astrup, P.; Wanstrup, J. (1972) Ultrastructural intimal changes in the rabbit aorta after a moderate carbon monoxide exposure. Atherosclerosis 16: 67-82.

Kleinman, M. T.; Leaf, D. A.; Kelly, E.; Caiozzo, V.; Osann, K.; O'Niell, T. (1998) Urban angina in the mountains: effects of carbon monoxide and mild hypoxemia on subjects with chronic stable angina. Arch. Environ. Health 53: 388-397.

Klimisch, H.-J.; Chevalier, H.-J.; Harke, H.-P.; Dontenwill, W. (1975) Uptake of carbon monoxide in blood of miniature pigs and other mammals. Toxicology 3: 301-310.
Koehler, R. C.; Jones, M. D., Jr.; Traystman, R. J. (1982) Cerebral circulatory response to carbon monoxide and hypoxic hypoxia in the lamb. Am. J. Physiol. 243: H27-H32.
Kurata, S.; Matsumoto, M.; Yamashita, U. (1996) Concomitant transcriptional activation of nitric oxide synthase and heme oxygenase genes during nitric oxide-mediated macrophage cytostasis. J. Biochem. 120: 49-52.
Landaw, S. A. (1973) The effects of cigarette smoking on total body burden and excretion rates of carbon monoxide. J. Occup. Med. 15: 231-235.
Landaw, S. A.; Callahan, E. W., Jr.; Schmid, R. (1970) Catabolism of heme in vivo: comparison of the simultaneous production of bilirubin and carbon monoxide. J. Clin. Invest. 49: 914-925.
Levasseur, L.; Galliot-Guilley, M.; Richter, F.; Scherrmann, J. M.; Baud, F. J. (1996) Effects of mode of inhalation of carbon monoxide and of normobaric oxygen administration on carbon monoxide elimination from the blood. Hum. Exp. Toxicol. 15: 898-903.
Levitt, M. D.; Ellis, C.; Levitt, D. G. (1994) Diurnal rhythm of heme turnover assessed by breath carbon monoxide concentration measurements. J. Lab. Clin. Med. 124: 427-431.
Lifshay, A.; Fast, C. W.; Glazier, J. B. (1971) Effects of changes in respiratory pattern on physiological dead space. J. Appl. Physiol. 31: 478-483.
Lipton, S. A.; Kim, W.-K.; Choi, Y.-B.; Kumar, S.; D'Emilia, D. M.; Rayudu, P. V.; Arnelle, D. R.; Stamler, J. S. (1997) Neurotoxicity associated with dual actions of homocysteine at the *N*-methyl-D-aspartate receptor. Proc. Natl. Acad. Sci. U. S. A. 94: 5923-5928.
Liu, Y.; Fechter, L. D. (1995) MK-801 protects against carbon monoxide-induced hearing loss. Toxicol. Appl. Pharmacol. 132: 196-202.
Lizasoain, I.; Moro, M. A.; Knowles, R. G.; Darley-Usmar, V.; Moncada, S. (1996) Nitric oxide and peroxynitrate exert distinct effects on mitochondrial respiration which are differentially blocked by glutathione or glucose. Biochem. J. 314: 877-880.
Longo, L. D.; Hill, E. P. (1977) Carbon monoxide uptake and elimination in fetal and maternal sheep. Am. J. Physiol. 232: H324-H330.
Ludbrook, G. L.; Helps, S. C.; Gorman, D. F.; Reilly, P. L.; North, J. B.; Grant, C. (1992) The relative effects of hypoxic hypoxia and carbon monoxide on brain function in rabbits. Toxicology 75: 71-80.
Lundh, B.; Cavallin-Ståhl, E.; Mercke, C. (1975) Nicotinic acid and the endogenous production of carbon monoxide. Acta Med. Scand. 197: 173-176.
Luomanmäki, K.; Coburn, R. F. (1969) Effects of metabolism and distribution of carbon monoxide on blood and body stores. Am. J. Physiol. 217: 354-363.
Luperchio, S.; Tamir, S.; Tannenbaum, S. R. (1996) NO-induced oxidative stress and glutathione metabolism in rodent and human cells. Free Radical Biol. Med. 21: 513-519.
Lynch, S. R.; Moede, A. L. (1972) Variation in the rate of endogenous carbon monoxide production in normal human beings. J. Lab. Clin. Med. 79: 85-95.
MacMillan, V. (1975) Regional cerebral blood flow of the rat in acute carbon monoxide intoxication. Can. J. Physiol. Pharmacol. 53: 644-650.
Maines, M. D. (1988) Heme oxygenase: function, multiplicity, regulatory mechanisms, and clinical applications. FASEB J. 2: 2557-2568.
Maines, M. D.; Mark, J. A.; Ewing, J. F. (1993) Heme oxygenase, a likely regulator of cGMP production in the brain: induction *in vivo* of HO-1 compensates for depression in NO synthase activity. Mol. Cell. Neurosci. 4: 398-405.
Manno, M.; Rugge, M.; Cocheo, V. (1992) Double fatal inhalation of dichloromethane. Hum. Exp. Toxicol. 11: 540-545.
Marks, G. S. (1994) Heme oxygenase: the physiological role of one of its metabolites, carbon monoxide and interactions with zinc protoporphyrin, cobalt protoporphyrin and other metalloporphyrins. Cell. Mol. Biol. (Paris) 40: 863-870.
Marthan, R.; Castaing, Y.; Manier, G.; Guenard, H. (1985) Gas exchange alterations in patients with chronic obstructive lung disease. Chest 87: 470-475.
Matsuoka, M.; Igisu, H.; Tanaka, I.; Hori, H.; Koga, M. (1993) Brain energy metabolites in mice after an acute exposure to carbon monoxide. Res. Commun. Chem. Pathol. Pharmacol. 81: 15-20.
Maurer, F. W. (1941) The effects of carbon monoxide anoxemia on the flow and composition of cervical lymph. Am. J. Physiol. 133: 170-179.
McCartney, M. L. (1990) Sensitivity analysis applied to Coburn-Forster-Kane models of carboxyhemoglobin formation. Am. Ind. Hyg. Assoc. J. 51: 169-177.
McClean, P. A.; Duguid, N. J.; Griffin, P. M.; Newth, C. J. L.; Zamel, N. (1981) Changes in exhaled pulmonary diffusing capacity at rest and exercise in individuals with impaired positional diffusion. Clin. Respir. Physiol. 17: 179-186.
McCoubrey, W. K., Jr.; Huang, T. J.; Maines, M. D. (1997) Isolation and characterization of a cDNA from the rat brain that encodes hemoprotein heme oxygenase-3. Eur. J. Biochem. 247: 725-732.
McGrath, J. J. (1988) Carbon monoxide studies at high altitude. Neurosci. Biobehav. Rev. 12: 311-314.

McGrath, J. J. (1992) Effects of altitude on endogenous carboxyhemoglobin levels. J. Toxicol. Environ. Health 35: 127-133.
McGrath, J. J.; Schreck, R. M.; Lee, P. S. (1993) Carboxyhemoglobin levels in humans: effects of altitude. Inhalation Toxicol. 5: 241-249.
Meilin, S.; Rogatsky, G. G.; Thom, S. R.; Zarchin, N.; Guggenheimer-Furman, E.; Mayevsky, A. (1996) Effects of carbon monoxide on the brain may be mediated by nitric acid. J. Appl. Physiol. 81: 1078-1083.
Mercke, C.; Lundh, B. (1976) Erythrocyte filterability and heme catabolism during the menstrual cycle. Ann. Intern. Med. 85: 322-324.
Mercke, C.; Cavallin-Ståhl, E.; Lundh, B. (1975a) Diurnal variation in endogenous production of carbon monoxide. Acta Med. Scand. 198: 161-164.
Mercke, C.; Cavallin-Ståhl, E.; Lundh, B. (1975b) Carbon monoxide production and reticulocyte count in normal women: effect of contraceptive drugs and smoking. Acta Med. Scand. 198: 155-160.
Mercke, C.; Cavallin-Ståhl, E.; Lundh, B. (1975c) Heme catabolism during short-term treatment with phenobarbital, diazepam and oxazepam. Acta Med. Scand. 198: 149-154.
Messmer, K. (1982) Oxygen transport capacity. In: Brendel, W.; Zink, R. A., eds. High altitude physiology and medicine. New York, NY: Springer-Verlag; pp. 117-122.
Meyer, J.; Prien, T.; Van Aken, H.; Bone, H.-G.; Waurick, R.; Theilmeier, G.; Booke, M. (1998) Arterio-venous carboxyhemoglobin difference suggests carbonmonoxide production by human lungs. Biochem. Biophys. Res. Commun. 244: 230-232.
Moore, E. G.; Gibson, Q. H. (1976) Cooperativity in the dissociation of nitric oxide from hemoglobin. J. Biol. Chem. 251: 2788-2794.
Morita, T.; Perrella, M. A.; Lee, M.-E.; Kourembanas, S. (1995) Smooth muscle cell-derived carbon monoxide is a regulator of vascular cGMP. Proc. Natl. Acad. Sci. U. S. A. 92: 1475-1479.
Motterlini, R.; Foresti, R.; Intaglietta, M.; Winslow, R. M. (1996) NO-mediated activation of heme oxygenase: endogenous cytoprotection against oxidative stress to endothelium. Am. J. Physiol. 270: H107-H114.
Muller, K. E.; Barton, C. N. (1987) A nonlinear version of the Coburn, Forster and Kane model of blood carboxyhemoglobin. Atmos. Environ. 21: 1963-1967.
Murphy, T. H.; Miyamoto, M.; Sastre, A.; Schnaar, R. L.; Coyle, J. T. (1989) Glutamate toxicity in a neuronal cell line involves inhibition of cystine transport leading to oxidative stress. Neuron 2: 1547-1558.
Nabeshima, T.; Yoshida, S.; Morinaka, H.; Kameyama, T.; Thurkauf, A.; Rice, K. C.; Jacobson, A. E.; Monn, J. A.; Cho, A. K. (1990) MK-801 ameliorates delayed amnesia, but potentiates acute amnesia induced by CO. Neurosci. Lett. 108: 321-327.
Nabeshima, T.; Katoh, A.; Ishimaru, H.; Yoneda, Y.; Ogita, K.; Murase, K.; Ohtsuka, H.; Inari, K.; Fukuta, T.; Kameyama, T. (1991) Carbon monoxide-induced delayed amnesia, delayed neuronal death and change in acetylcholine concentration in mice. J. Pharmacol. Exp. Ther. 256: 378-384.
Nathanson, J. A.; Scavone, C.; Scanlon, C.; McKee, M. (1995) The cellular Na^+ pump as a site of action for carbon monoxide and glutamate: a mechanism for long-term modulation of cellular activity. Neuron 14: 781-794.
Neas, L. M.; Schwartz, J. (1996) The determinants of pulmonary diffusing capacity in a national sample of U.S. adults. Am. J. Respir. Crit. Care Med. 153: 656-664.
Newby, M. B.; Roberts, R. J.; Bhatnagar, R. K. (1978) Carbon monoxide- and hypoxia-induced effects on catecholamines in the mature and developing rat brain. J. Pharmacol. Exp. Ther. 206: 61-68.
Niden, A. H.; Schulz, H. (1965) The ultrastructural effects of carbon monoxide inhalation on the rat lung. Virchows Arch. Pathol. Anat. Physiol. 339: 283-292.
Oka, A.; Belliveau, M. J.; Rosenberg, P. A.; Volpe, J. J. (1993) Vulnerability of oligodendroglia to glutamate: pharmacology, mechanisms, and prevention. J. Neurosci. 13: 1441-1453.
Okeda, R.; Funata, N.; Takano, T.; Miyazaki, Y.; Higashino, F.; Yokoyama, K.; Manabe, M. (1981) The pathogenesis of carbon monoxide encephalopathy in the acute phase—physiological and morphological correlation. Acta Neuropathol. 54: 1-10.
Ott, W. R.; Mage, D. T. (1978) Interpreting urban carbon monoxide concentrations by means of a computerized blood COHb model. J. Air Pollut. Control Assoc. 28: 911-916.
Pace, N.; Strajman, E.; Walker, E. L. (1950) Acceleration of carbon monoxide elimination in man by high pressure oxygen. Science (Washington, DC) 111: 652-654.
Pankow, D. (1996) Carbon monoxide formation due to metabolism of xenobiotics. In: Penney, D. G., ed. Carbon monoxide. Boca Raton, FL: CRC Press; pp. 25-43.
Pannen, B. H.; Bauer, M. (1998) Differential regulation of hepatic arterial and portal venous vascular resistance by nitric oxide and carbon monoxide in rats. Life Sci. 62: 2025-2033.
Parving, H.-H.; Ohlsson, K.; Buchardt Hansen, H. J.; Rörth, M. (1972) Effect of carbon monoxide exposure on capillary permeability to albumin and α_2-macroglobulin. Scand. J. Clin. Lab. Invest. 29: 381-388.
Pellegrini-Giampietro, D. E.; Cherici, G.; Alesiani, M.; Carla, V.; Moroni, F. (1990) Excitatory amino acid release and free radical formation may cooperate in the genesis of ischemia-induced neuronal damage. J. Neurosci. 10: 1035-1941.

Penn, A.; Currie, J.; Snyder, C. (1992) Inhalation of carbon monoxide does not accelerate arteriosclerosis in cockerels. Eur. J. Pharmacol. 228: 155-164.

Penney, D. G.; Davidson, S. B.; Gargulinski, R. B.; Caldwell-Ayre, T. M. (1988) Heart and lung hypertrophy, changes in blood volume, hematocrit and plasma renin activity in rats chronically exposed to increasing carbon monoxide concentrations. J. Appl. Toxicol. 8: 171-178.

Peters, T.; Jürgens, K. D.; Gunther-Jürgens, G.; Gros, G. (1994) Determination of myoglobin-diffusivity in intact skeletal muscle fibers: an improved microscope-photometrical approach. In: Vaupel, P.; Zander R.; Bruley, D. F., eds. Oxygen transport to tissue XV. Proceedings of the twentieth annual meeting of the International Society on Oxygen Transport to Tissue; August 1992; Mainz, Germany. New York, NY: Plenum Press; pp. 677-683. (Advances in experimental medicine and biology: v. 345).

Peterson, J. E.; Stewart, R. D. (1970) Absorption and elimination of carbon monoxide by inactive young men. Arch. Environ. Health 21: 165-171.

Peterson, J. E.; Stewart, R. D. (1975) Predicting the carboxyhemoglobin levels resulting from carbon monoxide exposures. J. Appl. Physiol. 39: 633-638.

Piantadosi, C. A.; Tatro, L.; Zhang, J. (1995) Hydroxyl radical production in the brain after CO hypoxia in rats. Free Radical Biol. Med. 18: 603-609.

Piantadosi, C. A.; Zhang, J.; Demchenko, I. T. (1997a) Production of hydroxyl radical in the hippocampus after CO hypoxia or hypoxic hypoxia in the rat. Free Radical Biol. Med. 22: 725-732.

Piantadosi, C. A.; Zhang, J.; Levin, E. D.; Folz, R. J.; Schmechel, D. E. (1997b) Apoptosis and delayed neuronal damage after carbon monoxide poisoning in the rat. Exp. Neurol. 147: 103-114.

Poderoso, J. J.; Cerreras, M. C.; Lisdero, C.; Riobó, N.; Schöpfer, F.; Boveris, A. (1996) Nitric oxide inhibits electron transfer and increases superoxide radical production in rat heart mitochondria and submitochondrial particles. Arch. Biochem. Biophys. 328: 85-92.

Robinson, N. B.; Barie, P. S.; Halebian, P. H.; Shires, G. T. (1985) Distribution of ventilation and perfusion following acute carbon monoxide poisoning. In: 41st annual forum on fundamental surgical problems held at the 71st annual clinical congress of the American College of Surgeons; October; Chicago, IL. Surg. Forum 36: 115-118.

Rodgers, P. A.; Vreman, H. J.; Dennery, P. A.; Stevenson, D. K. (1994) Sources of carbon monoxide (CO) in biological systems and applications of CO detection technologies. Semin. Perinatol. 18: 2-10.

Rodkey, F. L.; O'Neal, J. D.; Collison, H. A. (1969) Oxygen and carbon monoxide equilibria of human adult hemoglobin at atmospheric and elevated pressure. Blood 33: 57-65.

Roughton, F. J. W. (1970) The equilibrium of carbon monoxide with human hemoglobin in whole blood. In: Coburn, R. F., ed. Biological effects of carbon monoxide. Ann. N. Y. Acad. Sci. 174: 177-188.

Saltzman, B. E.; Fox, S. H. (1986) Biological significance of fluctuating concentrations of carbon monoxide. Environ. Sci. Technol. 20: 916-923.

Schoenfisch, W. H.; Hoop, K. A.; Struelens, B. S. (1980) Carbon monoxide absorption through the oral and nasal mucosae of cynomolgus monkeys. Arch. Environ. Health 35: 152-154.

Seki, T.; Naruse, M.; Naruse, K.; Yoshimoto, T.; Tanabe, A.; Imaki, T.; Hagiwara, H.; Hirose, S.; Demura, H. (1997) Interrelation between nitric oxide synthase and heme oxygenase in rat endothelial cells. Eur. J. Pharmacol. 331: 87-91.

Selvakumar, S.; Sharan, M.; Singh, M. P. (1992) Mathematical model for the exchange of gases in the lungs with special reference to carbon monoxide. Med. Biol. Eng. Comput. 30: 525-532.

Selvakumar, S.; Sharan, M.; Singh, M. P. (1993) A mathematical model for the elimination of carbon monoxide in humans. J. Theor. Biol. 162: 321-336.

Sharan, M.; Selvakumar, S.; Singh, M. P. (1990) Mathematical model for the computation of alveolar partial pressure of carbon monoxide. Int. J. Biomed. Comput. 26: 135-147.

Shimazu, T.; Ikeuchi, H.; Hubbard, G. B.; Langlinais, P. C.; Mason, A. D., Jr.; Pruitt, B. A., Jr. (1990) Smoke inhalation injury and the effect of carbon monoxide in the sheep model. J. Trauma 30: 170-175.

Siggaard-Andersen, J.; Bonde Petersen, F.; Hansen, T. I.; Mellemgaard, K. (1968) Plasma volume and vascular permeability during hypoxia and carbon monoxide exposure. Scand. J. Clin. Lab. Invest. Suppl. 103: 39-48.

Singh, J.; Moore-Cheatum, L. (1993) Gestational protein deficiency enhances fetotoxicity of carbon monoxide. In: Keen, C. L.; Bendich, A.; Willhite, C. C., eds. Maternal nutrition and pregnancy outcome. Ann. N. Y. Acad. Sci. 678: 366-368.

Singh, M. P.; Sharan, M.; Selvakumar, S. (1991) A mathematical model for the computation of carboxyhaemoglobin in human blood as a function of exposure time. Philos. Trans. R. Soc. Lond. B 334: 135-147.

Singh, J.; Smith, C. B.; Moore-Cheatum, L. (1992) Additivity of protein deficiency and carbon monoxide on placental carboxyhemoglobin in mice. Am. J. Obstet. Gynecol. 167: 843-846.

Singh, J.; Aggison, L., Jr.; Moore-Cheatum, L. (1993) Teratogenicity and developmental toxicity of carbon monoxide in protein-deficient mice. Teratology 48: 149-159.

Singleton, G. J.; Olsen, C. R.; Smith, R. L. (1972) Correction for mechanical dead space in the calculation of physiological dead space. J. Clin. Invest. 51: 2768-2772.

Smith, M. V. (1990) Comparing solutions to the linear and nonlinear CFK equations for predicting COHb formation. Math. Biosci. 99: 251-263.
Smith, M. V.; Hazucha, M. J.; Benignus, V. A.; Bromberg, P. A. (1994) Effect of regional circulation patterns on observed HbCO levels. J. Appl. Physiol. 77: 1659-1665.
Sokal, J. A.; Majka, J.; Palus, J. (1984) The content of carbon monoxide in the tissues of rats intoxicated with carbon monoxide in various conditions of acute exposure. Arch. Toxicol. 56: 106-108.
Sokal, J.; Majka, J.; Palus, J. (1986) Effect of work load on the content of carboxymyoglobin in the heart and skeletal muscles of rats exposed to carbon monoxide. J. Hyg. Epidemiol. Microbiol. Immunol. 30: 57-62.
Solanki, D. L.; McCurdy, P. R.; Cuttitta, F. F.; Schechter, G. P. (1988) Hemolysis in sickle cell disease as measured by endogenous carbon monoxide production: a preliminary report. Am. J. Clin. Pathol. 89: 221-225.
Song, S.-Y.; Okeda, R.; Funata, N.; Higashino, F. (1983) An experimental study of the pathogenesis of the selective lesion of the globus pallidus in acute carbon monoxide poisoning in cats: with special reference to the chronologic change in the cerebral local blood flow. Acta Neuropathol. 61: 232-238.
Stewart, R. D.; Peterson, J. E.; Baretta, E. D.; Bachand, R. T.; Hosko, M. J.; Herrmann, A. A. (1970) Experimental human exposure to carbon monoxide. Arch. Environ. Health 21: 154-164.
Stewart, R. D.; Peterson, J. E.; Fisher, T. N.; Hosko, M. J.; Baretta, E. D.; Dodd, H. C.; Herrmann, A. A. (1973) Experimental human exposure to high concentrations of carbon monoxide. Arch. Environ. Health 26: 1-7.
Stokes, D. L.; MacIntyre, N. R.; Nadel, J. A. (1981) Nonlinear increases in diffusing capacity during exercise by seated and supine subjects. J. Appl. Physiol.: Respir. Environ. Exercise Physiol. 51: 858-863.
Stone, J. R.; Marletta, M. A. (1994) Soluble guanylate cyclase from bovine lung: activation with nitric oxide and carbon monoxide and spectral characterization of the ferrous and ferric states. Biochemistry 33: 5636-5640.
Stork, R. L.; Bredle, D. L.; Chapler, C. K.; Cain, S. M. (1988) Regional hemodynamic responses to hypoxia in polycythemic dogs. J. Appl. Physiol. 65: 2069-2074.
Sugi, K.; Theissen, J. L.; Traber, L. D.; Herndon, D. N.; Traber, D. L. (1990) Impact of carbon monoxide on cardiopulmonary dysfunction after smoke inhalation injury. Circ. Res. 66: 69-75.
Tamayo, L.; López-López, J. R.; Castañeda, J.; González, C. (1997) Carbon monoxide inhibits hypoxic pulmonary vasoconstriction in rats by a cGMP-independent mechanism. Pfluegers Arch. 434: 698-704.
Thom, S. R. (1990) Carbon monoxide-mediated brain lipid peroxidation in the rat. J. Appl. Physiol. 68: 997-1003.
Thom, S. R. (1992) Dehydrogenase conversion to oxidase and lipid peroxidation in brain after carbon monoxide poisoning. J. Appl. Physiol. 73: 1584-1589.
Thom, S. R. (1993) Leukocytes in carbon monoxide-mediated brain oxidative injury. Toxicol. Appl. Pharmacol. 123: 234-247.
Thom, S. R.; Ischiropoulos, H. (1997) Mechanism of oxidative stress from low levels of carbon monoxide. Cambridge, MA: Health Effects Institute; research report no. 80.
Thom, S. R.; Ohnishi, S. T.; Ischiropoulos, H. (1994) Nitric oxide released by platelets inhibits neutrophil B_2 integrin function following acute carbon monoxide poisoning. Toxicol. Appl. Pharmacol. 128: 105-110.
Thom, S. R.; Xu, Y. A.; Ischiropoulos, H. (1997) Vascular endothelial cells generate peroxynitrite in response to carbon monoxide exposure. Chem. Res. Toxicol. 10: 1023-1031.
Thom, S. R.; Garner, S.; Fisher, D.; Ischiropoulos, H. (1998) Vascular nitrosative stress from CO exposure. In: Program and abstracts [of the] Undersea and Hyperbaric Medical Society annual scientific meeting: pre- and post-courses; May; Seattle, WA. Undersea Hyperbaric Med. 25(suppl.): 47.
Thom, S. R.; Ohnishi, S. T.; Fisher, D.; Xu, Y. A.; Ischiropoulos, H. (1999a) Pulmonary vascular stress from carbon monoxide. Toxicol. Appl. Pharmacol. 154: 12-19.
Thom, S. R.; Fisher, D.; Xu, Y. A.; Garner, S.; Ischiropoulos, H. (1999b) Role of nitric oxide-derived oxidants in vascular injury from carbon monoxide in the rat. Am. J. Physiol. 276: H984-H992.
Thomsen, H. K. (1974) Carbon monoxide-induced atherosclerosis in primates: an electron-microscopic study on the coronary arteries of *Macaca irus* monkeys. Atherosclerosis 20: 233-240.
Tikuisis, P. (1996) Modeling the uptake and elimination of carbon monoxide. In: Penney, D. G., ed. Carbon monoxide. Boca Raton, FL: CRC Press; pp. 45-67.
Tikuisis, P.; Buick, F.; Kane, D. M. (1987a) Percent carboxyhemoglobin in resting humans exposed repeatedly to 1,500 and 7,500 ppm CO. J. Appl. Physiol. 63: 820-827.
Tikuisis, P.; Madill, H. D.; Gill, B. J.; Lewis, W. F.; Cox, K. M.; Kane, D. M. (1987b) A critical analysis of the use of the CFK equation in predicting COHb formation. Am. Ind. Hyg. Assoc. J. 48: 208-213.
Tikuisis, P.; Kane, D. M.; McLellan, T. M.; Buick, F.; Fairburn, S. M. (1992) Rate of formation of carboxyhemoglobin in exercising humans exposed to carbon monoxide. J. Appl. Physiol. 72: 1311-1319.
Trischmann, U.; Klöckner, U.; Isenberg, G.; Utz, J.; Ullrich, V. (1991) Carbon monoxide inhibits depolarization-induced Ca rise and increases cyclic GMP in visceral smooth muscle cells. Biochem. Pharmacol. 41: 237-241.
Turner, D. M.; Lee, P. N.; Roe, F. J. C.; Gough, K. J. (1979) Atherogenesis in the White Carneau pigeon: further studies of the role of carbon monoxide and dietary cholesterol. Atherosclerosis 34: 407-417.

Tyuma, I.; Ueda, Y.; Imaizumi, K.; Kosaka, H. (1981) Prediction of the carbonmonoxyhemoglobin levels during and after carbon monoxide exposures in various animal species. Jpn. J. Physiol. 31: 131-143.

U.S. Environmental Protection Agency. (1978) Altitude as a factor in air pollution. Research Triangle Park, NC: Office of Research and Development, Environmental Criteria and Assessment Office; report no. EPA 600/9-78-015.

U.S. Environmental Protection Agency. (1991) Air quality criteria for carbon monoxide. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/8-90/045F.

U.S. Environmental Protection Agency. (1992) Review of the national ambient air quality standards for carbon monoxide: 1992 reassessment of scientific and technical information. OAQPS staff paper. Research Triangle Park, NC: Office of Air Quality Planning and Standards; report no. EPA-452/R-92-004.

Utz, J.; Ullrich, V. (1991) Carbon monoxide relaxes ileal smooth muscle through activation of guanylate cyclase. Biochem. Pharmacol. 41: 1195-1201.

Venkatram, A.; Louch, R. (1979) Evaluation of CO air quality criteria using a COHb model. Atmos. Environ. 13: 869-872.

Wagner, J. A.; Horvath, S. M.; Dahms, T. E. (1975) Carbon monoxide elimination. Respir. Physiol. 23: 41-47.

Wang, R. (1998) Resurgence of carbon monoxide: an endogenous gaseous vasorelaxing factor. Can. J. Physiol. Pharmacol. 76: 1-15.

Wang, R.; Wu, L.; Wang, Z. (1997a) The direct effect of carbon monoxide on K_{Ca} channels in vascular smooth muscle cells. Pfluegers Arch. 434: 285-291.

Wang, R.; Wang, Z.; Wu, L. (1997b) Carbon monoxide-induced vasorelaxation and the underlying mechanisms. Br. J. Pharmacol. 121: 927-934.

Webster, W. S.; Clarkson, T. B.; Lofland, H. B. (1968) Carbon monoxide-aggravated atherosclerosis in the squirrel monkey. Exp. Mol. Pathol. 13: 36-50.

Werner, B.; Lindahl, J. (1980) Endogenous carbon monoxide production after bicycle exercise in healthy subjects and in patients with hereditary spherocytosis. Scand. J. Clin. Lab. Invest. 40: 319-324.

West, J. B. (1990a) Ventilation/blood flow and gas exchange. 5th ed. Oxford, United Kingdom: Blackwell Scientific Publications.

West, J. B. (1990b) Respiratory physiology—the essentials. 4th ed. Baltimore, MD: Williams & Wilkins.

Wittenberg, B. A.; Wittenberg, J. B. (1993) Effects of carbon monoxide on isolated heart muscle cells. Cambridge, MA: Health Effects Institute; research report no. 62.

Woehlck, H. J.; Dunning, M. B., III; Kulier, A. H.; Sasse, F. J.; Nithipataikom, K.; Henry, D. W. (1997a) The response of anesthetic agent monitors to trifluoromethane warns of the presence of carbon monoxide from anesthetic breakdown. J. Clin. Monit. 13: 149-155.

Woehlck, H. J.; Dunning, M., III; Connolly, L. A. (1997b) Reduction in the incidence of carbon monoxide exposures in humans undergoing general anesthesia. Anesthesiology 87: 228-234.

Wyman, J.; Bishop, G.; Richey, B.; Spokane, R.; Gill, S. (1982) Examination of Haldane's first law for the partition of CO and O_2 to hemoglobin A_0. Biopolymers 21: 1735-1747.

Yamaya, M.; Sekizawa, K.; Ishizuka, S.; Monma, M.; Mizuta, K.; Sasaki, H. (1998) Increased carbon monoxide in exhaled air of subjects with upper respiratory tract infections. Am. J. Respir. Crit. Care Med. 158: 311-314.

Yoneda, I.; Watanabe, Y. (1997) Comparisons of altitude tolerance and hypoxia symptoms between nonsmokers and habitual smokers. Aviat. Space Environ. Med. 68: 807-811.

Zayasu, K.; Sekizawa, K.; Okinaga, S.; Yamaya, M.; Ohrui, T.; Sasaki, H. (1997) Increased carbon monoxide in exhaled air of asthmatic patients. Am. J. Respir. Crit. Care Med. 156: 1140-1143.

Zhu, N.; Weiss, H. R. (1994) Effect of hypoxic and carbon monoxide-induced hypoxia on regional myocardial segment work and O_2 consumption. Res. Exp. Med. 194: 97-107.

