



Air Quality Criteria for Carbon Monoxide

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

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Preface

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

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

CHAPTER 1. INTRODUCTION

Principal Author

Mr. James A. Raub—Project Manager and Coordinator for Heath Effects
National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors

Dr. Robert S. Chapman—Coordinator for Epidemiology Studies
National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Beverly M. Comfort—Coordinator for Indoor Air Emissions and Concentrations
National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. William G. Ewald—Coordinator for Measurement Methods
National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. David T. Mage—Coordinator for Population Exposure
National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Joseph P. Pinto—Coordinator for Atmospheric Chemistry, Sources, and Emissions
National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Reviewers

Mr. C. Barnett—New York Healthy Schools Network, 96 South Swan Street
Albany, NY 12210

Ms. Kelly M. Brown—Ford Motor Company, 17225 Federal Drive, Suite 145
Allen Park, MI 48101

Mr. Albert Donnay—MCS Referral & Resources, Inc., 508 Westgate Rd., Baltimore, MD 21229

Dr. Sandra E. Inkster—U.S. Consumer Product Safety Commission, 4330 East West Highway
Room 600, Bethesda, MD 02814

Authors, Contributors, and Reviewers

(cont'd)

Dr. David J. McKee—Office of Air Quality Planning and Standards (MD-15)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Nancy W. Newkirk—American Petroleum Institute, 1220 L Street, NW
Washington, DC 20005

Mr. Harvey M. Richmond—Office of Air Quality Planning and Standards (MD-15)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

CHAPTER 2. ANALYTICAL METHODS FOR MONITORING CARBON MONOXIDE

Principal Authors

Dr. Russell R. Dickerson—Department of Meteorology, The University of Maryland
College Park, MD 20742

Dr. David T. Mage—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors

Mr. William G. Ewald—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Joseph P. Pinto—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lance Wallace—National Exposure Research Laboratory
U.S. Environmental Protection Agency, Reston, VA 22092

Reviewers

Dr. Michael G. Apte—Indoor Environment Department
Lawrence Berkeley National Laboratory, Berkeley, CA 94720

Ms. Kelly M. Brown—Ford Motor Company, 17225 Federal Drive, Suite 145
Allen Park, MI 48101

Dr. Steven D. Colome—Integrated Environmental Services, Irvine, CA 92612-2935

Authors, Contributors, and Reviewers

(cont'd)

Dr. Thomas E. Dahms—Department of Anesthesiology, School of Medicine
St. Louis University Medical Center, St. Louis, MO 63110

Mr. Albert Donnay—MCS Referral & Resources, Inc., 508 Westgate Rd., Baltimore, MD 21229

Dr. Milan J. Hazucha—Department of Medicine
Center for Environmental Medicine and Lung Biology, The University of North Carolina
Chapel Hill, NC 27599

Dr. Michael T. Kleinman—Department of Community and Environmental Medicine
California College of Medicine, University of California, Irvine, CA 92697

Mr. Leon Langan—Langan Products, Inc., 2660 California Street, San Francisco, CA 94115

Dr. William A. McClenny—National Exposure Research Laboratory (MD-44)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Nancy W. Newkirk—American Petroleum Institute, 1220 L Street, NW
Washington, DC 20005

Dr. Leonard Newman—Environmental Chemistry Division
Brookhaven National Laboratory, Upton, NY 11973

Dr. Paul Roberts—Sonoma Technology, Inc., Petaluma, CA 94954

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

Principal Authors

Dr. Joseph P. Pinto—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Beverly M. Comfort—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Michael P. Zelenka—National Exposure Research Laboratory (MD-56)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Authors, Contributors, and Reviewers

(cont'd)

Contributors

Mr. Warren P. Freas—Office of Air Quality Planning and Standards (MD-14)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Alan H. Huber—National Exposure Research Laboratory (MD-56)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Reviewers

Dr. Michael G. Apte—Indoor Environment Department
Lawrence Berkeley National Laboratory, Berkeley, CA 94720

Dr. Irwin H. Billick—WEC Consulting, Ltd., Potomac, MD 20854

Ms. Kelly M. Brown—Ford Motor Company, 17225 Federal Drive, Suite 145
Allen Park, MI 48101

Mr. Tom Chapple—State of Alaska, Department of Environmental Conservation
555 Cordova Street, Anchorage, AK 99501

Dr. Steven D. Colome—Integrated Environmental Services, Irvine, CA 92612-2935

Mr. Albert Donnay—MCS Referral & Resources, Inc., 508 Westgate Rd., Baltimore, MD 21229

Dr. Peter G. Flachsbart—Department of Urban and Regional Planning
University of Hawaii at Manoa, Honolulu, HI 96822

Dr. Lawrence J. Folinsbee—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Mary Good—Municipality of Anchorage, Department of Health and Human Services
825 L Street, P.O. Box 196650, Anchorage, AK 99519

Mr. Hank Hove—Fairbanks North Star Borough, 809 Pioneer Road, P.O. Box 71267
Fairbanks, AK 99707

Dr. Sandra E. Inkster—U.S. Consumer Product Safety Commission, 4330 East West Highway
Room 600, Bethesda, MD 02814

Dr. Kai-Shen Liu—Environmental Health Laboratory
California Department of Health Services, Berkeley, CA 94704

Authors, Contributors, and Reviewers

(cont'd)

Mr. Thomas R. McCurdy—National Exposure Research Laboratory (MD-56)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Robert Morris—Department of Family Medicine
Tufts University School of Medicine, Boston, MA 02111

Ms. Nancy W. Newkirk—American Petroleum Institute, 1220 L Street, NW
Washington, DC 20005

Dr. Leonard Newman—Environmental Chemistry Division
Brookhaven National Laboratory, Upton, NY 11973

Dr. Paul Roberts—Sonoma Technology, Inc., Petaluma, CA 94954

Dr. Jed Waldman—California Department of Health Services, Berkeley, CA 94704

CHAPTER 4. POPULATION EXPOSURE TO CARBON MONOXIDE

Principal Author

Dr. Peter G. Flachsbart—Department of Urban and Regional Planning
University of Hawaii at Manoa, Honolulu, HI 96822

Contributor

Dr. David T. Mage—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Reviewers

Dr. Michael G. Apte—Indoor Environment Department
Lawrence Berkeley National Laboratory, Berkeley, CA 94720

Mr. C. Barnett—New York Healthy Schools Network, 96 South Swan Street
Albany, NY 12210

Dr. Irwin H. Billick—WEC Consulting, Ltd., Potomac, MD 20854

Authors, Contributors, and Reviewers

(cont'd)

Ms. Kelly M. Brown—Ford Motor Company, 17225 Federal Drive, Suite 145
Allen Park, MI 48101

Dr. Steven D. Colome—Integrated Environmental Services, Irvine, CA 92612-2935

Mr. Albert Donnay—MCS Referral & Resources, Inc., 508 Westgate Rd., Baltimore, MD 21229

Dr. Milan J. Hazucha—Department of Medicine
Center for Environmental Medicine and Lung Biology, The University of North Carolina
Chapel Hill, NC 27599

Dr. Sandra E. Inkster—U.S. Consumer Product Safety Commission, 4330 East West Highway
Room 600, Bethesda, MD 02814

Dr. Michael T. Kleinman—Department of Community and Environmental Medicine
California College of Medicine, University of California, Irvine, CA 92697

Dr. Kai-Shen Liu—Environmental Health Laboratory
California Department of Health Services, Berkeley, CA 94704

Mr. Thomas R. McCurdy—National Exposure Research Laboratory (MD-56)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Robert Morris—Department of Family Medicine
Tufts University School of Medicine, Boston, MA 02111

Ms. Nancy W. Newkirk—American Petroleum Institute, 1220 L Street, NW
Washington, DC 20005

Mr. Harvey M. Richmond—Office of Air Quality Planning and Standards (MD-15)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Jed Waldman—California Department of Health Services, Berkeley, CA 94704

Authors, Contributors, and Reviewers
(cont'd)

***CHAPTER 5. PHARMACOKINETICS AND MECHANISMS OF
ACTION OF CARBON MONOXIDE***

Principal Authors

Dr. Milan J. Hazucha—Department of Medicine
Center for Environmental Medicine and Lung Biology, The University of North Carolina
Chapel Hill, NC 27599

Dr. Stephen R. Thom—Institute for Environmental Medicine and
Department of Emergency Medicine, University of Pennsylvania, Philadelphia, PA 19104

Reviewers

Mr. C. Barnett—New York Healthy Schools Network, 96 South Swan Street
Albany, NY 12210

Ms. Kelly M. Brown—Ford Motor Company, 17225 Federal Drive, Suite 145
Allen Park, MI 48101

Dr. Steven D. Colome—Integrated Environmental Services, Irvine, CA 92612-2935

Dr. Thomas E. Dahms—Department of Anesthesiology
School of Medicine, St. Louis University Medical Center, St. Louis, MO 63110

Mr. Albert Donnay—MCS Referral & Resources, Inc., 508 Westgate Rd., Baltimore, MD 21229

Dr. Sandra E. Inkster—U.S. Consumer Product Safety Commission, 4330 East West Highway
Room 600, Bethesda, MD 02814

Dr. Michael T. Kleinman—Department of Community and Environmental Medicine
California College of Medicine, University of California, Irvine, CA 92697

Dr. James J. McGrath—Department of Physiology, School of Medicine
Texas Tech University Health Sciences Center, Lubbock, TX 79430

Ms. Nancy W. Newkirk—American Petroleum Institute, 1220 L Street, NW
Washington, DC 20005

Dr. Peter Tikuisis—Defence and Civil Institute of Environmental Medicine
1133 Sheppard Avenue, West, Toronto, Ontario, M3M 3B9, Canada

Authors, Contributors, and Reviewers

(cont'd)

CHAPTER 6. HEALTH EFFECTS OF EXPOSURE TO AMBIENT CARBON MONOXIDE

Principal Authors

Mr. James A. Raub—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Robert S. Chapman—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Reviewers

Mr. C. Barnett—New York Healthy Schools Network, 96 South Swan Street
Albany, NY 12210

Ms. Kelly M. Brown—Ford Motor Company, 17225 Federal Drive, Suite 145
Allen Park, MI 48101

Dr. Steven D. Colome—Integrated Environmental Services, Irvine, CA 92612-2935

Dr. Thomas E. Dahms—Department of Anesthesiology, School of Medicine
St. Louis University Medical Center, St. Louis, MO 63110

Mr. Albert Donnay—MCS Referral & Resources, Inc., 508 Westgate Rd., Baltimore, MD 21229

Dr. Lawrence J. Folinsbee—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Milan J. Hazucha—Department of Medicine
Center for Environmental Medicine and Lung Biology, The University of North Carolina
Chapel Hill, NC 27599

Dr. Jon M. Heuss—Air Improvement Resources, Inc., 7355 Rickett Drive
Washington, MI 48094

Dr. Sandra E. Inkster—U.S. Consumer Product Safety Commission, 4330 East West Highway
Room 600, Bethesda, MD 02814

Dr. Michael T. Kleinman—Department of Community and Environmental Medicine
California College of Medicine, University of California, Irvine, CA 92697

Authors, Contributors, and Reviewers

(cont'd)

Dr. Victor G. Laties—Environmental Medicine, University of Rochester Medical Center
School of Medicine and Dentistry, Rochester, NY 14642

Dr. James J. McGrath—Department of Physiology, School of Medicine
Texas Tech University Health Sciences Center, Lubbock, TX 79430

Dr. Robert Morris—Department of Family Medicine
Tufts University School of Medicine, Boston, MA 02111

Ms. Nancy W. Newkirk—American Petroleum Institute, 1220 L Street, NW
Washington, DC 20005

CHAPTER 7. INTEGRATIVE SUMMARY AND CONCLUSIONS

Principal Author

Mr. James A. Raub—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors

Dr. Robert S. Chapman—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Beverly M. Comfort—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. William G. Ewald—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. David T. Mage—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Joseph P. Pinto—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Authors, Contributors, and Reviewers

(cont'd)

Reviewers

Dr. Michael G. Apte—Indoor Environment Department
Lawrence Berkeley National Laboratory, Berkeley, CA 94720

Ms. Kelly M. Brown—Ford Motor Company, 17225 Federal Drive, Suite 145
Allen Park, MI 48101

Mr. Albert Donnay—MCS Referral & Resources, Inc., 508 Westgate Rd., Baltimore, MD 21229

Dr. Lawrence J. Folinsbee—National Center for Environmental Assessment (MD-52)
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Sandra E. Inkster—U.S. Consumer Product Safety Commission, 4330 East West Highway
Room 600, Bethesda, MD 02814

Dr. James J. McGrath—Department of Physiology, School of Medicine
Texas Tech University Health Sciences Center, Lubbock, TX 79430

Ms. Nancy W. Newkirk—American Petroleum Institute, 1220 L Street, NW
Washington, DC 20005

Dr. Stephen R. Thom—Institute for Environmental Medicine and
Department of Emergency Medicine, University of Pennsylvania, Philadelphia, PA 19104

Dr. Vanessa Vu—National Center for Environmental Assessment (8601D)
U.S. Environmental Protection Agency, 401 M St. SW, Washington, DC 20460

Dr. Jed Waldman—California Department of Health Services, Berkeley, CA 94704

**U.S. Environmental Protection Agency
Science Advisory Board
Clean Air Scientific Advisory Committee
Carbon Monoxide Review Panel**

Chair

Dr. Joe Mauderly—Director of External Affairs, Senior Scientist, and Director of National Environmental Respiratory Center, Lovelace Respiratory Research Institute
Albuquerque, NM 87108

Members

Mr. John Elston—Administrator, Office of Air Quality Management, State of New Jersey
Department of Environmental Protection and Energy, Trenton, NJ 08625

Dr. Philip K. Hopke—R.A. Plane Professor of Chemistry, Clarkson University
Potsdam, NY 13699

Dr. Eva J. Pell—Steimer Professor of Agriculture Sciences, Buckhout Laboratory
The Pennsylvania State University, University Park, PA 16802

Dr. Arthur C. Upton—Director, Independent Peer Review, CRESP
Environmental and Occupational Health Sciences Institute, Piscataway, NJ 08854

Dr. Sverre Vedal—Professor of Medicine, Vancouver General Hospital
Vancouver, BC Canada V57 3J5

Dr. Warren White—Senior Research Associate, Chemistry Department, Washington University
St. Louis, MO 63130

Consultants

Dr. Stephen M. Ayres—Director, International Health Programs
Virginia Commonwealth University/Medical College of Virginia, Richmond, VA 23284

Dr. Thomas E. Dahms—Professor and Director, Anesthesiology Research
Department of Anesthesiology, St. Louis University School of Medicine, St. Louis, MO 63110

Dr. Victor G. Laties—Professor Emeritus, Department of Environmental Medicine
University of Rochester Medical Center, Rochester, NY 14642

**U.S. Environmental Protection Agency
Science Advisory Board
Clean Air Scientific Advisory Committee
Carbon Monoxide Review Panel
(cont'd)**

Dr. Brian Leaderer—Professor, Division of Environmental Health Sciences
Yale University School of Medicine, New Haven, CT 06519

Dr. Lawrence D. Longo—Professor, School of Medicine, Department of Physiology
Center for Perinatal Biology, Departments of Physiology and Gynecology and Obstetrics
School of Medicine, Loma Linda University, Loma Linda, CA 92354

Designated Federal Official

Mr. Robert Flaak—Designated Federal Officer and Team Leader, Committee Operations Staff
U.S. Environmental Protection Agency, Science Advisory Board (1400), Washington, DC 20460

Staff Assistant

Ms. Diana Pozun—Management Assistant, U.S. Environmental Protection Agency
Science Advisory Board (1400), Washington, DC 20460

**U.S. Environmental Protection Agency
Project Team for Development of
Air Quality Criteria for Carbon Monoxide**

Scientific Staff

Mr. James A. Raub—Project Manager and Coordinator for Health Effects
National Center for Environmental Assessment (MD-52), Research Triangle Park, NC 27711

Dr. Joseph P. Pinto—Coordinator for Atmospheric Chemistry, Sources, and Emissions
National Center for Environmental Assessment (MD-52), Research Triangle Park, NC 27711

Dr. Robert S. Chapman—Coordinator for Epidemiology Studies
National Center for Environmental Assessment (MD-52), Research Triangle Park, NC 27711

Mr. William G. Ewald—Coordinator for Measurement Methods
National Center for Environmental Assessment (MD-52), Research Triangle Park, NC 27711

Ms. Beverly M. Comfort—Coordinator for Indoor Air Emissions and Concentrations
National Center for Environmental Assessment (MD-52), Research Triangle Park, NC 27711

Dr. David T. Mage—Coordinator for Population Exposure
National Center for Environmental Assessment (MD-52), Research Triangle Park, NC 27711

Ms. Ellie Speh—Office Manager, Environmental Media Assessment Group
National Center for Environmental Assessment (MD-52), Research Triangle Park, NC 27711

Technical Support Staff

Mr. Douglas B. Fennell—Technical Information Specialist
National Center for Environmental Assessment (MD-52), Research Triangle Park, NC 27711

Ms. Diane H. Ray—Technical Information Manager
National Center for Environmental Assessment (MD-52), Research Triangle Park, NC 27711

Mr. Richard N. Wilson—Clerk
National Center for Environmental Assessment (MD-52), Research Triangle Park, NC 27711

U.S. Environmental Protection Agency
Project Team for Development of
Air Quality Criteria for Carbon Monoxide
(cont'd)

Document Production Staff

Mr. John R. Barton—Document Processing Coordinator
OAO Corporation, Chapel Hill-Nelson Highway, Beta Building, Suite 210, Durham, NC 27713

Ms. Yvonne Harrison—Word Processor
OAO Corporation, Chapel Hill-Nelson Highway, Beta Building, Suite 210, Durham, NC 27713

Ms. Bettye Kirkland—Word Processor
OAO Corporation, Chapel Hill-Nelson Highway, Beta Building, Suite 210, Durham, NC 27713

Mr. David E. Leonhard—Graphic Artist
OAO Corporation, Chapel Hill-Nelson Highway, Beta Building, Suite 210, Durham, NC 27713

Ms. Carolyn T. Perry—Word Processor
OAO Corporation, Chapel Hill-Nelson Highway, Beta Building, Suite 210, Durham, NC 27713

Ms. Veda E. Williams—Graphic Artist
OAO Corporation, Chapel Hill-Nelson Highway, Beta Building, Suite 210, Durham, NC 27713

Technical Reference Staff

Mr. R. David Belton—Reference Specialist
OAO Corporation, Chapel Hill-Nelson Highway, Beta Building, Suite 210, Durham, NC 27713

Mr. John Bennett—Technical Information Specialist
OAO Corporation, Chapel Hill-Nelson Highway, Beta Building, Suite 210, Durham, NC 27713

Mr. William Hardman—Reference Retrieval and Database Entry Clerk
OAO Corporation, Chapel Hill-Nelson Highway, Beta Building, Suite 210, Durham, NC 27713

Ms. Sandra L. Hughey—Technical Information Specialist
OAO Corporation, Chapel Hill-Nelson Highway, Beta Building, Suite 210, Durham, NC 27713

Mr. Jian Ping Yu—Reference Retrieval and Database Entry Clerk
OAO Corporation, Chapel Hill-Nelson Highway, Beta Building, Suite 210, Durham, NC 27713

EXECUTIVE SUMMARY

Air Quality Criteria for Carbon Monoxide *External Review Draft*

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

Summary Findings

Monitoring

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

- Several adequate techniques exist for highly reliable monitoring of CO to ensure compliance with the NAAQS. The most reliable method for continuous measurement of CO in ambient air is the nondispersive infrared (NDIR) optical transmission technique, the technique on which the EPA-designated analytical reference methods are based. One category of NDIR monitors, the gas filter correlation monitor, is still the single most widely used analyzer for fixed-site monitoring stations.
- Determining CO levels at many nonurban locations requires substantially better performance than that required to demonstrate compliance with the NAAQS. Commercial CO-monitoring instruments, sometimes with minor modifications, can meet the measurement needs for supplying useful data on the distribution and trends of ambient CO and for modeling photochemical smog in places where ambient levels are significantly below the NAAQS.
- There are at this time commonly used and accepted procedures for generating CO measurement standards that are accurate to better than $\pm 2\%$ in the parts-per-million range and about $\pm 10\%$ 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 CO exposure. Although the use of optical methods (e.g., CO-Oximetry [CO-Ox]) is common for population sampling and clinical analyses of COHb, gas chromatography is the method of choice for measuring low COHb saturations (<5%) that are expected to occur with ambient CO exposures. The measurement of CO in exhaled breath has practical advantages for population exposure sampling but has a greater potential for error in the estimation of COHb than a 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 may be responsible for 20 to 40% of the ozone formed in nonurban areas. Ozone is an oxidant, a greenhouse gas, and a precursor of hydroxyl radicals. On balance, if CO increases, the net effect is to decrease hydroxyl radicals.
- Carbon monoxide is, therefore, an intermediary in determining the future concentrations of many environmentally important trace gases. The future of methane, a greenhouse gas, cannot be evaluated adequately or predicted without an accurate understanding of the global CO budget, which is not presently available. Similarly, predicting future concentrations of other environmentally important gases, such as the hydrochlorofluorocarbons that can deplete stratospheric ozone, depends on how well we understand the CO budget.
- Global background CO concentrations average about 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 since 1993.
- The average lifetime of CO in the atmosphere is about 2 mo, longer at high latitudes and shorter at low latitudes.
- In addition to direct emissions from fossil fuel and biomass burning, CO is produced in the atmosphere by the photochemical oxidation of anthropogenic and biogenic hydrocarbons. Because of uncertainties in reaction kinetics, the identification of reaction products, and the effects of heterogeneous processes, the accuracy of estimates of photochemical sources of CO are limited.

- The global emissions of CO are about 2.3×10^9 metric tons per year, amounting to an annual source of about 1.0×10^9 metric tons of carbon in the atmosphere, compared with a global anthropogenic input of 7.1×10^9 metric tons per year of carbon in carbon dioxide. Estimates of individual CO sources are uncertain by a factor of two or more; however, the total production of CO is known to within 25%, based on its estimated rate of destruction because of reactions with hydroxyl radicals.
- Emissions from various sources in developing countries are likely to be very significant but are not known at present.

Regional and Urban Air Quality

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

- Carbon monoxide plays an important role in atmospheric photochemistry in regional and urban environments. In urban areas, CO either can produce or destroy ozone, depending on the concentrations of nitrogen oxides and hydrocarbons. In numerical simulations of several urban air sheds, CO was found to be responsible for production of 10 to 20% of the ozone.
- The nationwide average annual second highest 8-h ambient CO concentration decreased from 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.
- Carbon monoxide levels in the geographically diverse metropolitan statistical areas (MSAs) of Denver, CO; Los Angeles, CA; New York, NY; and Phoenix, AZ, have decreased from 1986 through 1995. However, the nature of the diurnal and seasonal variations has remained essentially the same. These variations result largely from the interaction among motor vehicle emissions, traffic patterns, and meteorological parameters, such as wind speed and mixing height. [An analysis of air quality in Fairbanks, AK, is in progress.]
- In general, the spatial distribution of CO within these four air sheds was highly heterogeneous. For instance, correlations between time series of daily 8-h average maximum CO concentrations at different monitoring sites in the Denver, New York, and Los Angeles MSAs ranged from about 0 to 0.7, whereas corresponding correlations ranged from about 0.3 to 0.7 in the Phoenix MSA.

Indoor Air Quality

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

- Carbon monoxide occurs indoors directly through emissions from various indoor combustion sources or indirectly as a result of infiltration or ventilation from outdoor sources. In the absence of indoor sources, average CO concentrations generally will equal those in the surrounding ambient environment.
- Emissions of CO from the use of adequately vented combustion appliances (e.g., gas and oil furnaces, gas water heaters, gas dryers) will not contaminate indoor air unless the units or venting systems are malfunctioning.
- The major sources of CO in residential microenvironments are tobacco smoke, vehicle startup and idling in attached garages, and unvented or partially vented combustion appliances. Factors affecting emissions of CO from the use of combustion appliances in the home include the type of source (e.g., gas cooking stoves, unvented space heaters, wood stoves, fireplaces), appliance design, 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.
- Wood stoves and fireplaces emit CO during fire start-ups and maintenance, through leaks in the stove or venting system, and from back drafting. Carbon monoxide emissions are higher during the first stage of a fire because of increased fuel usage and lower combustion temperatures.
- Carbon monoxide emissions from tobacco smoke depend on the type of tobacco product (e.g., cigarette, cigar) and the degree to which tobacco is actively smoked. Concentrations of CO from the use of tobacco products will exceed background concentrations, but will vary based on differences in ventilation, the number of cigarettes or cigars smoked, and the smoking

1 rate. For example, it is possible for cigar smokers to raise indoor CO concentrations to more
2 than 9 ppm above ambient levels measured outside.

3 4 ***Population Exposure***

5
6 The reduction in automotive emissions brought about by the CAA have reduced in-traffic
7 CO exposures and traffic-related ambient CO concentrations well below those measured in the
8 past decade. Chapter 4 describes the reduction in human exposures to CO over the past decade,
9 brought about by the reduction in automotive emissions of CO. However, people are still
10 exposed to CO at concentration levels above the NAAQS in areas of high traffic density and in
11 indoor locations where tobacco is smoked and where combustion devices (e.g., stoves, heaters)
12 are not adequately vented.

- 13
14 • Fixed site monitors often are used in urban areas to measure the ambient concentrations to
15 which individuals in the surrounding areas may be exposed. These measurements tend to
16 overestimate 8-h exposure values for people living in areas of lower traffic and underestimate
17 the exposure of people living in areas of higher traffic.
- 18
19 • Neighborhood scale, fixed-site ambient CO monitoring may provide a reasonable estimate of
20 the average CO exposures for some people who are not exposed to tobacco smoke or other
21 sources of CO in their homes and occupations.
- 22
23 • Nonsmokers exposed to tobacco smoke, heavy traffic fumes, and indoor sources of CO will
24 have higher body burdens of CO (COHb) than would be predicted from ambient data alone.
- 25
26 • Emission reductions in CO mandated by the CAA amendments have led to significant
27 reductions in ambient CO concentrations and lower traffic-related exposures to CO from motor
28 vehicle exhaust, suggesting that estimates of current population exposure based on pre-1990
29 exposure studies may no longer apply. There currently is not a good estimate of CO exposure
30 distribution for the population.
- 31
32 • Personal CO exposures that exceed the level of the NAAQS will still occur in some
33 nonsmokers exposed to sources of CO not controlled by the CAA (e.g., recreational vehicles,
34 garages, poorly vented or malfunctioning indoor combustion sources) or exposed in their
35 occupations or hobbies to CO or to organic solvents that are metabolized to CO (e.g.,
36 methylene chloride).
- 37
38 • Modern CO exposure models adequately predict the average general population exposure but
39 still underpredict high CO exposures, indicating that further work is required to understand the
40 activities and emissions associated with these higher exposures.

41 42 ***Pharmacokinetics and Mechanisms of Action***

43
44 The action of CO in the body and the factors influencing its uptake, distribution to vital
45 tissues, and elimination, provide the foundation for measuring or predicting effects on organ

function. In Chapter 5, the basic principles of CO pharmacokinetics are reviewed, and the possible mechanisms for pathophysiologic effects at the cellular level are discussed.

- The most prominent pathophysiological effect of CO is hypoxemia caused by the binding of CO to hemoglobin. The formation of COHb reduces the oxygen-carrying capacity of blood and impairs release of oxygen from red blood cells to tissues. The brain and heart are especially sensitive to CO-induced hypoxia and cytotoxicity because these tissues have the highest resting oxygen requirements.
- Carbon monoxide is produced endogenously through heme degradation, metabolic processes of drugs, and degradation of unsaturated fatty acids, inhaled solvents and other xenobiotics. High altitude and many 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 the health status and metabolism of the exposed individual. The formation of COHb is reversible, but, because of a small blood-to-air CO pressure gradient and tight binding of CO to Hb, the elimination half-time is quite long, varying from 2 to 6.5 h.
- The physical and physiological variables affecting the rate of COHb formation and elimination have been integrated into empirical and mathematical models for estimating COHb levels from different conditions of exposure. The nonlinear Coburn-Forster-Kane equation is the most widely used predictive model of COHb formation and is still considered the best all-around model for COHb prediction.
- Intracellular binding of CO to hemoproteins, particularly myoglobin (Mb) found in heart and skeletal muscle, would be favored under conditions of low intracellular oxygen tension as COHb levels rise. The impact of ambient CO on intracellular CO uptake by Mb is not well understood.
- New investigations have expanded on the physiological effects of CO in two areas. First, there is a growing recognition that CO may play a role in normal neurotransmission and vasomotor control. Second, there also is increased interest in the ability of CO to cause free-radical-mediated changes in tissues. The impact of ambient CO on these processes and the role they may have in pathophysiology is not well understood.

Health Effects

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

- 1 • Blood COHb levels are the best known indicators of potential health risk; however, the lowest-
2 observed-effect levels depend on the method used for analysis. Gas chromatography (GC)
3 generally is regarded as more accurate than CO-Ox for measuring low (<5%) COHb
4 saturations.
5
- 6 • Maximal exercise duration and performance in healthy individuals has been shown to be
7 reduced at COHb levels of ≥ 2.3 and $\geq 4.3\%$ (GC), respectively. Performance decrements are
8 small, however, and likely to affect only competing athletes. No effects were observed during
9 submaximal exercise in healthy individuals at COHb levels as high as 15 to 20%.
10
- 11 • Decreased exercise tolerance has been observed consistently in patients with coronary artery
12 disease (CAD) and reproducible exercise-induced angina (chest pain) at COHb levels of 3 to
13 6% COHb (CO-Ox). The indicators of myocardial ischemia during exercise, such as
14 electrocardiographic changes and associated chest pain, were statistically significant in one
15 large multicenter clinical study at $\geq 2.4\%$ COHb (GC) and showed a dose-response relationship
16 with increasing COHb.
17
- 18 • An increase in the number and complexity of exercise-related arrhythmias (irregular heart
19 beats) has been observed at $\geq 6\%$ COHb (CO-Ox) in some people with CAD and a high level
20 of baseline ectopy (a chronic arrhythmia) that may present an increased risk of sudden death.
21
- 22 • In epidemiologic studies, daily fluctuations in ambient CO concentration have been associated
23 consistently with fluctuations in heart disease exacerbation. These associations have been
24 observed at ambient CO levels at or below the current CO standards. The influence on these
25 associations of ambient CO exposure, relative to CO exposure from nonambient sources, has
26 not been determined.
27
- 28 • Epidemiologic studies also suggest associations of short-term ambient CO exposure with
29 nonaccidental daily mortality, the great majority of which occurs in people at least 65 years of
30 age. As above, the relative influences on these associations of ambient and nonambient CO
31 have not been determined and the possibility that CO is acting as a marker for other
32 combustion-related pollutants cannot be ruled out.
33
- 34 • Laboratory animal studies indicate that acute CO poisoning can affect the growth and function
35 of the developing fetus. Epidemiologic studies show a limited association of subchronic
36 ambient CO exposure with low birth weight; however, these studies are not conclusive.
37
- 38 • Recent analyses indicate that significant behavioral impairments in healthy individuals should
39 not be expected until COHb levels exceed 20%; however, mild central nervous system effects
40 have been reported in the historical CO literature at COHb levels between 5 and 20%.
41
- 42 • Ambient levels of CO are not known to have any direct effects on lung tissue. Observed
43 epidemiologic associations of short-term ambient CO levels with daily respiratory illness
44 frequency cannot yet be interpreted with confidence.
45

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

Subpopulations Potentially At Risk

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

- Young, healthy nonsmokers are not at immediate risk from ambient CO exposure because only limitations at maximal exercise performance have been demonstrated at low COHb levels (<5%) that are predicted to result from ambient exposures. Effects have not been demonstrated on healthy individuals performing submaximal exercise that is more typical of daily human activity.
- Patients with reproducible exercise-induced angina (chest pain) are a sensitive group within the general population that is at increased risk of experiencing decreased exercise tolerance because of exacerbation of cardiovascular symptoms at ambient or near-ambient CO-exposure concentrations that result in COHb levels of 2.4% (GC) or higher.

1. INTRODUCTION

This document is an update of *Air Quality Criteria for Carbon Monoxide*, published by the U.S. Environmental Protection Agency (EPA) in 1991, and will serve as the basis for reevaluating the current National Ambient Air Quality Standards (NAAQS) for carbon monoxide (CO) set in 1994. Carbon monoxide is one of six ubiquitous ambient air pollutants covered by the Federal Clean Air Act (CAA) requiring an assessment of the latest scientific knowledge as a requisite step in the development of standards to protect public health and welfare. The present document is not intended as a complete and detailed literature review, but it does summarize relevant key information from the previous 1991 document and evaluates new information relevant to the CO NAAQS criteria development, based on pertinent published literature available through early 1999.

Carbon monoxide, a trace constituent of the troposphere, is produced by both natural processes and human activities. Because plants can both metabolize and produce CO, trace levels are considered a normal constituent of the natural environment. Although ambient concentrations of CO in the vicinity of urban and industrial areas can exceed global background levels, there are no reports of these currently measured levels of CO producing any adverse effects on plants or microorganisms. Ambient concentrations of CO, however, 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 gives an overview of the issues, methods, and procedures utilized in the preparation of the present document.

1.1 LEGISLATIVE REQUIREMENTS

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

1 criteria for pollutants that may reasonably be anticipated to endanger public health or welfare.
2 These air quality criteria are to reflect the latest scientific information useful in indicating the
3 kind and extent of all identifiable effects on public health or welfare that may be expected from
4 the presence of the pollutant in ambient air.

5 Section 109(a) of the CAA (U.S. Code, 1991) directs the Administrator of EPA to propose
6 and promulgate primary and secondary NAAQS for pollutants identified under Section 108.
7 Section 109(b)(1) defines a primary standard as one that the attainment and maintenance of
8 which, in the judgment of the Administrator, based on the criteria and allowing for an adequate
9 margin of safety, is requisite to protect the public health. The secondary standard, as defined in
10 Section 109(b)(2), must specify a level of air quality that the attainment and maintenance of
11 which, in the judgment of the Administrator, based on the criteria, is requisite to protect the
12 public welfare from any known or anticipated adverse effects associated with the presence of the
13 pollutant in ambient air.

14 Section 109(d) of the CAA (U.S. Code, 1991) requires periodic review and, if appropriate,
15 revision of existing criteria and standards. If, in the Administrator's judgment, EPA's review and
16 revision of criteria make appropriate the proposal of new or revised standards, such standards are
17 to be revised and promulgated in accordance with Section 109(b). Alternatively, the
18 Administrator may find that revision of the standards is inappropriate and conclude the review by
19 leaving the existing standards unchanged.

22 **1.2 REGULATORY BACKGROUND**

23 On April 30, 1971, EPA promulgated identical primary and secondary NAAQS for CO at
24 levels of 10 mg/m³ (9 ppm) for an 8-h average and 40 mg/m³ (35 ppm) for a 1-h average, not to
25 be exceeded more than once per year. The scientific basis for the primary standard, as described
26 in the first criteria document (National Air Pollution Control Administration, 1970), was a study
27 suggesting that low levels of CO exposure resulting in carboxyhemoglobin (COHb)
28 concentrations of 2 to 3% were associated with neurobehavioral effects in exposed subjects
29 (Beard and Wertheim, 1967).

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

**TABLE 1. NATIONAL AMBIENT AIR QUALITY STANDARDS
FOR CARBON MONOXIDE**

Date of Promulgation	Primary NAAQS	Averaging Time
August 1, 1994	9 ppm ^a (10 mg/m ³)	8-h ^b
	35 ppm ^a (40 mg/m ³)	1-h ^b

^a1 ppm = 1.145 mg/m³, 1 mg/m³ = 0.873 ppm at 25 °C, 760 mm Hg.

^bNot to be exceeded more than once per year.

Source: Federal Register (1994).

1880, EPA proposed certain changes in the standards based on scientific evidence reported in the revised criteria document for CO (U.S. Environmental Protection Agency, 1979). Such evidence indicated that the Beard and Wertheim (1967) study no longer should be considered as a sound scientific basis for the standard. Additional medical evidence accumulated since 1970, however, indicated that aggravation of angina pectoris and other cardiovascular diseases would occur at COHb levels as low as 2.7 to 2.9%. On August 18, 1980, EPA proposed changes to the standard (Federal Register, 1980) based on the findings of the revised criteria. The proposed changes included (1) retaining the 8-h primary standard level of 9 ppm, (2) revising the 1-h primary standard level from 35 ppm to 25 ppm, (3) revoking the existing secondary CO standards (because no adverse welfare effects have been reported at or near ambient CO levels), (4) changing the form of the primary standards from deterministic to statistical, and (5) adopting a daily interpretation for exceedances of the primary standards, so that exceedances would be determined on the basis of the number of days on which the 8- or 1-h average concentrations are above the standard levels.

The 1980 proposal was based in part on health studies conducted by Dr. Wilbert Aronow. In March 1983, EPA learned that the Food and Drug Administration (FDA) had raised serious questions regarding the technical adequacy of several studies conducted by Dr. Aronow on experimental drugs, leading FDA to reject use of the Aronow drug study data. Therefore, EPA convened an expert committee to examine the Aronow CO studies before any final decisions were made on the NAAQS for CO. In its report (Horvath et al., 1983), the committee concluded

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

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

9 The criteria review process was initiated again on July 22, 1987, and notice of availability
10 of the revised draft criteria document was published in the Federal Register (Federal Register,
11 1990) on April 19, 1990. This draft document included discussion of several new studies of
12 effects of CO on angina patients that had been initiated in light of the controversy discussed
13 above. The Clean Air Scientific Advisory Committee (CASAC) reviewed the draft criteria
14 document at a public meeting held on April 30, 1991. The EPA carefully considered comments
15 received from the public and from CASAC in preparing the final criteria document (U.S.
16 Environmental Protection Agency, 1991). On July 17, 1991, CASAC sent to the EPA
17 Administrator a "closure letter" outlining key issues and recommendations and indicating that the
18 document provided a scientifically balanced and defensible summary of the available knowledge
19 of effects of CO. A revised "staff paper" based on the scientific evidence was released for public
20 review in February 1992, followed by two CASAC review meetings held on March 5 and on
21 April 28, 1992. The CASAC came to closure on the final staff paper (U.S. Environmental
22 Protection Agency, 1992) in a letter to the Administrator dated August 11, 1992, indicating that it
23 provided a scientifically adequate basis for EPA to make a regulatory decision on the appropriate
24 primary NAAQS for CO. On August 1, 1994, EPA issued a final decision (Federal Register,
25 1994) that revisions of the NAAQS for CO were not appropriate at that time.

26 In keeping with the requirements of the CAA, EPA's National Center for Environmental
27 Assessment has begun to review and once again revise the criteria for CO.
28
29
30

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

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

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

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

30 The Administrator concluded that the lowest COHb level at which adverse effects have been
31 demonstrated in persons with angina is around 2.9 to 3.0%, representing an increase of 1.5%

COHb above baseline when using the CO-Ox to measure COHb. These data serve to establish the upper end of the range of COHb levels of concern. Taking into account the above data uncertainties, the less significant health endpoints, and less quantifiable data on other potentially sensitive groups, the lower end of the range was established at 2.0% COHb.

1.3.2 Relationship Between Carbon Monoxide Exposure and Carboxyhemoglobin Levels

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

1.3.3 Estimating Population Exposure

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

1.3.4 Decision on the Primary Standards

Based on the exposure analysis results described above, the Administrator of EPA concluded that relatively few people of the cardiovascular sensitive population group analyzed would experience COHb levels $\geq 2.1\%$ 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 scientific issues that are addressed in the revised air quality criteria document for CO. These issues are based on findings presented at symposia and workshops that were convened to assess the current state of understanding of the sources, atmospheric cycle, and health effects of CO and revised, as appropriate, by peer review comments received on earlier draft chapters of the criteria document.

1.4.1 Sources and Emissions

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

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

1.4.2 Atmospheric Chemistry

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

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., mol/m³ in SI units). Often in the literature, however, quantities of gaseous substances are expressed as volume mixing ratios, such as parts per million (ppm) or parts per billion (ppb). 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 in mol/m³ to the concentration in mol/m³ of all gaseous components in a given air volume (Seinfeld and Pandis, 1998). Thus, mixing ratio is a mole fraction that in SI units should be expressed as $\mu\text{mol/mol}$ for ppm, and nmol/mol for ppb. Throughout this document, however, mixing ratio will be referred to as concentration of CO in ppm or ppb 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 exposure does not correlate directly with CO concentrations determined by the fixed-site monitors alone. This is because of the mobility of people and the spatial and temporal variability of CO concentrations across a given area. The nature of differences between fixed-site and personal monitoring results should be given greater attention, especially in regard to interpreting the results of epidemiology studies.

Data from population field studies can be used to construct and test models of human exposure that account for time and activity patterns known to affect exposure to CO. New information from field monitoring studies needs to be incorporated into exposure models to better capture the observed personal exposure distributions, including the higher exposures found in the tail of exposure distribution.

A unique feature of CO exposure is that the dose an individual receives can be estimated by measuring COHb. 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 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. Secondary mechanisms related to intracellular uptake of CO have been the focus of recent research. Current knowledge summarized in this document suggests that the most likely protein other than hemoglobin to be inhibited functionally at relevant levels of COHb is myoglobin, found in heart and skeletal muscle. The extent of effects caused by 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 mainly for competing athletes. Clinical studies on subjects with reproducible exercise-induced angina have confirmed that adverse effects occur with postexposure COHb levels as low as 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

1 been shown to cause neurological problems weeks after recovery from the acute episode. It is
2 not known, however, if these late neurological sequelae, described as intellectual deterioration;
3 memory impairment; and cerebral, cerebellar, and mid-brain damage, result from long-term
4 exposure to low ambient levels of CO.

6 ***Developmental Toxicity***

7 Relatively high CO exposures of 150 to 200 ppm during gestation, leading to
8 approximately 15 to 25% COHb, produce reductions in birth weight, cardiomegaly, delays in
9 behavioral development, and disruption in cognitive function in newborn laboratory animals of
10 several species. Little data exist on humans exposed to CO for predicting a lowest-observed-
11 effect level for developmental effects. Studies relating human CO exposures from ambient
12 sources or cigarette smoking to reduced birth weight are of concern because of the risk for
13 developmental disorders; however, many of these studies have not considered all sources of CO
14 and may be confounded by other variables (e.g., smoke components, maternal behavior,
15 nutrition, genetics). Nevertheless, some health professionals have considered this evidence
16 sufficient to identify pregnant women, and the developing fetus, as at risk to ambient levels of
17 CO.

19 ***High-Altitude Effects***

20 There are relatively few reports on the effects of inhaling CO at high altitudes. Current
21 knowledge supports the possibility that the effects of hypoxic hypoxia and CO-hypoxia are at
22 least additive. The potential additive effects of CO exposure in sensitive individuals visiting at
23 high altitudes need to be considered.

25 **1.4.10 Carbon Monoxide Interaction with Drugs**

26 There remains little direct information on the possible enhancement of CO toxicity by
27 concomitant illegal and prescription drug use or abuse; however, there are some data on
28 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 the recommendations made by CASAC.

The main focus of this revised criteria document is on the evaluation and interpretation of more recent air quality, human exposure, and health effects issues. Therefore, the techniques used to present this information vary according to the state-of-science for the respective topics. For example, the analysis of ambient air quality is based on newly obtained air monitoring data and utilizes the previous analysis only for showing trends over time. As a result of the relatively dramatic decrease in ambient CO concentrations, population exposure to ambient CO also has declined. Human exposure studies conducted in the early 1980s and earlier distributions of COHb levels in the U.S. population that were relied on heavily in the previous assessment are no longer relevant to the current picture of ambient CO exposure in the 1990s. Thus, key information on population exposure must focus on the newer studies and on modeling results.

1 On the other hand, the health effects literature on CO has remained relatively static since the
2 previous 1991 assessment, except for provocative publications on cellular mechanisms of CO
3 action and on epidemiologic associations of ambient CO with mortality and morbidity in the
4 elderly population. Newly published studies on most of the other health outcomes reconfirm the
5 conclusions made in the last document and are incorporated into the previous summaries by
6 reference only.

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

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

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

24 Finally, a public peer-review workshop was convened on September 17 and 18, 1998, to
25 define key issues, to review early drafts of the criteria document chapters, and to ascertain and
26 discuss any pertinent new literature. The respective authors of the draft chapters or sections of
27 the document revised them on the basis of the workshop recommendations. The revised chapters
28 of the document were incorporated into the first external review draft released for public
29 comment and reviewed by CASAC on June 9, 1999. Necessary revisions were made in response
30 to public comments and CASAC recommendations before this Second External Review Draft of
31 the criteria document was released.

1.6 ORGANIZATION AND CONTENT OF THE DOCUMENT

The updated air quality criteria document for CO critically evaluates and assesses scientific information on air quality, human exposure, and health effects associated with exposure to the concentrations found in the environment. Emphasis has been placed on the development of a concise review of key information and a more interpretative discussion of the new scientific and technological data available since completion of the previous criteria document (U.S. Environmental Protection Agency, 1991). The references cited in the document should be reflective of the state of knowledge through early 1999 on those issues most relevant to review of the NAAQS for CO.

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

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

The document begins with this introduction (Chapter 1), which provides the regulatory history of CO and an understanding of the scientific basis for the current CO NAAQS. Information on analytical methods for monitoring CO (Chapter 2) covers the measurement of CO in ambient (outdoor) and indoor air, as well as methods for measuring breath CO and blood CO

1 levels in exposed individuals. Chapter 3 provides information on the atmospheric chemistry of
2 CO and typical sources, emissions, and concentrations found in the ambient and indoor
3 environments, topics addressed in separate chapters of the previous document. The remaining
4 chapters are similar to the previous document, covering topics on population exposure to CO
5 (Chapter 4), pharmacokinetics and mechanisms of action (Chapter 5), and health effects
6 (Chapter 6). The last chapter (Chapter 7) provides an overall integrative summary of key
7 findings and an evaluation of subpopulations potentially at risk from exposure to CO.
8

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2. ANALYTICAL METHODS FOR MONITORING CARBON MONOXIDE

2.1 INTRODUCTION

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

To promote uniform enforcement of the air quality standards set forth under the Clean Air Act as amended (U.S. Code, 1991), the U.S. Environmental Protection Agency (EPA) has established provisions under which analytical methods can be designated as “reference” or “equivalent” methods (Code of Federal Regulations, 1991a). Either a reference method or equivalent method for air quality measurements is required for acceptance of measurement data for National Ambient Air Quality Standards (NAAQS) compliance. An equivalent method for monitoring CO can be so designated when the method is shown to produce results equivalent to the approved reference monitoring method based on absorption of infrared radiation from a nondispersed beam.

The EPA-designated reference methods are automated methods utilizing the nondispersive infrared (NDIR) technique, generally accepted as being the most reliable, continuous method for the measurement of CO in ambient air. The official EPA reference methods (Code of Federal Regulations, 1991a) include eleven reference methods designated for use in determining compliance for CO. Before a particular NDIR instrument can be used in a reference method, it must be designated by the EPA as approved in terms of manufacturer, model number, components, operating range, etc. Several NDIR instruments have been so designated (Code of Federal Regulations, 1991a), including the gas filter correlation (GFC) technique, which was

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

3 4 5 **2.2 OVERVIEW OF TECHNIQUES FOR MEASUREMENT OF AMBIENT** 6 **CARBON MONOXIDE**

7 The NDIR technique is an automated and continuous method that is based on the specific
8 absorption of infrared radiation by the CO molecule (Feldstein, 1967). Most commercially
9 available analyzers incorporate a gas filter to minimize interferences from other gases; they
10 operate near atmospheric pressure, and the most sensitive analyzers are able to detect minimum
11 CO concentrations of about 0.02 ppm. Interferences because of carbon dioxide (CO₂) and water
12 vapor can be dealt with so as not to affect the data quality; a particle filter (Teflon® or nylon
13 composition is recommended), and desiccant in the inlet line improves reliability. Nondispersive
14 infrared analyzers are relatively insensitive to flow rate, require no wet chemicals, are sensitive
15 over wide concentration ranges, and have short response times. Nondispersive infrared analyzers
16 of the newer GFC type have overcome zero and span problems, as well as minor problems
17 caused by vibrations.

18 A more sensitive method for measuring low background levels is gas chromatography
19 (Bergman et al., 1975; Bruner et al., 1973; Dagnall et al., 1973; Porter and Volman, 1962;
20 Feldstein, 1967; Smith et al., 1975; Swinnerton et al., 1968; Tesarik and Krejci, 1974). This
21 technique is an automated, semicontinuous method where CO is separated from water, CO₂, and
22 hydrocarbons other than methane (CH₄) by a stripper column. Carbon monoxide and CH₄ then
23 are separated on an analytical column, and the CO is passed through a catalytic reduction tube,
24 where it is converted to CH₄. The CO (converted to CH₄) passes through a flame ionization
25 detector (FID), and the resulting signal is proportional to the concentration of CO in the air.
26 Mercury liberation detectors offer greater sensitivity and ease of operation than FID's.
27 (Section 2.4.4.3). These methods have no known interferences and can be used to measure levels
28 from 0.02 to 45 ppm.

29 Whichever method or instrument is used, it is essential that the results be evaluated by
30 frequent calibration with samples of known composition (Commins et al., 1977; Goldstein, 1977;
31 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/m³). Some instruments offer higher ranges, typically 0 to 100 ppm (0 to 115 mg/m³), or lower ranges such as 0 to 20 ppm (0 to 23 mg/m³). Higher ranges up to 1,000 ppm (1,145 mg/m³) 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 concentrations 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 has a detection limit around 50 ppb in addition to methods in current use. Suggested performance specifications for monitoring CO in nonurban environments are shown in Table 2-2.

2.3 GAS STANDARDS FOR CALIBRATION

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

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

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

Definitions:

Range: Nominal minimum and maximum concentrations that a method is capable of measuring.

Noise: The standard deviation about the mean of short duration deviations in output that are not caused by input concentration changes.

Lower detectable limit: The minimum pollutant concentration that produces a signal of twice the noise level.

Interference equivalent: Positive or negative response caused by a substance other than the one measured.

Zero drift: The change in response to zero pollutant concentration during continuous unadjusted operation.

Span drift: The percent change in response to an upscale pollutant concentration during continuous unadjusted operation.

Lag time: The time interval between a step change in input concentration and the first observable corresponding change in response.

Rise time: The time interval between initial response and 95% of final response.

Fall time: The time interval between initial response to a step decrease in concentration and 95% of final response.

Precision: Variation about the mean of repeated measurements of the same pollutant concentration expressed as one standard deviation about the mean.

Source: Code of Federal Regulations (1991a).

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

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

^aZero interval is the interval between measuring chemical zeros.

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

2.3.1 Pre-made Mixtures

2.3.1.1 Standard Reference Materials

Calibration gas standards of CO in air (certified at levels of approximately 12, 23, and 46 mg/m³ or (10, 20, and 40 ppm, respectively) or in nitrogen (N₂; 10 ppm to 13%) are obtainable from the Standard Reference Material Program of the National Institute of Standards and Technology (NIST), formerly the National Bureau of Standards, Gaithersburg, MD 20899. These Standard Reference Materials (SRMs) are supplied as compressed gas mixtures at about 135 bar (1,900 psi) in high-pressure aluminum cylinders containing 800 L (28 ft³) 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 $\pm 1\%$ 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 N₂, 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 ft³) of gas at STPD. Each cylinder is supplied with a certificate stating concentration and uncertainty. The concentrations are certified to be accurate to $\pm 1\%$ relative to the stated values (Guenther et al., 1996).

2.3.1.3 U.S. Environmental Protection Agency Protocol Gases

Calibration gas standards of CO in air or CO in N₂ 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

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

4 5 **2.3.1.5 Commercial Blends**

6 Calibration gas mixtures of CO in air or N₂ over a wide concentration range also can be
7 purchased commercially from many specialty gas companies. Some mixtures may have
8 “certification” documentation and some may not. These mixtures can be ordered in cylinders of
9 almost any size. Mild steel cylinders are to be avoided (U.S. Environmental Protection Agency,
10 1991).

11 The nominal values for CO concentration supplied by the vendor should be verified by
12 intercomparison with an SRM or other validated standard sample. A three-way intercomparison
13 has been made among the NIST SRM’s, commercial gas blends, and an extensive set of standard
14 gas mixtures prepared by gravimetric blending at EPA (Paulsell, 1976). Results of the
15 comparison showed that commercial gas blends are within $\pm 2\%$ of the true value represented by
16 a primary standard. Another study on commercial blends (Elwood, 1976) found poorer accuracy.
17 To achieve compatible results in sample analyses, different laboratories should interchange and
18 compare their respective working standards frequently.

19 20 **2.3.2 Laboratory Blended Mixtures**

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

29 Standard samples of CO in air also can be prepared by flowing gas dilution techniques.
30 In a versatile system designed for this purpose (Hughes et al., 1973), air at a pressure of about
31 0.7 to 7.0 bars (about 10 to 100 psi) above ambient is first purified and dried by passage through

1 cartridges of charcoal and silica gel, then is passed through a sintered metal filter into a flow
2 control and flowmeter system. The CO (or a mixture of CO in air that is to be diluted further),
3 also under pressure, is passed through a similar flow control and flowmeter system.

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

11 **2.3.3 Other Methods**

12 Permeation tubes have been used for preparing standard mixtures of such pollutant gases as
13 sulfur dioxide (SO₂) and nitrogen dioxide (O’Keeffe and Ortman, 1966; Scaringelli et al., 1970).
14 Permeation tubes are not used routinely in the United States for making CO standard samples and
15 are not recommended. In the permeation tube techniques, a sample of the pure gas under
16 pressure is allowed to diffuse through a calibrated partition at a defined rate into a diluent gas
17 stream to give a standard sample of known composition.

18 Another possible way to liberate known amounts of CO into a diluent gas is by thermal
19 decomposition of nickel tetracarbonyl [Ni(CO)₄]. However, an attempt to use this as a
20 gravimetric calibration source showed that the relation between CO output and weight loss of the
21 Ni(CO)₄ is nonstoichiometric (Stedman et al., 1976).

23 **2.3.4 Intercomparisons of Standards**

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

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

12 Careful intercomparisons of calibration gases indicate that accurate and consistent
13 standards can be made. Hughes et al. (1991) compared primary gas standards of CO in
14 N₂ produced by NIST and the National Physical Laboratory in the United Kingdom. These
15 standards, prepared gravimetrically, contained concentrations ratios ranging from 10 ppm to 8%.
16 In a blind intercomparison, the mean difference was 0.2%, well within the experimental
17 uncertainty of the techniques. Novelli et al. (1991) gravimetrically produced CO in zero air in
18 the range of 25 to 1,000 ppb from both pure CO and a NIST SRM; they found agreement to
19 within 1%. Agreement with commercially available NIST-traceable standards was within 3%.
20 Reasonable consistency (6% or better) was found with standards used by Australian, German,
21 Brazilian, and several American institutions. One Australian standard was found to be 22%
22 lower, although trouble with this standard had been reported previously (Weeks et al., 1989).
23 A reevaluation of the reference scale in the range of nonurban ambient concentrations (Novelli
24 et al., 1994) confirmed agreement to within 5% or better for the National Oceanic and
25 Atmospheric Administration (NOAA), NASA, and German groups.

26 Intercomparisons of TDLS and NDIR GFC techniques (Poulida et al., 1991; Fried et al.,
27 1991) indicated agreement within experimental uncertainty (better than 10% for typical
28 tropospheric concentrations of 100 to 1,000 ppb), when NIST-based standards were used to
29 calibrate both instruments. These experiments demonstrated good agreement in ambient and
30 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 concentrations ratios down to the lowest expected in the boundary layer, about 50 ppb, agreement among groups was typically better than 10 ppb; for higher mixing ratios the typical agreement was about 5%.

2.3.5 Infrared Absorption

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

2.4 MEASUREMENT IN AMBIENT AIR

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

2.4.1 Sampling System Components

Carbon monoxide monitoring requires a sample introduction system, an analyzer system, and a data recording system. A sample introduction system consists of a sampling probe, an intake manifold, tubing, and air movers. This system is needed to collect the air sample from the atmosphere and to transport it to the analyzer without altering the original concentration. It also may be used to introduce known gas concentrations in order to periodically check the reliability of the analyzer output. Construction materials for the sampling probe, intake manifold, and tubing should be tested to demonstrate that the test atmosphere composition or concentration is not altered significantly. It is recommended that sample introduction systems be fabricated from borosilicate glass or fluorinated ethylene propylene Teflon® (Code of Federal

Regulations, 1991b) if several pollutants are to be monitored. However, in monitoring for CO only, it has been reported (Wohlers et al., 1967) that no measurable pollutant losses were observed at the high (>1 L/min) sampling flow rates when sampling systems were constructed of tygon, polypropylene, polyvinylchloride, aluminum, or stainless steel piping. The sample introduction system should be constructed so that it presents no pressure drop to the analyzer. At low flow and low concentrations, such operation may require validation.

The analyzer system consists of the analyzer itself and any sample-preconditioning components that may be necessary. Sample preconditioning might require a moisture control system such as a Nafion[®] drying tube to help minimize the false positive response of the analyzer (e.g., the NDIR analyzer) to water vapor and a particulate filter to help protect the analyzer from clogging and possible chemical interference caused by particulate buildup in the sample lines or analyzer inlet. The sample preconditioning system also may include a flow metering and control device to control the sampling rate to the analyzer.

2.4.2 Quality Assurance Procedures for Sampling

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

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

A calibration curve is derived from the analyzer response obtained by introducing several successive test atmospheres of different known concentrations. One recommended method for generating CO test atmospheres is to use air containing no CO along with several known concentrations of CO in air or N₂ 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 CO₂ on a catalyst (Dickerson and Delany, 1988; Parrish et al., 1994). The number of standard gas mixtures (cylinders) necessary to establish a

1 calibration curve depends on the nature of the analyzer output. A multipoint calibration at five or
2 six different CO concentrations covering the operating range of the analyzer is recommended by
3 EPA (Code of Federal Regulations, 1991b; Federal Register, 1978). Alternatively, the multipoint
4 calibration is accomplished by diluting a known high-concentration CO standard gas with zero
5 gas in a calibrated flow dilution system.

6 Secondary calibration consists of a zero and upscale span of the analyzer. This is
7 recommended to be performed daily (Federal Register, 1978). If the analyzer response differs by
8 more than 2% from the certified concentrations, then the analyzer is adjusted accordingly.
9 Complete records of secondary calibrations should be kept to aid in data reduction and for use in
10 auditing. For high-sensitivity measurement, hourly zeros and weekly calibrations are
11 recommended.

12 Specific criteria for data selection and several instrument checks are available (Smith and
13 Nelson, 1973). Data recording involves recording in a standard format for data storage,
14 interchange of data with other agencies, or data analysis. Data analysis and interpretation usually
15 include a mathematical or statistical analysis of air quality data and a subsequent effort to
16 interpret results in terms of exposure patterns, meteorological conditions, characteristics of
17 emission sources, and geographic and topographic conditions.

18 Auditing procedures consist of several quality control checks and subsequent error analyses
19 to estimate the accuracy and precision of air quality measurements. The quality control checks
20 for CO include a data processing check, a control sample check, and a water vapor interference
21 check, which should be performed by a qualified individual independent of the regular operator.
22 The error analysis is a statistical evaluation of the accuracy and precision of air quality data.
23 Guidelines have been published by EPA (Smith and Nelson, 1973) for calculating an overall bias
24 and standard deviation of errors associated with data processing, measurement of control
25 samples, and water vapor interference, from which the accuracy and precision of CO
26 measurements can be determined. Since January 1, 1983, all state and local agencies submitting
27 data to EPA must provide estimates of accuracy and precision of the CO measurements based on
28 primary and secondary calibration records (Federal Register, 1978). The precision and accuracy
29 audit results through 1985 indicate that the 95% national probability limits for precision are
30 $\pm 9\%$, and the 95% national probability limits for accuracy are within $\pm 1.5\%$ 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/m³). 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.

1 Nondispersive infrared systems have several advantages. They are not sensitive to flow
2 rate, they require no wet chemicals, they are reasonably independent of ambient air temperature
3 changes, they are sensitive over wide concentration ranges, and they have short response times.
4 Further, NDIR systems may be operated by nontechnical personnel. Gas filter correlation
5 spectroscopy analyzers are used most frequently now in documenting compliance with ambient
6 air standards.

7 8 ***Gas-Filter Correlation Spectroscopy***

9 A GFC monitor (Burch et al., 1976) has the advantages of an NDIR instrument and the
10 additional advantages of smaller size, no interference from CO₂, and very small interference from
11 water vapor. A top schematic view of the GFC monitor is shown in Figure 2-1, showing the
12 components of the optical path for CO detection. During operation, air flows continuously
13 through the sample cell. Radiation from the source is directed by optical transfer elements
14 through the two main optical subsystems: (1) the rotating gas filter and (2) the optical multipass
15 (sample) cell. The beam exits the sample cell through interference filter FC, which limits the
16 spectral passband to a few of the strongest CO absorption lines in the 4.6-μm region. Detection
17 of the transmitted radiation occurs at the infrared detector, C.