CHAPTER 6

Health Effects of Exposure to Ambient Carbon Monoxide

6.1 Introduction

This chapter assesses the current understanding of health effects that may occur in individuals breathing carbon monoxide (CO) in ambient air. Concerns about the potential health effects of exposure to 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. Experimentally derived knowledge of CO health effects has been augmented in recent years by findings from a small, but growing, body of community epidemiology observational studies of human populations exposed to CO in ambient air. Additional 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 often used during experimental exposure and consequent levels of carboxyhemoglobin (COHb) saturation are much higher than typical of ambient human exposures. 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 is made in this chapter to compare CO health effect levels found in laboratory animal and human controlled-exposure studies. Epidemiologic studies of ambient CO exposure effects on human populations also are assessed in this chapter, and their reported are results considered in light of experimental study findings.

The next section of this chapter (Section 6.2) emphasizes CO effects in humans, especially cardiovascular effects of CO. The section begins with a discussion of epidemiologic studies (Section 6.2.1) because of their potential importance in assessing community health effects of ambient CO exposure. Section 6.2.1 emphasizes studies of ambient CO and heart disease exacerbation because short-term ambient CO concentrations have been associated more frequently with such exacerbation than with other health-related endpoints. For purposes of continuity in the epidemiologic discussion, Section 6.2.1 also addresses studies that have evaluated ambient CO in relation to health indices other than heart disease exacerbation, including studies of daily mortality, incidence of low birth weight, and daily frequency of respiratory illness.

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 the major scientific basis for U.S. Environmental Protection Agency (EPA) review of the levels and adequacy of the National Ambient Air Quality Standards (NAAQS) for CO. Although the scientific data 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 studies of neurobehavioral effects, which had earlier provided the scientific basis for the first CO NAAQS. Subsequent assessments of the neurobehavioral literature, however, have raised questions about both the methods and results of the early studies. Articles published since the last assessment in 1991 have been mostly reviews that attempt to explain the equivocal results found at low COHb levels and to provide a physiological basis for behavioral effects. The section on neurobehavioral effects (Section 6.3) illustrates 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 predominantly from experimental laboratory studies on 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, but none of the newly published studies draw into question the conclusions drawn from the previous 1991 assessment of these topics. Finally, a summary section (Section 6.9) provides a concise review of the key human health effects most clearly associated with exposure to ambient CO.

It should be noted that a review of the health effects literature on CO since the last assessment was published in 1991 finds many new published articles on CO poisoning, possibly reflecting increased 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 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 and the following chapter to present a snapshot of the full range of CO toxicity and to provide public health information about potential effects of accidental exposure to CO, particularly those exposures occurring indoors.

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 the 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 2 million have rheumatic fever or heart disease. Because the numbers of affected people are so high, even relatively small percentage increases in cardiovascular mortality or morbidity in the population could have a large impact on both public health and health care costs.

Carbon monoxide is notable among air pollutants because it is especially harmful in individuals with impaired cardiovascular systems. Persons with a normal cardiovascular system can tolerate substantial concentrations of CO, if they vasodilate in response to the hypoxemia produced by CO. In contrast, individuals unable to vasodilate in response to CO exposure may show evidence of ischemia at low concentrations of COHb. For this reason, experiments on healthy animals are unlikely to show effects at low CO concentrations of exposure. In the following discussion, the effects of CO on potentially susceptible population groups are explored through epidemiologic and controlled laboratory studies (for further discussion of subpopulations at risk, see Chapter 7).

6.2.1 Epidemiologic Studies of Cardiovascular and Other Disorders

6.2.1.1 Introduction

In recent years, many epidemiologic studies have shown associations of short-term ambient air pollution exposure with mortality, exacerbation of preexisting illness, and physiologic changes. The epidemiologic database regarding short-term ambient air pollution exposure is growing rapidly, and its interpretation is changing over time. As recently as the mid-1990s, many epidemiologic studies had reported associations of mortality and exacerbation of preexisting disease with ambient levels of particulate matter (PM), but relatively few had investigated or reported such associations with gaseous pollutants, including CO. Since then, however, investigators have given more thorough consideration to PM and gaseous pollutants and have frequently observed positive, statistically significant associations of harmful effects with both. Thus, although associations of PM with harmful effects continue to be observed, the roles of gaseous pollutants appear to be stronger than in previous evaluations.

Another important recent change relates to the biological plausibility of observed epidemiologic associations of ambient air pollution with harmful health outcomes. A few years ago, it was frequently argued that associations of low-level ambient air pollution with harmful health outcomes were biologically implausible. Now, with a considerable amount of new experimental evidence in hand, and after much new and sharpened thought on this issue, it is possible to hypothesize ways by which ambient exposure to one or multiple air pollutants could plausibly be involved in complex chains of biological events leading to harmful health effects in the most sensitive population groups.

In epidemiologic studies of ambient air pollution, small positive estimates of air pollutant health effects have been observed quite frequently, often being statistically significant at $\alpha = 0.05$.[1] If ambient air pollution actually promotes or produces harmful health effects, relatively small effect estimates would generally be expected on biological and epidemiologic grounds. Also, the magnitudes and significance levels of observed air pollution-related effects estimates have varied somewhat from place to place. This, too, would be expected if the observed epidemiologic associations reflect actual effects, because populations differ in characteristics that could affect susceptibility to air pollution health effects. These characteristics include demographic and socioeconomic factors, underlying health status, indoor-outdoor activities, diet, medical care systems and access to them, and exposure to risk factors other than ambient air pollution, such as extreme weather conditions. Thus, although it has been argued that epidemiologic studies are trustworthy only if they show relatively large effects estimates (e.g., large relative risks), if observed small effects estimates for ambient air pollution are sufficiently consistent and coherent across epidemiologic studies and comport well with plausibility considerations based on other findings, then the small effects estimates gain more credibility as likely reflecting underlying air pollution-health effects quantitative relationships. It should also be borne in mind that, in any large population exposed to ambient air pollution, even a small relative risk for a prevalent health disorder could calculate to a substantial public health burden attributable to air pollution exposure.

At the same time, important biological, epidemiologic, and statistical uncertainties remain in the current epidemiologic database for ambient CO and other air pollutants. Biologically and epidemiologically, it has not been confirmed that the magnitudes of observed statistical health effects

[1]The Greek letter alpha (α) is the probability of type I error that the investigator is willing to accept in judging whether a finding is statistically significant. Type I error (alpha error) is the error of rejecting a null hypothesis that is actually true. An alpha level of $\alpha = 0.05$ is often chosen in judging statistical significance. The *p value* is the probability of obtaining a test statistic as large or larger than the one actually observed, if the null hypothesis is true. (Examples of test statistics include the z-statistic, t-statistic, F-statistic, and chi-square statistic.) Evidence against the null hypothesis increases as the p value decreases. When an alpha level of $\alpha = 0.05$ is chosen, the finding is judged to be statistically significant if $p \leq 0.05$. In this chapter, the term "statistically significant" assumes an alpha level of $\alpha = 0.05$ ($p \leq 0.05$), unless stated otherwise.

estimates for ambient CO are quantitatively commensurate with actual underlying population susceptibility to CO exposure. Also, it has not been confirmed that the observed spatial variation in air pollution effects estimates reflects actual cross-population differences in susceptibility.

The ambient atmosphere contains numerous air pollutants, and there is increasing realization that health effects associated statistically with any single pollutant actually may be mediated by multiple components of the complex ambient mix. Specific attribution of effects to any single pollutant therefore may convey an overly simplistic notion of biological reality. Carbon monoxide is one of many air pollutants generated by combustion sources, including mobile sources. These pollutants include CO, PM, and nitrogen oxides, which have been considered in epidemiologic studies to date. These pollutants also include numerous volatile or semivolatile organic compounds, which have not yet been considered systematically in relation to the noncancer health outcomes usually associated with exposure to criteria air pollutants. In available epidemiologic studies, harmful health outcomes frequently are associated with multiple combustion-related or mobile-source-related air pollutants. Many investigators have raised the possibility that CO may be a surrogate or marker for a larger subset of the overall ambient air pollution mix, and some investigators have argued that ambient-level CO may be a biologically passive surrogate and that statistical associations of ambient CO with health effects may actually reflect effects of pollutants other than CO. However, most investigators have reserved judgment on this issue, and several have emphasized the need for further research on CO.

The health effects of long-term exposure to CO and other air pollutants have received little attention in epidemiologic studies and are not well understood as yet. Health effects of long-term exposure at present-day ambient pollutant levels, which are generally lower than past levels, are especially uncertain. Also, it is not known whether long-term exposure to ambient CO plays a role in the induction (incidence) of new cases of illness. Further research on long-term health effects of exposure to ambient CO and other pollutants is needed.

Important statistical issues need to be considered in critically assessing the available epidemiologic database for CO and other air pollutants. Many of these are especially pertinent to daily time series studies, which are the majority of the epidemiologic studies available for ambient CO and which form a large part of the epidemiologic database for other criteria air pollutants as well. Statistical uncertainties, coupled with existing biological and epidemiologic uncertainties, can pose difficulties in judging the quantitative accuracy of pollutant effect estimates themselves and, perhaps in some cases, their qualitative validity.

Key statistical issues that need to be considered include the following.

(1) *Sensitivity of effects estimates to different choices of statistical models/model specifications.* Effects estimates for CO and other air pollutants can vary, depending on different choices of statistical models or specifications for important model parameters. For example, as the following sections show, effects estimates for CO or other pollutants at times differ with different choices of metric for the same pollutant, with different choices of modeled covariates (independent variables), with different lag or moving-average structures for air pollutants and covariates, with different choices of time spans in nonparametric smoothing procedures, and with different choices of adjustment for autocorrelation and overdispersion in the data. Also, in parametric models, different choices of functional forms of modeled concentration-response relationships can lead to different interpretations of results. Furthermore, effects estimates for CO and other pollutants in single-pollutant models frequently differ from those derived from in multi-pollutant models. It is increasingly clear that ambient air pollution health effects may arise from exposure to multiple pollutants, and that single-pollutant models do not necessarily describe adequately the effects of ambient CO and other pollutants. Recent increased attention to multi-pollutant models is, therefore, highly appropriate. Even so, time series of ambient CO levels often are highly correlated with time series levels of other pollutants, such as PM. Thus, effects estimates for different pollutants remain subject to confounding in multi-pollutant models. Scientific consensus as to optimal modeling strategies for time series air pollution studies has not yet

been achieved. Application of nonparametric techniques, which generate exposure-response surfaces for more than one pollutant at a time, may well prove useful in future analyses. Nevertheless, however, much progress has been made in evaluating issues related to uncertainties associated with model selection and alternative specifications for important model parameters, as illustrated by U.S. EPA (1996) evaluations of time-series analyses of ambient PM exposure effects.

As mentioned above, small health effects estimates generally have been observed for ambient air pollutants, and small effects would be expected on biological and epidemiologic grounds. At the same time, because the effects estimates are small, they can be sensitive to different model specifications. These can calculate to substantial differences in estimated numbers of cases of illness or mortality attributable to ambient air pollution exposure. On balance, there remains uncertainty as to the proper choice of effects estimates to employ in estimating risks of exposure to ambient CO and other air pollutants in the human population.

(2) *Measurement error in ambient CO metrics*. In this document, Appendix 3-A and Sections 4.2.2 and 4.2.3 indicate that there is substantial spatial variability in ambient CO concentrations, and that fixed-site CO measurements may not adequately index widely varying actual population exposures to ambient CO. Current evidence also suggests that ambient CO is more spatially heterogeneous than other criteria pollutants assessed in epidemiologic studies to date (e.g., $PM_{2.5}$, PM_{10}, ozone [O_3]). In many instances, misclassification of exposure leads to downward bias in statistical effects estimates. Thus, effects estimates for ambient CO may be biased downward in available epidemiologic studies, and downward bias may be stronger for estimates of CO effects than for estimates of other pollutants' effects. However, this has not been confirmed. Further research is needed to quantify the degree to which fixed-site measurements of ambient CO and other pollutants overestimate or underestimate actual population exposures to these pollutants. This research will require characterization of relationships between fixed-site CO measurements and personal CO exposures over time. It will also require accurate apportionment of total CO exposure into CO exposures of ambient and nonambient origin. Further research also is needed to characterize influences of measurement error on estimates of air pollution effects in statistical models for CO and other ambient pollutants.

(3) *Potential confounding of air pollution and weather effects*. Meteorologic events and ambient air pollutant concentrations may be highly correlated on short time scales, even when longer time trends have been filtered. It is essential to model joint effects of air pollution and weather with great care. Such joint modeling has been conducted only rarely in time series studies of ambient air pollution. To date, simple additive or proportional assumptions generally have been made in modeling health effects of air pollutants and weather. These assumptions are not necessarily fully adequate, largely because health effects estimates for air pollutants are small and subject to large proportional differences with different model specifications. One example of recent efforts to model better possible complex relationships involving combinations of meteorological factors (e.g., temperature, barometric pressure, etc.) and to assess their impacts on air pollutant health effects estimates was the modeling of "synoptic weather pattern" effects in conjunction with ambient PM exposures (as described in U.S. EPA 1996). Application of nonparametric techniques to jointly model CO and meteorologic effects also may prove useful in future CO analyses.

(4) *Insufficient reporting of statistical uncertainty*. In available studies, statistical uncertainty generally has been assessed rather superficially, without formal consideration of the model tuning performed by the investigators. For example, lag times and averaging times for air pollutant metrics are sometimes selected to maximize statistical effects estimates for pollutants. This may, at times, lead to inflated reported effects estimates and, perhaps, unduly narrow confidence intervals for these estimates. In future studies, uncertainty arising from model tuning should be assessed more carefully. In this effort, resampling or simulation procedures, which would recreate the entire model estimation process,

should be considered as a means for evaluating the accuracy and robustness of reported effects estimates.

(5) *Health effects averaged over extended time periods*. None of the available time series studies of ambient CO are capable of assessing the incremental effect of pollutants over extended time periods. For example, current models cannot confidently predict whether reduction in pollution will decrease monthly rates of hospital admissions or mortality, even if they imply a reduction of admissions on days with low pollution. This public-health-related issue cannot be addressed by daily time series analysis, using only admission or mortality counts. In future studies, investigators also could consider time-averaged health effects over, say, 1 or 3 mo, in relation to pollution exposure metrics for the corresponding periods. Consideration of extended time-averaged health effects would tend to allow for detection of more chronic impacts beyond any short-term "harvesting" that might be observed in daily analyses. (In time series studies of air pollution, *harvesting* is a short-term elevation in the frequency of a health outcome during or just after a short period of elevated ambient air pollution, followed quickly by a short-term reduction in frequency of the same outcome below baseline frequency, then by a return to baseline. It has been argued that presence of harvesting would suggest that elevated air pollution exposure hastens occurrence of the health outcome by only a short time, but brings about little or no net increase in occurrence of the outcome. It also has been argued that absence of harvesting would suggest that, without the elevated air pollution exposure, the outcome might have been delayed for a long time or might not have occurred at all.)

To date, short-term fluctuations in ambient CO have been examined in time series studies of daily exacerbations of preexisting cardiovascular disease, mortality, and changes in respiratory illness frequency. Associations have been observed most frequently for short-term ambient CO fluctuations and exacerbation of heart disease (a subcategory of cardiovascular disease), as usually indexed by daily hospital admissions. These associations generally have been stronger during cold weather than during warm weather. These associations are biologically plausible to some degree. In heart disease patients, the coronary arteries usually are narrowed and unable to dilate normally. Increased hypoxic stress resulting from small increases in COHb saturation could conceivably lead to clinically apparent worsening of their illness. Cold temperatures also exacerbate hypoxic effects (e. g., as occurs at high altitude).

If observed associations of ambient CO with heart disease exacerbation prove to be real and specific to CO, they would be of genuine public health concern. In the United States in 1996, there were about 4,239,000 hospital discharges with heart disease as the first-listed diagnosis (Graves and Owings, 1998). Among these, about 2,262,000 (53.4%) were for ischemic heart disease (IHD), 825,000 (19.5%) for myocardial infarction (MI) or heart attack (a subcategory of IHD), 870,000 (20.5%) for congestive heart failure (CHF), and 618,000 (14.6%) for cardiac dysrhythmias. Also, there were 733,361 deaths caused by heart disease (Peters et al., 1998). Even a small percentage reduction in admissions or deaths caused by heart disease would result in a large number of avoided cases.

Even so, fluctuations in ambient CO levels would be expected to produce only very small changes in COHb saturation and only small changes in tissue oxygenation. Thus, the observed associations of ambient CO with heart disease exacerbation remain difficult to rationalize pathophysiologically. Also, such exacerbation has been associated not only with ambient CO, but also with other combustion-related ambient pollutants such as nitrogen dioxide (NO_2) and PM. Thus, the extent to which such exacerbation truly is attributable to ambient CO exposure is not yet clear.

Studies of short-term ambient CO levels and daily mortality have yielded mixed results. Observed associations of ambient CO with mortality are of potential public health concern because associations of ambient CO with heart disease exacerbation have been observed frequently, and because heart disease is the leading cause of death in the United States. For example, in the United States in 1996, 733,361 (31.7%) of all 2,314,690 deaths were caused by heart disease (Peters et al., 1998). Again, however, no firm pathophysiologic basis for reported ambient CO-mortality associations is apparent, and the degree of

correspondence between the reported statistical effects estimates in populations and real effects in individuals remains to be more firmly and plausibly delineated.

Some investigators have observed associations of short-term fluctuations in ambient CO with daily frequency of respiratory illness. In most cases, exacerbation of preexisting respiratory illness has been assessed, although some cases of acute respiratory infection constitute occurrence of new illness, especially in young people. The biological plausibility of these associations is tenuous, because there are as yet no demonstrated mechanisms by which ambient-level CO exposure could produce or promote harmful respiratory effects. Also, in epidemiologic studies to date, associations of ambient CO with respiratory disease frequency have been observed less consistently than with heart disease exacerbation. Nevertheless, the observed associations of ambient CO with respiratory disease frequency are worthy of discussion because they suggest that ambient CO exposure may not be specifically linked just with heart disease.

Two available U.S. studies suggest that subchronic ambient CO exposure averaged over about 3 mo. may be associated with increased incidence of low birth weight. These studies raise concern, because fetal hemoglobin (Hb) binds CO somewhat more strongly than does adult Hb, and because increased COHb saturation would be expected to impair tissue molecular oxygen (O_2) delivery more in the fetus than in the child or the adult (Longo, 1976). At the same time, these studies are not conclusive, and they are subject to potential confounding by unmeasured factors, such as maternal smoking, that are known to influence birth weight. Also, outdoor CO levels may be correlated with indoor levels of CO and other pollutants, which could be higher than outdoor levels, and which were not measured in these studies. Common socioeconomic factors could be associated with both ambient CO levels and such potential confounding variables.

Overall, then, recent epidemiologic studies have tended to increase concern regarding potential harmful effects of present-day ambient CO exposure, especially with respect to heart disease exacerbation, possibly with respect to mortality and low birth weight, and even, conceivably, with respect to increased frequency of respiratory illness. However, more research on the health effects of long- and short-term ambient CO exposure is strongly warranted to more clearly elucidate quantitative health risks ascribable to ambient CO specifically among those pollutants typically found in urban air mixes impacted by combustion processes. This research should assess effects not only of changes in COHb levels and tissue oxygenation, but also of CO dissolved in the blood and of CO in tissues other than blood, and it should assess effects of CO alone and as a component of the complex ambient air pollution mix.

Individual epidemiologic studies that have considered ambient CO are summarized and assessed below. Time series studies of short-term ambient CO are discussed first, in descending order of consistency of findings. Health-related outcomes are discussed in the following order: daily exacerbations of heart disease, daily mortality counts, and daily frequency of respiratory illness. Studies of subchronic ambient CO and reduction of birth weight are discussed after the time series studies.

6.2.1.2 Ambient Carbon Monoxide and Exacerbation of Heart Disease

Recent epidemiologic studies in the United States, Canada, and Europe suggest that short-term variations in ambient CO levels are associated with daily hospital admissions for heart disease. In several studies of such admissions, effects of lagged ambient air pollutant levels have been examined, in addition to effects of air pollutant levels on the same day as the admissions (0-day lag). When averaging times for ambient pollution metrics have been 24 h or shorter (e.g., 24-h average CO or daily maximum hourly CO), modeled effects of CO generally have been strongest with a 0-day lag. When averaging times have been longer than 24 h, CO effects generally have been strongest when the last day of the averaging period is lagged 0 days.

As mentioned above, observed associations of ambient CO with heart disease exacerbation have some biological plausibility and are of potential public health concern. However, these associations should be interpreted cautiously. The average daily 1-h maximum CO concentrations measured by stationary

monitors in the epidemiologic studies generally have been 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 even to measure accurately or, possibly, even to detect reliably. Even 8 h of exposure to 10 ppm CO with light to moderate exercise (ventilation about 20 L/min) would be expected to produce only a 1.0 to 2.0% increase in COHb saturation over the baseline level of about 0.5% COHb. Pathophysiologically, it remains difficult to reconcile such small expected ambient CO-induced changes in COHb saturation with reported increased overt exacerbation of heart disease in the community setting.

Also, epidemiologic studies of ambient CO have relied heavily on pollutant measurements at stationary outdoor monitors. Carbon monoxide levels at these monitors may not be correlated well with personal CO exposures and doses, especially in compromised persons such as cardiac patients, who spend much of their time indoors. Additional information on personal CO exposures and other individual characteristics, such as active and passive smoking, would be highly desirable in future epidemiologic studies of ambient CO. Furthermore, as discussed in Chapter 3, in most U.S. metropolitan areas, there is considerable spatial variation in 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 multi-site averaging of CO levels on statistical health effects estimates are not yet well understood.

The diagnostic category "heart disease" is smaller and more specific than the category "cardiovascular disease," which comprises heart disease and other disorders such as cerebrovascular disease (including stroke), hypertension (high blood pressure), and diseases of the blood vessels. To date, short-term variation in ambient CO levels has been more strongly associated with heart disease exacerbation than exacerbation of other cardiovascular diseases. At the same time, heart disease itself comprises several diagnostic subcategories, such as IHD (including MI, coronary artery atherosclerosis, and angina), heart failure (including CHF), and disturbances of cardiac rhythm (dysrhythmias, arrhythmias). In this document, the terms "ischemic heart disease" (or "IHD"), "coronary artery disease" (or "CAD"), and "coronary heart disease" may be considered interchangeable. The available epidemiologic database is not entirely consistent regarding the specific heart disease subcategories with which ambient CO levels are most strongly associated.

Morris et al. (1995) conducted a time-series analysis of ambient levels of gaseous air pollutants (CO, NO_2, sulfur dioxide [SO_2], and O_3), in relation to 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, 1986 to 1989. (Medicare covers only persons ≥65 years old.) 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 ambient 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. In almost all analyses, CO effects were stronger on the day of admission (0-day lag) than on previous days. In single-pollutant models, the effect of CO was statistically significant in all cities but Houston. In multi-pollutant models, the CO effect was significant in all cities but New York and Milwaukee. In the transition from single-pollutant to multi-pollutant models, effects of CO were more stable and retained statistical significance more frequently than effects of the other pollutants. Figure 2 from Morris et al. (1995), which shows nonparametrically smoothed exposure-response curves for ambient CO levels and CHF admission rates in each city, is reproduced in Figure 6-1. The authors estimated that, each year, approximately 3,250 hospital admissions for CHF could be attributed to the observed association with short-term elevations in ambient CO levels. (Note that the Y-axis in Figure 6-1 does not begin at zero. The exposure-response curves in this figure would appear somewhat less steep if the Y-axis began at zero.)

Schwartz and Morris (1995) examined air pollution and hospital admissions for heart disease (CHF, IHD, and cardiac dysrhythmias) in people aged 65 years and older in the Detroit metropolitan area from

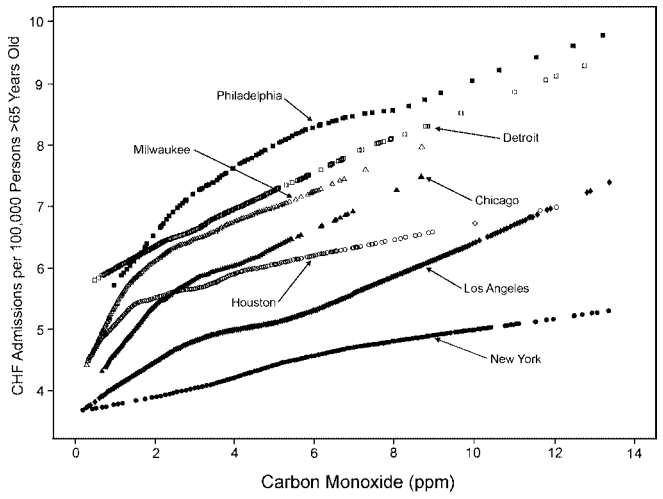

Figure 6-1. Nonparametric smoothing of the association between ambient levels of CO and hospital admissions for CHF among elderly people after adjustment for temperature, month, day of week, and year, 1986 through 1989.
Source: Morris et al. (1995).

1986 through 1989. Air quality data were available for CO, PM_{10}, O_3, and SO_2. For gaseous pollutants and PM_{10}, exposure metrics were the daily maximum 1-h concentration and the 24-h average concentration, respectively. The average of daily maximum 1-h CO concentrations over the whole study period was 2.4 ppm. The overall mean of 24-h average PM_{10} concentrations was 48.0 $\mu g/m^3$. Data were analyzed with Poisson auto-regressive models, with independent variables for temperature, dew point, month, and linear and quadratic time trends. For each pollutant, the "interquartile range" (IQR), i.e., the difference between the 25th and 75th percentiles of the distribution of ambient concentrations during the study period, was calculated. Relative risks for the health outcomes assessed were reported per increment in ambient concentration equal to each pollutant's IQR range.

Daily admissions for IHD were associated with IQR increases of 1.28 ppm for CO (relative risk [RR] = 1.010; 95% confidence interval [CI] = 1.001, 1.018), 32 $\mu g/m^3$ for PM_{10} (RR = 1.018; 95% CI = 1.005, 1.032), 18 ppb for SO_2 (RR = 1.014; 95% CI = 1.003, 1.026). However, both the CO and SO_2 effects lost statistical significance after controlling for PM_{10}, whereas the PM_{10} effect remained significant after controlling for the other pollutants. Daily admissions for congestive heart failure were associated independently and significantly with IQR increases in both CO (RR = 1.022; 95% CI = 1.010, 1.034) and PM_{10} (RR = 1.024; 95% CI = 1.004, 1.044). These results are summarized in Table 6-1. Effects of CO were stronger on the day of admission (0-day lag) than on previous days. No pollutant was found to be a significant risk factor for dysrhythmia admissions.

Table 6-1. Modeled Relative Risks of Interquartile Range Increases in Ambient Pollutant Concentrations for Daily Heart Disease Admissions in Persons ≥65 Years Old, Detroit, MI, 1986 to 1989

	Single-Pollutant Models				Two-Pollutant Models (including PM_{10} and CO or SO_2)[a]		
Disease Category	CO	SO_2	O_3	PM_{10}	CO	PM_{10}	SO_2
Congestive Heart Failure (Table 6)	1.022[b]	1.002	1.022	1.032[b]	1.022[b]	1.024[b]	
Ischemic Heart Disease (Table 4)	1.010[b]	1.014[b]	1.010	1.018[b]	1.006	1.016[b] 1.015[b]	1.009
Dysrhythmias	No Significant Pollutant Effects						

[a]For CHF, no model with PM_{10} and SO_2 was reported.
[b]Statistically significant at $\alpha = 0.05$.

Source: Modified from Schwartz and Morris (1995).

Ambient CO could be a surrogate for general combustion-related or mobile-source air pollution. In some locations, CO is highly correlated with PM during the winter months. The ambient PM_{10} level was associated with heart disease exacerbation in Schwartz and Morris (1995), but was not assessed in Morris et al. (1995). Also, ambient PM concentrations were associated with hospital admissions for both heart failure and IHD in Ontario, Canada (Burnett et al., 1995).

Pantazopoulou et al. (1995) investigated cardiac and respiratory disease exacerbation in the area of Athens, Greece, in relation to short-term ambient air pollution levels during 1988. The health outcomes analyzed were daily outpatient emergency department visits, and daily hospital admissions for cardiac and respiratory causes. Pollutant metrics were daily maximum 8-h moving average CO, daily maximum hourly NO_2, and 24-h average black smoke (BS), each averaged over multiple monitoring stations in the Athens area. Separate analyses were conducted for "winter" (January 1 to March 21 and September 22 to December 31) and "summer" (March 22 to September 21). Mean levels of CO for all available monitoring stations were 4.5 mg/m^3 (3.9 ppm) in winter and 3.4 mg/m^3 (3.0 ppm) in summer. These levels were quite high in comparison to current U.S. levels. Data were analyzed with multiple linear regression, with adjustment for meteorological and chronological variables. Only single-pollutant models were reported. The report did not mention lagged analysis, so effects were presumably reported for pollutant levels on the same day as the visit or admission.

Pollutant effects were reported as the modeled increment in the number of visits or admissions from the 5th to 95th percentile of the pollutant's concentration distribution during 1988. Winter and summer findings from Pantazopoulou et al. (1995) are summarized in Table 6-2. No pollutant had a statistically significant effect on any health outcome in summer. In contrast, all three pollutants had positive, statistically significant effects on both cardiac and respiratory "emergency admissions" (unscheduled hospital admissions) in winter. Pollution effects were stronger for admissions than for outpatient visits, and accounted for a higher proportion of respiratory admissions than cardiac admissions.

Separate analyses were conducted for CO effects when ambient CO levels were averaged across two, three, or five monitoring stations. Mean CO levels were 8.2, 6.5, and 5.2 mg/m^3 (7.2, 5.7, and 4.5 ppm), respectively. Interestingly, estimated 5th- to 95th-percentile increments in winter cardiac admissions were nearly identical in these different analyses (11.0, 11.4, and 11.2 admissions, respectively). Corresponding CO-related increments in winter respiratory admissions were also similar (9.9, 12.1, and 11.3 admissions, respectively). Effects of BS varied somewhat more than those of CO when averaged across different numbers of monitoring stations. These observations suggest that there may be less spatial variation in ambient CO in Athens than is typical for many U.S. locations, or that spatial heterogeneity in ambient CO levels may not always greatly distort CO-related health effects estimates, even when CO levels are averaged across multiple monitoring sites. The observations also underscore that further research is required on the effects of different choices of ambient pollutant metrics in time series studies.

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 analyzed range of diagnoses (International Classification of Diseases, Version 9 [ICD-9] codes 390 to 429) included heart disease, hypertension, rheumatic fever, and pulmonary circulatory disorders (U.S. Department of Health and Human Services, 1998). It did not include cerebrovascular disease or peripheral blood vessel diseases. Thus, heart disease constituted the large majority, but not all, of the analyzed disorders. The author assessed effects of CO, SO_2, O_3, NO_2, and PM_{10}, as measured at a single monitoring station. Poisson regression models included air pollution metrics, temperature, humidity, and day of week. Nonparametric smoothing was used to adjust for long-term temporal patterns. Exposure-to-admission lags of 0, 1, and 2 days were apparently assessed in different models, and effects estimates of pollutant levels on the same day as admission (0-day lag) were apparently reported. During the study, the medians of maximum hourly CO concentrations and of 24-h average PM_{10} concentrations 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.

Table 6-2. Modeled Effects of 5th- to 95th-Percentile Increments in Ambient Air Pollutant Concentrations on Daily Numbers of Cardiac and Respiratory Hospital Admissions in Single-Pollutant Models, by Season, Athens, Greece, 1998

		Winter (January 1-March 21 and September 22-December 31)			Summer (March 22-September 21)		
Disease Category	Pollutant	5th- to 95th-Percentile Increment ($\mu g/m^3$)[a]	Increase in Number of Admissions[b]	95% CI	5th- to 95th-Percentile Increment ($\mu g/m^3$)[a]	Increase in Number of Admissions[b]	95% CI
Cardiac	CO	8,200 (7.2 ppm)	11.0	3.4, 18.5	5,600 (4.9 ppm)	1.4	−5.5, 8.4
	BS	235	11.8	4.7, 18.9	134	3.0	−2.9, 8.9
	NO_2	76	11.2	3.3, 19.2	108	−0.06	−6.6, 6.5
Respiratory	CO	8,200 (7.2 ppm)	9.9	2.5, 17.4	5,600 (4.9 ppm)	2.2	−5.3, 11.5
	BS	235	9.2	2.0, 16.3	134	3.2	−4.0, 10.3
	NO_2	76	10.4	2.7, 18.2	108	3.9	−5.9, 10.2

[a]5th- to 95th-percentile increments in $\mu g/m^3$ as measured at two sites in central Athens.
[b]The average daily numbers of total cardiac admissions were 73.8 in winter and 63.9 in summer. The average daily numbers of total respiratory admissions were 41.8 in winter and 41.4 in summer.

Source: Modified from Pantazopoulou et al. (1995).

In Schwartz (1997), relative risk estimates of CO and PM_{10} for admissions were of similar magnitude, independent, additive, and statistically significant at $\alpha = 0.05$. In a model assessing both pollutants simultaneously, the estimated percentage increases in admissions across the IQRs of CO and PM_{10} levels were 2.33 and 2.37%, respectively. The IQRs of ambient CO and PM_{10} were 1.66 ppm and 23 $\mu g/m^3$, respectively. Effects estimates for both pollutants appeared to be quite stable across seasons and did not appear to be confounded with the meteorologic parameters assessed. There were no appreciable associations of admissions with ambient levels of SO_2, O_3, or NO_2.

Burnett et al. (1997a) examined temporal relationships between short-term ambient air pollution levels and hospitalizations for CHF in the elderly (persons $\geq$65 years of age) in the 10 largest Canadian cities, during the 11-year period 1981 to 1991. The average daily number of CHF admissions was 39 in the 134 catchment hospitals. Time series random-effects models, adjusted for long-term time trends, seasonal and subseasonal temporal variation, and day-of-week effects, were used to explore the relationship between hospitalizations and the ambient air pollutants CO, NO_2, SO_2, O_3, and coefficient of haze (COH, an optical index of ambient PM concentration). Fixed-effects models also were employed. 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 on the day of admission (0-day lag) was associated most strongly with hospitalization for CHF. Over the study period, the relative risk across all cities was 1.065 (95% CI = 1.028, 1.104) for an increase from 1 to 3 ppm CO (the overall IQR of the ambient CO concentration distribution). Associations 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 and weather variables than were the estimates for CO. The authors noted that CO could 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.

A summary of the Burnett et al. (1997a) study results is presented for each city in Table 6-3, which is slightly modified from Table 5 of the published report. The authors employed both random-effects models and fixed-effects models to estimate RRs of ambient CO (from 1 to 3 ppm) for CHF admissions in each city. These RRs varied substantially across cities, were generally somewhat larger in single-pollutant models than in two-pollutant models, and were slightly larger in fixed-effects models than in random-effects models. The across-cities average RR ranged from 1.058 (two-pollutant random-effects models) to 1.086 (single-pollutant fixed-effects models). Modeled city-specific relative risk was not correlated statistically significantly with city-specific study mean CO concentration or with city population (as calculated by the authors of the present document).

Burnett et al. (1997b) investigated summertime ambient air pollution in relation to unscheduled hospital admissions for cardiac and respiratory diseases in Toronto, Ontario, Canada, in the summers of 1992, 1993, and 1994 (total 388 days). Hourly measurements of CO, O_3, SO_2, NO_2, and COH were available from multiple monitoring stations. Daily measurements of fine and coarse PM (8:00 a.m. to 8:00 a.m.) were available from a dichotomous sampler at a downtown site chosen to be representative of the Toronto area. Measurements of COH also were available. Levels of PM_{10} were calculated as the sum of daily fine and coarse PM mass. Ambient CO levels were low; the mean and 95th percentile of the daily 1-h maximum CO concentration were 1.8 and 3.2 ppm, respectively.

In data analysis, pollutant concentrations were lagged 0 to 4 days before admission in separate models. Additional pollutant metrics were computed as multi-day average ambient concentrations, with the last day of the averaging period lagged 0 to 2 days before admission. The number of days in the averaging period, and the last day of the period, varied from pollutant to pollutant. In single-pollutant models, there were positive, usually significant, effects of all pollutants on both cardiac and respiratory admissions. Many two-pollutant models, each with one particulate metric and one gaseous pollutant metric,were constructed. In these, there was little evidence of a CO effect on cardiac or respiratory admissions. Effects of CO remained slightly positive, but were not statistically significant. Effects of PM

Table 6-3. Canadian City-Specific Relative Risks of a Change in Daily Maximum 1-Hour Carbon Monoxide Levels from 1 ppm to 3 ppm for Congestive Heart Failure in the Elderly, Based on Random Effects Models (Random) and a Fixed Effect Analysis of Each City Separately (Fixed), for Selected Model Specifications

			Model Specification			
			CO		CO, NO_2, Temperature, Dew Point	
City	Population[a] ($\times 10^5$)	CO[b] (ppm)	Fixed	Random	Fixed	Random
Montreal	24.6	2.0	1.05	1.05	1.04	1.04
Ottawa	8.0	2.5	1.23	1.16	1.18	1.12
Toronto	31.4	2.7	1.19	1.16	1.17	1.12
Hamilton	4.2	2.0	1.04	1.05	1.05	1.05
London	3.3	1.7	1.00	1.02	0.99	1.01
Windsor	3.2	2.0	1.01	1.02	1.01	1.02
Winnipeg	5.9	1.6	1.05	1.05	0.99	1.01
Edmonton	7.2	2.7	1.06	1.06	1.02	1.04
Calgary	8.1	3.3	1.01	1.04	0.99	1.02
Vancouver	14.0	2.5	1.22	1.17	1.22	1.15
Average	10.99	2.30	1.086	1.078	1.066	1.058

[a] Based on 1986 census.
[b] Average of daily maximum 1-h ambient concentrations of carbon monoxide.

Source: Modified from Burnett et al. (1997a).

metrics adjusted for CO were similar to PM effects in single-pollutant models. The gaseous pollutant least sensitive to adjustment for PM metrics was O_3, and the gaseous pollutant that most attenuated PM effects was NO_2. The authors hypothesized that the absence of a CO effect may have reflected the fact that summertime ambient CO levels were low and emphasized the potential importance of the overall ambient air pollution mix. They recommended that "all available air pollution measures be considered in assessing the effects of any single pollutant on health."

Poloniecki et al. (1997) investigated cardiovascular hospital admissions in relation to ambient air pollution concentrations 1 day before admission in London, UK, from April 1, 1987, to March 31, 1994. Pollutant metrics were 24-h mean CO, BS, SO_2, and NO_2 and hourly mean O_3 between 9:00 a.m. and 5:00 p.m. Measurements of all gaseous pollutants were taken from a single site in central London. Measurements of BS were taken from one central site and four suburban sites. Median and 90th-percentile CO concentrations were 0.9 and 1.8 ppm, respectively. Corresponding BS concentrations were 12 and 22 $\mu g/m^3$. Health outcomes considered were admissions for all cardiovascular diseases and for the following seven diagnostic subgroups: (1) MI, (2) other IHD, (3) heart failure, (4) angina, (5) cardiac dysrhythmia, (6) cerebrovascular disease, and (7) other circulatory diseases.

Analytical models were adjusted for day of week, holidays, an influenza epidemic in 1989, and several temporal cycles ranging from 20 days to the whole study period. Pollutant concentration, temperature, and humidity one day before admission (1-day lag) also were entered into the models. Single-pollutant Poisson models were constructed for each health outcome. In these models, CO was positively and statistically significantly associated with admissions for all cardiovascular diseases, MI, and other

circulatory diseases. Black smoke was significantly associated with admissions for all cardiovascular diseases, MI, and angina. Admissions for all cardiovascular diseases and MI were significantly associated with all pollutants except O_3. The only diagnostic subgroup signficantly associated with more than one pollutant was MI. Admissions for heart failure, other IHD, and cerebrovascular disease were not significantly associated with any pollutants.

Additional single-pollutant and two-pollutant Poisson models were constructed for MI during the warm season (April through September) and the cool season (October through March). Ambient air pollution levels were not reported separately by season. In the warm season, there were no significant associations of air pollution with MI admissions ($p > 0.25$). In the cool season, CO was positively and significantly associated with MI in the single-pollutant model and the two-pollutant model with O_3. The same was true for all other pollutants except O_3, and SO_2 was significant in all two-pollutant models. The p values and regression coefficients from Table 4 of Poloniecki et al. (1997), which show pollutant effects in single-pollutant and two-pollutant models in the cool season, are presented in Table 6-4.

Table 6-4. Acute Myocardial Infarction: One- and Two-Pollutant Models with Cool Season[a,b], London, UK, April 1, 1987, to March 31, 1994

	Second Pollutant				
Test Pollutant	O_3	NO_2	SO_2	CO	BS
O_3 (ppb)					
p Value	***0.22***	0.72	0.91	0.93	0.95
Coefficient	***−0.0013***	0.0004	0.0001	−0.0001	0.0001
NO_2 (ppb)					
p Value	0.0004[c]	***0.0020[c]***	0.15	0.84	0.23
Coefficient	0.0022	***0.0013***	0.0008	0.0002	0.0008
SO_2 (ppb)					
p Value	0.0005[c]	0.03[c]	***0.0004[c]***	0.02[c]	0.03[c]
Coefficient	0.0025	0.0015	***0.0021***	0.0020	0.0015
CO (ppb)					
p Value	0.001[c]	0.15	0.39	***0.02[c]***	0.38
Coefficient	0.0324	0.0205	0.0083	***0.0227***	0.0100
Black smoke ($\mu g/m^3$)					
p Value	0.0006[c]	0.23	0.10	0.13	***0.002[c]***
Coefficient	0.0033	0.0014	0.0015	0.0019	***0.0024***

[a]Diagonal elements (bold italics) are single-pollutant models; off-diagonal elements are test pollutant modeled with a second pollutant
[b]Cool season is October to March. Coefficient = Poisson regression coefficient—for example, percent admissions per unit of pollutant = [exp (coeff) − 1] × 100.
[c]$p < 0.05$.

Source: Modified from Poloniecki et al. (1997). The original table shows results in both cool and warm seasons.

This study suggests that, during the cool season in London, short-term elevations in ambient air pollution levels are related to cardiac hospital admissions, especially MI admissions, 1 day later. Unlike North American investigators, Poloniecki et al. (1997) reported no association of ambient CO with heart failure. Even so, there is some consistency between the European and North American studies.

Specifically, these studies show positive, statistically significant relationships of ambient CO concentration and other pollutant concentrations with hospital admissions for heart disease, and these relationships tend to be sronger for heart disease than other types of cardiovascular disease such as stroke.

Poloniecki et al. (1997) present a balanced discussion of consistencies and inconsistencies in the available epidemiologic database regarding ambient air pollution. They emphasize the potential for confounding of air pollution and meteorologic effects. They state, "With so much potential for confounding, and with a good many conflicting results to be found in the scientific literature, we chose to place the statistical emphasis on the direction and consistency of the relations (p values) rather than on estimating the size of effects from the models which produce the largest effects, as has usually been done." They also state that their results make a case for further study of CO.

In Poloniecki et al. (1997), a statistically significant association of ambient CO with angina admissions might well have been expected, because ambient CO was associated significantly with MI admissions, and because CO exposure reduces the time to angina onset in experimental studies of exercising cardiac patients (see Section 6.2.2). Failure to observe an association of ambient CO with angina could be interpreted as a caveat on the observed association of ambient CO with MI. It is also conceivable that the 1-day lag employed in data analysis was not an optimum lag time for detection of any association of ambient CO exposure and angina that might have existed.

Morris and Naumova (1998) investigated joint effects of short-term ambient CO concentration and ambient temperature on daily hospital admissions for CHF in people $\geq$65 years of age, in Cook County (Chicago), IL, from 1986 through 1989. Data were analyzed with general linear models (GLM) and general additive models (GAM). The pollutant metrics assessed 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. The PM_{10} levels were measured at only one station on 80% of study days. The 25th and 75th percentiles of daily maximum hourly CO, over the whole study period, were 1.81 and 3.05 ppm, respectively. The corresponding percentiles of 24-h average PM_{10} were 28 and 51 $\mu g/m^3$, respectively. In addition to the pollutant metrics, 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 pollutant except O_3 was associated positively and statistically significantly with CHF 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, 1.12), as compared to RR = 1 at a hypothetical, modeled CO concentration of zero. Associations of CO and other pollutants with admissions were strongest on the day of admission (0-day lag) and weakened rapidly with successively longer lag times.

The authors conducted a detailed analysis to assess effects of ambient CO at different temperatures. These effects 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 multi-pollutant GLM, RRs for CHF admissions at the 75th percentile of maximum hourly CO concentration were 1.09 (95% CI = 1.01, 1.18), 1.07 (95% CI = 1.01, 1.13), and 1.01 (95% CI = 0.92, 1.11) when maximum temperature was <40, 40 to 75 °F, and >75 °F, respectively. Figure 3 in Morris and Naumova (1998) shows temperature-specific exposure-response curves for percentiles of ambient CO distributions and relative risk of CHF admission in single-pollutant and multi-pollutant models. This figure is reproduced in Figure 6-2. The authors hypothesized that CHF patients may be unusually susceptible to CO effects, and that cardiovascular and other stresses imposed by cold weather may heighten this susceptibility.

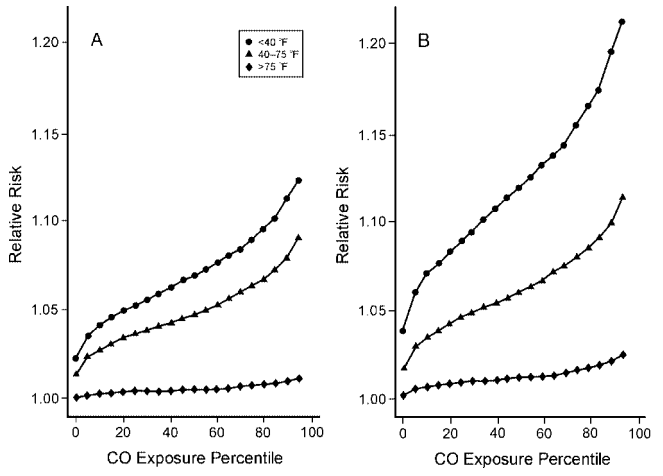

Figure 6-2. The relative risk associated with the exposure percentiles of CO at specific temperature strata, based on results of the (A) multi-pollutant and (B) single-pollutant generalized linear models of hospital admissions for heart failure among the elderly in Chicago, IL, 1986 to 1989. (Note that curves are plotted by percentiles of ambient CO concentrations, not measured concentrations. Temperature-specific percentiles of CO concentrations were not reported.)
Source: Morris and Naumova (1998).

Morris and Naumova (1998) is one of the few time series studies that has modeled temperature-specific effects estimates for air pollutant metrics. It is an unusually strong time series study, and its findings regarding ambient CO effects on CHF admissions are therefore of unusual interest and concern. However, even these findings should be interpreted cautiously. For example, as the authors point out, fixed-site CO measurements do not give exact estimates of individual subjects' total CO exposures. Discrepancies between estimated and actual total CO exposures may be greatest in cold weather, when indoor CO levels may be higher than in warm weather, and when CHF patients may spend more time indoors. 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. Thus, the observed stronger associations of ambient CO with CHF in colder weather might reflect an underlying effect of increased total CO dose in colder weather, rather than a specific effect of ambient CO exposure. Finally, the observed associations could reflect a true effect of ambient CO fluctuations, superimposed on higher baseline CO doses from nonambient sources during colder weather.

As mentioned above, Burnett et al. (1997b) did not observe an association of ambient CO with cardiac admissions. However, their results do not necessarily contradict those of Morris and Naumova (1998), who observed a strong association of CO with CHF admissions at cold temperatures but little or no association at warm ones. Pantazopoulou et al. (1995) and Poloniecki et al. (1997) also observed associations of CO and other air pollutants with cardiac admissions during cooler weather but not during warmer weather. Thus, these four studies generate the hypothesis that ambient CO effects on heart disease exacerbation are stronger during cooler weather than during warmer weather, a hypothesis that should be tested further in future studies.

Yang et al. (1998) studied cardiovascular hospital admissions in relation to short-term CO levels in Reno-Sparks, NV, during 6 years (1989 to 1994). The study area is about 4,400 ft above sea level. At this elevation, the effect of COHb on tissue O_2 delivery might well differ from that at sea level. Exposure to a given concentration of ambient CO might be expected to reduce tissue O_2 delivery more at this elevation than at sea level. The range of ICD-9 codes studies (390 to 459.99) included heart disease and other cardiovascular disorders such as stroke and hypertension. The modeled daily CO metric was the highest of the 1-h average CO concentrations occurring between midnight and noon. The mean of this metric over the study period was 3.09 ppm. Data were analyzed with weighted least-squares regression and autoregressive integrated moving average (ARIMA) regression for time series data. Models were adjusted with dummy variables for day of week and month of year. Wind speed and the previous day's minimum temperature also were considered. Carbon monoxide effects estimates were reported for the ambient CO level on the day of admission (0-day lag). Pollutants other than CO were not considered.

The authors stated, "All hospital admissions for CV [cardiovascular disease] and IHD were significantly associated with CO concentrations...." Tabular displays of results were limited to all CV and

IHD admissions. No results were reported for other diagnostic subcategories. Modeled CO effects on admissions were larger in males than females and did not differ significantly by age. The significance levels of CO effects are somewhat difficult for the reader to discern. Table 5 of Yang et al. (1998) suggests that regression results were highly significant ($p < 0.006$). However, the text states, "According to the ARIMA models, CV and IHD hospital admissions increased 1.19% (95% CI = 0.99, 1.39%) and 2.83% (95% CI = 2.07, 3.60%), respectively, for each 1 ppm increase in the 1-h maximum CO level...." This suggests much clearer significance of the CO effect on IHD admissions than for the effect of CO on total cardiovascular admissions. Overall, this report suggests an association of short-term ambient CO levels with cardiovascular admissions, especially IHD admissions, at an elevation of 4,400 ft. The report does not enable inference as to effects of pollutants other than CO.

Schwartz (1999) evaluated effects of short-term ambient CO and PM_{10} exposure on daily hospital admissions for cardiovascular disease (ICD-9 codes 390 to 429) in persons aged at least 65 years, in eight U.S. counties over 3 years, 1988 to 1990. The analyzed health outcomes were the same as in Schwartz (1997) (i.e., ICD-9 codes 390 to 429). The eight study locations were Chicago, IL; Colorado Springs, CO; Minneapolis and St. Paul MN; New Haven, CT; and Seattle, Spokane, and Tacoma, WA. Previous findings from Tucson, AZ, also were summarized (Schwartz, 1997). Aerometric data were taken from population-oriented CO monitors (neighborhood scale), rather than from compliance monitors, which may be located away from population centers. Daily maximum 1-h CO levels and 24-h average PM_{10} levels were analyzed, apparently only on the same day as admissions (0-day lag). During the study period, 50th-percentile CO and PM_{10} metrics ranged from 2.0 to 4.7 ppm and 23 to 37 $\mu g/m^3$, respectively, across the study locations. The IQRs of the ambient CO and PM_{10} metrics, across all eight locations during the study period, were about 1.75 ppm and 25 $\mu g/m^3$, respectively. Pollutants other than CO and PM_{10} were not analyzed.

Poisson regression was employed with locally weighted regression scatter plot smoothing (LOESS) to adjust for effects of temperature, dew point, and seasonal patterns. Effects estimates were reported as percentage increases in admissions over approximate IQRs of ambient pollutant concentrations. In all study locations, both CO and PM_{10} levels were associated positively with daily cardiac admissions. Carbon monoxide effects were statistically significant in seven of nine locations, and PM_{10} effects were significant in six of nine locations. Relative effects of CO and PM_{10} differed widely among locations. Overall, the interquartile percentage increase in admissions for CO was 2.79% (95% CI = 1.89 to 3.68), and that for PM_{10} was 2.48% (95% CI = 1.81 to 3.14). Effects estimates for CO and PM_{10} were not related to the location-specific correlation between these two pollutants' concentrations, suggesting their effects on cardiac admissions were at least partially independent. Table 3 of Schwartz (1999), which shows modeled ambient CO and PM_{10} effects in all eight study locations and in Tucson, is reproduced with slight modification in Table 6-5. In two-pollutant models, effects estimates for CO and PM_{10} were somewhat smaller than in single-pollutant models. Pollution effects estimates were not reported for diagnostic subcategories (e.g., IHD and heart failure).

This study's findings leave a general impression of similar, but partially independent statistical effects of short-term ambient CO and PM_{10} on total cardiac admissions in the elderly. At the same time, it is not clear why CO exerted a substantially larger statistical effect than PM_{10} on admissions in Minneapolis, but no CO effect was evident in the adjacent location of St. Paul. It is also not clear why the LOESS seasonal smoothing window was 34% longer in St. Paul than in Minneapolis. Similarly, CO had a larger effect than PM_{10} on admissions in Seattle, whereas the reverse was true in nearby Tacoma. Furthermore, the seasonal smoothing window in Seattle was 34% longer than in Tacoma.

Schwartz (1999) points out that, although CO is a known "cardiovascular toxin," cardiac effects in experimental studies of humans have been observed only at higher than ambient CO levels. He states that one would expect to observe CO effects at lower levels in epidemiologic studies because epidemiology examines the entire population, which comprises a broader range of disease states and exposure to potential effects modifiers than do experimental subject groups. He also raises the possibility that ambient CO may

Table 6-5. Modeled Percentage Increases in Hospital Admissions for Heart Disease, Associated with Interquartile Range Increases in Ambient PM_{10} (25 $\mu g/m^3$)and Carbon Monoxide (1.75 ppm) in Eight Locations, Across These Locations, and in Tucson, AZ, 1988 to 1990

City	PM_{10}	95% CL	CO	95% CL	Window[a]
Chicago, IL	2.31	1.31,3.33	2.84	1.59,4.10	76
Colorado Springs, CO	2.76	−3.2,9.09	0.51	−2.41,3.51	180
Minneapolis, MN	2.03	−1.87,6.09	4.09	1.59,6.65	143
New Heaven, CT	2.87	1.04,4.73	3.04	1.18,4.93	172
St. Paul, MN	4.19	1.44,7.00	0.74	−1.84,3.39	191
Seattle, WA	1.77	−0.07,3.64	4.22	2.44,6.02	161
Spokane, WA	3.28	0.43,6.21	2.71	0.69,4.78	145
Tacoma, WA	2.63	0.47,2.63	1.84	0.24,3.46	120
Across the Locations Above	2.48	1.81,3.14	2.79	1.89,3.68	NA
Tucson, AZ	2.99	0.55,5.50	2.94	0.54,5.71	83

[a]Size of window (in days) for LOESS smoothing of time to control season.

Source: Modified from Schwartz (1999).

be a marker for automotive pollution, and states, "One potential constituent of automotive [pollution] that may have acute cardiovascular toxicity is the volatile and semivolatile organic aerosols.... Hence, CO may be serving as a proxy for these compounds. Nevertheless, associations between cardiovascular hospital admissions and CO have been seen in more than 20 North American cities,...suggesting that a better understanding of this pollutant should have a high priority."

Burnett et al. (1999) assessed daily unscheduled hospital admissions for eight types of cardiovascular and respiratory disease exacerbation in Toronto, Canada, in relation to short-term ambient air pollution exposure over 15 years, 1980 to 1994. Daily average concentrations of CO, NO_2, SO_2, and O_3 were obtained from four monitoring stations. Daily average concentrations of fine PM ($PM_{2.5}$), coarse PM ($PM_{10-2.5}$), and PM_{10} were estimated from total suspended particles (TSP) and sulfate levels measured at a single central station. Daily average COH levels were measured at the same station. The cardiovascular disease types were IHD, heart failure, cardiac dysrhythmias, cerebrovascular disease (including stroke), and peripheral circulatory disorders. The respiratory disease types were asthma, obstructive lung disease, and respiratory infection.

Data were analyzed with general additive models, with accommodation for over- or underdispersion from Poisson variation. The data were prefiltered with a 31-day LOESS smoother. LOESS smoothers also were employed to adjust for effects of temperature and relative humidity. Models were adjusted for day-of-week effects. Exploratory models were run to select climate variables for final models. The report did not present seasonal air pollution effects estimates. Pollution metrics were 1-, 2-, or 3-day averages, with the final day of the averaging period lagged 0 to 2 days before admission. All possible single-pollutant models were run for each disease type. Pollutant metrics were constructed to give the log of relative risk per unit

change in pollutant concentration. Pollutant effects were reported as the percentage increase in total daily hospital admissions, from zero concentration to the mean pollutant concentration during the study period.

In the single-pollutant models (Table 3 in Burnett et al., 1999), pollutant effects estimates were weak or negative for cerebrovascular disease and peripheral circulatory disease, so these two disease types were not considered in subsequent multi-pollutant analyses. This left only three heart disease categories and three respiratory disease categories for further consideration. In single-pollutant models, the CO effect in each of these six categories was strongest for a 1- or 2-day averaging time, ending on the same day as the admission (0-day lag).

The authors constructed multi-pollutant models in an effort to ascertain effects of the overall ambient air pollution mix and to estimate health benefits that would follow air pollution reduction. They selected pollutant metrics from the single-pollutant models for inclusion in the multi-pollutant models. For each pollutant, they selected the averaging period and lag that yielded the largest ratio of log-relative risk to standard error (largest T-ratio or t-statistic). They constructed two sets of multi-pollutant models. In the first set (Table 4 in Burnett et al., 1999), four models were run for each of the six cardiac and respiratory disease categories. In one of these four models, all PM metrics were excluded. In each of the other three models, the investigators forced inclusion of only one PM metric ($PM_{2.5}$, $PM_{10-2.5}$, or PM_{10}). After these constraints were imposed, gaseous pollutants were entered into each of the 24 models using stepwise regression. Specific gaseous pollution metrics in final models were selected using the Akaike Information Criterion.

In this first set of multi-pollutant models, inclusion of gaseous pollutants led to substantially smaller PM effects estimates than observed in single-pollutant models. Also, modeled percentage increases in admissions (PIAs) with a PM metric in the model were only moderately larger than corresponding increases with no PM metric in the model. The maximum diagnosis-specific percentage increase in the PIA with a PM metric in the model, over the PIA with no PM metric, ranged from 7.4% for IHD to 28.1% for respiratory infection. These increases were larger for respiratory diseases (average = 21.0%) than for heart diseases (average = 8.5%).

In the second set of multi-pollutant models (Table 5 in Burnett et al., 1999), all gaseous and PM metrics competed equally for inclusion, and no metric was constrained to be included or excluded. In these models, percentage increases in diagnosis-specific hospital admissions, at the mean concentrations of included pollutants, ranged from 9.29% (IHD) to 14.45% (respiratory infection). Effects of CO and NO_2, which are generated by mobile sources, largely were confounded. Carbon monoxide, but not NO_2, was included in models for asthma, obstructive lung disease, and dysrhythmias, and NO_2, but not CO, was included for IHD. Both CO and NO_2 were included as independent predictors for heart failure. Taken together, effects estimates for CO and NO_2 were larger and more frequently statistically significant for heart diseases than for respiratory diseases.