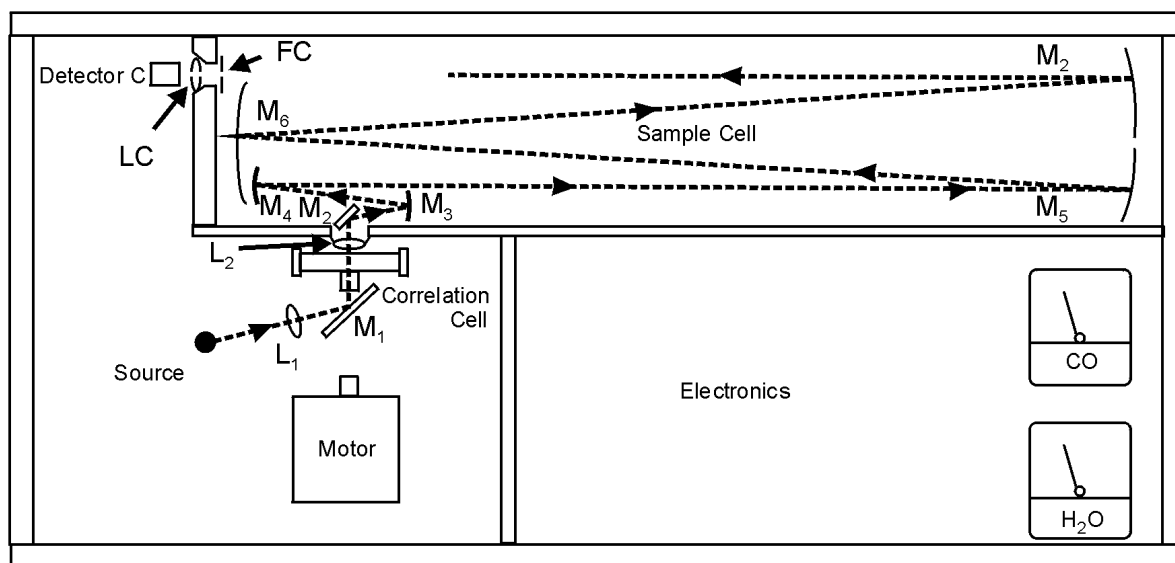
18 The gas correlation cell is constructed with two compartments: one compartment is filled
19 with 0.5 atm CO, and the second compartment is filled with pure N₂. Radiation transmitted
20 through the CO is completely attenuated at wavelengths where CO absorbs strongly. The
21 radiation transmitted through the N₂ is reduced by coating the exit window of the cell with a
22 neutral attenuator so that the amounts of radiation transmitted by the two cells are made
23 approximately equal in the passband that reaches the detector.

24 In operation, radiation passes alternately through the two cells as they are rotated to
25 establish a signal modulation frequency. If CO is present in the sample, the radiation transmitted
26 through the CO is not appreciably changed, whereas that through the N₂ cell is changed. This
27 imbalance is linearly related to CO concentrations in ambient air.

28 29 ***Enhanced Performance***

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

A.



B.

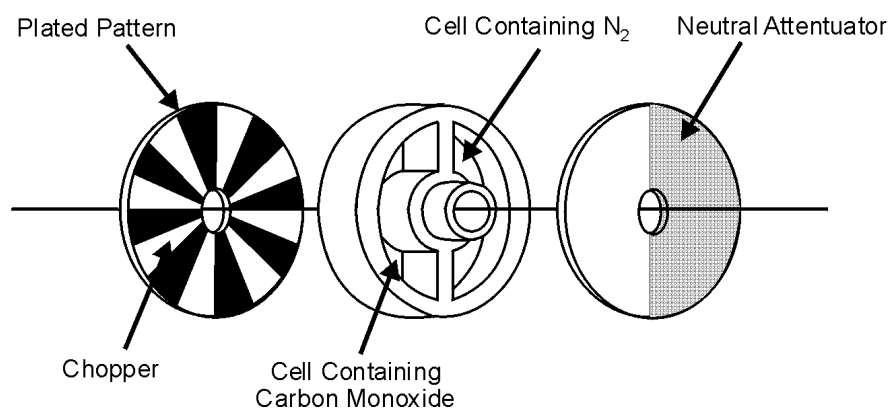


Figure 2-1. Schematic diagram of GFC monitor for CO. A = optical layout (M denotes mirror reflector, and L denotes lens); B = detail of correlation cell.

Source: Chaney and McClenny (1977).

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

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

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

12 The greatest source of potential error in monitoring CO in the 0.1-ppm range is background
13 drift. The stability of the instruments with respect to changes in calibration (span) is adequate,
14 but the background (zero) drifts on time scales of minutes to hours in response to, among other
15 factors, instrument temperature. This drift can be accounted for most easily by frequent chemical
16 zeroing with an oxidizer that converts CO to CO₂.

18 **2.4.4.2 Gas Chromatography-Flame Ionization**

19 Carbon monoxide can be measured in either ambient air samples collected every few
20 minutes or in air from grab samples stored under pressure in inert canisters. Carbon monoxide in
21 air samples is dried, preconcentrated, reduced to methane, and detected by flame ionization
22 (GC/FID) (Heidt, 1978; Greenberg et al., 1984; Hoell et al., 1987). Uncertainty on the order of
23 10 ppb or 10% of the observation can be obtained routinely.

25 **2.4.4.3 Mercury Liberation**

26 This technique, involving reaction with hot mercuric oxide to give elemental mercury
27 vapor, was developed early this century (Moser and Schmid, 1914; Beckman et al., 1948;
28 McCullough et al., 1947; Mueller, 1954; Palanos, 1972; Robbins et al., 1968) and is now
29 available commercially (e.g., Trace Analytical Inc., Menlo Park, CA). The method is
30 temperature and pressure sensitive, and operation in the continuous mode requires elimination of
31 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 to over 1,000 ppb, has a detection limit below 10 ppb, and the reported uncertainty is about 2%.

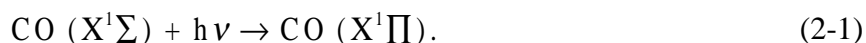
2.4.4.4 Tunable Diode Laser Spectroscopy

Tunable diode lasers (TDLs) produce IR radiation with a line width that is narrow compared with typical absorption lines of atmospheric trace gases. Absorption of IR radiation by a single rotational line in the 4.6- μm band can be exploited to measure CO with high precision and rapid response and without interferences; the sharp focus on a narrow spectral region provides great selectivity. Air samples are measured over open paths through the ambient air (Chaney et al., 1979) or by pulling air samples through an orifice into a long-path cell maintained at a pressure well below ambient (Sachse et al., 1987; Fried et al., 1991; Roths et al., 1996). Radiation from a TDL is modulated over a very narrow wavelength region such that absorption by CO produces an AC signal. The background is measured by catalytic oxidation of CO to CO₂.

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

2.4.4.5 Resonance Fluorescence

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



1 Atmospheric CO absorbs radiation in the 150-nm range from a radio frequency discharge lamp,
2 and fluorescence from the excited CO is detected by a photo-multiplier tube. The lamp generates
3 a plasma in a continuous flow of CO₂ in argon. Limits to the sensitivity of this instrument are set
4 by interference from water vapor, continuum Raman scattering by oxygen (O₂), and by drift in
5 the lamp intensity. The pressure in the fluorescence chamber must be maintained between 7 and
6 9 mbar air to balance interference from O₂ and signal from CO.

7 Recent improvements (Gerbig et al., 1999) have reduced the detection limit to 3 ppb for a
8 response time of as short as a few seconds. The high sensitivity and small size of the instrument
9 are desirable for measurements from aircraft. Before the instrument is practical for air pollution
10 monitoring, its stability must be improved. As the lamp window degrades, sensitivity is lost,
11 such that after about 200 h of operation, a factor of two loss in the span can be expected.

13 **2.4.5 Intercomparisons of Methods**

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

21 **2.4.6 Other Methods of Analysis**

22 Color changes induced by reaction of a solid or liquid date back to Haldane (1897-1898)
23 and were reviewed extensively in the previous criteria document. Examples include the colored
24 silver sol method, the NIST colorimetric indicating gel, the length-of-stain indicator tube, and
25 frontal analysis (U.S. Environmental Protection Agency, 1991).

26 More recently developed electrochemical techniques show highly improved resolution and
27 specificity (e.g., Langan, 1992; Lee et al., 1992a, Ott et al., 1995). Electrochemical sensors
28 operate by measuring the current of a small fuel cell, and because of their reduced size and power
29 requirements have been used extensively in exposure and indoor research studies (see
30 Section 2.5). Precision of from 0.2 to 2 ppm has been reported. Further independent evaluation

1 and intercomparison, followed by publication in the reviewed scientific literature is called for to
2 determine the sensitivity, stability, and selectivity of electrochemical methods, in order to
3 establish equivalency to the NDIR instrument by EPA for use in compliance monitoring.
4
5

6 **2.5 MEASUREMENT USING PERSONAL MONITORS**

7 Monitors at fixed locations provide useful information on ambient CO concentrations and
8 their variability and trends, but cannot measure personal exposure. Information on personal
9 exposure, including home, in-transit, and work-related concentrations is needed for
10 epidemiologic studies. The previous criteria document (U.S. Environmental Protection Agency,
11 1991) reviewed the state of the science of personal monitors as of about 1986. Since that time,
12 the devices have been further developed and refined.

13 One technique involves an ion-exchange Y-type zeolite, with zinc ion as the adsorbent.
14 The adsorbent is desorbed thermally, converted to methane, and analyzed using GC-FID (e.g.,
15 Lee et al., 1992b,c; Lee and Yanagisawa, 1992, 1995). Apte (1997) reviewed several of these
16 devices and described passive samplers based on transition metal compound color changes
17 measured spectrochemically. The method suffers an interference from ethylene, but provides
18 adequate performance (sensitivity of 10 ppm-h and precision of 20% or better) for health studies.
19 Substantial work remains for most passive samplers on stability and response to temperature,
20 humidity, and interferences. These techniques lack the response speed and sensitivity for
21 ambient air monitoring.

22 Numerous field studies on personal exposure have been conducted with electrochemical
23 sensors (Akland et al., 1985; Ott et al., 1986; Wallace et al., 1988; Ott et al., 1994; Klepeis et al.,
24 1999; McBride et al., 1999); some are described in Chapters 3 and 4. These studies show that
25 spatial and temporal variability, and the effects of microenvironments can have a major impact
26 on the level of CO exposure.

27 Carbon monoxide emissions from vehicles can be measured rapidly with a remote sensing
28 IR technique (Bishop et al., 1989; Stedman and Bishop, 1996) in which CO is measured near
29 4.3 μm and CO₂ at 3.6 μm ; a third wavelength is used as a reference for intensity. The
30 instrument has been evaluated in a double blind intercomparison with on-board NDIR, and the
31 two methods agreed well within experimental uncertainty (Lawson et al., 1990). Surveys

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

2.6.1 Carboxyhemoglobin Measurements

Direct reading of COHb 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 $\pm 1\%$ 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

1 the use of threshold limits of 3% COHb for nonsmokers and 10% COHb for smokers when
2 classifying subjects for treatment.

3 The performance of the various early versions of the CO-Ox instruments for measuring
4 blood COHb was reviewed in Section 8.5 of U.S. Environmental Protection Agency (1991).
5 These and later instruments, of different design from different manufacturers, used several
6 wavelengths of light for simultaneous measurement of Hb, O₂Hb, COHb and methemoglobin
7 (Freeman and Steinke, 1993; Gong, 1995; Bailey et al., 1997). Vreman et al. (1993) and
8 Mahoney et al. (1993) confirmed that considerable difficulties were encountered for COHb
9 concentrations below 5% (a region with which most environmental studies of nonsmokers are
10 concerned), and the authors concluded that the CO-Ox is unreliable for environmental studies.
11 Some versions of the CO-Ox also were found to be influenced by bilirubin and by fetal
12 hemoglobin, presenting difficulty in diagnosing newborn infants with jaundice (Vreman and
13 Stevenson, 1994; Stevenson and Vreman, 1997). Shepard and McMahan (1996) present a highly
14 detailed analysis of the causes and effects of oximeter errors in blood gas analyses.

15 Recent CO-Ox developments have been a new six-wavelength instrument (Instrumentation
16 Laboratory, 1999) used by Kimmel et al. (1999) and a 128-wavelength instrument (Krarup, 1998)
17 both of which identify and correct for possible interferences. The latter instrument is still under
18 formal independent evaluation, and, although peer-reviewed published results of comparison
19 testing are expected to be forthcoming shortly, the only article currently in press is in German,
20 in a non-peer reviewed journal (Krarup, 1999). It is possible that comparison of the results on
21 the same sample using the new multi-wavelength instrument and older fewer-wavelength
22 instruments may show that the new instruments measure lower COHb if they better correct for
23 the positive interferences of various non-COHb species in the blood, such as varying fractions of
24 fetal hemoglobin and sulfhemoglobin. This would be consistent with the report that some
25 laboratories, as cited above, accepted 5 to 6% COHb from oximeter readings as normal for
26 nonsmokers.

27 For a research study to relate health effects or breath CO to COHb, the method of choice is
28 GC analysis of the CO gas released from the blood when COHb is dissociated (U.S.
29 Environmental Protection Agency, 1991; Van Dam and Daenenes, 1994; Lloyd and Rowe,
30 1999). The reader, therefore, is alerted to the difference between end-tidal breath CO to blood
31 COHb relationships when the COHb is determined by CO-Ox or by 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 U.S. Environmental Protection Agency (1991). A common type of instrument in use for rapidly screening large numbers of people for CO exposures or measuring breath CO distributions is the electrochemical analyzer. The subject performs an inhalation-breathhold maneuver and exhales through a mouthpiece into the instrument inlet. The end tidal breath is retained for analysis, and the reading in ppm CO can be converted to COHb through a calibration curve or nomogram provided with the instrument.

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

Lee et al. (1991) developed a TDLS system that was well suited for measuring low levels of CO in breath. The system also can detect the abundance of isotopic CO ($^{13}\text{C}^{16}\text{O}$), 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

1 expelled after breath holding for 20 s, thus obtaining alveolar air undiluted by dead space air.
2 The sampler was unaffected by humidity; however, the rather low efficiency of collection (50%)
3 and the resulting fairly high detection limit of 3.2 ppm may limit the utility of the sampler for
4 environmental studies.

5 6 **2.6.3 Relationships of Breath Carbon Monoxide to Blood** 7 **Carboxyhemoglobin**

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

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

28 Lee et al. (1994) performed a study of CO-COHb relationships at altitude in Boulder.
29 A total of 13 nonsmoking adults were exposed to 9 ppm CO for both 1 and 8 h. Blood was
30 sampled and end-tidal breath samples were taken after a 10-s breathhold. Mean COHb values
31 prior to exposure were 0.65% and, after exposure for the 1- and 8-h periods were 1.2 and 2.2%,

1 respectively. The corresponding mean CO levels in the breath samples were about 2.4, 4.4, and
2 8.2 ppm (uncorrected for the ≈ 0 ppm ambient CO in inhaled air), respectively, as shown in
3 Figure 2-2. The slope of 3.65 ppm per 1% COHb saturation after a 10-s breathhold at altitude is
4 somewhat smaller than previous estimates of about 5 ppm CO per 1% COHb, but the previous
5 estimates were based on a 20-s breathhold near sea level that maximizes the end-tidal CO if the
6 inhaled air had a CO concentration below the 20-s end-tidal breath CO (Jones et al., 1958).

7 8 **2.6.4 Summary of the Relationship Between Biological Measurements of** 9 **Carbon Monoxide**

10 The use of CO-Ox to measure COHb provides useful information regarding values of
11 COHb in populations being studied for clinical diagnosis. However, the range of COHb values
12 obtained with this optical method for blood collected from nonsmokers is greater than that
13 obtained from a split sample analyzed for COHb by research laboratory GC. Therefore, the
14 greater potential exists with the CO-Ox for having an incorrect absolute value for COHb, as well
15 as an incorrectly broadened range of values, when used in population studies. In addition, it is
16 not clear exactly how sensitive the CO-Ox techniques are to small changes in COHb at the low
17 CO end of the COHb dissociation curve. Interferences (e.g., from variable levels of oxygen
18 saturation of hemoglobin [O_2Hb]) and nonlinear phenomena appear to have a very significant
19 influence on the COHb reading at low COHb concentrations in a sample, suggesting nonlinearity
20 or a disproportionality in the absorption spectra of different species of Hb (e.g., HbA [adult], HbF
21 [fetal], HbS [sickle], HbZH [Zurich]). Gas chromatography continues to be the method of choice
22 for measuring COHb in a research setting, although, with care, a CO-Ox can be specially
23 calibrated by GC analysis of calibration-standard blood samples prepared with low COHb
24 concentrations (Allred et al., 1991).

25 The measurement of exhaled breath CO has the advantages of ease, speed, precision
26 (provided the required correction for CO in the inhaled air is made), and greater subject
27 acceptance than the invasive measurement of blood COHb. Breath CO measurement on
28 randomly chosen people can be related to the blood COHb by use of an empirical relationship
29 developed by simultaneous measurements of COHb (preferably by GC) and breath CO using the
30 identical procedure for the breath collection that is used in the population study. The empirical
31 relationships developed with different breath holding techniques will differ from the theoretical

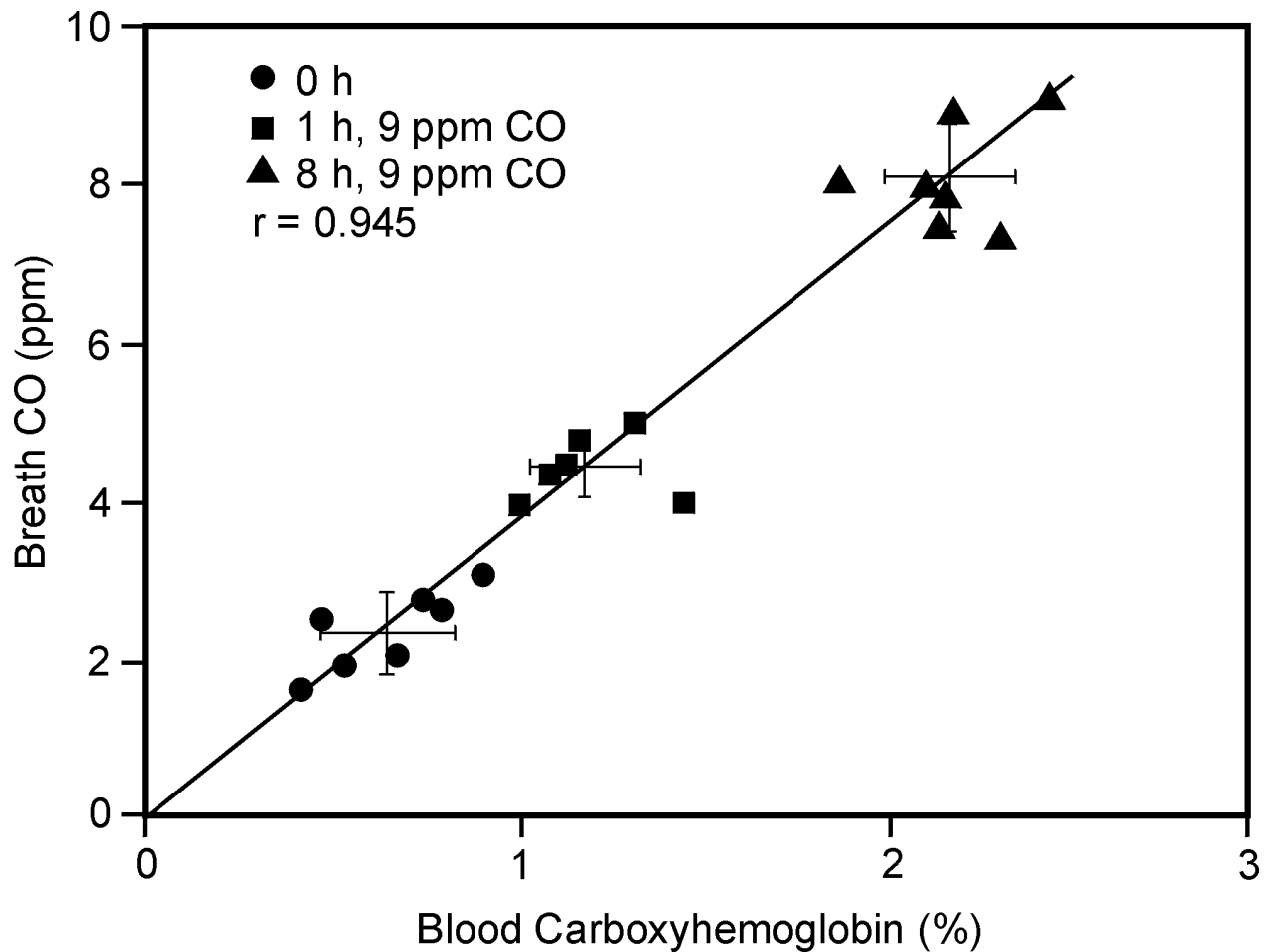


Figure 2-2. The correlation between an end-tidal breath CO concentration after a 10-s breathhold and blood COHb levels expressed as individual data points as well as mean \pm standard deviation. The breath concentration was not corrected for the concentration of CO in the inhaled air (Smith, 1977; Wallace,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

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

1 Haldane equilibrium relationship for the reaction $\text{CO} + \text{O}_2\text{Hb} \leftrightarrow \text{O}_2 + \text{COHb}$, which depends on
 2 the ratio of adult- to fetal-hemoglobin (HbA:HbF). This is because the Haldane relationship is
 3 for in vitro static equilibrium, and the empirical end-tidal breath CO-blood COHb relationship is
 4 for an in vivo dynamic equilibrium that depends on how long the breath is held and on the
 5 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 Chemical Transport Models (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

1 information regarding mean values in populations being studied or as an aid in clinical diagnosis.
2 It has been shown, however, that the range of values obtained with this optical method will be
3 greater than that obtained with other more accurate methods, especially at COHb levels <5%.
4 Gas chromatography continues to be the method of choice for measuring COHb.

5 The measurement of exhaled breath has the advantages of ease, speed, precision, and
6 greater subject acceptance than measurement of blood COHb. However, the accuracy of the
7 breath measurement procedure and the validity of the in vitro Haldane relationship between
8 breath and blood still remains in question, especially at low environmental CO concentrations.
9

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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. In indoor environments with sources such as properly operating unvented combustion sources, malfunctioning or misused combustion appliances, automobile exhaust from attached garages, and cigarettes and, in outdoor environments such as urban areas where emissions from motor vehicles or wood burning can cause high concentrations to exist, carbon monoxide is of direct concern because of health effects resulting from human exposure to these high concentrations. Human exposures to CO are discussed in Chapter 4.

Carbon monoxide in less polluted air is of interest because of its importance to atmospheric chemistry. Carbon monoxide can affect the formation of ozone (O₃) 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 O₃ and the energy budget of the atmosphere. Changes in CO levels, therefore, may contribute to widespread changes in atmospheric chemistry and indirectly affect global climate. In this chapter, the global scale aspects of CO are discussed first, and then the discussion proceeds to successively smaller scales. An overview of the major sources and sinks of CO and the resulting CO distribution on a global basis and the importance of CO to tropospheric chemistry is presented in Section 3.2, followed by a discussion of nationwide emissions of CO in Section 3.3. Nationwide trends in ambient CO levels and related discussions on CO air quality are presented in Section 3.4, and concentrations and sources of CO in indoor environments are discussed in Section 3.5.

3.2 THE GLOBAL CYCLE OF CARBON MONOXIDE

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

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

Sources and Sinks	Notes
Sources	
Fossil fuel combustion	Transportation and coal, oil, and natural gas burning.
Biomass burning	Agricultural clearing, wood and refuse burning, and forest fires. ^a
CH ₄ oxidation	Wetlands, ^a agriculture (rice cultivation, animal husbandry, and biomass burning), landfills, coal mining, and natural gas and petroleum industry.
NMHC oxidation	Transportation (alkanes, alkenes, 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 catalogued.

^aSources and sinks that have large natural components.

Carbon monoxide is formed as an intermediate product during the photochemical oxidation of methane and non-methane hydrocarbons (NMHCs) to CO₂. Major sources of methane are summarized in the second column of Table 3-1. Likewise, major sources of NMHCs, whose oxidation produces CO, are given. In addition, the photooxidation of organic matter in surface waters (oceans, lakes, and rivers) and on the soil surface occurs. Carbon monoxide is lost primarily by reaction with atmospheric OH radicals and by uptake by soil microorganisms.

1 More detailed descriptions of the nature of individual sources of primary CO shown in
2 Table 3-1 and estimates of the strengths of these sources, along with similar material for
3 nonchemical sinks of CO, are given in Section 3.2.2. Carbon monoxide concentrations and
4 trends in the background atmosphere are discussed in Section 3.2.1, and the atmospheric
5 chemistry of CO, including the formation of secondary CO, is discussed in Section 3.2.3.
6

7 **3.2.1 Global Background Concentrations of Carbon Monoxide**

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

21 Surface measurements of CO concentrations are made routinely as part of the National
22 Oceanic and Atmospheric Administration’s Climate Monitoring Diagnostics Laboratory
23 (NOAA/CMDL) Global Cooperative Air Sampling Network (e.g., Hofmann et al., 1996).
24 Carbon monoxide flask samples are collected weekly in flasks or continuously with in situ gas
25 chromatographs at about 40 remote sites around the world. These sites are located primarily in
26 the marine boundary layer, with a few located in continental areas. The latitudinal and seasonal
27 variations in CO levels are summarized in the three-dimensional diagram shown in Figure 3-1
28 (National Oceanic and Atmospheric Administration, 1999). Annual average CO mixing ratios
29 are about 120 ppb in the Northern Hemisphere and about 40 ppb in the Southern Hemisphere.
30 Seasonal maxima in CO mixing ratios occur during late winter in both hemispheres, and minima

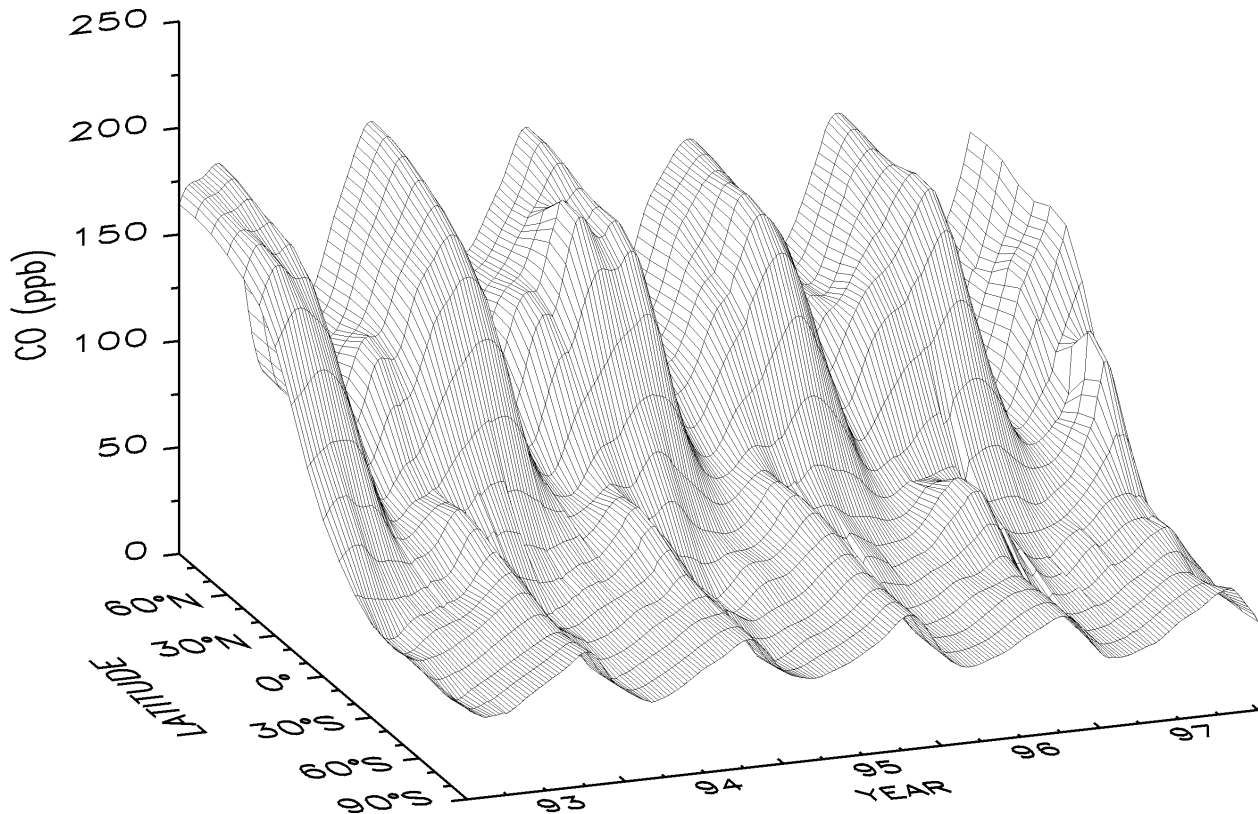


Figure 3-1. Latitudinal and seasonal variability in CO concentrations obtained in the NOAA/CMDL monitoring network.

Source: National Oceanic and Atmosphere Administration (1999a).

1 occur during late summer, with about a factor of two variation between maximum and minimum
 2 values. Carbon monoxide is well mixed in high latitudes of both the Northern Hemisphere and
 3 the Southern Hemisphere. A steep gradient in CO mixing ratios exists between about 30° north
 4 (N) latitude and about 10° south (S) latitude. Carbon monoxide concentrations range from a
 5 minimum of about 30 ppb during summer in the Southern Hemisphere to about 200 ppb at high
 6 latitudes in the Northern Hemisphere during winter. Thus, CO concentrations in remote areas of
 7 the Northern Hemisphere are only a small fraction (≈ 1 to 2%) of those of concern to human
 8 health (as given by the National Ambient Air Quality Standards [NAAQS] for CO of 9 ppm for
 9 the second highest, nonoverlapping 8-h average concentration).

1 There were sufficient data on tropospheric air quality trends to suggest that CO
2 concentrations measured at global background sites were increasing at $1.2 \pm 0.6\%$ per year from
3 1981 to 1986, based on data collected by the Oregon Graduate Institute (OGI), this increase
4 presumably resulted from anthropogenic activities (Khalil and Rasmussen, 1988a). From 1987
5 until 1992, global background levels of CO declined at a rate of about $-2.6 \pm 0.8\%$ per year
6 (Khalil and Rasmussen, 1994), whereas Novelli et al. (1994) determined a rate of decrease in CO
7 of $-6.5 \pm 0.8\%$ per year from 1990 to 1993 and later results reported by NOAA/CMDL indicate
8 that background levels of CO continued to decline although at a lower rate of $-2.6 \pm 0.2\%$ per
9 year from 1990 to 1995 (Novelli et al., 1998). Hypotheses to explain these observations include
10 reductions in fossil fuel combustion (Bakwin et al., 1994; Novelli et al., 1994; Khalil and
11 Rasmussen, 1994) and tropical biomass burning (Yung et al., 1999). Possible increases in
12 tropospheric OH levels resulting from enhanced transmission of solar ultraviolet radiation caused
13 by stratospheric O₃ depletion may have been an additional factor (Fuglestad et al., 1994; Bekki
14 et al., 1994). More recent data for changes in global background CO levels are shown in
15 Figure 3-2. The data from 1993 to 1997 do not show clearly any stable upward or downward
16 trend.

17 Because direct measurements of sufficient precision for defining trends have come into use
18 only within the last 15 to 20 years, estimates of longer term trends in CO levels must come from
19 indirect means. Rinsland and Levine (1985) derived an increase in the mean tropospheric CO
20 abundance of about 2% per year from 1950 to 1984, based on an examination of solar spectra
21 captured on photographic plates in Europe. Column CO abundances obtained over Zvenigorod,
22 Russia from 1974 through 1997 have increased by about 1% per year (Yurganov et al., 1999),
23 while measurements obtained with a similar technique over the Alps have indicated decreases in
24 CO of $-0.18 \pm 0.16\%$ per year from 1984 to 1995 compared to a change of $-0.95 \pm 0.32\%$ per
25 year from 1984 to 1993. The difference arises mainly from a pronounced minimum during the
26 second half of 1992 and 1993 (depending on the fitting function (Mahieu et al., 1997). Thus,
27 there is still considerable uncertainty in defining global trends for CO based on differences in
28 trends found in specific regions.

29 Carbon monoxide concentrations measured in air bubbles trapped in the ice sheets of
30 Greenland and Antarctica have been used as proxies for CO concentrations in ambient air at the

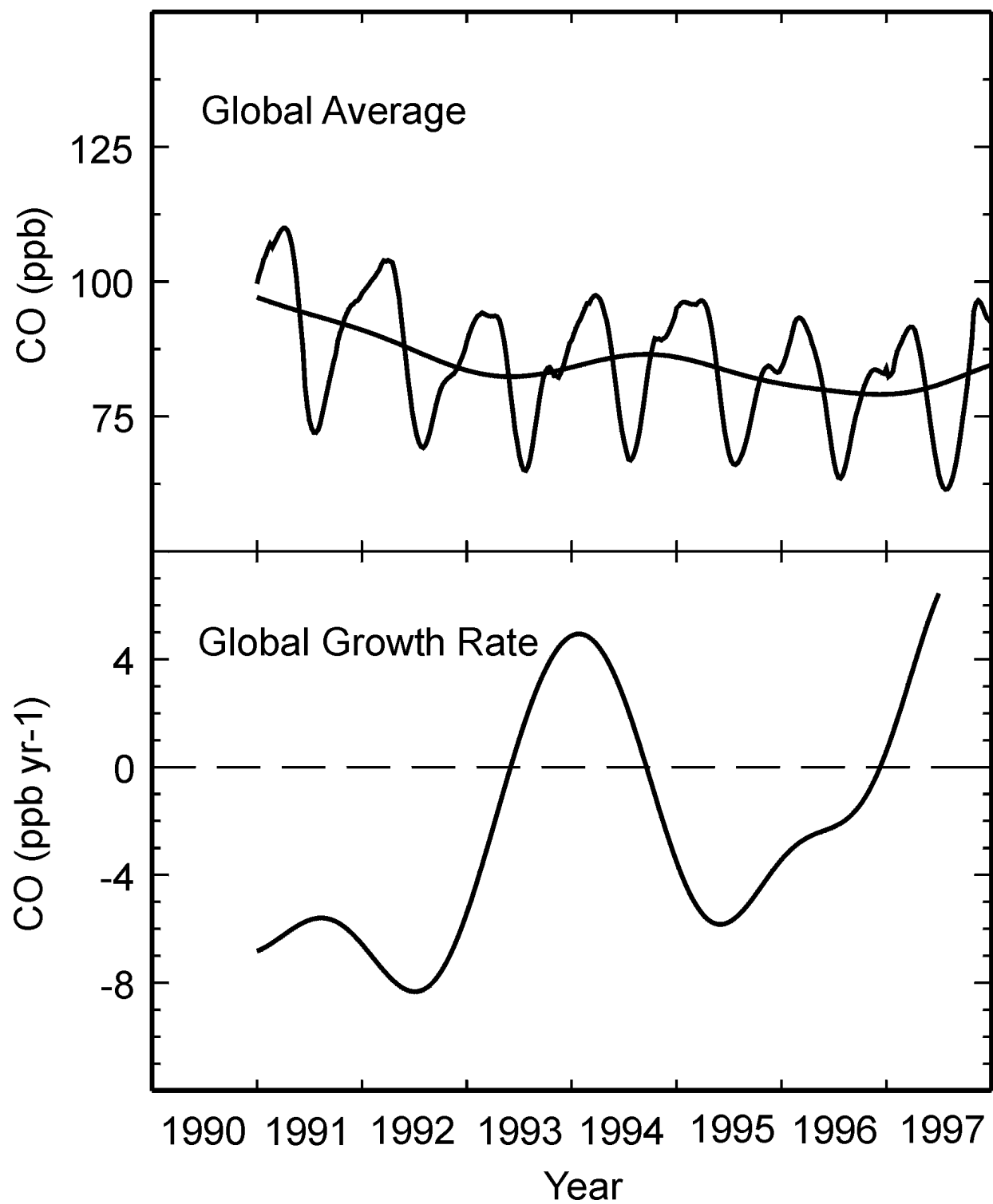


Figure 3-2. Global background average CO levels (upper) and growth rates for global background average CO (lower).

Source: National Oceanic and Atmospheric Administration (1999b).

time the air bubbles were sealed from the atmosphere (Haan et al., 1996). Carbon monoxide concentrations derived this way for the preindustrial era (roughly corresponding to the year 1850, when anthropogenic activities should not have influenced significantly the atmospheric composition) are about 90 ppb for the high-latitude Northern Hemisphere and are about 50 ppb for the high-latitude Southern Hemisphere. 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 mixing ratios 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 carbon dioxide (CO₂). 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.

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

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

^aEstimate includes 150 Tg/year from stationary sources.

^bEstimate includes 100 Tg/year from stationary sources.

^cValues in parentheses represent ratio of maximum to minimum estimate of source term.

1 This latter source is of significance only in eastern Europe and in developing countries of Africa
2 and Asia (especially China). However, it also should be noted that the importance of this source
3 has been declining as heating needs are met increasingly by centralized power plants.

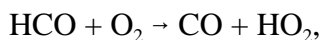
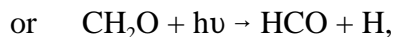
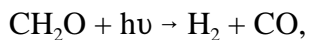
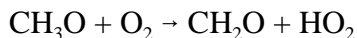
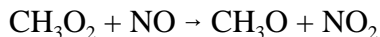
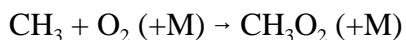
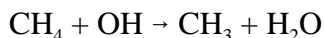
4 Biomass burning consists of wildfires and the burning of vegetation to clear new land for
5 agriculture and population resettlement; to control the growth of unwanted plants on pasture
6 land; to dispose of agricultural and domestic waste; and as fuel for cooking, heating, and water
7 sterilization. Most wildfires are the result of human activities with only a small fraction (10 to
8 30%) initiated by lightning (Andreae, 1991). Biomass burning exhibits strong seasonality, with
9 most biomass burned during the local dry season. The smoldering phase of combustion yields
10 higher emissions factors than the flaming phase. Lobert et al. (1991) found, in controlled
11 combustion chamber experiments with a wide variety of vegetation types, that, on average,
12 84% of CO was produced during the smoldering phase and 16% during the flaming phase of
13 combustion. Smoldering conditions are more prevalent during the burning of large pieces of
14 vegetation, such as trees, compared with grasses. Nonetheless, most CO is produced in the
15 tropics by savanna burning (mainly in Africa), followed by burning forests, fuel wood, and
16 agricultural waste. Less than 20% of the CO produced by biomass burning originates in middle
17 and high latitudes (Andreae, 1991).

18 The other sources of CO shown in Table 3-2 all have large natural components. Carbon
19 monoxide may be evolved from the photodecomposition of organic matter in surface waters
20 (such as oceans, rivers, and lakes) and the soil surface. Soils can act as a source or a sink for
21 carbon monoxide, depending on soil moisture, the intensity of sunlight reaching the soil surface,
22 and soil temperature (e.g., Inman et al., 1971; Conrad and Seiler, 1985). Soil uptake of CO
23 occurs because of anaerobic bacteria (Inman et al., 1971). Emissions of CO from soils appear to
24 occur by abiotic processes, such as thermodecomposition or photodecomposition of organic
25 matter. In general, warm and moist conditions found in most soils favor CO uptake, whereas hot
26 and dry conditions as found in deserts and some savannas favor the release of CO (King, 1999).
27 The value reported for soil emissions in Table 3-2 is based on very limited data, and hence it is
28 difficult even to assign uncertainty bounds (Conrad, 1996). Moxley and Cape (1997)
29 hypothesized that from 20 to 80% of CO in the stable nocturnal boundary layer (calculated
30 heights between 40 and 220 m) could have been depleted by soil microorganisms during
31 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 CO₂ 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 produced by human activity and a value of two-thirds for the fraction of CH₄ produced by human activity (Houghton et al., 1992), 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 CH₄ 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 CH₄ emissions from the various source categories shown in Table 3-1 can be found in the Intergovernmental Panel on Climate Change report (Houghton et al., 1992). Methane oxidation can be summarized by the following sequence of reactions:



where M is a mediator (e.g., nitrogen, O₂, argon, CO₂). The photolysis of formaldehyde (CH₂O) proceeds by two pathways, the first yields molecular hydrogen (H₂) plus CO (55%), and the

1 second yields atomic hydrogen (H) plus the formyl radical (HCO) (45%), where the percentages
2 are given for overhead sun conditions (Rogers, 1990). Formyl radicals then react with molecular
3 oxygen (O_2) to form the hydroperoxy radical (HO_2) plus CO. In addition, the reaction of the
4 methyl peroxy radical (CH_3O_2) with HO_2 radicals, forming methyl hydroperoxide (CH_3OOH),
5 needs to be considered, especially in low nitrogen oxide (NO_x) environments. The heterogeneous
6 removal of soluble intermediate products, such as CH_3OOH , CH_2O , and radicals, decreases the
7 yield of CO from the oxidation of CH_4 .

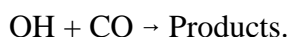
8 Although the oxidation of CH_2O nearly always results in CO formation (except for the
9 formation of small quantities of formic acid in the reaction of CH_2O with HO_2), the oxidation of
10 acetaldehyde (CH_3CHO) does not always yield two CO molecules. The photolysis of CH_3CHO
11 also involves pathways that produce molecules and radicals, namely $CH_4 + CO$ and $CH_3 + HCO$.
12 Estimates of the yield of CO from the photooxidation of CH_4 and CH_3 are subject to the same
13 considerations outlined above. The reaction of CH_3CHO with OH radicals can yield acetyl
14 radicals (CH_3CO). The acetyl radicals then will participate with O_2 in a termolecular
15 recombination reaction to form acetyl peroxy radicals, which then can react with nitric oxide
16 (NO) to form $CH_3 + CO_2$ (or the acetyl peroxy radicals can react with nitrogen dioxide (NO_2) to
17 form peroxy acetyl nitrate [PAN]). Thus, one of the carbon atoms can be oxidized directly to
18 CO_2 without passing through CO. The yield of CO depends on the OH concentration and the
19 photolysis rate of CH_3CHO , as well as on the abundance of NO, as acetyl peroxy radicals also
20 can react with HO_2 and other hydrogen-bearing radicals.

21 Estimates of the yield of CO from the oxidation of more complex hydrocarbons requires
22 the calculation of the yields of CH_2O , CH_3CHO , CH_3CO , and analogous radicals from the
23 oxidation of the parent molecule. Likewise, the extent of heterogeneous removal of soluble
24 intermediate products needs to be considered in the oxidation of more complex hydrocarbons.
25 However, in contrast to simple hydrocarbons containing one or two carbon atoms, detailed
26 kinetic information is lacking about the gas phase oxidation pathways of many anthropogenic
27 hydrocarbons (e.g., aromatic compounds, such as benzene and toluene), biogenic hydrocarbons
28 (e.g., isoprene, the monoterpenes), and their intermediate oxidation products (e.g., epoxides,
29 nitrates, carbonyl compounds). As much as 30% of the carbon in hydrocarbons in many urban
30 areas is in the form of aromatic compounds (Grosjean and Fung, 1984; Seila et al., 1989). Yet
31 mass balance analyses performed on irradiated smog chamber mixtures of aromatic hydrocarbons

1 indicate that only about one-half of the carbon is in the form of compounds that can be identified.
2 Reactions that have condensible products, such as those occurring during the oxidation of
3 terpenes, also need to be considered because these reactions produce secondary organic
4 particulate matter, thereby reducing the potential yield of CO.

5 The yield of CO from the oxidation of CH₄ is about 0.9, and it is about 0.4 from the
6 oxidation of ethane and propane, on a per carbon basis from estimates based on atmospheric
7 model results (Kanakidou et al., 1991). Jacob and Wofsy (1990) estimated that 1 mole of CO is
8 produced by the oxidation of 1 mole of isoprene (corresponding to a conversion factor of 0.2 on a
9 per carbon basis) for low NO_x levels. For higher NO_x levels, they estimated that 3 moles of CO
10 are produced per mole of isoprene oxidized (corresponding to a conversion factor of 0.6 on a per
11 carbon basis). Isoprene accounts for most of the CO produced by the photochemical oxidation of
12 NMHCs shown in Table 3-2.

13 The major pathway removing CO from the atmosphere is by its reaction with OH radicals.
14 There have been numerous determinations of the rate coefficient for this reaction. The most
15 recent evaluation of kinetics data for use in atmospheric modeling (National Aeronautics and
16 Space Administration, Panel for Data Evaluation, 1997) recommends a value of 1.5×10^{-13}
17 $(1 + 0.6 P_{\text{atm}}) \text{ cm}^3 \text{ molecules}^{-1} \text{ s}^{-1}$, with a value of $0 \pm 300 \text{ K}$ for E/R for the reaction



21 This reaction proceeds through two channels. The bimolecular channel yields H + CO₂, whereas
22 the addition channel leads to the formation of a carboxyl radical (HOCO). In the presence of O₂,
23 the HOCO intermediate is converted to HO₂ + CO₂. Therefore, for atmospheric purposes, the
24 products of the reaction OH + CO can be taken to be HO₂ and CO₂.

25 Estimates of OH radical concentrations can be used along with the rate coefficient given
26 above to calculate the lifetime of CO in the atmosphere. Measurements of OH radical
27 concentrations in situ (Hard et al., 1992; Mount and Williams, 1997; Poppe et al., 1994) in the
28 lower troposphere show that their levels are highly site specific and are highly variable in space
29 and time. Typical mid-latitude noontime values during summer (when OH concentrations are at
30 their highest levels) range from about 5 to $10 \times 10^6 \text{ OH/cm}^3$ and are much lower during other
31 times of the day and during other seasons. As a result, it is difficult to derive average values that

would be meaningful for use in calculating the atmospheric lifetime of long-lived species that react with OH radicals, based on direct measurements. Modeling the atmospheric distribution of methyl chloroform (CH_3CCl_3) has been used to derive diurnal and global average OH values for calculating the atmospheric lifetimes of long-lived species by comparing predictions to observations (Prinn et al., 1992). Average OH values derived in this manner are about 8×10^5 OH/cm³. 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/cm³ in 1978 and 1.07×10^6 OH/cm³ 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 CH₄ emissions, and derived an overall change of 6% in OH levels 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 should also be noted that Prinn et al. (1995) had found little or no trend in OH based on methychloroform data.

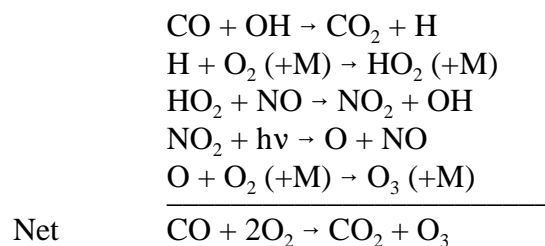
The resulting globally averaged atmospheric lifetime of CO is then approximately 2 mo. Shorter lifetimes are found in the tropics, whereas longer lifetimes are found at higher latitudes. During winter at high latitudes, CO is essentially inert. The CO lifetime is shorter than the characteristic time 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 CO level of 3×10^6 in urban areas) and in indoor environments, where OH levels 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

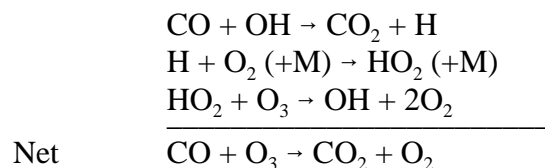
effect (e.g., CH₄) or can deplete stratospheric O₃ (e.g., methyl chloride [CH₃Cl], methyl bromide [CH₃Br], and hydrochlorofluorocarbons, such as difluorochloromethane). Because of the importance of CO in determining OH levels, interest has focused on the possible effects of increases in anthropogenic CO emissions on the concentrations of gases such as 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 CH₄ emissions constant, that the mixing ratio of CH₄ at the surface increased by about 12% (corresponding to a mean increase of 0.56% per year), and that the mixing ratio of CH₄ at the surface increased by about 30% (corresponding to a mean increase of 1.3% per year) for an increase in surface CO mixing ratio of 2% per year. However, based on the trend results reported earlier, Brühl and Crutzen (1998) have examined the consequences of decreases in CO levels for atmospheric chemistry. They found, by decreasing CO emissions linearly by about 20% between 1990 and 2000, that the CO reductions could lead to a significant decrease (≈25%) in the growth rate of CH₄ and even to a decrease in CH₄ levels in the case of constant CH₄ emissions. An accurate knowledge of the sources and sinks of carbon monoxide in the atmosphere is therefore necessary for assessing the effects of future increases in anthropogenic CO emissions on the concentrations of the above-mentioned radiatively and photochemically important trace species. However, because of nonlinearities introduced into the calculation of OH radical concentrations by short-lived NO_x (e.g., Hameed et al., 1979), an accurate assessment of these effects awaits the development of three-dimensional chemistry and transport models incorporating the spatial variability of NO_x (e.g., Kanakidou and Crutzen, 1993).

In the free troposphere, in the absence of significant quantities of NMHCs, the effects of CO on tropospheric O₃ can be summarized as shown below.

Atmospheric Reactions Leading to O₃ Production



Atmospheric Reactions Leading to O₃ Destruction



The oxidation of CO by OH could lead to the production or destruction of O₃, depending on the ratio of NO to HO₂ concentrations. Based on current values of rate coefficients for the reactions of HO₂ with NO and O₃, in regions where NO levels are greater than about 10 ppt, the oxidation of CO leads to O₃ formation, whereas, in areas where NO levels are less than about 10 ppt, the oxidation of CO leads to O₃ destruction. Nitric oxide levels less than 10 ppt typically are found over the tropical oceans (Carroll et al., 1990). A rough estimate of the fraction of O₃ 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 HO₂ 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 NO₂ by HO₂ radicals produced by the reaction of CO with OH radicals) represents 20 to 40% of the production of O₃ on a global basis.

The effects of CO on O₃ 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, HO₂). 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 O₃ 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 O₃ 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 O₃ 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 VOCs and that oxidize NO to NO₂, that CO accounted for about 17.5% of the O₃ 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 O₃ involving each of the above species, caution should be exercised in attempting to estimate the effects of variations in CO levels on O₃ 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 (NET) 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 lawn equipment, construction equipment, trains, aircraft, boats, ships, recreational equipment, logging equipment, and agricultural equipment. From 1988 to 1997, the contribution of onroad sources decreased from 61 to 57%, while 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 air quality criteria document (AQCD) for CO. It can be seen from inspection of Table 3-3 that the values for 1990 have been revised upward in the interim to 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, 1993) 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. Exhaust emission rates were found to increase significantly, 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

TABLE 3-3. U.S. NATIONWIDE 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, 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. NATIONWIDE 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
On-Road 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
Non-Road Engines and Vehicles	14,698	14,820	15,376	15,368	15,652	15,828	16,050	16,271	16,409	16,755
Non-Road 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. NATIONWIDE CARBON MONOXIDE EMISSIONS
(thousands of short tons)

(THOUSANDS OF SHORT TONS)										
Source Category			1988	1989	1990	1991	1992	1993	1994	1995
Non-Road 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
Non-Road 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. NATIONWIDE 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:

^aCoal Burning

^bNatural Gas Burning

^cResidential wood burning

^dCarbon black manufacturing

^eFerrous metal production

^fRefineries

^gWood, 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).

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

6 In addition, it should be noted that Table 3-3 does not include formation of secondary CO,
7 such as from the oxidation of isoprene. Annual emissions of isoprene in the contiguous United
8 States are about 17.2 Tg/year (Pierce and Dudek, 1996). A source of CO of 7.1 Tg/year can be
9 calculated using the conversion factor of 0.20 for C in isoprene to C in CO estimated by Jacob
10 and Wofsy (1990). This value would add about 9% to the estimated U.S. emissions for CO in
11 1995, shown in Table 3-3. The oxidation of anthropogenic and other natural NMHCs may
12 supply an additional 2 to 3 Tg CO per year.

13 A number of techniques, such as roadside tunnel sampling and the remote sensing of
14 individual motor vehicle emissions have been applied in the past several years at a number of
15 locations throughout the United States to test CO emissions estimates and to derive emissions
16 factors (i.e., emissions per unit distance traveled). Two major points have been realized on the
17 basis of these studies: first, that a small percentage of motor vehicles are responsible for most of
18 the emissions, and, second, that CO and hydrocarbon emissions had been systematically
19 underestimated by as much as a factor of two in emissions factor models. As a result of these
20 studies, a number of revisions have been made to emissions inventories.

21 Roadside remote sensing data indicate that about 50% of CO and NMHC emissions are
22 produced by only about 10% of the vehicles (Lawson et al., 1990; Stephens and Cadle, 1991).
23 These “superemitters” are typically older, poorly maintained vehicles. Bishop and Stedman
24 (1996) also found that the most important variables governing CO emissions are fleet age and
25 owner maintenance. There are also a surprising number of newer vehicles that are classified as
26 superemitters. Possible reasons are related to tampering with emissions control systems to
27 improve mileage, the use of contaminated fuels that may interfere with the proper operation of
28 emissions control systems, and the lack of maintenance of emissions control equipment and the
29 failure of emissions control equipment. In addition to the above activities, so-called off-cycle
30 operations also can result in enhanced emissions relative to those conditions for which emissions
31 testing is usually done. For example, rapid accelerations have been shown to increase emissions

1 relative to less stressful driving modes. Roadside remote sensing of motor vehicle emissions
2 have also been used to evaluate the effectiveness of inspection and maintenance programs
3 (Zhang et al., 1996; Stedman et al., 1997; Stedman et al., 1998).

4 A comparison of emissions factors computed on the basis of tunnel measurements in
5 Van Nuys, CA, during the South Coast Air Quality Study in 1987 with those calculated by
6 emissions inventory models indicated that CO emissions were underpredicted by emissions
7 models (i.e., the Emissions Factor 7C [EMFAC7C] model, which is similar to MOBILE3) by a
8 factor of 2.7, and hydrocarbon emissions were underestimated by a factor of 3.8 (Ingalls et al.,
9 1989; Pierson et al., 1990). A reinterpretation of the Van Nuys tunnel data by Pollack et al.
10 (1998) indicated that emissions factors calculated using MOBILE5a were only a few percent
11 greater than the ambient tunnel data indicated (21.3 versus 20.9 g/mi), compared with a factor of
12 two difference using EMFAC7F (9.6 versus 20.9 g/mi). Likewise, a comparison of emission
13 factors computed on the basis of measurements in the Fort McHenry, MD, and Tuscarora, PA,
14 tunnels with those calculated by emissions models (MOBILE4.1 and MOBILE5) indicated that
15 both versions of the MOBILE model gave predictions within $\pm 50\%$ of observations most of the
16 time (Pierson et al., 1996). However, it should be noted that emissions in tunnels arise from
17 vehicles in warmed-up or hot-stabilized operation. Cold and hot start emissions, which are
18 important components of the emissions inventory, generally are not present in tunnels and thus
19 are not evaluated in these studies.

20 Comparisons of ambient air quality data with predictions of emissions factor models have
21 been made for conditions when ambient concentrations result primarily from local emissions
22 with minimal photochemical processing and minimal transport from locations with different
23 source characteristics. The optimal time to obtain such conditions is during the early morning,
24 when ambient concentrations of CO, non-methane organic compounds (NMOCs), and NO_x
25 typically peak and are dominated by local mobile source emissions (Fujita et al., 1992). These
26 comparisons have been performed in California for the Los Angeles Basin (Fujita et al., 1992),
27 the San Joaquin Valley, and San Francisco Bay Area (Magliano et al., 1993), and for the
28 Lake Michigan air quality region (Korc et al., 1993). A fairly consistent picture of
29 underpredictions of ambient CO to NO_x and NMOC to NO_x ratios by emissions factor models,
30 after allowing for the effects of atmospheric processing and transport, emerged from these
31 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/NO_x 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 largely arisen through the process of model development, evaluation and further refinement.

Stationary sources account for approximately 23% of nationwide CO emissions. 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 (1988, 1989) have shown that during the winter in Medford, OR, and in Olympia, WA, the contribution of wood burning to CO levels 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 account for 20 to 40% of excess over nonurban background CO levels.

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/m³), and the second highest nonoverlapping 8-h value is less than or equal to 9 ppm (10 mg/m³). Nationwide trends in ambient CO concentrations are presented in Section 3.4.1, diurnal variations in ambient CO levels are presented in Section 3.4.2, and a more detailed characterization of the spatial and temporal variability in ambient CO concentrations in selected urban areas are presented in 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 (Shadwick et al., 1997, 1998a,b,c). The results of similar analyses for the Fairbanks, AK, Metropolitan Statistical Area will be included in this section when they become available.

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 immediate monitoring needs. These NAMS and SLAMS sites conform to uniform criteria for monitor siting, instrumentation, and quality assurance. "Other" monitors may be Special Purpose Monitors, monitors at industrial sites, monitors on tribal lands, etc. Although state and local air programs may require extensive monitoring to document and measure the local impacts of CO emissions, only two NAMS sites are required in urbanized areas with populations greater than 500,000. Two categories of NAMS sites are required: (1) peak concentration areas (microscale), such as major traffic corridors, street canyons, and major arterial streets, and (2) areas with high population and traffic densities (middle scale or neighborhood scale).

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. 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 in 1996. 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 past 20 years (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



Figure 3-3. Locations of sites in the nationwide ambient CO monitoring network, 1997.

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

1 in the composite mean of the annual second highest 8-h average concentration for
 2 184 monitoring sites that reported ambient air quality data in at least 17 of the past 20 years,
 3 1978 to 1997. All monitoring sites are weighted equally when computing the nationwide
 4 composite mean concentration. This selection criterion maximizes the number of sites available
 5 for trend analyses. This subset of sites yields good geographical coverage with sites from more
 6 than 90 cities in 39 states. Each year, site leases are lost, or sites are discontinued, and new sites
 7 come online; therefore, the 184 long-term-trend sites compose only one-third of the currently
 8 active CO monitors. The solid line in Figure 3-4 shows the trend in the composite mean for a
 9 larger database of 368 sites that have reported ambient CO monitoring data in at least 8 of the
 10 past 10 years. Missing annual second-highest CO concentration data for the second through

**TABLE 3-4. SITES NOT MEETING THE 8-HOUR CARBON MONOXIDE
NATIONAL AMBIENT AIR QUALITY STANDARD, 1993 TO 1997**

Location	Airs Site ID	1993		1994		1995		1996		1997	
		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
Callexico, 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**

Location	Airs Site ID	1993		1994		1995		1996		1997	
		2nd Max ^a	No. Exc. ^b	2nd Max	No. Exc.	2nd Max	No. Exc.	2nd Max	No. Exc.	2nd Max	No. Exc.
Newark, NJ	060375001	9.6	2	11.3	6	8.7	0	10.5	5	7.9	1
	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-WW	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).

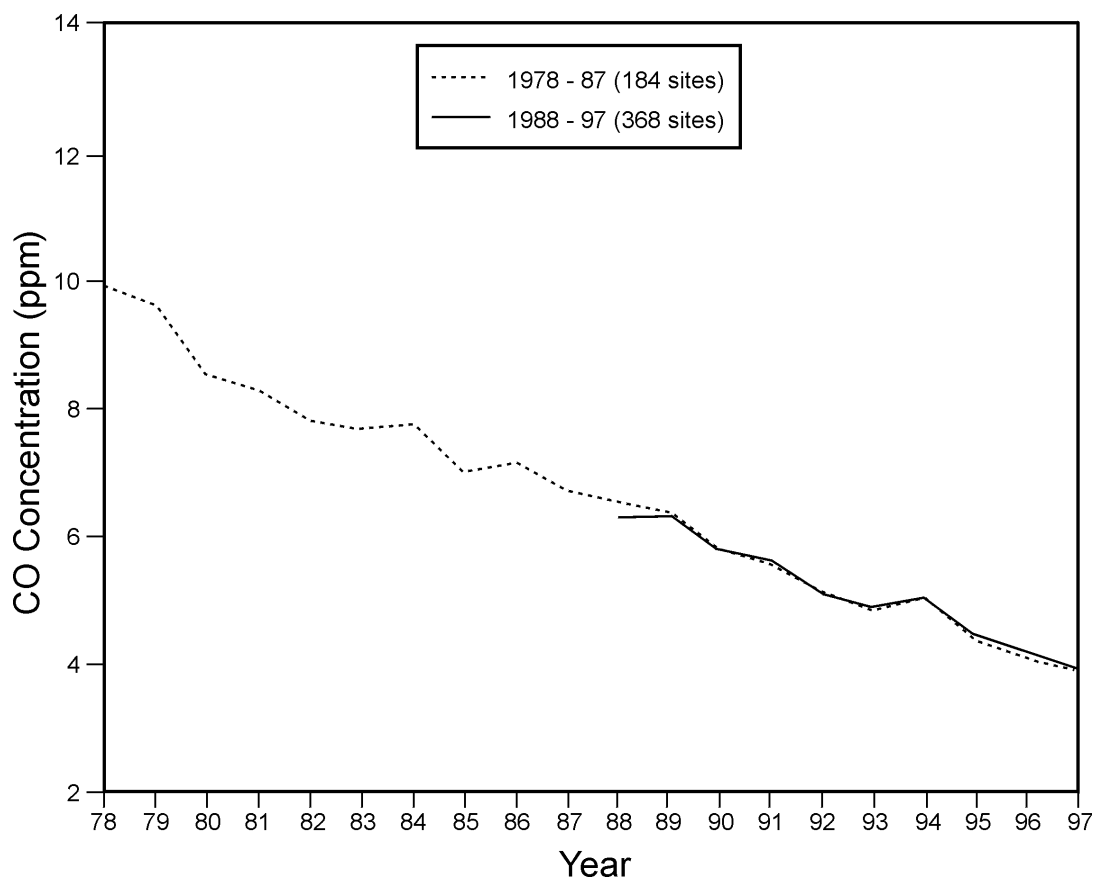


Figure 3-4. Nationwide composite average of the annual second highest 8-h CO concentrations, 1978 to 1997.