Table 6-6 summarizes modeled effects of CO in single-pollutant models and modeled effects of CO and other pollutants in multi-pollutant models as taken from Tables 3 and 5 of Burnett et al. (1999). No PM metric was included in multi-pollutant models for IHD and heart failure (which accounted for 73.9% of all U.S. hospital admissions for heart disease in 1996). When a PM metric was included, the contribution of the modeled PM effect to the overall pollution-associated increase in admissions ranged from 19.3% (dysthythmias) to 42.1% (respiratory infection). The average contribution of PM metrics to the air-pollution-associated percentage increase in heart disease admissions was only 6.4% ([0% + 0% + 19.3%] / 3). If weighted by the number of admissions for each of the three analyzed heart disease categories in the United States in 1996 (see Section 6.2.1.1), this contribution would calculate to only 3.2%. The average contribution of PM metrics to percentage increases in respiratory disease admissions was 34.2%. Fine PM was included in models for dysrhythmias and respiratory infection, and coarse PM was included for asthma and obstructive lung disease. No more than one PM metric was included for any disease, and PM_{10} was not included for any disease. Ozone was associated much more strongly with respiratory disease admissions

Table 6-6. Modeled Percentage Increases in Hospitalizations at Mean Pollutant Concentrations in Single- and Multi-Pollutant Models, Toronto, Canada, 1980 to 1994

Disease Category	Single-Pollutant Models (Table 3)							Multi-Pollutant Models (Table 5)					
	CO (1.2 ppm)[a]	NO_2 (25.2 ppb)[a]	SO_2 (5.4 ppb)[a]	O_3 (19.5 ppb)[a]	PM_{10} (30 $\mu g/m^3$)[a]	$PM_{2.5}$ (18 $\mu g/m^3$)[a]	$PM_{10-2.5}$ (12 $\mu g/m^3$)[a]	CO	NO_2	SO_2	O_3	PM	All Pollutants
Heart Disease													
Dysrhythmias	8.99(3.60)[b]	5.33(1.73)	0.80(1.43)	3.51(1.71)	5.00(3.03)	4.33(2.91)	2.47(1.88)	7.00(2.50)	—[c]	—	3.34(1.63)	2.47[d](1.49)	12.81
Heart Failure	8.33(5.71)	9.48(6.33)	1.93(3.85)	1.42(1.42)	5.75(3.51)	4.70(3.20)	3.77(2.79)	4.09(2.08)	6.89(3.44)	—	—	—	10.98
Ischemic Heart Disease	7.31(6.46)	9.73(8.40)	2.32(6.13)	0.61(0.99)	4.97(5.55)	5.73(6.08)	1.81(3.02)	—	8.34(6.10)	0.95(2.07)	—	—	9.29
Respiratory Disease													
Asthma	5.35(3.92)	3.33(2.37)	1.01(1.76)	6.32(4.63)	5.27(3.39)	4.60(3.22)	5.25(4.20)	4.00(3.86)	—	—	4.99(3.48)	4.00[e](3.04)	12.99
Obstructive Lung Disease	2.93(1.48)	2.21(1.07)	0.03(0.05)	7.29(4.23)	4.11(2.44)	3.42(1.89)	6.07(3.26)	3.00(1.52)	—	—	6.08(2.74)	3.86[e](1.90)	12.94
Respiratory Infection	5.00(4.25)	6.89(5.53)	2.40(5.04)	4.42(4.29)	8.35(5.96)	7.64(6.09)	4.44(4.00)	—	4.44(3.31)	—	3.93(3.80)	6.08[d](4.46)	14.45

[a]Overall study means of pollutant metrics are in parentheses.
[b]T-statistics for pollutant effects estimates are in parentheses, and are approximately equal to Z-statistics. Two-tailed Z-statistics of 1.96 or greater, and 2.58 or greater, denote statistical significance at $\alpha = 0.05$ and $\alpha = 0.01$, respectively.
[c]A dash denotes that the indicated pollutant was not included in the multi-pollutant model.
[d]The PM metric included was $PM_{2.5}$ (fine PM).
[e]The PM metric included was $PM_{2.5-10}$ (coarse PM).

Source: Modified from Burnett et al. (1999).

than with heart disease admissions. Single-pollutant model effects of SO_2 could be explained largely by inclusion of other pollutants.

In Burnett et al. (1999), PM metrics were estimated, not measured. Thus, the findings are subject to quantitative uncertainty regarding specific pollutant effects and regarding gaseous pollution effects relative to PM effects. Modeled effects of PM may have been biased downward, but this is not certain. Also, the extent to which findings in Toronto can be generalized to other locations is not clear. Nevertheless, this report presents an unusually comprehensive effort to examine multi-pollutant effects across a variety of health outcomes. This study, like many other recent studies, emphasizes the importance of considering both gaseous and particulate pollutants in data analyses. It underscores the importance of gaseous pollutants as contributors to health effects attributable to the overall ambient air pollution mix, especially in relation to heart disease exacerbation. Also, unless both gaseous pollutants and PM are taken into account, modeled effects estimates for single pollutants are likely to be inaccurate. Furthermore, using effects estimates derived from multi-pollutant models may compensate, at least partly, for confounding of effects among individual pollutants in estimating potential public health risks.

Time series studies of ambient CO and daily exacerbations of heart disease are summarized in Table 6-7.

6.2.1.3 Ambient Carbon Monoxide and Daily Mortality Counts

Epidemiologic studies of the relationship between CO exposure and daily mortality are not 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 cardiovascular disease, but potential confounders were not controlled thoroughly. In contrast, Kuller et al. (1975) observed no association between ambient CO levels and cardiovascular disease or sudden death in Baltimore, MD.

Kinney and Özkaynak (1991) investigated effects of short-term variation in ambient air pollution levels on daily nonaccidental, nonviolent deaths in Los Angeles County over 10 years, 1970 through 1979. The mean daily death count was 152; of these, 87 (57%) and 8 (5%) resulted from cardiovascular and respiratory causes, respectively. Pollution metrics were "daily maximum" CO, daily maximum hourly total oxidants (O_3 in 1979), 24-h average SO_2, NO_2, and KM (a particulate metric similar to British smoke, related to elemental carbon), and visual extinction coefficient (B_{ext}, related to fine particulate). In multiple regression models, adjusted for meteorology and temporal patterns, there were statistically significant associations of total and cardiovascular mortality with temperature, oxidants (lagged 1 day) and the automotive pollutants CO, NO_2, and KM (each lagged 0 days). Levels of the latter three pollutants were too highly intercorrelated to enable confident assessment of their separate effects. Respiratory mortality was associated with temperature but not with any pollution metric, although the power to test for pollutant effects was limited by small numbers of daily respiratory deaths.

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 ambient particles, 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.

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., TSP, SO_2, NO_2, BS) 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

Table 6-7. Summary of Time Series Studies of Ambient Carbon Monoxide and Daily Frequency of Heart Disease Exacerbation

Reference	Health Outcomes, Study Locations, Period of Study	Ambient Air Pollutants Assessed and Pollutant Concentrations	Findings: Single-Pollutant Models	Findings: Multiple-Pollutant Models	Comments
Morris et al. (1995)	Daily Medicare hospital admissions for CHF, seven U.S. cities, 1986-1989	CO, NO_2, SO_2, O_3. The average of daily maximum 1-h CO ranged from 1.8 ppm in Milwaukee, WI, to 5.6 ppm in New York, NY.	RR for CHF admissions, per 10-ppm increase in CO, ranged from 1.10 in New York to 1.37 in Los Angeles, CA. The CO effect was statistically significant in all cities but Houston, TX. CO effects were usually strongest with a 0-day lag.	The effect of CO was more stable and retained statistical significance more often than other pollutants' effects.	PM effects were not assessed in this study. The authors estimated that about 3,250 CHF admissions (about 0.4% of all CHF admissions) could be attributed to short-term increases in ambient CO.
Schwartz and Morris (1995)	Daily hospital admissions for CHF, IHD, and cardiac dysrhythmias in persons ≥65 years old, Detroit, MI, 1986-1989	CO, PM_{10}, O_3, SO_2. The average of daily maximum 1-h CO = 2.4 ppm. The average of 24-h average PM_{10} = 48.0 $\mu g/m^3$.	RRs for CHF admissions, per IQR increase in pollutant level, were 1.022 for CO and 1.024 for PM_{10}. RRs for IHD admissions were 1.010 for CO and 1.018 for PM_{10}. Ambient air pollution was not associated with dysrhythmia admissions.	Effects of CO and PM_{10} on CHF admissions were independent and statistically significant (RR = 1.022 for CO and 1.024 for PM_{10}). Effects of PM_{10} on IHD admissions retained statistical significance, but effects of CO and SO_2 did not.	CO effects on admissions were strongest with a 0-day lag.
Pantazo-poulou et al. (1995)	Daily emergency department visits and hospital admissions for cardiac and respiratory causes, Athens, Greece, 1988	Daily maximum 8-h moving average CO, daily maximum hourly NO_2, 24-h average BS. Mean CO = 4.5 mg/m^3 in winter and 3.4 mg/m^3 in summer.	In winter, all three pollutants were statistically significantly associated with cardiac and respiratory hospital admissions. Air pollution effects were stronger for admissions than for emergency department visits. Ambient air pollution was not associated with admissions or visits in summer.	None reported.	Ambient CO levels were high in comparison to current U.S. levels. The report did not mention lagged analysis, so effects presumably were reported for a 0-day lag.

Table 6-7 (cont'd). Summary of Time Series Studies of Ambient Carbon Monoxide and Daily Frequency of Heart Disease Exacerbation

Reference	Health Outcomes, Study Locations, Period of Study	Ambient Air Pollutants Assessed and Pollutant Concentrations	Findings: Single-Pollutant Models	Findings: Multiple-Pollutant Models	Comments
Schwartz (1997)	Daily cardiovascular hospital admissions in persons ≥65 years old, Tucson, AZ, 1988-1990	CO, PM_{10}, SO_2, NO_2, O_3. Medians of daily maximum hourly CO and 24-h average PM_{10} concentrations = 3.03 ppm and 39 $\mu g/m^3$, respectively. The IQRs for CO and PM_{10} were about 1.7 ppm and 23 $\mu g/m^3$, respectively.	Effects of CO and PM_{10} on admissions were of similar magnitude and statistically significant. Admissions were not appreciably associated with SO_2, O_3, or NO_2.	In a model that included both CO and PM_{10}, percentage increases in admissions, per IQR increase in pollutant level, were 2.33% for CO and 2.37% for PM_{10}.	Admissions for heart disease constituted most, but not all, of the admissions considered in this analysis.
Burnett et al. (1997a)	Daily hospitalizations for CHF in persons ≥65 years old, 10 Canadian cities, 1981-1991	CO, SO_2, NO_2, O_3, COH. Mean daily 1-h maximum CO = 2.32 ppm. Mean daily 8-h maximum CO = 1.59 ppm.	The effect of CO on hospitalizations was stronger than effects of other pollutants. The effect of CO was strongest with a 0-day lag.	The effect of CO was less sensitive to simultaneous adjustment for other pollutants and meteorologic variables than were effects of non-CO pollutants.	Size-specific PM metrics were not assessed. The authors noted that CO could be acting as a surrogate for transportation-related air pollutants.
Burnett et al. (1997b)	Daily hospital admissions for cardiac and respiratory diseases, Toronto, Canada, summers of 1992-1994	CO, fine PM ($PM_{2.5}$), coarse PM ($PM_{10-2.5}$), PM_{10} (calculated), COH, O_3, SO_2, NO_2. Mean and 95th percentile of daily 1-h maximum CO = 1.8 ppm and 3.2 ppm, respectively.	All pollutants had positive effects on cardiac and respiratory admissions. Effects were usually statistically significant.	CO had little effect on admissions in two-pollutant models that included one PM metric and one gaseous pollutant metric. PM effects were relatively insensitive to adjustment for gaseous pollutants.	Ambient CO levels were low. This partially may explain the lack of association of CO with admissions in this study.

Table 6-7 (cont'd). Summary of Time Series Studies of Ambient Carbon Monoxide and Daily Frequency of Heart Disease Exacerbation

Reference	Health Outcomes, Study Locations, Period of Study	Ambient Air Pollutants Assessed and Pollutant Concentrations	Findings: Single-Pollutant Models	Findings: Multiple-Pollutant Models	Comments
Poloniecki et al. (1997)	Daily cardiovascular hospital admissions, London, England, April 1, 1987-March 31, 1994. Admissions were divided into seven diagnostic subgroups. Air pollution effects on admissions for MI were analyzed separately in warm and cool seasons.	24-h mean CO, BS, SO_2, NO_2. Hourly mean O_3 between 9:00 a.m. and 5:00 p.m. Median and 90th percentile CO levels = 0.9 and 1.8 ppm, respectively. Median and 90th percentile BS levels = 12 and 22 $\mu g/m^3$, respectively.	Over all seasons, CO was statistically significantly associated with admissions for all cardiovascular diseases and MI. BS was significantly associated with admissions for all cardiovascular diseases, MI, and angina. No pollutant was associated with MI admissions in the warm season.	Two-pollutant models were constructed. In the cool season, CO and BS were significantly associated with MI admissions in models that included O_3. In the model that included CO and BS, neither pollutant had a significant effect on MI admissions.	Pollutant effects were analyzed with a 1-day lag. This report presents a balanced discussion of strengths and limitations of time series studies. Emphasizes potential for confounding of air pollution and meteorologic effects.
Morris and Naumova (1998)	Daily hospital admissions for CHF in persons ≥65 years old, Chicago, IL, 1986-1989	Daily maximum hourly CO, NO_2, SO_2, O_3, and 24-h average PM_{10}. Mean and 75th percentile CO = 2.51 and 3.05 ppm, respectively. Mean and 75th percentile PM_{10} = 41 and 51 $\mu g/m^3$, respectively.	In single-pollutant GLMs, all pollutants but O_3 were significantly associated with CHF admissions. In GLMs stratified on ambient temperature, CO effects were strongest in the lowest temperature range (<40 °F) and weakest in the highest temperature range (>75 °F). CO effects were also strongest at lower temperatures in a generalized additive model that generated a joint CO-temperature effects surface.	In a GLM that included all pollutants, only CO was significantly associated with admissions. In temperature-stratified GLMs, CO effects were somewhat smaller than in single-pollutant GLMs, but clearly still were associated inversely with ambient temperature.	Data were analyzed with unusual attention to joint effects of ambient air pollution and temperature. Pollutant effects on admissions were strongest with a 0-day lag, and decreased rapidly with successively longer lag times.

Table 6-7 (cont'd). Summary of Time Series Studies of Ambient Carbon Monoxide and Daily Frequency of Heart Disease Exacerbation

Reference	Health Outcomes, Study Locations, Period of Study	Ambient Air Pollutants Assessed and Pollutant Concentrations	Findings: Single-Pollutant Models	Findings: Multiple-Pollutant Models	Comments
Yang et al. (1998)	Daily cardiovascular hospital admissions, Reno, NV, 1989-1994	CO only. Mean CO = 3.09 ppm.	The effect of ambient CO (0-day lag) on IHD admissions and cardiovascular admissions was statistically significant.	None reported.	CO effects on admissions were analyzed only with a 0-day lag.
Schwartz (1999)	Daily cardiovascular hospital admissions in persons ≥65 years old, eight U.S. counties, 1988-1990 (Results from Tucson, AZ, also were summarized.)	CO, PM_{10}. The median of daily maximum hourly CO ranged from 2.0 ppm (Chicago, IL) to 4.7 ppm (Spokane, WA). The median 24-h average PM_{10} ranged from 23 $\mu g/m^3$ (Colorado Springs, CO) to 37 $\mu g/m^3$ (New Haven, CT; Spokane, WA; and Tacoma, WA). The overall IQRs for CO and PM_{10} were about 1.75 ppm and 25 $\mu g/m^3$, respectively.	Effects of CO on admissions were statistically significant in seven of nine locations. PM_{10} effects were significant in six of nine locations. CO and PM_{10} effects on admissions appeared to be at least partially independent.	In two-pollutant models, effects estimates for CO and PM_{10} were slightly smaller than in single-pollutant models.	Pollutant effects on admissions were apparently analyzed only with a 0-day lag. Interpretation of findings is complicated by observations of different relative effects of CO and PM_{10}, and different lengths of LOESS smoothing windows, in adjacent and nearby locations.
Burnett et al. (1999)	Daily hospital admissions for five categories of cardiovascular disease and three categories of respiratory disease, Toronto, Canada, 1980-1994	Measured daily average CO, NO_2, SO_2, O_3, COH. Estimated daily average PM_{10}, fine PM, coarse PM. Overall means of pollutant metrics: CO = 1.2 ppm; PM_{10} = 30 $\mu g/m^3$; fine PM = 18 $\mu g/m^3$; coarse PM = 12 $\mu g/m^3$.	All possible single-pollutant models were constructed. CO effects on admissions were strongest with a 1-day or 2-day averaging time, ending on the same day as admission (0-day lag). Pollutant effects were weak or negative for cerebrovascular disease and peripheral circulatory disease.	In two-pollutant models, PM effects were substantially smaller than in single-pollutant models. In multi-pollutant models, CO and NO_2 effects were usually confounded, but CO and NO_2 contributed independently to admissions for heart failure. PM metrics accounted for 6.4% and 34.2% of the overall ambient air pollution effect on admissions for cardiovascular and respiratory diseases, respectively.	This report employs a thorough, logical strategy for sequential use of single-pollutant and multi-pollutant models to estimate air pollution-related health risks. The authors emphasized the importance of considering the overall ambient air pollution mix in data analysis.

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, BS, and CO were averaged over all available monitoring stations. Autoregressive models were used, with log-transformed daily mortality as the dependent variable and with adjustment for temperature, relative humidity, year, season, day of week, and serial correlations in mortality. Separate models for log(SO_2), log(BS), and log(CO) yielded statistically significant effects estimates ($p < 0.001$). Air pollution measurements lagged by 1 day were associated most strongly with daily mortality. In a multi-pollutant model, SO_2 and BS were independent predictors of mortality, although 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 Air Pollution and Health—A European Approach (APHEA) 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 over 5 years, 1987 to 1991. 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 maximum 8-h ambient CO concentration was 1.10 (95% CI = 1.05, 1.15). This finding may be attributable to yet unknown health effects of ambient levels of CO, to the presence of highly compromised susceptible groups in the population, or, again, to CO acting as a surrogate for other combustion-generated air pollutants. Also, ambient CO concentrations were high during this study, and this may have predisposed toward observing a positive statistical effect of CO on mortality.

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. Maximum ambient PM_{10} concentrations ranged from 339 to 500 μg/m^3 across the monitoring stations in 1989. Ambient concentrations of CO and fine PM were not reported. Total daily mortality (excluding death by injury and poisoning) was regressed on daily maximum 8-h average CO, 24-h average fine PM, humidity, and temperature, using Poisson regression. When all days were included in the model, effects of CO, humidity, and temperature were statistically significant, but the fine PM effect was not. When the model included only days with fine PM levels under 150 μg/m^3, the fine PM effect also became significant. The authors constructed maps showing standardized mortality ratios for total and respiratory mortality in different zones of the Santiago area. They reasoned from these maps, together with the regression analyses described above, that ambient air pollution exposure might well be a more important risk factor than socioeconomic status for total mortality and respiratory mortality in adults. However, no analytical models included environmental and socioeconomic variables simultaneously. Cardiovascular mortality was not assessed.

Wietlisbach et al. (1996) assessed associations 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 CO, TSP, SO_2, NO_2, and O_3 were obtained in each city (TSP and O_3 measurements were not available in Geneva). For each pollutant except O_3, the 3-day moving average ambient concentration, ending on the day of death (0-day lag), was used in the analysis. A 1-day average was used for O_3. The study mean daily average CO ranged from 0.95 mg/m^3 (0.83 ppm) in Basel to 1.93 mg/m^3 (1.68 ppm) in Geneva. The study mean daily average TSP was 46.2 μg/m^3 in Zurich and 45.2 μg/m^3 in Basel. Single-pollutant Poisson models were used to regress daily death counts on pollutant levels in each city, controlling for time trends, seasonal factors, and weather variables.

In the Wietlisbach et al. (1996) study, air pollution-mortality associations in single-pollutant models were generally somewhat stronger in the elderly than in the population as a whole and were somewhat stronger for respiratory mortality than cardiovascular mortality. Associations of mortality with CO were somewhat weaker than with TSP, NO_2, and SO_2. In Zurich, TSP and NO_2 were associated statistically significantly with total daily mortality; TSP, NO_2, and CO were associated significantly with mortality in the elderly; all five pollutants were associated significantly with respiratory mortality (the association with O_3 was negative); and no pollutants were associated significantly with cardiovascular mortality. In Basel, all pollutants but O_3 were associated significantly with total mortality; all pollutants were associated signficantly with mortality in the elderly; TSP and NO_2 were associated significantly with respiratory mortality; and all pollutants but O_3 were associated significantly with cardiovascular mortality. In Geneva, SO_2 and NO_2 were associated significantly with total mortality; SO_2, NO_2, and CO were associated significantly with mortality in the elderly and with respiratory mortality; and TSP and SO_2 were associated significantly with cardiovascular mortality. 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 24-h average 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 overall study mean of 24-h average ambient CO concentrations was 1.18 ppm. Overall means of estimated PM_{10} and fine PM concentrations were 30.2 and 18.0 $\mu g/m^3$, respectively. 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 2-day moving average was selected as the optimum metric 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 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 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 multi-pollutant 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 frequency attributable to combined exposure to all four pollutants differed widely among cities, 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 reducing mortality. It is not possible to interpret this study quantitatively, because metrics of PM and PM constituents were not included in the analyses. At the same time, these 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 ambient CO, other ambient gaseous pollutants, and PM.

There have been few studies of ambient CO and mortality in children. Saldiva et al. (1994, 1995) observed no association between CO and daily mortality among children or the elderly in São Paulo, Brazil, after adjusting for nitrogen oxides and PM_{10}, although Pereira et al. (1998) did report a 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, although intrauterine mortality was associated somewhat less strongly with CO than with other pollutants. 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.

Time series studies of ambient CO and daily mortality counts are summarized in Table 6-8.

6.2.1.4 Ambient Carbon Monoxide and Frequency of Respiratory Illness

Short-term variation in ambient CO levels has been reported in several studies to be associated with daily variation in indices of respiratory illness frequency. In most cases, these indices reflect exacerbation of preexisting respiratory illness. Significant positive associations of ambient CO with respiratory illness frequency have been observed less often than with heart disease exacerbation. Also, there is as yet no demonstrated biological mechanism by which CO at ambient exposure levels could plausibly promote respiratory illness exacerbation or new respiratory illness. Therefore, observed associations of ambient CO with such exacerbation should be interpreted very cautiously and, by no means, should be considered confirmed. At the same time, it is appropriate to discuss these associations because they indicate that short-term ambient CO exposure may not be specifically linked epidemiologically only with heart disease. The correct interpretation of this apparent lack of specificity is not yet known. On one hand, it could suggest that short-term ambient CO exposure effects are not confined to the cardiovascular system. On the other hand, it could also be taken as a caveat in regard to the observed associations of ambient CO with heart disease exacerbation because, although the pathophysiologic connection of CO with respiratory disease is more tenuous than with heart disease, statistical associations of CO with respiratory disease frequency have nevertheless been reported.

Sunyer et al. (1991) investigated daily emergency department visits for chronic obstructive pulmonary disease in Barcelona, Spain, in relation to short-term ambient air pollution levels during 1985 and 1986. Emergency department visits for asthma were excluded. Pollutants considered were daily average and daily maximum hourly SO_2, daily average BS, and daily maximum hourly CO, NO_2, and O_3. Ambient levels of CO were quite low during the study: yearly mean of daily maximum hourly levels = 5.4 mg/m^3 (4.7 ppm), and 98th percentile = 14.9 mg/m^3 (13.0 ppm). In single-pollutant regression models adjusted for meteorology, season, and day of week, positive, statistically significant effects estimates were observed most consistently for SO_2 lagged 0 or 1 day, but not 2 days. Effects were significant for both daily average and maximum hourly SO_2 levels. Effects of BS and CO were also positive and statistically significant ($p < 0.01$). Effects of NO_2 and O_3 were not significant. Air pollution effects on visits were weaker in fall than in other seasons. Effects of SO_2 remained positive and significant even when days with daily average SO_2 above 72 μg/m^3 (181 days, 24.8% of all 730 study days) were excluded from analysis.

Gordian et al. (1996) examined relationships between short-term ambient air pollution levels and daily outpatient visits for asthma, bronchitis, and upper respiratory illness (e.g., sore throat, sinusitis, earache, rhinitis) in Anchorage, AK, from May 1992 to March 1994. Numbers of visits were derived from medical insurance claims by state and municipal employees and their dependents. Measurements of CO were made only during winter months. An increase of 10 μg/m^3 in PM_{10} was associated with a 3 to 6% increase in visits for asthma and a 1 to 3% increase in visits for upper respiratory illness. Winter CO concentrations were associated with increased numbers of visits for bronchitis and upper respiratory illness, but not for asthma. At the same time, these CO concentrations were tightly correlated with overall automobile exhaust emissions, including NO_2, fine particles, and VOCs such as benzene. Thus, visits for respiratory illness could not be linked specifically to ambient CO exposure.

Yang et al. (1997) investigated asthma emergency room visits in Reno, NV, in relation to short-term ambient air pollution levels during 3 years, 1992 to 1994. Analytical methods were similar to those used in Yang et al. (1998). Briefly, there was a positive, statistically significant association of visits with

Table 6-8. Summary of Time Series Studies of Ambient Carbon Monoxide and Daily Mortality Counts

Reference	Health Outcomes, Study Locations, Period of Study	Ambient Air Pollutants Assessed and Pollutant Concentrations	Findings: Single-Pollutant Models	Findings: Multiple-Pollutant Models	Comments
Kinney and Özkaynak (1991)	Daily nonaccidental, nonviolent deaths from all causes, cardiovascular causes, and respiratory causes, Los Angeles County, CA, 1970-1979	"Daily maximum" CO, daily maximum hourly total oxidants, 24-h average SO_2, NO_2, KM, and visual extinction coefficient. Mean annual levels of daily maximum CO decreased over time (11.2 ppm in 1970, 6.1 ppm in 1979).	None reported.	In two-pollutant models, total mortality and cardiovascular mortality were associated statistically significantly with total oxidants (1-day lag) and each of the following pollutants: CO, NO_2, and KM.	Levels of CO, NO_2, and KM were highly correlated. Numbers of respiratory deaths were too small to give powerful tests of ambient pollutant effects on respiratory mortality. Size-specific PM metrics were not available.
Ito et al. (1995)	Daily nonaccidental deaths in Los Angeles County, CA, and Cook County (Chicago), IL, 1985-1990	Daily maximum 1-h CO. PM_{10}, O_3. Ambient CO concentrations were not reported.	An association of mortality with CO (2-day lag) was observed in Los Angeles, but not in Cook County.	None reported for CO.	The authors concluded that mortality risk estimates for PM_{10} depend on the choice of monitoring sites to include in analysis.
Ito and Thurston (1996)	Daily nonaccidental deaths in population subgroups (e.g. race- and sex-specific deaths), Cook County (Chicago), IL, 1985-1990	CO, PM_{10}, O_3, SO_2. Mean and 90th percentile ambient CO levels = 2.05 and 3.25 ppm, respectively. Mean and 90th percentile PM_{10} levels = 40.7 and 65.0 $\mu g/m^3$, respectively.	Total mortality was associated most consistently with PM_{10} and O_3. There was no consistent association of CO with mortality.	None reported for CO.	Air pollution effects on mortality were especially pronounced in black women.
Kelsall et al. (1997)	Daily mortality (excluding external causes) in persons <65, 65-74, and ≥75 years old, Philadelphia, PA, 1974-1988	CO, TSP, SO_2, NO_2, O_3. The mean and 75th percentile of daily CO levels = 1.74 and 2.05 ppm, respectively. Mean and 75th percentile TSP = 67.3 and 82.0 $\mu g/m^3$, respectively.	CO was maximally predictive of mortality with a 3-day lag. TSP, SO_2, lagged CO, and O_3 had positive effects on mortality.	Lagged CO was not associated statistically significantly with mortality.	The effect of TSP on mortality increased with increasing age.

Table 6-8 (cont'd). Summary of Time Series Studies of Ambient Carbon Monoxide and Daily Mortality Counts

Reference	Health Outcomes, Study Locations, Period of Study	Ambient Air Pollutants Assessed and Pollutant Concentrations	Findings: Single-Pollutant Models	Findings: Multiple-Pollutant Models	Comments
Verhoeff et al. (1996)	Total daily deaths in Amsterdam, The Netherlands, 1986-1992	CO, PM_{10}, BS, SO_2, O_3. Mean and 75th percentile of daily average CO = 0.97 and 1.21 mg/m^3, respectively. Mean and 75th percentile of PM^{10} = 39 and 45 $\mu g/m^3$, respectively.	Modeled effects of CO were not statistically significant and did not change appreciably with lags of 0, 1, and 2 days.	Effects of CO were not statistically significant in models that also included BS or PM_{10}. Effects of BS were somewhat stronger than effects of PM_{10}.	Modeled effects of particulate metrics were somewhat stronger than effects of gaseous pollutant metrics.
Touloumi et al. (1994)	Daily all-cause mortality, Athens, Greece, 1984-1988	Daily average CO, BS, SO_2. Mean annual ambient CO levels ranged from 4.63 mg/m^3 (1988) to 6.92 mg/m^3 (1984).	CO, BS, and SO_2 were associated with mortality. Mortality-pollutant associations were strongest with a 1-day lag.	Addition of CO to a model with BS and SO_2 metrics did not improve the model's ability to predict mortality.	
Salinas and Vega (1995)	Daily deaths, Santiago, Chile, 1988-1991	CO, fine PM. Ambient concentrations were not reported.	None reported.	When all days were included, CO was statistically significantly associated with daily deaths, but fine PM was not. When analysis was restricted to days with fine PM <150 $\mu g/m^3$, both pollutants were associated significantly with deaths.	
Burnett et al. (1998b)	Daily nonaccidental mortality, 11 Canadian cities, 1980-1991	CO, NO_2, O_3, SO_2. Overall mean of daily average ambient CO = 1.0 ppm, ranging from 0.4 ppm in London, Ontario, to 1.5 ppm in Toronto.	Modeled effects estimates for ambient CO were more consistent across cities than were estimates for other pollutants.	CO effects estimates were substantially smaller than in single-pollutant models. Inclusion of SO_2 and NO_2 explained much of the CO-associated effect on daily mortality.	Analyses did not include PM metrics, so quantitative effects of gaseous pollutants cannot be inferred with confidence.
Wietlisbach et al. (1996)	Daily deaths from all causes, respiratory causes, and cardiovascular causes, Zurich, Basel, and Geneva, Switzerland, 1984-1989	Daily CO, TSP, SO_2, NO_2, O_3. Mean ambient CO levels in Zurich, Basel, and Geneva were 1.25, 0.95, and 1.93 mg/m^3 (1.09, 0.83, and 1.68 ppm), respectively. Mean TSP levels in Zurich and Basel were 46.2 and 45.2 $\mu g/m^3$, respectively.	Associations of mortality with CO were statistically significant, but somewhat smaller than with TSP, SO_2, and NO_2. CO effects appeared strongest with a 3-day lag.	When all pollutants were modeled simultaneously, their estimated effects were unstable and were not statistically significant.	TSP measurements were not available in Geneva.

Table 6-8 (cont'd). Summary of Time Series Studies of Ambient Carbon Monoxide and Daily Mortality Counts

Reference	Health Outcomes, Study Locations, Period of Study	Ambient Air Pollutants Assessed and Pollutant Concentrations	Findings: Single-Pollutant Models	Findings: Multiple-Pollutant Models	Comments
Saldiva et al. (1995)	Daily deaths in persons ≥65 years old, São Paulo, Brazil, May 1990-April 1991	CO, PM_{10}, NO_x, SO_2, O_3. Mean daily CO and PM_{10} = 6.18 ppm and 82.4 $\mu g/m_3$, respectively.	Modeled effects of CO and SO_2 were statistically significant at $\alpha = 0.05$. Effects of PM_{10} and NO_x were significant at $\alpha = 0.01$.	The modeled PM_{10} effect was statistically significant at $\alpha = 0.01$. Effects of other pollutants were not significant.	
Saldiva et al. (1994)	Daily deaths from respiratory causes in children <5 years old, São Paulo, Brazil, May 1990-April 1991	CO, PM_{10}, NO_x, SO_2, O_3. Mean daily CO and PM_{10} = 6.18 ppm and 82.4 $\mu g/m_3$, respectively.	None reported (see Comments).	In a model with all pollutants, the effects estimate for CO was small, negative, and not statistically significant (see Comments). There was a strong association of childhood respiratory mortality with NO_x.	It is not entirely clear whether the reported pollutant effects estimates are from single-pollutant or multi-pollutant models.
Pereira et al. (1998)	Daily intrauterine mortality occurring after 28 weeks of gestation, São Paulo, Brazil, 1991-1992	CO, PM_{10}, NO_2, SO_2, O_3. Mean and maximum ambient CO levels = 5.7 and 12.5 ppm, respectively. Mean and maximum PM_{10} levels = 65.0 and 192.8 $\mu g/m^3$, respectively.	The modeled effects of CO and SO_2 were statistically significant at $\alpha = 0.10$. The effect of NO_2 was significant at $\alpha = 0.01$.	In a model with all pollutants, the effect of NO_2 was significant at $\alpha = 0.01$, and effects of other pollutants were not significant. The overall air pollution effect was best explained by a composite air pollution index that incorporated ambient levels of NO_2, CO, and SO_2.	The authors' use of a composite air pollution index is of interest. Even so, the reported results are difficult to interpret quantitatively, because the most spontaneous abortions occur before 28 weeks of gestation. In a second study, ambient CO levels, adjusted for passive smoking and birth weight, were associated significantly with cord blood CO levels at $\alpha = 0.01$.

the ambient O_3 level lagged 0 days, but not 1 or 2 days. Visits were not associated with ambient CO or PM_{10} levels.

Two reports investigating asthma exacerbation in relation to short-term ambient levels of CO and other air pollutants, published in 1999 by University of Washington investigators (Sheppard et al., 1999; Norris et al., 1999), highlight difficulties inherent in efforts to specify single-pollutant effects in populations exposed to complex ambient air pollution mixes. Sheppard et al. (1999) considered admissions for asthma to 23 greater Seattle hospitals from 1987 through 1994 in persons aged <65 years. Fifty-four percent of these admissions occurred in persons less than 20 years old. Pollutants considered were daily average CO, PM_{10}, $PM_{2.5}$ (fine PM), $PM_{10-2.5}$ (coarse PM), SO_2, and daily maximum 8-h average O_3. The CO monitors were located in street canyons, not residential areas. The PM_{10} was measured with both the EPA reference method and with light-scattering nephelometry. Fine PM levels were estimated largely from PM_{10} measurements. Coarse PM levels were calculated as the difference between PM_{10} and fine PM levels. The PM measurements from residential sites were given higher weight (80%) than those from an industrial site (20%). During the study period, 50th-percentile ambient levels of average CO, PM_{10}, fine PM, and coarse PM were quite moderate (1.7 ppm and 27, 13, and 14 $\mu g/m^3$, respectively). Data were analyzed to treat all measured pollutants evenhandedly. Semiparametric Poisson regression models were used and included dummy variables for day of week. Multiple lag times were considered; for each pollutant, the lag time showing the strongest statistical association with admissions was selected. Single- and two-pollutant models were constructed, and pollutant effects estimates were reported over IQRs of ambient pollutant concentrations.

In single-pollutant models, CO lagged 3 days and O_3 lagged 2 days were associated most strongly with asthma admissions. Associations of admissions with PM_{10}, fine PM, and coarse PM, each lagged 1 day, were also positive and statistically significant. The association of admissions with SO_2 (lagged 0 days) was positive but not significant. In season-specific, two-pollutant models, generally similar effects were observed for CO lagged 3 days and fine PM lagged 1 day. Over all seasons, effects of both pollutants were positive and significant. Both pollutants were positively, and at least marginally significantly, associated with admissions in fall, winter, and spring. Both pollutants were negatively associated with admissions in summer. Sheppard et al. (1999) stated, "In striving for a balanced approach to all measured pollutants..., we observed unexpected associations for CO that dominated the PM effects. Nevertheless,... there is no evidence for an effect [of CO] on the underlying physiology of asthma. CO may be an important environmental indicator of incomplete combustion, particularly from mobile sources."

Norris et al. (1999) investigated short-term ambient air pollution and emergency department visits for asthma in Seattle children aged <18 years, from September 1995 through December 1996. Analyses were conducted for the entire study population, for urban children (in whom the reported overall annual hospitalization rate was more than 600/100,000), and for suburban children (in whom the reported overall rate was less than 100/100,000). Pollutants considered were daily average CO, PM_{10}, and PM_1 (as measured by nephelometer); hourly average SO_2; and daily maximum hourly average and daily average NO_2. During the study period, mean ambient levels of CO, PM_{10}, and fine PM were 1.6 ppm, 21.7 $\mu g/m^3$, and 12 $\mu g/m^3$ (estimated), respectively. There were too few O_3 measurements to include in analytical models. Relative risks were reported over IQRs of pollutant concentrations. Lag times of 0 through 4 days were considered. Models were adjusted with dummy variables for day of week, smoothing splines for time trends (approximately a 2-mo moving average), ambient temperature, and dew point temperature.

Pollutant effects on asthma visits usually were reported with a 1-day lag. In single-pollutant models, effects of PM_1 and PM_{10} were consistently positive and at least marginally statistically significant. Effects of CO were also consistently positive, but not significant in the urban children. Effects of daily average NO_2, lagged 2 days, were positive and marginally significant. Mixed results were observed for other pollution metrics. In multi-pollutant models, effects of PM_1 and PM_{10} remained positive and statistically significant, but SO_2 and NO_2 effects did not retain significance. Multi-pollutant models did not include CO

because CO was assumed a priori to be a surrogate for stagnant conditions. Norris et al. (1999) stated, "In summary, this study found a small but significant association between air pollution and increased ED [emergency department] visits for asthma.... PM and CO concentrations...were associated with increased childhood ED visits for asthma and represent the daily variation in incomplete combustion products...."

The exclusion of CO from multi-pollutant models by Norris et al. (1999) appears dubious, because both they and Sheppard et al. (1999) observed statistically significant associations of both PM and CO with asthma exacerbation in single-pollutant models. The assumption that CO is a surrogate for stagnant conditions may well be valid, but no rationale was presented for why the same assumption could not be made for the other combustion-related air pollutants that were included in the multi-pollutant models. Also, if ambient CO is merely a biologically inert fellow-traveler with ambient PM, it would be difficult to understand why, in Sheppard et al. (1999), the CO-asthma association was strongest when lagged 3 days, whereas the PM-asthma association was strongest when lagged only 1 day. Furthermore, although it is true that there is no known biological mechanism by which CO at ambient levels could exacerbate asthma, the mechanistic linkage of combustion-related, nonbiological PM with asthma exacerbation remains to be more clearly elucidated as well. Finally, the authors' assumption that children under 18 years old are more "susceptible" than the general population is somewhat questionable, because short-term elevations in ambient air pollution levels have been associated most strongly with unequivocally harmful health effects in the elderly, and because asthma death rates and case-fatality rates are higher in adults than in children.

Time series studies of ambient CO and daily frequency of respiratory illness are summarized in Table 6-9.

6.2.1.5 Ambient Carbon Monoxide and Low Birth Weight

Low birth weight (typically defined as birth weight $\leq$2,500 g) is associated with infant mortality and childhood morbidity and may predict increased risk of morbidity into adulthood (Joseph and Kramer, 1996; Institute of Medicine, 1985). Although low birth weight is probably not a direct cause of these harmful outcomes, it is a useful marker for developmental disturbances that are more directly responsible (Weinberg and Wilcox, 1998).

Alderman et al. (1987) conducted a case-control study of birth weight in relation to ambient CO concentration in Denver, CO, from 1975 through 1983. The CO metric was the time-weighted geometric mean ambient CO level as measured in the mother's neighborhood during the last 3 mo of gestation. The large majority of mothers lived within 2 mi of their neighborhood monitoring sites. Median and 95th percentile CO concentrations ranged among monitoring sites from 0.5 to 3.6 ppm and 0.8 to 4.8 ppm, respectively. Air pollutants other than CO were not considered in analysis. Individual-level data on maternal age, race, education, marital status, parity, and prior pregnancy history were available from birth certificates, but data on mother's personal CO exposure and smoking were not available. Ambient CO exposures were divided into quintiles and analyzed with Mantel-Haenszel methods, adjusting for mother's race and education. No association of ambient CO level with frequency of birth weight $\leq$2,500 g was observed in these analyses. After consultation with exposure assessment experts, the investigators divided subjects into two groups for whom the monitoring data were considered to reflect true CO exposure more and less accurately. Separate analyses of these two groups were conducted. Interestingly, there was more suggestion of a positive, monotonic CO effect in the former group (p value for chi-square test of trend equaled 0.07 [marginally significant]) than in the latter group (p = 0.56 [not significant]).

Ritz and Yu (1999) assessed low birth weight in southern California, in relation to ambient CO levels, from 1989 through 1993. The health outcome analyzed was incidence of birth weight <2,500 g in singleton babies born at term (37 to 44 weeks of gestation), treated as a dichotomous variable. Birth weights <1,000 g and >5,500 g were excluded. The main exposure variable was the average ambient CO level from 6:00 to 9:00 a.m. during the third trimester of pregnancy, as measured at the South Coast Air Quality Management District (SCAQMD) monitoring station nearest the mother's residence. This metric

Table 6-9. Summary of Time Series Studies of Ambient Carbon Monoxide and Daily Frequency of Respiratory Illness

Reference	Health Outcomes, Study Locations, Period of Study	Ambient Air Pollutants Assessed and Pollutant Concentrations	Findings: Single-Pollutant Models	Findings: Multiple-Pollutant Models	Comments
Sunyer et al. (1991)	Daily emergency department visits for chronic obstructive pulmonary disease (excluding asthma), Barcelona, Spain, 1985 and 1986	Daily maximum hourly CO, NO_2, O_3, SO_2. Daily average SO_2, BS. Mean CO = 5.4 mg/m^3. 98th percentile CO = 14.9 mg/m^3. Mean BS = 72.9 μg/m^3.	SO_2 exerted the strongest pollutant effects. BS and CO also had statistically significant positive effects.	None reported.	
Gordian et al. (1996)	Insurance claims for daily outpatient visits for asthma, bronchitis, and upper respiratory illness (URI), Anchorage, AK, May 1992-March 1994	PM_{10}, CO (fall/winter only). Mean PM_{10} = 45.5 μg/m^3. Mean CO = 2.5 ppm.	PM_{10} was associated with increased numbers of visits for asthma and URI. Fall/winter CO was associated with increased numbers of visits for bronchitis and URI.	Models that included PM_{10} and CO simultaneously produced essentially the same results as single-pollutant models. This suggests that CO and PM_{10} effects were at least partly independent.	Effects of CO could not be separated confidently from effects of other automotive pollutants, including benzene.
Yang et al. (1997)	Daily emergency room visits for asthma, Reno, NV, 1992-1994	CO, PM_{10}, O_3. Mean CO = 4.6 ppm. Mean PM_{10} (gravimetric) = 38.0 μg/m^3.	Asthma visits were associated with daily maximum O_3 lagged 0 days, but not 1 or 2 days. Visits were not associated with CO.	None reported.	
Sheppard et al. (1999)	Daily hospital admissions for asthma in persons aged <65 years, Seattle, WA, 1987-1994	Daily average CO, PM_{10}, fine PM, coarse PM, SO_2. Daily maximum 8-h average O_3.	The strongest associations were observed for CO lagged 3 days and O_3 lagged 2 days. Associations also were observed for PM metrics lagged 1 day.	In two-pollutant models, similar effects were observed for CO lagged 3 days and fine PM lagged 1 day. Over all seasons, effects of CO and fine PM were positive and statistically significant	CO and fine PM exerted similar statistical effects, with different lags. The authors noted that CO may be an indicator of incomplete combustion, especially from mobile sources.

Table 6-9 (cont'd). Summary of Time Series Studies of Ambient Carbon Monoxide and Daily Frequency of Respiratory Illness

Reference	Health Outcomes, Study Locations, Period of Study	Ambient Air Pollutants Assessed and Pollutant Concentrations	Findings: Single-Pollutant Models	Findings: Multiple-Pollutant Models	Comments
Norris et al. (1999)	Daily emergency department visits for asthma in persons aged <18 years, Seattle, WA, September 1995-December 1996	Daily average CO, PM_{10}, PM_{1}. Hourly average SO_2. Daily average and daily maximum hourly average NO_2. Daily average fine PM (estimated). Daily average CO = 1.6 ppm. Daily average PM_{10} = 21.7 $\mu g/m^3$. Daily average PM_{1} = 0.4 m^{-1}.	Effects of PM_{1} and PM_{10} (1-day lag) were positive and at least marginally statistically significant. Effects of CO (1-day lag) were positive, not always significant. Effects of NO_2 (2-day lag) were marginally significant.	CO was not included in multi-pollutant models. In these models, effects of PM_{1} and PM_{10} retained statistical significance, but effects of gaseous pollutants did not.	This study and Sheppard et al. (1999), show generally similar statistical effects of PM metrics and CO on daily frequency of asthma exacerbations.

was chosen after consultation with SCAQMD aerometric experts. Births were included only if the mother's residential zip code was entirely or largely within 2 mi of one of 18 SCAQMD stations. The large majority of study mothers lived within 2 mi of the nearest station. Thus, this study, like that of Alderman et al. (1987), addressed the fact that ambient CO levels often exhibit considerable spatial variability. The overall average third-trimester ambient CO level was 2.6 ppm; average CO levels ranged from 1.44 to 3.72 ppm across the monitoring stations. Data were analyzed with logistic regression, adjusting for gestational age, parity, time since previous birth, infant's gender, and mother's age, educational level, and ethnic group. Ecological variables for commuting habits, constructed from census data for the respective zip codes, also were included.

A total of 125,573 term births (92.1% of 136,376 eligible births) was included in analysis. Birth weight was <2,500 g in 2,813 (2.2%) of these. The analysis predicted a 22% increase in incidence of low birth weight among babies born to mothers with average ambient CO exposure above the 95th percentile of 5.5 ppm (odds ratio 1.22 [95% CI 1.03, 1.44]). This rose to 33% when first births were excluded and to 54% for mothers <20 years old. Average ambient CO levels during the first and second trimesters and during all trimesters combined were not associated with low birth weight incidence.

Measurements of O_3, NO_2, and PM_{10} were made at six of the 18 monitoring stations. Multi-pollutant models were constructed for subjects living near these six stations. In these models, ambient third-trimester ambient CO levels were categorized into 0 to 50th percentile (reference category), 50 to 95th percentile (2.2 to 5.5 ppm), and >95th percentile (>5.5 ppm). The authors stated, "The effects of CO appeared more pronounced after adjustment for concurrent exposures to NO_2, PM_{10}, and ozone," although specific effects estimates for the non-CO pollutants were not reported. In the multi-pollutant models, incidence of low birth weight consistently increased with increasing ambient CO level. Effects estimates for the highest CO exposure category achieved statistical significance for births after the first birth and for births to mothers <20 years old, but not for all births.

Ritz and Yu (1999) provide justification for their choices of study population, exposure period (third trimester), pollution averaging time (6:00 to 9:00 a.m.), and allowable distance of subjects' residences from monitoring stations. They identify important, relevant unmeasured factors such as maternal smoking, nutrition, prepregnancy weight, adverse pregnancy experience, and occupational history. They acknowledge that confounding because of these factors is possible. They also argue that their study design and analytical approach render serious confounding unlikely.

Taken together, the Alderman et al. (1987) and Ritz and Yu (1999) studies tend to raise concern as to whether contemporary ambient CO exposure is a risk factor for low birth weight. The findings have some biological plausibility because the CO binding affinity of fetal Hb is somewhat greater than that of adult Hb, and, at a given level of CO exposure, tissue O_2 delivery is reduced more in the fetus than in the child or the adult, in whom fetal Hb has been replaced by adult Hb (Longo, 1976). The observation by Pereira et al. (1998) of an association of ambient CO concentration with cord blood COHb level reinforces this concern. Both Alderman et al. (1987) and Ritz and Yu (1999) recommend further research with individual-level measurements of CO exposure and relevant covariates.

At the same time, the Alderman et al. (1987) and Ritz and Yu (1999) studies are not conclusive because neither study controlled for relevant covariates at the individual level. Lack of control for lead exposure is noteworthy in this regard because lead, like CO, is associated with mobile sources. Furthermore, lead is associated with a variety of harmful reproductive outcomes, including low birth weight (U.S. Environmental Protection Agency, 1986, 1990). Potential confounding by lead exposure may be of particular concern for the Alderman et al. (1987) study, which assessed births occurring at least a decade earlier than those assessed in the Ritz and Yu (1999) study.

Studies of ambient CO and low birth weight are summarized in Table 6-10.

Table 6-10. Summary of Epidemiologic Studies of Ambient Carbon Monoxide and Low Birth Weight

Reference	Health Outcomes, Study Locations, Period of Study	Ambient Air Pollutants Assessed and Pollutant Concentrations	Findings: Single-Pollutant Models	Findings: Multiple-Pollutant Models	Comments
Alderman et al. (1987)	Case-control study of birth weight, Denver, CO, 1975-1983	Time-weighted geometric mean ambient CO level during the last 3 mo of gestation (third trimester of pregnancy). The median CO ranged from 0.5 to 3.6 ppm across monitoring sites.	No association of ambient CO with birth weight <2,500 g was observed in the study population as a whole. A marginally statistically significant association was observed in subjects for whom ambient CO exposure estimates were considered to be relatively accurate.	None reported.	Data on mother's smoking, personal CO exposure, and other relevant characteristics were not available.
Ritz and Yu (1999)	Large ecologic study of incidence of birth weight <2,500 g, southern California, 1989-1993	Mean ambient CO level from 6:00-9:00 a.m. during the third trimester of pregnancy. Overall average ambient CO = 2.6 ppm (range across 18 monitoring stations = 1.44-3.72 ppm). PM_{10}, O_3, and NO_2 measurements were available from six of the 18 monitoring stations.	Analysis predicted a 22% increase in low birth weight incidence in mothers with average ambient CO exposure above the 95th percentile of 5.5 ppm. The CO effect was stronger for births after the first birth, and in mothers <20 years old, than in the study population as a whole.	Effects of CO appeared more pronounced than in single-pollutant models. Low birth weight incidence was monotonically related to estimated ambient CO exposure. Effects of CO in the highest exposure category were statistically significant for births after the first birth, and in mothers <20 years old.	Data on mother's smoking, personal CO exposure, and other relevant characteristics were not available. Despite this, the authors argued thoughtfully that observed CO effects were unlikely to be seriously confounded with unmeasured factors.

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 those 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).

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 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 6-3). 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.

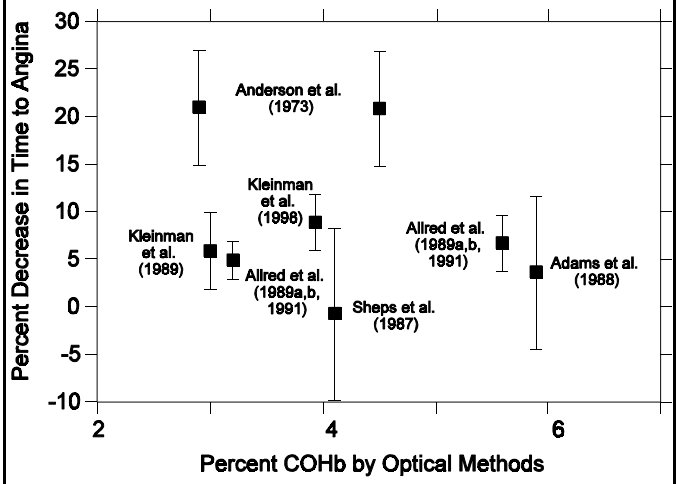

Figure 6-3. The effect of CO exposure on time to onset of angina. For comparison across studies, data are presented as mean percent differences between air- and CO-exposure days for individual subjects calculated from each study. Bars indicate calculated standard errors of the mean. The COHb levels were 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).

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 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 (n = 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 6-3). 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 IHD, 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 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 ($\leq$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 an MI (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 IHD 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 this does not occur at lower COHb levels (Sheps et al., 1990, 1991; Chaitman et al., 1992; Dahms et al., 1993). This finding, combined with the 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), suggests 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 affect adversely the cardiovascular system. The lowest-observed-effect level (LOEL) varies, depending on the exposure regime used and species tested (see Table 6-11). 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 Hb concentration and hematocrit ratio, probably representing compensation for the reduction in oxygen transport caused by CO. At high CO concentrations, excessive increases in Hb and hematocrit may impose an additional workload on the heart and compromise blood flow to the tissues.

There is conflicting evidence suggesting that CO exposure may enhance 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 ($\approx$20%) COHb saturations (U.S. Environmental

Table 6-11. Estimated Lowest-Observed-Effect Levels for Cardiovascular Effects of Exposure of Laboratory Animals to Carbon Monoxide

Health Effect Category	LOEL		Duration	Species	Reference
	CO (ppm)	COHb (%)			
Cardiovascular effects					
Cardiac rhythm	50	2.6	6 weeks[a]	Dog	Preziosi et al. (1970)
Cardiomegaly	200	15.8	30 days[a]	Rat	Penney et al. (1974)
Hemodynamics	150	7.5	30 min	Rat	Kanten et al. (1983)
Hematology	100	9.3	46 days[a]	Rat	Penney et al. (1974)
Atherosclerosis and thrombosis	250	20.0	10 weeks[b]	Rabbit	Davies et al. (1976)

[a]Continuous daily exposure.
[b]Intermittent daily exposure, 4 h/day.

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, vasodilation in the brain (and increased blood supply) occurs sufficiently 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 adequately compensates not only for the oxygen supply decrease caused by reduced arterial O_2 content (CaO_2), but it 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 seen by combining the information of Doblar et al. (1977) from goats and Langston et al. (1996) from sheep into one graph (see Figure 6-4). Although information from Jones and

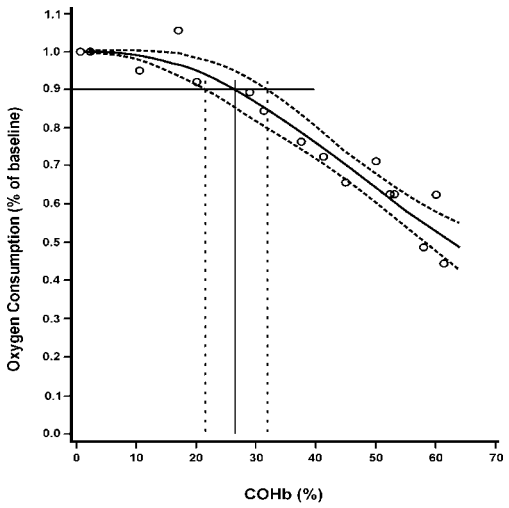

Figure 6-4. The relationship between COHb and $CMRO_2$ for goats and sheep. Means from Doblar et al. (1977) were taken from their Tables 1 and 3, and $CMRO_2$ values were transformed to percent of baseline. Figures 1 and 3 of Langston et al. (1996) were converted digitally (Summasketch III graphical 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 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.

Traystman (1984) and associated studies was expressed as a function of CaO_2, not COHb, and was difficult to incorporate into Figure 6-4 and the associated analysis, their data corroborate those of the other workers.

From Figure 6-4, 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 in Figure 6-4.

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 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 that is 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 in 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 CO NAAQS 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; Putz, 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 on 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 not replicable.

Benignus (1994) performed extensive meta-analyses of the CO-behavioral literature. Only double-blind human CO studies were included (see Section 10.4.2 of U.S. Environmental Protection Agency, 1991). 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 rat experiments and corrected for the effects of hypothermia. The COHb for rats was estimated from exposure conditions by use of a rat-specific version of the Coburn-Forster-Kane Equation (Benignus and Annau, 1994). 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 present purposes using the same dose-effect model (a logit) as for the $CMRO_2$ data above (originally a different function was used); the results are plotted in Figure 6-5. With the logit function, it is estimated that a 10% decrement should be produced in rats by ≈25% COHb (95% confidence limits of ≈20 to 30%). Data from all available double-blind human studies also were converted to percent of baseline and plotted (Figure 6-6), along with the logit curve fitted to the rat data (from Figure 6-5).

The human data plotted in Figure 6-6 were mostly not statistically significant (thin solid lines) and seem, as a group, not to have a dose-related trend of decrements; thus, 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 (thin dashed lines) by the authors of the original reports.

The low-COHb significant results plotted in Figure 6-6 invariably were reported in studies in which only a few levels of COHb were evaluated. The two studies in which more and higher COHb levels were tested invariably did not find statistically significant effects, even at much higher levels. Furthermore, for

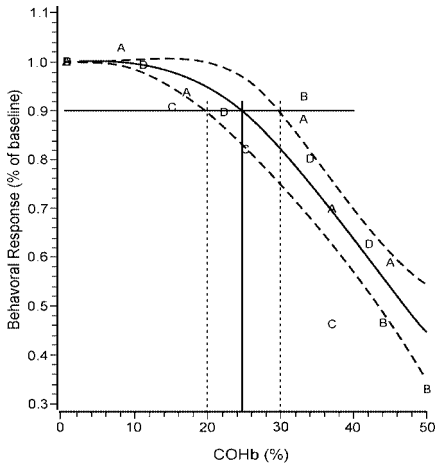

Figure 6-5. The relationship between COHb and behavior: effects in rats. Points plotted are the hypothermia-corrected means from four studies of effects of COHb in rats in which COHb was estimated by a rat-specific version of the Coburn-Forster-Kane Equation (see Benignus, 1994). The solid line is a best-fit logit curve to the rat data. The dashed lines are 95% confidence limits. The data points are means from various studies coded by letter as follows: A = Ator (1982), B = Ator et al. (1976), C = Smith et al. (1976), and D = Merigan and McIntire (1976).

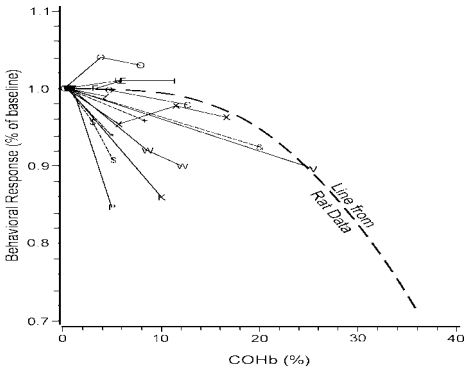

*Figure 6-6. The relationship between COHb and behavior: effects in humans compared to rats. Points plotted are means from various human studies. The heavy dashed line is the line fitted to rat data as shown in Figure 6-5. The points for the human data are connected by thin lines to depict the dose-effect curve found in each study. Solid thin lines are from studies in which no significant effect was found; dashed lines are from studies in which a significant effect was reported. The data points are coded such that alphabetic symbols are from nonsignificant studies and other symbols from significant studies. Investigators are coded as follows: X = Benignus et al. (1990), C = Benignus et al. (1977), K = Groll-Knapp et al. (1982), U = Harbin et al. (1988), O = Otto et al. (1979), W = Ramsey (1973), P = Roche et al. (1981), E = Stewart et al. (1973), V = Stewart et al. (1970), & = Weir et al. (1973), Z = Wright et al. (1973), + = Benignus et al. (1987), $ = Putz et al. (1976), * = Putz et al. (1979).*

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 replication. 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 wider range, dose-effect patterns 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, 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 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.

Behavioral work should be encouraged to determine whether reliable decrements in behavior truly are associated with low levels of COHb. However, any new experiments should involve several CO exposure levels, including one high enough to produce changes. In addition, inclusion of some other procedure or a reference dose of some other active substance would serve to verify the sensitivity of the behavior under study, thereby facilitating interpretation of any negative data collected at the chosen COHb levels. Studies that do not satisfy these specifications most likely would be unfruitful and only further confuse the present understanding of the published literature. In addition, other experiments should be designed to contribute to the understanding of how $CMRO_2$ relates to COHb elevation and behavioral changes.

Behaviors implicated by the research findings involve 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 better evidence of reliable behavioral effects are published, preferably in studies that demonstrate dose-related changes, conclusions must be formed from the extant set of experimental data.

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 also could be important. Interactions such as these are understood from physiological theory and could be given quantitative estimates through the use of physiological simulation using whole-body physiological models that are currently under development.

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. 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 suggest that exposure to lower levels of CO, leading to $\leq$10% COHb, should not have much of an effect on the developing fetus until possibly later in gestation when the embryo is much larger and more dependent on transport of oxygen by red blood cells (Robkin, 1997). In addition, results from a multicenter, prospective study (Koren et al., 1991) of fetal outcome following mild to moderate accidental CO poisoning in pregnancy suggest 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 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 use, lead exposure, alcohol consumption, genetic background, maternal general health, 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 between 6 and 23 h per day during the first trimester of pregnancy (Gestational Days 8 through 18). 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 56% 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; Shimazu et al., 1990). 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 generally 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 (≤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. No new studies have been published at CO levels relevant to ambient exposures. 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 (Żebro 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, Hb (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 IHD 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 these 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 only be hypothesized.

The mechanism by which long-term adaptation may occur, if it can be demonstrated in humans, is assumed to be increased Hb concentration via an increase in hemopoiesis. This alteration in Hb 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 Hb 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 (Longo, 1977), 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 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, excerpted from the last review, still applies because nothing significant has appeared in the recently published literature.

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 relevant concentrations of 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, 1999; Burnett et al., 1997a,b; Morris and Naumova, 1998; Burnett et al., 1999) 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 (>100 ppm) 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 (CO_2), 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).

All of the studies discussed above involve interactions with exogenous exposure to CO. There are endogenous sources of CO (e.g., heme degradation, peroxidative degradation of unsaturated fatty acids, xenobiotic metabolism) that also can lead to increased COHb saturation. These are discussed in more detail in Section 5.3 of this document. Possibly one of the greatest concerns regarding potential risk in the population comes from inhalation exposure to the halogenated hydrocarbons widely used as solvents, especially the dihalomethanes (e.g., methylene chloride [dichloromethane], dibromomethane,

diiodomethane, and bromochloromethane). There is some indication from the older literature (Fodor and Roscovanu, 1976) that oral exposure to trihalogenated methane derivatives also will lead to increased COHb. Other volatile solvents (e.g., carbon tetrachloride, chloroform, methanol) were tested in laboratory animals, but none produced increased levels of COHb (Pankow, 1996).