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

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 inter-site 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 percentile concentrations CO concentrations for each year are indicated, respectively, by the bottom, middle, and top lines of each box. For example, 10% of the

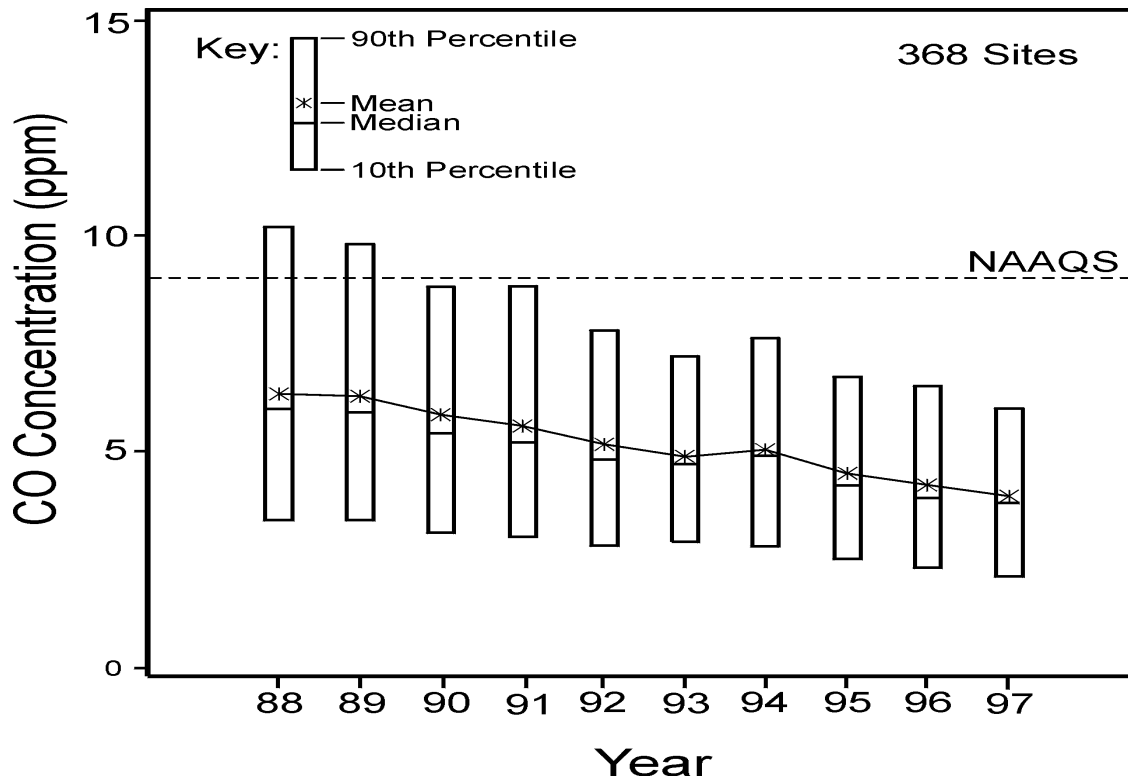


Figure 3-5. Variability in the annual second highest 8-h CO concentrations across all sites in the United States, 1988 to 1997.

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

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 “x” 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 levels 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 levels measured in populated areas over the past decade is also reflected at least at one continental background site at Shenandoah National Park, VA (Hallock-Waters et al., 1999).

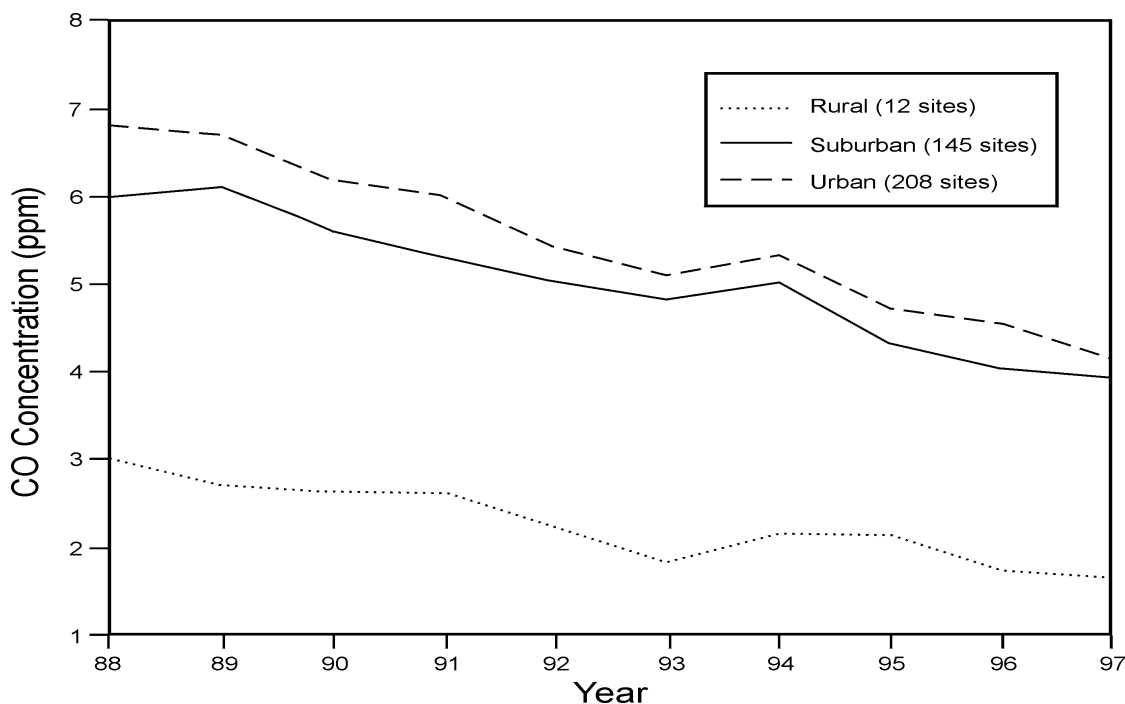


Figure 3-6. Composite average of the annual second highest 8-h CO concentrations for rural, suburban, and urban sites, 1988 to 1997.

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

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 mainly from CO emitted into the relatively shallow morning boundary layer by motor vehicles (e.g., Fujita et al., 1992). The CO mixing ratios decline towards mid-afternoon, as the height of the atmospheric mixing layer increases and then increase again with the onset of the evening rush hour. Carbon monoxide levels fall off less rapidly after the afternoon peak because the mixing layer height decreases during evening and nighttime. There is a general decrease in CO levels during the night because of a lack of fresh emissions combined with processes such as mixing with CO-poor areas and deposition to the surface. The downward trend in CO concentrations from 1987 to 1996 is apparent for all times of the day. Especially notable is the decrease in 7 to

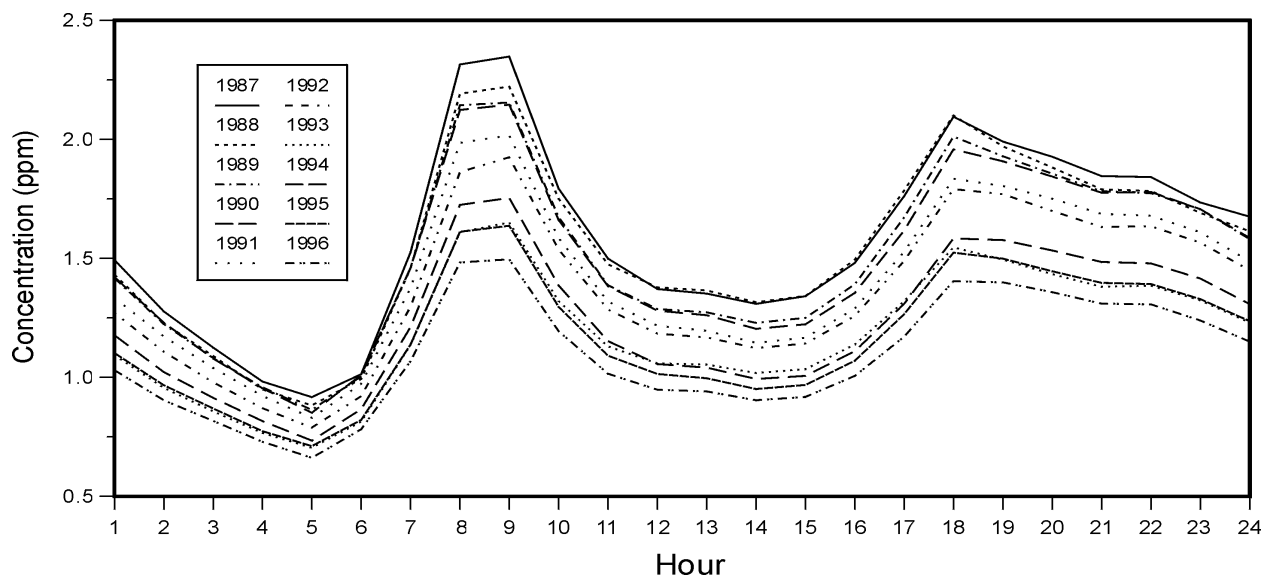


Figure 3-7. Diurnal variation of nationwide composite hourly average CO concentrations for winter (December to February), 1987 to 1996.

Source: Cohen and Iwamiya (1998).

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 sum the numbers of these events by hour of the day over the course of a year. Hourly average CO data were taken from AIRS to construct running 8-h averages for 1996.

In the previous AQCD for CO (U.S. Environmental Protection Agency, 1991b), which summarized ambient monitoring data through 1988, six stations in six major cities, with prominent patterns of 8-h exceedances, were selected to demonstrate the variability in the circadian patterns of exceedances using the above technique; some peaked in daylight hours and 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 No.	1988	1996	1997	1997 data completeness
Lynwood, CA	06 037 1301	392	110	62	Jan-Dec/97
Hawthorne, CA	06 037 5001	163	19	2	Jan-Dec/97
Las Vegas, NV	32 003 0557	102	3	0	Jan-Mar/97
New York City, NY	36 061 0081	123	NA ^a	0	Jan-June, Oct-Dec/97
Steubenville, OH	39 081 1012	152	0	0	Jan-Sep/97
Spokane, WA	53 063 0040	169	1	0	Jan-Dec/97

^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 indeterminant.

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

At the Lynwood station, the running-average exceedances have declined from 392 in 1988 to 110 in 1996 (22 nonoverlapping exceedances); the majority of exceedances in 1996 occurred in the hours between midnight and sunrise, as they had in 1988. They occurred in the months of January, February, November, and December.

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

Only a small number of stations have several running-average exceedances; however, these recurrent high levels are attributed to unusual local situations. A prime example is the

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

^aCalibrations normally are done at 4 a.m., thus values are interpolated.

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 cities in the continental United States (New York, NY; Denver, CO; Phoenix, AZ; and Los Angeles, CA) and results will be reported for Fairbanks, AK, as they become available. These five cities 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 United States has been the locations of studies either characterizing personal exposure to CO or relating health outcomes to air pollution levels.

Hourly average CO data obtained from EPA's AIRS were used to calculate running 8-h averages for 1986 to 1996. Only valid hourly average values were used to compose the 8-h average. In the case that less than six valid hourly average values were used to compose the 8-h average, the 8-h average was set to a missing value. The six valid hourly average values in an 8-h window corresponds to 75% data capture in the 8-h window.

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

1 A map of Denver showing the locations of CO monitoring sites is given in Figure 3-8. The
2 average diurnal variation in CO concentrations at the Denver-Broadway site during the winter
3 months of November through February for the period 1986 through 1995 is given in Figure 3-9.
4 The monthly average diurnal variation in CO at this site for weekdays from May 1986 through
5 May 1987 is shown in Figure 3-10, whereas the same quantity for the period 1995 to 1996 is
6 shown in Figure 3-11. Central tendency statistics for the daily 8-h max CO concentration for the
7 winter season from 1986 to 1995 at the Broadway site are given in Figure 3-12.

8 A map of Los Angeles showing the locations of CO monitoring sites is shown in
9 Figure 3-13. The average diurnal variation in CO concentrations at the Los Angeles-Lynwood
10 site during the winter months of November through February for the period 1986 through 1995 is
11 given in Figure 3-14. Central tendency statistics for the daily 8-h max CO concentration for the
12 winter season from 1986 to 1995 at the Broadway site are given in Figure 3-15 and for the
13 Los Angeles-Barstow site are given in Figure 3-16. The average diurnal variation in CO
14 concentrations at the Los Angeles-Hawthorne site during the winter months of November
15 through February for the period 1986 through 1995 is given in Figure 3-17 and for the
16 Los Angeles-El Toro site in Figure 3-18. The monthly average diurnal variation at the
17 Los Angeles-Anaheim site from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993,
18 and 1995 to 1996 is shown in Figure 3-19.

19 A map of the New York Metropolitan area showing the locations of CO monitoring sites is
20 given in Figure 3-20. The monthly average diurnal variation at the New York-Flatbush site from
21 May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996 is shown in
22 Figure 3-21. The average diurnal variation in CO concentrations at the New York-Manhattan
23 site during the winter months of November through February for the period 1986 through 1995 is
24 given in Figure 3-22. The monthly average diurnal variation at the New York-Manhattan site
25 from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996 is shown in
26 Figure 3-23 and for the New York-Morristown, NJ, site in Figure 3-24.

27 A map of Phoenix showing the locations of CO monitoring sites is given in Figure 3-25.
28 The monthly average diurnal variation at the Los Angeles-Anaheim site from May through May
29 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996 is shown in Figure 3-26. Central
30 tendency statistics for the daily 8-h max CO concentration for the winter season from 1986 to
31 1995 at the east Butler site are given in Figure 3-27. The monthly average diurnal variation at the

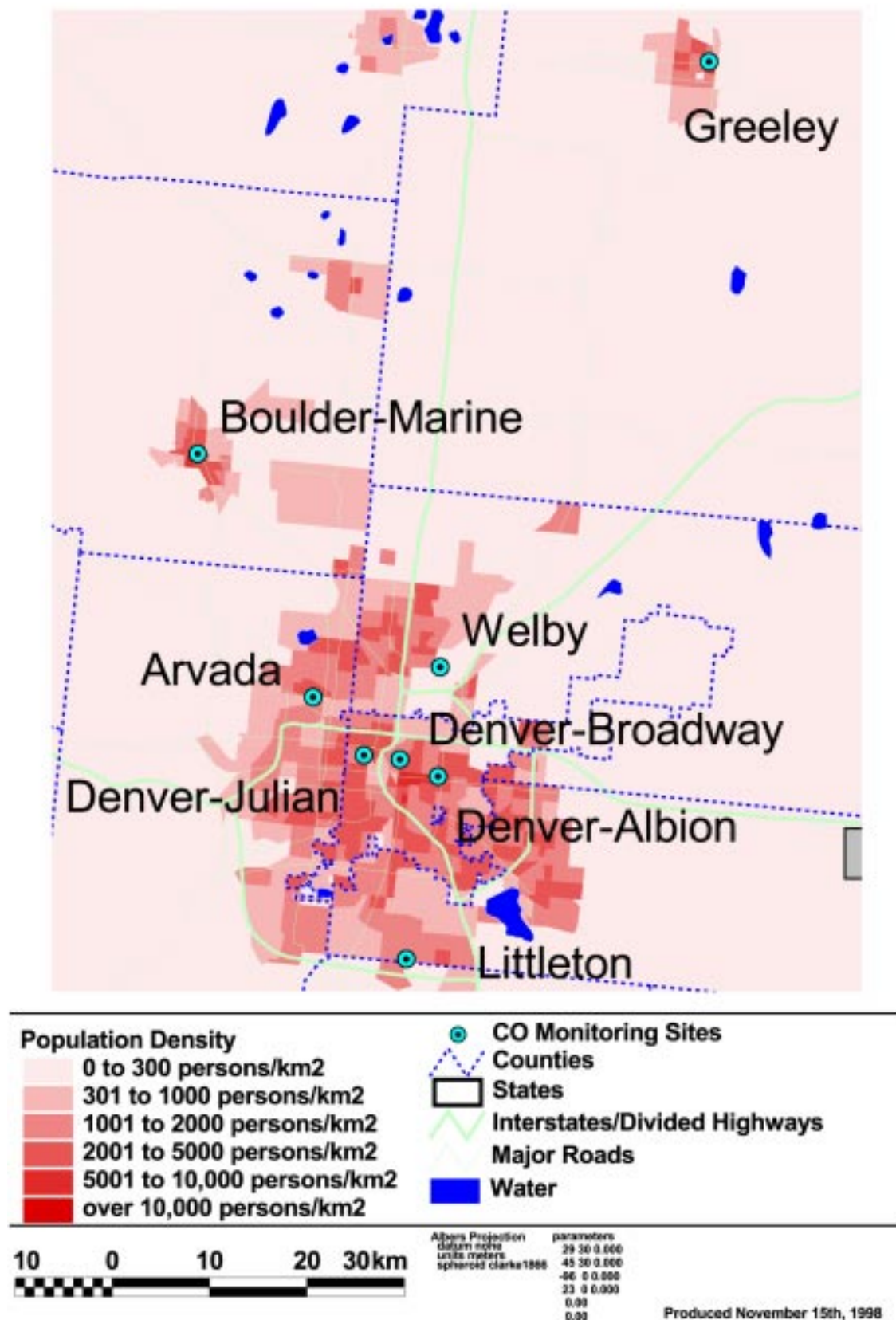


Figure 3-8. Map of Denver showing locations of CO monitoring sites.

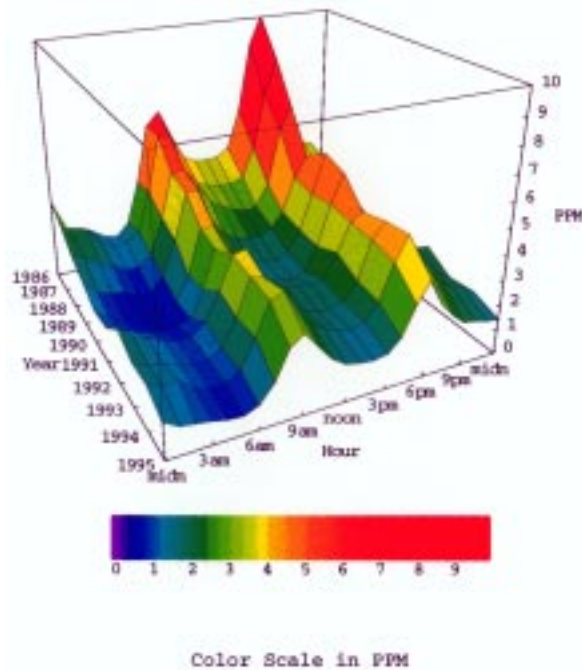


Figure 3-9. Average diurnal variation in CO at the Denver-Broadway site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986/87 through 1995/96, and the z-axis shows CO concentration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

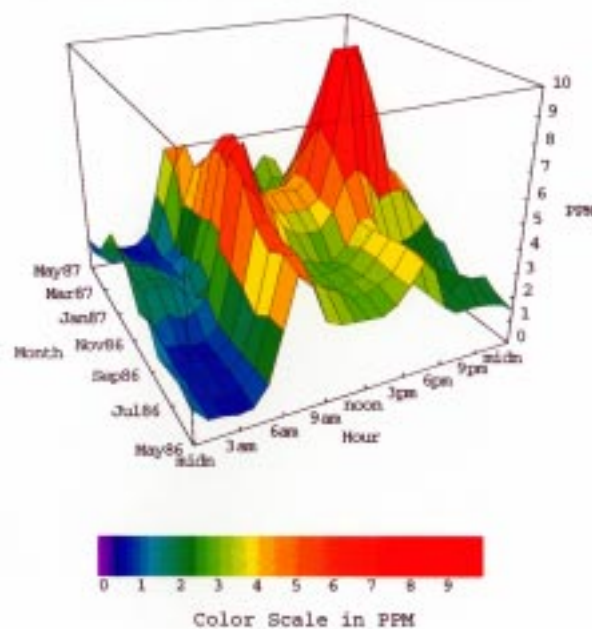


Figure 3-10. Monthly average diurnal variation in CO at the Denver-Broadway site for weekdays from May 1986 through May 1987. The abscissa shows the time of day, the ordinate shows the month of the year, and the z-axis shows CO concentration in ppm.

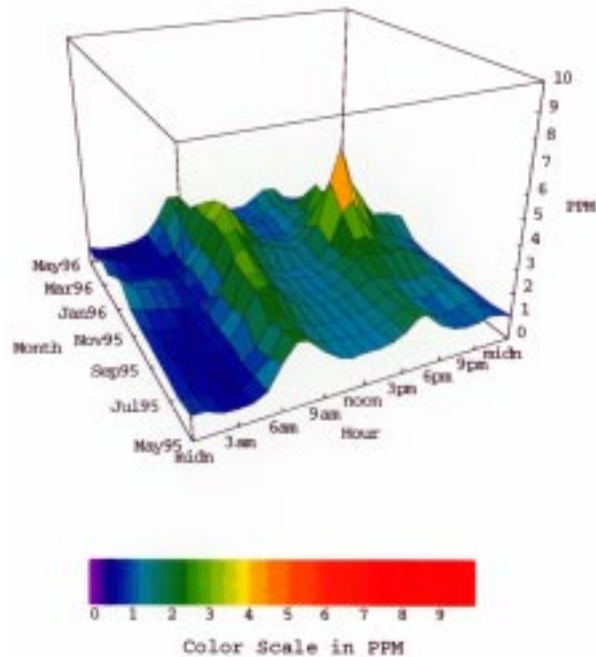


Figure 3-11. Monthly average diurnal variation in CO at the Denver-Broadway site for weekdays from May 1995 through May 1996. The abscissa shows the time of day, the ordinate shows the month of the year, and the z-axis shows CO concentration in ppm.

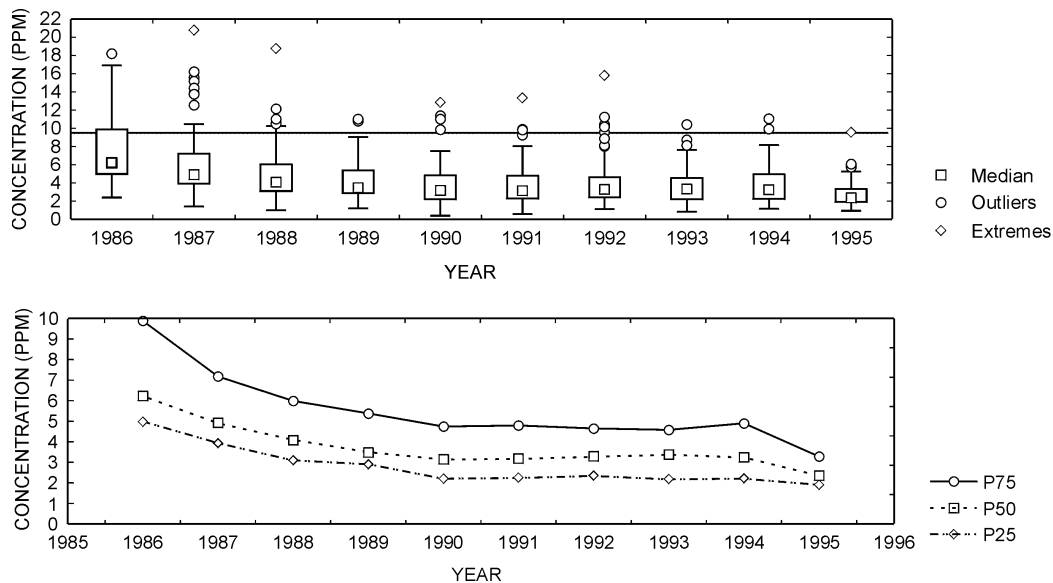


Figure 3-12. Central tendency statistics for the daily 8-h max CO concentration at the Denver-Broadway site during the winter season from 1986 to 1995. The top graph shows box plots (with 10, 25, 50, 75, and 90 percentile values) for the entire time series. Each circle (outlier) or diamond (extreme)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

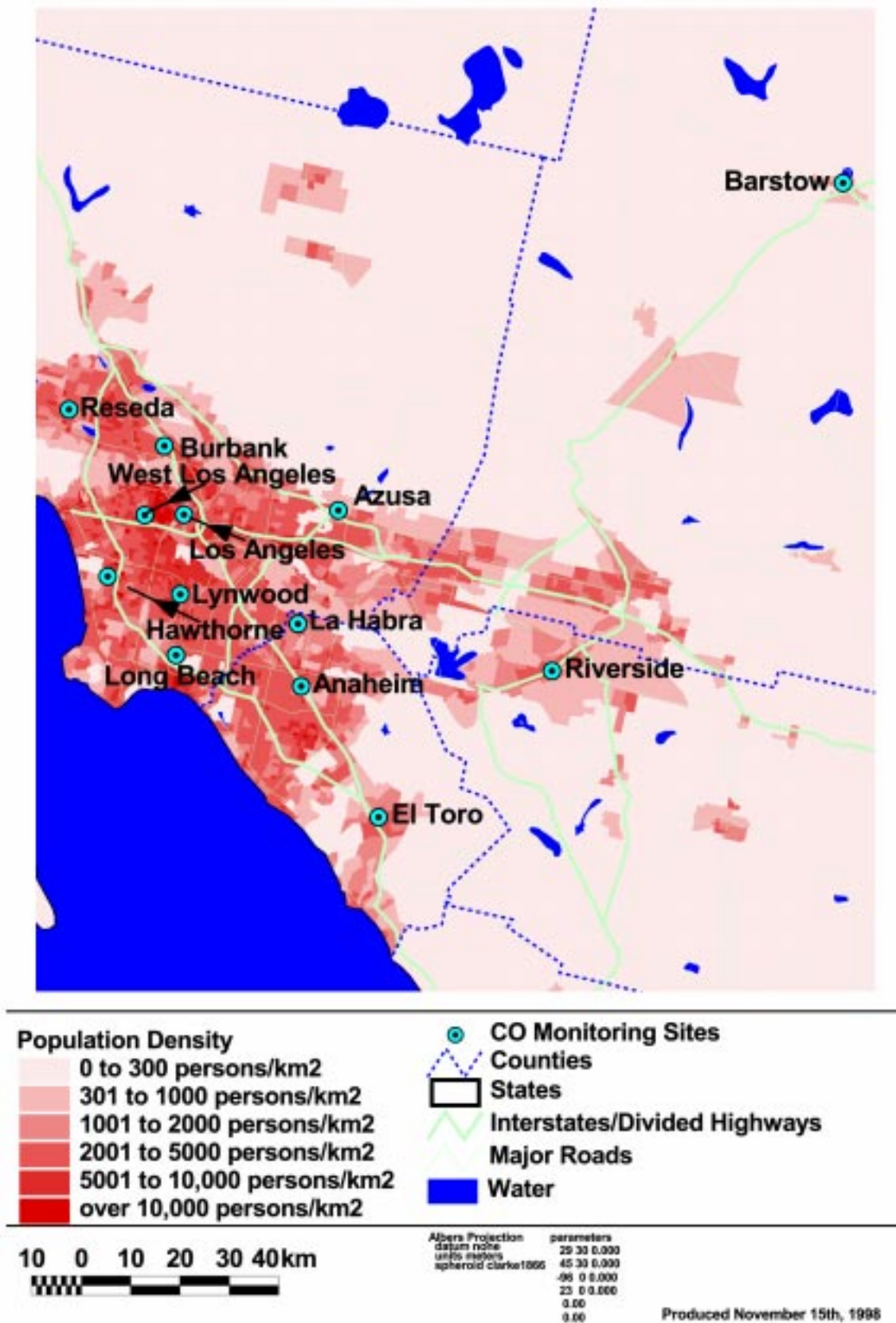


Figure 3-13. Map of Los Angeles showing locations of CO monitoring sites.

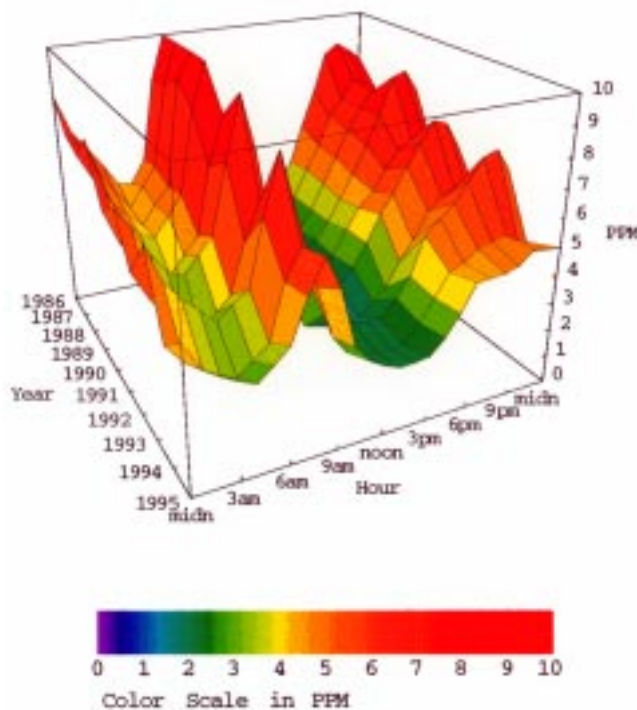


Figure 3-14. Average diurnal variation in CO at the Los Angeles-Lynwood site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986/87 through 1995/96, and the z-axis shows CO concentration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

Phoenix-West site from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996 is shown in Figure 3-28 and at the Phoenix-South site in Figure 3-29.

Analysis of ambient CO data obtained in the four geographically diverse metropolitan statistical areas of Denver, Los Angeles, New York, and Phoenix has shown that urban CO levels have decreased over the past 10 years. However, there have been instances where the downward trend has reversed itself on a year-to-year basis. Although the number of violation days has declined for these cities, and the seasonally averaged peak concentrations generally do not exceed 8 ppm, at least one exceedance of 9 ppm for the maximum daily 8-h average for CO has occurred in 1995/1996 (the final year in this analysis) in all four of these cities.

Data obtained from different monitoring sites within a given MSA show a large degree of variability. During 1996, for example, annual mean CO concentrations ranged from 0.4 to

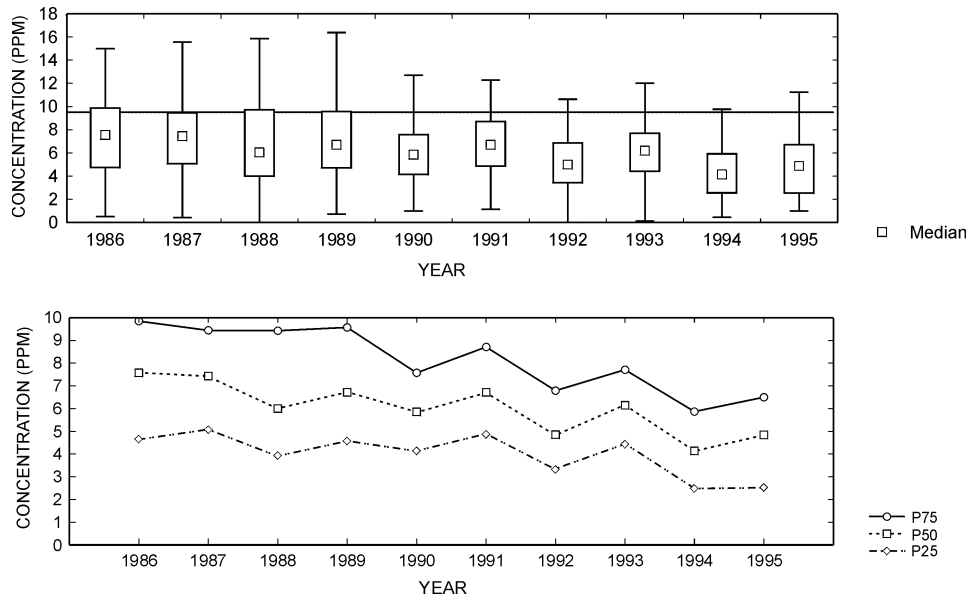


Figure 3-15. Central tendency statistics for the daily 8-h max CO concentration at the Los Angeles-Hawthorne site during the winter season from 1986 to 1995. The top graph shows box plots (with 10, 25, 50, 75, and 90 percentile values) for the entire time series. The horizontal line shows the current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

1 1.5 ppm in the Denver MSA, 0.4 to 3.2 ppm in the Los Angeles CMSA, 0.6 to 3.7 in the New
2 York CMSA, and 0.7 to 3.4 in the Phoenix MSA. Carbon monoxide concentrations during the
3 cold season (November through February) range from 5 to 20% higher than the annual average in
4 each MSA. However, it should be noted that, despite decreasing CO concentrations, the nature
5 of the diurnal and seasonal variation observed at each monitoring site has remained remarkably
6 constant over the 10-year period covered in this analysis. At all the sites investigated here, it is
7 clear that the diurnal and seasonal variations in CO observed in these MSAs result largely from
8 the interaction between motor vehicle emissions and meteorological parameters that, at times,
9 can be conducive to the buildup of CO near the surface. The diurnal concentration profiles in
10 most cases show a very distinctive two-peaked structure for weekdays. The peaks correspond to
11 both the morning and evening rush hour commutes. Frequently, the morning peak is higher than
12 the evening peak at any given site because the height of the mixed layer is much lower during the
13 morning, thus inhibiting vertical mixing that would have diluted CO. In the late afternoon and

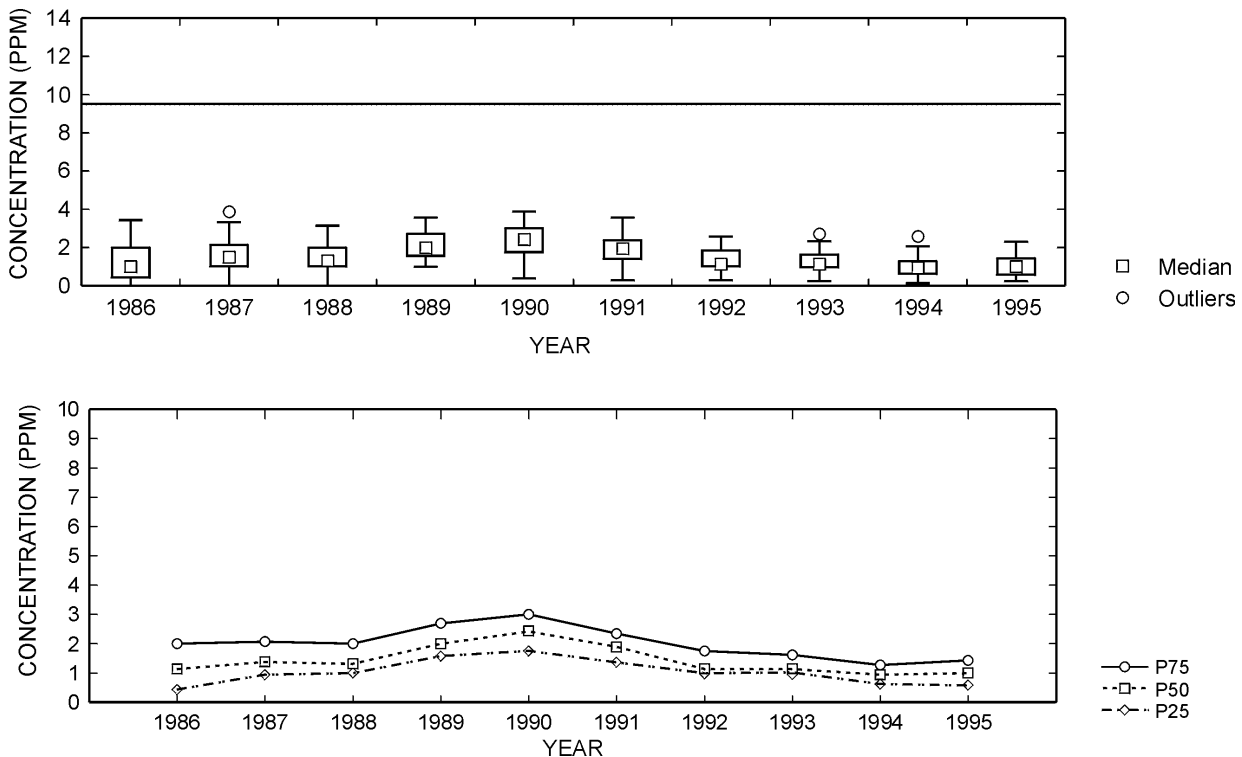


Figure 3-16. Central tendency statistics for the daily 8-h max CO concentration at the Los Angeles-Barstow site during the winter season from 1986 to 1995. The top graph shows box plots (with 10, 25, 50, 75, and 90 percentile values) for the entire time series. Each circle (outlier) refers to an individual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

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 3-13 or other locations, such as the Denver or New York MSAs. In the Los Angeles and Phoenix metropolitan areas CO concentrations often remain until midnight at levels reached during the evening rush hour. Then, although these concentrations gradually diminish

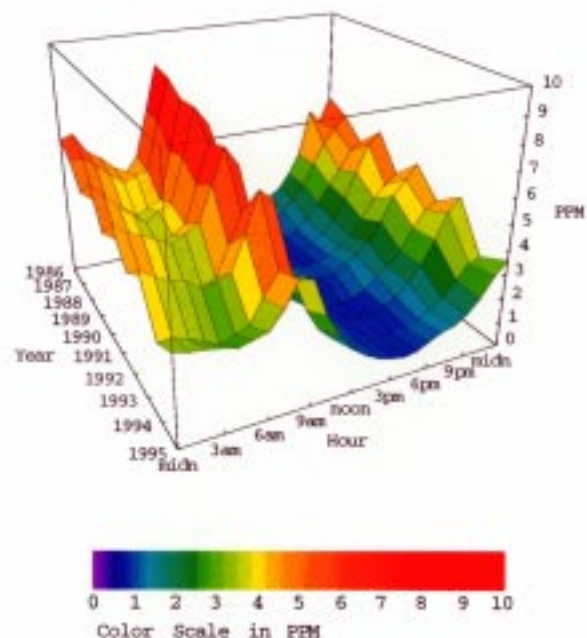


Figure 3-17. Average diurnal variation in CO at the Los Angeles-Hawthorne site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986/87 through 1995/96, and the z-axis shows CO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

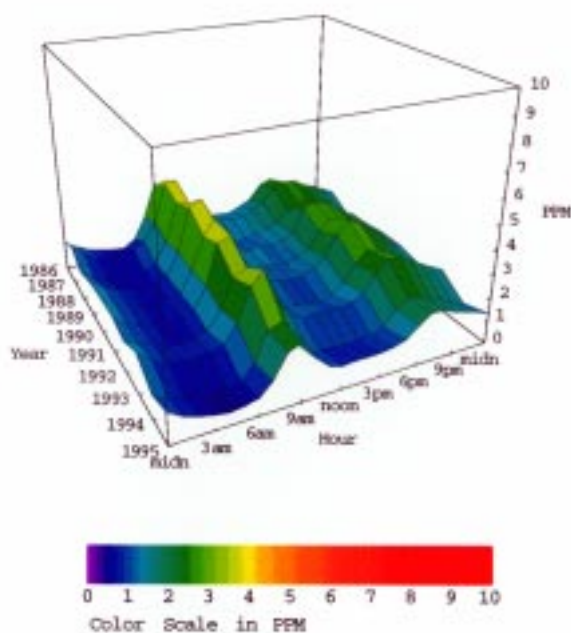


Figure 3-18. Average diurnal variation in CO at the Los Angeles-El Toro site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986/87 through 1995/96, and the z-axis shows CO concentration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

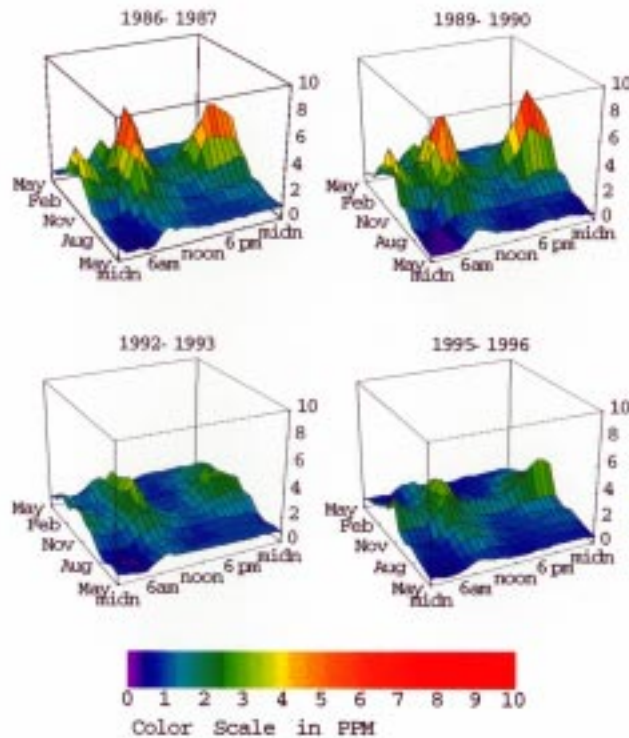


Figure 3-19. Monthly average diurnal variation in CO at the Los Angeles-Anaheim site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and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

throughout the night, they do not drop to the low afternoon levels (typically no more than 1 to 2 ppm, often less than this amount) before they begin to increase again because of the morning rush hour. This pattern is shown quite well in Figure 3-26, which depicts the seasonal, diurnal concentration profile for the Central Phoenix site.

In general, the highest values of ambient CO were found during the wintertime (defined as the months of November through February, inclusive) in all of the MSAs included here. There were a few sites in the New York Metropolitan Area where a wintertime peak in CO was not discernable; the site on Flatbush Avenue in Brooklyn (Figure 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.

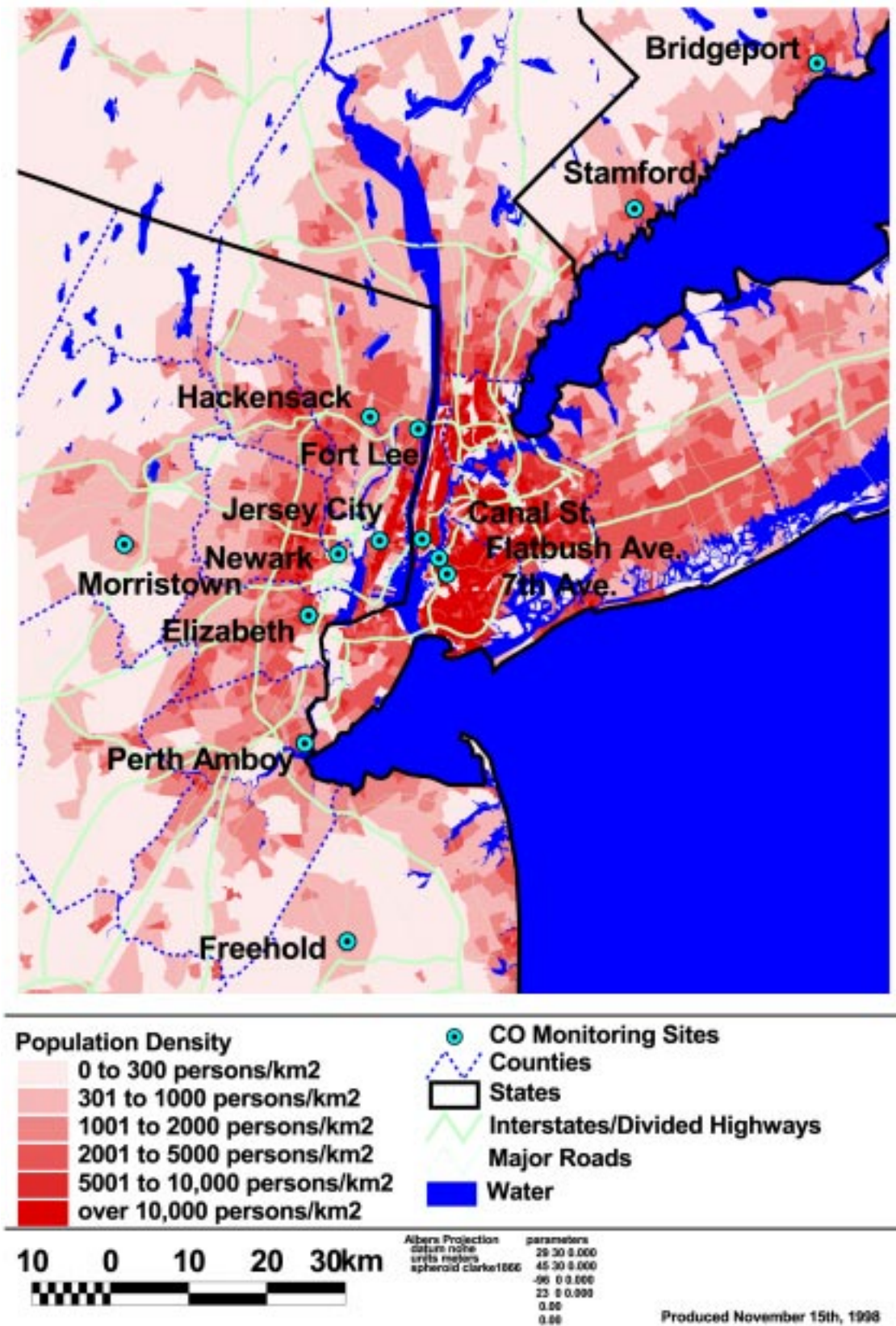


Figure 3-20. Map of New York showing locations of CO monitoring sites.

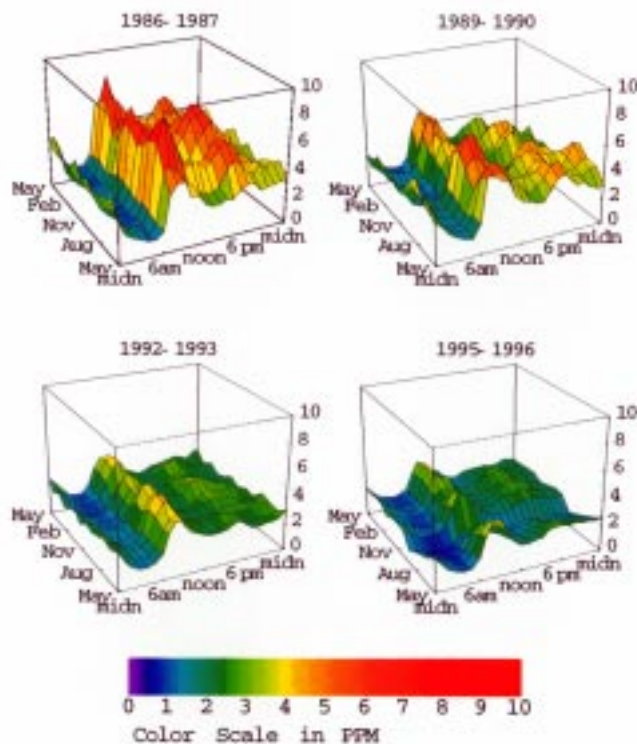


Figure 3-21. Monthly average diurnal variation in CO at the New York-Flatbush site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the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

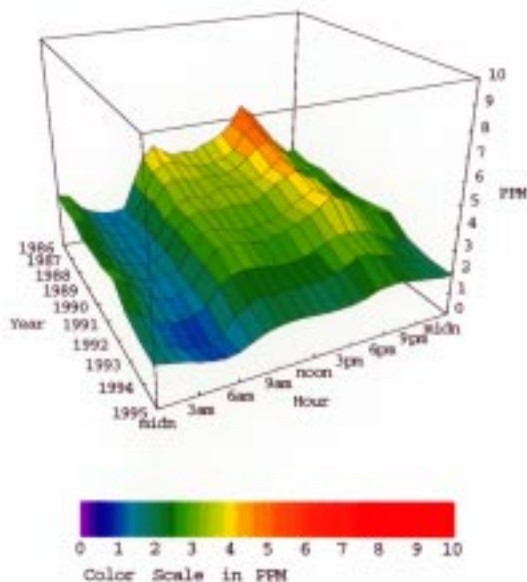


Figure 3-22. Average diurnal variation in CO at the New York-Manhattan site for weekdays during the winter season (November through February). The abscissa shows the time of day from midnight to midnight, the ordinate shows years from the winter of 1986/87 through 1995/96, and the z-axis shows CO concentration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

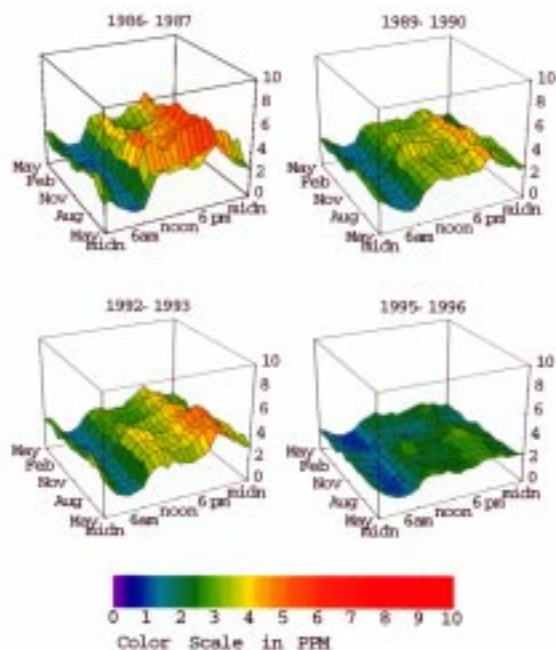


Figure 3-23. Monthly average diurnal variation in CO at the New York-Manhattan site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and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

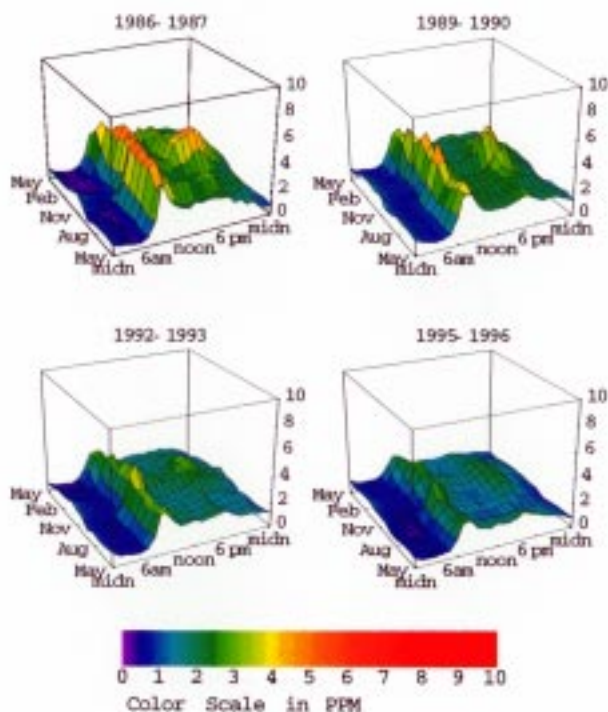


Figure 3-24. Monthly average diurnal variation in CO at the New York-Morristown, NJ, site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year,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

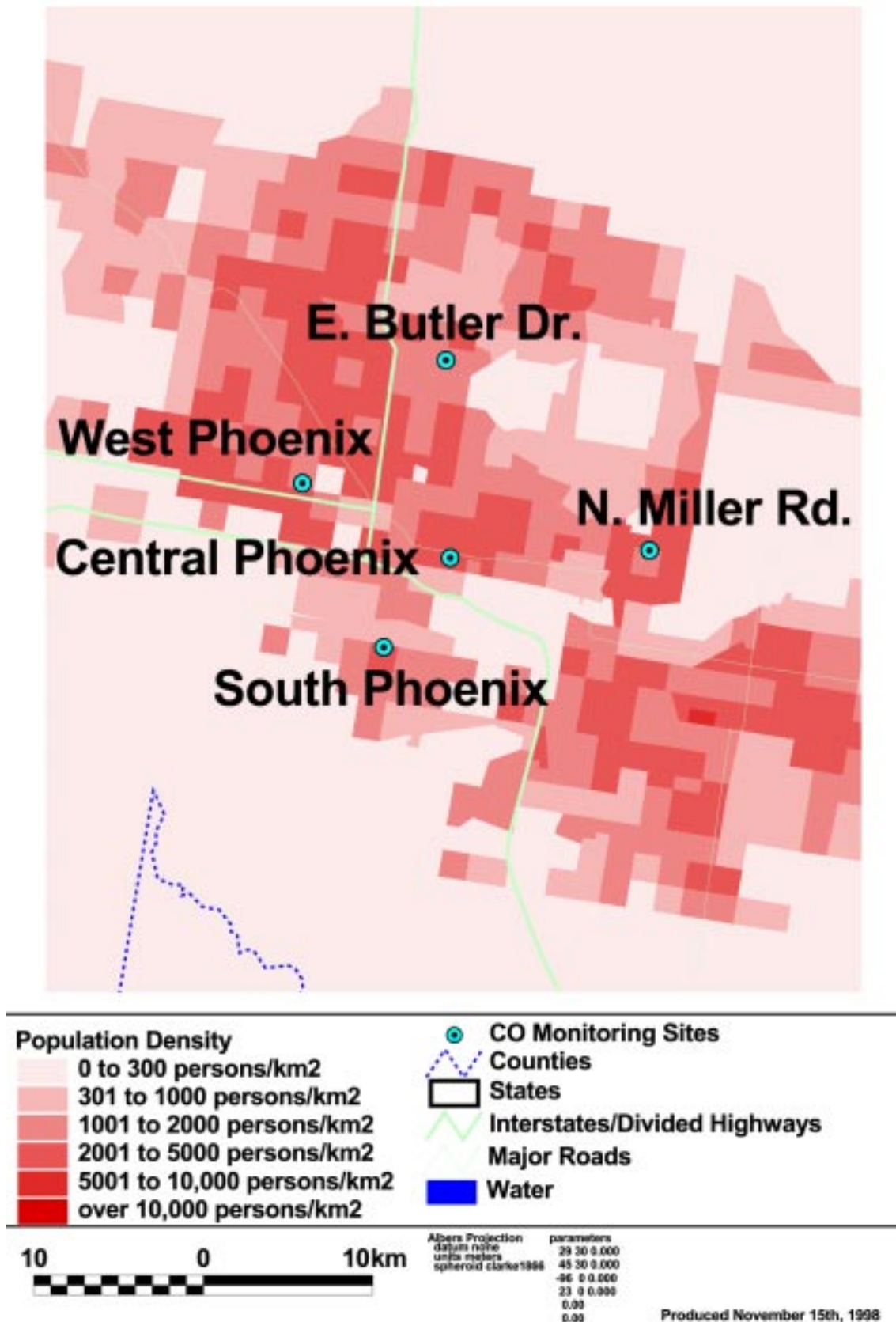


Figure 3-25. Map of Phoenix showing locations of CO monitoring sites.

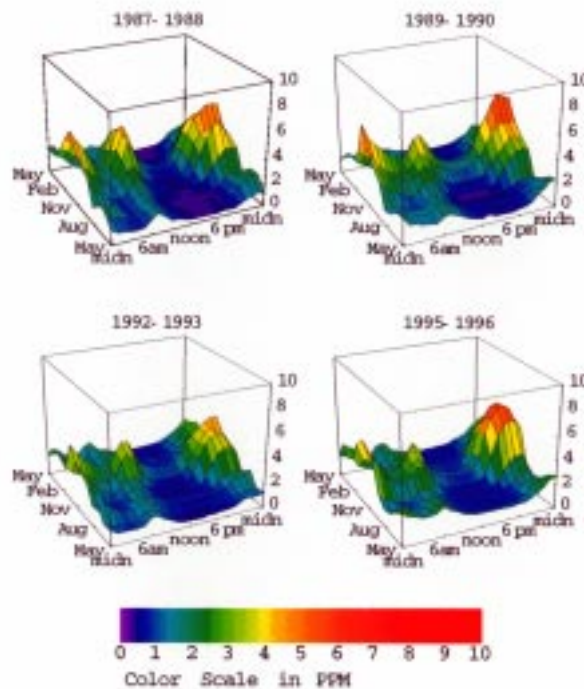


Figure 3-26. Monthly average diurnal variation in CO at the Phoenix-Central site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the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

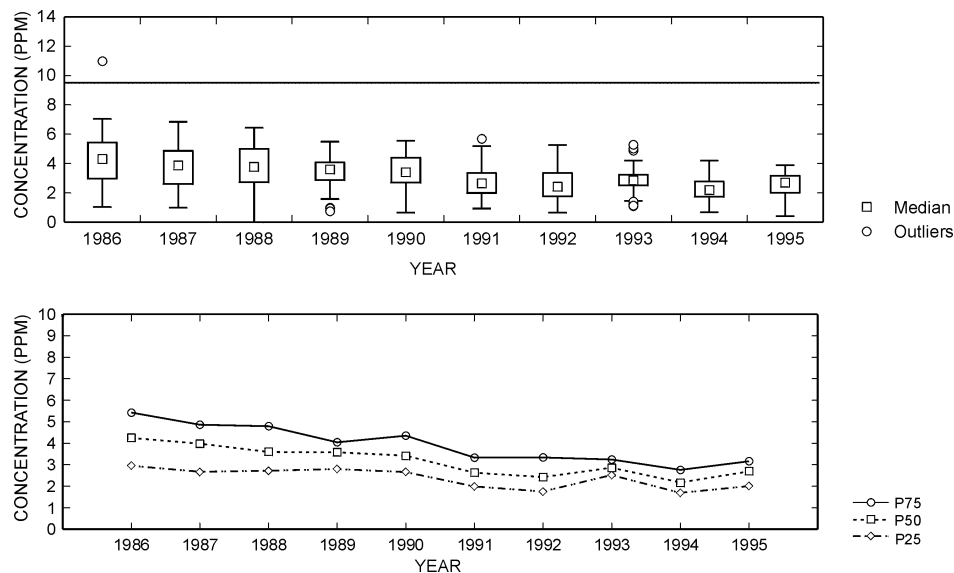


Figure 3-27. Central tendency statistics for the daily 8-h max CO concentration at the Phoenix-East Butler site during the winter season from 1986 to 1995. The top graph shows box plots (with 10, 25, 50, 75, and 90 percentile values) for the entire time series. Each circle (outlier) refers to an individual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

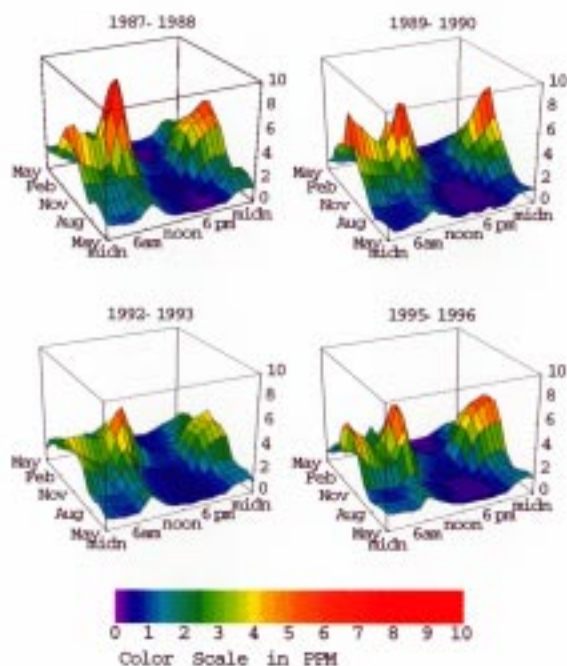


Figure 3-28. Monthly average diurnal variation in CO at the Phoenix-West site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis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

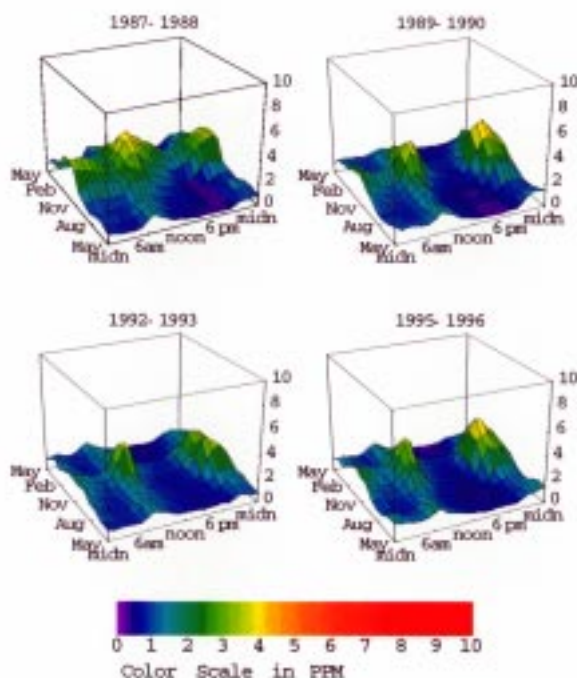


Figure 3-29. Monthly average diurnal variation in CO at the Phoenix-South site for weekdays from May through May 1986 to 1987, 1989 to 1990, 1992 to 1993, and 1995 to 1996. On each graph, the abscissa shows the time of day from midnight to midnight, the ordinate shows the month of the year, and the z-axis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

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

The general United States population spends up to 95% of its time indoors. In recent years, more emphasis has been placed on the evaluation of pollutant sources, emissions, and concentrations in indoor environments to aid in the evaluation of total human exposure. It is particularly important to evaluate carbon monoxide concentrations in indoor environments because indoor exposure may represent a significant portion of the total CO exposure.

The following sections focus on the sources and emission rates of CO in indoor environments. Concentrations of CO in various indoor environments also will be discussed. Emphasis is placed on the evaluation of manufacturer recommended uses of combustion appliances and consumer products and the resulting CO emissions and concentrations. Accidental sources and concentrations will be mentioned only briefly. This section will only summarize those studies discussed in the previous criteria document. The reader is referred to the 1991 Air Quality Criteria for Carbon Monoxide (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, cigarette combustion, woodburning stoves, and automotive vehicles 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 gas cooking stoves were highly variable among burners on a single gas cooking range and between gas stoves. Improperly adjusted gas stoves (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 contribute a negligible amount of CO to the indoor environment.

Carbon monoxide emissions from unvented gas and kerosene space heaters were also 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 versus

convective and catalytic unvented gas units. For unvented kerosene space heaters, emissions were higher for the radiant heaters.

Limited information was available on CO emissions from woodburning stoves. However, nonairtight woodburning stoves can contribute substantial amounts of CO into the indoor environment. Carbon monoxide from cigarette combustion showed little variability among the different brands, but could also 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.

3.5.2 Unvented Combustion Sources and Estimated Emissions Rates

Carbon monoxide occurs in indoor environments directly through emissions from various indoor combustion sources or indirectly as a result of infiltration or ventilation from outdoor sources. Unvented, partially vented, and improperly vented combustion appliances and consumer products represent the primary sources of CO emissions in the indoor environment. Table 3-8 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.