Methylene chloride provides the greatest potential exposure to the population because it has been used widely as a paint remover, degreaser, and aerosol propellant (Wilcosky and Simonsen, 1991). When inhaled, it will undergo metabolic breakdown by cytochrome P-450 in liver to form CO, chloride, and CO_2. Increased levels of CO from metabolic breakdown of exogenous chemicals will increase COHb measured in the blood and add to the increased COHb levels resulting from exogenous CO exposure (DiVincenzo and Kaplan, 1981a,b; Kurppa et al., 1981). The metabolism to CO can be saturated, leading to a slower elimination of COHb than after CO exposure (Pankow, 1996). In addition, any co-exposures to other chemicals or drugs that affect cytochrome P-450 also will affect COHb saturation (Kim and Kim, 1996; Wirkner et al., 1997).

6.8.4 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, passive smoking will be closer to pure CO exposure than active smoking, 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; He et al., 1999). The data suggest that nonsmokers exposed to ETS had a relative risk of CVD of approximately 1.3 (95% CI of 1.2 to 1.4). The association of CVD with prolonged exposure to ETS could 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). Unfortunately, given the size of this association (25 to 30%) compared to active smoking ($\approx$75%) and the inherent problems with the studies, it is still not known, with accuracy, how much, or even whether, exposure to ETS increases the risk of CVD (Bailar, 1999).

6.9 Summary

The effects of 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. 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 by controlled exposure studies to be associated with the low COHb levels (< 5%) that are expected to occur from exposure to ambient CO are summarized in Table 6-12. As shown in that table, 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%.

Table 6-12. Key Health Effects of Carbon Monoxide Demonstrated by Controlled-Exposure Studies

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 (CAD)	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 CAD	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 CAD and high baseline ectopy (chronic arrhythmia)	Sheps et al. (1990)
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.

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 are detectable by electrocardiographic (ECG) changes (ST depression) and associated angina, were statistically significant in one study at $\geq$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 $\geq$6% COHb (CO-Ox) in some people with CAD and high levels of baseline ectopy (a chronic arrhythmia) that may present an increased risk of sudden death.

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.

In addition to the controlled-exposure study findings highlighted in Table 6-12 for key human health effects most clearly demonstrated to be associated with COHb levels expected to occur from ambient or near-ambient level CO exposures, certain newly emerging community epidemiology study results warrant note here, as well. In time series epidemiologic studies, investigators have reported statistically significant associations of short-term ambient CO concentrations with daily frequencies of heart disease exacerbation in the elderly. Such associations have been observed most consistently during cold weather. Also, some investigators have observed associations of short-term ambient CO levels with daily mortality counts and with daily frequencies of respiratory illness. Results from experimental laboratory studies of high level exposures to CO, and occupational reports of increased morbidity and mortality in workers routinely exposed to combustion products, raise the possibility of community-level associations of ambient CO with harmful health outcomes. However, the available epidemiologic database must be considered inconclusive as to whether the reported statistical associations reflect actual and specific health effects of ambient CO exposure. As discussed above, short-term fluctuations in ambient CO at current U.S. levels would produce only very small changes in COHb levels. The rather low (typically <5.0 ppm) average daily maximum ambient CO levels evaluated in the epidemiologic analyses would be projected to increase COHB levels by barely detectable amounts with 1-h exposures and even 8-h exposures to 10 ppm CO with light to moderate exercise would produce only a 1.0% to 2.0% increase in COHb over the baseline level of about 0.5%. On pathophysiologic grounds, it remains difficult to reconcile such small expected changes in COHB concentrations with statistically detectable exacerbation of preexisting illness or with increased mortality at the community level.

Also, the epidemiologic database itself exhibits some degree of internal inconsistency. Specifically, the available studies suggest a considerably stronger association of ambient CO with cardiac morbidity than with respiratory morbidity. In view of this, a stronger association of ambient CO with cardiovascular mortality than with respiratory mortality might well be expected. In fact, however, the available database shows no such preferential association with cardiovascular mortality. Indeed, associations of ambient CO with respiratory mortality have been observed at least as frequently as with cardiovascular mortality. Further research is needed on short- and long-term exposure to ambient CO and other combustion-related air pollutants, and on the relative influence of exposure to pollutants from nonambient sources. In future epidemiologic studies of CO and other air pollutants, cause-specific relationships of pollution with morbidity and mortality should be characterized more thoroughly, and the consistency of findings on morbidity with findings on mortality should be critically assessed.

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 more 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, increasing risks for nonsmoking co-workers and family members. Carbon monoxide poisoning from indoor exposures to higher than ambient CO levels occurs frequently, has more severe consequences, and often is overlooked.

References

Abbatiello, E. R.; Mohrmann, K. (1979) Effects on the offspring of chronic low exposure carbon monoxide during mice pregnancy. Clin. Toxicol. 14: 401-406.

Adams, K. F.; Koch, G.; Chatterjee, B.; Goldstein, G. M.; O'Neil, J. J.; Bromberg, P. A.; Sheps, D. S.; McAllister, S.; Price, C. J.; Bissette, J. (1988) Acute elevation of blood carboxyhemoglobin to 6% impairs exercise performance and aggravates symptoms in patients with ischemic heart disease. J. Am. Coll. Cardiol. 12: 900-909.

Alderman, B. W.; Baron, A. E.; Savitz, D. A. (1987) Maternal exposure to neighborhood carbon monoxide and risk of low infant birth weight. Public Health Rep. 102: 410-414.

Allred, E. N.; Bleecker, E. R.; Chaitman, B. R.; Dahms, T. E.; Gottlieb, S. O.; Hackney, J. D.; Pagano, M.; Selvester, R. H.; Walden, S. M.; Warren, J. (1989a) Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. N. Engl. J. Med. 321: 1426-1432.

Allred, E. N.; Bleecker, E. R.; Chaitman, B. R.; Dahms, T. E.; Gottlieb, S. O.; Hackney, J. D.; Hayes, D.; Pagano, M.; Selvester, R. H.; Walden, S. M.; Warren, J. (1989b) Acute effects of carbon monoxide exposure on individuals with coronary artery disease. Cambridge, MA: Health Effects Institute; research report no. 25.

Allred, E. N.; Bleecker, E. R.; Chaitman, B. R.; Dahms, T. E.; Gottlieb, S. O.; Hackney, J. D.; Pagano, M.; Selvester, R. H.; Walden, S. M.; Warren, J. (1991) Effects of carbon monoxide on myocardial ischemia. Environ. Health Perspect. 91: 89-132.

American Heart Association. (1997) 1998 heart and stroke statistical update. Dallas, TX: American Heart Association.

Anderson, E. W.; Andelman, R. J.; Strauch, J. M.; Fortuin, N. J.; Knelson, J. H. (1973) Effect of low-level carbon monoxide exposure on onset and duration of angina pectoris: a study in ten patients with ischemic heart disease. Ann. Intern. Med. 79: 46-50.

Annau, Z.; Fechter, L. D. (1994) The effects of prenatal exposure to carbon monoxide. In: Needleman, H. L.; Bellinger, D., eds. Prenatal exposure to toxicants: developmental consequences. Baltimore, MD: Johns Hopkins University Press; pp. 249-267. (Annau, Z., ed. The Johns Hopkins series in environmental toxicology).

Ator, N. A. (1982) Modulation of the behavioral effects of carbon monoxide by reinforcement contingencies. Neurobehav. Toxicol. Teratol. 4: 51-61.

Ator, N. A.; Merigan, W. H., Jr.; McIntire, R. W. (1976) The effects of brief exposures to carbon monoxide on temporally differentiated responding. Environ. Res. 12: 81-91.

Bailar, J. C., III. (1999) Passive smoking, coronary heart disease, and meta-analysis [letter]. N. Engl. J. Med. 340: 958-959.

Bascom, R.; Bromberg, P. A.; Costa, D. L.; Devlin, R.; Dockery, D. W.; Frampton, M. W.; Lambert, W.; Samet, J. M.; Speizer, F. E.; Utell, M. (1996) Health effects of outdoor air pollution [part 2]. Am. J. Respir. Crit. Care Med. 153: 477-498.

Bassan, M. M. (1990) Sudden cardiac death [letter to the editor]. N. Engl. J. Med. 322: 272.

Benignus, V. A. (1993) Importance of experimenter-blind procedure in neurotoxicology. Neurotoxicol. Teratol. 15: 45-49.

Benignus, V. A. (1994) Behavioral effects of carbon monoxide: meta analyses and extrapolations. J. Appl. Physiol. 76: 1310-1316.

Benignus, V. A. (1996) Behavioral effects of carbon monoxide exposure: results and mechanisms. In: Penney, D. G., ed. Carbon monoxide. Boca Raton, FL: CRC Press; pp. 211-238.

Benignus, V. A.; Annau, Z. (1994) Carboxyhemoglobin formation due to carbon monoxide exposure in rats. Toxicol. Appl. Pharmacol. 128: 151-157.

Benignus, V. A.; Otto, D. A.; Prah, J. D.; Benignus, G. (1977) Lack of effects of carbon monoxide on human vigilance. Percept. Mot. Skills 45: 1007-1014.

Benignus, V. A.; Muller, K. E.; Barton, C. N.; Prah, J. D. (1987) Effect of low level carbon monoxide on compensatory tracking and event monitoring. Neurotoxicol. Teratol. 9: 227-234.

Benignus, V. A.; Muller, K. E.; Malott, C. M. (1990) Dose-effects functions for carboxyhemoglobin and behavior. Neurotoxicol. Teratol. 12: 111-118.

Benowitz, N. L. (1997) The role of nicotine in smoking-related cardiovascular disease. Preventive Med. 26: 412-417.

Blair, P. S.; Fleming, P. J.; Bensley, D.; Smith, I.; Bacon, C.; Taylor, E.; Berry, J.; Golding, J.; Tripp, J. (1996) Smoking and the sudden infant death syndrome: results from 1993-5 case-control study for confidential inquiry into stillbirths and deaths in infancy. Br. Med. J. 313: 195-198.

Brooke, O. G.; Anderson, H. R.; Bland, J. M.; Peacock, J. L.; Stewart, C. M. (1989) Effects on birth weight of smoking, alcohol, caffeine, socioeconimic factors, and psychosocial stress. Br. Med. J. 298: 795-801.

Burnett, R. T.; Dales, R.; Krewski, D.; Vincent, R.; Dann, T.; Brook, J. R. (1995) Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am. J. Epidemiol. 142: 15-22.

Burnett, R. T.; Dales, R. E.; Brook, J. R.; Raizenne, M. E.; Krewski, D. (1997a) Association between ambient carbon monoxide levels and hospitalizations for congestive heart failure in the elderly in 10 Canadian cities. Epidemiology 8: 162-167.

Burnett, R. T.; Cakmak, S.; Brook, J. R.; Krewski, D. (1997b) The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environ. Health Perspect. 105: 614-620.

Burnett, R. T.; Cakmak, S.; Raizenne, M. E.; Stieb, D.; Vincent, R.; Krewski, D.; Brook, J. R.; Philips, O.; Ozkaynak, H. (1998a) The association between ambient carbon monoxide levels and daily mortality in Toronto, Canada. J. Air Waste Manage. Assoc. 48: 689-700.

Burnett, R. T.; Cakmak, S.; Brook, J. R. (1998b) The effect of the urban ambient air pollution mix on daily mortality rates in 11 Canadian cities. Can. J. Public Health 89: 152-156.

Burnett, R. T.; Smith-Doiron, M.; Stieb, D.; Cakmak, S.; Brook, J. R. (1999) Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. Arch. Environ. Health 54: 130-139.

Burns, T. R.; Greenberg, S. D.; Cartwright, J.; Jachimczyk, J. A. (1986) Smoke inhalation: an ultrastructural study of reaction to injury in the human alveolar wall. Environ. Res. 41: 447-457.

Busey, W. M. (1972) Chronic exposure of albino rats to certain airborne pollutants. New York, NY: Coordinating Research Council, Inc.; report no. CRC-APRAC-CAPM-6-68-6.

Carratù, M. R.; Renna, G.; Giustino, A.; De Salvia, M. A.; Cuomo, V. (1993) Changes in peripheral nervous system activity produced in rats by prenatal exposure to carbon monoxide. Arch. Toxicol. 67: 297-301.

Carratù, M. R.; Cagiano, R.; De Salvia, M. A.; Trabace, L.; Cuomo, V. (1995) Developmental neurotoxicity of carbon monoxide. In: Degen, G. H.; Seiler, J. P.; Bentley, P., eds. Toxicology in transition: proceedings of the 1994 EUROTOX congress; August 1994; Basel, Switzerland. Arch. Toxicol. Suppl. 17: 295-301.

Carratù, M. R.; Cagiano, R.; Cortese, I.; Renna, G.; Siro Brigiani, G.; Trabace, L.; Cuomo, V. (1996) Myelination disorders produced by prenatal exposure to moderate carbon monoxide concentrations in rat offspring. Fundam. Clin. Pharmacol. 10: 172.

Cary, R.; Clarke, S.; Delic, J. (1997) Effects of combined exposure to noise and toxic substances—critical review of the literature. Ann. Occup. Hyg. 41: 455-465.

Chaitman, B. R.; Dahms, T. E.; Byers, S.; Carroll, L. W.; Younis, L. T.; Wiens, R. D. (1992) Carbon monoxide exposure of subjects with documented cardiac arrhythmias. Cambridge, MA: Health Effects Institute; research report no. 52.

Chen, S.; Weller, M. A.; Penney, D. G. (1982) A study of free lung cells from young rats chronically exposed to carbon monoxide from birth. Scanning Electron Microsc. 2: 859-867.

Cohen, S. I.; Deane, M.; Goldsmith, J. R. (1969) Carbon monoxide and survival from myocardial infarction. Arch. Environ. Health 19: 510-517.

Cooper, K. R.; Alberti, R. R. (1984) Effect of kerosene heater emissions on indoor air quality and pulmonary function. Am. Rev. Respir. Dis. 129: 629-631.

Crocker, P. J.; Walker, J. S. (1985) Pediatric carbon monoxide toxicity. J. Emerg. Med. 3: 443-448.

Dahms, T. E.; Younis, L. T.; Wiens, R. D.; Zarnegar, S.; Byers, S. L.; Chaitman, B. R. (1993) Effects of carbon monoxide exposure in patients with documented cardiac arrhythmias. J. Am. Coll. Cardiol. 21: 442-450.

Davies, D. M.; Smith, D. J. (1980) Electrocardiographic changes in healthy men during continuous low-level carbon monoxide exposure. Environ. Res. 21: 197-206.

Davies, R. F.; Topping, D. L.; Turner, D. M. (1976) The effect of intermittent carbon monoxide exposure on experimental atherosclerosis in the rabbit. Atherosclerosis 24: 527-536.

De Luca, A.; Pierno, S.; Tricarico, D.; Carratù, M. R.; Cagiano, R.; Cuomo, V.; Camerino, D. C. (1996) Developmental changes of membrane electrical properties of rat skeletal muscle fibers produced by prenatal exposure to carbon monoxide. Environ. Toxicol. Pharmacol. 2: 213-221.

De Salvia, M. A.; Cagiano, R.; Carratù, M. R.; Di Giovanni, V.; Trabace, L.; Cuomo, V. (1995) Irreversible impairment of active avoidance behavior in rats prenatally exposed to mild concentrations of carbon monoxide. Psychopharmacology (Berlin) 122: 66-71.

DeLucia, A. J.; Whitaker, J. H.; Bryant, L. R. (1983) Effects of combined exposure to ozone and carbon monoxide (CO) in humans. In: Lee, S. D.; Mustafa, M. G.; Mehlman, M. A., eds. International symposium on the biomedical effects of ozone and related photochemical oxidants; March; Pinehurst, NC. Princeton, NJ: Princeton Scientific Publishers, Inc.; pp. 145-159. (Advances in modern environmental toxicology: v. 5).

Di Giovanni, V.; Cagiano, R.; De Salvia, M. A.; Giustino, A.; Lacomba, C.; Renna, G.; Cuomo, V. (1993) Neurobehavioral changes produced in rats by prenatal exposure to carbon monoxide. Brain Res. 616: 126-131.

DiVincenzo, G. D.; Kaplan, C. J. (1981a) Effect of exercise or smoking on the uptake, metabolism, and excretion of methylene chloride vapor. Toxicol. Appl. Pharmacol. 59: 141-148.

DiVincenzo, G. D.; Kaplan, C. J. (1981b) Uptake, metabolism, and elimination of methylene chloride vapor by humans. Toxicol. Appl. Pharmacol. 59: 130-140.

Dill, D. B.; Alexander, W. C.; Myhre, L. G.; Whinnery, J. E.; Tucker, D. M. (1985) Aerobic capacity of D.B. Dill, 1928-1984. Fed. Proc. 44: 1013.

Doblar, D. D.; Santiago, T. V.; Edelman, N. H. (1977) Correlation between ventilatory and cerebrovascular responses to inhalation of CO. J. Appl. Physiol.: Respir. Environ. Exercise Physiol. 43: 455-462.

Doi, R.; Tanaka, H. (1984) Effects of carbon monoxide exposure on the distribution of methylmercury in mice. J. Toxicol. Sci. 9: 11-22.

Douglas, A. S.; Allan, T. M.; Helms, P. J. (1996) Seasonality and the sudden infant death syndrome during 1987-9 and 1991-3 in Australia and Britain. Br. Med. J. 312: 1381-1383.

Drinkwater, B. L.; Raven, P. B.; Horvath, S. M.; Gliner, J. A.; Ruhling, R. O.; Bolduan, N. W.; Taguchi, S. (1974) Air pollution, exercise, and heat stress. Arch. Environ. Health 28: 177-181.

Edling, C.; Axelson, O. (1984) Risk factors of coronary heart disease among personnel in a bus company. Int. Arch. Occup. Environ. Health 54: 181-183.

Ekblom, B.; Huot, R. (1972) Response to submaximal and maximal exercise at different levels of carboxyhemoglobin. Acta Physiol. Scand. 86: 474-482.

Engen, T. (1986) The combined effect of carbon monoxide and alcohol on odor sensitivity. Environ. Int. 12: 207-210.

Evans, R. G.; Webb, K.; Homan, S.; Ayres, S. M. (1988) Cross-sectional and longitudinal changes in pulmonary function associated with automobile pollution among bridge and tunnel officers. Am. J. Ind. Med. 14: 25-36.

Fechter, L. D. (1995) Combined effects of noise and chemicals. Occup. Med. State of the Art Rev. 10: 609-621.

Fechter, L. D.; Young, J. S.; Carlisle, L. (1988) Potentiation of noise induced threshold shifts and hair cell loss by carbon monoxide. Hear. Res. 34: 39-47.

Fechter, L. D.; Liu, Y.; Pearce, T. A. (1997) Cochlear protection from carbon monoxide exposure by free radical blockers in the guinea pig. Toxicol. Appl. Pharmacol. 142: 47-55.

Fein, A.; Grossman, R. F.; Jones, J. G.; Hoeffel, J.; McKay, D. (1980) Carbon monoxide effect on alveolar epithelial permeability. Chest 78: 726-731.

Fisher, A. B.; Hyde, R. W.; Baue, A. E.; Reif, J. S.; Kelly, D. F. (1969) Effect of carbon monoxide on function and structure of the lung. J. Appl. Physiol. 26: 4-12.

Fodor, G. G.; Roscovanu, A. (1976) Erhoehter Blut-CO-Gehalt bei Mensch und Tier durch inkorperierte halogenierte Kohlenwasserstoffe [Increased blood CO content in humans and animals caused by incorporated halogenated hydrocarbons]. Zentralbl. Bakteriol. Parasitenkd. Infektionskrankh. Hyg. Abt. 1: Orig. Reihe B 162: 34-40.

Fodor, G. G.; Winneke, G. (1972) Effect of low CO concentrations on resistance to monotony and on psychomotor capacity. Staub Reinhalt. Luft 32: 46-54.

Franco, P.; Groswasser, J.; Sottiaux, M.; Broadfield, E.; Kahn, A. (1996) Decreased cardiac responses to auditory stimulation during prone sleep. Pediatrics 97: 174-178.

Glantz, S. A.; Parmley, W. W. (1991) Passive smoking and heart disease: epidemiology, physiology, and biochemistry. Circulation 83: 1-12.

Gliner, J. A.; Raven, P. B.; Horvath, S. M.; Drinkwater, B. L.; Sutton, J. C. (1975) Man's physiologic response to long-term work during thermal and pollutant stress. J. Appl. Physiol. 39: 628-632.

Goldsmith, J. R.; Landaw, S. A. (1968) Carbon monoxide and human health. Science (Washington, DC) 162: 1352-1359.

Gordian, M. E.; Özkaynak, H.; Xue, J.; Morris, S. S.; Spengler, J. D. (1996) Particulate air pollution and respiratory disease in Anchorage, Alaska. Environ. Health Perspect. 104: 290-297.

Graves, E. J.; Owings, M. F. (1998) 1996 summary: National Hospital Discharge Survey. Hyattsville, MD: National Center for Health Statistics; DHHS publication no. (PHS) 98-1250. (Advance data from vital and health statistics; no. 301). Available: www.cdc.gov/nchs/data/ad301.pdf [2000, June 8].

Groll-Knapp, E.; Haider, M.; Jenkner, H.; Liebich, H.; Neuberger, M.; Trimmel, M. (1982) Moderate carbon monoxide exposure during sleep: neuro- and psychophysiological effects in young and elderly people. Neurobehav. Toxicol. Teratol. 4: 709-716.

Groll-Knapp, E.; Haider, M.; Kienzl, K.; Handler, A.; Trimmel, M. (1988) Changes in discrimination learning and brain activity (ERP's) due to combined exposure to NO and CO in rats. Toxicology 49: 441-447.

Grover, R. F.; Weil, J. V.; Reeves, J. T. (1986) Cardiovascular adaptation to exercise at high altitude. Exercise Sport Sci. Rev. 14: 269-302.

Hackney, J. D.; Linn, W. S.; Mohler, J. G.; Pedersen, E. E.; Breisacher, P.; Russo, A. (1975a) Experimental studies on human health effects of air pollutants: II. four-hour exposure to ozone alone and in combination with other pollutant gases. Arch. Environ. Health 30: 379-384.

Hackney, J. D.; Linn, W. S.; Law, D. C.; Karuza, S. K.; Greenberg, H.; Buckley, R. D.; Pedersen, E. E. (1975b) Experimental studies on human health effects of air pollutants: III. two-hour exposure to ozone alone and in combination with other pollutant gases. Arch. Environ. Health 30: 385-390.

Hagberg, M.; Kolmodin-Hedman, B.; Lindahl, R.; Nilsson, C.-A.; Norstrom, A. (1985) Irritative complaints, carboxyhemoglobin increase and minor ventilatory function changes due to exposure to chain-saw exhaust. Eur. J. Respir. Dis. 66: 240-247.

Hanley, D. F.; Wilson, D. A.; Traystman, R. J. (1986) Effect of hypoxia and hypercapnia on neurohypophyseal blood flow. Am. J. Physiol. 250: H7-H15.

Harbin, T. J.; Benignus, V. A.; Muller, K. E.; Barton, C. N. (1988) The effects of low-level carbon monoxide exposure upon evoked cortical potentials in young and elderly men. Neurotoxicol. Teratol. 10: 93-100.

He, J.; Vupputuri, S.; Allen, K.; Prerost, M. R.; Hughes, J.; Whelton, P. K. (1999) Passive smoking and the risk of coronary heart disease—a meta-analysis of epidemiologic studies. N. Engl. J. Med. 340: 920-926.

Helfaer, M. A.; Traystman, R. J. (1996) Cerebrovascular effects of carbon monoxide. In: Penney, D. G., ed. Carbon monoxide. Boca Raton, FL: CRC Press; pp. 69-86.

Hexter, A. C.; Goldsmith, J. R. (1971) Carbon monoxide: association of community air pollution with mortality. Science (Washington, DC) 172: 265-267.

Hinderliter, A. L.; Adams, K. F., Jr.; Price, C. J.; Herbst, M. C.; Koch, G.; Sheps, D. S. (1989) Effects of low-level carbon monoxide exposure on resting and exercise-induced ventricular arrhythmias in patients with coronary artery disease and no baseline ectopy. Arch. Environ. Health 44: 89-93.

Hoppenbrouwers, T.; Calub, M.; Arakawa, K.; Hodgman, J. E. (1981) Seasonal relationship of sudden infant death syndrome and environmental pollutants. Am. J. Epidemiol. 113: 623-635.

Horvath, S. M. (1981) Impact of air quality in exercise performance. Exercise Sport Sci. Rev. 9: 265-296.

Horvath, S. M.; Dahms, T. E.; O'Hanlon, J. F. (1971) Carbon monoxide and human vigilance: a deleterious effect of present urban concentrations. Arch. Environ. Health 23: 343-347.

Horvath, S. M.; Raven, P. B.; Dahms, T. E.; Gray, D. J. (1975) Maximal aerobic capacity at different levels of carboxyhemoglobin. J. Appl. Physiol. 38: 300-303.

Howard, G.; Wagenknecht, L. E.; Burke, G. L.; Diez-Roux, A.; Evans, G. W.; McGovern, P.; Nieto, J.; Tell, G. S. (1998) Cigarette smoking and progression of atherosclerosis: the atherosclerosis risk in communities (ARIC) study. JAMA J. Am. Med. Assoc. 279: 119-124.

Hugod, C. (1979) Effect of exposure to 0.5 ppm hydrogen cyanide singly or combined with 200 ppm carbon monoxide and/or 5 ppm nitric oxide on coronary arteries, aorta, pulmonary artery, and lungs in the rabbit. Int. Arch. Occup. Environ. Health 44: 13-23.

Hugod, C. (1980) The effect of carbon monoxide exposure on morphology of lungs and pulmonary arteries in rabbits: a light- and electron-microscopic study. Arch. Toxicol. 43: 273-281.

Hutter, C. D. D.; Blair, M. E. (1996) Carbon monoxide—does fetal exposure cause sudden infant death syndrome? Med. Hypotheses 46: 1-4.

Institute of Medicine. (1985) Preventing low birthweight. Washington, DC: National Academy Press.

Ito, K.; Thurston, G. D. (1996) Daily PM_{10}/mortality associations: an investigation of at-risk subpopulations. J. Exposure Anal. Environ. Epidemiol. 6: 79-95.

Ito, K.; Kinney, P.; Thurston, G. D. (1995) Variations in PM-10 concentrations within two metropolitan areas and their implications for health effects analyses. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 735-745.

Jarvis, M. J. (1987) Uptake of environmental tobacco smoke. In: O'Neill, I. K.; Brunnemann, K. D.; Dodet, B.; Hoffmann, D., eds. Environmental carcinogens: methods of analysis and exposure measurement, v. 9 - passive smoking. Lyon, France: International Agency for Research on Cancer; pp. 43-58. (IARC scientific publications no. 81).

Jedrychowski, W.; Flak, E. (1996) Confronting the prenatal effects of active and passive tobacco smoking on the birth weight of children. Cent. Eur. J. Public Health 4: 201-205.

Jones, M. D., Jr.; Traystman, R. J. (1984) Cerebral oxygenation of the fetus, newborn, and adult. Semin. Perinatol. 8: 205-216.

Joseph, K. S.; Kramer, M. S. (1996) Review of the evidence on fetal and early childhood antecedents of adult chronic disease. Epidemiol. Rev. 18: 158-174.

Kahn, A.; Groswasser, J.; Sottiaux, M.; Rebuffat, E.; Franco, P.; Dramaix, M. (1993) Prone or supine body position and sleep characteristics in infants. Pediatrics 91: 1112-1115.

Kalmaz, E. E.; Saunders, P. J.; Kalmaz, G. D. (1993) Effects of carbon monoxide on arterial endothelial permeability and its possible relation to arterial disease. J. Occup. Med. Toxicol. 2: 31-39.

Kanten, W. E.; Penney, D. G.; Francisco, K.; Thill, J. E. (1983) Hemodynamic responses to acute carboxyhemoglobinemia in the rat. Am. J. Physiol. 244: H320-H327.

Katsumata, Y.; Aoki, M.; Oya, M.; Yada, S.; Suzuki, O. (1980) Liver damage in rats during acute carbon monoxide poisoning. Forensic Sci. Int. 16: 119-123.

Kawachi, I.; Colditz, G. A.; Speizer, F. E.; Manson, J. E.; Stampfer, M. J.; Willett, W. C.; Hennekens, C. H. (1997) A prospective study of passive smoking and coronary heart disease. Circulation 95: 2374-2379.

Kelsall, J. E.; Samet, J. M.; Zeger, S. L.; Xu, J. (1997) Air pollution and mortality in Philadelphia, 1974-1988. Am. J. Epidemiol. 146: 750-762.

Kemp, J. S.; Livne, M.; White, D. K.; Arfken, C. L. (1998) Softness and potential to cause rebreathing: differences in bedding used by infants at high and low risk for sudden infant death syndrome. J. Pediatr. 132: 234-239.

Khosla, S.; Laddu, A.; Ehrenpreis, S.; Somberg, J. C. (1994) Cardiovascular effects of nicotine: relation to deleterious effects of cigarette smoking. Am. Heart J. 127: 1669-1672.

Kim, Y. C.; Carlson, G. P. (1983) Effect of carbon monoxide inhalation exposure in mice on drug metabolism in vivo. Toxicol. Lett. 19: 7-13.

Kim, S. K.; Kim, Y. C. (1996) Effect of a single administration of benzene, toluene or *m*-xylene on carboxyhaemoglobin elevation and metabolism of dichloromethane in rats. J. Appl. Toxicol. 16: 437-444.

Kinney, P. L.; Özkaynak, H. (1991) Associations of daily mortality and air pollution in Los Angeles County. Environ. Res. 54: 99-120.

Kinney, P. L.; Ito, K.; Thurston, G. D. (1995) A sensitivity analysis of mortality/PM_{10} associations in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 59-69.

Kizakevich, P. N.; Hazucha, M.; Van Hoose, L.; McCartney, M. L.; Bolick, K.; Jochem, W. J.; Clayton, C. A.; Alexander, B. V.; Boehleche, B.; Hackney, A. J.; Sheps, D. S.; Clapp, L. (1994) Noninvasive ambulatory assessment of cardiac function and myocardial ischemia in healthy subjects exposed to carbon monoxide. Frederick, MD: U.S. Army Medical Research and Materiel Command; contract no. DAMD17-91-C-1007.

Klein, J. P.; Forster, H. V.; Stewart, R. D.; Wu, A. (1980) Hemoglobin affinity for oxygen during short-term exhaustive exercise. J. Appl. Physiol.: Respir. Environ. Exercise Physiol. 48: 236-242.