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

3.5.2.1 Gas Cooking Ranges and 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. Average annual household fuel consumption has been estimated at 5,000 ft³ for ranges with standing pilots (Johnson et al., 1992). Menkedick et al. (1993) reported annual household fuel consumption of 2,180 ft³ (± 890 ft³) 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 ft³ ($\pm 1,830$ ft³). The average fuel consumption was also affected by the age of

**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 (ms + ss) ^d	National Research Council (1986) Rickert et al. (1984)

^aNG = natural gas, P = propane.

^bOne kJ (kiloJoule) is the equivalent of 3.485 ft³ of natural gas.

^cFuel consumption rates not provided for most studies.

^dms + ss = mainstream and sidestream smoke.

the occupants (older adults used the range more frequently for preparing meals than did young adults) and the presence or absence of a standing pilot, and showed a seasonal trend. A recent study by Spicer and Billick (1996) evaluated CO emissions from a gas 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 older gas ranges with standing pilot lights (Billick et al., 1994, 1996). Study details are included in the section on indoor concentrations.

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

**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.

3.5.2.2 Emissions from Unvented Space Heaters

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

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 test house in Chicago, IL. The house was a 1-story, 3-bedroom with a full basement, single-family dwelling. Total square footage was 2,300 sq ft. Eight burner experiments and three pilot light

experiments were conducted. Heaters were (1) 10,000 BTU-h blue-flame convective, (2) 15,000 BTU-h (max.) radiant-tile (infrared), (3) 14,000 BTU-h (max.) fan-forced blue-flame convective, and (4) 16,000 BTU-h perforated-tube convective heaters. 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 7.9 $\mu\text{g}/\text{BTU}$ for fan-forced models to 182.1 $\mu\text{g}/\text{BTU}$ for the perforated tube (CO emissions enhanced by leaky gas pressure regulating valve) and 57.9 $\mu\text{g}/\text{BTU}$ for the infrared unit. Carbon monoxide concentrations in the test house are discussed in the section addressing CO concentrations associated with indoor sources. Spicer and Billick (1996) reported CO emissions indexes of 19.1 and 28.7 $\mu\text{g}/\text{kJ}$ for a convective blue-flame space heater. An emission index of 44.1 $\mu\text{g}/\text{kJ}$ 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, kerosene lamp, an oil lamp, and several candles. The fuel used for the portable gas stove was butane and 1-K grade kerosene was used in the kerosene space heater. 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. The test for the portable stove and the kerosene heater was conducted in a room with a volume of 19 m³. Both the lamp tests and the candle tests were conducted in a 0.15 m³ chamber. 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 emission rates for the portable gas stove and kerosene heater were 33.6 ± 15.0 and 226.7 ± 100 mg/h, respectively. 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. The height of the wick did not affect the emission of CO from either the kerosene lamp or the oil lamp. Several recent studies on CO emissions evaluated emissions from prototype units; a brief discussion of the results of these studies follows.

The Gas Research Institute evaluated the emissions of CO, NO, NO₂, and unburned hydrocarbons (UHC) from a vented and an unvented prototype space heater. The heater design was a Pyrocore ceramic fiber radiant burner. Emission goals were 5.5 $\mu\text{g}/\text{kJ}$ (20 ppm) CO, 4.0 $\mu\text{g}/\text{kJ}$ (13.5 ppm) NO, 0.7 $\mu\text{g}/\text{kJ}$ (1.5 ppm) NO₂, and 0.8 $\mu\text{g}/\text{kJ}$ (5.0 ppm) UHC. Both units had cross-flow room air circulation fans. The samples collected from the unvented space heater were corrected for dilution effects. Emission rates were estimated using a single-equation

1 mass-balance model. Carbon monoxide emissions ranged from 0.6 to $>27.5 \mu\text{g/kJ}$ (2.0 to
2 >100 ppm), based on the amount of excess air and the firing rate values (Duret and Tidball,
3 1990).

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

8 The Institute of Gas Technology, along with Maxon Corporation, designed and tested an air
9 heater based on the cyclonic combustion concept. This technology included premixed high-
10 excess air, and cyclonic combustion with flame stabilization, in conjunction with optimized
11 nozzle velocity control. Carbon monoxide emissions were 1.6 to $5.9 \mu\text{g/kJ}$ (1.0 to 3.6 ppm at
12 15% O_2) (Xiong et al., 1991).

14 **3.5.2.3 Woodstoves and Fireplaces**

15 A few studies have evaluated the emission of CO from woodstove or fireplace use. Carbon
16 monoxide may enter the indoor environment during fire start-up and tending and through leaks in
17 the stove or venting system. Carbon monoxide emissions are higher during the first stage of a
18 fire because of increasing amounts of fuel being burned and inadequate temperature conditions.
19 Such intermittent emissions makes it difficult to accurately determine CO emission rates.
20 Mueller Associates (1985) reported CO emission ranges of 0.07 to 0.375 g/h for wood heaters.
21 Jaasma et al. (1995) conducted a study designed to evaluate the effectiveness of custom-built
22 glass doors for fireplaces in reducing CO emissions under conditions of negative pressure. The
23 glass doors decreased spillage of CO; however, decreasing the leakiness of the glass doors did
24 not always reduce CO spillage. Tests with the glass doors closed had CO emission rates of 2 to
25 36 g/h (highest levels represented leaking glass doors). Carbon monoxide emissions on the order
26 of 70 g/h were noted for glass-door-opened tests under negative pressure.

27 Carbon monoxide also may enter the indoor environment through backdrafting when the
28 natural draft is overcome by depressurization. Depressurization generally occurs during fire
29 start-up, but also may occur during operation of other equipment such as kitchen and bathroom
30 exhaust fans and clothes dryers. Nagda et al. (1996) summarized the results of several studies on
31 emissions of pollutants into living compartments as a result of house depressurization. Carbon

monoxide emissions were found to be insignificant. Tiegs and Bighouse (1994) evaluated CO spillage from a woodstove under chamber and in-house conditions. They reported CO leakage into the indoor environment by nonairtight woodstoves during conditions of negative pressure.

3.5.2.4 Environmental Tobacco Smoke

Carbon monoxide emissions from the combustion of tobacco occurs in the indoor environment when smokers exhale the inhaled or mainstream smoke (ms) and from the emission of sidestream smoke (ss) from smoldering tobacco products. The majority of the CO emissions are from sidestream smoke. Ott et al. (1992) reported a sidestream-to-mainstream ratio of ≈ 3 . The amount of CO emitted will vary based on the type of tobacco product (cigarette/cigar), the degree to which tobacco is actively smoked, and the amount of smoke being absorbed by the lungs (Klepeis et al., 1996; Akbar-Khanzadeh and Greco, 1996).

The Federal Trade Commission compiled data on 933 varieties of cigarette manufactured and sold in the United States in 1992. These data were provided by the various cigarette manufacturers. Carbon monoxide emission rates for the brands of cigarettes reported ranged from <0.5 to 23.0 mg per cigarette (cigarettes emitting 23.0 mg were unfiltered brands) (Federal Trade Commission, 1994). Klepeis et al. (1995, 1996) measured CO concentrations in airport smoking lounges under real life conditions. They estimated CO emissions to be 78 mg per cigarette (ms and ss) 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 (ms and ss) was reported by Ott et al. (1992). Löfroth et al. (1989) estimated a CO emission rate of 67 mg per cigarette (ss) 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; ms and ss) 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 for 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 or 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 (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 expect to exhibit 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 were also generally higher than unvented kerosene heaters and gas cooking stoves (Koontz and Nagda, 1987; Research Triangle Institute, 1990; Leaderer et al., 1984; Davidson et al., 1987).

Indoor concentrations of CO from the use of nonairtight woodburning stoves can contribute as much as 9 ppm to the average indoor CO level (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 (mechanical ventilation) and 41 ppm (natural ventilation) have been measured in automobiles (Harke and Peters, 1974). However, while 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. Information on the number of households using combustion appliances in the United States in 1995 appear in Table 3-9.

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

^aBased on 96,650,000 occupied housing units with heating fuel. Values in parenthesis represent use of fuel type as secondary heating fuel.

^bBased on 97,406,000 occupied housing units with cooking fuel.

^cBased on 46,577,000 occupied housing units with central air conditioning.

^dBased on 70,756,000 occupied housing units with central air conditioning.

^eBased on 97,522,000 occupied housing with hot piped water.

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

The major sources of CO in residential environments are unvented gas or kerosene appliances. 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 in households where gas cooking stoves have continuously burning pilots or are

1 used improperly as a primary or secondary source of heat. Koontz et al. (1992) reported the
2 results of a survey conducted in 1985 and 1991 designed to determine the prevalence of kitchen
3 fans and the factors affecting their use and the impact of other cooking appliances (i.e.,
4 microwave ovens, toaster ovens, hot plates) on the use of the range for cooking. The authors
5 reported a 27% increase in the use of gas ranges without standing pilot lights between 1985 and
6 1991 and a 20% reduction in the use of both electric and gas stoves for cooking. Ninety-five
7 percent of the households surveyed reported having another form of cooking appliance in
8 addition to the gas range, and, of this number, 55 to 65% reported using the stove less often.
9 There were, however, more people using a gas range for purposes of supplemental heating than
10 there were using electric ranges for that purpose (11% versus 3.6%). Estimates of gas cooking
11 stove usage range from 30 to 60 min/day. Table 3-10 contains information on the prevalence of
12 gas cooking stoves in the United States.

13 The use of unvented space heaters represent a significant source of CO in indoor
14 environments. Data from the National Health and Nutrition Examination Survey estimated that
15 13.7 million adults used unvented combustion space heaters between 1988 and 1994. Based on
16 the information obtained in the survey, an estimated 13.2% of the adult population in the
17 southern United States used unvented combustion space heaters. An estimated 5.9% of the adult
18 population in the Midwest, 4.2% in the Northeast, and 2.5% in the West used unvented space
19 heaters (Figure 3-30) (Slack and Heumann, 1997). The use of more unvented combustion space
20 heaters in the South also was reported in earlier studies by U.S. Department of Housing and
21 Urban Development (1987), U.S. Environmental Protection Agency (1992), and Williams et al.
22 (1992). This may be because in areas with relatively mild winters, combustion space heaters are
23 used frequently as the primary source of heat. The U.S. Census Bureau estimated that
24 1,055,000 and 1,159,000 households used kerosene or another liquid fuel as primary and
25 secondary heating fuels, respectively, in 1995 (U.S. Census Bureau, 1999). The U.S.
26 Environmental Protection Agency (1990) estimated that kerosene heaters are used 16.7 h/day in
27 southern states as primary sources of heat and, in regions where the heaters are used as secondary
28 heat sources, estimated use ranges from 2.6 to 10.7 h/day.

29 The AER, the balance of the flow of air in and out of a microenvironment, is based on the
30 fraction of air that enters the microenvironment through infiltration through unintentional
31 openings in the building envelope, natural ventilation through any designed opening in the

TABLE 3-10. PREVALENCE OF GAS COOKING RANGES

Fuel	Region	Number of Households (total)	Percentage of Households	Comments	Reference
Gas	U.S. households (1985)	929 (2,323)	41	Twenty percent of the 924 households had electronic pilots in 1985. Twenty-seven percent of the households had electronic pilots in 1991, based on 886 respondents from the 1985 survey.	Koontz et al. (1992)
Natural gas	U.S. households (1993)	33,813,000 (94,363,000)	36		U.S. Census Bureau (1998)
Natural gas	California (1991, 1992)	142 (293)	52	Fifty-two percent of the households examined used gas for cooking. Fifty-one percent of the households using gas cooking stoves had electronic pilots.	Wilson et al. (1993)
Natural gas	Los Angeles, CA (1995)	2,614,000 (3,165,200)	82		U.S. Census Bureau (1998)
	Denver, CO (1995)	151,300 (770,600)	20		
Natural gas	Washington, DC (1982-1983)	609,029 (953,714)	64	Results are estimates of the pollution using gas cooking stoves compared to the total population.	Johnson (1984) Hartwell et al. (1984)
	Denver, CO (1982-1983)	85,542 (345,163)	25		
Natural gas	U.S. households (1995)	35,001,000 (97,406,000)	40		U.S. Census (1999)

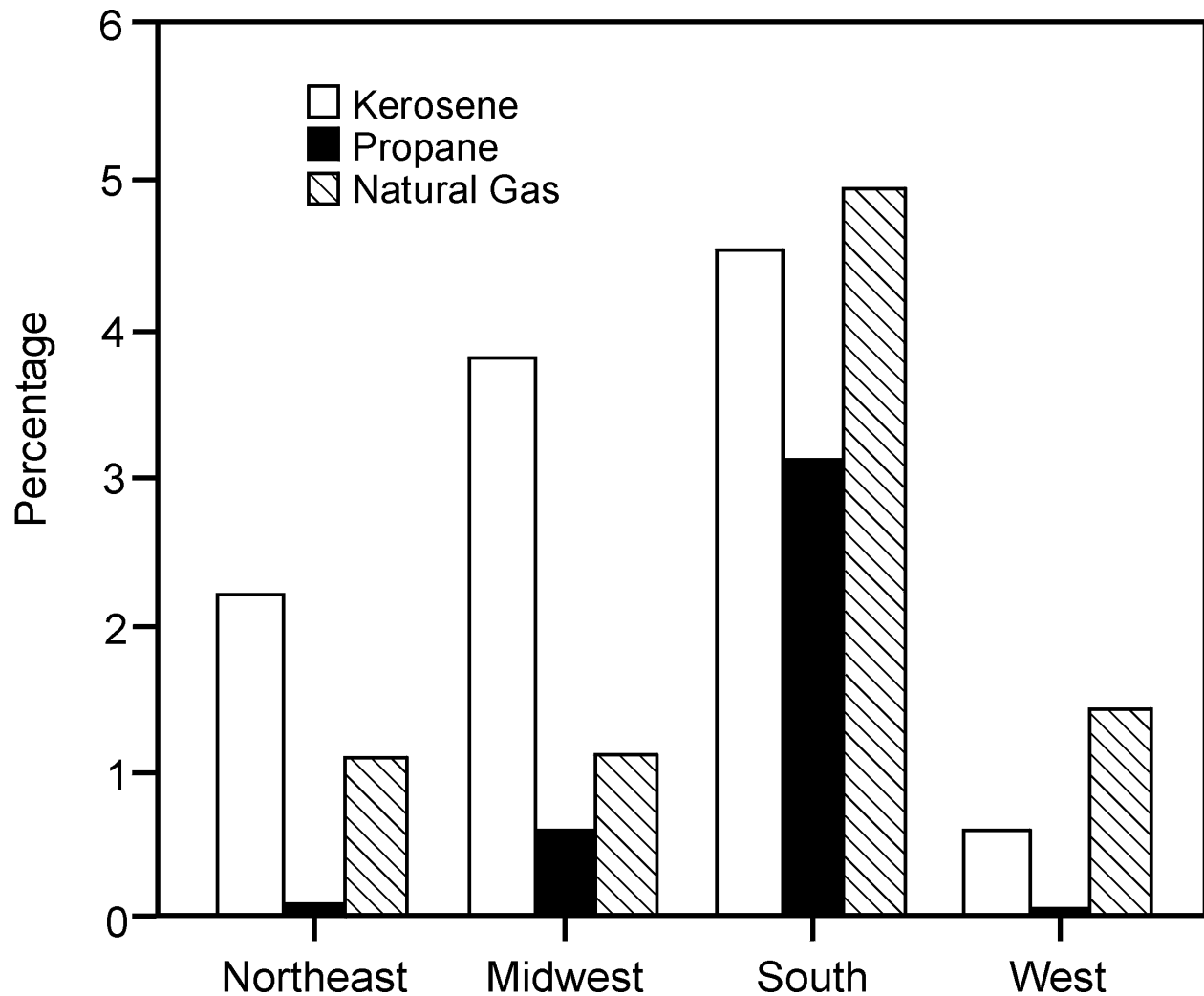


Figure 3-30. Percentage of U.S. households using unvented combustion heaters, by type of fuel, stratified by region (Third National Health and Nutrition Examination Survey, 1988 to 1994).

Source: Slack and Heumann (1997).

1 building envelope (doors, windows), and forced ventilation systems. Infiltration is the dominant
 2 mechanism for residential air exchange. Forced ventilation is typically the dominant mechanism
 3 for air exchange in nonresidential buildings. Natural ventilation, airflow through doors and
 4 opened windows, is seasonal (Koontz and Rector, 1995). Air exchange rates for some residential
 5 buildings are listed in Table 3-11. Air exchange rates varied depending on the outside

TABLE 3-11. RESIDENTIAL AIR EXCHANGE RATES

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

1 temperature, geographical location, type of cooking fuel used, type of heating system used, and
2 building type (Colome et al., 1994). Homes with gas cooking stoves with standing pilots and gas
3 wall furnaces had the highest AER. Homes with gas stoves without pilots had higher AER than
4 electric stoves. Also, homes with forced air furnaces had higher AER than electric homes.

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

$$\frac{dC_{IN}}{dt} = v C_{OUT} + \frac{S}{V} - v C_{IN} . \quad (3-1)$$

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 3-31). The findings illustrated in Figure 3-31 are for only a limited number of model runs, sources, and building conditions.

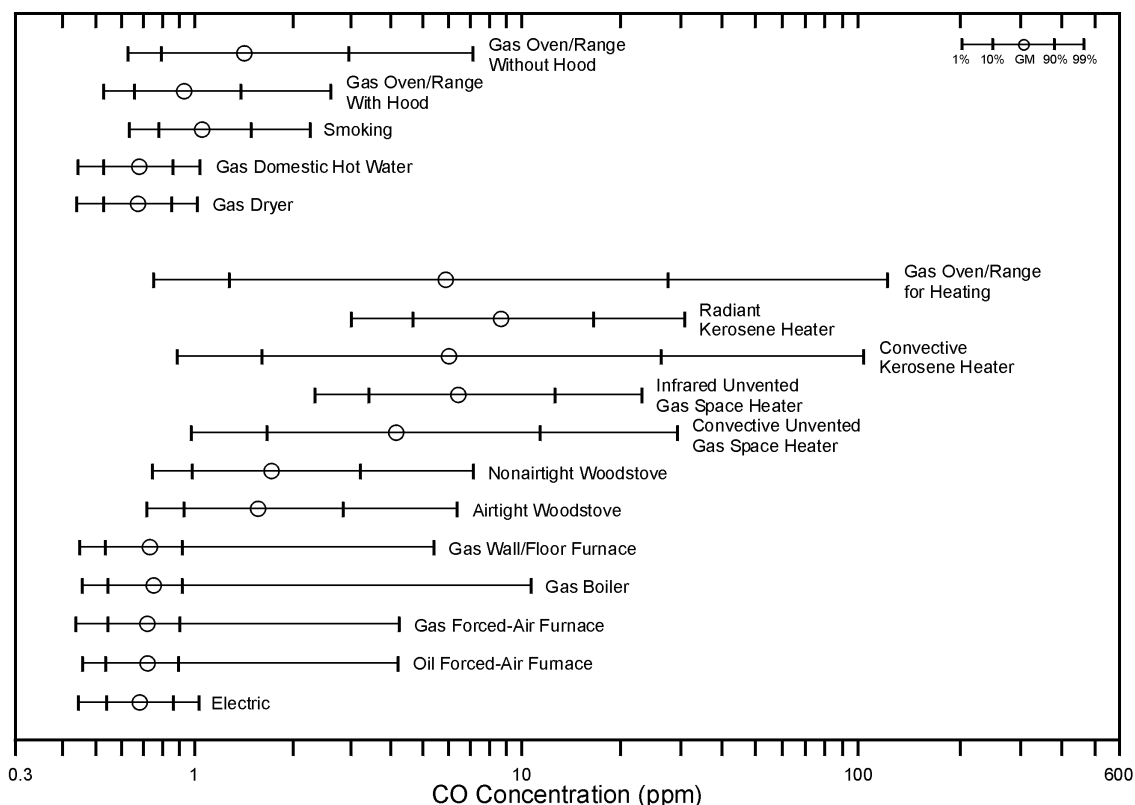


Figure 3-31. Modeled indoor CO concentration distributions in houses with only one indoor combustion pollutant source.

Source: Traynor et al. (1989).

3.5.4.3 Microenvironmental Monitoring Studies

Residential Carbon Monoxide Concentrations Related to Indoor Sources

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

1 The Gas Research Institute, Pacific Gas and Electric Company, San Diego Gas and Electric
2 Company, and Southern California Gas Company initiated indoor monitoring of 293 randomly
3 selected homes. Monitoring was for a single 48-h period. Carbon monoxide levels indoors were
4 reported to be closely associated with levels outdoors for most of the residences monitored.
5 However, 13 homes had CO concentrations above 9 ppm, and concentrations in one home
6 exceeded 35 ppm. Homes with gas ranges with standing pilot lights had higher CO
7 concentrations than did homes with gas ranges with electronic pilot lights or electric ranges.
8 Homes with standing pilots had a 0.56-ppm increase in net CO. Indoor minus outdoor CO
9 concentrations for six averaging times were used to rank homes. Using that criterion, 21 of the
10 293 homes studied were selected for case studies. The higher CO seen in these homes possibly
11 was associated with occupant smoking, the use of gas stoves for heating purposes, infiltration
12 from attached garages, the type of heating system used (homes with gas wall furnaces had higher
13 CO), the building type and size (smaller multi-family homes had higher CO than larger single-
14 family homes), use of gas appliances, and more than one CO source. The average AER varied by
15 type of heating system (wall furnaces > forced-air > electric) and building type (multi-family
16 units > single-family units) (Billick et al., 1994, 1996; Colome et al., 1994). The CO descriptive
17 statistics for homes in this study are given in Table 3-12.

18 The Research Triangle Institute (1990) monitored CO concentrations in 400 homes for
19 3 days in Suffolk and Onondaga Counties, NY. Homes in Suffolk County were monitored in
20 January and February. The selected homes in Onondaga County were monitored in February,
21 March, and April. The average room volume was assumed to be 50 m³. The average AER was
22 0.59 h⁻¹. Carbon monoxide monitors were placed in the primary living space and close to the
23 source. Approximately half of the homes used gas cooking stoves. Kerosene heaters had to be
24 operated at least 3 h/day to qualify as a CO source, and the woodstove or fireplace had to be
25 operated an average of 2 h/day. Any reported usage of gas stoves qualified them as sources. The
26 average CO concentration in the primary living area was 2.23 ± 0.17 ppm (results for
27 209 homes). Use of both gas stoves and kerosene space heaters was associated with increased
28 CO. Homes using woodstoves or fireplaces had lower CO than did homes without woodstoves
29 or fireplaces (see Figure 3-32). An explanation for the finding of higher CO in homes without
30 wood stoves and fireplaces was not provided. Lower CO levels may have been associated with
31 an increased air exchange rate. Also, CO emissions for the use of wood stoves and fireplaces are

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

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

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

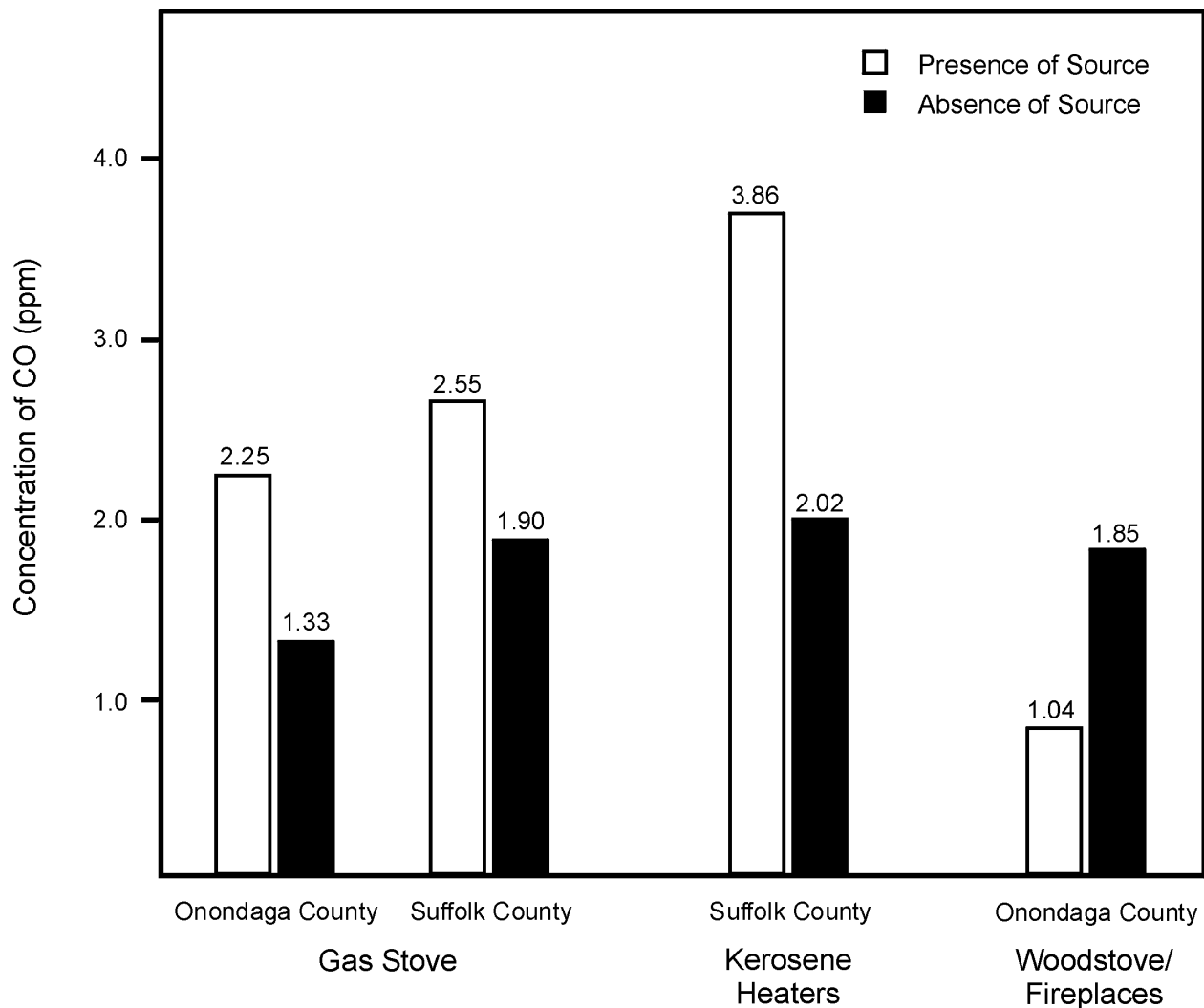


Figure 3-32. Arithmetic mean CO concentrations by presence or absence of combustion source. Homes in Suffolk County were monitored in January and February and in Onondaga County in February, March, and April.

Source: Research Triangle Institute (1990).

intermittent and will generally only occur during fire start-up and tending or through leaks in the stove or venting system.

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 single-family, one-story, three-bedroom dwelling with a full basement, comprising 1,150 ft² per level. Eight burner experiments and three pilot light experiments were conducted. Heaters were operated for 8 h followed by a 15-h decay period. The pilot studies were conducted over a 48-h period. Fans were used to distribute emissions throughout the house, excluding the basement. The highest CO concentrations were seen with the radiant-tile heater (13.4 ppm), and the lowest CO concentrations were reported with the fan-forced unit (0.9 ppm). Two of the tests using the blue-flame convective units were affected by gas leakage, resulting in CO concentrations of 4.7 and 4.8 ppm. The test not affected by the leakage had a CO concentration of 2.7 ppm. The maximum CO concentration in the test house from use of the perforated-tube convective heater was 31.9 ppm. Carbon monoxide concentrations during the pilot light experiments did not exceed 2.0 ppm.

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

Carbon monoxide concentrations in eight single-wide mobile homes (150 to 255 m³) 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 m²) 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 \pm 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 \pm 1.4 ppm. Peaks usually were observed at the end of the combustion period. The AER averaged 0.47 h⁻¹ when the unit was in operation. Homes with the radiant and multistage units had higher CO than homes with convective heaters. Average 1-h levels of CO for convective units ranged from 1.3 to 5.3 ppm. One-hour average CO concentrations for radiant and multistage units ranged from 1.1 to 28.3 ppm and 16.0 to 50.0 ppm, respectively.

Carbon Monoxide Concentrations Related to Environmental Tobacco Smoke

Carbon monoxide concentrations in environments where smoking occurs exceed background CO concentrations. 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 period ranged from 2.8 to 13.5. The room volumes ranged from 238 to 803 m³, with AERs of 12.8 and 15.8 h⁻¹. Holcomb (1993) reviewed the literature on tobacco smoke in various indoor environments and evaluated those data the authors defined as generated under real-life conditions. Carbon monoxide concentrations ranged from 0.1 to 10.2 ppm depending on the indoor environment. The results are outlined in Table 3-13. Löfroth et al. (1989) reported CO concentrations in a chamber test for cigarettes (1 cigarette) smoked every 15 to 30 min. The chamber volume was 13.6 m³, with a set AER of 3.55 h⁻¹. The cigarette mass was 1.2 g, and mass smoked was 0.9 to 1.0 g. Smoking duration was ≈12 min per cigarette. Carbon monoxide concentrations averaged 1.56 and 2.17 ppm for the 30-min tests and 4.16 ppm for the 15-min test.

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

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

Source: Holcomb (1993).

Carbon monoxide concentrations 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.

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

8 ***Carbon Monoxide Concentrations Associated with Motor Vehicles***

9 In the United States, motor vehicles dominate total anthropogenic emissions of CO. Older
10 vehicles are likely to remit more CO than newer models. However, when the newer models with
11 catalytic converters are started, the fuel-air mixture is rich to facilitate ignition and to improve
12 cold engine operation. Also, the catalytic convertor is not warm enough to function efficiently
13 (Marr et al., 1998). Emission rates for combustion vehicles are discussed in Section 3.3 of this
14 chapter.

15 Several studies have monitored the CO concentrations inside a moving vehicle under
16 various operating conditions. Chan et al. (1989, 1991) evaluated CO, NO_x, O₃, and VOCs inside
17 two moving vehicles (a 1983 and a 1987 model). Tailpipe emissions were higher for the older
18 model. Driving routes were selected to represent three distinct traffic patterns; urban traffic, high
19 traffic, and rural traffic. Inside ventilation was (1) windows and vents closed and air
20 conditioning on; (2) windows and vents closed and fan on; or (3) front windows half opened,
21 vent and fan on. Average CO concentrations for 70 samples, including both cars and all driving
22 routes, were 11.3 ppm. The in-vehicle concentrations were almost four times higher than
23 ambient CO (3.0 ppm). Carbon monoxide concentrations in the rural traffic pattern were
24 significantly less than either the urban and high-traffic patterns. Carbon monoxide in urban and
25 high-traffic patterns was not significantly different. The lowest CO concentrations were
26 measured when the windows were open; however, the concentration difference between the
27 different ventilation modes was only 1.0 ppm. Ott et al. (1994) reported an average CO
28 concentration of 10.2 ppm in the inside compartment of a moving vehicle for 93 trips under
29 urban highway conditions at varying times of the day. A more detailed discussion of this study
30 appears in the chapter on human exposure. Higher CO concentrations were reported both inside
31 and outside of moving vehicles in Sacramento and Los Angeles than those measured at roadside

1 and ambient monitoring stations. Carbon monoxide concentrations inside vehicles ranged from
2 nondetectable to 6 ppm (Rodes et al., 1998). In-vehicle CO from deployment of four different air
3 bags was reported by Wheatley et al. (1997). The time-weighted-average CO concentration
4 ranged from 174 to 370 ppm. Peak CO concentrations occurred 2 min after deployment.

5 Kern et al. (1990) measured CO concentrations in a poorly sealed, detached garage from
6 operation of an emissions-controlled (catalytic reactor and oxygen sensor) and an emissions-
7 uncontrolled vehicle (carbureted, without a catalytic reactor). Two tests were conducted: Test 1,
8 poorly sealed garage door with a 3-in. crack, and Test 2, garage door sealed with rags. Carbon
9 monoxide concentrations in the poorly sealed garage reached 4,700 ppm for the uncontrolled car
10 versus 2,000 ppm for the controlled car. When the garage was better sealed, CO concentrations,
11 after 110 min of operation, reached 8,400 ppm for the uncontrolled vehicle versus 3,600 ppm for
12 the controlled vehicle.

13 Amendola and Hanes (1984) evaluated the concentration of CO in automotive repair shops
14 based on seasonal conditions and as a function of work environment size. Monitoring was
15 conducted in a small service station (1 to 2 bays), a large service station (>2 bays), and an
16 automobile dealership. The 8-h time-weighted average during warm weather ranged from 3.3 to
17 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
18 dealership; however, the authors noted that CO concentrations were affected by the type of
19 ventilation used in the facility, volume and type of repairs, and employee work habits, such as
20 minimizing engine run time.

23 **3.6 SUMMARY**

24 Carbon monoxide is produced by the incomplete combustion of burning fossil and biomass
25 fuels. Approximately 70% of the CO produced globally is the result of human activities. Carbon
26 monoxide in the atmosphere is of both primary and secondary origin. The photochemical
27 oxidation of CH₄ and NMHCs accounts for almost one-half of the total source strength of CO.
28 The uncertainty in estimates of the magnitudes of individual CO sources ranges from a factor of
29 two to three.

30 Atmospheric CO concentrations in remote areas of the world have been increasing at the
31 rate of about 1% per year throughout most of the industrial era. This increase reflects the growth

1 of anthropogenic emissions from the combustion of fossil and biomass fuels and increased
2 agriculture to feed the expanding world population. However, CO levels decreased for several
3 years from the late 1980s to the early 1990s. The reasons for this decline are not clear, although
4 several factors may be involved. Since then, there has been no clear trend in CO levels.

5 Carbon monoxide plays an important role in atmospheric chemistry because it is the major
6 reactant for OH radicals. Reaction with OH radicals is the loss mechanism for many trace gases
7 that are responsible for contributing to the greenhouse effect (e.g., CH₄) and for depleting
8 stratospheric O₃ (e.g., CH₃Cl, and CH₃Br). Thus, increases in CO concentrations can suppress
9 OH radical levels and allow the concentrations of these trace gases contributing to global-scale
10 environmental problems to increase, even if trace gas emissions are constant. Conversely,
11 decreases in global average CO concentrations can stabilize or even reverse the growth rates of
12 the trace gases mentioned above.

13 Carbon monoxide may be responsible for 20 to 40% of the O₃ formed in the background or
14 “clean” troposphere. In addition, CO may have been responsible for 10 to 20% of the O₃ formed
15 during smog episodes in the few urban areas that have been examined. Obviously, the
16 photochemistry must be examined in more cities before any more general statements about the
17 importance of CO for urban air chemistry can be made.

18 Emissions from transportation dominate other sources of CO within the United States.
19 Even though CO in urban areas results largely from motor vehicle emissions, a sizable fraction of
20 the CO observed in rural air may be produced by the photochemical oxidation of isoprene and
21 other NMHCs, at least according to one model study. Residential wood burning may be an
22 important source of CO in a number of urban areas. The uncertainties in the magnitudes of
23 individual sources in the nationwide and worldwide emission inventories are comparable (i.e.,
24 roughly a factor of between two and three).

25 There has been a consistent decrease in the nationwide annual second highest maximum
26 8-h composite average ambient CO concentration over the past 20 years, from about 11 ppm in
27 1977 to about 4 ppm in 1996. This improvement in CO quality occurred despite a 121% increase
28 in vehicle miles traveled, a 29% increase in population, and a 104% increase in gross domestic
29 product in the United States over the same period. During the past 10 years, the composite mean
30 annual CO second maximum 8-h concentration decreased 37% at 190 urban sites, 37% at
31 142 suburban locations, and 48% at 10 rural monitoring sites. Hourly average CO concentrations

1 decreased from 2.0 ppm to 1.2 ppm over the past 10 years. Despite uncertainties in the
2 calculations of CO emissions, the decline in ambient CO concentrations in the United States
3 reflects the controls placed on automotive emissions. These declines are seen clearly in the
4 trends in CO levels during times of day when CO concentrations result mainly from mobile
5 source emissions.

6 The patterns and trends of observed CO reflect reductions in the CO emissions of the past
7 11 years. However, it is important to note that the reported concentrations from the monitoring
8 sites are representative only of the air quality in their neighborhoods. Also, although personal
9 exposure to CO from mobile sources also should be decreasing, the CO values from the
10 monitoring sites are not equivalent to personal exposures. The same ratios of personal to
11 monitored CO from past studies in urban areas with CO emissions dominated by mobile sources
12 may remain applicable today, but continued validation is needed.

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

20 In 1995, an estimated 40% of the United States population used gas for cooking. Carbon
21 monoxide emissions from gas ranges vary from range to range for both the top burners and the
22 oven burners and are dependent on the type of pilot light, the fuel consumption rate, the
23 frequency of use, and the operating condition. Older gas ranges with standing pilot lights emit
24 more CO than do newer units with electronic pilot lights. Carbon monoxide emissions from the
25 use of gas cooking stoves are 15 to 215 and 53 to 344 $\mu\text{g}/\text{kJ}$ for range top burners with
26 blue-flame and yellow-tipping operating conditions, respectively. Emissions from oven use
27 ranged from 12 to 226 $\mu\text{g}/\text{kJ}$ for blue-flame and 54 to 62 $\mu\text{g}/\text{kJ}$ for yellow-tipping. Carbon
28 monoxide emissions for both burner and oven standing pilots were only reported for blue flame
29 operating conditions and ranged from 28 to 56 and 209 to 322 $\mu\text{g}/\text{kJ}$ for burners and ovens,
30 respectively. Estimates of fuel consumption range from 5,000 to 5,710 ft^3/year for burners and
31 standing pilots. Annual pilot light fuel consumption for standing pilots has been estimated to be

3,530 ft³/y. A steady decrease in the emission of CO from pilot lights will likely occur with the replacement of older gas ranges with new models without standing pilots. Given the decrease in the number of individuals using gas stoves, the amount of time spent cooking on gas stoves, and the replacement of gas stoves with standing pilots with electronic pilots, it is likely that CO emission from gas stoves will continue to decrease. Also, with the advent of other cooking appliances (e.g., microwaves, toaster ovens, heating plates), the use of ranges in meal preparation is decreasing. Estimates of gas stove usage range from 30 to 60 min/day. Carbon monoxide emissions from gas water heaters and furnaces are generally negligible, but less efficient models will emit more CO than the more efficient ones.

The use of well-maintained, energy-efficient gas stoves will result in only intermittent, small increases in CO concentrations. In one report, CO concentrations from gas stove usage ranged from 0.65 to >9.0 ppm. The high levels of CO likely were associated with the presence of multiple CO sources, the use of the gas stove as a supplemental heat source, infiltration from ambient sources, and the building type (multi-family units versus single-family units). Short-term peak concentrations have been noted as high as 120 ppm.

Emissions from unvented space heaters are a function of the appliance design, combustion efficiency, length and frequency of use, and the fuel type and consumption rate. Unvented gas and kerosene space heaters generate the highest CO emissions and concentrations in the indoor environment. Data covering the years 1988 to 1994 indicate that 13.7 million adults used unvented space heaters in the United States. The largest percentage of unvented space heaters were in southern states. Data from a recent survey by the U.S. Census Bureau indicates that 1.06 million households used unvented space heaters (heating fuel described and kerosene or other liquid fuel) during 1995 as the primary heat source and 1.2 million households used unvented space heaters as a secondary heat source. Catalytic gas and convective kerosene space heaters emit the smallest amount of CO. Radiant and infrared unvented space heaters emit higher amounts of CO. The CO concentration from the use of a radiant-tile gas unit was 13.4 ppm, compared with 0.9 ppm for a convective gas unit. However, CO concentrations also depend on the frequency and duration of use of the space heater. Higher CO is found in homes where unvented space heaters are the primary heat source (up to 37 ppm) versus homes where unvented space heaters are used to supplement another heat source (<9.0 ppm). The decreasing usage of unvented space heaters is likely to result in decreased CO emissions from this source.

1 Available studies on woodstoves and fireplaces indicate that CO is emitted from fire
2 start-up and maintenance, leaks in the stove and venting system, and through backdrafting when
3 the natural draft is overcome by depressurization. The average CO source strength for airtight
4 stoves ranged from 0.08 to 0.27 g/h (10 to 140 cm³/h) versus 0.32 to 2.18 g/h (220 to
5 1,800 cm³/h) for nonairtight stoves. Carbon monoxide emissions of 0.07 to 0.375 g/h were
6 reported for wood heaters.

7 Carbon monoxide from the combustion of tobacco products occurs in the indoor
8 environment primarily through sidestream smoke. The Center for Disease Control estimated that
9 29% of the U.S. population smoked in 1995. An estimated 487 billion cigarettes were sold
10 during that year. An estimated 4.4 billion cigars were sold in the U.S. in 1997, compared to
11 3.8 billion in 1996. Emissions will vary based on the type and brand of tobacco product.
12 Concentrations of CO in environments where smoking occurs will exceed background
13 concentrations but will be dependent on the CO emission rate of the tobacco product, number of
14 cigarettes smoked, smoking rate, size of the indoor compartment, ventilation rate, and ambient
15 CO concentrations.

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

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4. POPULATION EXPOSURE TO CARBON MONOXIDE

4.1 INTRODUCTION

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

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

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

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

1 everyone is exposed to a global background level of CO in the ambient air on the order of
2 0.1 ppm (see Section 3.2). These combined sources constitute a reference or baseline exposure
3 as reflected in an endogenous COHb level on the order of 0.5% that varies individually, based on
4 physiological differences. These differences reflect variation in basal metabolisms and other
5 metabolic sources, as discussed in detail in Sections 5.3 and 5.4. This chapter discusses the
6 exposure of nonsmokers to CO. Smokers are excluded, because they represent a source of CO,
7 and because of their higher baseline levels of COHb and adaptive response to elevated COHb.

8 The study of population exposure is multidisciplinary, and the definition of personal
9 exposure has evolved over time (Ott, 1982; Duan, 1982; Liou, 1990; U.S. Environmental
10 Protection Agency, 1992a; Last et al., 1995; Zartarian et al., 1997). A recent definition offered
11 by Zartarian et al. (1997) states that exposure is the contact between an agent and a target at a
12 specified contact boundary, defined as a surface in space containing at least one exposure point
13 (a point at which contact occurs). Using this definition, this chapter assumes that an inhaled CO
14 molecule (the agent) reaches a human (the target) at the lining of the lung (the contact boundary)
15 where CO exchange takes place between air and blood. In actual field studies, the air in the
16 immediate vicinity of the target is often assumed to be well mixed, such that a measured CO
17 concentration in the air can be assumed to represent a non-smoking person's actual exposure
18 from CO inhalation.

19 This chapter is concerned only with CO exposures that occur at concentrations capable of
20 increasing COHb levels above a reference baseline level. Besides exposure to CO concentrations
21 above the background level, human COHb levels can be elevated because of metabolic
22 degradation of many drugs, solvents (e.g., methylene chloride), and other compounds to CO.
23 For details see Section 5.3. Because the endogenous production of CO from drugs and solvents
24 may continue for several hours, it can prolong any cardiovascular stress from COHb. Moreover,
25 the maximum COHb level from an endogenous CO production can last up to twice as long a
26 comparable COHb levels caused by comparable exposures to exogenous CO (Wilcosky and
27 Simonsen, 1991; Agency for Toxic Substances and Disease Registry, 1993). Hence, the
28 literature on exposure to methylene chloride also is discussed in this chapter.

29 Descriptive studies of exposure typically report: average and peak concentrations to which
30 people are exposed, the temporal aspects of exposure (i.e., averaging times), where exposures
31 occurred (i.e., outdoor and indoor microenvironments), and the sources of microenvironmental

exposures that add to ambient air intrusion (e.g., motor vehicles, gas appliances, etc.). Explanatory studies 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. 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 (e.g., accidental exposure to undiluted motor vehicle exhaust). Chapter 6 discusses relevant health effects due to 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 last prior CO air quality criteria document (AQCD). 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 levels of the NAAQS. The conclusion also examines the extent to which CO exposures have changed since the 1991 AQCD.

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 1991 CO AQCD, with the primary purpose of this edition of the AQCD being to focus on more recent studies; and (2) the results of older studies may no longer be indicative of current population exposures, given the major reductions in vehicle emissions during the last 30 years, social changes affecting commuting patterns, 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 currently thought to be at greatest risk from exposure to ambient CO levels are those with ischemic heart disease who have stable exercise-induced angina pectoris (cardiac chest pain). Individuals with this disease represented about 3% of the U.S. population in 1994. Studies show that earlier time to onset of cardiac chest pain occurred in these people while they exercised during exposures to CO concentrations that produced levels of COHb in the bloodstream in the range of 2 to 3% (U.S. Environmental Protection Agency, 1991). The National Health and Nutrition Examination Survey (NHANES) II study reported that 6.4% of the U.S. population who never smoked had COHb levels above 2.1%, based on a national random sample of people (n = 3,141) ranging in age from 12 to 74 years (Radford and Drizd, 1982). The NHANES II study was done in the late 1970s when ambient CO concentrations were much higher (see Figure 3-3).

4.2.2 Estimates of Population Exposure Based on Fixed-Site Monitors

In the United States, 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 12.7 million people lived in seven counties where ambient CO levels exceeded the NAAQS in 1996 and, thus, were at increased risk of exposure to CO levels above the NAAQS (U.S. Environmental Protection Agency, 1998a). The

1 estimate was made by combining census data on county populations with data on violations of
2 the CO NAAQS recorded by stationary monitors. Previous studies have shown why such
3 estimates should not be interpreted as assessments of population exposure to CO, for the two
4 reasons discussed below:

5 (1) Ambient CO concentrations are not spatially homogeneous within the area monitored.

6 For example, Ott and Eliassen (1973) reported average CO levels ranging from 5.2 to
7 14.2 ppm for sidewalks along congested streets of downtown San Jose, CA. Corresponding
8 CO averages at fixed-site monitors were only 2.4 to 6.2 ppm. A decade later, Ott and
9 Flachsbart (1982) found a narrower gap between simultaneous CO measurements from
10 fixed-site and personal exposure monitors deployed at indoor and outdoor commercial
11 settings in five California cities.

12 (2) In the absence of indoor CO sources and immediate outdoor sources (i.e., idling motor
13 vehicles), indoor CO concentrations tend to equal outdoor concentrations over the long term.
14 In buildings with mechanical ventilation systems, the timing and scheduling of outdoor
15 “make-up” air into the building affects ratios of indoor-outdoor concentrations both in the
16 short and long term (Yocom, 1982). For example, when make-up air was introduced into an
17 air-conditioned building during morning rush hours (when outdoor CO levels were high),
18 indoor CO concentrations exceeded outdoor levels for the remainder of the day (Yocom
19 et al., 1971). In the presence of indoor sources such as gas appliances, indoor CO
20 concentrations often exceed the outdoor levels (U.S. Environmental Protection Agency,
21 1991). Many American homes use gas (natural gas and liquid propane) for space heating,
22 cooking, heating water, and drying clothes. In a 1985 Texas study of a low-socioeconomic
23 population, CO concentrations were greater than or equal to 9 ppm in 12% of surveyed
24 homes. Residential CO concentrations were high where unvented gas space heaters were
25 used as the primary heat source (Koontz and Nagda, 1988).

26 These facts take on added significance given that many Americans spend most of their time
27 indoors (Szalai, 1972; Chapin, 1974; Meyer, 1983; Johnson, 1989; Schwab et al., 1990). Hence,
28 studies of actual personal exposure to CO are preferred over crude estimates of population
29 exposure to ambient CO, in determining what risk CO poses to public health from a total
30 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 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

1 on highways have not yet diffused into residential areas. A negative net value simply indicates
2 that the microenvironment has a lower positive CO concentration than the outdoor environment
3 at a given moment.

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

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

23 Direct studies of general populations are rare because of their expense and the logistical
24 problems of monitor distribution. Two examples for CO were those done in Denver and
25 Washington during the winter of 1982 and 1983 (Akland et al., 1985). In both studies, the target
26 population included noninstitutionalized, nonsmoking residents, 18 to 70 years of age, who lived
27 in the city's metropolitan area, an estimated 1.2 million adults in Washington and 500,000 in
28 Denver. In both cities, the composite network of fixed-site monitors overestimated the 8-h
29 exposures of people with low-level personal exposures and underestimated the 8-h exposures of
30 people with high-level personal exposures. With respect to the underestimates, over 10% of the
31 daily maximum 8-h personal exposures in Denver exceeded the NAAQS of 9 ppm, and about 4%

1 of maximum 8-h personal exposures in Washington exceeded 9 ppm. The end-expired breath
2 CO levels were in excess of 10 ppm, which is roughly equivalent to about 2% COHb in about
3 12.5% of the Denver participants and about 10% (after corrections were made for instrumental
4 measurement drift) of the Washington participants. Simultaneous CO measurements at fixed-site
5 monitors exceeded 9 ppm only 3% of the time in Denver and never exceeded 9 ppm in
6 Washington (Akland et al., 1985).

7 The Denver and Washington studies identified certain activities associated with higher CO
8 exposures. The two highest average CO concentrations occurred when subjects were inside a
9 parking garage and when traveling by car. Those who commuted 6 h or more per week had
10 higher average exposures than those who commuted less than 6 h per week. Table 4-1 shows
11 that higher mean CO concentrations occurred for travel by motor vehicle (motorcycle, bus, car,
12 and truck) than by walking and bicycle, and that high indoor concentrations above the 8-h
13 NAAQS of 9 ppm occurred in public garages, service stations or motor vehicle repair facilities.
14 Denver had higher average CO concentrations than Washington for all microenvironments
15 because of Denver's higher altitude and colder winter climate (Ott et al., 1992).

17 **4.2.4 Population Exposure Models**

18 Many studies developed computer models to predict exposure in both general and special
19 populations (U.S. Environmental Protection Agency, 1991). These models are important because
20 it is impossible and impractical to know the hourly and daily exposure of every person in a
21 population on a real-time basis. Models of human exposure are empirically derived
22 mathematical relationships, theoretical algorithms, or hybrids of these two. To support policy
23 decisions related to the setting of ambient and emission standards, EPA supported development
24 of two general population exposure models: (1) the NAAQS Exposure Model (NEM) and (2) the
25 Simulation of Human Activity and Pollutant Exposure (SHAPE) model. These models assume
26 that an individual's total CO exposure over a specified time interval can be estimated as the sum
27 of the average concentration within a microenvironment, multiplied by the amount of time spent
28 in that microenvironment (Duan, 1982).

29 The SHAPE model used a stochastic approach to simulate the exposure of an individual
30 over a 24-h period (Ott, 1984). The model replicates a person's daily activity pattern by
31 sampling from probability distributions representing the chance of entry, time of entry, and time

**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	Mean ¹ (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

TABLE 4-1 (cont'd). CARBON MONOXIDE CONCENTRATIONS IN SELECTED MICROENVIRONMENTS OF DENVER, CO, 1982 AND 1983
(Listed in descending order of mean CO concentration)

Microenvironment	Number	Mean ^a (ppm)	Standard Error (ppm)
Indoor (cont'd)			
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).

spent in 22 different microenvironments. Transition probabilities determine a person's movement from one microenvironment to another. The model assumes that microenvironmental concentrations reflect the contribution of an ambient concentration and a component representing CO sources within each microenvironment. Because SHAPE relies on field surveys of representative populations, the data requirements of the model are fairly extensive.

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

1 Unlike SHAPE, which uses diary data from each person in a population, the NEM model
2 aggregates people into cohorts. The NEM model has evolved over time from deterministic to
3 probabilistic versions. As described elsewhere (Johnson and Paul, 1983; Paul and Johnson,
4 1985), the deterministic version of NEM simulates movements of selected groups (cohorts) of an
5 urban population through a set of exposure districts or neighborhoods and through different
6 microenvironments. Cohorts are identified by district of residence and, if applicable, district of
7 employment, as well as by age-occupation group and activity pattern subgroup. The NEM uses
8 empirical adjustment factors for indoor and in-transit microenvironments, and accumulates
9 exposure over 1 year. Although deterministic NEM was able to estimate central tendencies in
10 total exposure accurately, it did less well estimating the associated uncertainty caused by
11 variation in time spent in various microenvironments (Quackenboss et al., 1986) or to variation
12 in microenvironmental concentrations (Akland et al., 1985). Paul et al. (1988) discussed
13 advancements in the deterministic version of NEM.

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

21 McCurdy (1995) examined the history of both the NEM and pNEM models and the role
22 they have played in reviews of criteria air pollutants such as CO. The EPA used pNEM/CO,
23 rather than the SHAPE model, in its previous review of the CO NAAQS (U.S. Environmental
24 Protection Agency, 1992b). At the request of the Clean Air Scientific Advisory Committee, as
25 part of that review, EPA performed a limited evaluation of the predictions of pNEM/CO against
26 observed data for subjects of the Denver, CO, study (Johnson et al., 1992). That evaluation
27 concluded that there was generally good agreement between the distributions of observed and
28 predicted 1-h daily maximum exposures, but that the model tended to underpredict the highest
29 8-h daily maximum exposures (i.e., >12 ppm) and overpredict the lowest 8-h daily maximum
30 exposures (i.e., <5 ppm). Extending the earlier evaluation of the pNEM/CO model, Law et al.
31 (1997) performed 20 simulated runs, the average values of which were used for evaluation

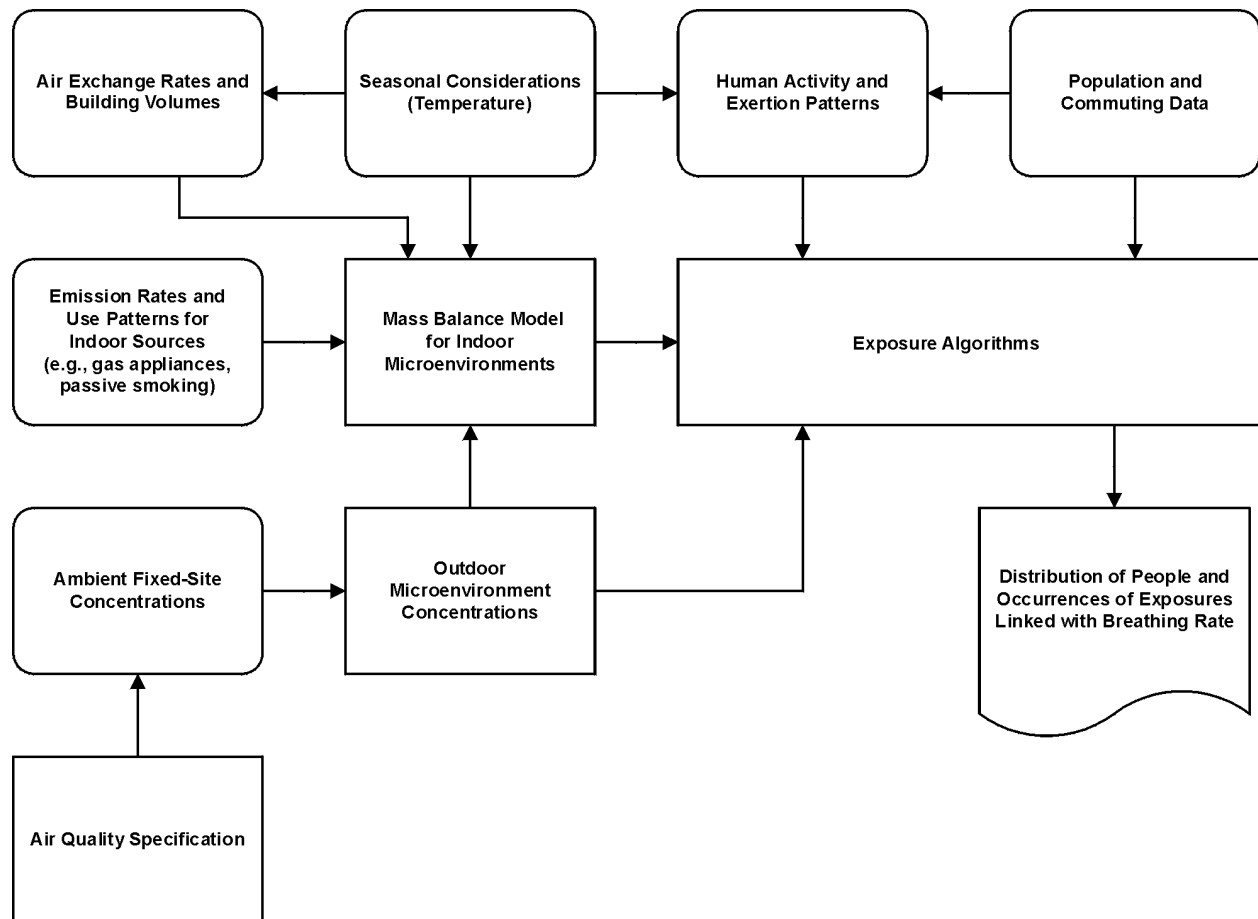


Figure 4-1. Conceptual overview of pNEM.

Source: Johnson et al. (1999).

1 purposes. Based on this evaluation, Law et al. (1997) reported the predicted and observed
 2 population exposure cumulative frequency distributions (CFD), with and without gas stove use.
 3 Figures 4-2 and 4-3 show that, regardless of gas stove use, pNEM/CO overpredicted the CFD at
 4 low exposures and underpredicted the CFD at high exposures for 8-h daily maximum exposures.
 5 The proportion of the Denver population exposed at or above 9 ppm (8-h NAAQS) was 12.7%
 6 (observed) versus 9.9% (highest predicted) for those with gas stoves and 13.3% (observed)
 7 versus 8.8% (highest predicted) for those without gas stoves. Similar results were reported for
 8 the 1-h daily maximum exposures, with and without gas stove use. The proportion of the Denver
 9 population exposed at or above 35 ppm (1-h NAAQS) was 3.2% (observed) versus 1.2% (highest

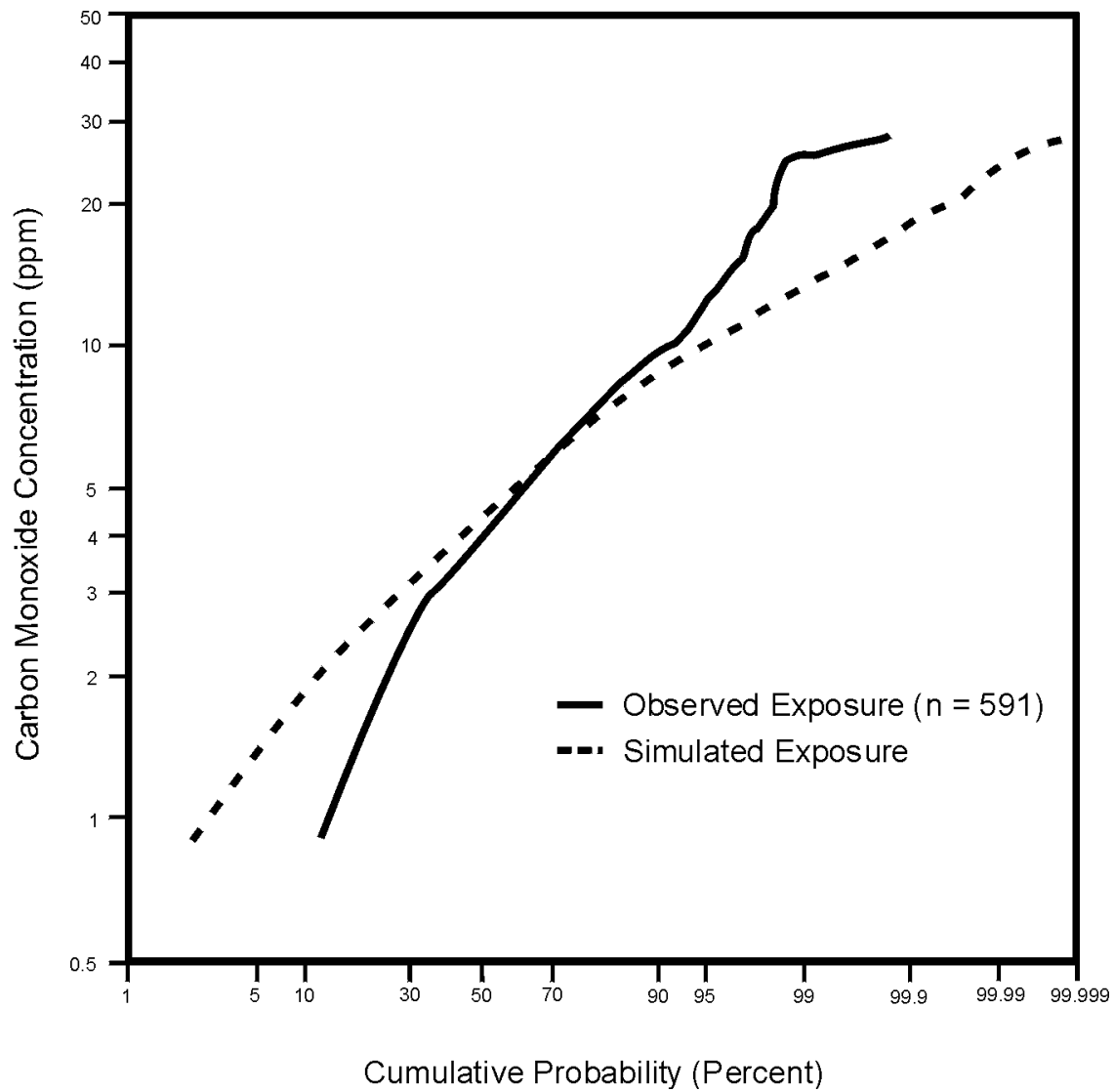


Figure 4-2. Observed versus simulated 8-h daily maximum exposure for persons residing in homes with gas stoves in Denver, CO.

Source: Law et al. (1997).

1 predicted) for those with gas stoves and 2.1% (observed) versus 1.1% (highest predicted) for
 2 those without gas stoves. Relatively close agreement between simulated and observed PEM data
 3 occurred for CO concentrations near the average exposure, within the range of 6 to 13 ppm for
 4 the 1-h case and within 5.5 to 7.0 ppm for the 8-h case.

5

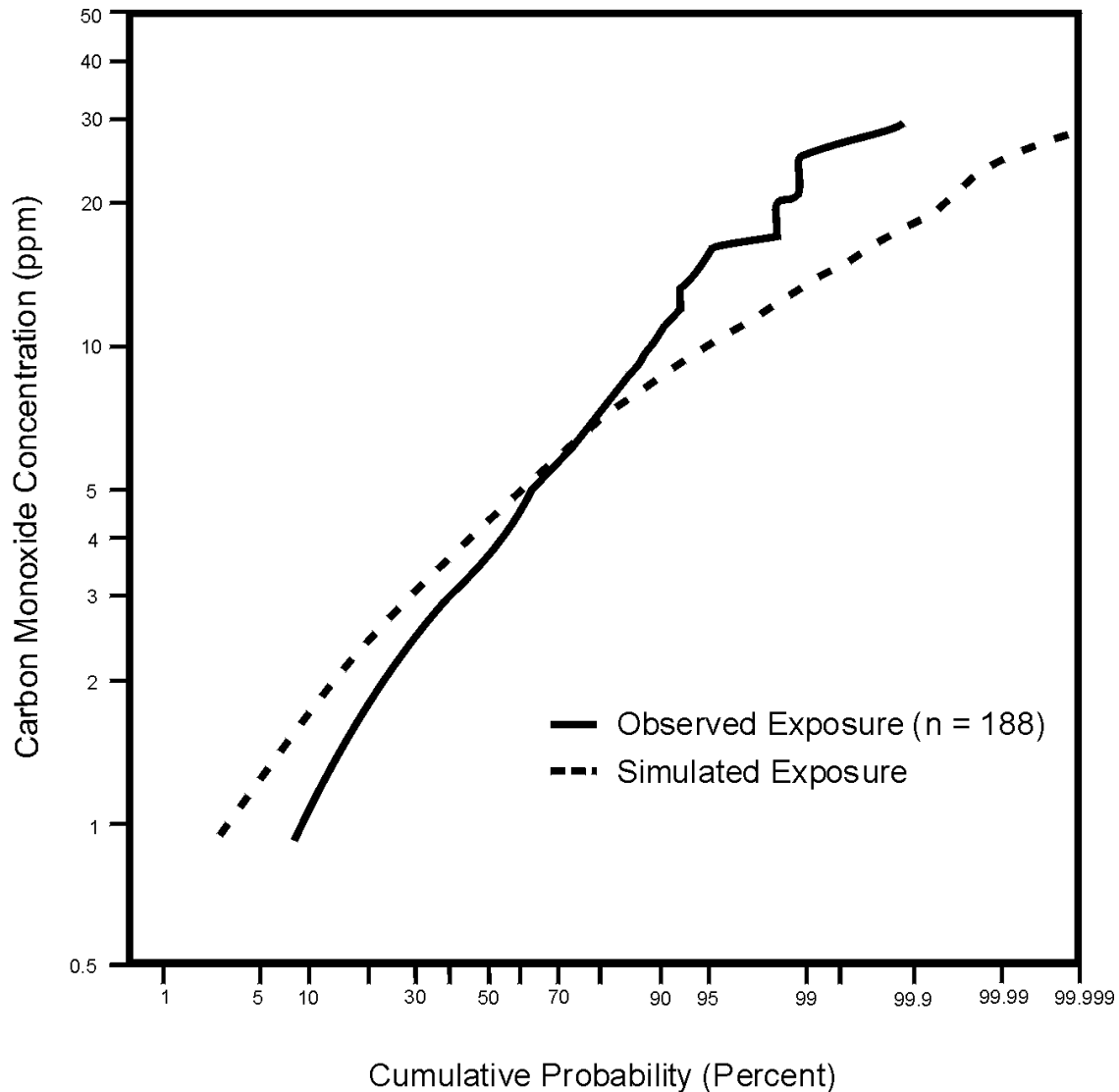


Figure 4-3. Observed versus simulated 8-h daily maximum exposure for persons residing in homes without gas stoves in Denver.

Source: Law et al. (1997).

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

(1) 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, wood stoves, etc.) that may have impacted observed levels using personal monitors.

(2) While 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, CO; and Washington, DC) 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.

Presently, EPA's Office of Air Quality Planning and Standards is in the process of revising the pNEM/CO model.

Given this evaluation and EPA's mandate under the Clean Air Act 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, in order 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 Clean Air Act.

4.3 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 last CO AQCD 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 measure the concentration and amount of CO inhaled by a smoker in a field study. As such, smokers have higher baseline levels of COHb than nonsmokers and an adaptive response to elevated COHb.

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

8 **4.3.1 Nonoccupational Exposures**

9 This subsection focuses on nonoccupational CO exposures that occur because of a variety
10 of human activities that require contact with sources of CO emissions such as motor vehicles and
11 fuel-burning tools and appliances. Section 3.5 discusses studies where CO has been measured by
12 area monitors in indoor microenvironments because such measurements constitute an indirect
13 exposure estimate. In addition, this section discusses studies of breath CO in populations and
14 studies of exposure to methylene chloride because it increases COHb levels.

16 **4.3.1.1 Exposure to Carbon Monoxide from Motor Vehicles**

17 This subsection presents nonoccupational studies of exposure to CO concentrations from
18 motor vehicles. Because these studies date to the mid-1960s, many of them were reviewed in the
19 1991 CO AQCD, and, therefore, they are not again reviewed here. Subsection 4.4.2.2 examines
20 the effects of progressively tighter CO emission standards on passenger cabin exposure. This
21 subsection focuses on other factors that affect the CO exposure of motorists and bicyclists.

22 Several studies done prior to 1991 reported passenger exposure to engine or tailpipe
23 emissions of CO (Amiro, 1969; Clements, 1978; Ziskind et al., 1981). More recently, Hampson
24 and Norkool (1992) reported that 20 of 68 children were treated for accidental CO poisoning
25 after riding in the back of eight pickup trucks in Seattle, WA, between 1986 and 1991.
26 Seventeen of the 20 children rode under a rigid closed canopy attached to the bed of the truck,
27 and the other three rode beneath a tarpulin. Six pickups had known exhaust system leaks; three
28 had rear-end tailpipes, and three had side-mounted tailpipes. For the 20 children, average COHb
29 levels measured in an emergency room were 18.2% (mean) (2.4%) (standard error), and levels
30 ranged from 1.6 to 37.0% COHb.

1 Studies done both before and after 1991 continue to show that fixed-site monitors
2 underestimate in-vehicle CO exposures. Flachsbart (1995) reported that 14 of 16 in-vehicle
3 exposure studies performed in the United States between 1965 and 1992 simultaneously
4 measured both ambient and passenger cabin concentrations. Regardless of the study, Table 4-2
5 shows that the mean CO concentrations inside vehicles always exceeded the mean ambient CO
6 concentrations measured at fixed-site monitors. The ratio between a study's mean in-vehicle CO
7 concentration and its mean ambient CO concentration fell between 2 and 5 for most studies,
8 regardless of when the study was done, but exceeded 5 for two studies done during the early
9 1980s. Of the more recent studies, Chan et al. (1991) found that median CO concentrations were
10 11 ppm inside test vehicles driven on hypothetical routes in Raleigh, NC during August and
11 September 1988, but median ambient concentrations were only 2.8 ppm at fixed-site monitors.
12 Fixed-site samples were collected about 30 to 100 m from the midpoint of each route.

13 Flachsbart (1995) proposed that the results of the 16 studies could be explained partly by
14 different study approaches (direct versus indirect) and by other aspects of study design, including
15 choice of city, season of the year, the surveyed road's functional type and location, travel mode,
16 and vehicular ventilation. For example, by pairing three direct studies with three indirect studies
17 (as shown in Table 4-2) that were done at the same time, Flachsbart showed that the mean
18 in-vehicle exposure measured by the direct approach was always lower than that measured by the
19 indirect approach. Although direct studies sampled real populations engaged in a variety of trips
20 in all types of traffic, most indirect studies focused on hypothetical commuters with higher
21 exposures in rush hour traffic. In another example, a comparison of Studies 8 through 10 in
22 Table 4-2 shows the effect of roadway type. Study 9 had a sizeable component of residential
23 driving, which may explain why the mean in-vehicle CO exposure of 7.7 ppm for Study 9 was
24 lower than the mean exposures for Studies 8 and 10. When Study 9 data were disaggregated by
25 roadway location, mean CO concentrations were 10 ppm for major commuting routes and
26 5.5 ppm for drives in residential areas. The mean concentration of 10 ppm for major commuting
27 routes in Study 9 is similar to the mean CO concentrations reported for arterial highways by other
28 studies (i.e., 9.8 ppm for Study 8 and 10.6 ppm for Study 10), which also were done during the
29 early 1980s.

30 Like earlier studies, recent ones also have looked at effects of different routes and travel
31 modes on CO exposure. Chan et al. (1991) reported significantly different in-vehicle exposures

TABLE 4-2. SUMMARY OF STUDIES OF IN-VEHICLE EXPOSURE AND AMBIENT CARBON MONOXIDE CONCENTRATIONS, 1965 AND 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	3.8	±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 | 9. Denver, CO; Los Angeles, CA; Phoenix, AZ; Stamford, CT |
| 2. Chicago, IL; Cincinnati, OH; Denver, CO; St. Louis, MO; Washington, DC | 10. Honolulu, HI |
| 3. 14 cities | 11. Denver, CO; Washington, DC |
| 4. Los Angeles, CA | 12. Washington, DC |
| 5. Boston, MA | 13. Los Angeles, CA |
| 6. Washington, DC | 14. Raleigh, NC |
| 7. Los Angeles, CA | 15. Menlo Park, Palo Alto, and Los Altos, CA |
| 8. Menlo Park, Palo Alto, and Los Altos, CA | 16. New Jersey Turnpike and Route 18, NJ |

Notes (numbers shown in parentheses are CO concentrations in ppm):

^aRange or one standard deviation except as noted.

^bChicago (37); Cincinnati (21); Denver (40); St. Louis (36); Washington (25).

^cAtlanta (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).

^dDenver (10.3); Los Angeles (8.5); Phoenix (6.7); Stamford (5.2); commuting and residential driving microenvironments weighted by sample size.

^eRange across all cities studied.

^fDenver (8.0); Washington (5.0).

^gRange in standard error for all cities studied.

Source: Flachsbarth (1995).

1 to CO for standardized drives on three routes that varied in traffic volume and speed. The
2 median in-vehicle CO concentration was 13 ppm for 30 samples in the downtown area of
3 Raleigh, which had heavy traffic volumes, slow speeds, and frequent stops. The next highest
4 concentrations (median = 11 ppm, n = 34) occurred on an interstate beltway that had moderate
5 traffic volumes and high speeds, and the lowest concentrations (median = 4 ppm, n = 6) occurred
6 on rural highways with low traffic volumes and moderate speeds. Similarly, Dor et al. (1995)
7 reported CO exposures of 12 ppm for 19 trips lasting an average of 82 min on a route through
8 central Paris, France, which was 2 to 3 ppm higher than the mean exposure for 30 trips split
9 between two suburban routes. In terms of travel modes, both Joumard (1991) and Dor et al.
10 (1995) found differences in CO exposures for public and private modes of travel in French cities
11 and towns, confirming findings made earlier in the United States by Flachsbart et al. (1987).

12 Ott et al. (1994) developed statistical models of passenger cabin exposure to CO
13 concentrations from highway emissions, based on 88 trips taken during a 13.5-mo period in 1980
14 and 1981. All trips occurred in one vehicle with windows set in a “standard position” as it
15 traveled an arterial highway (El Camino Real) in the San Francisco Bay Area of California. The
16 models are noteworthy because they examined the explanatory power of nine variables. The best
17 model predicted the average CO exposure per trip as a function of just two variables: (1) traffic
18 conditions as measured by the proportion of travel time stopped and (2) a seasonal trend term
19 expressed as a cosine function of the day of the year on which the trip was taken (adjusted
20 $R^2 = 0.67$). A model that included ambient CO concentrations from a fixed-site monitor slightly
21 improved the explanatory power of the model (adjusted $R^2 = 0.71$).

22 Flachsbart (1999a) developed a set of statistical models of passenger exposure to CO
23 concentrations inside a motor vehicle as it traveled a coastal artery (the Kalanianaʻole Highway)
24 in Honolulu, HI. All trips occurred during morning periods over a 6-mo period in 1981 and
25 1982. The 6.2-km study site was divided into three links. The models predicted the average CO
26 concentration inside the vehicle’s passenger cabin on the third link as a function of several
27 variables. Based on data for 80 trips, the three most powerful models (adjusted $R^2 = 0.69$) were
28 nonlinear combinations of several variables: the average CO concentration inside the cabin for
29 the second link; wind speed and direction; and either travel time, vehicle speed, or the estimated
30 motor vehicle CO emission factor for the third link. Several nonlinear models were based on
31 data for 62 trips for which nonzero, ambient CO concentrations were available. For this smaller

1 database, the most practical models (adjusted $R^2 = 0.67$) combined three variables: (1) the
2 ambient CO concentration; (2) the second-link travel time; and (3) either the travel time, vehicle
3 speed, or CO emission factor for the third link. The models showed that cabin exposure was
4 strongly affected by travel time and average vehicle speed, both of which were affected by the
5 time that the test vehicle entered each link of the highway. This implied that stochastic
6 simulations of exposure (e.g., the SHAPE model by Ott et al. [1988]) should not assume that trip
7 times and commuter exposures are independent of trip-starting times.

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

22 Because the California study design purposely emphasized scenarios likely to result in high
23 in-vehicle emissions, the study results can not easily be compared to results of the 16 studies in
24 Table 4-2. Mean CO concentrations inside both test vehicles were reported for each scenario
25 based on only two to four commutes in each city. These concentrations ranged from less than
26 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
27 total of 16 trips in Los Angeles. As in similar studies, the means of ambient CO concentrations
28 measured at fixed-site monitors fell below the means of in-vehicle CO levels in both cities, and
29 typically were less than the MQL of the portable monitor. Because ambient CO levels vary from
30 city to city, the study computed microenvironmental concentrations of test vehicles by
31 subtracting ambient from interior CO levels to estimate CO exposure resulting solely from

1 roadway emissions. They found average microenvironmental concentrations to be higher in
2 Los Angeles (4.6 to 4.9 ppm) than in Sacramento (2.1 to 3.1 ppm) during rush hour trips on
3 freeways; but, there was little difference in average microenvironmental concentrations between
4 freeway and arterial trips during rush hour trips in both cities. Based on preliminary analysis of
5 five trips, the study reported that CO concentrations could reach short-term peaks, ranging from
6 ~15 to 70 ppm, when the vehicle trailed gasoline-powered delivery trucks and older sedans.

7 The CO exposure of cycling as a travel mode has been studied and compared to the
8 exposure of motorists. In England, Bevan et al. (1991) reported that the mean CO exposure of
9 cyclists in Southampton was 10.5 ppm, based on 16 runs over two 6-mi routes that took an
10 average of 35 min to complete. Note that the CO exposures of European cyclists may not be
11 comparable to cyclists' exposures in the United States because installation of catalytic converters
12 on new cars in Europe occurred in 1988, about 13 years after their introduction in the United
13 States (Faiz et al., 1996). In The Netherlands, Van Wijnen et al. (1995) compared exposures of
14 volunteers serving as both car drivers and cyclists on several routes in Amsterdam during winter
15 and spring. For a given route, the mean personal 1-h CO concentrations were always higher for
16 car drivers than for cyclists regardless of when sampling occurred during the year. However, a
17 volunteer breathed 2.3 times more air per minute on average as a cyclist than as a car driver.
18 When adjusted for variation in breathing rate, the range in median 1-h averaged uptakes of CO of
19 cyclists (2.4 to 3.2 mg) approached that of car drivers (2.7 to 3.4 mg).

20 Studies have quantified the effect of traffic volume and speed on in-vehicle CO exposure.
21 Flachsbart et al. (1987) reported that in-vehicle CO exposures fell by 35% when test vehicle
22 speeds increased from 10 to 60 mph on eight commuter routes in Washington, DC. In a similar
23 study of typical commuter routes in central Riyadh, Saudi Arabia, Koushki et al. (1992) found
24 that in-vehicle CO exposures fell by 36% when vehicle speeds increased from 14 to 55 km/h
25 (8.7 to 34.2 mph). They also found that mean in-vehicle CO concentrations increased by 71.5%
26 when traffic volumes increased from 1,000 to 5,000 vehicles per hour. Mean CO levels ranged
27 from 30 to 40 ppm averaged over trips of 25 to 43 min during peak hours, and ranged from 10 to
28 25 ppm for trips of 15 to 20 min during off-peak hours.

29 The effects of diurnal and seasonal variation on in-vehicle CO exposure were not discussed
30 completely in the 1991 CO AQCD. Studies of diurnal effects on in-vehicle exposure during peak
31 travel periods have been inconclusive because they did not control for covariation in traffic

1 volumes and speeds, ambient CO concentrations, or meteorological conditions (e.g.,
2 temperatures, wind speeds) during different periods of the day. In Los Angeles, CA,
3 Haagen-Smit (1966) found evidence that CO exposures during afternoon commutes were greater
4 than those during morning commutes. Similar results were later found by Cortese and Spengler
5 (1976) in Boston, MA, by Wallace (1979) in Washington, DC, and by Dor et al. (1995) in Paris,
6 France. However, contrary evidence was reported by Holland (1983) for four U.S. cities, and by
7 Joumard (1991) in France. Recently, Rodes et al. (1998) compared commuter exposures for
8 morning and evening rush hour periods for 12 freeway trips in two California cities. Ambient
9 CO levels were subtracted from in-vehicle CO levels to estimate the vehicle's
10 microenvironmental concentration. In Los Angeles, microenvironmental concentrations during
11 evening commutes were about 25% lower than morning values because of higher wind speeds.
12 In Sacramento, such concentrations during evening trips were slightly higher than morning
13 values because of higher traffic congestion levels. In another recent study, Alm et al. (1999)
14 reported that the geometric mean CO concentration of 11 morning trips (3.1 ppm) exceeded that
15 of 12 afternoon trips (2.0 ppm) on a standard route in Kuopio, Finland, but attributed this
16 difference to weather and traffic variables.

17 Seasonal variation in ambient temperatures, wind conditions, and traffic volumes affect
18 passenger cabin exposure to CO, as shown in studies by Shikiya et al. (1989) in southern
19 California, Ott et al. (1994) in northern California, Dor et al. (1995) in France, and Flachsbart
20 (1999a) in Hawaii. Ott et al. (1994) and Dor et al. (1995), who both measured exposures for an
21 entire year, reported that they were generally higher in the fall and winter than in the spring and
22 summer. Such results usually are attributed to colder temperatures in temperate climates, which
23 increase CO emissions per vehicle mile during winter months. In Hawaii, where temperatures
24 are never cold enough to have a substantial effect on motor vehicle emissions, Flachsbart (1999a)
25 found that traffic flows and wind speeds had reinforcing effects on passenger cabin exposures to
26 CO concentrations on a coastal highway in Honolulu. During late fall, exposures were low
27 because traffic flows were light and wind speeds low. During winter and spring, exposures were
28 relatively higher because traffic flows were greater and winds calmer than during the fall.

29 In 1984, the U.S. Department of Transportation ordered a gradual phase-in of airbag
30 technology on passenger cars for safety reasons, and made dual airbags mandatory for all cars
31 beginning September 1, 1997. Based on deployment of four different airbags, Wheatley et al.

(1997) reported that the time-weighted-average (TWA) CO concentration ranged from 174 to 370 ppm. Peak CO concentrations occurred 2 min after deployment.

4.3.1.2 Exposure to Carbon Monoxide in Recreational Vehicles

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

In the second study, 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. At distances greater than 25 ft, centerline exposures tended to increase with greater speeds. At 15 ft off centerline, average concentrations fell sharply to levels of 0 to 7.5 ppm. When the snowmobiler drove alone, the average concentration minus the background concentration was 1.3 to 3.0 ppm. Background concentrations ranged from 0.2 to 0.5 ppm.

Snowmobile tourism has become a booming business across the nation and in several national parks. Over 87,000 tourists traveled by snowmobile in Yellowstone National Park (Wilkinson, 1995) during the winter of 1993 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

1 a catalyst emits far less (0.01 to 0.04 g/mi) at speeds of 10 to 40 mph. There are no federal laws
2 regulating the exhaust from snowmobile engines, and states are preempted from implementing
3 snowmobile emission standards. The typical snowmobile utilizes a two-stroke engine, because it
4 is less expensive than a four-stroke engine and provides a high power:weight ratio. However, a
5 two-stroke engine produces relatively high emissions of CO (Snook and Davis, 1997).

7 **4.3.1.3 Residential Exposure to Carbon Monoxide**

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

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

20 Mumford et al. (1991) and Williams et al. (1992) assessed CO exposure to emissions from
21 unvented portable kerosene heaters in eight small mobile homes with no gas appliances and low
22 air exchange rates. Each home was monitored for an average of 6.5 h per day for 3 days per
23 week for 4 weeks. For 2 weeks, the heater was on, and, for 2 weeks, it was off. When the heater
24 was turned on, it was in use for an average of 4.5 h. When the heater was in use, study
25 participants (all nonsmokers) spent most of their time in the family room or kitchen. Sampling
26 took place in the living area about 1.5 to 3 m from the heater. The mean 8-h CO concentrations
27 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)
28 when it was off. Peaks usually were observed at the end of the combustion period. The ambient
29 CO level measured 0.5 h prior to heater use ranged from 0 to 8 ppm. When the heater was on,
30 three of the eight homes had 8-h average CO levels that exceeded the NAAQS, and one home
31 routinely had levels of 30 to 50 ppm.

1 In joint studies, Wilson et al. (1993a,b) and Colome et al. (1994) reported CO exposures for
2 a random sample of California homes that used gas appliances during a 48-h period from
3 December 1991 to April 1992. For periods of 48 h, the median CO concentration was 1.2 ppm
4 (indoors) and 0.8 ppm (outdoors), and the median of the maximum 8-h average CO concentration
5 was 2.0 ppm (indoors) and 1.4 ppm (outdoors). Of surveyed homes, 13 of 286 homes (4.5%) had
6 indoor CO concentrations above the NAAQS of 9 ppm for 8 h, and 8 of 282 homes (2.8%) had
7 outdoor CO concentrations above this standard. Although most of the exceedances occurred in
8 the Los Angeles basin, these percentages could be low because the basin was under-represented
9 in the statewide sample. The study did not translate these percentages into statewide estimates.

10 Figures 4-4 and 4-5 show log-probability plots of the 1-h and 8-h maximum indoor minus
11 outdoor CO concentrations, respectively, for a common sample of 277 homes. These Figures
12 show that 17 homes (6.1%) had 1-h maximum concentrations indoors that were at least 5 ppm
13 higher than outdoor levels, and that 10 homes (3.6%) had 8-h maximum CO concentrations
14 indoors that were at least 5 ppm higher than outdoor levels. They suggest that a small percentage
15 of California homes would still have indoor CO problems even if outdoor CO levels at these
16 homes complied with federal ambient standards. Using univariate regression analysis, outdoor
17 CO concentrations explained approximately 55% of the variation found in indoor CO
18 concentrations. Higher net indoor CO levels (indoor minus outdoor CO concentrations) were
19 traced to several factors: space heating with gas ranges and gas-fired wall furnaces, use of gas
20 ranges with continuous gas pilot lights, small home volumes, and smoking cigarettes. The study
21 reported that several factors may have contributed to higher indoor net CO levels: malfunctioning
22 gas furnaces, automobile exhausts leaking into the home from attached garages and carports,
23 improper use of gas appliances (e.g., gas fireplaces), and improper installation of gas appliances
24 (e.g., forced air unit ducts).

25 In an area monitoring study, Kern et al. (1990) measured CO concentrations in a poorly
26 sealed, detached garage from operation of an emissions controlled (catalytic reactor and oxygen
27 sensor) and an emissions uncontrolled vehicle (carbureted and no catalytic reactor). Two tests
28 were conducted: Test 1 involved a poorly sealed garage door with a 3-in. opening, and Test 2
29 sealed the garage door with rags. The CO concentrations in the poorly sealed garage reached
30 4,700 ppm for the car without emission controls versus 2,000 ppm for the car with controls.

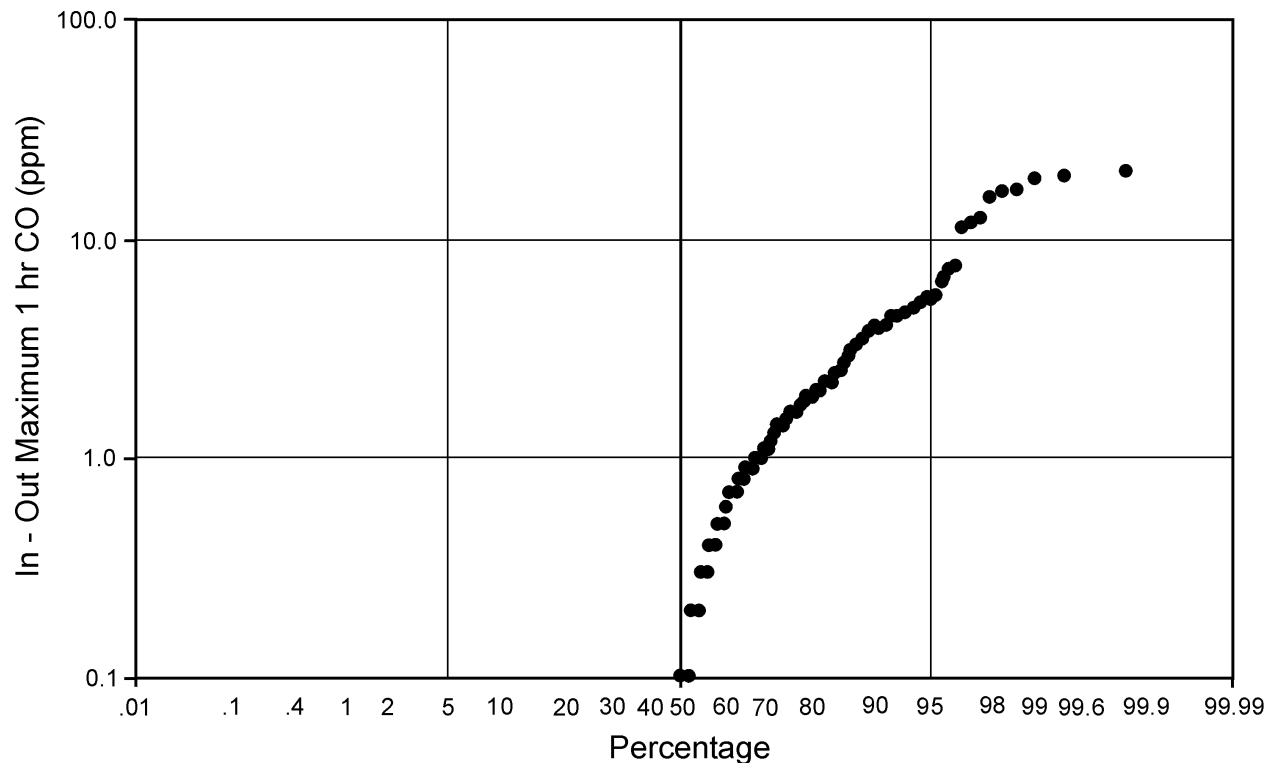


Figure 4-4. Log-probability plot of the maximum 1-h indoor minus outdoor CO concentrations based on a random sample of 277 homes that used gas appliances in California, 1991 and 1992. (Only those indoor minus outdoor values greater than or equal to 0.1 ppm are shown.)

Source: Wilson et al. (1993a).

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

3 Unintentional deaths caused by CO poisonings have been studied in California,
 4 New Mexico, and Washington. Two California studies collected data for the 1979 to 1988
 5 period. In the first, Liu et al. (1993) reported that 13.3% of 444 deaths were caused by improper
 6 use of charcoal grills and hibachies, of which 54% occurred inside motor vehicles (e.g., a van or
 7 recreational camper) and 46% in residential structures (e.g., homes, apartments, shacks, tents).
 8 Relative to their share of the state population, higher death rates occurred among Asians, blacks,
 9 males, and people aged 20 to 39. In the second study, Girman et al. (1998) identified specific

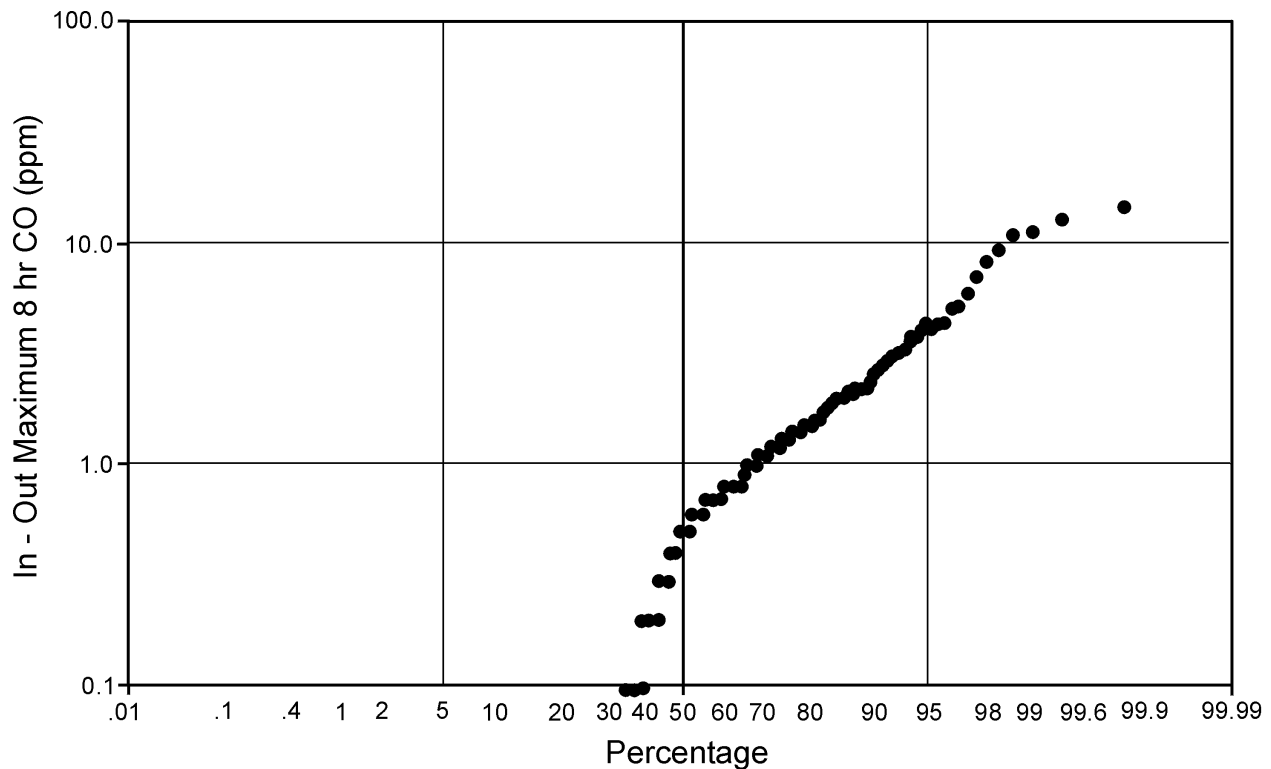


Figure 4-5. Log-probability plot of the maximum 8-h indoor minus outdoor CO concentrations based on a random sample of 277 homes that used gas appliances in California, 1991 and 1992. (Only those indoor minus outdoor values greater than or equal to 0.1 ppm are shown.)

Source: Wilson et al. (1993a).

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, and 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 to listen 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.

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

8 The National Center for Health Statistics (NCHS) and the U.S. Consumer Product Safety
9 Commission (CPSC) estimated that 212 deaths in 1992 were caused by fuel-burning appliances
10 used in the home. Of these deaths, 13 involved use of gasoline-powered appliances (National
11 Center for Health Statistics and U.S. Consumer Product Safety Commission, 1992). The CPSC
12 also estimated that 3,900 CO injury accidents occurred in 1994, of which about 400 were
13 associated with the use of gasoline-powered engines or tools (National Institute for Occupational
14 Safety and Health, 1996). In response to the problem, several federal government agencies
15 issued a joint alert concerning exposure to CO emitted by these sources (National Institute for
16 Occupational Safety and Health, 1996). These sources involved use of pressure washers, air
17 compressors, concrete-cutting saws, electric generators, floor buffers, power trowels, water
18 pumps, and welding equipment. Unintentional CO poisonings frequently happened indoors even
19 when people took precautions to ventilate the building.
20

21 **4.3.1.4 Exposure to Carbon Monoxide at Commercial Facilities**

22 Although motorists may turn off their engines during refueling, people still may be exposed
23 to CO concentrations from idling cars and other cars entering and leaving the fueling area of the
24 station. Wilson et al. (1991) randomly sampled 100 self-service filling stations and, for
25 comparison, took convenience samples at 10 parking garages and 10 nearby office buildings in
26 Los Angeles, Orange, Riverside, and San Bernardino counties of Southern California. They took
27 5-min samples of 13 motor vehicle air pollutants including CO in each microenvironment and in
28 the ambient environment. Microenvironmental and ambient concentrations were measured on
29 the same day but not simultaneously. The highest median CO concentration occurred in parking
30 garages (11.0 ppm), followed by service stations (4.3 ppm), and office buildings (4.0 ppm). The
31 median ambient CO concentration was 2.0 ppm.

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

9 Several studies of CO exposure in commercial facilities were not cited in the 1991 CO
10 AQCD. First, Kwok (1981) reported episodes of CO poisoning among skaters inside four arenas
11 in Ontario, Canada. Mean CO levels ranged from 4 to 81 ppm for periods of about 80 min. The
12 CO levels in the spectator areas ranged from 90 to 100% of levels on the rink. The ice
13 resurfacing machines lacked catalytic emission controls. Second, both Sorensen (1986) and
14 Miller et al. (1989) reported CO concentrations greater than 100 ppm in ice rinks from the use of
15 gas resurfacing machines. High concentrations were attributed to poorly maintained machines
16 and to an ice rink without sufficient ventilation. Third, based on data collected in the Quebec
17 city area, Lévesque et al. (1990) developed a linear relationship between CO exposure and the
18 CO concentration in exhaled breath (see Section 4.3.1.5 for discussion of CO exposure and
19 breath CO relationships) but could not eliminate other factors affecting the relationship. In a
20 later study, Lévesque et al. (1991) measured the alveolar CO of 14 male adult nonsmokers who
21 played ice hockey, but who were not exposed in occupational settings. Rink CO concentrations
22 ranged from 0 to 76.2 ppm. The study again found a linear relationship between exposure and
23 absorbed CO such that, for each 10 ppm of CO in the indoor air, the players absorbed enough CO
24 to raise alveolar CO by 4.1 ppm or about 0.76% COHb.

25 In the United States, surveys of CO exposure were done at ice arenas in Vermont,
26 Massachusetts, Wisconsin, and Washington. For a rink in Massachusetts, Lee et al. (1993)
27 showed that excessive CO concentrations can occur even with well-maintained equipment and
28 fewer resurfacing operations if ventilation is inadequate. Average CO levels were less than
29 20 ppm over 14 h, with no significant source of outdoor CO. Ventilation systems could not
30 disperse pollutants emitted and trapped by temperature inversions and low air circulation at ice
31 level. In another study, Lee et al. (1994) reported that CO concentrations measured inside six

1 enclosed rinks in the Boston area during a 2-h hockey game ranged from 4 to 117 ppm, whereas
2 outdoor levels were about 2 to 3 ppm, and the alveolar CO of hockey players increased by an
3 average of 0.53 ppm per 1 ppm CO exposure over 2 h. Fifteen years earlier, Spengler et al.
4 (1978) found CO levels ranging from 23 to 100 ppm in eight enclosed rinks in the Boston area,
5 which suggests that CO exposure levels in ice arenas have not improved.

6 In a letter, Paulozzi et al. (1991) reported that 25 people exposed to CO during a Vermont
7 high-school ice hockey game had mean COHb levels of 8.9%, but did not report if any of them
8 were smokers. Although Paulozzi et al. (1991) was unable to measure CO concentrations at the
9 game, Smith et al. (1992) reported CO levels of 150 ppm (no averaging time was given) at an
10 indoor ice-hockey rink in Wisconsin. To document the extent of the problem in Vermont,
11 Paulozzi et al. (1993) measured CO during eight high-school games in the state, and reported that
12 average CO levels for the entire game ranged from <5 to 101 ppm, with a mean of 35 ppm.
13 Hampson (1996) reported a maximum CO level of 354 ppm inside an ice arena in Seattle in
14 March 1996. Based on data for 17 persons whose tobacco use was not reported, the average
15 COHb level was 8.6% (range 3.3 to 13.9%). The source of CO was a malfunction in a
16 20-year-old ice resurfacing machine. Hampson also reported that CO may have diffused into an
17 adjacent bingo hall through an open door. In view of these studies, the State of Minnesota
18 declared in Regulation No. 4635 that CO measurements taken 20 min after ice resurfacing must
19 be less than 30 ppm.

20 Studies also have been done in sports arenas that allow motor vehicles. Boudreau et al.
21 (1994) reported CO levels for three indoor sporting events (i.e., monster-truck competitions and
22 tractor pulls) in Cincinnati, OH. The CO measurements were taken before and during each event
23 at different elevations in the public seating area of each arena with most readings obtained at the
24 midpoint elevation where most people were seated. Average CO concentrations over 1 to 2-h
25 ranged from 13 to 23 ppm before the event to 79 to 140 ppm during the event. Measured CO
26 levels were lower at higher seating levels. The ventilation system was operated maximally, and
27 ground-level entrances were completely open.

28 High CO levels also have been found at motor vehicle competitions in Canada. In a study
29 not cited in the 1991 CO AQCD, Luckurst and Solkoski (1990) recorded CO concentrations at
30 two tractor-pull events in Winnipeg, Manitoba. The mean of instantaneous concentrations at
31 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 were determined at five stations located at different points in the arena. The TWA concentrations ranged from 19.1 to 38.0 ppm, with higher levels during the second half of the show. High CO concentrations forced a health official to interrupt the event seven times to help clear the air. Covariance analysis showed that CO levels were related to the initial CO concentration, the event duration, motor size, and especially the number of motorcycles on the track.

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

The 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 can also be related to percentage of blood COHb by a calibration curve constructed by simultaneous blood sampling and end-tidal breath sampling. Because the CO air quality standards are intended to protect the nonsmoking public from attaining a level of 2.1% COHb (U.S. Environmental Protection Agency, 1992b), these end-tidal breath CO measurements can demonstrate whether nonsmoking subjects have been recently protected from reaching this level. 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 if 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 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

1 the results of different studies may be related to different breath collection methods and different
2 breath CO measurement techniques.

3 Lando et al. (1991) collected breath samples of 4,647 workers using MiniCO breath kits
4 (Model 1000, Catalyst Research Corporation, Owings Mills, MD). The latter part of a breath
5 was collected in a balloon following a 15-s breathhold but the method of analysis was not
6 described. Although the authors cite Jarvis et al. (1980) for this method, Jarvis et al. (1980) used
7 the Jones et al. (1958) method that requires a 20-s breathhold. Furthermore, these data are
8 uncorrected for the amount of CO in the maximal inhalation prior to the breathhold step (Smith,
9 1977; Wallace, 1983). Consequently, these data are not compatible with other studies using
10 20-s for the breathhold time and corrected data. Mean CO levels (Table 4-3) ranged from
11 4.2 (± 1.66 standard deviation [SD]) ppm for never-smokers to 33.3 (± 11.22 SD) ppm for heavy
12 smokers (25 cigarettes/day or more). Based on cutoffs of 3 and 6 ppm above ambient, a larger
13 number of ex-smokers (1.7 to 3.3%) than never-smokers (0.4 to 1.9%) appeared to be falsely
14 reporting their smoking status.

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

24 Seufert and Kiser (1996) measured CO levels in the end-tidal breath after a 10-s breathhold
25 of 126 crew members of a nuclear submarine just before and just after a 62-h submerged period.
26 The CO level in the submarine (called “ambient” by the authors) increased from 2.6 ppm to
27 9.2 ppm in the fan room and in two other spaces. The authors state that the increase was caused
28 primarily by cigarette smoke from the 40 smokers aboard because auxiliary diesel engines were
29 not used during the submersion period. The nonsmokers’ breath CO increased from 9 to 21 ppm.
30 Although the authors did not comment on the considerable difference between the nonsmokers’
31 breath CO of 21 ppm and the measured “ambient” concentration of only 9.2 ppm, it may have

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 (1 to 15 cigarettes/day)	M	14.3	15.6	14.0	13.79
	SD	8.40	8.94	8.70	7.21
	n	238	48	131	59
Moderate smokers (16 to 24 cigarettes/day)	M	24.7	24.6	25.4	23.4
	SD	10.47	11.72	10.06	9.67
	n	351	97	180	74
Heavy smokers (25 cigarettes/day or more)	M	33.3	32.6	34.1	33.0
	SD	11.22	9.61	12.73	10.50
	n	273	95	117	61

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

Source: Lando et al. (1991).

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 instrumental systems. Operation of an atmospheric revitalization system that removed CO also may have contributed to a lower monitored “ambient” CO than the CO nonsmokers were exposed to in the nonmonitored duty sections.

Zayas 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 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 ppm of CO in the air inhaled for the breathhold.

4.3.1.6 Nonoccupational Exposure to Methylene Chloride

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

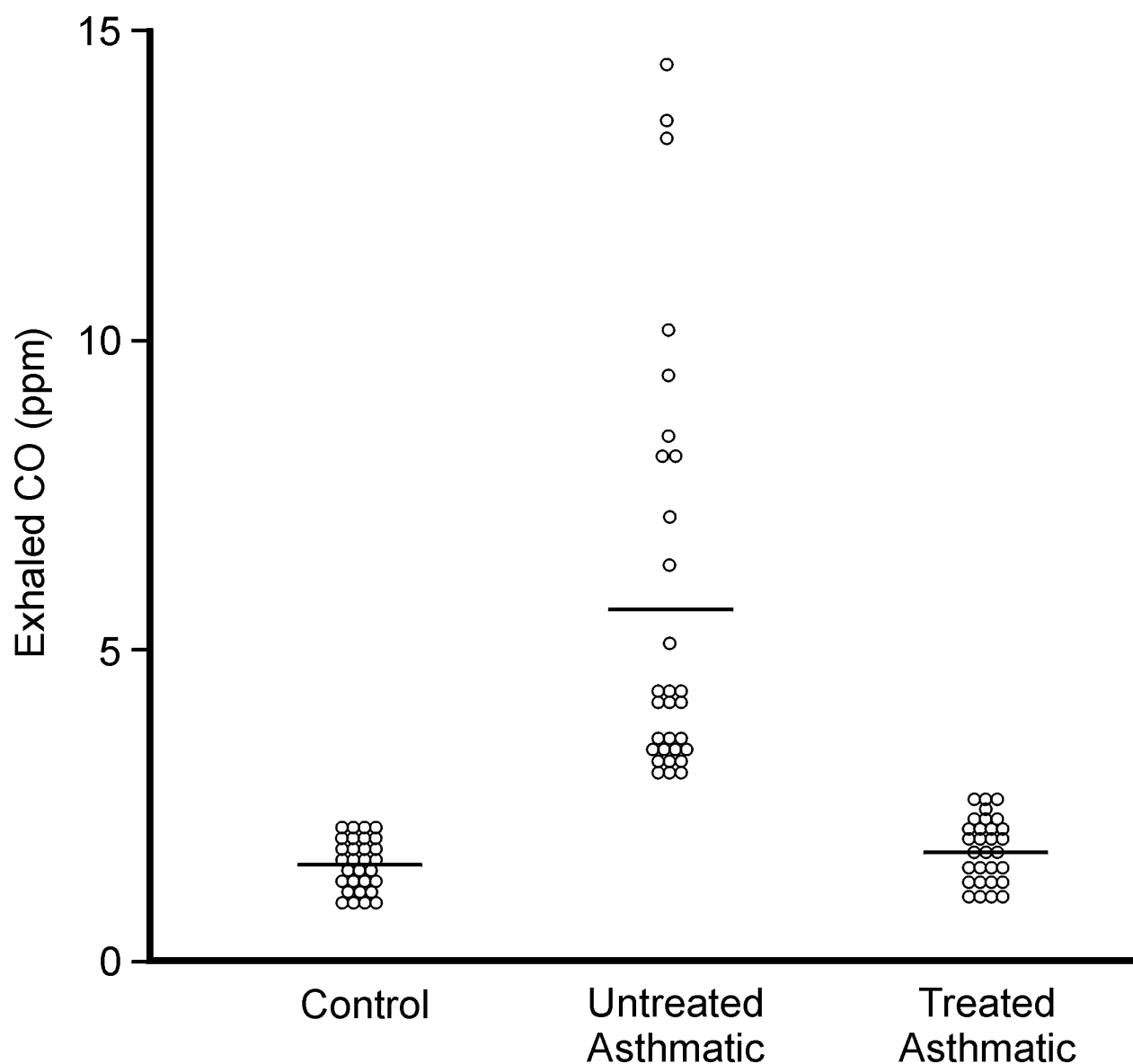


Figure 4-6. Excess CO concentrations in the exhaled air of nonsmoking control subjects (n = 30), untreated asthmatics (n = 30), and treated asthmatics (n = 30). The values shown were determined by subtracting the background level from the observed reading. “Untreated” means no inhaled corticosteroids,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

Source: Zayasu et al. (1997).

1 ingested in drinking water or inhaled when it volatilizes during showering and laundering
2 (Agency for Toxic Substances and Disease Registry, 1993).

3 Exposure to about 500 ppm of methylene chloride for several hours can elevate COHb
4 levels to 15%. Increases in COHb levels can be detected in the blood of nonsmokers about
5 30 min after exposure to methylene chloride. Stewart et al. (1972) demonstrated that elevated
6 COHb levels were proportional to a series of controlled exposures to methylene chloride. In a
7 controlled experiment, Stewart and Hake (1976) observed postexposure levels of COHb ranging
8 from 5 to 10% after 3 h of use of a liquid-gel paint remover containing 80% methylene chloride
9 and 20% methanol by weight. Concurrent exposure to methylene chloride and methanol
10 prolongs the period of elevated COHb in the body (Stewart and Hake, 1976; Buie et al., 1986;
11 Wilcosky and Simonsen, 1991). Peterson (1978) reported COHb levels of up to about 10%
12 saturation after inhalation of methylene chloride concentrations ranging from 50 to 500 ppm over
13 5 days for 7.5 h per day.

15 **4.3.2 Occupational Exposures**

16 This subsection discusses occupational exposures to CO and methylene chloride.

18 **4.3.2.1 Exposures to Carbon Monoxide in the Workplace**

19 A survey by the National Institute for Occupational Safety and Health (NIOSH) found that
20 3.5 million workers in the private sector potentially are exposed to CO primarily from motor
21 exhaust. The number of persons potentially exposed to CO in the work environment is greater
22 than that for any other physical or chemical agent (Pedersen and Sieber, 1988). In 1992, there
23 were 900 work-related CO poisonings resulting in death or illness in private industry as reported
24 by the U.S. Bureau of Labor Statistics (as cited in National Institute for Occupational Safety and
25 Health, 1996). Three risk factors affect industrial occupational exposure: (1) the work
26 environment is located in a densely populated area that has high background (i.e., ambient) CO
27 concentrations; (2) the work environment produces CO as a product or by-product of an
28 industrial process, or the work environment tends to accumulate CO concentrations that may
29 result in occupational exposures; and (3) the work environment involves exposure to methylene
30 chloride, which is metabolized to CO in the body. Proximity to fuel combustion of all types
31 elevates CO exposure for certain occupations: airport employees; auto mechanics; small

gasoline-powered tool operators (e.g., users of chainsaws); charcoal meat grillers; construction workers; crane deck operators; firefighters; forklift operators; parking garage or gas station attendants; policemen; taxi, bus, and truck drivers; toll booth and roadside workers; and warehouse workers (U.S. Environmental Protection Agency, 1991).

Studies of firefighters are discussed briefly below because these studies were not discussed in the 1991 CO AQCD. Other occupational studies of CO exposure are summarized in Table 4-4, 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, 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.

4.3.2.2 Exposures to Methylene Chloride in the Workplace

Certain occupations expose workers to organic solvents such as methylene chloride. The solvent is widely used as a degreaser, paint remover, aerosol propellant, and blowing agent for

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

^aNA = not available, INT = interior of vehicle, NS = nonsmokers, and IM = inside mask.

Source: Adapted from Apte (1997) and updated.

polyurethane foams. It is used as an extractant for foods and spices, a grain fumigant, and a low-pressure refrigerant. It also is used in the manufacturing of synthetic fibers, photographic film, polycarbonate plastics, pharmaceuticals, printed circuit boards, and inks. More than one million workers have significant potential for exposure to methylene chloride (Agency for Toxic Substances and Disease Registry, 1993). Moreover, the highest levels of exposure to methylene chloride often occur in the workplace. To protect worker health, the 8-h TWA threshold limit value for methylene chloride was set at 50 ppm by the American Conference of Governmental Industrial Hygienists. Exposure at this concentration leads to COHb levels of about 1.9% in experimental subjects. Exposure to 500 ppm for several hours may elevate COHb levels as high as 15%. An 8-h exposure to about 500 mg/m³ (3.5 mg/m³ = 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/m³ of methylene chloride for 7.5 h was associated with a COHb level of 6.8% in eight volunteers. Exposure to methylene chloride also can be fatal. Leikin et al. (1990) reported fatalities of two people who were exposed to unknown concentrations of methylene chloride while they removed paint in an enclosed space. Death was caused not by CO poisoning, but by solvent-induced narcosis. Before they died, their COHb levels continued to rise following cessation of exposure despite treatment by high levels of oxygen.

4.3.3 Activity Pattern Studies

In assessing population exposure, studies of human activity patterns over a fixed time period (e.g., 24 h) are necessary to determine how many people potentially are exposed to sources of an air pollutant, and how long people spend in activities that involve use of these sources. Accordingly, this section reviews studies of human activity patterns that pertain to

1 population exposure to CO and methylene chloride. Previous studies reviewed in the 1991 CO
2 AQCD reported that many Americans spent most of their time indoors at home, school, or work,
3 etc. (Szalai, 1972; Chapin, 1974; Meyer, 1983; Johnson, 1989; Schwab et al., 1990). Although
4 more recent activity pattern studies largely confirm this finding, their sampling and questionnaire
5 designs provide new insights. This section reviews, in chronological order, newer studies that
6 include two surveys of activity patterns in California, a similar survey of preadolescents in six
7 states, a comparative study between California and the nation, a study in southwest England,
8 a Boston study, and a recent survey at the national level.

9 10 **4.3.3.1 Activity Patterns of California Residents**

11 The California Air Resources Board (CARB) conducted two surveys to determine the
12 activity patterns of California residents. In each case, projectable probability samples were
13 drawn from English-speaking households who had telephones. The first surveyed 1,762 adults
14 and adolescents over 11 years of age from fall 1987 through summer 1988 (Wiley et al., 1991a;
15 Jenkins et al., 1992), and the second surveyed 1,200 children under age 11 from April 1989
16 through February 1990 (Wiley et al., 1991b; Phillips et al., 1991). Using telephone interviews,
17 both surveys asked participants to complete a 24-h diary for the preceding day. People ages
18 9 and over responded directly to the interview, and the primary adult careprovider responded for
19 young children. The diaries enabled estimates of time spent in various activities and locations,
20 and determinations of whether respondents used or were near sources of pollutants, including
21 consumer products, combustion appliances, and motor vehicles.

22 Similar to previous studies, the results showed that all age groups spent most of their time
23 indoors. Adults and adolescents in California spent, on average, 87% of their time indoors (62%
24 at home and 25% elsewhere), and only 6% of their time outdoors. They also spent 7% of their
25 time in transit mostly in a car, van, or pickup truck. Compared to adults and adolescents,
26 children spent a similar amount of time indoors (86%), but more time at home (76%) and
27 outdoors (10%), and less time indoors elsewhere (10%) and in transit by car, van or pickup truck
28 (4%). About 46% of nonsmoking adults/adolescents reported being near others' tobacco smoke
29 at some time during the day.

30 Table 4-5 summarizes results of the two California surveys for various microenvironments
31 pertinent to CO exposure. For each microenvironment, the table shows the mean and range in

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

NA = not available.

^a Note: 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).

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.

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 1987-88	Children 1989-90
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 gas 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
Environmental Tobacco Smoke (ETS)		
Nonsmokers near ETS at any time during the day:		
Adults (18 years or older)	43	
Youths (12 to 17 years)	64	
Adults and youths (12 years and older)	46	
Youths (0 to 11 years)		38

^aNote: 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.

^bPotential methylene chloride exposure.

^cData presented for adult respondents (age 18 years or older) only.

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

4.3.3.2 Activity Patterns of Children in Six States

In 1990 and 91, Silvers et al. (1994) surveyed the activities of preadolescent children (ages 5 to 12 years) from a projectable probability sample of 1,000 households in six states. These states included three on the East Coast (New Jersey, New York, and Pennsylvania) and three on the West Coast (California, Oregon, and Washington). Comparisons between this study known as the Children's Activity Survey (CAS) and the CARB children's study are possible because both were done over an entire year at about the same time, and both used a retrospective time diary for a 24-h day. Both studies reported very similar results in terms of the mean hours per day spent by preadolescent children for locations designated "indoors" (21.5 h for CARB versus 21.7 h for CAS) and "at home" (18.0 h for CARB versus 17.8 h for CAS). For each study, these results varied by ± 1 h for different seasons of the year. There was variation in specific activities (e.g., the CAS study reported that preadolescents spent less time per day "riding in a vehicle" in California [0.52 h] than they did in the five other states [0.82 h], when the five were combined as a group). The CAS study did not report time spent near other CO sources.

4.3.3.3 A Comparative Study Between California and the Nation

Robinson and Thomas (1991) compared results of activity pattern studies, one conducted by CARB in California in 1987 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.

4.3.3.4 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).

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

Using activity diary data from 150 households that participated in a 1991 Boston survey, Vadarevu and Stopher (1996) tested several hypotheses about household travel. One study hypothesis was that there are significant differences in mean time allocations of activities among different "life-cycle groups" based on age, working status, and household size. They tested the theory that life-cycle stage affects which activities fall into mandatory, flexible, and optional categories; how much time can be allocated to different activities; and which household member does each activity. They found that time allocated by households to specific activities varied according to whether the household consisted of a single working adult, multiple adults, a young family, an older family, or a nonworking adult. However, they found no significant differences among the life-cycle groups or between any life-cycle group and the population mean in terms of the total time spent in mandatory activities (work, work-related, school, and certain at-home activities), which required on average 21 h per day. The amount of time spent in all flexible, optional, and travel activities was about 3 h per day.

4.3.3.6 The National Human Activity Pattern Survey

The U.S. Environmental Protection Agency'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 9,386 respondents, 38.3% reported having a gas range or oven at home, and another 23.7% said that the range/oven had a burning pilot light. In terms of motor vehicle use, 10% of 6,560 people (7.0% of total sample) spent more than 175 min per day inside a car, and 10% of 1,172 people (1.2% of total sample) spent more than 180 min inside a truck, pickup, or van. Of those who were inside a car and knew they had angina (n = 154 respondents), 10% of them spent more than 162 min per day inside a car. The survey also asked about sources of household pollutants. Of 4,723 respondents, 10.5% were exposed to solvents, 10.4% to open flames, and 8.4% to "gas-diesel" powered equipment; 6.3% of these respondents were in a garage or indoor parking lot; and 5.7% reported that someone smoked cigarettes at home. Only 1.8% of 4,663 respondents reported having a kerosene space heater at home.

4.4 MAJOR FACTORS AFFECTING POPULATION EXPOSURE

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

4.4.1 Federal Policies Affecting Transportation and Air Quality in Urban Areas

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

Since the mid-1960s, major construction projects intended to expand highway capacities have been opposed in some metropolitan areas. Opponents claimed that these projects promoted urban sprawl and induced motor vehicle travel that raised regional air pollutant emissions. To address these concerns, the 1990 CAA amendments state that transportation actions (plans, programs, and projects) cannot create new NAAQS violations, increase the frequency or severity of existing NAAQS violations, nor delay attainment of the NAAQS (U.S. Code, 1990). Pursuant thereto, the U.S. Environmental Protection Agency promulgated its Transportation Conformity Rule. Complementary provisions of the 1991 Intermodal Surface Transportation Efficiency Act offered financial incentives under the Congestion Management and Air Quality (CMAQ) improvement program. Under CMAQ, metropolitan planning organizations were offered federal funds to improve air quality by implementing transportation control measures (TCMs). Examples of TCMs include programs to promote car and van pooling, flextime, special lanes for high occupancy vehicles, and parking restrictions.

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, 1998b]), the study inferred how much TCMs would change average speeds of motor vehicles and CO emissions therefrom. The direct effect of TCMs on commuter exposure to CO has received only

1 limited study. Flachsbart (1989) found that priority (with-flow and contra-flow) lanes were
2 effective in reducing exposure to motor vehicle exhaust on a coastal artery in Honolulu.
3 Compared to commuter CO exposure in adjacent but congested lanes, exposure in priority lanes
4 was about 18% less for those in carpools, 28% less for those in high-occupancy vehicles (e.g.,
5 vanpools), and 61% less for those in express buses. These differences occurred possibly because
6 commuters in priority lanes traveled faster than those in the congested lanes. Faster vehicles
7 created more air turbulence, which may have helped to disperse pollutants surrounding vehicles
8 in priority lanes. Furthermore, these differences existed even though the priority lanes were often
9 downwind of the congested lanes. Although higher speeds were related to lower exposures in
10 priority lanes, differences in exposure also could have been caused by differences in vehicle type
11 and ventilation, both of which were not controlled.

12 More recently, Rodes et al. (1998) compared the CO concentrations of two test vehicles
13 driven on standardized routes that included a freeway carpool lane in Los Angeles. One vehicle
14 used the carpool lane and the other the unrestricted lanes. Each vehicle repeatedly drove its route
15 for both the morning and evening rush-hour periods of one day, and CO measurements were
16 taken continuously both inside and outside of each vehicle. Because the vehicles had different
17 air exchange rates, comparisons of external CO levels measured at the base of the windshield are
18 appropriate. Based on these measurements, the average CO concentration of the vehicle in the
19 noncarpool lane (5.6 ppm) was twice as high as that of the vehicle in the carpool lane (2.8 ppm).
20 For a hypothetical 30-mi commute, exposure in the noncarpool lane (measured in parts per
21 million-minutes) was estimated to be 187% greater than exposure in the carpool lane. The study
22 suggests that carpoolers may have lower total CO exposure for their entire commute, because
23 they are exposed to lower CO concentrations and spend less time commuting in heavy traffic.
24 However, the study did not account for the extra time to collect nonfamily members of a carpool.

25 Models to estimate the direct effects of TCMs on commuter CO exposure are not apparent
26 in the literature. However, Flachsbart (1999a) developed a series of statistical models to predict
27 passenger cabin exposure to CO based on trip variables for a 3.85-mi, Honolulu artery divided
28 into three links. Based on data for 80 trips, the most practical models of third-link exposure
29 (adjusted correlation coefficient $[R^2] = 0.69$) combined three variables: (1) the ambient CO
30 concentration; (2) the second-link travel time; and (3) either the travel time, vehicle speed, or CO
31 emission factor for the third link. The models showed that the vehicle's travel time and average

1 speed and the CO emission factor for a given link of the roadway had equal ability to predict
2 passenger cabin exposure to CO on the third link because of mathematical relationships among
3 these three predictor variables.
4

5 **4.4.2 Federal and State Policies Affecting Temporal Trends in Exposure**

6 Studies show significant temporal trends in population exposure to CO concentrations from
7 motor vehicle emissions based on different indicators. One indicator is unintentional death rates
8 from CO poisoning, and another is based on direct measurements of passenger cabin exposure to
9 CO concentrations from traffic emissions. Table 4-7 summarizes data on these indicators from
10 several U.S. studies and shows the federal and California tailpipe CO emission standards by
11 model year for comparison. In Table 4-7, the net mean CO concentration value represents the
12 microenvironmental component of total exposure. This value equals the mean in-vehicle CO
13 concentration, minus the mean ambient CO concentration as recorded simultaneously at a
14 fixed-site monitor.
15

16 **4.4.2.1 Effects of Motor Vehicle Emission Standards on Unintentional Death Rates**

17 Based on death certificate reports compiled by the National Center for Health Statistics,
18 Cobb and Etzel (1991) reported statistics on the annual rate of unintentional deaths from CO
19 poisoning in the United States. As shown in Table 4-7, the annual death rate per 100,000
20 population declined from 0.67 in 1979 to 0.39 in 1988. Motor vehicle exhaust gas accounted for
21 6,552 deaths or 56.7% of the total 11,547 unintentional deaths occurring during the 10-year
22 period. The highest death rates per 100,000 persons occurred among males, blacks, the elderly,
23 and residents of northern states. Monthly variation in death rates indicated a seasonal pattern,
24 with January fatalities routinely about two to five times higher than in July.

25 Although mortality is not a health effect used in setting the NAAQS for CO, the Cobb and
26 Etzel (1991) study still has value in its revelations about cofactors of personal exposure to high
27 CO levels. Moreover, the study speculated that declining death rates could be attributed in part
28 to automaker compliance with the motor vehicle CO emission standards of the CAA. They
29 argued that tighter CO emission standards may enable cars to emit exhaust into an enclosed space
30 for a longer period of time before CO builds up to toxic levels.
31

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

^aMean in-vehicle CO concentration minus mean ambient CO concentration.

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

4.4.2.2 Effects of Motor Vehicle Emission Standards on Passenger Cabin Exposure

Based on a review of 16 U.S. studies that occurred between 1965 and 1992, Flachsbart (1995) reported a long-term, downward trend in commuter exposure levels (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 commuter CO exposures in cities during these time periods, then exposures fell 92% over this 27-year period. This reduction implies that CO exposure levels reported in the past for a particular place and time in the United States may not be indicative of current exposures.