Kleinman, M. T. (1992) Health effects of carbon monoxide. In: Lippmann, M., ed. Environmental toxicants: human exposures and their health effects. New York, NY: Van Nostrand Reinhold; pp. 98-118.

Kleinman, M. T.; Leaf, D. (1991) Effects of exposure to low-level carbon monoxide at high altitude in sensitive subjects. Sacramento, CA: California Air Resources Board.

Kleinman, M. T.; Davidson, D. M.; Vandagriff, R. B.; Caiozzo, V. J.; Whittenberger, J. L. (1989) Effects of short-term exposure to carbon monoxide in subjects with coronary artery disease. Arch. Environ. Health 44: 361-369.

Kleinman, M. T.; Leaf, D. A.; Kelly, E.; Caiozzo, V.; Osann, K.; O'Niell, T. (1998) Urban angina in the mountains: effects of carbon monoxide and mild hypoxemia on subjects with chronic stable angina. Arch. Environ. Health 53: 388-397.

Klonoff-Cohen, H. S.; Edelstein, S. L.; Lefkowitz, E. S.; Srinivasan, I. P.; Kaegi, D.; Chang, J. C.; Wiley, K. J. (1995) The effect of passive smoking and tobacco exposure through breast milk on sudden infant death syndrome. JAMA J. Am. Med. Assoc. 273: 795-798.

Knisely, J. S.; Rees, D. C.; Salay, J. M.; Balster, R. L.; Breen, T. J. (1987) Effects of intraperitoneal carbon monoxide on fixed-ratio and screen-test performance in the mouse. Neurotoxicol. Teratol. 9: 221-225.

Knisely, J. S.; Rees, D. C.; Balster, R. L. (1989) Effects of carbon monoxide in combination with behaviorally active drugs on fixed-ratio performance in the mouse. Neurotoxicol. Teratol. 11: 447-452.

Koike, A.; Wasserman, K. (1992) Effect of acute reduction in oxygen transport on parameters of aerobic function during exercise. Ann. Acad. Med. Singapore 21: 14-22.

Koike, A.; Wasserman, K.; Armon, Y.; Weiler-Ravell, D. (1991) The work-rate-dependent effect of carbon monoxide on ventilatory control during exercise. Respir. Physiol. 85: 169-183.

Kolarzyk, E. (1994a) The effect of acute carbon monoxide poisoning on the respiratory system efficiency. I. Values of spirometric parameters in different degrees of poisoning. Int. J. Occup. Med. Environ. Health 7: 225-235.

Kolarzyk, E. (1994b) The effect of acute carbon monoxide poisoning on the respiratory system efficiency. II. Types of ventilatory disorder and dynamics of changes according to the severity of carbon monoxide poisoning. Int. J. Occup. Med. Environ. Health 7: 237-243.

Kolarzyk, E. (1995) Regulation of breathing in cases of acute carbon monoxide poisoning. Int. J. Occup. Med. Environ. Health 8: 89-101.

Koren, G.; Sharav, T.; Pastuszak, A.; Garrettson, L. K.; Hill, K.; Samson, I.; Rorem, M.; King, A.; Dolgin, J. E. (1991) A multicenter, prospective study of fetal outcome following accidental carbon monoxide poisoning in pregnancy. Reprod. Toxicol. 5: 397-403.

Koskela, R.-S. (1994) Cardiovascular diseases among foundry workers exposed to carbon monoxide. Scand. J. Work Environ. Health 20: 286-293.

Kritz, H.; Schmid, P.; Sinzinger, H. (1995) Passive smoking and cardiovascular risk. Arch. Intern. Med. 155: 1942-1948.

Kuller, L. H.; Radford, E. P.; Swift, D.; Perper, J. A.; Fisher, R. (1975) Carbon monoxide and heart attacks. Arch. Environ. Health 30: 477-482.

Kurppa, K.; Kivisto, H.; Vainio, H. (1981) Dichloromethane and carbon monoxide inhalation: carboxyhemoglobin addition, and drug metabolizing enzymes in rat. Int. Arch. Occup. Environ. Health 49: 83-87.

Kuska, J.; Kokot, F.; Wnuk, R. (1980) Acute renal failure after exposure to carbon monoxide. Mater. Med. Pol. (Engl. Ed.) 12: 236-238.

Langston, P.; Gorman, D.; Runciman, W.; Upton, R. (1996) The effect of carbon monoxide on oxygen metabolism in the brains of awake sheep. Toxicology 114: 223-232.

LeVois, M. E.; Layard, M. W. (1995) Publication bias in the environmental tobacco smoke/coronary heart disease epidemiologic literature. Regul. Toxicol. Pharmacol. 21: 184-191.

Leaf, D. A.; Kleinman, M. T. (1996a) Urban ectopy in the mountains: carbon monoxide exposure at high altitude. Arch. Environ. Health 51: 283-290.

Leaf, D. A.; Kleinman, M. T. (1996b) Acute exposure to carbon monoxide does not affect plasma lipids, lipoproteins, and apolipoproteins. Angiology 47: 337-341.

Lebowitz, M. D.; Collins, L.; Holberg, C. J. (1987) Time series analyses of respiratory responses to indoor and outdoor environmental phenomena. Environ. Res. 43: 332-341.

Levin, B. C. (1996) New research avenues in toxicology: 7-gas N-gas model, toxicant suppressants, and genetic toxicology. In: Chaturvedi, A. K.; Sanders, D. C.; Higgins, E. A., eds. Proceedings of the international colloquium on advances in combustion toxicology; April 1995; Oklahoma City, OK. Toxicology 115: 89-106.

Levin, B. C.; Paabo, M.; Gurman, J. L.; Harris, S. E.; Braun, E. (1987a) Toxicological interactions between carbon monoxide and carbon dioxide. Presented at: 16th conference of toxicology, Air Force Medical Research Laboratory; October 1986; Dayton, OH. Toxicology 47: 135-164.

Levin, B. C.; Paabo, M.; Gurman, J. L.; Harris, S. E. (1987b) Effects of exposure to single or multiple combinations of the predominant toxic gases and low oxygen atmospheres produced in fires. Fundam. Appl. Toxicol. 9: 236-250.

Levin, B. C.; Paabo, M.; Gurman, J. L.; Clark, H. M.; Yoklavich, M. F. (1988) Further studies of the toxicological effects of different time exposures to the individual and combined fire gases—carbon monoxide, hydrogen cyanide, carbon dioxide and reduced oxygen. In: Polyurethanes 88: proceedings of the SPI 31st annual technical/marketing conference; October; Philadelphia, PA. Society of the Plastics Industry, Inc.; pp. 249-252.

Longo, L. D. (1976) Carbon monoxide: effects on oxygenation of the fetus in utero. Science (Washington, DC) 194: 523-525.

Longo, L. D. (1977) The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. Am. J. Obstet. Gynecol. 129: 69-103.
Luke, B. (1994) Maternal-fetal nutrition. Clin. Obstet. Gynecol. 37: 93-109.
Lutz, L. J. (1983) Health effects of air pollution measured by outpatient visits. J. Fam. Pract. 16: 307-313.
MacDorman, M. F.; Cnattingius, S.; Hoffman, H. J.; Kramer, M. S.; Haglund, B. (1997) Sudden infant death syndrome and smoking in the United States and Sweden. Am. J. Epidemiol. 146: 249-257.
Martin, T. R.; Bracken, M. B. (1986) Association of low birth weight with passive smoke exposure in pregnancy. Am. J. Epidemiol. 124: 633-642.
May, D. S.; Kelly, J. J.; Mendlein, J. M.; Garbe, P. L. (1991) Surveillance of major causes of hospitalization among the elderly, 1988. Morb. Mortal. Wkly. Rep. 40: 7-21.
McGrath, J. J. (1982) Physiological effects of carbon monoxide. In: McGrath, J. J.; Barnes, C. D., eds. Air pollution—physiological effects. New York, NY: Academic Press; pp. 147-181.
McGrath, J. J. (1992) Effects of altitude on endogenous carboxyhemoglobin levels. J. Toxicol. Environ. Health 35: 127-133.
McGrath, J. J.; Lee, P.; Schreck, R. M. (1991) Effects of altitude on expired breath carbon monoxide levels. Presented at: 84th annual meeting and exhibition of the Air & Waste Management Association; June; Vancouver, BC, Canada. Pittsburgh, PA: Air & Waste Management Association; paper no. 91-138.2.
McGrath, J. J.; Schreck, R. M.; Lee, P. S. (1993) Carboxyhemoglobin levels in humans: effects of altitude. Inhalation Toxicol. 5: 241-249.
McMillan, D. E.; Miller, A. T., Jr. (1974) Interactions between carbon monoxide and *d*-amphetamine or pentobarbital on schedule-controlled behavior. Environ. Res. 8: 53-63.
Medical College of Wisconsin. (1974) Exposure of humans to carbon monoxide combined with ingestion of ethyl alcohol and the comparison of human performance when exposed for varying periods of time to carbon monoxide. Milwaukee, WI: Medical College of Wisconsin; report no. MCOW-ENVM-CO-74-2.
Melius, J. M. (1995) Cardiovascular disease among firefighters. Occup. Med.: State of the Art Rev. 10: 821-827.
Mennear, J. H. (1993) Carbon monoxide and cardiovascular disease: an analysis of the weight of evidence. Regul. Toxicol. Pharmacol. 17: 77-84.
Merigan, W. H.; McIntire, R. W. (1976) Effects of carbon monoxide on responding under a progressive ratio schedule in rats. Physiol. Behav. 16: 407-412.
Michaels, D.; Zoloth, S. R. (1991) Mortality among urban bus drivers. Int. J. Epidemiol. 20: 399-404.
Min, H. Y.; Wei, Z.; Quan, Q. M.; Rong, Z. (1992) Correlation between hemorheological parameters and viscoelasticity of thrombus in rats after exposure to carbon monoxide. Clin. Hemorheol. 12: 593-598.
Mitchell, D. S.; Packham, S. C.; Fitzgerald, W. E. (1978) Effects of ethanol and carbon monoxide on two measures of behavioral incapacitation of rats. Proc. West. Pharmacol. Soc. 21: 427-431.
Mitchell, E. A.; Ford, R. P. K.; Stewart, A. W.; Taylor, B. J.; Becroft, D. M. O.; Thompson, J. M. D.; Scragg, R.; Hassall, I. B.; Barry, D. M. J.; Allen, E. M.; Roberts, A. P. (1993) Smoking and the sudden death syndrome. Pediatrics 91: 893-896.
Montgomery, M. R.; Rubin, R. J. (1971) The effect of carbon monoxide inhalation on in vivo drug metabolism in the rat. J. Pharmacol. Exp. Ther. 179: 465-473.
Montgomery, M. R.; Rubin, R. J. (1973) Oxygenation during inhibition of drug metabolism by carbon monoxide or hypoxic hypoxia. J. Appl. Physiol. 35: 505-509.
Moore, L. G.; Rounds, S. S.; Jahnigen, D.; Grover, R. F.; Reeves, J. T. (1982) Infant birth weight is related to maternal arterial oxygenation at high altitude. J. Appl. Physiol.: Respir. Environ. Exercise Physiol. 52: 695-699.
Morris, R. D.; Naumova, E. N. (1998) Carbon monoxide and hospital admissions for congestive heart failure: evidence of an increased effect at low temperatures. Environ. Health Perspect. 106: 649-653.
Morris, R. D.; Naumova, E. N.; Munasinghe, R. L. (1995) Ambient air pollution and hospitalization for congestive heart failure among elderly people in seven large US cities. Am. J. Public Health 85: 1361-1365.
Murphy, S. D. (1964) A review of effects on animals of exposure to auto exhaust and some of its components. J. Air Pollut. Control Assoc. 14: 303-308.
Murray, F. J.; Schwetz, B. A.; Crawford, A. A.; Henck, J. W.; Staples, R. E. (1978) Teratogenic potential of sulfur dioxide and carbon monoxide in mice and rabbits. In: Mahlum, D. D.; Sikov, M. R.; Hackett, P. L.; Andrew, F. D., eds. Developmental toxicology of energy-related pollutants: proceedings of the seventeenth annual Hanford biology symposium; October 1977; Richland, WA. Oak Ridge, TN: U.S. Department of Energy, Technical Information Center; pp. 469-478.

National Research Council. (1986) Environmental tobacco smoke: measuring exposures and assessing health effects. Washington, DC: National Academy Press.
Niden, A. H.; Schulz, H. (1965) The ultrastructural effects of carbon monoxide inhalation on the rat lung. Virchows Arch. Pathol. Anat. Physiol. 339: 283-292.
Norris, G.; Young-Pong, S. N.; Koenig, J. Q.; Larson, T. V.; Sheppard, L.; Stout, J. W. (1999) An association between fine particles and asthma emergency department visits for children in Seattle. Environ. Health Perspect. 107: 489-493.
Olds, D. (1997) Tobacco exposure and impaired development: a review of the evidence. Ment. Retard. Dev. Disabil. Res. Rev. 3: 257-269.
Olds, D. L.; Henderson, C. R.; Tatelbaum, R. (1994a) Intellectual impairment in children of women who smoke cigarettes during pregnancy. Pediatrics 93: 221-227.
Olds, D. L.; Henderson, C. R.; Tatelbaum, R. (1994b) Prevention of intellectual impairment in children of women who smoke cigarettes during pregnancy. Pediatrics 93: 228-233.
Otto, D. A.; Benignus, V. A.; Prah, J. D. (1979) Carbon monoxide and human time discrimination: failure to replicate Beard-Wertheim experiments. Aviat. Space Environ. Med. 50: 40-43.
Pankow, D. (1996) Carbon monoxide formation due to metabolism of xenobiotics. In: Penney, D. G., ed. Carbon monoxide. Boca Raton, FL: CRC Press; pp. 25-43.
Pankow, D.; Ponsold, W.; Fritz, H. (1974) Combined effects of carbon monoxide and ethanol on the activities of leucine aminopeptidase and glutamic-pyruvic transaminase in the plasma of rats. Arch. Toxicol. 32: 331-340.
Pantazopoulou, A.; Katsouyanni, K.; Kourea-Kremastinou, J.; Trichopoulos, D. (1995) Short-term effects of air pollution on hospital emergency outpatient visits and admissions in the greater Athens, Greece area. Environ. Res. 69: 31-36.
Paulson, O. B.; Parving, H.-H.; Olesen, J.; Skinhoj, E. (1973) Influence of carbon monoxide and of hemodilution on cerebral blood flow and blood gases in man. J. Appl. Physiol. 35: 111-116.
Peacock, J. L.; Bland, J. M.; Anderson, H. R.; Brooke, O. G. (1991a) Cigarette smoking and birthweight: type of cigarette smoked and a possible threshold effect. Int. J. Epidemiol. 20: 405-412.
Peacock, J. L.; Bland, J. M.; Anderson, H. R. (1991b) Effects on birthweight of alcohol and caffeine consumption in smoking women. J. Epidemiol. Commun. Health 45: 159-163.
Penn, A. (1993) Determination of the atherogenic potential of inhaled carbon monoxide. Cambridge, MA: Health Effects Institute; research report number 57.
Penn, A.; Currie, J.; Snyder, C. (1992) Inhalation of carbon monoxide does not accelerate arteriosclerosis in cockerels. Eur. J. Pharmacol. 228: 155-164.
Penney, D. G. (1988) A review: hemodynamic response to carbon monoxide. Environ. Health Perspect 77: 121-130.
Penney, D. G., ed. (1996a) Carbon monoxide. Boca Raton, FL: CRC Press.
Penney, D. G. (1996b) Effects of carbon monoxide exposure on developing animals and humans. In: Penney, D. G., ed. Carbon monoxide. Boca Raton, FL: CRC Press; pp. 109-144.
Penney, D.; Benjamin, M.; Dunham, E. (1974) Effect of carbon monoxide on cardiac weight as compared with altitude effects. J. Appl. Physiol. 37: 80-84.
Pereira, L. A. A.; Loomis, D.; Conceição, G. M. S.; Braga, A. L. F.; Arcas, R. M.; Kishi, H. S.; Singer, J. M.; Böhm, G. M.; Saldiva, P. H. N. (1998) Association between air pollution and intrauterine mortality in São Paulo, Brazil. Environ. Health Perspect. 106: 325-329.
Peters, K. D.; Kochanek, K. D.; Murphy, S. L.; (1998) Deaths: final data for 1996. Atlanta, GA: U.S. Centers for Disease Control and Prevention, National Center for Health Statistics. (National vital statistics reports: v. 47, no. 9). Available: www.cdc.gov/nchswww/releases/98facts/98sheets/finmort.htm [2000, June 8].
Pirnay, F.; Dujardin J.; Deroanne, R.; Petit, J. M. (1971) Muscular exercise during intoxication by carbon monoxide. J. Appl. Physiol. 31: 573-575.
Poloniecki, J. D.; Atkinson, R. W.; Ponce de Leon, A.; Anderson, H. R. (1997) Daily time series for cardiovascular hospital admissions and previous day's air pollution in London, UK. Occup. Environ. Med. 54: 535-540.
Ponsonby, A.-L.; Dwyer, T.; Gibbons, L. E.; Cochrane, J. A.; Wang, Y.-G. (1993) Factors potentiating the risk of sudden infant death syndrome associated with the prone position. N. Engl. J. Med. 329: 377-382.
Preziosi, T. J.; Lindenberg, R.; Levy, D.; Christenson, M. (1970) An experimental investigation in animals of the functional and morphologic effects of single and repeated exposures to high and low concentrations of carbon monoxide. Ann. N. Y. Acad. Sci. 174: 369-384.
Prigge, E.; Hochrainer, D. (1977) Effects of carbon monoxide inhalation on erythropoiesis and cardiac hypertrophy in fetal rats. Toxicol. Appl. Pharmacol. 42: 225-228.
Putz, V. R. (1979) The effects of carbon monoxide on dual-task performance. Hum. Factors 21: 13-24.

Putz, V. R.; Johnson, B. L.; Setzer, J. V. (1976) Effects of CO on vigilance performance: effects of low level carbon monoxide on divided attention, pitch discrimination, and the auditory evoked potential. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health; report no. NIOSH-77-124.

Putz, V. R.; Johnson, B. L.; Setzer, J. V. (1979) A comparative study of the effects of carbon monoxide and methylene chloride on human performance. J. Environ. Pathol. Toxicol. 2: 97-112.

Ramsey, J. M. (1973) Effects of single exposures of carbon monoxide on sensory and psychomotor response. Am. Ind. Hyg. Assoc. J. 34: 212-216.

Raven, P. B.; Drinkwater, B. L.; Horvath, S. M.; Ruhling, R. O.; Gliner, J. A.; Sutton, J. C.; Bolduan, N. W. (1974a) Age, smoking habits, heat stress, and their interactive effects with carbon monoxide and peroxyacetylnitrate on man's aerobic power. Int. J. Biometeorol. 18: 222-232.

Raven, P. B.; Drinkwater, B. L.; Ruhling, R. O.; Bolduan, N.; Taguchi, S.; Gliner, J.; Horvath, S. M. (1974b) Effect of carbon monoxide and peroxyacetyl nitrate on man's maximal aerobic capacity. J. Appl. Physiol. 36: 288-293.

Ritz, B.; Yu, F. (1999) The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. Environ. Health Perspect. 107: 17-25.

Robertson, G.; Lebowitz, M. D. (1984) Analysis of relationships between symptoms and environmental factors over time. Environ. Res. 33: 130-143.

Robkin, M. A. (1997) Carbon monoxide and the embryo. Int. J. Dev. Biol. 41: 283-289.

Roche, S.; Horvath, S.; Gliner, J.; Wagner, J.; Borgia, J. (1981) Sustained visual attention and carbon monoxide: elimination of adaptation effects. Hum. Factors 23: 175-184.

Rockwell, T. J.; Weir, F. W. (1975) The interactive effects of carbon monoxide and alcohol on driving skills. Columbus, OH: The Ohio State University Research Foundation; CRC-APRAC project CAPM-9-69.

Rodkey, F. L.; Collison, H. A. (1979) Effects of oxygen and carbon dioxide on carbon monoxide toxicity. J. Combust. Toxicol. 6: 208-212.

Roth, R. A., Jr.; Rubin, R. J. (1976a) Role of blood flow in carbon monoxide- and hypoxic hypoxia-induced alterations in hexobarbital metabolism in rats. Drug Metab. Dispos. 4: 460-467.

Roth, R. A., Jr.; Rubin, R. J. (1976b) Comparison of the effect of carbon monoxide and of hypoxic hypoxia. II. Hexobarbital metabolism in the isolated, perfused rat liver. J. Pharmacol. Exp. Ther. 199: 61-66.

Roth, R. A., Jr.; Rubin, R. J. (1976c) Comparison of the effect of carbon monoxide and of hypoxic hypoxia. I. In vivo metabolism, distribution and action of hexobarbital. J. Pharmacol. Exp. Ther. 199: 53-60.

Rubin, D. H.; Leventhal, J. M.; Krasilnikoff, P. A.; Weile, B.; Berget, A. (1986) Effect of passive smoking on birth-weight. Lancet (8504): 415-417.

SAS Institute Inc. (1990) The NLIN procedure. In: SAS/STAT® user's guide, version 6, fourth edition. Volume 2. Cary, NC: SAS Institute Inc.; pp. 1135-1193.

Saldiva, P. H. N.; Lichtenfels, A. J. F. C.; Paiva, P. S. O.; Barone, I. A.; Martins, M. A.; Massad, E.; Pereira, J. C. R.; Xavier, V. P.; Singer, J. M.; Böhm, G. M. (1994) Association between air pollution and mortality due to respiratory diseases in children in São Paulo, Brazil: a preliminary report. Environ. Res. 65: 218-225.

Saldiva, P. H. N.; Pope, C. A., III; Schwartz, J.; Dockery, D. W.; Lichtenfels, A. J.; Salge, J. M.; Barone, I.; Böhm, G. M. (1995) Air pollution and mortality in elderly people: a time-series study in São Paulo, Brazil. Arch. Environ. Health 50: 159-163.

Salinas, M.; Vega, J. (1995) The effect of outdoor air pollution on mortality risk: an ecological study from Santiago, Chile. World Health Stat. Q. 48: 118-125.

Sardinas, A.; Wang Miller, J.; Hansen, H. (1986) Ischemic heart disease mortality of fireman and policemen. Am. J. Public Health 76: 1140-1141.

Schoendorf, K. C.; Kiely, J. L. (1992) Relationship of sudden infant death syndrome to maternal smoking during and after pregnancy. Pediatrics 90: 905-908.

Schwartz, J. (1997) Air pollution and hospital admissions for cardiovascular disease in Tucson. Epidemiology 8: 371-377.

Schwartz, J. (1999) Air pollution and hospital admissions for heart disease in eight U.S. counties. Epidemiology 10: 17-22.

Schwartz, J.; Morris, R. (1995) Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am. J. Epidemiol. 142: 23-35.

Schwartz, P. J.; Stramba-Badiale, M.; Segantini, A.; Austoni, P.; Bosi, G.; Giorgetti, R.; Grancini, F.; Marni, E. D.; Perticone, F.; Rosti, D.; Salice, P. (1998) Prolongation of the QT interval and the sudden infant death syndrome. N. Engl. J. Med. 338: 1709-1761.

Scragg, R.; Mitchell, E. A.; Taylor, B. J.; Stewart, A. W.; Ford, R. P. K.; Thompson, J. M. D.; Allen, E. M.; Becroft, D. M. O. (1993) Bed sharing, smoking, and alcohol in the sudden infant death syndrome. Br. Med J. 307: 1312-1318.

Secker-Walker, R. H.; Vacek, P. M.; Flynn, B. S.; Mead, P. B. (1997) Smoking in pregnancy, exhaled carbon monoxide, and birth weight. Obstet. Gynecol. 89: 648-653.

Shephard, R. J. (1983) Carbon monoxide: the silent killer. Springfield, IL: Charles C. Thomas. (American lecture series no. 1059).

Shephard, R. J. (1984) Athletic performance and urban air pollution. Can. Med. Assoc. J. 131: 105-109.

Sheppard, D.; Distefano, S.; Morse, L.; Becker, C. (1986) Acute effects of routine firefighting on lung function. Am. J. Ind. Med. 9: 333-340.

Sheppard, L.; Levy, D.; Norris, G.; Larson, T. V.; Koenig, J. Q. (1999) Effects of ambient air pollution on nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. Epidemiology 10: 23-30.

Sheps, D. S.; Adams, K. F., Jr.; Bromberg, P. A.; Goldstein, G. M.; O'Neil, J. J.; Horstman, D.; Koch, G. (1987) Lack of effect of low levels of carboxyhemoglobin on cardiovascular function in patients with ischemic heart disease. Arch. Environ. Health 42: 108-116.

Sheps, D. S.; Herbst, M. C.; Hinderliter, A. L.; Adams, K. F.; Ekelund, L. G.; O'Neil, J. J.; Goldstein, G. M.; Bromberg, P. A.; Dalton, J. L.; Ballenger, M. N.; Davis, S. M.; Koch, G. G. (1990) Production of arrhythmias by elevated carboxyhemoglobin in patients with coronary artery disease. Ann. Intern. Med. 113: 343-351.

Sheps, D. S.; Herbst, M. C.; Hinderliter, A. L.; Adams, K. F.; Ekelund, L. G.; O'Neil, J. J.; Goldstein, G. M.; Bromberg, P. A.; Ballenger, M.; Davis, S. M.; Koch, G. (1991) Effects of 4 percent and 6 percent carboxyhemoglobin on arrhythmia production in patients with coronary artery disease. Cambridge, MA: Health Effects Institute; research report no. 41.

Shimazu, T.; Ikeuchi, H.; Hubbard, G. B.; Langlinais, P. C.; Mason, A. D., Jr.; Pruitt, B. A., Jr. (1990) Smoke inhalation injury and the effect of carbon monoxide in the sheep model. J. Trauma 30: 170-175.

Singh, J. (1986) Early behavioral alterations in mice following prenatal carbon monoxide exposure. Neurotoxicology 7: 475-481.

Singh, J.; Moore-Cheatum, L. (1993) Gestational protein deficiency enhances fetotoxicity of carbon monoxide. In: Keen, C. L.; Bendich, A.; Willhite, C. C., eds. Maternal nutrition and pregnancy outcome. Ann. N. Y. Acad. Sci. 678: 366-368.

Singh, J.; Aggison, L., Jr.; Moore-Cheatum, L. (1993) Teratogenicity and developmental toxicity of carbon monoxide in protein-deficient mice. Teratology 48: 149-159.

Sinha, A. K.; Klein, J.; Schultze, P.; Weiss, J.; Weiss, H. R. (1991) Cerebral regional capillary perfusion and blood flow after carbon monoxide exposure. J. Appl. Physiol. 71: 1196-1200.

Smith, C. J.; Steichen, T. J. (1993) The atherogenic potential of carbon monoxide. Atherosclerosis (Shannon, Irel.) 99: 137-149.

Smith, M. D.; Merigan, W. H.; McIntire, R. W. (1976) Effects of carbon monoxide on fixed-consecutive-number performance in rats. Pharmacol. Biochem. Behav. 5: 257-262.

Snella, M.-C.; Rylander, R. (1979) Alteration in local and systemic immune capacity after exposure to bursts of CO. Environ. Res. 20: 74-79.

Spitzer, W. O.; Lawrence, V.; Dales, R.; Hill, G.; Archer, M. C.; Clark, P.; Abenhaim, L.; Hardy, J.; Sampalis, J.; Pinfold, S. P.; Morgan, P. P. (1990) Links between passive smoking and disease: a best-evidence synthesis. Clin. Invest. Med. 13: 17-42.

Steenland, K. (1992) Passive smoking and the risk of heart disease. JAMA J. Am. Med. Assoc. 267: 94-99.

Steenland, K.; Thun, M.; Lally, C.; Heath, C., Jr. (1996) Environmental tobacco smoke and coronary heart disease in the American Cancer Society CPS-II cohort. Circulation 94: 622-628.

Stern, F. B.; Lemen, R. A.; Curtis, R. A. (1981) Exposure of motor vehicle examiners to carbon monoxide: a historical prospective mortality study. Arch. Environ. Health 36: 59-66.

Stern, F. B.; Halperin, W. E.; Hornung, R. W.; Ringenburg, V. L.; McCammon, C. S. (1988) Heart disease mortality among bridge and tunnel officers exposed to carbon monoxide. Am. J. Epidemiol. 128: 1276-1288.

Stewart, R. D.; Peterson, J. E.; Baretta, E. D.; Bachand, R. T.; Hosko, M. J.; Herrmann, A. A. (1970) Experimental human exposure to carbon monoxide. Arch. Environ. Health 21: 154-164.

Stewart, R. D.; Newton, P. E.; Hosko, M. J.; Peterson, J. E. (1973) Effect of carbon monoxide on time perception. Arch. Environ. Health 27: 155-160.

Stewart, R. D.; Newton, P. E.; Kaufman, J.; Forster, H. V.; Klein, J. P.; Keelen, M. H., Jr.; Stewart, D. J.; Wu, A.; Hake, C. L. (1978) The effect of a rapid 4% carboxyhemoglobin saturation increase on maximal treadmill exercise. New York, NY: Coordinating Research Council, Inc.; report no. CRC-APRAC-CAPM-22-75.

Ström, J.; Alfredsson, L.; Malmfors, T. (1995) Carbon monoxide: causation and aggravation of cardiovascular diseases—a review of the epidemiologic and toxicologic literature. Indoor Environ. 4: 322-333.

Sunyer, J.; Antó, J. M.; Murillo, C.; Sáez, M. (1991) Effects of urban air pollution on emergency room admissions for chronic obstructive pulmonary disease. Am. J. Epidemiol. 134: 277-286.

Surgeon General of the United States. (1983) The health consequences of smoking: cardiovascular disease - a report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health; publication no. DHHS(PHS) 84-50204.

Surgeon General of the United States. (1986) The health consequences of involuntary smoking: a report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Office on Smoking and Health; publication no. DHHS (CDC) 87-8398.

Thom, S. R.; Ischiropoulos, H. (1997) Mechanism of oxidative stress from low levels of carbon monoxide. Cambridge, MA: Health Effects Institute; research report no. 80.

Thom, S. R.; Xu, Y. A.; Ischiropoulos, H. (1997) Vascular endothelial cells generate peroxynitrite in response to carbon monoxide exposure. Chem. Res. Toxicol. 10: 1023-1031.