In the United States, the effect of progressively tighter CO emission standards on in-vehicle CO exposures over time is readily apparent in Table 4-7. 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 equal to the 92% reduction in commuter exposure reported above for the same period. Further analysis reveals that net mean exposure data and the applicable emission standard data in Table 4-7 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 1980-1981 on a suburban highway near San Jose. They reported a mean CO concentration of 9.8 ppm for trips of 35 to 45 min. In 1991-1992, Ott et al. (1993) resurveyed this highway using a methodology similar to

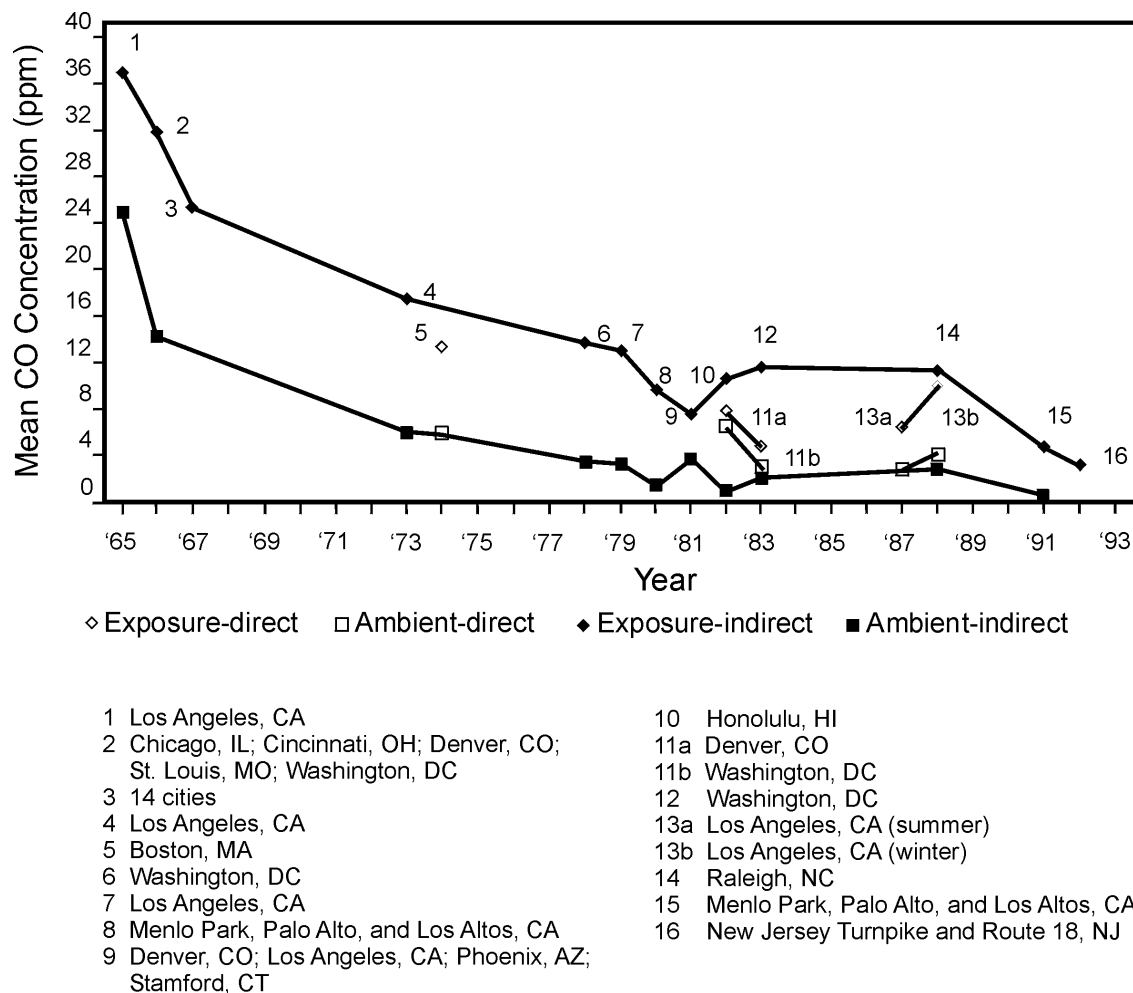


Figure 4-7. Trends in ambient CO concentrations and in-vehicle CO exposures, 1965 to 1992. (The upper and lower lines are provided to make a clear distinction between exposure and ambient CO data reported for each city; these lines do not imply that results for cities are related.)

Source: Flachsbart (1995).

1 their previous study to determine in-vehicle exposure trends. They reported that the mean
 2 in-vehicle CO concentration had dropped to 4.6 ppm or 47% of the mean value estimated
 3 11 years earlier. They attributed the exposure reduction to replacement of older vehicles with
 4 newer ones that have lower CO emission factors. This reduction is particularly significant, as

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

3 For this highway, Yu et al. (1996) developed a mathematical model known as the STREET
4 model to predict trends in CO emissions and exposures. Based on fleet turnover and no changes
5 in the 1990 California motor vehicle CO emission standards, the model predicted that the median
6 CO concentrations would drop from 3.9 ppm in 1991 and 1992 to 1.6 to 1.8 ppm in 2002 and
7 2003. At the 99% percentile, the model predicted that the CO concentrations would drop from
8 10 ppm in 1991 and 1992 to 4.0 to 4.6 ppm in 2002 and 2003. This prediction was based on an
9 additional expected reduction of up to 60% in tailpipe emissions of CO primarily because of
10 continued replacement of older cars with newer, low-emission vehicles. However, these
11 predictions could be too low because the study did not anticipate the phenomenal growth in sport
12 utility vehicle (SUV) use in California during the 1990s. The certified CO emissions of SUVs
13 exceed that of standard passenger cars.

14 Similar studies of commuter CO exposure were done by Flachsbart et al. (1987) in the
15 United States, Koushki et al. (1992) in Saudi Arabia, Fernández-Bremauntz and Ashmore
16 (1995a,b) in Mexico, and Dor et al. (1995) in France. These studies used similar methods of data
17 collection and analysis, with one exception. Smoking was allowed for some trips in the Saudi
18 study, but was not allowed in the other studies. Table 4-8 shows typical values of the net mean
19 CO concentration by travel mode for three of the studies. The net mean CO concentration for the
20 Saudi study could not be determined. The net CO concentrations for each travel mode in Mexico
21 City were much higher than for comparable modes in both Washington and Paris, where net CO
22 concentrations were similar. The similarity between the U.S. and French studies occurred even
23 though catalytic converters existed on 62% of American cars in 1982 (U.S. Department of
24 Commerce, 1983) but were not yet common on French cars in 1992 (Dor et al., 1995).

25 The reasons for the similarity in results between the U.S. and French studies are not readily
26 apparent. However, passenger cabin exposure levels in North and Central America can be
27 explained partly by comparing the history of automotive emission standards in the United States
28 and Mexico. The United States initiated nationwide emission standards on new passenger cars in
29 1968 and adopted progressively tighter controls throughout the 1970s (Johnson, 1988). By the
30 1975 model year, catalytic converters became standard equipment on new passenger cars.

**TABLE 4-8. TYPICAL NET MEAN CARBON MONOXIDE CONCENTRATION RANGES BY TRAVEL MODE
FOR CITIES IN THREE COUNTRIES^{a,b}**

Travel Mode	Washington, DC, USA (1983)		Mexico City, Mexico (1991)		Paris, France (1991-92)	
	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.

^bNet mean CO concentration = mean in-vehicle CO concentration, minus mean ambient CO concentration.

NA = not available.

Source: Adapted from Flachsbart (1999b).

1 Mexico adopted a tailpipe CO emission standard of 47.0 g/mi for the 1975 model year, and,
2 by the 1993 model year, Mexico finally reached parity with the 1981 U.S. standard of 3.4 g/mi.

4 **4.4.3 Social Changes Affecting Human Activity Patterns**

5 Between 1965 and 1985, the Americans' Use of Time Project at the University of
6 Maryland reported that average time spent in travel for leisure trips increased from 2.7 to
7 3.1 h per week (Cornish et al., 1991). Despite this trend, there is evidence that average
8 commuting times between home and work have remained stable. The decennial census
9 collected travel time data for the first time in 1980. By 1990, the census showed that the
10 nation's average commuting time of 21.7 min in 1980 increased only 40 s to 22.4 min in 1990.
11 Although the number of workers who commuted 45 min or more increased from 10.9 million in
12 1980 to 13.9 million in 1990, the mean travel time of this commuter cohort actually decreased
13 slightly from 59.6 min in 1980 to 58.5 min in 1990. One reason for this is that more people
14 were taking their morning commute from home to work during the "shoulder hours" from 6 to
15 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
16 hours accounted for about 37% of worker trip starts, whereas the "peak hour" accounted for
17 only 32% of all trip starts (Pisarski, 1992).

18 Typically, average commuting times in large metropolitan regions are greater than those
19 nationwide. In the Washington, DC metropolitan region, for example, the average daily
20 commuting time for all modes of travel between home and work was 62 min per day in 1957
21 (Bello, 1958). This value increased to 69 min per day by 1968 and fell slightly to 68.3 min in
22 1987 and 1988 when the region was resurveyed. The stability in daily commuting times
23 between the 1968 and the 1987 and 1988 surveys was achieved by an increase in travel speed.
24 This increase in travel speed offset greater travel distances between home and work that
25 occurred during that 20-year period. For those who commuted alone by automobile in
26 Washington, the average Euclidean, round-trip travel distance from home to work increased
27 from 13.8 miles in 1968 to 16.1 miles in 1987 and 1988. However, the average trip speeds of
28 solo commuters in Washington also increased (i.e., by 10.7% for home-to-work trips and by
29 20.3% for work-to-home trips) to offset increased commuting distance (Levinson and Kumar,
30 1994). This increase in trip speeds is significant because passenger cabin exposure to CO

1 concentrations has been shown in a separate study to be inversely related to travel speed in the
2 Washington area (Flachsbart et al., 1987).

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

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

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

4.5 CONCLUSIONS

This chapter has reviewed studies of population exposure to carbon monoxide, including some key studies from the previous CO AQCD, 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 last AQCD and some current gaps in knowledge about population exposure to CO. The previous CO AQCD 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, occupational and residential sources of unvented fuel combustion, or 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/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

1 vehicles are expected to drop further in the near future. However, those projections could be too
2 low because the study did not anticipate or account for the phenomenal growth in sport utility
3 vehicle (SUV) use during the 1990s. The certified CO emissions of SUVs presently exceed
4 those of standard passenger cars, and the U.S. Environmental Protection Agency did not propose
5 tighter emission standards for SUVs until 1999.

6 Likewise, there are uncertainties over the extent to which population exposure to CO has
7 changed in other ways since the 1991 AQCD. First, there are no apparent trend studies of CO
8 exposure in other important microenvironments (e.g., indoor parking garages, pedestrian
9 sidewalks on commercial streets, or home environments affected by greater use of microwaves
10 for cooking in lieu of gas ranges). Second, the net effect of various travel behavior trends on
11 commuter CO exposure is uncertain. Trends noted in this chapter include disproportionately
12 high growth rates in vehicle miles of travel, growth in travel during “shoulder” hours of
13 peak-traffic periods, and growing use of personal computers for telecommuting and
14 teleshopping from home in lieu of trips by motor vehicles. These trends and their implications
15 for exposure suggest that the results of earlier personal CO monitoring studies, such as those of
16 Akland et al. (1985) summarized in Table 4-1, are probably no longer indicative of present CO
17 levels and population exposures. These types of personal exposure studies would need to be
18 redone to determine current CO exposure levels of similar urban populations.

19 The 1991 CO AQCD reported that people are exposed to elevated CO levels in certain
20 indoor microenvironments (e.g., unventilated parking garages, motor vehicles with leaky
21 exhaust systems, and small homes with unvented gas stoves and space heaters). More recent
22 studies in California homes indicate that elevated CO concentrations still exist and can be
23 caused by several factors such as attached garages and carports, ranges with continuous gas pilot
24 lights, improper use and installation of gas appliances, especially in small homes (Wilson
25 et al.,1993a,b; Colome et al.,1994). Also, recent studies have found elevated CO concentrations
26 when people ride certain types of recreational vehicles (i.e., snowmobiles and power boats),
27 gather indoors to barbecue food (sometimes to cope with electrical power outages), and watch
28 sporting events held at indoor arenas. High-level exposures may occur inside arenas when they
29 are used for ice skating, motocross and monster-truck competitions, and tractor-pulls. Vehicles
30 used in these competitions often lack any type of emission controls. In some cases, ventilation
31 alone has not lowered CO sufficiently to safe levels at these events. Moreover, recent studies

1 report that high-level CO exposures can occur when people use unregulated gasoline-powered
2 appliances, engines, and tools, (e.g., chainsaws), even under ventilated conditions.

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

14 In analyzing activity patterns, the California and national studies both analyzed activities
15 by conventional social categories (e.g., gender, age, race, etc.). In a travel behavior study,
16 Vadarevu and Stopher (1996) used a different social construct that revealed significant
17 differences in activity patterns among different life-cycle groups defined by age, working status,
18 and household size. Hence, although their study did not focus on CO exposure assessment
19 per se, it still has useful lessons for the design and analysis of activity pattern studies. Their
20 study also revealed that modern urban people make continuous tradeoffs in their activity
21 patterns and household-role allocations (in terms of who gets to do what and when) in response
22 to ongoing social and technological changes. However, the effects of these activity and role
23 adjustments by householders on personal CO exposure still needs to be documented by
24 empirical study.

25 In light of the above, population exposure models (e.g., pNEM/CO and SHAPE) may need
26 to sample from distributions that more accurately represent current microenvironmental CO
27 concentrations and time budgets and add certain high exposure level microenvironments (e.g.,
28 tobacco smoke exposure while in a vehicle, or sporting events involving motor vehicles at
29 indoor arenas) to their current list. In the future, simulation models of exposure should consider
30 that trip times and commuter exposures are not independent of trip-starting times, and that the
31 distribution of CO exposure is homogeneous for all types of commuters. As evidence of the

1 former, Flachsbart (1999a) showed that a commuter's travel time and CO exposure inside a
2 passenger car for a trip from home to work was related to trip departure time. Not surprisingly,
3 travel during off-peak hours (i.e., the “shoulder” periods) to avoid congested traffic resulted in
4 both less travel time and CO exposure. As evidence of the latter, carpoolers can reduce their
5 CO exposure if they use high-occupancy vehicle lanes on highways, as shown by both
6 Flachsbart (1989) in Hawaii and by Rodes et al. (1998) in Southern California.

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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. Furthermore, the animal data at least partially fill the knowledge gaps for which no human data are currently available in these areas of research. Despite some well recognized interspecies differences in the toxicokinetics of CO, the basic mechanisms of CO toxicity between animals and humans are similar and in many respects close to identical (Tyuma et al., 1981; Benignus and Annau, 1994;

1 Kimmel et al., 1999). The discussion of interspecies differences as they relate to humans may
2 aid in interpretation of data and elucidation of mechanisms; however, for the material presented
3 in this chapter, it is not essential and is well beyond the scope of this document. Despite
4 interspecies differences, especially in the uptake and elimination kinetics of CO, extrapolation of
5 observations from animals to man as applied in this chapter, even with its many assumptions,
6 may be useful in identifying potential pathophysiologic and histotoxic processes associated with
7 CO exposure.

10 **5.2 ABSORPTION, DISTRIBUTION, AND PULMONARY ELIMINATION**

11 **5.2.1 Pulmonary Uptake**

12 Although CO is not one of the respiratory gases, the similarity of physico-chemical
13 properties of CO and oxygen (O₂) permits an extension of the findings of studies on the kinetics
14 of transport of O₂ to those of CO. The rate of formation and elimination of COHb, its
15 concentration in blood, and its catabolism is controlled by numerous physical factors and
16 physiological mechanisms. The relative contribution of these mechanisms to the overall COHb
17 kinetics will depend on the environmental conditions, the physical activity of an individual, and
18 many other physiological processes, some of which are complex and still poorly understood
19 (see Section 5.4 for details). All of the pulmonary uptake occurs at the respiratory bronchioles,
20 alveolar ducts, and sacs. The rate of CO uptake depends on the rate of COHb formation. At the
21 low concentration of CO in inhaled air, the rate of uptake and the rate of COHb formation could,
22 for all practical purposes, be considered to be qualitatively the same.

24 **5.2.1.1 Mass Transfer of Carbon Monoxide**

25 The mass transport of CO between the airway opening (mouth and nose) and the red blood
26 cell (RBC) hemoglobin (Hb) is predominantly controlled by physical processes. The CO transfer
27 to the Hb-binding sites is accomplished in two sequential steps: (1) transfer of CO in a gas
28 phase, between the airway opening and the alveoli; and (2) transfer in a “liquid” phase, across the
29 air-blood interface, including the RBC. In the gas phase, the key mechanisms of transport are
30 convective flow, by the mechanical action of the respiratory system, and diffusion in the acinar

1 zone of the lung (Engel et al., 1973). Subsequent molecular diffusion of CO across the
2 alveolo-capillary membrane along the CO pressure gradient, plasma, and RBC is the virtual
3 mechanism of the liquid phase. The principal transport pathways and body stores of CO are
4 shown in Figure 5-1 (Coburn, 1967).

6 **5.2.1.2 Effects of Dead Space and Ventilation/Perfusion Ratio**

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

15 The inefficiency of gas mixing and a consequent decrease in the effectiveness of alveolar
16 gas exchange is aggravated by ventilation/perfusion (\dot{V}_A/\dot{Q}) mismatch. Because of the gravity
17 dependence of ventilation and even more of perfusion in an upright posture, regional \dot{V}_A/\dot{Q} ratios
18 will range from 0.6 (at the base of the lung) to 3.0 (at the apex), the overall value being 0.85.
19 As a result, the \dot{V}_A/\dot{Q} ratio is the principal variable controlling gas exchange, and any inequalities
20 not only will impair transfer of gases to the blood but also will interfere with unloading of gases
21 from the blood into the alveolar air. In humans, a change in posture to recumbent or horizontal,
22 or exercise will increase the uniformity of \dot{V}_A/\dot{Q} ratios and promote more efficient gas exchange,
23 whereas increased resting lung volume, increased airway resistance, decreased lung compliance,
24 and, generally, any lung abnormality will aggravate \dot{V}_A/\dot{Q} ratio inequality.

25 The simplest indicator of the \dot{V}_A/\dot{Q} ratio inequalities is the volume of physiological dead
26 space (V_D), which comprises both the anatomical and alveolar dead space. The alveolar dead
27 space results from reduced perfusion of alveoli, relative to their ventilation (Singleton et al.,
28 1972). Both right-to-left and physiological shunts under normal conditions contribute little to
29 \dot{V}_A/\dot{Q} inequality (West, 1990a). An increase in tidal volume or respiratory frequency, or both,

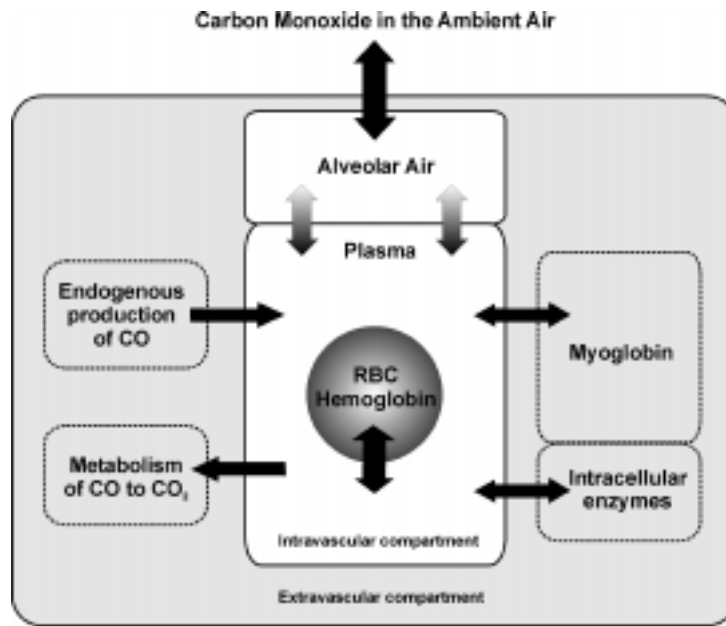


Figure 5-1. Diagrammatic presentation of CO uptake and elimination pathways and CO body stores.

Source: Adapted from Coburn (1967).

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. In order to reach the Hb-binding sites, CO and other gas molecules have to pass across the alveolo-capillary membrane, diffuse through the plasma, pass across the RBC membrane, and finally enter the RBC stroma before reaction between CO and Hb can take place. The molecular transfer across the membrane and the blood phase is governed by general physico-chemical laws, particularly by Fick's first law of diffusion (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 by immediate and tight binding of CO to Hb. The rapidity of CO binding to Hb keeps a low partial pressure of CO within the RBC, thus maintaining a high pressure differential between air and blood and consequent diffusion of CO into blood. Subsequent inhalation of CO-free air reverses the gradient (higher CO pressure on the blood side than alveolar air), and CO is released into alveolar air. The air-blood pressure gradient for CO is usually much higher than the blood-air gradient; therefore, the CO uptake will be a proportionately faster process than CO elimination. The rate of CO release also will be affected by metabolic and endogenous production of CO.

Diurnal variations in CO diffusion capacity of the lung ($D_L\text{CO}$) 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 CO_2 , ventilatory pattern, O_2 consumption, blood flow, functional residual capacity, etc. (Forster, 1987). Diffusion seems to be relatively independent of lung volume within the midrange of vital capacity. However, at extreme volumes, the differences in diffusion rates could be significant; at total lung capacity, diffusion is higher, whereas, at residual volume, it is lower than the average (McClellan et al., 1981). In a supine position at rest, $D_L\text{CO}$ has been shown to be significantly higher than that at rest in a sitting position (McClellan et al., 1981). Carbon monoxide diffusion increases with exercise, and, at maximum work rates, diffusion will be maximal regardless of body position. This increase is attained 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 might 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 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 of CO and duration of exposure. Experimental exposures of the oronasal cavity in monkeys to very high concentrations of CO for a very short period of time (5 s) increased the blood COHb level to <3.5%. Comparative exposures of the whole lung, however, elevated COHb to almost 60% (Schoenfisch et al., 1980). Thus diffusion of CO across the airway mucosa will contribute little if at all to overall COHb concentration.

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 O₂. However, the CO chemical affinity (represented by the Haldane coefficient, M) for Hb is about 218 (210 to 250) times greater than that of O₂ (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 O₂ would form equal parts of O₂Hb and COHb (50% of each), which would be achieved by breathing air containing 21% oxygen and 650 ppm CO. Moreover, the ratio of COHb to O₂Hb is proportional to the ratio of their respective partial pressures, PCO and PO₂. The relationship between the affinity constant M and PO₂ and PCO, first expressed by Haldane (1897-1898), has the following form:

$$\text{COHb} / \text{O}_2\text{Hb} = M \times (\text{PCO} / \text{PO}_2). \quad (5-1)$$

At equilibrium, when Hb is maximally saturated by O₂ and CO at their respective gas tensions, the M value for all practical purposes is independent of pH, CO₂, temperature, and 2,3-diphosphoglycerate (Wyman et al., 1982; Gronlund and Garby, 1984).

Under dynamic conditions, competitive binding of O₂ 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 O₂. However, CO not only occupies O₂-binding sites, molecule for molecule, thus reducing the amount of available O₂, but also alters the characteristic relationship between O₂Hb and PO₂, 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

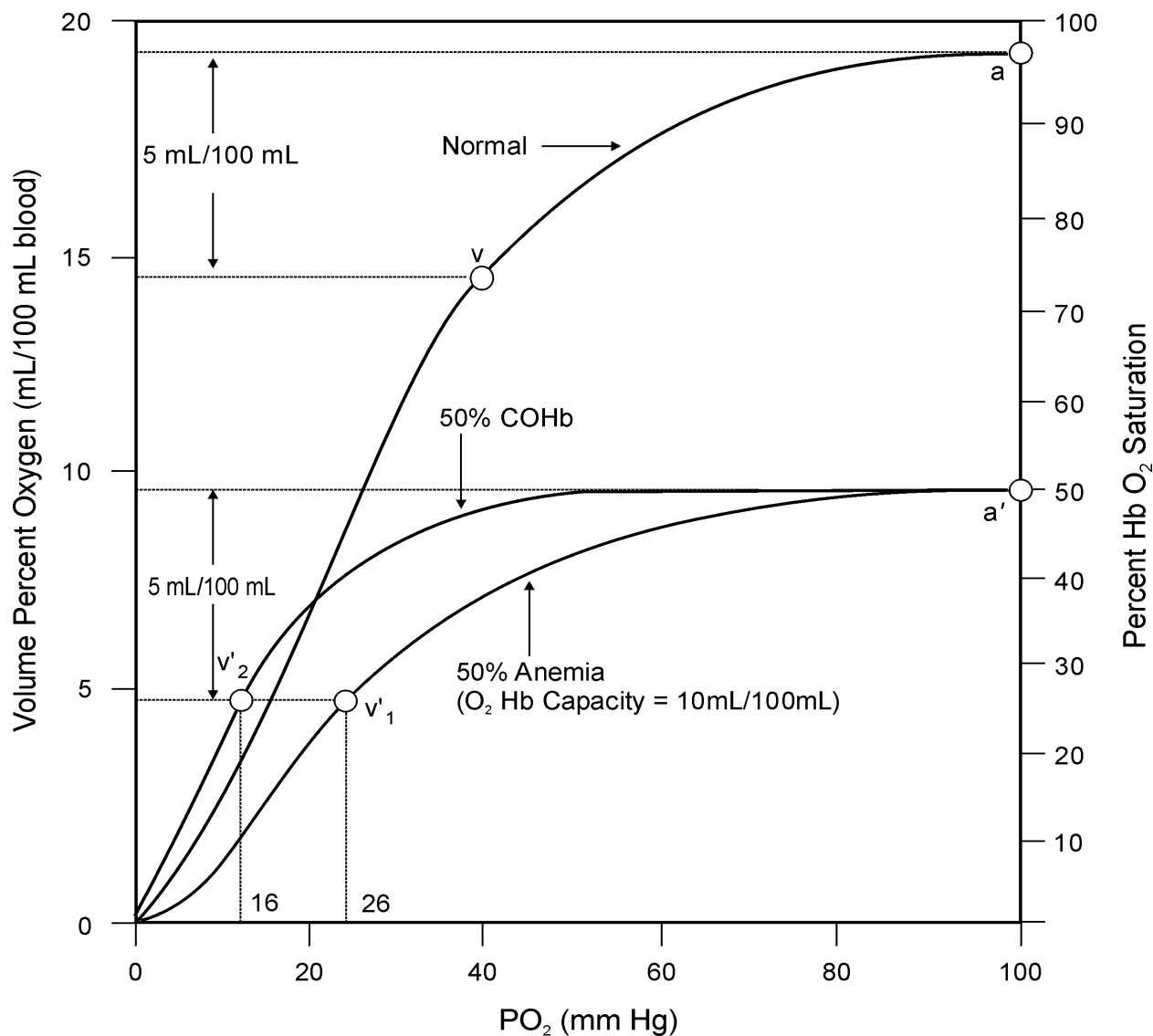


Figure 5-2. Oxyhemoglobin dissociation curve of normal human blood, of blood containing 50% COHb, and of blood with only 50% Hb because of anemia. See the text for additional details.

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

- 1 PO_2 . The v represents the venous PO_2 of healthy individuals after extraction of 5 vol % of O_2 .
- 2 With increasing concentration of COHb in blood, the dissociation curve is shifted gradually to
- 3 the left, and its shape is transformed into a near rectangular hyperbola. Because the shift occurs

over a critical saturation range for release of O_2 to tissues, a reduction in O_2Hb by CO 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 Fig. 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 found that over the range of 2 to 35% COHb, 77% of total body CO remains in the vascular compartment on the average. The rest of CO diffused to extravascular tissues, primarily skeletal muscle where it is bound to Mb. Compared to dogs, the extravascular CO stores in men are smaller and account for <16% of total body CO. Similarly to animals, no shift between blood and extravascular compartments was found at low <4% COHb (Coburn, 1967; Luomanmäki and Coburn, 1969).

5.2.2.3 Heart and Skeletal Muscle

Myoglobin (Mb), as a respiratory hemoprotein of muscular tissue, will undergo a reversible reaction with CO in a manner similar to O_2 . Greater affinity of O_2 for Mb than Hb (hyperbolic versus S-shaped dissociation curve) is, in this instance, physiologically beneficial because a small drop in tissue PO_2 will release a large amount of O_2 from O_2Mb . The main function of Mb is thought to be a temporary store of O_2 and to act as a diffusion facilitator between hemoglobin and the tissues (Peters et al., 1994).

Myoglobin has a CO affinity constant approximately eight-times lower than hemoglobin ($M = 20$ to 40 versus 218 , respectively) (Haab and Durand-Arczynska, 1991; Coburn and

1 Mayers, 1971). As with Hb, the combination velocity constant between CO and Mb is only
2 slightly lower than that for O₂, but the dissociation velocity constant is much lower than that for
3 O₂. The combination of greater affinity (Mb is 90% saturated at PO₂ of 20 mmHg) and lower
4 dissociation velocity constant for CO favors retention of CO in the muscular tissue. Thus, a
5 considerable amount of CO potentially can be stored in the skeletal muscle (Luomanmäki and
6 Coburn, 1969). The binding of CO to Mb (COMb) in heart and skeletal muscle in vivo has been
7 demonstrated at levels of COHb below 2% in heart and 1% in skeletal muscle (Coburn, 1973;
8 Coburn and Mayers, 1971). At rest, the COMb/COHb ratio (0.4 to 1.2) does not increase with an
9 increase in COHb up to 50% saturation and appears to be independent of the duration of
10 exposure (Sokal et al., 1984). During exercise, the relative rate of CO binding increases more for
11 Mb than for Hb, and CO will diffuse from blood to skeletal muscle (Werner and Lindahl, 1980);
12 consequently, the COMb/COHb will increase for both skeletal and cardiac muscles (Sokal et al.,
13 1986). A similar shift in CO has been observed under hypoxic conditions because a fall in
14 myocyte intracellular PO₂ below a critical level will increase the relative affinity of Mb to CO
15 (Coburn and Mayers, 1971). Consequent reduction in O₂ storage capacity of Mb may have a
16 profound effect on the supply of O₂ to the tissue. Apart from Hb and Mb, other hemoproteins
17 will react with CO. However, the exact role of such compounds on O₂-CO kinetics still needs to
18 be ascertained. For more discussion on this topic, see Section 5.6.1.

20 **5.2.2.4 The Brain and Other Tissues**

21 The concentration of CO in brain tissue has been found to be about 30- to 50-times lower
22 than that in blood. During the elimination of CO from brain, the above ratio of concentrations
23 was still maintained (Sokal et al., 1984). However, the energy requirement of brain tissue is very
24 high and varies greatly with local metabolism. Because oxygen demand also is coupled to local
25 functional activity, which at times may be very high, and because the brain's oxygen storage is
26 minimal, any degree of hypoxia if uncompensated will have a detrimental effect on brain
27 function. The primary effects of low, ambient concentrations of CO on other organs (e.g., liver,
28 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 involved in modulating the rate of COHb decline in blood were done at moderate COHb levels, the physiologic mechanisms involved in CO elimination kinetics are also effected at lower blood COHb including levels resulting from ambient exposures. The elimination rate of CO from an equilibrium state will follow a monotonically decreasing, second-order (logarithmic or exponential) function (Pace et al., 1950). The rate, however, may not be constant when the steady-state conditions have not yet been reached. Particularly after very short and high CO exposures, it is possible that COHb decline could be biphasic, and it can be approximated best by a double-exponential function; the initial rate of decline or “distribution” might be considerably faster than the later “elimination” phase (Wagner et al., 1975). The reported divergence of the COHb decline rate in blood and in exhaled air suggests that the CO elimination rates from extravascular pools are slower than those reported for blood (Landaw, 1973). Although the absolute elimination rates are associated positively with the initial concentration of COHb, the relative elimination rates appear to be independent of the initial concentration of COHb (Wagner et al., 1975).

The same factors that govern CO uptake will affect CO elimination. This suggests that the Coburn-Forster-Kane (CFK) model (see Section 5.5.1) may be suitable to predict CO elimination as well. Surprisingly, few studies tested this application. When breathing air, the CFK model predicted very well the COHb decline. However, at a higher partial pressure of O₂ in humidified inspired air (P_IO₂) or under hyperbaric O₂ 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

1 during waking hours. Although no ventilation variables were obtained during the study, the
2 day-to-night differences have been attributed to lower ventilation rates at sleep. The authors
3 speculate that the sex differences in elimination half-time are related to the skeletal muscle mass
4 and intrinsically to the amount of Mb (Deller et al., 1992). The half-time elimination rate
5 appears to be independent of the CO exposure source (e.g., fire, CO intoxication). Normobaric
6 O₂ administered to fire victims and CO-poisoned individuals resulted in about the same CO
7 elimination half-time, 91 and 87 min, respectively (Levasseur et al., 1996).

8 Increased inhaled concentrations of O₂ accelerated elimination of CO; by breathing
9 100% O₂, the half-time was shortened by almost 75% (Peterson and Stewart, 1970). The average
10 half-life of COHb in individuals with very low COHb level (1.16%) breathing hyperbaric O₂ was
11 26 min, compared with 71 min when breathing normobaric O₂ (Jay and McKindly, 1997). The
12 elevation of PO₂ to 3 atm reduced the half-time to about 20 min, which is approximately a
13 14-fold decrease over that seen when breathing room air (Britten and Myers, 1985; Landaw,
14 1973). Although the washout of CO can be somewhat accelerated by an admixture of 5% carbon
15 dioxide (CO₂) in O₂, hyperbaric O₂ treatment is more effective in facilitating displacement of CO.
16 Therefore, hyperbaric oxygen is used as a treatment of choice in CO poisoning. A mathematical
17 model of COHb elimination that takes into account P_IO₂ has been developed but not yet validated
18 (Singh et al., 1991; Selvakumar et al., 1993).

21 **5.3 TISSUE PRODUCTION AND METABOLISM OF CARBON** 22 **MONOXIDE**

23 In the process of natural degradation of RBC hemoglobin to bile pigments, a carbon atom is
24 separated from the porphyrin nucleus and, subsequently, is catabolized by heme oxygenase (HO)
25 into CO. The major site of heme breakdown and, therefore, the major production organ of
26 endogenous CO is the liver (Berk et al., 1976). The spleen and the erythropoietic system are
27 other important catabolic generators of CO. Because the amount of porphyrin breakdown is
28 stoichiometrically related to the amount of endogenously formed CO, the blood level of COHb or
29 the concentration of CO in the alveolar air have been used with mixed success as quantitative
30 indices of the rate of heme catabolism (Landaw et al., 1970; Solanki et al., 1988). Diurnal
31 variations in endogenous CO production are significant, reaching a maximum around noon and a

1 minimum around midnight (Levitt et al., 1994; Mercke et al., 1975a). Week-to-week variations
2 of CO production are greater than day-to-day or within-day variations for both males and females
3 (Lynch and Moede, 1972; Mercke et al., 1975b).

4 Any disturbance leading to accelerated destruction of RBCs and accelerated breakdown of
5 other hemoproteins would lead to increased production of CO. Hematomas, intravascular
6 hemolysis of RBCs, blood transfusion, and ineffective erythropoiesis all will elevate COHb
7 concentration in blood. In females, COHb levels fluctuate with the menstrual cycle; the mean
8 rate of CO production in the premenstrual, progesterone phase is almost doubled
9 (Delivoria-Papadopoulos et al., 1974; Mercke and Lundh, 1976). Neonates and pregnant women
10 also showed a significant increase in endogenous CO production related to increased breakdown
11 of RBCs. Degradation of RBCs under pathologic conditions such as anemia (hemolytic,
12 sideroblastic, and sickle cell), thalassemia, Gilbert's syndrome with hemolysis, and other
13 hematological diseases also will accelerate CO production (Berk et al., 1974; Solanki et al.,
14 1988). In patients with hemolytic anemia, the CO production rate was 2- to 8-times higher, and
15 blood COHb concentration was 2- to 3-times higher than in healthy individuals (Coburn et al.,
16 1966). Anemias also may develop under many pathophysiologic conditions characterized by
17 chronic inflammation, such as malignant tumors or chronic infections (Cavallin-Ståhl et al.,
18 1976) (see also Section 5.4.3).

19 Not all endogenous CO comes from RBC degradation. Other hemoproteins, such as Mb,
20 cytochromes, peroxidases, and catalase, contribute approximately 20 to 25% to the total amount
21 of CO (Berk et al., 1976). Approximately 0.4 mL/h of CO is formed by Hb catabolism, and
22 about 0.1 mL/h originates from nonhemoglobin sources (Coburn et al., 1963; 1964). This will
23 result in a blood COHb concentration between 0.4 and 0.7% (Coburn et al., 1965).

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

30 Another mechanism that will increase CO production is a stimulation of HO and
31 subsequent degradation of cytochrome P-450-dependent, mixed-function oxidases. Several types

1 of compounds such as a carbon disulfide and sulfur-containing chemicals (parathion and
2 phenylthiourea) will act on different moieties of the P-450 system leading to an increase in
3 endogenous CO (Landaw et al., 1970). Other sources of CO involving HO activity include
4 auto-oxidation of phenols, photooxidation of organic compounds and lipid peroxidation of cell
5 membrane lipids (Rodgers et al., 1994). The P-450 system also is involved in oxidative
6 dehalogenation of dihalomethanes, widely used solvents in homes and industry (Kim and Kim,
7 1996). Metabolic degradation of these solvents and other xenobiotics results in the formation of
8 CO that can lead to very high (>10%) COHb levels (Manno et al., 1992; Pankow, 1996).

9 Ascent to high elevations will increase the endogenous level of COHb in both humans and
10 animals (McGrath, 1992; McGrath et al., 1993). The baseline COHb level has been shown to be
11 positively dependent on altitude (McGrath, 1992). Assuming the same endogenous production
12 of CO at altitude as at sea level, the increase in COHb most likely is consequent to a decrease in
13 PO₂ (McGrath et al., 1993). Whether other variables, such as an accelerated metabolism or a
14 greater pool of hemoglobin, transient shifts in body stores, or a change in the elimination rate of
15 CO are contributing factors, remains to be explored. Animal studies suggest that the elevated
16 basal COHb production is not a transient phenomenon but persists through a long-term
17 adaptation period (McGrath, 1992).

18 In recent years, new discoveries in molecular biology identified the CO molecule as being
19 involved in many physiological responses, such as smooth muscle relaxation, inhibition of
20 platelet aggregation, and as a neural messenger in the brain (for details, see Sections 5.6 and 5.7).
21 Most recently, several studies reported yet another function of CO, that of a possible marker of
22 inflammation in individuals with upper respiratory tract infection (Yamaya et al., 1998) and
23 bronchiectasis (Horvath et al., 1998a), and in asthmatics (Zayasu et al., 1997; Horvath et al.,
24 1998b). In the Zayasu et al. (1997) study, the investigators found that exhaled concentrations of
25 CO in asthmatics taking corticosteroids were about the same as in healthy individuals (1.7 and
26 1.5 ppm, respectively), whereas, in asthmatics who did not use corticosteroids, the average CO
27 concentration was 5.7 ppm. The authors speculate that one of the anti-inflammatory effects of
28 corticosteroids is the down-regulation of HO. Whether asthmatics have an increased COHb level
29 was not measured in this study or reported in other studies. Patients with chronic inflammatory
30 lung disease, such as bronchiectasis may produce a substantial amount of CO (e.g., 11.8 ppm).
31 As with asthma, induction of heme oxygenase appears to be the primary mechanism involved in

the production of CO (Horvath et al., 1988). 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 O₂ 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 O₂ requires adjustment of the cardiopulmonary system, so that an increased demand for O₂ is met with an adequate supply of O₂. Depending on the intensity of exercise, the physiologic changes may range from minimal, involving primarily the respiratory system, to substantial, involving extensively the respiratory, cardiovascular, and other organ systems, inducing local as well as systemic changes. Exercise will improve the \dot{V}_A/\dot{Q} ratio in the lung, increase the respiratory exchange ratio (RER), increase cardiac output, increase D_LCO, mobilize RBC reserves from the spleen and induce other compensatory changes. Heavy exercise will cause a decrease in plasma volume leading to hemoconcentration and a subsequent decrease in blood volume. Of the many mechanisms operating during exercise, the two most important physiologic variables are (1) the alveolar ventilation (\dot{V}_A) and (2) cardiac output. Although some physiologic changes during exercise may impair CO loading into blood (e.g., relative decrease in D_LCO during severe exercise), the majority of the changes will facilitate CO transport. Thus, by increasing gas exchange efficiency, exercise also will promote CO uptake. Consequently, the rate of CO uptake and of COHb formation will be proportional to the intensity of exercise. During a transition period from rest to exercise while exposed to CO (500 ppm/10 min), the diffusing capacity and CO uptake were reported to rise faster than O₂ consumption for each exercise intensity (Kinker et al., 1992).

1 Apart from physiological factors, the concentration of CO, as well as the rate of change of
2 CO concentration in an individual's immediate environment, can have a significant impact on
3 COHb. For example, at intersections with idling and accelerating cars, pedestrians will be
4 exposed for a short period of time to higher CO concentrations than those present at other places
5 on the same street. Around home, an individual working with a chain saw, lawnmower, or other
6 gasoline-powered tools will be exposed transiently to higher, and occasionally to much higher
7 (e.g., breathing near the exhaust of a chain saw), concentrations of CO (up to 400 ppm) (Bünger
8 et al., 1997). In indoor environments, exposure to elevated CO from unventilated gas appliances
9 or from environmental tobacco smoke may increase transiently the COHb level of a previously
10 unexposed individual. Occupationally, there are many instances and conditions under which
11 workers may be exposed briefly to moderate-to-high levels of CO from operating equipment or
12 other sources. Despite the shortness of each exposure episode, such transients may result in a
13 relatively high COHb concentration. As an example, exposure for 5 min or less of a resting
14 individual to 7,600 ppm CO in inhaled air will result in almost 20% COHb (Benignus et al.,
15 1994). On repeated brief exposures to high CO, the COHb will increase further until the
16 concentrations in inhaled CO and in blood reach equilibrium. Once the distribution of CO within
17 body stores is complete, the COHb will remain constant, unless the ambient CO concentration
18 changes (either up or down) again. As is the CO uptake, so is the elimination of CO from blood
19 governed by the gas concentration gradient between blood and alveolar air. However, the
20 elimination of CO from blood is a much slower process (see Section 5.2.3) and, therefore, will
21 take many hours of breathing clean air before the baseline COHb value is reached.

22 Recently, a unique source of CO exposure was identified. It has been found repeatedly that
23 the use of volatile anesthetics (fluranes) in closed-circuit anesthetic machines, when CO₂
24 absorbent (soda lime) is dry, can result in a significant production of CO caused by a degradation
25 of the anesthetic and subsequent exposure of a patient to CO (up to 7.0% COHb) (Woehlck et al.,
26 1997a,b).

28 **5.4.2 Altitude**

29 Altitude may have a significant influence on the COHb kinetics (U.S. Environmental
30 Protection Agency, 1978). These changes are consequent to compensatory and adaptive
31 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 (FVC, FEF_{25-75}) will be reduced as well (Ge et al., 1997). The maximal aerobic capacity and total work performance will decrease, and the RER will increase (Horvath et al., 1988). Redistribution of blood from skin to organs and within organs from blood into extravascular compartments, as well as an increase in cardiac output, will promote CO loading (Luomanmäki and Coburn, 1969). Because of a decrease in plasma volume (hemoconcentration), the Hb concentration will be higher than at sea level (Messmer, 1982). The blood electrolytes and acid-base equilibrium will be readjusted, facilitating transport of O_2 . Thus, for the same CO concentration as at sea level, these compensatory changes will favor CO uptake and COHb formation (Burki, 1984). By the same token, the adaptive changes will affect not only CO uptake but CO elimination as well. Carboxyhemoglobin levels at altitude has been shown to be increased in both laboratory animals and humans (McGrath, 1992; McGrath et al., 1993). Breathing CO (9 ppm) at rest at altitude has produced higher COHb levels than those at sea level (McGrath et al., 1993). Surprisingly, exercise in a CO atmosphere (50 to 150 ppm) at altitude appeared either to suppress COHb formation or to shift the CO storage, or both. The measured COHb levels were lower than those found under similar conditions of exercise and exposure at sea level (Horvath et al., 1988).

The short-term acclimatization (within a week or two) will stabilize the compensatory changes. During a prolonged stay at high altitude (over a few months), most of the early adaptive changes gradually will revert to the sea level values, and long-term adaptive changes, such as an increase in tissue capillarity and myoglobin content in the skeletal muscle, begin to take place. Smokers appear to tolerate short-term hypoxic hypoxia caused by high altitude (7,620 m

[25,000 ft]) much better than nonsmokers, who experience more severe subjective symptoms and a greater decline in task performance (Yoneda and Watanabe, 1997). Perhaps smokers, because of chronic hypoxemia (because of chronically elevated COHb), develop partial tolerance to hypoxic hypoxia. Although the mechanisms of COHb formation in hypoxic hypoxia and CO hypoxia are different, the resultant decrease in O₂ 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 equilibrium 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 O₂ transport mechanisms (Ludbrook et al., 1992; Zhu and Weiss, 1994). Recently, Kleinman et al. (1998) demonstrated that the effects of CO and simulated altitude were not synergistic but additive.

5.4.3 Physical Characteristics

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

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

1 In pregnancy, increased requirement for iron may lead to iron deficiency and anemia
2 (for further details see Section 5.4.3). Pregnant women who smoked showed a more pronounced
3 shift of the O₂ dissociation curve to the left (\approx 5% COHb) than one would expect from the same
4 COHb concentration in nonpregnant women. Thus, increased O₂ affinity, combined with
5 decreased O₂-carrying capacity of blood of CO-exposed women, may promote fetal hypoxia
6 (Grote et al., 1994). Animal studies found that protein deficiency in pregnant mice had no
7 modulating effect on maternal COHb but resulted in a greater concentration of placental COHb
8 (Singh et al., 1993; Singh and Moore-Cheatum, 1993; Singh et al., 1992).

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

13 Whether the dynamics of COHb formation and elimination or the absolute COHb levels for
14 the same exposure conditions are different in any way between races have not been studied.
15 Blacks have lower diffusion capacity than whites (Neas and Schwartz, 1996), which transiently
16 will slow CO loading and unloading. It also is well documented that the black population has a
17 higher incidence of sickle cell anemia, which may be a risk factor for CO hypoxia (see
18 Section 5.4.4 below).

20 **5.4.4 Health Status**

21 An individual with any pathophysiologic condition that reduces the blood O₂ content will
22 be at a greater risk from CO exposure because additional reduction in the O₂-carrying capacity of
23 blood resulting from COHb formation will increase hypoxemia. Depending on the severity of
24 initial hypoxia, exposure to CO may lower the O₂ content to the point where O₂ delivery to the
25 tissues becomes insufficient.

26 One group of disorders that encompasses a range of etiologically varied diseases
27 characterized by a reduction in total blood Hb and subsequent insufficiency to meet O₂ demands
28 are the anemias. Anemia is a result of either impaired formation of RBCs or increased loss or
29 destruction of RBCs. The former category includes disorders of altered O₂ affinity,
30 methemoglobinemias, and diseases with functionally abnormal and unstable hemoglobins.
31 By far, the most prevalent disorder in this group is a single-point mutation of Hb (Hb S), causing

sickle cell diseases, the most typical of which is a sickle cell anemia. The O₂-carrying capacity of individuals afflicted with sickle cell anemia is reduced not only because of a smaller amount of Hb, but also the O₂ dissociation curve is shifted to the right, reducing the O₂ affinity as well. Initial compensation involves primarily the cardiovascular system. The cardiac output will increase as both heart rate and stroke volume increase.

The opposite condition of anemia is polycythemia, an increased number of RBCs in blood. Although in polycythemia the total amount of hemoglobin generally is elevated, under certain conditions the arterial O₂ saturation may be decreased, leading to a higher risk of additional hypoxia when exposed to CO (Foster et al., 1978; Stork et al., 1988).

One of the characteristic symptoms of chronic obstructive pulmonary disease (COPD) is increased V_D and \dot{V}_A/\dot{Q} inequality (Marthan et al., 1985). Subsequently, impaired gas mixing because of poorly ventilated lung zones will result in decreased arterial O₂ saturation and hypoxemia. These pathophysiologic conditions will slow both CO uptake and elimination. Any COHb formation will further lower the O₂ content of blood and increase hypoxemia. Because COPD patients very often operate at the limit of their O₂ transport capability, exposure to CO may compromise severely tissue oxygenation.

Because O₂ extraction by the myocardium is high, a greater O₂ 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 O₂ demand during physical activity. If this compensatory mechanism is further compromised by decreased O₂ 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 O₂ 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):

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

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 question their utility in practical applications (Tikuissis, 1996).

Several 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, the 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 O₂Hb is constant:

$$V_b \frac{d[\text{COHb}]_t}{dt} = \dot{V}_{\text{CO}} - \frac{[\text{COHb}]_0 P_{\bar{c}}\text{O}_2}{[\text{O}_2\text{Hb}]M} \left(\frac{1}{\frac{1}{D_L} + \frac{1}{\dot{V}_A}} \right) + \left(\frac{P_I\text{CO}}{\frac{1}{D_L} + \frac{1}{\dot{V}_A}} \right), \quad (5-3)$$

where V_b is blood volume in milliliters; $[\text{COHb}]_t$ 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; $[\text{COHb}]_0$ is the COHb concentration at time zero in milliliters CO per milliliter blood, STPD; $[\text{O}_2\text{Hb}]$ is the oxyhemoglobin concentration in milliliters O₂ per milliliter blood, STPD; $P_{\bar{c}}\text{O}_2$ is the average partial pressure of O₂ in lung capillaries in millimeters of mercury; \dot{V}_A is the alveolar ventilation in ml/min, STPD; D_L is the lung diffusing capacity of CO in ml/min/mmHg, STPD; and $P_I\text{CO}$ 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 O₂ and CO combine with Hb from the same pool, higher COHb values do affect the amount of Hb available for bonding with O₂. Such interdependence can be modeled by substituting (1.38 Hb- [COHb]) for [O₂Hb], 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:

$$\frac{d[\text{COHb}]_t}{dt} = \frac{\dot{V}_{\text{CO}}}{V_b} + \frac{1}{V_b\beta} \left(P_i \text{CO} - \frac{[\text{COHb}]_0 P_{\bar{c}} \text{O}_2}{[\text{O}_2 \text{Hb}] M} \right), \quad (5-4)$$

where β is $(1/D_L) + (P_B - 47)/\dot{V}_A$, and P_B is the barometric pressure in millimeters of mercury.

The nonlinear CFK model is more accurate physiologically but has no explicit solution.

Therefore, interactive or numerical integration methods must be used to solve the equation (Muller and Barton, 1987; Johnson et al., 1992). One of the requirements of the method is that the volumes of all gases be adjusted to the same conditions (e.g., STPD) (Muller and Barton, 1987; Tikuisis et al., 1987a,b).

In general, the linear CFK equation is a better approximation to the nonlinear equation during the uptake of CO than during the elimination of CO. As long as the linear CFK equation is used to predict COHb levels at or below 6% COHb, the solution to the nonlinear CFK model will deviate no more than $\pm 0.5\%$ COHb (Smith, 1990). Over the years, it has been empirically determined that minute ventilation and the $D_L\text{CO}$ have the greatest influence on the CO uptake and elimination. The relative importance of other physiologic variables will vary with exposure conditions and health status. A comprehensive evaluation of fractional sensitivities of physiologic variables for both the linear and nonlinear CFK equation shows that each variable will exert its maximal influence at different times of exposure (McCartney, 1990). The analysis found that only the fractional concentration of CO in inhaled air, in parts per million ($F_i\text{CO}$) 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 hemoglobin. The fractional

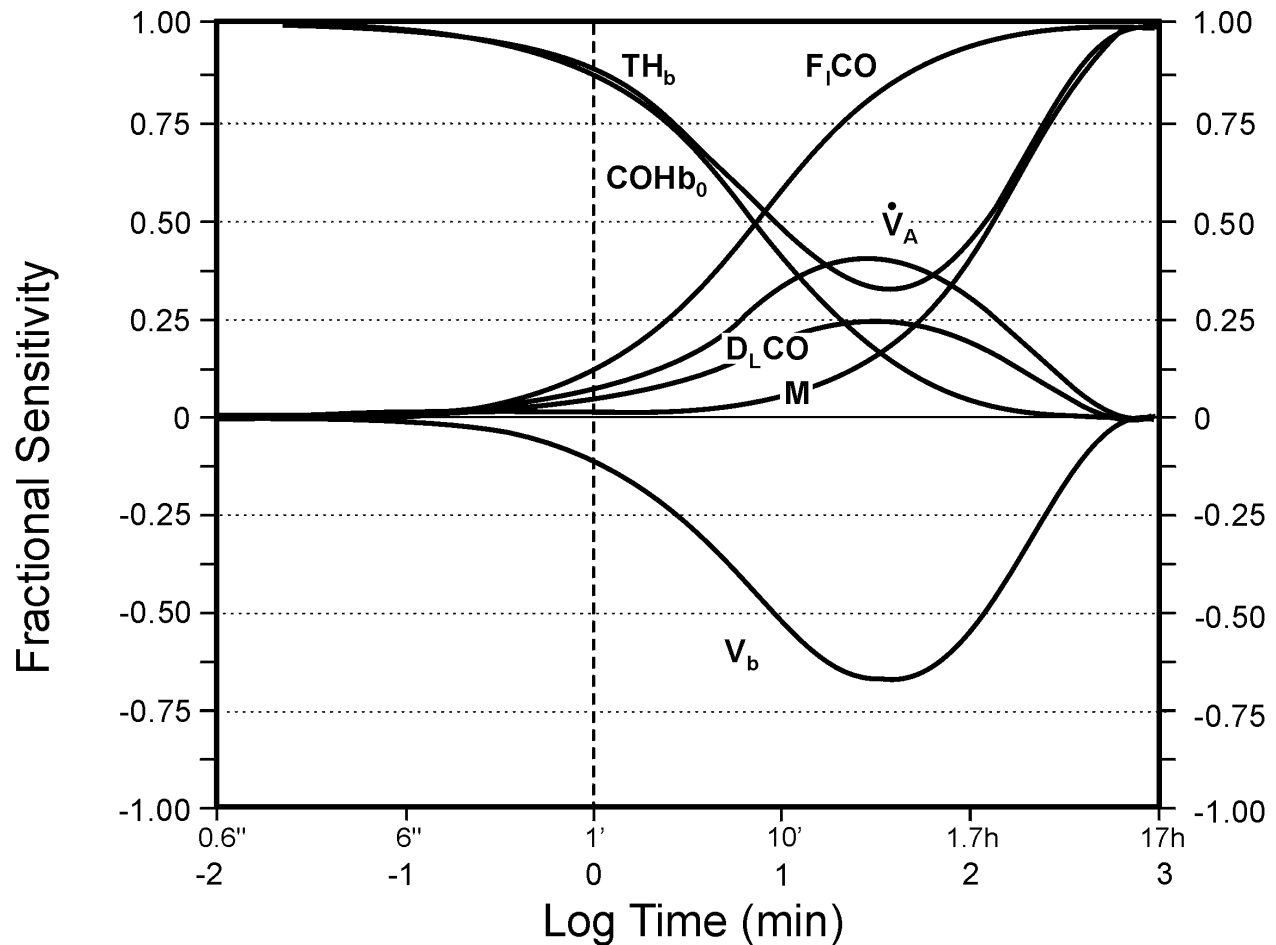


Figure 5-3. Plot of fractional sensitivities of selected variables versus time of exposure (see text for details).

Source: Modified from McCartney (1990).

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 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 both measured directly and 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 exercise the agreement between the predicted and measured COHb values was good (correlation coefficient $[r] > 0.74$).

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

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

A series of studies has tested the accuracy of the CFK equation under transient exposure conditions that would violate several assumptions of the CFK model, specifically the assumption of a single, well-mixed vascular compartment. These studies were designed to simulate everyday conditions (e.g., environmental, occupational, military) that may involve frequent but brief (75 s to 5 min) exposures to high (667 to 7,500 ppm) CO concentrations at rest and exercise. Moreover, the experiments were designed to test the accuracy of the CFK equation under transient exposure conditions during the CO uptake and early elimination phase from arterial and

1 venous blood. Attempts were made to measure directly some of the key physiologic parameters
2 of the CFK equation for each subject (Tiku et al., 1987a,b; Benignus et al., 1994). The
3 studies have shown that during and immediately following exposure, the arterial COHb was
4 considerably higher (1.5 to 6.1%), and the venous COHb was considerably lower (0.8 to 6%)
5 than the predicted COHb. The observed COHb differences between arterial and venous blood
6 ranged from 2.3 to 12.1% COHb among individuals (Benignus et al., 1994). The overprediction
7 of venous COHb increased during exercise ($\approx 10\%$ of the true value). Provided that the total CO
8 dose (concentration \times time) is the same and within the time constant for the CO uptake and
9 elimination, the COHb value was found to be the same, regardless of the pattern of exposure.
10 Because \dot{V}_A affects both the equilibrium and the rate at which it is achieved, inconsistencies in
11 the estimates or conversion of gas volumes (ATPS and BTPS to STPD) will affect the predicted
12 values. The interindividual and intraindividual disparities between measured and predicted
13 COHb values were attributed primarily to delays in mixing of arterial and venous blood and
14 differences in cardiac output; but, other factors such as lung wash-in also contribute to this
15 phenomenon. Modification of the CFK equation by adjusting for regional differences in blood
16 flow produced a model that predicted with much greater accuracy both the arterial ($<0.7\%$ COHb
17 difference) and venous ($<1\%$ COHb difference) COHb during transient uptake and elimination of
18 CO from blood (Smith et al., 1994).

19 Although the CO concentrations used in these studies are several orders of magnitude
20 higher than the usual CO concentrations found in ambient air, under certain conditions (see
21 Section 5.4.1) people can be exposed briefly (<10 min) to such (or even higher) levels of CO in
22 their immediate environment. Because the physiologic mechanisms (but not the kinetics) of
23 COHb formation are independent of CO concentration, high COHb transients, particularly in
24 at-risk individuals, could be of clinical importance. Even briefly, higher arterial COHb may lead
25 to functional impairment of the hypoxia-sensitive brain and heart (see Sections 5.2.2.3 and
26 5.2.2.4). In these situations, the predicted instantaneous arterial COHb level will be substantially
27 underestimated.

28 29 **5.5.1.4 Application of Coburn-Forster-Kane Models**

30 To obviate measurements of CFK equation parameters, many of which are complex
31 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 O₂ uptake by the body, which was in turn related to an activity level, a simplified linear form of the CFK model was developed (Bernard and Duker, 1981). The model was used subsequently to draw simple nomograms of predictive relationship between pairs of variables, but the accuracy of the nomograms was not experimentally tested.

The need for more accurate COHb prediction under more complex physiologic or exposure conditions requires either modification or expansion of the CFK model. Benignus (1995) combined a physiological model of respiratory gas exchange, MACPUF (Ingram et al., 1987), with the CFK model. The new model allows for continuous output and input of 60 cardiopulmonary variables, including F_ICO. The usefulness of the model is particularly in its ability to continuously update COHb concentration in response to dynamically changing physiologic parameters. The model also allows COHb prediction under 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 a transient CO uptake and early elimination phase. The model incorporated regional differences in blood flow, particularly in the forearm, because the forearm is used most frequently for blood sampling. This more elaborate model performed extremely well in predicting blood COHb. Although the model was validated on a small number of subjects using the same experimental setting, the validation was not performed under more demanding conditions of physical activity and varying CO concentrations.

To accurately predict COHb in individuals exposed to dihalomethanes, which are a source of endogenous CO (see Section 5.3), the CFK model was extended to account for the CO production caused by oxidation of a parent chemical (Andersen et al., 1991). The model developed and validated on rats employed a variety of exposure scenarios to dichloromethane.

1 It subsequently was tested on six volunteers exposed to dichloromethane, where, after adjustment
2 of a few parameters, the COHb level was predicted remarkably well. After further validation,
3 this model has potential use in predicting accurately COHb caused by exogenous and endogenous
4 CO originating from different sources (e.g., Hb degradation, metabolism of dihalomethanes,
5 inhaled CO).

6 Reexpression of the solution of the CFK model from units of percent COHb to parts per
7 million of CO allows the examination of a variety of CO concentration profiles, while keeping a
8 simple preselected target COHb as a constant. Application of the transformed model to urban
9 hourly averaged CO concentrations that just attained alternative 1-h and 8-h CO NAAQS showed
10 that, depending on the air quality pattern used, between 0.01 to 10% of the population may
11 exceed a target 2.1% COHb level in blood without ambient CO concentrations ever exceeding
12 the standard. By including transients, the models predicted COHb more accurately, particularly
13 when built into the 8-h running averages (Venkatram and Louch, 1979; Biller and Richmond,
14 1982, 1992). Actually, the ambient CO concentrations could be averaged over any time period
15 less than or equal to the half-life of COHb (Saltzman and Fox, 1986).

18 **5.6 INTRACELLULAR EFFECTS OF CARBON MONOXIDE**

19 **5.6.1 Introduction**

20 Traditional concepts for CO pathophysiology have been based on the high affinity of CO
21 for deoxyhemoglobin and consequent reduction of O₂ delivery. This mechanism is relevant for
22 high CO concentrations, but it is less likely to be relevant to the concentrations of CO currently
23 found in the ambient environment. This section will summarize recently published information
24 on biochemical mechanisms that is not related to an impairment of oxygen delivery from
25 elevations in COHb. Some of the studies outlined in this section were done with cells in culture
26 and others with laboratory rats. To be relevant to human exposures from environmental
27 contamination, it is important to note what concentrations of CO are likely to occur in vivo.
28 Lung parenchyma represents a special situation where cells may be exposed to ambient CO
29 without the reduction in concentration associated with hemoglobin-bound CO. Elsewhere in the
30 body, only a fraction of COHb will dissociate to elevate extravascular CO concentrations. This

elevation is in the range of approximately 2 to 10 nM when the COHb concentration is from 0.8 to 3.8% (Coburn, 1970b; Göthert, 1970). The COHb values near steady state conditions in laboratory rats are close to values for humans (Kimmell, 1999). This strengthens the potential for human relevance in recent animal studies showing 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 myoglobin, cytochrome c oxidase, cytochrome P-450, dopamine β hydroxylase, and tryptophan oxygenase (Coburn and Forman, 1987). Inhibition of these enzymes could have adverse effects on cell function.

Carbon monoxide acts as a competitive inhibitor, hence biological effects depend on the partial pressures of both CO and O₂. The cellular hemoprotein with the highest relative affinity for CO over that for O₂ is myoglobin. Carbon monoxide will inhibit myoglobin-facilitated oxygen diffusion, but physiological compromise is seen only with high concentrations of COMb. Wittenberg and Wittenberg (1993) found that high-energy phosphate production was inhibited in isolated cardiac myocytes, maintained at a physiologically relevant oxygen concentration, when COMb exceeded 40%. The authors estimated that formation of sufficient COMb to impair oxidative phosphorylation in vivo would require a COHb level of 20 to 40%.

Coefficients for binding CO versus O₂ 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) (Cocconi et al., 1988). It is unclear, however, whether this could arise under physiological conditions and CO concentrations produced endogenously. The competition between CO and O₂ for cytochrome c oxidase was well outlined in the previous review (U.S. Environmental Protection Agency, 1991), but some additional information has been published. Based on its Warburg partition coefficient of between 5 and 15, CO binding is favored only in situations where oxygen

tension is extremely low (Coburn and Forman, 1987). Carbon monoxide binding to cytochrome c oxidase in vivo will occur when COHb is high (ca. 50%), a level that causes both systemic hypotension as well as impaired oxygen delivery (Brown and Piantadosi, 1992). Mitochondrial dysfunction, possibly linked to cytochrome inhibition, has been shown to inhibit energy production, and it also may be related to enhanced free radical production (Piantadosi et al., 1995; 1997a). There has been no new information published since the last air quality criteria document that pertains to the effects of CO on dopamine β hydroxylase or tryptophan oxygenase.

5.6.3 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 (\cdot 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 \cdot NO, and the exposure will cause death by a \cdot 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 \cdot NO concentration and production of peroxynitrite (Thom et al., 1994; Thom et al., 1997). Peroxynitrite is a relatively long-lived, strong oxidant that is produced by the near diffusion-limited reaction between \cdot NO and superoxide radical (Huie and Padjama, 1993).

The mechanism by which CO concentrations of 11 nM or more cause an elevation of steady-state \cdot NO concentrations appears to be based on altered intracellular “routing” of \cdot NO in endothelial cells and platelets. It is well established that the association and dissociation rate constants of \cdot NO with hemoproteins exceed the rate constants for O₂ or CO (Gibson et al., 1986). However, Moore and Gibson (1976) found that when CO was incubated with nitrosyl (\cdot NO)-myoglobin or \cdot NO-hemoglobin, CO slowly displaced the \cdot NO. Carbon monoxide replacement occurred even when there was excess \cdot 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 \cdot NO. These conditions, including the presence of thiols, exist in cells exposed to environmentally relevant concentrations of CO. Exposures to up to 1,070 nM CO do not alter the rate of production of \cdot NO by platelets and

endothelial cells, yet liberation of $\cdot\text{NO}$ was enhanced by CO (Thom and Ischiropoulos, 1997; Thom et al., 1994; Thom et al., 1997).

Carbon monoxide will increase the concentration of $\cdot\text{NO}$ 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 $\cdot\text{NO}$ 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 $\cdot\text{NO}$ production, as it was inhibited in rats pretreated with N^ω -nitro-L-arginine methyl ester (L-NAME), a nitric oxide synthase inhibitor. Production of $\cdot\text{NO}$ -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 $\cdot\text{NO}$ or peroxynitrite may perturb mitochondrial function. Peroxynitrite inhibits electron transport at complexes I through III, and $\cdot\text{NO}$ 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 $\cdot\text{NO}$ 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

1 to CO at concentrations found in ambient air. Moreover, enzyme conversion was not a primary
2 effect of CO. Rather, it only occurred following sequestration and activation of circulating
3 leukocytes (Thom, 1993).

5 **5.6.4 Stimulation of Guanylate Cyclase**

6 In recent years, CO has been demonstrated to play a physiological role in vasomotor control
7 and neuronal signal transduction (Morita et al., 1995; Ingi et al., 1996). Carbon monoxide is
8 produced endogenously by oxidation of organic molecules, but the predominant source is from
9 the degradation of heme (Rodgers et al., 1994). The rate-limiting enzyme for heme metabolism
10 is heme oxygenase (HO), which converts heme to biliverdin, free iron, and CO. Three isoforms
11 of HO have been characterized. The HO-1 is an inducible enzyme found in vascular endothelial
12 cells, smooth muscle cells, bronchoalveolar epithelium, and pulmonary macrophages. The HO-1
13 is induced by its substrate, heme, as well as $\cdot\text{NO}$, H_2O_2 , several cytokines, and lipopolysaccharide
14 (Arias-Díaz et al., 1995; Durante et al., 1997; Morita et al., 1995; Motterlini et al., 1996). The
15 HO-2 is a constitutive enzyme found in certain neurons within the central nervous system,
16 testicular cells, and vascular smooth muscle cells (Marks, 1994). Little is known about HO-3,
17 which was recently identified in homogenates from a number of organs (McCoubrey et al.,
18 1997).

19 A main physiological role for CO is thought to be regulation of soluble guanylate cyclase
20 activity. Both CO and $\cdot\text{NO}$ can activate guanylate cyclase, although activation by CO is
21 approximately 30-fold lower (Stone and Marletta, 1994). In neuronal cells possessing both heme
22 oxygenase and nitric oxide synthase, regulation of cyclic guanosine monophosphate (cGMP)
23 synthesis is mediated in a reciprocal fashion by producing either CO or $\cdot\text{NO}$ (Ingi et al., 1996;
24 Maines et al., 1993). A compensatory interrelationship between nitric oxide synthase and heme
25 oxygenase also has been found in endothelial cells and activated macrophages, although its
26 functional significance is unknown (Kurata et al., 1996; Seki et al., 1997). In macrophages,
27 cGMP synthesis promotes chemotaxis, and cGMP-mediated synthesis and secretion of tumor
28 necrosis factor α has been linked to both CO and $\cdot\text{NO}$ (Arias-Díaz et al., 1995; Belenky et al.,
29 1993). Carbon monoxide causes smooth muscle relaxation by stimulating soluble guanylate
30 cyclase (Utz and Ullrich, 1991; Wang et al., 1997b). Smooth muscle relaxation also may occur
31 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 O₂ delivery (Kanten et al., 1983; MacMillan, 1975). However, a portion of the observed increases in cerebral blood flow are independent of perturbations in O₂ supply (Koehler et al., 1982). In a setting where cellular oxidative metabolism was not impaired by CO, elevations in cerebral blood flow appeared to be mediated by •NO (Meilin et al., 1996). Whether the mechanism was the same as that outlined in the section above, which causes oxidative stress, remains to be determined.

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

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

16 **5.7.2 Mitochondrial Dysfunction and Altered Production of High-Energy** 17 **Intermediates**

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

26 Carbon monoxide binding to mitochondrial cytochromes of respiring cells in vitro has been
27 documented only when either the CO concentration was extraordinarily high, or O_2 tension was
28 extremely low, such that the CO/O_2 ratio exceeded 12:1 (Coburn and Forman, 1987). Following
29 CO exposure and removal to fresh air, CO diffuses out from cells, and mitochondrial function is
30 restored. This process is enhanced by inspiration of hyperbaric oxygen (Brown and Piantadosi,
31 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 have been exposed to relatively low CO concentrations for many hours at a time, capillary leakage of macromolecules from the lungs and systemic vasculature have been documented, but the presence of an hypoxic stress was

questioned (Kjeldsen et al., 1972; Maurer, 1941; Parving et al., 1972; Siggaard-Andersen et al., 1968).

In light of the physiological role for CO in vasomotor control, protracted exposures may be prone to disturb vascular homeostasis, giving rise to pathophysiological responses. 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 has been shown following exposures of rats to 50 ppm or more for 1 h, and the process is mediated by \cdot 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 \cdot NO, resulting from exposures to lower CO concentrations contribute to oxidative or nitrosative stress in vivo. Important differences in the patterns of leakage from pulmonary and systemic vascular beds suggest that they may be caused by different mechanisms. For example, systemic vascular leakage was present for several hours after CO exposure, and the leakage resolved within 18 h, whereas pulmonary vascular leakage was not measurable until 18 h after CO exposure, and it resolved by 48 h. Both pulmonary and systemic vascular leakage occurred after hour-long exposures to CO, but not when exposures lasted for only 30 min, and vascular changes were not different whether rats were exposed to just 50 ppm or as much as 1,000 ppm CO. These are recent observations and further investigations are required before their relevance to environmental CO contamination can be assessed adequately. Moreover, it should be emphasized that the vascular leakage observed in lungs and systemic microvasculature following exposures to CO at concentrations as low as 50 ppm may have no pathophysiological impact if regional lymphatics can sustain a higher flow so that edema does not occur (Thom et al., 1998, 1999a,b).

5.8 OTHER EFFECTS OF CARBON MONOXIDE

Among the most concerning pathophysiological effects of CO is its propensity for causing brain damage. There has been considerable effort focussed on potential mechanisms for this process. With regard to ambient air standards, however, it is important to note that recent studies were done with high CO concentrations. Carbon monoxide poisoning is not a “pure” pathological process, as injuries may be precipitated by a combination of cardiovascular effects linked to hypoperfusion or frank ischemia, COHb-mediated hypoxic stress, and intracellular effects, including free radical production and oxidative stress. For example, CO poisoning causes elevations of glutamate and dopamine in experimental models and human fatalities (Arranz et al., 1997; Ishimaru et al., 1991, 1992; Nabeshima et al., 1990, 1991; Newby et al., 1978; Piantadosi et al., 1997b). These elevations occur because of the CO-associated cardiovascular compromise and, possibly, other direct CO-mediated effects. Based on the effects of agents that block the N-methyl-D-aspartate (NMDA) receptor, elevations of glutamate in experimental CO poisoning have been linked to a delayed type (but not an acute type) of amnesia, to loss of CA1 neurons in the hippocampus of mice, and to loss of glutamate-dependent cells in the inner ear of rats (Ishimaru et al., 1991, 1992; Liu and Fechter, 1995; Nabeshima et al., 1990, 1991). Antioxidants can protect against CO-mediated cytotoxicity of glutamate-dependent nerve cells (Fechter et al., 1997). Mechanisms of glutamate neurotoxicity include excessive calcium influx, free radical-mediated injury that may include calcium-calmodulin-dependent activation of cytosolic NO synthase, and lipid peroxidation. Moderate stimulation by excitatory amino acids may cause mitochondrial dysfunction with impaired synthesis of adenosine triphosphate and production of reactive O₂ 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 O₂ 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 O₂-carrying capacity of blood and impairs release of O₂ from O₂Hb to tissues. In addition to tissue hypoxia, ultimate diffusion of CO to cells may affect adversely their function. The brain and heart tissues are particularly sensitive to CO-induced hypoxia and cytotoxicity. The rate of COHb formation and elimination depends on many physical and physiological factors. The same factors that govern CO uptake determine CO elimination as well. The flow of CO between blood and either alveolar air or the tissues, and vice versa, is governed by the CO concentration gradient between these compartments. Because of a small blood-to-air CO gradient, and tight binding of CO to Hb, the elimination half-time is quite long, varying from 2.0 to 6.5 h. Apart from the CO concentration in ambient air, the principal determinants of CO uptake are minute ventilation and lung diffusion capacity. Thus, any physiological conditions that affect these variables (e.g., exercise, age) also will affect the kinetics of COHb. Both the physical and physiological variables have been integrated into many empirical and mathematical models of COHb formation and elimination under static and dynamic conditions of ambient CO concentration and physiologic function. The nonlinear CFK equation is the most widely used predictive model of COHb formation, and it still is considered the best all-around model for COHb prediction. Altitude may have a significant influence on COHb kinetics. The effects of hypoxic hypoxia (altitude) and CO-induced hypoxia appear to be additive. Adaptation to altitude will moderate COHb formation. In addition to exogenous sources of CO, the gas also is produced endogenously through catabolism of Hb, metabolic processes of drugs, and degradation of inhaled solvents and other xenobiotics. This last source may lead to very high (up to 50%) COHb concentrations. Many disorders, particularly anemias of any etiology, will predispose affected individuals to CO hypoxia. Furthermore, patients with a variety of cardiopulmonary (e.g., COPD, CAD) and chronic inflammatory diseases may be at increased risk because of elevated COHb.

Apart from impaired O₂ delivery to the tissues because of COHb formation, recent studies of CO pathophysiology suggest cytotoxic effects independent of O₂. 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,

1 there is insufficient information available to influence decisions on ambient air quality standards.
2 The second area of investigation of CO is related to its propensity for causing
3 free-radical-mediated changes in tissues. Mechanisms for these changes have been linked to both
4 mitochondria and to a CO-mediated disturbance of intracellular “buffering” of endogenously
5 generated free radicals (e.g., $\cdot\text{NO}$). The role these mechanisms play in pathophysiology currently
6 is being investigated. Where dose-response studies are available, the concentrations of CO that
7 cause adverse effects in animals exceed current NAAQS.
8

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6. HEALTH EFFECTS OF EXPOSURE TO AMBIENT CARBON MONOXIDE

6.1 INTRODUCTION

Concerns about the potential health effects of exposure to carbon monoxide (CO) have been addressed in extensive controlled-exposure studies and more limited population-exposure studies. Under varied experimental protocols, considerable information has been obtained on the toxicity of CO, its direct effects on blood and tissues, and the manifestations of these effects in the form of changes in organ function. This chapter assesses the current understanding of health effects that may occur in individuals breathing 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 used during exposure and consequent levels of carboxyhemoglobin (COHb) saturation are much higher than typically would be experienced by ambient exposures of humans. The laboratory animal studies, therefore, must be interpreted with caution. However, they can be useful for exploring the properties and possible mechanisms of an effect much more thoroughly and extensively than is possible in humans. An effort is made in this chapter to compare the health effect levels for CO found in laboratory animal and human controlled-exposure studies.

A review of the health effects literature on CO since the last assessment was published in 1991 finds many published articles on CO poisoning, possibly reflecting 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 a snapshot of the full range of CO toxicity and to provide public

1 health information about potential effects of accidental exposure to CO, particularly those
2 exposures occurring indoors.

3 The next section of this chapter (Section 6.2) addresses cardiovascular effects of CO. The
4 section begins with a discussion of epidemiologic studies (Section 6.2.1), because of their
5 potential importance in assessing community health effects of ambient CO exposure.
6 Section 6.2.1 emphasizes studies of ambient CO and heart disease exacerbation, because
7 short-term ambient CO concentrations have been associated more frequently with such
8 exacerbation than with other health-related endpoints. For purposes of continuity in the
9 epidemiologic discussion, Section 6.2.1 also addresses studies that have evaluated ambient CO in
10 relation to health indices other than heart disease exacerbation. These are daily mortality,
11 incidence of low birth weight, and daily frequency of respiratory illness.

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

19 Next in importance to cardiovascular effects, but of questionable impact for the young and
20 healthy population, are studies of neurobehavioral effects, which had earlier provided the
21 scientific basis for the first CO NAAQS. Subsequent assessments of the neurobehavioral
22 literature, however, have raised questions about both the methods and results of the early studies.
23 Articles published since the last assessment in 1991 have been mostly reviews that attempt to
24 explain the equivocal results found at low COHb levels, and to provide a physiological basis for
25 behavioral effects. The section on neurobehavioral effects (Section 6.3) illustrates the difficulty
26 in studying an organ system with exquisite compensatory responses to a reduced oxygen supply
27 (hypoxia).

28 The rest of the chapter summarizes current knowledge about developmental toxicity
29 (Section 6.4), acute pulmonary effects (Section 6.5), other systemic effects of CO (Section 6.6),
30 physiologic responses to CO exposure (Section 6.7), and combined exposure of CO with other
31 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. No new published studies are known to draw into question the conclusions drawn from the previous literature review of these topics. Finally, a summary section (Section 6.9) provides a concise review of the key human health effects most clearly associated with exposure to ambient CO.

6.2 CARDIOVASCULAR EFFECTS

Cardiovascular disease (CVD) is the leading cause of death in the United States (American Heart Association, 1997; U.S. Centers for Disease Control and Prevention, 1997). An estimated 58 million people in the United States ($\approx 20\%$ of the population) have one or more types of CVD (American Heart Association, 1997). For the major diseases within this category of total CVD, about 50 million Americans have high blood pressure, 14 million have ischemic (coronary) heart disease, 5 million have heart failure, 4 million have cerebrovascular disease (stroke), and 1.8 million have rheumatic fever or heart disease. 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. 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

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. These studies have increased concern as to whether ambient air pollution exposure can promote, and perhaps even produce, harmful health outcomes, even when ambient pollutant concentrations do not exceed current U.S. air quality standards.

1 The epidemiologic database regarding short-term ambient air pollution exposure is growing
2 rapidly, and its interpretation is changing over time. As recently as the mid-1990s, many
3 epidemiologic studies had reported associations of mortality and exacerbation of pre-existing
4 disease with ambient levels of particulate matter (PM), but relatively few had investigated or
5 reported such associations with gaseous pollutants, including CO. Since then, however,
6 investigators have given more thorough consideration to PM and gaseous pollutants, and have
7 frequently observed positive, statistically significant associations of harmful effects with both.
8 Thus, although associations of PM with harmful effects continue to be observed, the role of
9 gaseous pollutants appears to be stronger than it did in previous evaluations.

10 Another important recent change relates to the biological plausibility of observed
11 epidemiologic associations of ambient air pollution with harmful health outcomes. A few years
12 ago, it was frequently argued that associations of low-level ambient air pollution with harmful
13 health outcomes were biologically implausible. Now, with a considerable amount of new
14 experimental evidence in hand, and after much new and sharpened thought on this issue, it is
15 possible to hypothesize ways by which ambient exposure to multiple air pollutants could
16 plausibly be involved in the complex chain of biological events leading to harmful health effects
17 in the human population.

18 In epidemiologic studies of ambient air pollution, small positive estimates of air pollutant
19 health effects have been observed quite consistently. These estimates have frequently been
20 statistically significant at $\alpha = 0.05$. If ambient air pollution actually promotes or produces
21 harmful health effects, relatively small effect estimates would generally be expected on
22 biological and epidemiologic grounds. Also, the magnitudes and significance levels of observed
23 air pollution-related effects estimates have varied somewhat from place to place. This would
24 also be expected if the observed epidemiologic associations denote actual effects, because
25 populations differ in characteristics that could affect susceptibility to air pollution health effects.
26 These characteristics include demographic and socioeconomic factors, underlying health status,
27 indoor-outdoor activities, diet, medical care systems and access to them, and exposure to risk
28 factors other than ambient air pollution, such as extreme weather conditions.

29 Thus, though it has been argued that epidemiologic studies are trustworthy only if they
30 show relatively large effects estimates (e.g., large relative risks), and that the observed effects
31 estimates for ambient air pollution are not sufficiently constant across epidemiologic studies,

1 these arguments have only limited weight in relation to ambient air pollution studies. It should
2 also be borne in mind that in any large population exposed to ambient air pollution, even a small
3 relative risk for a prevalent health disorder could calculate to a substantial public health burden
4 attributable to air pollution exposure.

5 At the same time, important biological, epidemiologic, and statistical uncertainties remain
6 in the current epidemiologic database for ambient CO and other air pollutants. Biologically and
7 epidemiologically, it has not been confirmed that the magnitudes of observed statistical health
8 effects estimates for ambient CO are quantitatively commensurate with actual underlying
9 population susceptibility to CO exposure. Also, it has not been confirmed that the observed
10 spatial variation in air pollution effects estimates reflects actual cross-population differences in
11 susceptibility.

12 The ambient atmosphere contains numerous air pollutants, and there is increasing
13 realization that health effects associated statistically with any single pollutant may actually be
14 mediated by multiple components of the complex ambient mix. Specific attribution of effects to
15 any single pollutant may therefore convey an overly simplistic notion of biological reality.
16 Carbon monoxide is one of many air pollutants generated by combustion sources, including
17 mobile sources. These pollutants include CO, PM, and nitrogen oxides, which have been
18 considered in epidemiologic studies to date. These pollutants also include numerous volatile or
19 semivolatile organic compounds, which have not yet been systematically considered in relation to
20 the non-cancer health outcomes usually associated with exposure to criteria air pollutants.
21 In available epidemiologic studies, harmful health outcomes are frequently associated with
22 multiple combustion-related or mobile source-related air pollutants. Many investigators have
23 raised the possibility that CO may be a surrogate or marker for a larger subset of the overall
24 ambient air pollution mix. Some investigators have argued that CO is a biologically passive
25 surrogate, and that statistical associations of CO with health effects actually reflect effects of
26 pollutants other than CO. However, most investigators have reserved judgment on this issue, and
27 several investigators have emphasized the need for further research on CO.

28 The health effects of long-term exposure to CO and other air pollutants have received little
29 attention in epidemiologic studies, and are not well understood as yet. Health effects of long-
30 term exposure at present-day ambient pollutant levels, which are generally lower than past levels,
31 are especially uncertain. Also, it is not known whether long-term exposure to ambient CO plays

1 a role in the induction (incidence) of new cases of illness. Further research on long-term health
2 effects will be important both to understand better how the public may be protected against such
3 effects, and to provide an epidemiologic context in which to assess the plausibility, accuracy, and
4 validity of the short-term effects estimates.

5 Important statistical uncertainties also remain in the available epidemiologic database for
6 CO and other air pollutants. Many of these are especially pertinent to daily time series studies,
7 which are the majority of the epidemiologic studies available for ambient CO, and which are a
8 large part of the epidemiologic database for other criteria air pollutants. These statistical
9 uncertainties, coupled with existing biological and epidemiologic uncertainties, raise some
10 questions as to the quantitative accuracy of the pollutant effects estimates themselves, and
11 perhaps in some cases as to their qualitative validity. This, in turn, contributes to scientific
12 uncertainty regarding estimates of potential public health impacts of current U.S. CO levels.

13 Unresolved statistical issues include those described below.

14 (1) *Large proportional differences in air pollutant effects estimates with different model*
15 *specifications.* As discussed above, small health effects estimates have generally been
16 observed for ambient air pollutants, and small effects would indeed be expected on
17 biological and epidemiologic grounds. At the same time, because the effects estimates are
18 small, they are subject to large proportional differences with different choices of statistical
19 models. They are also subject to changes in statistical significance level. As the following
20 sections show, for CO and other air pollutants, effects estimates are sensitive to many model
21 selection choices: (1) for different metrics for the same pollutant; (2) for different choices of
22 covariates in single-pollutant models; (3) for a given pollutant in single-pollutant and multi-
23 pollutant models; (4) for a given pollutant in different multi-pollutant models; (5) for
24 different lag or moving-average structures for CO, co-pollutants, and covariates; (6) for the
25 functional form of the modeled concentration-response relationship; and (7) with different
26 adjustments for autocorrelation and overdispersion in the statistical estimation procedure.
27 It seems quite likely that pollutant effects estimates in multi-pollutant models are more
28 biologically and epidemiologically sound than those in single-pollutant models. However,
29 even this has not been demonstrated, and scientific consensus as to optimal modeling
30 strategies for time series air pollution studies has not yet been achieved. Therefore, the

choice of effects estimates to employ in risk assessments for short-term ambient air pollution effects remains open to question.

(2) *Potential confounding of air pollution and weather effects.* Meteorologic events and ambient air pollutant concentrations may be highly correlated on short time scales, even after 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 have generally been made in modeling health effects of air pollutants and weather. These assumptions are not fully adequate, largely because health effects estimates for air pollutants are small and subject to large proportional differences with different model specifications.

(3) *Insufficient reporting of statistical uncertainty.* In available studies, statistical uncertainty has generally 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 have usually been selected to maximize statistical effects estimates for pollutants. This may have led not only to unrealistically large reported effects estimates, but also to unduly narrow confidence intervals for these estimates. In future studies, uncertainty arising from model tuning should be more carefully assessed. In this effort, resampling or simulation procedures, which would recreate the entire model estimation process, should be considered.

(4) *Health effects averaged over extended time periods.* None of the available time series air pollution studies is capable of assessing the incremental effect of pollutants over extended time periods. For example, current models cannot determine whether reduction in pollution will decrease monthly rates of hospital admissions or mortality, even if they predict 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 could consider time-averaged health effects over, say, one month or three months, in relation to pollution exposure metrics for the corresponding periods. Consideration of extended time-averaged health effects would also tend to attenuate 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

1 health outcome during or just after a short period of elevated ambient air pollution, followed
2 quickly by a short-term reduction in frequency of the same outcome below baseline
3 frequency, then by a return to baseline. It has been argued that presence of harvesting would
4 suggest that elevated air pollution exposure hastens occurrence of the health outcome by a
5 short time, but brings about little or no net increase in occurrence of the outcome. It also has
6 been argued that absence of harvesting would suggest that without the elevated air pollution
7 exposure, the outcome might have been delayed for a long time, or might not have occurred
8 at all.)

9 To date, short-term fluctuations in ambient CO have been examined in time series studies
10 of daily exacerbations of preexisting cardiovascular disease, mortality, and changes in respiratory
11 illness frequency. Subchronic ambient CO levels, averaged over about 3 mo, also have been
12 examined in relation to frequency of low birth weight. Associations have been observed most
13 frequently for short-term ambient CO fluctuations and exacerbation of heart disease
14 (a subcategory of cardiovascular disease), as usually indexed by daily hospital admissions. These
15 associations are biologically plausible to some degree. In heart disease patients, the coronary
16 arteries usually are narrowed and unable to dilate normally. Increased hypoxic stress resulting
17 from small increases in COHb saturation could conceivably lead to clinically apparent worsening
18 of their illness.

19 If observed associations of ambient CO with heart disease exacerbation prove to be real and
20 specific to CO, they would be of genuine public health concern. In the U.S. in 1996, there were
21 about 4,239,000 hospital discharges with heart disease as the first-listed diagnosis (Graves and
22 Owings, 1998). Among these, about 2,262,000 (53.4%) were for ischemic heart disease,
23 825,000 (19.5%) for myocardial infarction or heart attack (a subcategory of ischemic heart
24 disease), 870,000 (20.5%) for congestive heart failure, and 618,000 (14.6%) for cardiac
25 dysrhythmias. Also, there were 733,361 deaths caused by heart disease (Peters et al., 1998).
26 Even a small percentage reduction in admissions or deaths caused by heart disease would result
27 in a large number of avoided cases.

28 Even so, fluctuations in ambient CO levels would be expected to produce only very small
29 changes in COHb saturation, and only small changes in tissue oxygenation. Thus, the observed
30 associations of ambient CO with heart disease exacerbation remain difficult to rationalize
31 pathophysiologically. Also, such exacerbation has been associated not only with ambient CO,

1 but also with other combustion-related ambient pollutants such as NO₂ and PM. Thus, the extent
2 to which such exacerbation is truly attributable to ambient CO exposure is not yet clear.

3 Studies of short-term ambient CO levels and daily mortality have yielded mixed results.
4 Observed associations of ambient CO with mortality are of potential public health concern
5 because associations of ambient CO with heart disease exacerbation have been observed
6 frequently, and because heart disease is the leading cause of death in the United States. For
7 example, in the United States in 1996, 733,361 (31.7%) of all 2,314,690 deaths were caused by
8 heart disease (Peters et al., 1998). Again, however, there is not a firm pathophysiologic basis for
9 the observed CO-mortality associations, and the degree of correspondence between statistical
10 effects estimates in populations and real effects in individuals has not yet been determined.

11 Two available U.S. studies suggest that subchronic ambient CO exposure may be
12 associated with increased incidence of low birth weight. These studies raise concern, because
13 fetal hemoglobin binds CO somewhat more strongly than does adult hemoglobin, and because
14 increased COHb saturation would be expected to impair tissue O₂ delivery more in the fetus than
15 in the child or the adult (Longo, 1976). At the same time, these studies are not conclusive. They
16 are subject to potential confounding by unmeasured factors, such as maternal smoking, that are
17 known to influence birth weight. Also, outdoor CO levels may be correlated with indoor levels
18 of CO and other pollutants, which could be higher than outdoor levels, and which were not
19 measured in these studies. Common socioeconomic factors could be associated with both
20 ambient CO levels and such potential confounding variables.

21 Some investigators have observed associations of short-term fluctuations in ambient CO
22 with daily frequency of respiratory illness. In most cases, exacerbation of preexisting respiratory
23 illness has been assessed, though some cases of acute respiratory infection constitute occurrence
24 of new illness, especially in young people. The biological plausibility of these associations is
25 tenuous, because there are as yet no demonstrated mechanisms by which ambient-level CO
26 exposure could produce or promote harmful respiratory effects. Also, in epidemiologic studies to
27 date, associations of ambient CO with respiratory disease frequency have been observed less
28 consistently than with heart disease exacerbation. Nevertheless, the observed associations of
29 ambient CO with respiratory disease frequency are worthy of discussion, because they suggest
30 that ambient CO exposure may not be specifically linked with heart disease.

Overall, then, recent epidemiologic studies have raised the level of 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, further research on the health effects of long-term and short-term ambient CO exposure is strongly warranted. 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. 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 discussed below in the following order of health outcomes: (1) daily exacerbation of heart disease, (2) daily mortality, (3) incidence of low birth weight, and (4) daily frequency of respiratory illness.

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 variation in ambient CO levels is 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, 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 maximum CO concentrations measured by stationary monitors in the epidemiologic studies have generally 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. 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 1.0-2.0% 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 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. CO levels at these monitors may not be well correlated 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 exposure 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 ischemic heart disease (including myocardial infarction, coronary artery atherosclerosis, and angina), heart failure, and disturbances of cardiac rhythm (dysrhythmias). 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, nitrogen dioxide [NO₂], sulfur dioxide [SO₂], and ozone [O₃]), in relation to Medicare hospital admissions for congestive heart failure (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. The average daily maximum 1-h CO levels (mean \pm standard deviation [SD]) ranged from 1.8 (\pm 1.0) ppm in Milwaukee to 5.6 (\pm 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, CO effects were more stable, and more frequently retained statistical significance, than effects of the other pollutants. Figure 2 from Morris et al. (1995), which shows 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 congestive heart failure could be attributed to the observed association with short-term elevations in ambient CO levels.

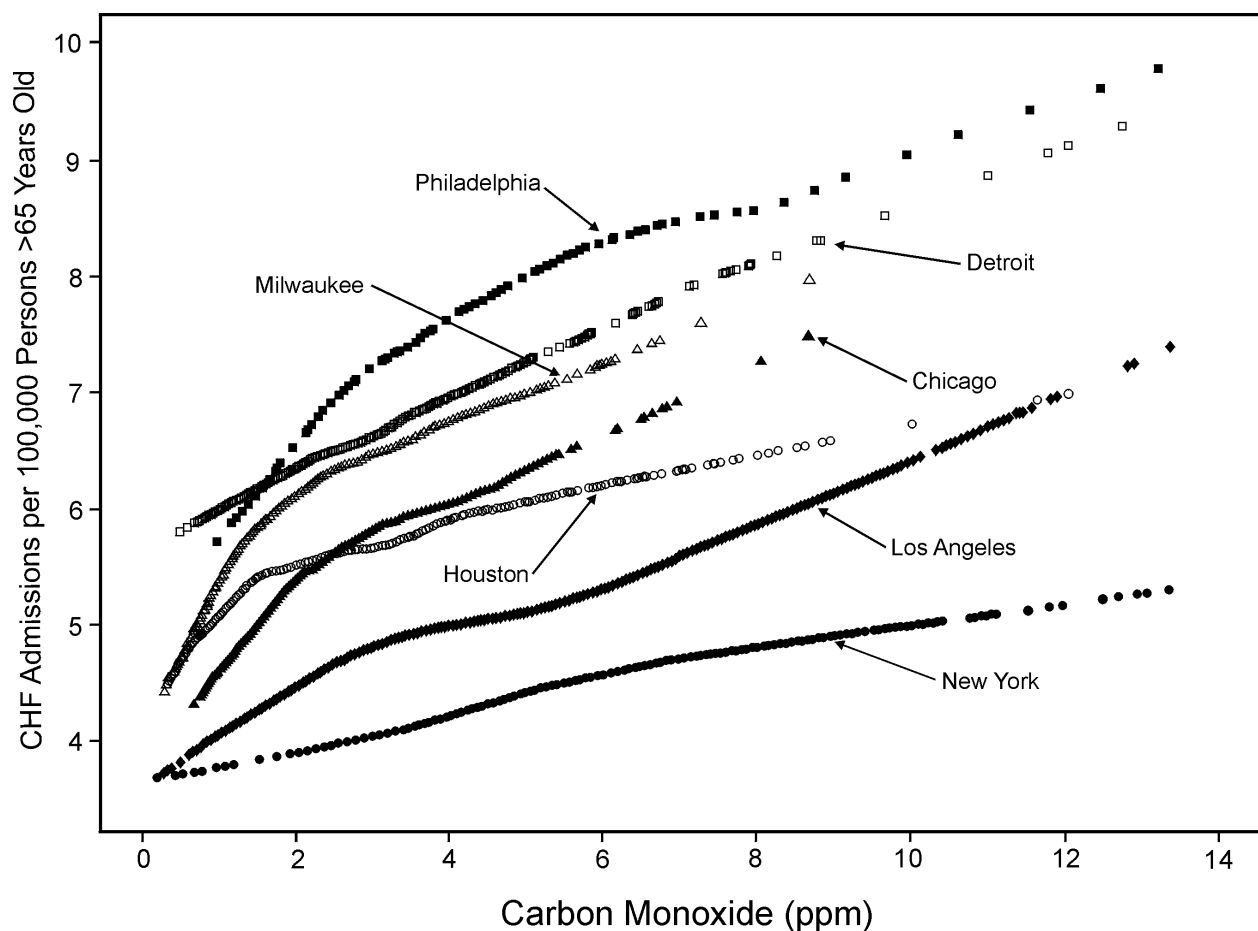


Figure 6-1. Lowess smoothing of the association between ambient levels of CO and hospital admissions for congestive heart failure (CHF) among elderly people after adjustment for temperature, month, day of week, and year, 1986 through 1989.

Source: Morris et al. (1995).

1 Schwartz and Morris (1995) examined air pollution and hospital admissions for heart
2 disease (congestive heart failure, ischemic heart disease, and cardiac dysrhythmias) in people
3 aged 65 years or older in the Detroit metropolitan area during the years 1986 through 1989.
4 Air quality data were available for PM₁₀ on 82% of possible days and for O₃ on 85% of possible
5 days. Data were available for SO₂ and CO on all days during the study period. The mean PM₁₀
6 was 48.0 µg/m³, the mean O₃ was 41.0 ppb, the mean SO₂ was 25.4 ppb, and the mean CO was
7 2.4 ppm. Data were analyzed with Poisson auto-regressive models, with independent variables
8 for temperature, dew point, month, and linear and quadratic time trends. For each pollutant, the
9 difference between the 25th and 75th percentiles of the distribution of ambient concentrations
10 during the study period (the “interquartile range”) was calculated. Relative risks for the health
11 outcomes assessed were reported per increment in ambient concentration equal to each
12 pollutant’s interquartile range.

13 Daily admissions for ischemic heart disease were associated with interquartile range
14 increases of 32 µg/m³ for PM₁₀ (relative risk [RR] = 1.018; 95% confidence interval [CI] 1.005,
15 1.032), 18 ppb for SO₂ (RR = 1.014; 95% CI 1.003, 1.026), and 1.28 ppm for CO (RR = 1.010;
16 95% CI 1.001, 1.018). However, both the CO and SO₂ effects lost statistical significance after
17 controlling for PM₁₀, whereas PM₁₀ remained significant after controlling for the other pollutants.
18 Daily admissions for heart failure were associated independently and significantly with
19 interquartile range increases in both PM₁₀ (RR = 1.024; 95% CI 1.004, 1.044) and CO
20 (RR = 1.022; 95% CI 1.010, 1.034). These results are summarized in Table 6-1. Effects of CO
21 were stronger on the day of admission (0-day lag) than on previous days. No pollutant was a
22 significant risk factor for dysrhythmia admissions, and O₃ was not a significant risk factor for
23 admissions in any heart disease category.

24 Ambient CO could be a surrogate for general combustion-related or mobile-source air
25 pollution. In some locations, CO is highly correlated with PM during the winter months. The
26 ambient PM₁₀ level was associated with heart disease exacerbation in Schwartz and Morris
27 (1995), but was not assessed in Morris et al. (1995). Also, ambient PM concentrations were
28 associated with hospital admissions for both heart failure and ischemic heart disease in Ontario,
29 Canada (Burnett et al., 1995).

30 Pantazopoulou et al. (1995) investigated cardiac and respiratory disease exacerbation in the
31 area of Athens, Greece, in relation to short-term ambient air pollution levels during 1988. The

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

Disease Category	Single-Pollutant Models				Two-Pollutant Models (including PM ₁₀ and CO or SO ₂) ^a		
	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						

^aFor congestive heart failure, no model with PM₁₀ and SO₂ was reported.

^bStatistically significant at $\alpha = 0.05$.

Source: Modified from Schwartz and Morris (1995).

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 NO₂, and 24-h average black smoke (BS), each averaged over multiple monitoring stations in the Athens area. Mean levels of CO for all available monitoring stations were 4.5 mg/m³ in winter and 3.4 mg/m³ in summer. 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. Separate analyses were conducted for “winter” (January 1 to March 21 and September 22 to December 31) and “summer” (March 22 to September 21).

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.

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

Disease Category	Pollutant	Winter (January 1-March 21 and September 22-December 31)			Summer (March 22-September 21)		
		5th to 95th Percentile Increment ($\mu\text{g}/\text{m}^3$) ^a	Increase in Number of Admissions ^b	95% CI	5th to 95th Percentile Increment ($\mu\text{g}/\text{m}^3$) ^a	Increase in Number of Admissions ^b	95% CI
Cardiac	CO	8,200	11.0	3.4, 18.5	5,600	1.4	-5.5, 8.4
	Black Smoke	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	9.9	2.5, 17.4	5,600	2.2	-5.3, 11.5
	Black Smoke	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

^a5th- to 95th-percentile increments in $\mu\text{g}/\text{m}^3$ as measured at two sites in central Athens.

^bThe 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).

1 In contrast, all three pollutants had positive, statistically significant effects on both cardiac and
2 respiratory “emergency admissions” (unscheduled hospital admissions) in winter. Pollution
3 effects were stronger for admissions than outpatient visits, and accounted for a higher proportion
4 of respiratory admissions than cardiac admissions.

5 Separate analyses were conducted for CO effects when ambient CO levels were averaged
6 across two, three, or five monitoring stations (mean CO levels were 8.2, 6.5, and 5.2 mg/m³,
7 respectively). Interestingly, estimated 5th- to 95th-percentile increments in winter cardiac
8 admissions were nearly identical in these different analyses (11.0, 11.4, and 11.2 admissions,
9 respectively). Corresponding CO-related increments in winter respiratory admissions were also
10 similar (9.9, 12.1, and 11.3 admissions, respectively). Effects of BS varied somewhat more than
11 those of CO when averaged across different numbers of monitoring stations. These observations
12 suggest that spatial variation in ambient CO may be smaller in Athens than in many U.S.
13 locations, or that spatial heterogeneity in ambient CO levels may not always greatly distort
14 CO-related health effects estimates, even when CO levels are averaged across multiple
15 monitoring sites. The observations also underscore that further research is required on the effects
16 of different choices of ambient pollutant metrics in time series studies.

17 Schwartz (1997) examined relationships of short-term ambient air pollution levels with
18 cardiovascular hospital admissions in people at least 65 years old in Tucson, AZ, from 1988
19 through 1990. The analyzed range of diagnoses (International Classification of Diseases,
20 Version 9 [ICD-9] codes 390 to 429) included heart disease, hypertension, rheumatic fever, and
21 pulmonary circulatory disorders. It did not include cerebrovascular disease or peripheral blood
22 vessel diseases. Thus, heart disease constituted the large majority, but not all, of the analyzed
23 disorders. The author assessed effects of CO, SO₂, O₃, NO₂, and PM₁₀, as measured at a single
24 monitoring station. Poisson regression models included air pollution metrics, temperature,
25 humidity, and day of week. Nonparametric smoothing was used to adjust for long-term temporal
26 patterns. Exposure-to-admission lags of 0, 1, and 2 days were apparently assessed in different
27 models, and effects estimates of pollutant levels on the same day as admission (0-day lag) were
28 apparently reported. During the study, the median of maximum hourly CO concentrations and
29 the median of 24-h average PM₁₀ concentrations were 3.03 ppm and 39 µg/m³, respectively. The
30 correlation between PM₁₀ and SO₂ was lower than in eastern U.S. cities.

1 In Schwartz (1997), relative risk estimates of CO and PM₁₀ for admissions were of similar
2 magnitude, independent, additive, and statistically significant at $\alpha = 0.05$. In a model assessing
3 both pollutants simultaneously, the estimated percentage increases in admissions (PIAs) across
4 the interquartile ranges of CO and PM₁₀ levels were 2.33 and 2.37%, respectively. Effects
5 estimates for both pollutants appeared to be quite stable across seasons, and did not appear to be
6 confounded with the meteorologic parameters assessed. There were no appreciable associations
7 of admissions with ambient levels of SO₂, O₃, or NO₂.

8 Burnett et al. (1997a) examined temporal relationships between short-term ambient air
9 pollution levels and hospitalizations for congestive heart failure (CHF) in the elderly (individuals
10 >64 years of age) in 10 Canadian cities, during the 11-year period 1981 through 1991. The
11 average daily number of CHF admissions was 39 in the 134 catchment hospitals. A time series
12 analysis adjusted for long-term time trends, seasonal and subseasonal temporal variation, and
13 day-of-week effects was used to explore the relationship between cardiopulmonary illness and
14 the ambient air pollutants CO, NO₂, SO₂, O₃, and coefficient of haze (COH, an optical index of
15 ambient PM concentration). After stratifying by month of the year and adjusting for temperature,
16 dew point, and other pollutants, the log of the daily 1-h maximum CO concentration on the day
17 of admission (0-day lag) had the strongest statistical association with hospitalization for CHF.
18 The relative risk was 1.065 (95% CI = 1.028, 1.104) for an increase from 1 to 3 ppm CO
19 (the interquartile range of the ambient CO concentration distribution). Associations of other
20 pollutants with admissions also were observed in single-pollutant models. However, risk
21 estimates for these other pollutants were more sensitive to simultaneous adjustment for multiple
22 pollutants and weather variables than were the estimates for CO. Burnett et al. (1997a) present a
23 nonparametrically smoothed exposure-response function for daily maximum hourly CO level and
24 adjusted daily CHF admissions (Figure 6-2). The authors noted that CO could be acting as a
25 marker for pollution from transportation sources in general, and that independent effects of
26 non-CO pollutants could not be ruled out.

27 Burnett et al. (1997b) investigated summertime ambient air pollution in relation to
28 unscheduled hospital admissions for cardiac and respiratory diseases in Toronto, Ontario,
29 Canada, in the summers of 1992, 1993, and 1994 (total 388 days). Hourly measurements of CO,
30 O₃, SO₂, NO₂, and COH were available from multiple monitoring stations. Daily measurements
31 of fine and coarse PM (8:00 a.m.-8:00 a.m.) were available from a dichotomous sampler at a

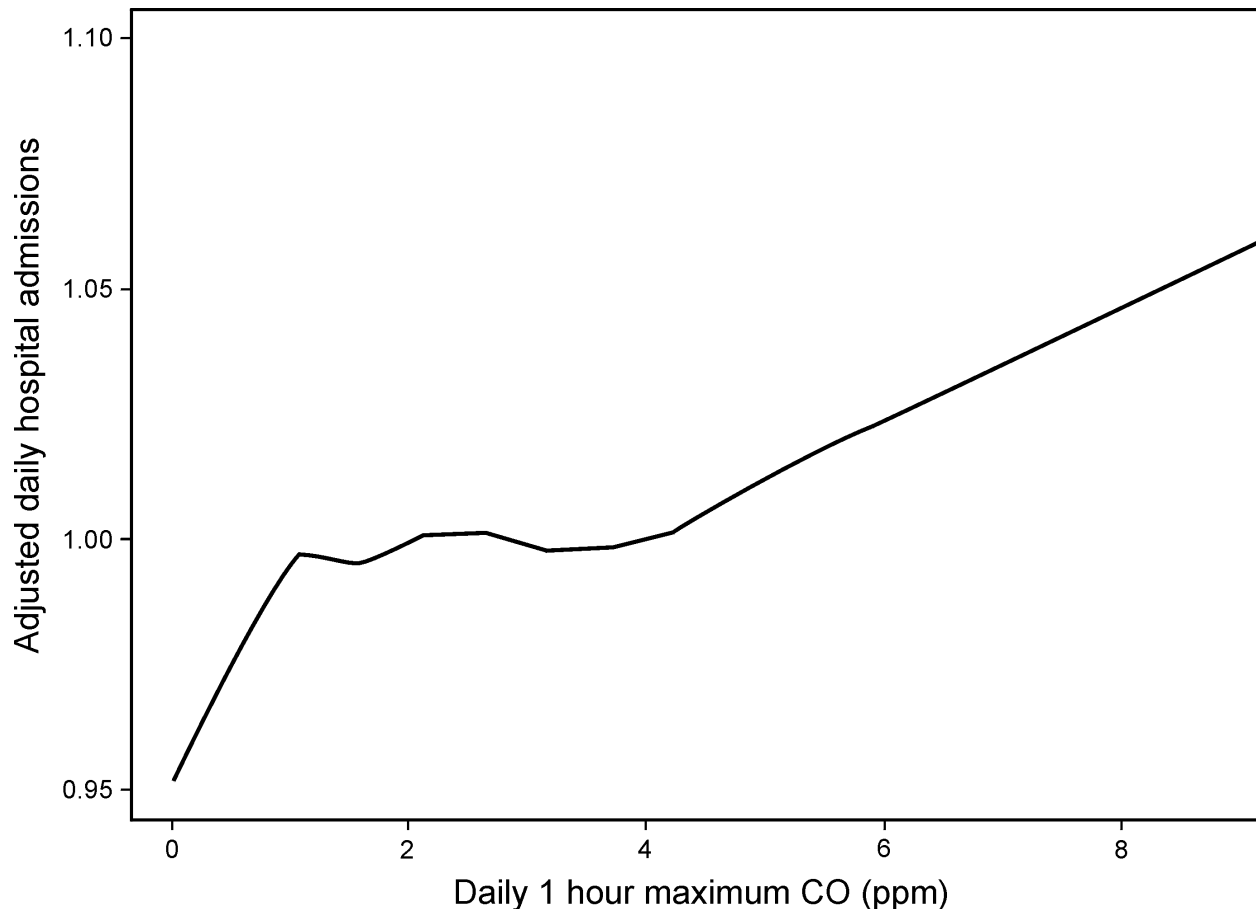


Figure 6-2. Nonparametric smoothed curve of adjusted hospitalization rates for congestive heart failure in the elderly plotted against daily 1-h maximum CO levels in 10 Canadian cities, 1981 to 1991. Hospitalization rates are adjusted for long-term time trends, seasonal and subseasonal variations, and day of week effects and are normalized to unity for each city separately.

Source: Burnett et al. (1997a).

downtown site chosen to be representative of the Toronto area. Measurements of COH were also available. The PM_{10} levels 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. Additional pollutant metrics were computed as multiday 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 its last day, 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 metrics adjusted for CO were similar to PM effects in single-pollutant models. The gaseous pollutant least sensitive to adjustment for PM metrics was O₃. The gaseous pollutant that most attenuated PM effects was NO₂. The authors hypothesized that the absence of a CO may result from the fact that summertime ambient CO levels are low and emphasized the potential importance of the overall ambient air pollution mix, recommending 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 one day before admission in London, UK, from April 1, 1987, to March 31, 1994. Pollutant metrics were 24-h mean CO, BS, SO₂, and NO₂, and hourly mean O₃ 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 µg/m³. Health outcomes considered were admissions for all cardiovascular diseases and for the following seven diagnostic subgroups: myocardial infarction (MI), other ischemic heart disease, heart failure, angina, cardiac dysrhythmia, cerebrovascular disease, and 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 were also entered into the models (1-day lag). 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 O₃, which

1 was generally negatively, but not significantly, associated with these admissions. The only
2 diagnostic subgroup significantly associated with more than one pollutant was MI. Admissions
3 for heart failure, other ischemic heart disease, and cerebrovascular disease were not significantly
4 associated with any pollutants.

5 Additional single-pollutant and two-pollutant Poisson models were constructed for MI
6 during the warm season (April through September) and the cool season (October through March).
7 In the warm season, there were no significant associations of air pollution with MI admissions
8 ($p > 0.25$). In the cool season, CO was positively and significantly associated with MI in the
9 single-pollutant model and the two-pollutant model with O₃. The same was true for all other
10 pollutants except O₃, and SO₂ was significant in all two-pollutant models. P-values and
11 regression coefficients from Table 4 of Poloniecki et al. (1997), which show pollutant effects in
12 single-pollutant and two-pollutant models, and which show the marked differences in modeled
13 air pollution effects between the cool and warm seasons, are presented in Table 6-3.

14 This study suggests that, in London, short-term elevations in ambient air pollution levels
15 are related to cardiac hospital admissions, especially MI admissions, 1 day later. The authors
16 systematically evaluated pollution effects on different diagnostic subgroups of CV disease, and,
17 unlike North American investigators, reported no association of ambient CO with congestive
18 heart failure. Even so, there is some consistency between the European and North American
19 studies. Specifically, these studies show positive, statistically significant relationships of
20 ambient CO concentration, and other pollutant concentrations, with hospital admissions for heart
21 disease, and these relationships tend to be stronger for heart disease than other types of
22 cardiovascular disease such as stroke. Also, effects of CO on heart disease exacerbation have
23 consistently been strongest with a 0-day lag for the ambient CO metric. Poloniecki et al. (1997)
24 evaluated effects of air pollution only with a 1-day lag. Thus, though it is not certain, modeled
25 CO effects may have been biased downward in this study.

26 Poloniecki et al. (1997) present a balanced discussion of consistencies and inconsistencies
27 in the available epidemiologic database regarding ambient air pollution. They emphasize the
28 potential for confounding of air pollution and meteorologic effects, despite conscientious efforts
29 to model these effects appropriately. They state, “Significant associations [of air pollution with

TABLE 6-3. ACUTE MYOCARDIAL INFARCTION: ONE AND TWO POLLUTANT MODELS WITH COOL AND WARM SEASON^{a,b}, LONDON, UK, APRIL 1, 1987 TO MARCH 31, 1994

Test Pollutant	Second pollutant				
	O ₃	NO ₂	SO ₂	CO	BS
O ₃ (ppb)					
Cool season:					
P Value	<i>0.22</i>	0.72	0.91	0.93	0.95
Coefficient	<i>-0.0013</i>	0.0004	0.0001	-0.0001	0.0001
Warm season:					
P Value	<i>0.48</i>	0.39	0.26	0.34	0.34
Coefficient	<i>-0.0005</i>	-0.0006	-0.0009	-0.0009	-0.0007
NO ₂ (ppb)					
Cool season:					
P Value	0.0004 ^c	<i>0.0020^c</i>	0.15	0.84	0.23
Coefficient	0.0022	<i>0.0013</i>	0.0008	0.0002	0.0008
Warm season:					
P Value	0.49	<i>0.53</i>	0.65	0.90	0.63
Coefficient	0.0004	<i>0.0003</i>	-0.0003	0.0001	0.0003
SO ₂ (ppb)					
Cool Season:					
P Value	0.0005 ^c	0.03 ^c	<i>0.0004^c</i>	0.02 ^c	0.03 ^c
Coefficient	0.0025	0.0015	<i>0.0021</i>	0.0020	0.0015
Warm season:					
P Value	0.70	0.49	<i>0.53</i>	0.32	0.58
Coefficient	0.0004	0.0009	<i>0.0006</i>	0.0013	0.0006
CO (ppb)					
Cool season:					
P Value	0.001 ^c	0.15	0.39	<i>0.02^c</i>	0.38
Coefficient	0.0324	0.0205	0.0083	<i>0.0227</i>	0.0100
Warm season:					
P Value	0.63	0.63	0.55	<i>0.40</i>	0.39
Coefficient	0.0112	0.0154	-0.0160	<i>0.0187</i>	0.0243
Black smoke (μg/m ³)					
Cool Season:					
P Value	0.0006 ^c	0.23	0.10	0.13	<i>0.002^c</i>
Coefficient	0.0033	0.0014	0.0015	0.0019	<i>0.0024</i>
Warm season:					
P Value	0.84	0.96	0.86	0.79	<i>0.82</i>
Coefficient	-0.0003	0.0001	0.0003	-0.0006	<i>0.0003</i>

^aDiagonal elements (bold italics) are single-pollutant models; off-diagonal elements are test pollutant modeled with a second pollutant

^bCool season is October to March, and warm season is April to September. Coefficient = Poisson regression coefficient—for example, percent admissions per unit of pollutant = [exp (coeff) -1] × 100.

^cP < 0.05.

Source: Modified from Poloniecki et al. (1997).

1 health outcomes] might...arise solely because factors that affect the clearance and creation of air
2 pollution—such as the weather and driving motor vehicles—also have a direct effect on human
3 behavior and on acute health outcomes...Although we have modelled temperature and humidity,
4 there are other factors—for example, wind and rain—which affect air pollution and also affect
5 the amount of physical exercise taken and the duration of time spent outdoors, where levels of air
6 pollution are generally different from indoors. With so much potential for confounding, and with
7 a good many conflicting results to be found in the scientific literature, we chose to place the
8 statistical emphasis on the direction and consistency of the relations (P values) rather than on
9 estimating the size of effects from the models which produce the largest effects, as has usually
10 been done.” Thus, these authors recognize the high degree of uncertainty inherent in ostensibly
11 quantitative estimates of effects of individual pollutants in time series studies.

12 Poloniecki et al. (1997) also present the following assessment of observed associations of
13 CO with heart disease exacerbation: “The present results...make a case for further study of CO.
14 Average concentrations over one hour at a kerbside monitor can reach 25 ppm [in the UK].
15 Breathing CO at 50 ppm for one hour increased carboxyhaemoglobin by a factor of two, and
16 reduced symptom limited exercise capacity in patients with stable angina...Thus the risk of
17 myocardial ischaemia when pushing a lawn mower or or shovelling snow is increased by the
18 proximity of an internal combustion engine. We have shown that fluctuations in...CO are an
19 additional risk factor for myocardial infarction in the population, and this effect could be due to
20 an increased risk of infarction during exercise when environmental concentrations of CO have
21 risen within the preceding 24 hours.”

22 Morris and Naumova (1998) investigated joint effects of short-term ambient CO
23 concentration and ambient temperature on daily hospital admissions for CHF in people >64 years
24 of age, in Cook County (Chicago), IL, from 1986 through 1989. Data were analyzed with
25 general linear models (GLM) and general additive models (GAM). The pollutant metrics
26 assessed were daily maximum hourly levels of CO, NO₂, SO₂, and O₃, as well as 24-h average
27 PM₁₀. For each day of the study, gaseous pollutant measurements were averaged across Cook
28 County’s eight monitoring stations, six of which were in downtown Chicago. The PM₁₀ levels
29 were measured at only one station on 80% of study days. In addition to these pollutant variables,
30 models included variables for daily maximum hourly temperature, day of week, month of year,
31 and year of study.

1 In single-pollutant GLMs, the level of each pollutant except O₃ was associated positively
2 and statistically significantly with CHF admissions on the same day. In a GLM that included all
3 pollutants, only CO was associated significantly with admissions. In this model, the RR for CHF
4 admission at the 75th percentile of maximum hourly CO concentration was 1.08 (95% CI 1.03,
5 1.12), as compared to RR = 1 at CO concentration of zero. Associations of CO and other
6 pollutants with admissions were strongest on the day of admission (0-day lag), and weakened
7 rapidly with successively longer lag times.

8 The authors conducted a detailed and thoughtful analysis to assess effects of ambient CO at
9 different temperatures. These effects were analyzed in three ways: (1) inclusion of a
10 CO-temperature interaction term in GLM; (2) simultaneous inclusion of a CO term and a
11 temperature term in GAM, generating an additive CO-temperature effects surface; and
12 (3) analysis with stratification on daily maximum ambient temperature (<40°, 40 to 75°, and
13 >75° F). Effects of CO on CHF admissions were consistently associated inversely with
14 temperature (stronger effects at lower temperatures). For example, in a multipollutant GLM,
15 RRs for CHF admissions at the 75th percentile of maximum hourly CO concentration were
16 1.09 (1.01, 1.18), 1.07 (1.01, 1.13), and 1.01 (0.92, 1.11) when maximum temperature was <40,
17 40 to 75°, and >75° F, respectively. Figure 3 in Morris and Naumova (1998) shows
18 temperature-specific exposure-response curves for percentiles of ambient CO distributions and
19 relative risk of CHF admission in single-pollutant and multi-pollutant models. This figure is
20 reproduced in Figure 6-3. The authors hypothesized that CHF patients may be unusually
21 susceptible to CO effects, and that cardiovascular and other stresses imposed by cold weather
22 may heighten this susceptibility.

23 Morris and Naumova (1998) is one of the few time series studies that have jointly analyzed
24 effects of ambient air pollution and weather, and thereby not forced statistical models to generate
25 single effects estimates for air pollutant metrics. It is an unusually strong time series study, and
26 its findings regarding ambient CO effects on CHF admissions are therefore of unusual interest
27 and concern. However, even these findings should be interpreted cautiously. For example, as
28 the authors point out, fixed-site CO measurements do not give exact estimates of individual
29 subjects' total CO exposures. Discrepancies between estimated and actual total CO exposures
30 may be greatest in cold weather, when indoor CO levels may be higher than in warm weather,
31 and when CHF patients may spend more time indoors. Also, a given day-to-day difference in

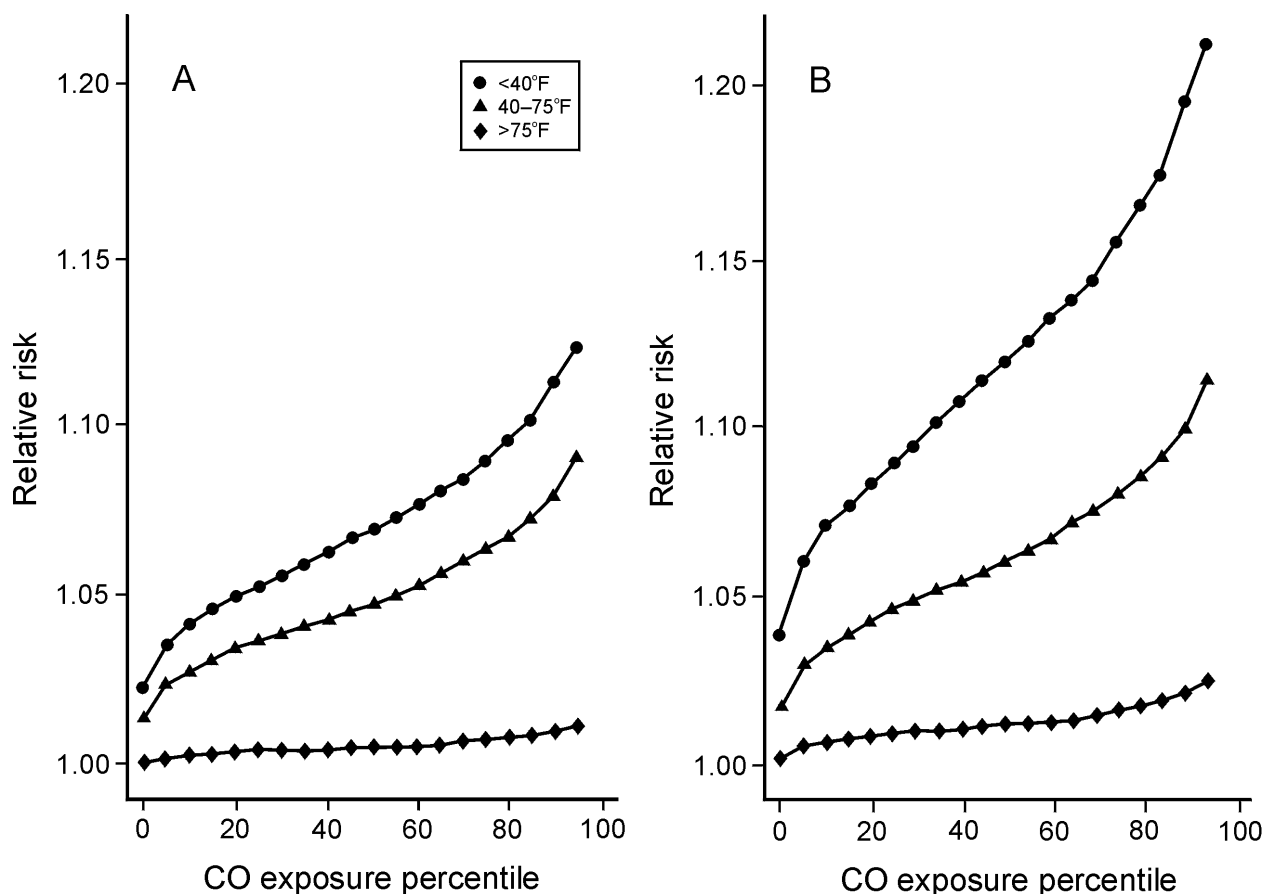


Figure 6-3. The relative risk associated with the exposure percentiles of CO at specific temperature strata, based on results of the (A) multi-pollutant and (B) single-pollutant generalized linear models of hospital admissions for heart failure among the elderly in Chicago, IL, 1986 to 1989.