Topping, D. L.; Fishlock, R. C.; Trimble, R. P.; Storer, G. B.; Snoswell, A. M. (1981) Carboxyhaemoglobin inhibits the metabolism of ethanol by perfused rat liver. Biochem. Int. 3: 157-163.

Touloumi, G.; Pocock, S. J.; Katsouyanni, K.; Trichopoulos, D. (1994) Short-term effects of air pollution on daily mortality in Athens: a time-series analysis. Int. J. Epidemiol. 23: 957-967.

Touloumi, G.; Samoli, E.; Katsouyanni, K. (1996) Daily mortality and "winter type" air pollution in Athens, Greece — a time series analysis within the APHEA project. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Commun. Health 50(suppl. 1): S47-S51.

Turino, G. M. (1981) Effect of carbon monoxide on the cardiorespiratory system. Carbon monoxide toxicity: physiology and biochemistry. Circulation 63: 253A-259A.

U.S. Centers for Disease Control and Prevention. (1997) Mortality patterns—preliminary data, United States, 1996. Morb. Mortal. Wkly. Rep. 46: 941-944.

U.S. Department of Health and Human Services. (1998) International classification of diseases, ninth revision (ICD-9). Hyattsville, MD: U.S. Centers for Disease Control and Prevention, National Center for Health Statistics.

U.S. Environmental Protection Agency. (1979) Air quality criteria for carbon monoxide. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA-600/8-79-022.

U.S. Environmental Protection Agency. (1984) Revised evaluation of health effects associated with carbon monoxide exposure: an addendum to the 1979 EPA air quality criteria document for carbon monoxide. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA-600/8-83-033F.

U.S. Environmental Protection Agency. (1986) Air quality criteria for lead. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA-600/8-83/028aF-dF. 4v.

U.S. Environmental Protection Agency. (1990) Air quality criteria for lead: supplement to the 1986 addendum. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/8-89/049F.

U.S. Environmental Protection Agency. (1991) Air quality criteria for carbon monoxide. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/8-90/045F.

U.S. Environmental Protection Agency. (1996) Air quality criteria for particulate matter. Research Triangle Park, NC: National Center for Environmental Assessment-RTP Office; report nos. EPA/600/P-95/001aF-cF. 3v. Available from: NTIS, Springfield, VA; PB96-168224.

Verhoeff, A. P.; Hoek, G.; Schwartz, J.; Van Wijnen, J. H. (1996) Air pollution and daily mortality in Amsterdam. Epidemiology 7: 225-230.

Vogel, J. A.; Gleser, M. A. (1972) Effect of carbon monoxide on oxygen transport during exercise. J. Appl. Physiol. 32: 234-239.

Wall, M. A.; Johnson, J.; Jacob, P.; Benowitz, N. L. (1988) Cotinine in the serum, saliva, and urine of nonsmokers, passive smokers, and active smokers. Am. J. Public Health 78: 699-701.

Wang, X.; Ding, H.; Ryan, L.; Xu, X. (1997) Association between air pollution and low birth weight: a community-based study. Environ. Health Perspect. 105: 514-520.

Weinberg, C. R.; Wilcox, A. J. (1998) Reproductive epidemiology. In: Rothman, K. J.; Greenland, S., eds. Modern epidemiology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; pp. 585-608.

Weir, F. W.; Rockwell, T. H.; Mehta, M. M.; Attwood, D. A.; Johnson, D. F.; Herrin, G. D.; Anglen, D. M.; Safford, R. R. (1973) An investigation of the effects of carbon monoxide on humans in the driving task: final report. Columbus, OH: The Ohio State University Research Foundation; contract no. 68-02-0329 and CRC-APRAC project CAPM-9-69.

Weiser, P. C.; Morrill, C. G.; Dickey, D. W.; Kurt, T. L.; Cropp, G. J. A. (1978) Effects of low-level carbon monoxide exposure on the adaptation of healthy young men to aerobic work at an altitude of 1,610 meters. In: Folinsbee, L. J.; Wagner, J. A.; Borgia, J. F.; Drinkwater, B. L.; Gliner, J. A.; Bedi, J. F., eds. Environmental stress: individual human adaptations. New York, NY: Academic Press, Inc.; pp. 101-110.

Weiss, S. T. (1996) Cardiovascular effects of environmental tobacco smoke. Circulation 94: 599.

Weissbecker, L.; Carpenter, R. D.; Luchsinger, P. C.; Osdene, T. S. (1969) In vitro alveolar macrophage viability: effect of gases. Arch. Environ. Health 18: 756-759.

Wells, A. J. (1994) Passive smoking as a cause of heart disease. J. Am. Coll. Cardiol. 24: 546-554.

Wen, S. W.; Goldenberg, R. L.; Cutter, G. R.; Hoffman, H. J.; Cliver, S. P.; Davis, R. O.; DuBard, M. B. (1990) Smoking, maternal age, fetal growth, and gestational age at delivery. Am. J. Obstet. Gynecol. 162: 53-58.

Werner, R. M.; Pearson, T. A. (1998) What's so passive about smoking? Secondhand smoke as a cause of atherosclerotic disease [editorial]. JAMA J. Am. Med. Assoc. 279: 157-158.

Wietlisbach, V.; Pope, C. A., III; Ackermann-Liebrich, U. (1996) Air pollution and daily mortality in three Swiss urban areas. Soz. Praeventivmed. 41: 107-115.

Wilcosky, T. C.; Simonsen, N. R. (1991) Solvent exposure and cardiovascular disease. Am. J. Ind. Med. 19: 569-586.

Wirkner, K.; Damme, B.; Poelchen, W.; Pankow, D. (1997) Effect of long-term ethanol pretreatment on the metabolism of dichloromethane to carbon monoxide in rats. Toxicol. Appl. Pharmcol. 143: 83-88.

Wouters, E. J. M.; de Jong, P. A.; Cornelissen, P. J. H.; Kurver, P. H. J.; van Oel, W. C.; van Woensel, C. L. M. (1987) Smoking and low birth weight: absence of influence by carbon monoxide? Eur. J. Obstet. Gynecol. Reprod. Biol. 25: 35-41.

Wright, G.; Randell, P.; Shephard, R. J. (1973) Carbon monoxide and driving skills. Arch. Environ. Health 27: 349-354.

Yang, L.; Zhang, W.; He, H.; Zhang, G. (1988) Experimental studies on combined effects of high temperature and carbon monoxide. J. Tongji Med. Univ. 8: 60-65.

Yang, W.; Jennison, B. L.; Omaye, S. T. (1997) Air pollution and asthma emergency room visits in Reno, Nevada. Inhalation Toxicol. 9: 15-29.

Yang, W.; Jennison, B. L.; Omaye, S. T. (1998) Cardiovascular disease hospitalization and ambient levels of carbon monoxide. J. Toxicol. Environ. Health Part A 55: 185-196.

Young, J. S.; Upchurch, M. B.; Kaufman, M. J.; Fechter, L. D. (1987) Carbon monoxide exposure potentiates high-frequency auditory threshold shifts induced by noise. Hear. Res. 26: 37-43.

Zarén, B.; Lindmark, G.; Gebre-Medhin, M. (1996) Maternal smoking and body composition of the newborn. Acta Paediatr. 85: 213-219.

Żebro, T.; Wright, E. A.; Littleton, R. J.; Prentice, A. I. D. (1983) Bone changes in mice after prolonged continuous exposure to a high concentration of carbon monoxide. Exp. Pathol. 24: 51-67.

Zhu, B.-Q.; Parmley, W. W. (1995) Hemodynamic and vascular effects of active and passive smoking. Am. Heart J. 130: 1270-1275.

CHAPTER 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 [Hb], myoglobin [Mb], 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 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 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 the amount of air removed and replaced per unit of time for gas exchange), 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 the high affinity of CO for 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, especially if exposure is to varying concentrations of CO over extended periods of time. 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 disorders, however, that can make an individual more susceptible to the potential adverse effects of low levels of CO, especially during exercise. Occlusive vascular disease (e.g., coronary heart disease, cerebrovascular disease) limits blood flow to the tissues, obstructive lung disease (e.g., bronchitis, emphysema, asthma) 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 affected body tissues. A reduction in oxygen delivery caused by elevated COHb levels, combined with impaired air or blood flow to the diseased tissues, will further reduce organ system function and limit exercise capacity.

The existing 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 reduce the risk of adverse health effects in the population groups most sensitive to the presence of CO in the ambient air. The term “ambient air” is interpreted to mean outdoor air measured 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 a summary of the key factors discussed 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 CO 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 the staff paper and associated assessments that will help to evaluate the adequacy of the existing CO NAAQS.

7.2 Environmental Sources

Carbon monoxide is produced by both natural and anthropogenic processes. About half of the atmospheric CO is released at the earth's surface from fossil fuel and biomass burning, and the rest is produced as the result of photochemical reactions in the atmosphere. About two-thirds of the CO in the atmosphere arises from human activities; natural processes account for the remaining one-third. 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, CO concentrations in remote marine areas increased at approximately 1% per year. More recent reports, however, show that CO concentrations in these locations declined rapidly between 1988 and 1993. Since 1993, the downward trend in CO has slowed or leveled off, depending on the measurement laboratory, 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 thought 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 at 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, 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 and other combustion engine sources, for example, riding behind high emitters or in a vehicle with a defective exhaust system and using lawnmowers, weeders, tillers, or other garden equipment. 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 are associated with vehicle startup and idling in attached garages and the use of unvented gas or kerosene space heaters where peak concentrations of CO as high or higher than 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 in a particular locale, and the findings of more recent studies suggest that results from pre-1990 studies in major cities across the United States are no longer applicable. For example, commuter exposure to motor vehicle exhaust fell from a historically high value of 37 ppm CO in Los Angeles, CA, during 1965 to a low value of 3 ppm CO on the New Jersey Turnpike in 1992. 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.

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 Hb to form COHb that, when elevated above the endogenous level, is a specific biomarker of CO exposure. 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 should be closely representative of any longer continuous exposures. In real-life situations, 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).

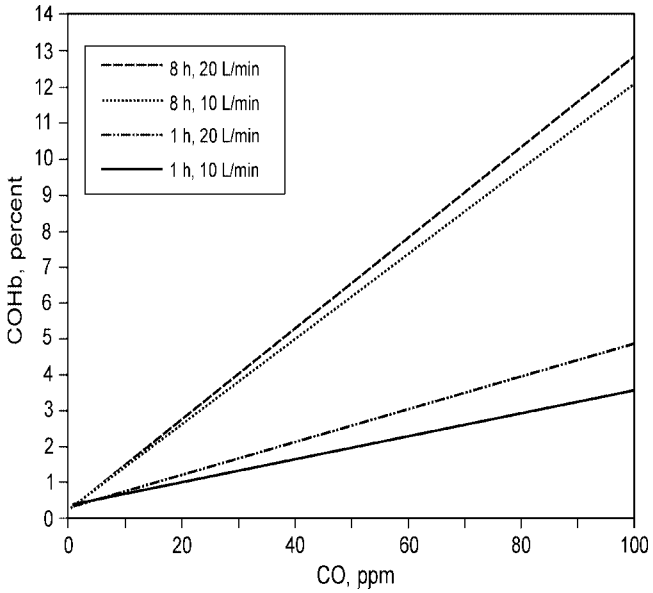

Figure 7-1. Predicted COHb levels resulting from 1- and 8-h exposures to CO at rest (minute ventilation rate of 10 L/min) and with light exercise (20 L/min) are based on the Coburn-Forster-Kane equation, using the following assumed parameters for nonsmoking adults: altitude = 0 ft, initial COHb level = 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.

Evaluation of human CO exposure situations indicates that occupational exposures in some workplaces, or exposures in homes with faulty or unvented combustion sources, can exceed 100 ppm CO, 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 rarely by the general public under ambient conditions. More frequently, short-term exposures to less than 25 to 50 ppm CO occur in 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.

Table 7-1. Predicted Carbon Monoxide Exposures in the Population

Exposure Conditions[c]	Predicted COHb Response[a,b]: 1 h, Light Exercise	Predicted COHb Response[a,b]: 8 h, Light Exercise
Nonsmoking adults exposed to 25 to 50 ppm	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 assumed parameters of the Coburn-Forster-Kane equation (Coburn et al., 1965).
[b] Light exercise at 20 L/min.
[c] Exposures are steady state.

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-pack-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 passive exposure to tobacco smoke, have been taken into account. In addition, as the result of their higher baseline COHb levels, smokers actually 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 raise the chronically elevated COHb levels resulting from smoking.

7.5 Mechanisms of Carbon Monoxide Activity

A clear mechanism of action underlying the 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 systemic hypotension induced by hypoxia, may cause identifiable health effects.

Carbon monoxide will bind to intracellular hemoproteins such as 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 when intracellular PO_2 decreases with increasing COHb levels. The hemoprotein most likely 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 hemoproteins may secondarily precipitate oxidative stress. The health risks associated with this mechanism have not been clearly established.

7.6 Health Effects of Carbon Monoxide

This document deals primarily with the relatively low concentrations of CO that may 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. The morbidity and mortality resulting from the latter exposures are described in several recent reports (Jain, 1990; Penney, 1996; Ernst and Zibrak, 1998).

The health effects from exposure to low CO concentrations, such as the levels found in ambient air, are considerably less threatening than those occurring in frank poisoning from high CO concentrations. Effects of exposure to excessive ambient air levels of CO are summarized 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 $\leq$5%, because of the large variability and potentially 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 segment depression). At 5% COHb (CO-Ox) or higher, some healthy individuals may experience impaired psychomotor performance; however, there is too much variability in response across studies that have tested the same concentrations of CO, and research conducted since the last criteria document review (U.S. Environmental Protection Agency, 1991) 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.

Some recent epidemiologic studies have reported findings suggestive of ambient CO levels being associated with increased exacerbation of heart disease in the population. However, these findings must be considered to be inconclusive at this time because of questions concerning (a) internal inconsistencies and overall coherence of the epidemiologic results, (b) how well the community average ambient CO levels used in the studies (typically derived from a few fixed-site monitors) index either spatially widely variable ambient CO levels or personal exposures often augmented by indoor-generated CO sources, (c) the extremely small changes (from virtually undetectable up to ca 1.0%) in COHb over baseline levels projected (see Figure 7-1) to occur with the low average ambient CO concentrations (most all < 5 ppm; daily max 1-h values) reported in the studies, and (d) the pathophysiologic implausibility of any harmful effects being exerted at such levels. Putting the ambient CO levels into perspective, exposures to cigarette smoke or to combustion exhaust gases from small engines and recreational vehicles typically raise COHb to levels much higher than levels resulting from mean ambient CO exposures, and, for most people, exposures to indoor sources of CO often exceed controllable outdoor exposures. The possibility has been posed that the

average ambient CO levels used as exposure indices in the epidemiology studies may be surrogates for ambient air mixes impacted by combustion sources and/or other constituent toxic components of such mixes. More research will be needed to clarify better CO's role.

7.7 Subpopulations Potentially at Risk from Exposure to Ambient Carbon Monoxide

As can be seen from the preceding section, CO-related health effects are most likely to occur in individuals who are physiologically stressed, either by exercise or by medical conditions that can make them more susceptible to low levels of CO.

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 2.4% (GC). Healthy individuals also 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 heart failure; people with peripheral vascular or cerebrovascular disease; individuals with hematologic 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 with 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. Limited epidemiologic findings suggest some association of subchronic ambient CO exposure with low birth weight, but the data are not conclusive. 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. Thus, many healthy individuals at 75 years of age are on the borderline with respect to being able to meet daily metabolic requirements for ordinary activities. It is quite possible, therefore, that even low levels of CO exposure might be enough to critically impair oxygen delivery to the tissues in this aging population and limit daily metabolic requirements. 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 a Risk Factor

7.7.2.1 Subjects with Heart Disease

As discussed in Chapter 6, cardiovascular disease comprises many types of medical disorders, including heart disease, cerebrovascular disease (e.g., stroke), hypertension (high blood pressure), and peripheral vascular diseases. Heart disease, in turn, comprises several types of disorders, including ischemic heart disease (i.e., coronary heart disease [CHD], CAD, myocardial infarction, and angina), congestive heart failure, and disturbances of cardiac rhythm (dysrhythmias and arryhthmias). Heart disease patients often have markedly reduced circulatory capacity and reduced ability to compensate for increased circulatory demands during exercise and other stress. Therefore, they are especially susceptible to harmful effects from the reduction in oxygen-carrying capacity of the blood. Exogenous CO exposure causes such reduction and, thus, could have serious consequences in heart disease patients.

Coronary heart disease remains the major cause of death and disability in industrialized societies. In the United States, CHD is the single largest killer of both males and females, causing 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 CHD, with increased 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. Exercise-induced angina pectoris (chest pain) occurs in many of them. Among all patients with diagnosed CAD, the predominant type of ischemia, as identified by ST segment depression, is asymptomatic (i.e., silent). Also, patients who

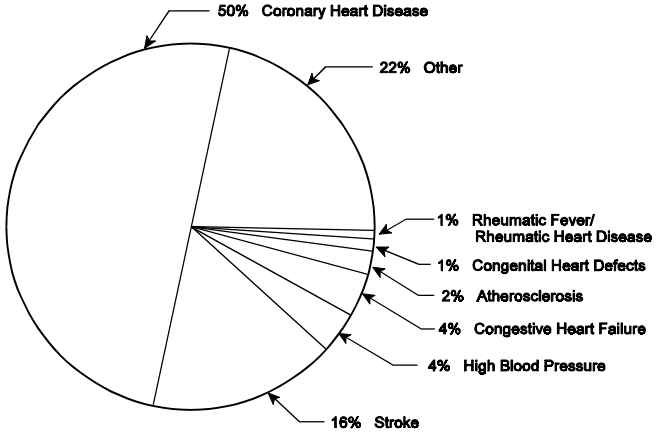

Figure 7-2. Percentage breakdown of deaths from cardiovascular diseases in the United States (1996 mortality statistics).
Source: American Heart Association (1997); National Center for Health Statistics (1995).

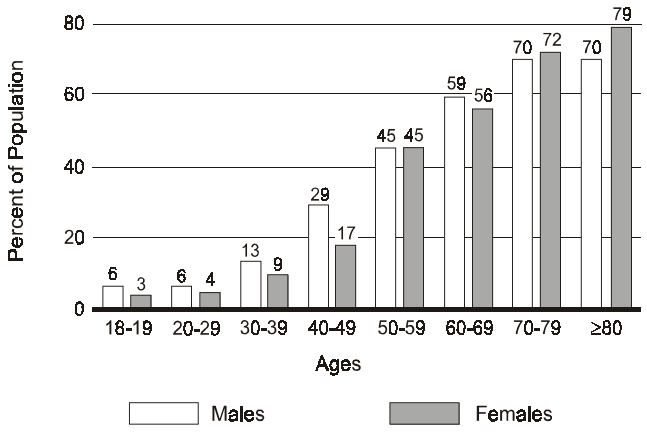

Figure 7-3. Estimated prevalence of cardiovascular disease by age and sex for the United States, 1988 to 1991.
Source: American Heart Association (1997); Collins (1997); Adams and Marano (1995).

experience angina typically have additional ischemic episodes that are asymptomatic. Unfortunately, some individuals in the population have CAD 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 exercise stress testing; 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, should be sensitive to a decrease in oxygen-carrying capacity induced by CO exposure.

Heart failure is a major and growing public health problem. Almost 5 million Americans have heart failure, and about 400,000 new cases occur each year (American Heart Association, 1997). Because the prevalence of heart failure increases with age, prolongation of life expectancy in the general population would be expected to increase the magnitude of the problem over the next few decades. The etiology of heart failure is diverse, but the most common secondary conditions observed in hospitalized patients are CHD, hypertension, chronic obstructive pulmonary disease, diabetes, and cardiomyopathy (Croft et al., 1997). The exacerbation of some of these secondary conditions by CO are not well known; however, any heart failure patients with CAD, for example, might be especially sensitive to CO exposure.

7.7.2.2 Subjects with Other Vascular Diseases

Vascular disease, including cerebrovascular disease, is present in both males and females 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 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 (lameness) 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 determine more precisely the sensitivity to CO of individuals with vascular disease.

7.7.2.3 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. Anemia is more prevalent in pregnant 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 Hb S is 12 days compared to an average of 120 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.

7.7.2.4 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 ($\approx$30%) continue to smoke and may have baseline COHb levels of 4 to 8%. The COPD patients with hypoxia are also more likely to have CO cause 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. Epidemiologic observations on the relationship between short-term ambient CO levels and the frequency of respiratory disease cannot yet be interpreted with confidence.

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 address meaningfully 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 at 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 possible that the combination of hypoxic hypoxia and hypoxia resulting from ambient exposure to CO could reduce birth weight further at high altitude and conceivably modify future development, available data are not adequate to confirm 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 inadequately vented combustion sources, 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 does not warrant changing the conclusions of the previous document. The principal cause of CO-induced effects at low levels of exposure still is thought to be increased COHb formation and the consequent reduction of oxygen delivery to the body's organs and tissues. The air quality criteria used to support the existing CO NAAQS were primarily those data obtained from experimental studies of nonsmoking coronary artery disease patients during exercise. These studies identified adverse effects with CO exposures that lead to COHb levels of 2.4% (GC) or higher. Young, healthy individuals appear to be at little or no health risk because of ambient CO exposure. In these individuals, the only observed effect of CO exposures resulting in <5% COHb has been reduction of maximal exercise. No effects of CO exposures in this range have been observed in healthy individuals performing submaximal exercise at levels typical of normal human activities. Greater concern, therefore, has focused on subpopulations in which biological and pathophysiologic considerations would suggest increased susceptibility to low-level CO exposure. Indeed, recent epidemiologic studies that have become available since publication of the previous document are stimulating increased scientific interest regarding ambient CO exposures as a potential risk factor for exacerbation of heart disease, mortality, and low birth weight. Results of these studies argue for further research on the health effects of ambient CO exposure. This research should address CO alone and CO as a component of the overall ambient air pollution mixture. Nevertheless, the epidemiologic studies remain subject to considerable biological and statistical uncertainty, and the available epidemiologic database does not provide convincing evidence that further selective reduction of ambient CO levels would substantially benefit public health.

References

Adams, P. F.; Marano, M. A. (1995) Current estimates from the National Health Interview Survey, 1994. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics; publication no. 6-1521. (Vital and health statistics: v. 10, no. 193). Available: www.cdc.gov/nchs/products/pubs/pubd/series/sr10/199-190/se10_193.htm [2000, February 28].

Akland, G. G.; Hartwell, T. D.; Johnson, T. R.; Whitmore, R. W. (1985) Measuring human exposure to carbon monoxide in Washington, D.C., and Denver, Colorado, during the winter of 1982-1983. Environ. Sci. Technol. 19: 911-918.

American Heart Association. (1997) 1998 heart and stroke statistical update. Dallas, TX: American Heart Association.

Coburn, R. F.; Forster, R. E.; Kane, P. B. (1965) Considerations of the physiological variables that determine the blood carboxyhemoglobin concentration in man. J. Clin. Invest. 44: 1899-1910.

Collins, J. G. (1997) Prevalence of selected chronic conditions: United States, 1990-1992. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics; publication no. 97-1522. (Vital and health statistics: v. 10, no. 194). Available: www.cdc.gov/nchs/data/sr10_194.pdf [2000, February 28].

Croft, J. B.; Giles, W. H.; Pollard, R. A.; Casper, M. L.; Anda, R. F.; Livengood, J. R. (1997) National trends in the initial hospitalization for heart failure. J. Am. Geriatr. Soc. 45: 270-275.

Ernst, A.; Zibrak, J. D. (1998) Carbon monoxide poisoning. N. Engl. J. Med. 339: 1603-1608.

Federal Register. (1994) National ambient air quality standards for carbon monoxide—final decision. F. R. (August 1) 59: 38,906-38,917.

Jain, K. K. (1990) Carbon monoxide poisoning. St. Louis, MO: Warren H. Green, Inc.

National Center for Health Statistics. (1995) Health, United States, 1994. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service; publication no. 95-1232. Available: www.cdc.gov/nchs/data/hus_94.pdf [2000, February 28].

Penney, D. G., ed. (1996) Carbon monoxide. Boca Raton, FL: CRC Press.

Radford, E. P.; Drizd, T. A. (1982) Blood carbon monoxide levels in persons 3-74 years of age: United States, 1976-80. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics; publication no. (PHS) 82-1250. (Advance data from vital and health statistics: no. 76).

U.S. Centers for Disease Control and Prevention. (1997) Mortality patterns—preliminary data, United States, 1996. Morb. Mortal. Wkly. Rep. 46: 941-944.

U.S. Environmental Protection Agency. (1991) Air quality criteria for carbon monoxide. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/8-90/045F.

APPENDIX A

Abbreviations and Acronyms

AER	Air exchange rate
AIRS	Aerometric Information Retrieval System
ATPS	Ambient temperature and pressure, saturated with water vapor
α	Alpha, the level of acceptable Type 1 error
BS	Black smoke
BTPS	Body temperature and pressure, saturated with water vapor at 37 °C
cGMP	Cyclic guanosine monophosphate
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-Forster-Kane
CH_3	Methyl radical
CH_4	Methane
CHAD	Consolidated Human Activity Database
CH_3Br	Methyl bromide
CH_3CCl_3	Methyl chloroform
CH_3CHO	Acetaldehyde
CH_3Cl	Methyl chloride

CH_3CO	Acetyl radical
CHD	Coronary heart disease
CHF	Congestive heart failure
CH_2O	Formaldehyde
CH_3O_2	Methyl peroxy radical
CH_3OOH	Methyl hydroperoxide
CI	Confidence interval
CMAQ	Congestion Management and Air Quality
$CMRO_2$	Cerebral metabolic rate for oxygen
CMSA	Consolidated metropolitan statistical area
CO	Carbon monoxide
CO_2	Carbon dioxide
COH	Coefficient of haze
COHb	Carboxyhemoglobin
COMb	Carboxymyoglobin
CO-Ox	CO-Oximetry or CO-Oximeter
COPD	Chronic obstructive pulmonary disease
CPSC	Consumer Product Safety Commission
CRM	Certified Reference Material
CTM	Chemical Transport Model
CVD	Cardiovascular disease
D_LCO	Diffusing capacity for carbon monoxide
ECG	Electrocardiogram
ED	Effective dose for a specific decrement in function
ED	Emergency department
EMFAC7C	Emissions Factor 7C
EPA	U.S. Environmental Protection Agency
ETS	Environmental tobacco smoke
F_ICO	Fractional concentration of carbon monoxide in inhaled air

FDA	Food and Drug Administration
FID	Flame ionization detection or detector
FTP	Federal testing procedures
GAM	General additive model
GC	Gas chromatography or gas chromatograph
GFC	Gas filter correlation
GLM	General linear model
hυ	Photon
H	Atomic hydrogen
H_2	Molecular hydrogen
Hb	Hemoglobin
HCN	Hydrogen cyanide
HCO	Formyl radical
HO	Heme oxygenase
HO1	Isoform of heme oxygenase
HO_2	Hydroperoxy radical
H_2O_2	Hydrogen peroxide
HOCO	Carboxyl radical
ICD	International Classification of Diseases
IHD	Ischemic heart disease
IQR	Interquartile range
IR	Infrared
LOEL	Lowest-observed-effect level
LOESS	Locally weighted regression scatter plot smoothing
M	Haldane coefficient
Mb	Myoglobin
MI	Myocardial infarction
ML	Mercury liberation
MQL	Minimum quantification limit

MSA	Metropolitan Statistical Area
n	Number
N	North
N_2	Molecular nitrogen
NAAQS	National Ambient Air Quality Standards
NAMS	National Air Monitoring Station
NASA	National Aeronautics and Space Administration
NDIR	Nondispersive infrared
NEM	National Ambient Air Quality Standards Exposure Model
NHANES	National Health and Nutrition Examination Survey
NHAPS	National Human Activity Pattern Survey
$Ni(CO)_4$	Nickel tetracarbonyl
NIST	National Institute of Standards and Technology
NMDA	N-methyl-D-aspartate
NMHC	Non-methane hydrocarbon
NMi	Nederland Meetinstitut (i.e., Dutch Bureau of Standards)
NMOC	Non-methane organic compounds
NO	Nitric oxide
$^{\bullet}NO$	Nitric oxide free radical
NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
NOAA/CMDL	National Oceanic and Atmospheric Administration Climate Monitoring Diagnostics Laboratory
NTRM	National Institute of Standards and Technology Traceable Reference Material
O	Atomic oxygen
O_2	Molecular oxygen
O_3	Ozone
OH	Hydroxyl radical
O_2Hb	Oxyhemoglobin

p	Probability
P_{atm}	Pressure in atmospheres
pNEM	Probabilistic National Ambient Air Quality Standards Exposure Model
P_B	Barometric pressure
PAH	Polyaromatic hydrocarbon
PAN	Peroxyacetyl nitrate
PCO	Partial pressure of carbon monoxide
PEM	Personal exposure monitor
PIA	Percentage increases in hospital admissions
PM	Particulate matter
PM_1	Particulate matter with an aerodynamic diameter ≤ 1 µm
$PM_{2.5}$	Particulate matter with an aerodynamic diameter ≤ 2.5 µm
PM_{10}	Particulate matter with an aerodynamic diameter ≤ 10 µm
$P_{\bar{c}}O_2$	Average partial pressure of oxygen in lung capillaries in millimeters of mercury
P_IO_2	Partial pressure of oxygen in humidified inspired air
PO_2	Partial pressure of oxygen
PRM	Primary Reference Material
$\dot{Q}$	Perfusion
r	Linear regression correlation coefficient
R^2	Multiple correlation coefficient
RBC	Red blood cell
RER	Respiratory exchange ratio
RR	Relative risk
S	South
SCAQMD	South Coast Air Quality Management District
SD	Standard deviation
SHAPE	Simulation of Human Activity and Pollutant Exposure
SI	International System of Units
SIDS	Sudden infant death syndrome

SLAMS	State and Local Air Monitoring Station
SO_2	Sulfur dioxide
SRM	Standard Reference Materials
ST	Segment of the electrocardiogram
STEL	Short-term exposure limit
STPD	Standard temperature and pressure, dry
SUV	Sport utility vehicle
TCM	Transportation Control Measure
TDL	Tunable diode laser
TDLS	Tunable diode laser spectroscopy
Tg	Teragram
THb	Total blood concentration of hemoglobin
TSP	Total suspended particulate
TWA	Time-weighted average
URI	Upper respiratory illness
UV	Ultraviolet
$\dot{V}_A$	Alveolar ventilation
V_b	Blood volume
$\dot{V}_{co}$	Endogenous carbon monoxide production rate
V_D	Volume of physiological dead space
VMT	Vehicle miles of travel