Source: Morris and Naumova (1998).

1 ambient CO level could reflect a greater day-to-day difference in total CO exposure in cold
2 weather than in warm weather. Thus, the observed stronger associations of ambient CO with
3 CHF in colder weather might reflect an underlying effect of increased total CO dose in colder
4 weather, and not an effect of ambient CO exposure per se. Finally, the observed associations
5 could indeed reflect a true effect of ambient CO fluctuations, superimposed on higher baseline
6 CO doses from nonambient sources during colder weather.

1 As mentioned above, Burnett et al. (1997b) did not observe an association of ambient CO
2 with cardiac admissions. However, their results do not contradict those of Morris and Naumova
3 (1998), who observed a strong association of CO with congestive heart failure admissions at cold
4 temperatures but little or no association at warm ones. Pantazopoulou et al. (1995) and
5 Poloniecki et al. (1997) also observed associations of CO and other air pollutants with cardiac
6 admissions during cooler weather but not during warmer weather. Thus, these four studies
7 generate the hypothesis that ambient CO effects on heart disease exacerbation are stronger during
8 cooler weather than during warmer weather. This hypothesis should be tested further in future
9 studies.

10 Yang et al. (1998) studied cardiovascular hospital admissions in relation to short-term CO
11 levels in Reno-Sparks, NV, over 6 years (1989 to 1994). The study area is about 4,400 ft above
12 sea level. At this elevation, the effect of COHb on tissue O₂ delivery might differ from that at sea
13 level. The studied range of ICD-9 codes, 390 to 459.99, included heart disease and other
14 cardiovascular disorders such as stroke and hypertension. The mean measured ambient CO level
15 during the study period was 3.09 ppm. Data were analyzed with weighted least-squares
16 regression and autoregressive integrated moving average (ARIMA) regression for time series
17 data. The CO metric was the average of the highest value of the maximum hourly CO levels at
18 all five local monitoring stations from midnight to noon. Models were adjusted with dummy
19 variables for day of week and month of year. Wind speed and the previous day's minimum
20 temperature were also considered. CO effects estimates were reported for the ambient CO level
21 on the day of admission (0-day lag). Pollutants other than CO were not considered in the
22 analysis.

23 The authors stated, "All hospital admissions for CV [cardiovascular disease] and IHD
24 [ischemic heart disease] were significantly associated with CO concentrations..." Tabular
25 displays of results were limited to all CV admissions and IHD admissions. No results were
26 reported for other diagnostic subcategories. Modeled CO effects on admissions were larger in
27 males than females, and did not differ significantly by age. The significance levels of CO effects
28 are somewhat difficult for the reader to discern. The tabular summary of regression results
29 (Table 5) suggests very high significance levels ($p < 0.006$); units of regression coefficients were
30 not given. However, the text states, "According to the ARIMA models, CV and IHD hospital
31 admissions increased 1.19% (95% CI: 0.99, 1.39%) and 2.83% (95% CI: 2.07, 3.60%),

1 respectively, for each 1 ppm increase in the 1-h maximum CO level....” This suggests only
2 marginal significance of the effect of CO on total cardiovascular admissions, and clear
3 significance of the CO effect on IHD admissions. On balance, this report suggests an association
4 of short-term ambient CO levels with cardiovascular admissions, especially IHD admissions, at
5 an elevation of 4,400 ft. The report does not enable inference as to effects of pollutants other
6 than CO.

7 Schwartz (1999) evaluated effects of short-term ambient CO and PM₁₀ exposure on daily
8 hospital admissions for cardiovascular disease (ICD-9 codes 390 to 429) in persons aged at least
9 65 years, in eight U.S. counties over 3 years, 1988 to 1990. The analyzed health outcomes were
10 the same as in Schwartz (1997) (i.e., ICD-9 codes 390 to 429). The eight study locations were
11 Chicago, IL; Colorado Springs, CO; Minneapolis and St. Paul MN; New Haven, CT; and Seattle,
12 Spokane, and Tacoma, WA. Previous findings from Tucson, AZ, also were summarized
13 (Schwartz, 1997). During the study period, 50th-percentile CO and PM₁₀ levels ranged from
14 2.0 to 4.7 ppm and 23-37 $\mu\text{g}/\text{m}^3$, respectively, across the study locations. Pollutants other than
15 CO and PM₁₀ were not analyzed, though the author stated: “The emphasis is on locations in the
16 western United States, because western locations have been less studied, because the correlation
17 between PM₁₀ and O₃ usually is negative versus positive in the east, and because SO₂
18 concentrations are much lower in the west.” (Even so, the dataset included the four nonwestern
19 locations of New Haven, Chicago, Minneapolis, and St. Paul.) Daily maximum 1-h CO levels
20 and 24-h average PM₁₀ levels were considered, apparently only on the same day as admissions
21 (0-day lag). Aerometric data were taken from population-oriented CO monitors, as presumably
22 opposed to compliance monitors, which may be located away from population centers. Poisson
23 regression was employed, with LOESS smoothing to adjust for effects of temperature, dew point,
24 and seasonal patterns. Effects estimates were reported as percentage increases in admissions
25 (PIAs) over approximate interquartile ranges of ambient pollutant concentrations.

26 In all study locations, both CO and PM₁₀ levels were positively associated with daily
27 cardiac admissions. CO effects were statistically significant in seven of nine locations, and PM₁₀
28 effects were significant in six of nine locations. Relative effects of CO and PM₁₀ differed widely
29 among locations. Overall, the interquartile PIA for CO was 2.79% (95% C.I. 1.89 to 3.68), and
30 that for PM₁₀ was 2.48% (1.81 to 3.14). Effects estimates for CO and PM₁₀ were not related to
31 the location-specific correlation between these two pollutants’ concentrations, suggesting that

their effects on cardiac admissions were at least partially independent. Table 3 of Schwartz (1999), which shows modeled ambient CO and PM₁₀ effects in all eight study locations and in Tucson, is reproduced with slight modification in Table 6-4. In two-pollutant models, effects estimates for CO and PM₁₀ were somewhat smaller than in single-pollutant models. Pollution effects estimates were not reported for diagnostic subcategories (e.g., ischemic heart disease and heart failure). This study's findings leave a general impression of similar, partially independent statistical effects of short-term ambient CO and PM₁₀ on total cardiac admissions in the elderly.

TABLE 6-4. MODELED PERCENTAGE INCREASES IN HOSPITAL ADMISSIONS FOR HEART DISEASE, ASSOCIATED WITH INTERQUARTILE RANGE INCREASES IN AMBIENT PM₁₀ AND CO LEVELS, 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 Locations	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

^aSize of window (in days) for LOESS smoothing of time to control season.

Source: Modified from Schwartz (1999).

At the same time, it is not clear why CO exerted a substantially larger statistical effect than PM₁₀ on admissions in Minneapolis, while the reverse was true in the adjacent location of St. Paul. It is also not clear why the LOESS seasonal smoothing window was 34% longer in

1 St. Paul than in Minneapolis. Similarly, CO had a larger effect than PM₁₀ on admissions in
2 Seattle, while the reverse was true in nearby Tacoma. Furthermore, the seasonal smoothing
3 window in Seattle was 34% longer than in Tacoma.

4 Schwartz (1999) points out that while CO is a known “cardiovascular toxin,” cardiac
5 effects in experimental studies of humans have been observed only at higher than ambient CO
6 levels. He states that one would expect to observe CO effects at lower levels in epidemiologic
7 studies, because epidemiology examines the entire population, which comprises a broader range
8 of disease states and exposure to potential effects modifiers than do experimental subject groups.
9 He also raises the possibility that ambient CO may be a marker for automotive pollution, and
10 states, “One potential constituent [of automotive pollution]...that may have acute cardiovascular
11 toxicity is the volatile and semivolatile organic aerosols...CO may be serving as a proxy for these
12 compounds. Nevertheless, associations between cardiovascular hospital admissions and CO
13 have been seen in more than 20 North American cities,...suggesting that a better understanding of
14 this pollutant should have a high priority.”

15 Burnett et al. (1999) assessed daily unscheduled hospital admissions for eight types of
16 cardiovascular and respiratory disease exacerbation in Toronto, Canada, in relation to short-term
17 ambient air pollution exposure over 15 years, 1980 to 1994. Daily average concentrations of CO,
18 NO₂, SO₂, and O₃ were obtained from four monitoring stations. Daily average concentrations of
19 fine PM (PM_{2.5}), coarse PM (PM_{10-2.5}), and PM₁₀ were estimated from TSP and sulfate levels
20 measured at a single central station. Daily average COH levels were measured at the same
21 station. The cardiovascular disease types were ischemic heart disease, heart failure, cardiac
22 dysrhythmias, cerebrovascular disease (including stroke), and peripheral circulatory disorders.
23 The respiratory disease types were asthma, obstructive lung disease, and respiratory infection.

24 Data were analyzed with general additive models, with accommodation for over- or under-
25 dispersion from Poisson variation. The data were prefiltered with a 31-day LOESS smoother.
26 The LOESS smoothers also were employed to adjust for effects of temperature and relative
27 humidity. Models were adjusted for day-of-week effects. Exploratory models were run to
28 provide parsimonious choices of climate variables in final models. The report did not present
29 seasonal air pollution effects estimates. Pollution metrics were 1-, 2-, or 3-day averages, with the
30 final day of the averaging period lagged 0 to 2 days before admission. All possible single-
31 pollutant models were run for each disease type. Pollutant metrics were constructed to give the

1 log of relative risk per unit change in pollutant concentration. Pollutant effects were reported as
2 the percentage increase in total daily hospital admissions, from zero concentration to the mean
3 pollutant concentration during the study period.

4 In the single-pollutant models (Table 3 in Burnett et al., 1999), pollutant effects estimates
5 were weak or negative for cerebrovascular disease and peripheral circulatory disease, so these
6 two disease types were not considered in subsequent multi-pollutant analyses. This left only
7 three heart disease categories and three respiratory disease categories for further consideration.
8 In single-pollutant models, the CO effect in each of these six categories was strongest for a
9 1- or 2-day averaging time, ending on the same day as the admission (0-day lag).

10 The authors constructed multi-pollutant models in an effort to ascertain effects of the
11 overall ambient air pollution mix, and to estimate health benefits that would follow air pollution
12 reduction. They selected pollutant metrics from the single-pollutant models for inclusion in the
13 multi-pollutant models. For each pollutant, they selected the averaging period and lag that
14 yielded the largest ratio of log-relative risk to standard error (largest T-ratio or t-statistic). They
15 constructed two sets of multi-pollutant models. In the first set (Table 4 in Burnett et al., 1999),
16 four models were run for each of the six cardiac and respiratory disease categories. In one of
17 these four models, all PM metrics were excluded. In each of the other three models, the
18 investigators forced inclusion of one and only one PM metric ($PM_{2.5}$, $PM_{10-2.5}$, or PM_{10}). After
19 these constraints were imposed, gaseous pollutants were entered into each of the 24 models using
20 stepwise regression. Specific gaseous pollution metrics in final models were selected using the
21 Akaike Information Criterion (AIC).

22 In this first set of multi-pollutant models, inclusion of gaseous pollutants led to
23 substantially smaller PM effects estimates than observed in single-pollutant models. Also,
24 modeled percentage increases in admissions (PIAs) with a PM metric in the model were only
25 moderately larger than corresponding increases with no PM metric in the model. The maximum
26 diagnosis-specific percentage increase in the PIA with a PM metric in the model, over the PIA
27 with no PM metric, ranged from 7.4% for ischemic heart disease to 28.1% for respiratory
28 infection. These increases were larger for respiratory diseases (average = 21.0%) than for heart
29 diseases (average = 8.5%).

30 In the second set of multi-pollutant models (Table 5 in Burnett et al., 1999), all gaseous and
31 PM metrics competed equally for inclusion, and no metric was constrained to be included or

1 excluded. In these models, percentage increases in diagnosis-specific hospital admissions, at the
2 mean concentrations of included pollutants, ranged from 9.29% (IHD) to 14.45% (respiratory
3 infection). Effects of CO and NO₂, which are both generated by mobile sources, were largely
4 confounded. CO but not NO₂ was included in models for asthma, obstructive lung disease, and
5 dysrhythmias, and NO₂ but not CO was included for IHD. Both CO and NO₂ were included as
6 independent predictors for heart failure. Taken together, effects estimates for CO and NO₂ were
7 larger, and more frequently statistically significant, for heart diseases than for respiratory
8 diseases.

9 Table 6-5 summarizes modeled effects of CO in single-pollutant models, and modeled
10 effects of CO and other pollutants in multi-pollutant models, as taken from Tables 3 and 5 of
11 Burnett et al. (1999). No PM metric was included in multi-pollutant models for the heart
12 diseases IHD and heart failure (which accounted for 73.9% of all U.S. hospital admissions for
13 heart disease in 1996). When a PM metric was included, the contribution of the modeled PM
14 effect to the overall pollution-associated increase in admissions ranged from 19.3%
15 (dysrhythmias) to 42.1% (respiratory infection). The average contribution of PM metrics to the
16 air pollution-associated percentage increase in heart disease admissions was thus only 6.4%
17 $([0\% + 0\% + 19.3\%] / 3)$. If weighted by the number of admissions for each of the three
18 analyzed heart disease categories in the United States in 1996 (see Section 6.2.1.1), this
19 contribution would calculate to only 3.2%. The average contribution of PM metrics to
20 percentage increases in respiratory disease admissions was 34.2%. Fine PM was included in
21 models for dysrhythmias and respiratory infection, and coarse PM was included for asthma and
22 obstructive lung disease. PM₁₀ was not included for any disease, and no more than one PM
23 metric was included for any disease. Ozone was associated much more strongly with respiratory
24 disease admissions than with heart disease admissions. Single-pollutant model effects of SO₂
25 could be largely explained by inclusion of other pollutants.

26 In Burnett et al. (1999), modeled PM metrics were not measured directly. Thus, the
27 findings are subject to quantitative uncertainty regarding specific pollutant effects, and regarding
28 gaseous pollution effects relative to PM effects. Modeled effects of PM may have been biased
29 downward, but this is not certain. Also, the extent to which findings in Toronto can be
30 generalized to other locations is not clear. Nevertheless, this report presents the most
31 comprehensive effort to date to examine multi-pollutant effects across a variety of health

TABLE 6-5. MODELED PERCENTAGE INCREASES IN HOSPITALIZATIONS AT MEAN POLLUTANT CONCENTRATIONS^a IN SINGLE-POLLUTANT AND MULTI-POLLUTANT MODELS, TORONTO, CANADA, 1980 TO 1994

Disease Category	Single-Pollutant Models (Table 3)							Multi-Pollutant Models (Table 5)					
	CO	NO ₂	SO ₂	O ₃	PM ₁₀	PM _{2.5}	PM _{10-2.5}	CO	NO ₂	SO ₂	O ₃	PM	All Pollutants
<u>Heart Disease</u>													
Dysrhythmias	8.99(3.60)	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)	— ^b	—	3.34(1.63)	2.47 ^c (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
<u>Respiratory Disease</u>													
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 ^d (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 ^d (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 ^c (4.46)	14.45

^aT-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.

^bA dash denotes that the indicated pollutant was not included in the multi-pollutant model.

^cThe PM metric included was PM_{2.5} (fine PM).

^dThe PM metric included was PM_{2.5-10} (coarse PM).

Source: Modified from Burnett et al. (1999).

1 outcomes. This study, like many other recent studies, emphasizes the importance of considering
2 both gaseous and particulate pollutants in data analyses and underscores the importance of
3 gaseous pollutants as contributors to health effects attributable to the overall ambient air
4 pollution mix, especially in relation to heart disease exacerbation. Also, unless both gaseous
5 pollutants and PM are taken into account, modeled effects estimates for single pollutants are
6 likely to be inaccurate. Also, using effects estimates derived from multipollutant models may
7 accommodate, at least partly, for confounding of effects among individual pollutants in
8 estimating potential public health risks.

9 10 **6.2.1.3 Ambient Carbon Monoxide and Daily Mortality**

11 Epidemiologic studies of the relationship between CO exposure and daily mortality are not
12 conclusive. Early studies in Southern California (Goldsmith and Landaw, 1968; Cohen et al.,
13 1969; Hexter and Goldsmith, 1971) suggested an association between atmospheric levels of CO
14 and increased mortality from cardiovascular disease, but potential confounders were not
15 controlled thoroughly. In contrast, Kuller et al. (1975) observed no association between ambient
16 CO levels and cardiovascular disease or sudden death in Baltimore, MD.

17 Kinney and Özkaynak (1991) investigated effects of short-term variation in ambient air
18 pollution levels on daily nonaccidental, nonviolent deaths in Los Angeles County over 10 years,
19 1970 through 1979. The mean daily death count was 152; of these, 87 (57%) and 8 (5%) resulted
20 from cardiovascular and respiratory causes, respectively. Pollution metrics were daily maximum
21 CO, daily maximum hourly total oxidants (O_3 in 1979), 24-h average SO_2 , NO_2 , and KM
22 (a particulate metric similar to British Smoke, related to elemental carbon), and visual extinction
23 coefficient (B_{ext} , related to fine particulate). In multiple regression models, adjusted for
24 meteorology and temporal patterns, there were statistically significant associations of total and
25 cardiovascular mortality with temperature, oxidants (lagged 1 day), and the automotive pollutants
26 CO, NO_2 , and KM (each lagged 0 days). Levels of the latter three pollutants were too highly
27 intercorrelated to enable confident assessment of their separate effects. Respiratory mortality
28 was associated with temperature but not with any pollution metric, though the power to test for
29 pollutant effects was limited by small numbers of daily respiratory deaths.

30 More recent time series studies in North and South America and in Europe have also
31 yielded mixed results in relating day-to-day variations in CO levels with daily mortality.

1 For example, no relationship was found between CO and daily mortality in Los Angeles,
2 Chicago, or Philadelphia (Ito et al., 1995; Kinney et al., 1995; Ito and Thurston, 1996; Kelsall
3 et al., 1997) after adjusting for particles (i.e., PM₁₀), time trends, and weather. Verhoeff et al.
4 (1996) found no relationship between 24-h average CO concentrations and daily mortality in
5 Amsterdam, with or without adjustment for PM₁₀ and other pollutants.

6 Three other studies (Touloumi et al., 1994; Salinas and Vega, 1995; Wietlisbach et al.,
7 1996) showed small, statistically significant relationships between CO and daily mortality.
8 However, effects of other pollutants (e.g., total suspended particles [TSP], SO₂, NO₂, black
9 smoke) and of meteorologic variables (e.g., temperature, relative humidity) were also significant.
10 Further research will be needed to determine whether low-level CO exposure actually is
11 increasing mortality (particularly in the elderly population), whether CO is a surrogate marker for
12 some other mobile-source or combustion-related pollutant, or whether CO is a surrogate for the
13 overall combustion-related or automotive pollution mix.

14 Touloumi et al. (1994) investigated air pollution and daily all-cause mortality in Athens
15 from 1984 through 1988. Daily mean pollution indicators for SO₂, black smoke, and CO were
16 averaged over all available monitoring stations. Autoregressive models were used, with log-
17 transformed daily mortality as the dependent variable, and with adjustment for temperature,
18 relative humidity, year, season, day of week, and serial correlations in mortality. Separate
19 models for log(SO₂), log(smoke), and log(CO) yielded statistically significant effects estimates
20 ($p < 0.001$). Air pollution measurements lagged by 1 day were most strongly associated with
21 daily mortality. In a multipollutant model, SO₂ and smoke were independent predictors of
22 mortality, though to a lesser extent than temperature and relative humidity. Addition of an
23 independent variable for CO concentration did not improve this model's ability to predict daily
24 mortality, suggesting that CO may be a surrogate marker for other mobile-source or combustion-
25 related pollutants.

26 In one of the Air Pollution and Health—A European Approach (APHEA) studies in
27 Athens, Touloumi et al. (1996) observed a distinct positive association of ambient CO levels
28 with daily mortality. Ambient CO concentrations were compiled from three fixed outdoor
29 monitoring stations. Median, mean, and maximum 8-h CO levels were 6.1 mg/m³ (5.3 ppm),
30 6.6 mg/m³ (5.8 ppm), and 24.9 mg/m³ (21.7 ppm), respectively. The relative risk for daily
31 mortality of a 10 mg/m³ (9 ppm) increase in the daily ambient air CO concentration was

1 1.10 (95% CI = 1.05, 1.15). This finding may be attributable to yet-unknown health effects of
2 low levels of CO, to the presence of highly compromised susceptible groups in the population,
3 or, again, to CO acting as a surrogate for other combustion-generated air pollutants.

4 Salinas and Vega (1995) examined the effect of urban air pollution on daily mortality in
5 Metropolitan Santiago, Chile, from 1988 through 1991. Measurements of maximum 8-h average
6 CO; maximum hourly O₃; daily mean SO₂, PM₁₀, and PM_{2.5}; and meteorologic variables were
7 obtained from five monitoring stations. Total and respiratory disease-specific deaths were
8 assessed, calculating the risk of death by municipality and month of the year using age-adjusted
9 standardized mortality ratios, and controlling for socioeconomic status. Daily death counts were
10 regressed on pollutant levels, using Poisson regression and controlling for temperature and
11 relative humidity. There were geographic differences, independent of socioeconomic and living
12 conditions, in both total mortality and disease-specific mortality (e.g., pneumonia, chronic
13 obstructive pulmonary disease, asthma). The daily number of deaths was significantly associated
14 with ambient CO, ambient suspended particles, and humidity, and also was associated with
15 temperature when the model included all days with complete data during the 4-year period. The
16 associations remained significant for those days with PM_{2.5} levels below 150 µg/m³.

17 Wietlisbach et al. (1996) assessed the association between daily mortality and air pollution
18 in metropolitan Zurich, Basel, and Geneva, Switzerland, from 1984 through 1989. Daily counts
19 were obtained for total mortality, mortality in people 65 years of age or older, and respiratory and
20 cardiovascular disease mortality. Daily measurements of weather variables and TSP, SO₂, NO₂,
21 CO, and O₃ were obtained in each city. Poisson models were used to regress daily death counts
22 on pollutant levels, controlling for time trends, seasonal factors, and weather variables. Positive,
23 statistically significant associations were found between daily mortality and TSP, SO₂, and NO₂.
24 The strongest associations were observed with 3-day moving averages. Somewhat weaker
25 associations were observed in each city between mortality in people 65 years of age or older and
26 measured average daily CO concentrations (mean = 1 to 2 mg/m³ [1 to 2 ppm], max = 5 to
27 8 mg/m³ [4 to 7 ppm]). Associations with O₃ were weak and inconsistent. When all pollutants
28 were modeled simultaneously, the regression coefficients were unstable and not statistically
29 significant.

30 In two recent studies, Burnett and colleagues investigated associations of CO and other
31 pollutants with daily nonaccidental mortality in Canada. In one study (Burnett et al., 1998a), the

investigators assessed the roles of average daily concentrations of ambient CO, other gaseous pollutants, sulfates, TSP, COH, estimated PM_{2.5} and PM₁₀, and meteorology in Toronto from 1980 through 1994. The time series was adjusted for long-term trends and temporal cycles. Effects of several different exposure-to-mortality lags were explored, and the final choice of lags was based on the Akaike Information Criterion. A 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 O₃ 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, NO₂, O₃, and SO₂) with daily nonaccidental mortality in 11 Canadian cities from 1980 through 1991. In single-pollutant models, relative risks of CO for mortality were more consistent across cities than were relative risks of the other pollutants. However, in multipollutant models, CO-associated relative risks decreased substantially, and NO₂ and SO₂ appeared to explain much of the CO effect on mortality. The estimated percentage increase in mortality risk attributable to combined exposure to all four pollutants differed widely 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 direct measurements 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 PM₁₀, though Pereira et al. (1998) did

observe a limited relationship of ambient CO concentration with intrauterine mortality. Interestingly, in the latter study, COHb levels in cord blood were correlated with short-term ambient CO levels, even though intrauterine mortality was associated somewhat 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.

6.2.1.4 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). Though 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, between 1989 and 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 to the mother's residence. This metric 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, the study design, like that of Alderman et al. (1987), addressed the fact that in the United States at least, ambient CO levels are often heterogeneous over large distances. 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 study 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 O₃, NO₂, and PM₁₀ were made at 6 of the 18 monitoring stations. Multi-pollutant models were constructed for subjects living near these 6 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 NO₂, PM₁₀, 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, Alderman et al. (1987) and Ritz and Yu (1999) 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 hemoglobin is somewhat greater than that of adult hemoglobin, and, at a given level of CO exposure, tissue O₂ delivery is reduced more in the fetus than in the child or the adult, in whom fetal hemoglobin has been replaced by adult hemoglobin (Longo, 1976). The observation by Pereira et al. (1998) of an association of ambient CO concentration with cord blood COHb level reinforces this concern. (Of course, the fetus might also be unusually susceptible to hypoxia from exposure to agents other than CO.) Both Alderman et al. (1987) and Ritz and Yu (1999) recommend further research with individual-level measurements of CO exposure and relevant covariates.

6.2.1.5 Ambient Carbon Monoxide and Frequency of Respiratory Illness

Short-term variation in ambient CO levels has been associated in several studies with daily variation in indices of respiratory illness frequency. In most cases, these indices reflect exacerbation of preexisting respiratory illness. Associations of ambient CO with respiratory illness frequency have been observed less frequently 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 should by no means be considered confirmed. At the same time, it is appropriate to discuss these associations because they indicate that ambient CO exposure is not specifically linked epidemiologically with heart disease. The correct interpretation of this lack of specificity

1 is not yet known. On one hand, it could suggest that short-term ambient CO exposure effects are
2 not confined to the cardiovascular system. On the other hand, it could be taken as a caveat on the
3 observed associations of ambient CO with heart disease exacerbation, because even though the
4 pathophysiologic connection of CO with respiratory disease is more tenuous than with heart
5 disease, statistical associations of CO with respiratory disease frequency are nevertheless
6 observed.

7 Sunyer et al. (1991) investigated daily emergency department (ED) visits for chronic
8 obstructive pulmonary disease (COPD) in Barcelona, Spain, in relation to short-term ambient air
9 pollution levels, during 1985 and 1986. ED visits for asthma were excluded. Pollutants
10 considered were daily average and daily maximum hourly SO₂, daily average black smoke (BS),
11 and daily maximum hourly CO, NO₂, and O₃. Ambient levels of CO were quite low during the
12 study (yearly mean of daily maximum hourly levels = 5.4 mg/m³, and 98th percentile
13 = 14.9 mg/m³). In single-pollutant regression models adjusted for meteorology, season, and day
14 of week, positive, statistically significant effects estimates were most consistently observed for
15 SO₂ lagged 0 or 1 day, but not 2 days. Effects were significant for both daily average and
16 maximum hourly SO₂ levels. Effects of BS and CO were also positive and statistically
17 significant ($p < 0.01$). Effects of NO₂ and O₃ were not significant. Air pollution effects on visits
18 were weaker in fall than in other seasons. Effects of SO₂ remained positive and significant even
19 when days with daily average SO₂ above 72 mg/m³ (181 days, 24.8% of all 730 study days) were
20 excluded from analysis.

21 Gordian et al. (1996) examined relationships between short-term ambient air pollution
22 levels and daily outpatient visits for asthma, bronchitis, and upper respiratory illness (e.g., sore
23 throat, sinusitis, earache, rhinitis) in Anchorage, AK, from May 1992 to March 1994. Numbers
24 of visits were derived from medical insurance claims by state and municipal employees, and their
25 dependents. Measurements of CO were made only during winter months. Briefly, an increase of
26 10 mg/m³ in PM₁₀ was associated with a 3 to 6% increase in visits for asthma, and a 1 to 3%
27 increase in visits for upper respiratory illness. Winter CO concentrations were associated with
28 increased numbers of visits for bronchitis and upper respiratory illness, but not for asthma.
29 At the same time, these CO concentrations were tightly correlated with overall automobile
30 exhaust emissions, including NO₂, fine particles, and VOCs such as benzene. Thus, visits for
31 respiratory illness could not be linked specifically to ambient CO exposure.

1 Yang et al. (1997) investigated asthma emergency room visits in Reno, NV, in relation to
2 short-term ambient air pollution levels over 3 years, 1992 to 1994. Analytical methods were
3 similar to those used in Yang et al. (1998). Briefly, there was a positive, statistically significant
4 association of visits with the ambient O₃ level lagged 0 days, but not 1 or 2 days. Visits were not
5 associated with ambient CO or PM₁₀ levels.

6 Two reports investigating asthma exacerbation in relation to short-term ambient levels of
7 CO and other air pollutants have been published in 1999 by University of Washington
8 investigators (Sheppard et al., 1999; Norris et al., 1999). Taken together, these reports highlight
9 the difficulties inherent in efforts to specify single-pollutant effects in populations exposed to the
10 complex ambient air pollution mix. Sheppard et al. (1999) considered admissions for asthma to
11 23 greater Seattle hospitals from 1987 through 1994 in persons aged <65 years. Fifty-four
12 percent of these admissions occurred in persons less than 20 years old. Pollutants considered
13 were daily average CO, PM₁₀, PM_{2.5} (fine PM), PM_{10-2.5} (coarse PM), and SO₂, and daily
14 maximum 8-h average O₃. The CO monitors were located in street canyons, not residential areas.
15 PM₁₀ was measured with both the EPA reference method and with light-scattering nephelometry.
16 Fine PM levels were largely estimated from PM₁₀ measurements. Coarse PM levels were
17 calculated as the difference between PM₁₀ and fine PM levels. The PM measurements from
18 residential sites were given higher weight (80%) than those from an industrial site (20%).
19 During the study period, 50th-percentile ambient levels of average CO, PM₁₀, fine PM, and
20 coarse PM were quite moderate (1.7 ppm and 27, 13, and 14 μg/m³, respectively).

21 Data were analyzed to treat all measured pollutants even-handedly. Semiparametric
22 Poisson regression models were used and included dummy variables for day of week. Multiple
23 lag times were considered; for each pollutant, the lag time showing the strongest statistical
24 association with admissions was selected. Single- and two-pollutant models were constructed,
25 and pollutant effects estimates were reported over interquartile ranges of ambient pollutant
26 concentrations.

27 In single-pollutant models, CO lagged 3 days and O₃ lagged 2 days were associated most
28 strongly with asthma admissions. Associations of admissions with PM₁₀, fine PM, and coarse
29 PM, each lagged 1 day, were also positive and statistically significant. The association of
30 admissions with SO₂ (lagged 0 days) was positive but not significant. In season-specific,
31 two-pollutant models, generally similar effects were observed for CO lagged 3 days and fine PM

1 lagged 1 day. Over all seasons, effects of both pollutants were positive and significant. Both
2 pollutants were positively, and at least marginally significantly, associated with admissions in
3 fall, winter, and spring. Both pollutants were negatively associated with admissions in summer.
4 Sheppard et al. (1999) stated, “In striving for a balanced approach to all measured pollutants...,
5 we observed unexpected associations for CO that dominated the PM effects. Nevertheless,...,
6 there is no evidence for an effect [of CO] on the underlying physiology of asthma. CO may be an
7 important environmental indicator of incomplete combustion, particularly from mobile sources.”

8 Norris et al. (1999) investigated short-term ambient air pollution and emergency
9 department (ED) visits for asthma in Seattle children aged <18 years, from September 1995
10 through December 1996. Analyses were conducted for the entire study population, for urban
11 children (in whom the reported overall annual hospitalization rate was more than 600/100,000)
12 and for suburban children (in whom the reported overall rate was less than 100/100,000).
13 Pollutants considered were daily average CO, PM₁₀, and PM₁ (as measured by nephelometer),
14 hourly average SO₂, and daily maximum hourly average and daily average NO₂. During the
15 study period, mean ambient levels of CO, PM₁₀, and fine PM were 1.6 ppm, 21.7 µg/m³, and
16 12 µg/m³ (estimated), respectively. There were too few O₃ measurements to include in analytical
17 models. Relative risks were reported over interquartile ranges of pollutant concentrations. Lag
18 times of 0 through 4 days were considered. Models were adjusted with dummy variables for day
19 of week, smoothing splines for time trends (approximately a 2-mo moving average), ambient
20 temperature, and dew point temperature.

21 Pollutant effects on asthma visits were usually reported with a 1-day lag. In single-
22 pollutant models, effects of PM₁ and PM₁₀ were consistently positive and at least marginally
23 statistically significant. Effects of CO were also consistently positive, but not significant in the
24 urban children. Effects of daily average NO₂, lagged 2 days, were positive and marginally
25 significant. Mixed results were observed for other pollution metrics. In multipollutant models,
26 effects of PM₁ and PM₁₀ remained positive and statistically significant, but SO₂ and NO₂ effects
27 did not retain significance. Multipollutant models did not include CO because CO was assumed
28 a priori to be a surrogate for stagnant conditions. Norris et al. (1999) stated, “In summary, this
29 study found a small but significant association between air pollution and increased ED visits for
30 asthma...PM and CO concentrations...were associated with increased childhood ED visits for
31 asthma and represent the daily variation in incomplete combustion products....”

1 The exclusion of CO from multi-pollutant models by Norris et al. (1999) appears dubious,
2 because both they and Sheppard et al. (1999) observed statistically significant associations of
3 both PM and CO with asthma exacerbation in single-pollutant models. The assumption that CO
4 is a surrogate for stagnant conditions may well be valid, but no rationale was presented for why
5 the same assumption could not be made for the other combustion-related air pollutants that were
6 included in the multipollutant models. Also, if ambient CO is merely a biologically inert fellow-
7 traveler with ambient PM, it would be difficult to understand why, in Sheppard et al. (1999), the
8 CO-asthma association was strongest when lagged 3 days, whereas the PM-asthma association
9 was strongest when lagged only 1 day. Furthermore, although it is true that there is no known
10 biological mechanism by which CO at ambient levels could exacerbate asthma, the mechanistic
11 linkage of combustion-related, nonbiological PM with asthma exacerbation remains to be more
12 clearly elucidated.

13 Norris et al. (1999) conclude, “Results from this study...show significant increases of ED
14 asthma visits...with daily PM_{2.5} concentrations substantially below the...standard of 15 µg/m³
15 annually.” Although this statement is reasonable enough, it does not mention that associations of
16 asthma exacerbation with ambient CO levels were also observed, that ambient CO levels were
17 also below the existing CO standards, and that PM_{2.5} levels were largely estimated, whereas CO
18 levels were measured directly. Finally, the authors’ assumption that children under 18 years old
19 are more “susceptible” than the general population is somewhat questionable, because short-term
20 elevations in ambient air pollution levels have been most strongly associated with unequivocally
21 harmful health effects in the elderly, and because asthma death rates and case-fatality rates are
22 higher in adults than in children. Taken together, Sheppard et al. (1999) and Norris et al. (1999)
23 show generally similar degrees of association of short-term fluctuations in ambient CO and PM
24 levels with frequency of asthma exacerbation in Seattle.

26 **6.2.2 Controlled Laboratory Studies**

27 The most extensive human experimental studies on the cardiovascular effects of CO have
28 been those conducted in predominantly young, healthy, nonsmoking subjects during exercise.
29 Previous assessments of these effects (U.S. Environmental Protection Agency, 1979, 1984, 1991;
30 Horvath, 1981; Sheppard, 1983, 1984) have identified what appears to be a linear relationship
31 between the level of COHb in the blood and decrements in human exercise performance,

1 measured as maximal oxygen uptake. Short-term maximal exercise performance significantly
2 decreases at COHb levels ranging from 5 to 20% (Pirnay et al., 1971; Vogel and Gleser, 1972;
3 Ekblom and Huot, 1972; Weiser et al., 1978; Stewart et al., 1978; Klein et al., 1980; Koike and
4 Wasserman, 1992). One study (Horvath et al., 1975) observed a marginal decrease in maximal
5 exercise performance at a COHb level as low as 4.3% COHb. Short-term maximal exercise
6 duration also has been shown to be significantly reduced at COHb levels ranging from 2.3 to
7 20% (Ekblom and Huot, 1972; Drinkwater et al., 1974; Raven et al., 1974a,b; Horvath et al.,
8 1975; Weiser et al., 1978; Koike and Wasserman, 1992). The observed decreases in maximal
9 exercise performance and duration, however, are so small that they are only of concern primarily
10 for competing athletes, rather than for healthy people conducting everyday activities at less than
11 maximal exercise levels. In fact, no significant effects on oxygen uptake or on exercise
12 ventilation and heart rate were reported during submaximal exercise at COHb saturations as high
13 as 15 to 20% (see Section 10.3.2 in U.S. Environmental Protection Agency, 1991), especially at
14 work rates below the metabolic acidosis threshold (Koike et al., 1991).

15 Of greater concern at more typical ambient CO levels are certain cardiovascular effects
16 during exercise that are likely to occur in a smaller, but sizeable, segment of the general
17 population having a deficiency of blood supply (ischemia) to the heart muscle. This group of
18 patients with coronary artery disease (CAD) and reproducible exercise-induced angina (chest
19 pain) is regarded as the most sensitive risk group for CO-exposure effects. Several important
20 studies (Anderson et al., 1973; Sheps et al., 1987; Adams et al., 1988; Kleinman et al., 1989;
21 Allred et al., 1989a,b, 1991) have provided the cardiovascular database for CO in CAD patients.
22 In these studies, discussed in detail in the previous document (see Section 10.3.2 in U.S.
23 Environmental Protection Agency, 1991), significant ischemia was measured subjectively by the
24 time of exercise required for the development of angina (time of onset of angina) and objectively
25 by the time required to demonstrate a 1-mm change in the ST segment of the electrocardiogram.
26 Adverse effects were found with postexposure COHb levels as low as 3 to 6% when compared
27 on the basis of optical measurements (Figure 6-4). This represents incremental increases of
28 1.5 to 4.4% COHb from preexposure baseline levels. Effects on silent ischemia episodes
29 (no chest pain), which represent the majority of episodes in these patients, have not been studied.

30 Only one new study has become available since publication of the 1991 document. As part
31 of an investigation of CO exposure at high altitude, 17 men with documented CAD and stable

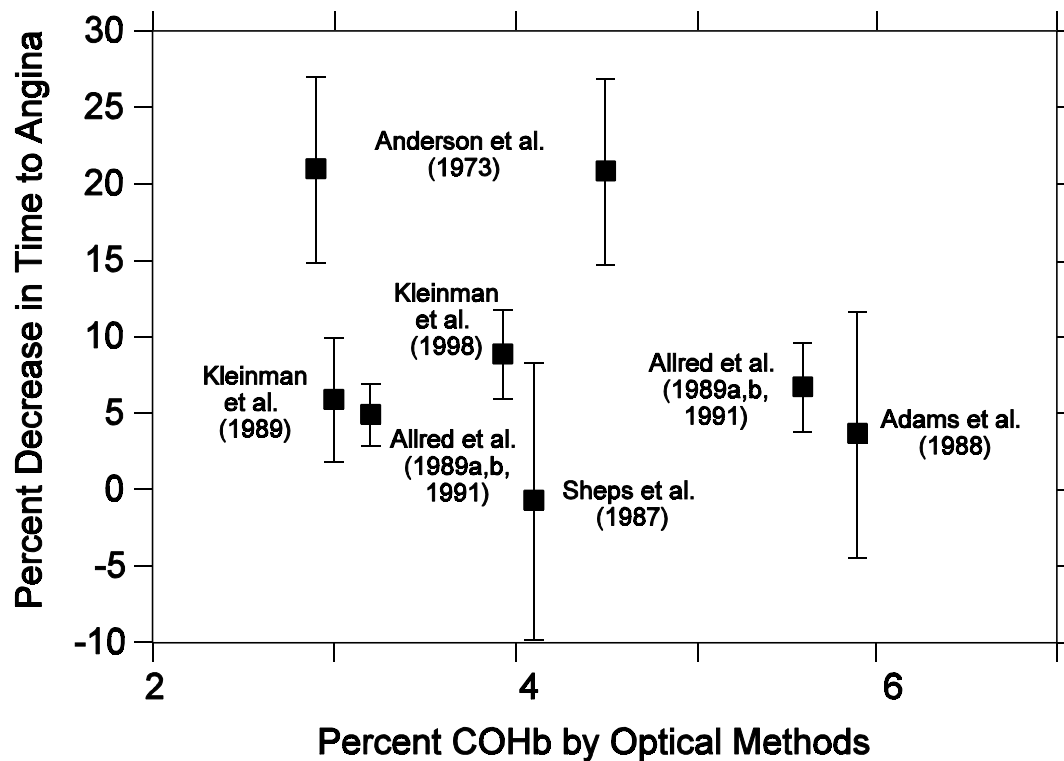


Figure 6-4. The effect of CO exposure on time to onset of angina. For comparison across studies, data are presented as mean percent differences between air- and CO-exposure days for individual subjects calculated from each study. Bars indicate calculated standard errors of the mean. The COHb levels were 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).

angina performed exercise stress tests after random 2-h exposures to either clean air or 100 ppm CO at sea level (Kleinman et al., 1998; Leaf and Kleinman, 1996a; Kleinman and Leaf, 1991). The methods used were similar to those previously reported by Kleinman et al. (1989). Group mean COHb levels measured by CO-Oximetry (CO-Ox) were 0.6 ± 0.3 (SD)% and 3.9 ± 0.5 (SD)% for clean air and CO exposures, respectively. Repeated measures analysis of variance for a subgroup ($n = 13$) with angina on all test days demonstrated a statistically significant ($p < 0.05$) decrease of $9.1 \pm 0.6\%$ 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 6-4). There was no statistically significant effect on ST segment change, on the duration of angina, or on hemodynamic factors such as blood pressure and heart rate.

Despite clearly demonstrable effects of low-level CO exposure in patients with ischemic heart disease, the adverse health consequences of these types of effects are very difficult to predict in the at-risk population of individuals with heart disease. There is a wide distribution of 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 a myocardial infarction (heart attack), a fatal arrhythmia (abnormal heart rhythm), or slight but cumulative myocardial damage.

Exposures to low levels of CO resulting in 5 to 20% COHb do not produce significant changes in cardiac rhythm or conduction during rest or exercise in healthy humans (Davies and Smith, 1980; Kizakevich et al., 1994). Effects of CO on resting and exercise-induced ventricular arrhythmia in patients with CAD are dependent on their clinical status. Hinderliter et al. (1989) reported no effects of 4 and 6% COHb in patients with ischemic heart disease who did not have chronic arrhythmia (ectopy) during baseline monitoring. In more severely compromised individuals with higher levels of baseline ectopy, exposures to CO that produce 6% COHb have been shown to significantly increase the number and complexity of arrhythmias (Sheps et al., 1990), but not at lower COHb levels (Sheps et al., 1990, 1991; Chaitman et al., 1992; Dahms et al., 1993). This finding, combined with epidemiologic evidence of CO-related morbidity and mortality noted above, and the morbidity and mortality studies of workers who are routinely exposed to combustion products (e.g., Stern et al., 1981, 1988; Edling and Axelson, 1984; Sardinas et al., 1986; Michaels and Zoloth, 1991; Koskela, 1994; Melius, 1995; Ström et al.,

1995) suggest that CO exposure may provide an increased risk of hospitalization or death in patients with more severe heart disease.

There also is evidence from experimental studies with laboratory animals that CO can adversely affect the cardiovascular system. The lowest-observed-effect level (LOEL) varies, depending on the exposure regime used and species tested (see Table 6-6). Results from animal studies (reviewed in U.S. Environmental Protection Agency, 1979, 1991; Turino, 1981; McGrath, 1982; Penney, 1988, 1996a) suggest that inhaled CO can cause disturbances in cardiac rhythm and conduction in healthy and cardiac-impaired animals that are consistent with the human data. Results from animal studies (U.S. Environmental Protection Agency, 1991) also indicate that inhaled CO can increase hemoglobin concentration and hematocrit ratio, probably representing compensation for the reduction in oxygen transport caused by CO. At high CO concentrations, excessive increases in hemoglobin and hematocrit may impose an additional workload on the heart and compromise blood flow to the tissues.

TABLE 6-6. ESTIMATED LOWEST-OBSERVED-EFFECT LEVELS FOR 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)
Schedule-controlled behavior	330	25.0	2 h	Rat	Merigan and McIntire (1976)
Developmental effects	60	6.0	21 days ^a	Rat	Prigge and Hochrainer (1977)
Lung morphology and function	5,000	60.0	15 min	Rat	Niden and Schulz (1965)

^aContinuous daily exposure.

^bIntermittent daily exposure, 4 h/day.

1 There is conflicting evidence that CO exposure enhances development of atherosclerosis in
2 laboratory animals, but most studies show no measurable effect when the animals are fed normal
3 diets without added cholesterol, even at high ($\approx 20\%$) COHb saturations (U.S. Environmental
4 Protection Agency, 1979, 1991; Penn et al., 1992; Penn, 1993; Mennear, 1993; Smith and
5 Steichen, 1993; Ström et al., 1995). Similarly, the possibility that CO promotes significant
6 changes in lipid metabolism that may accelerate atherosclerosis is suggested in only a few
7 laboratory animal studies (see Table 10-7 in U.S. Environmental Protection Agency, 1991) but
8 not in humans (Leaf and Kleinman, 1996b); however, any such effect must be subtle at most.
9 More recent in vitro studies utilizing cell culture techniques have explored the hypothesis that
10 CO causes cellular oxidative stress and leads to injuries of the vascular endothelium that may
11 precipitate atherosclerosis (Thom and Ischiropoulos, 1997; Thom et al., 1997). Unfortunately,
12 the ability of environmentally relevant CO concentrations to mediate this activity in the intact
13 organism has not been evaluated. Finally, CO probably inhibits rather than promotes platelet
14 aggregation (U.S. Environmental Protection Agency, 1991; Min et al., 1992), lending support to
15 forensic observations that thrombosis is not a prominent feature of CO-mediated injury.
16 In general, there are few data to indicate that an atherogenic effect of exposure is likely to occur
17 in human populations at frequently encountered levels of ambient CO.

20 **6.3 CENTRAL NERVOUS SYSTEM AND BEHAVIORAL EFFECTS**

21 **6.3.1 Brain Oxygen Metabolism**

22 **6.3.1.1 Whole Brain**

23 It has been documented amply in the literature that, as COHb is formed, vasodilation in the
24 brain (and increased blood supply) occurs in such proportions so as to keep the supply of oxygen
25 (O_2) to the brain constant (Helfaer and Traystman, 1996; U.S. Environmental Protection Agency,
26 1991). The increased blood flow is sufficient to compensate not only for the oxygen supply
27 decrease caused by reduced arterial O_2 content (CaO_2) but is also sufficient to compensate for the
28 increased difficulty of extraction of O_2 because of the shifted oxyhemoglobin dissociation curve.
29 This compensatory vasodilation appears to be effective from low levels to very high levels of
30 COHb (at least up to 60%) and is similar in the fetus, neonate, and healthy adult.

1 Despite the compensatory regulation of O₂ supply to the brain, it appears that
2 O₂ consumption, measured as the cerebral metabolic rate for O₂ (CMRO₂), is reduced as COHb
3 rises. The reason for this is unclear, but the fact is well documented (Doblar et al., 1977; Jones
4 and Traystman, 1984; U.S. Environmental Protection Agency, 1991; Langston et al., 1996). The
5 amount of reduction in CMRO₂ as a function of COHb can be seen by combining the information
6 of Doblar et al. (1977) from goats and Langston et al. (1996) from sheep into one graph (see
7 Figure 6-5). Although information from Jones and Traystman (1984) and associated studies was
8 expressed as a function of CaO₂, not COHb, and was difficult to incorporate into Figure 6-5 and
9 the associated analysis, their data corroborate those of the other workers.

10 From Figure 6-5, it may be seen that the CMRO₂ does not decrease to 90% of baseline until
11 ≈27% COHb (95% confidence limits were ≈21 to 32% COHb). The data from sheep and goats
12 agreed with the results of Paulson et al. (1973), who reported that the mean human CMRO₂ did
13 not decrease significantly, even for COHb up to 20%. Because Paulson et al. (1973) did not
14 report the value of their means, it was not possible to include their results as data points in
15 Figure 6-5.

16 17 **6.3.1.2 Subregions of the Brain**

18 There are a number of reports of the blood-flow response to COHb of subregions of the
19 brain (U.S. Environmental Protection Agency, 1991). The results generally demonstrate that
20 some areas of the brain have less baseline blood flow than others, and that the COHb-
21 compensatory increase in blood flow is not the same for all areas. Generally, however, the
22 percent increases over baseline are nearly the same for all areas except the neurohypophysis
23 (Hanley et al., 1986). It is important to note that the latter area serves homeostatic and not
24 ongoing behavioral functions. Thus, it would appear that the subregions of the brain have
25 compensatory increased blood flow in the presence of COHb similar to the whole brain. To be
26 sure, all possible regions of the brain have not been tested, but no evidence to indicate otherwise
27 has been found.

28 Work by Sinha et al. (1991), measuring regional capillary perfusion and blood flow in the
29 presence of COHb elevation, indicates that the problem of compensation for COHb-reduced
30 CaO₂ is not as simple as indicated above. Blood flow was measured using radiolabeled dye and
31 capillary morphology was measured by fluorescence microscopy. With these methods, there

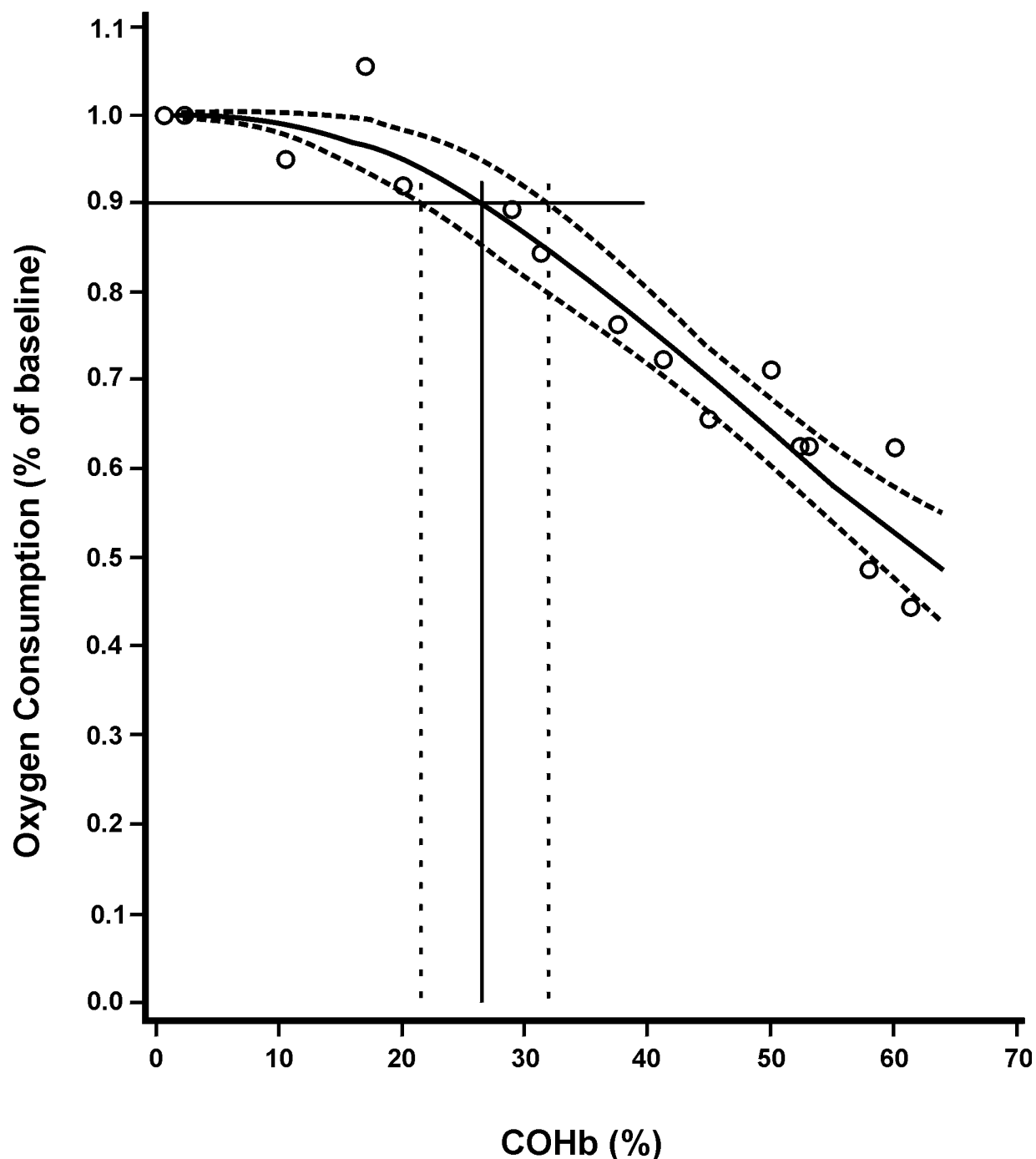


Figure 6-5. The relationship between COHb and CMRO_2 . Means from Doblar et al. (1977) were taken from their Tables 1 and 3, and CMRO_2 values were transformed to percent of baseline. Figures 1 and 3 of Langston et al. (1996) were converted digitally (Summasketch III graphical to digital conversion) and also were transformed to percent of baseline. Data from both sources were merged into the same database and a logit function was fitted to the data using SAS, PROC NLIN (SAS Institute Inc., 1990). The solid line is the best fit, dashed lines are the 95% confidence limits, and the points plotted are means from the published studies.

1 appeared to be an increase in the number of perfused capillaries and in the amount of blood flow
2 as COHb increased. Thus, not only may more blood be delivered, but increased capillary
3 perfusion would decrease the diffusion distance to the tissue.

4 Presumably the compensatory mechanisms in subareas of the brain would work in a
5 manner similar to that of the whole brain and thus would show similar decreases in CMRO₂ as
6 COHb increases. No corroborative studies, however, have been reported in the literature.

7 Better and more detailed documentation of regional CMRO₂ in humans as well as other
8 species seems appropriate, but does not have high priority because not much evidence exists to
9 suggest that the results would differ from whole-brain results. It appears that what is needed is
10 not more descriptive work, but an effort should be made to understand the mechanism by which
11 COHb elevation reduces CMRO₂. Furthermore, information is needed about brain conditions
12 under which brain compensatory mechanisms might be impaired (e.g., injury, inflammation,
13 ailments associated with aging and co-exposure to other pollutants). If such information were
14 available, specific theoretical (biologically based) predictions could be made, and behavioral
15 experiments designed to test them.

17 **6.3.2 Behavioral Effects of Carbon Monoxide**

18 The effects of CO on behavior, especially the ability to perform certain time discrimination
19 tasks, provided the scientific basis for the first CO NAAQS in 1971 (see Section 1.2). As further
20 research data became available, however, the results on human behavior at low levels of CO
21 exposure (<5% COHb) were called into question and subsequently dismissed as the basis for the
22 standard (U.S. Environmental Protection Agency, 1979). After reviewing available studies, the
23 previous criteria document (U.S. Environmental Protection Agency, 1991) concluded that effects
24 on behavior were demonstrated unambiguously in both humans and laboratory animals at COHb
25 elevations above 20%. Below this level, the results were less consistent. The document also
26 concluded, however, that it seems unwise to ignore the historical evidence in favor of effects on
27 human performance at COHb levels between 5 and 20% (e.g., Horvath et al., 1971; Fodor and
28 Winneke, 1972; Putz et al., 1976, 1979; Benignus et al., 1987). Even if behavioral effects are
29 small or occasional, they may be important to the performance of critical tasks.

30 Behavioral experiments with the effects of elevated COHb frequently have been marred by
31 methodological problems. In particular, experiments employing single-blind designs were shown

1 to be 2.5 times as likely to find significant results as similar studies employing double-blind
2 methods (Benignus, 1993, 1996). This problem was noted previously, and reports of findings of
3 behavioral effects of CO were summarized with respect to whether a double-blind procedure had
4 been followed (see Table 10-25 of U.S. Environmental Protection Agency, 1991). From this
5 summary, it was concluded that, at most, there was credible evidence for effects on only three
6 (somewhat artificially defined) categories of behavior: (1) tracking, (2) vigilance, and
7 (3) continuous performance. Even within these categories, considering only double-blind
8 studies, it was noted that less than 50% of all studies found significant effects. Furthermore,
9 most of the double-blind experiments reporting significant results were unreplicable.

10 Benignus (1994) performed extensive meta-analyses of the CO-behavioral literature.
11 Because single-blind studies were likely to include many type I errors (results erroneously
12 declared significant), only double-blind human CO studies were included. In this report, two
13 dose-effect curves were estimated from the literature by converting all behavioral endpoints to
14 percent of baseline. A dose-effect curve for COHb and behavior was estimated from rat
15 experiments and corrected for the effects of hypothermia. The COHb for rats was estimated from
16 exposure conditions by use of a rat-specific version of the Coburn-Forster-Kane Equation
17 (Benignus and Annau, 1994). Another dose-effect curve was estimated from the human
18 literature on hypoxic hypoxia, which was converted to equivalent COHb via equal arterial
19 oxygen contents and corrected for effects of hypocapnia. These two curves virtually overlapped
20 each other. Human data points from CO-behavior experiments then were plotted onto the curve
21 fitted to the rat CO data (no curve was fitted to human data because of the small effect sizes and
22 small COHb levels). The conclusion from this meta-analysis was that human behavioral
23 impairments of 10% (ED-10) should not be expected until COHb exceeds 20%.

24 Data for the rat studies from Benignus (1994) were refitted for present purposes using the
25 same dose-effect model (a logit) as for the CMRO₂ data above (originally a different function
26 was used). The results are plotted in Figure 6-6, in which the different studies are coded by
27 letters. With the logit function, it is estimated that a 10% decrement should be produced in rats
28 by ca. 25% COHb (95% confidence limits of ≈20 to 30%). Data from all available double-blind
29 human studies also were converted to percent of baseline and plotted (Figure 6-7) along with the
30 logit curve fitted to the rat data (from Figure 6-6). The human data plotted in Figure 6-7 were
31 mostly not statistically significant (thin solid lines) and seem, as a group, not to have a

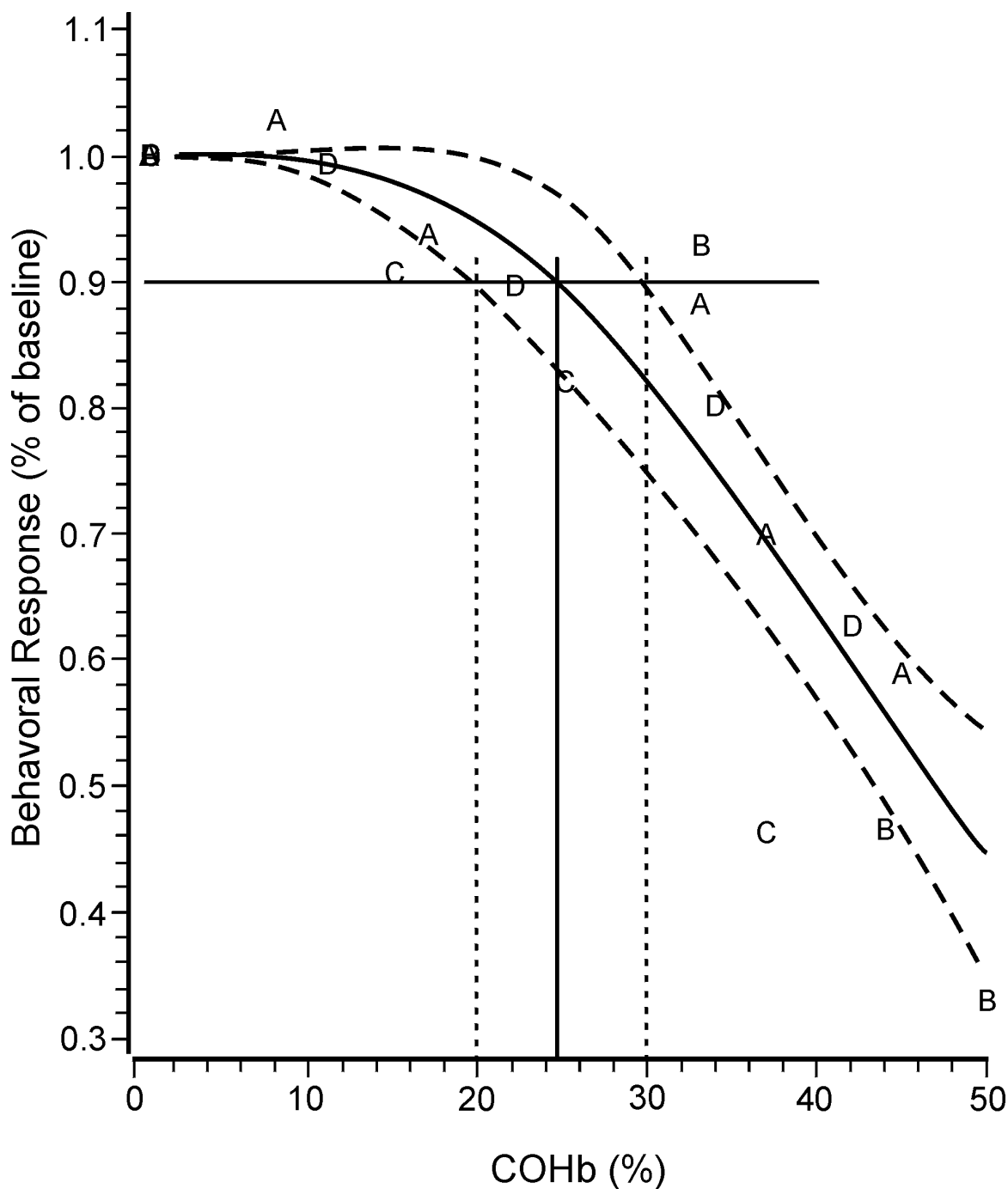


Figure 6-6. The relationship between COHb and behavior: effects in rats. Points plotted are the hypothermia-corrected means from four studies of effects of COHb in rats in which COHb was estimated by a rat-specific version of the Coburn-Forster-Kane Equation (see Benignus, 1994). The solid line is a 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).

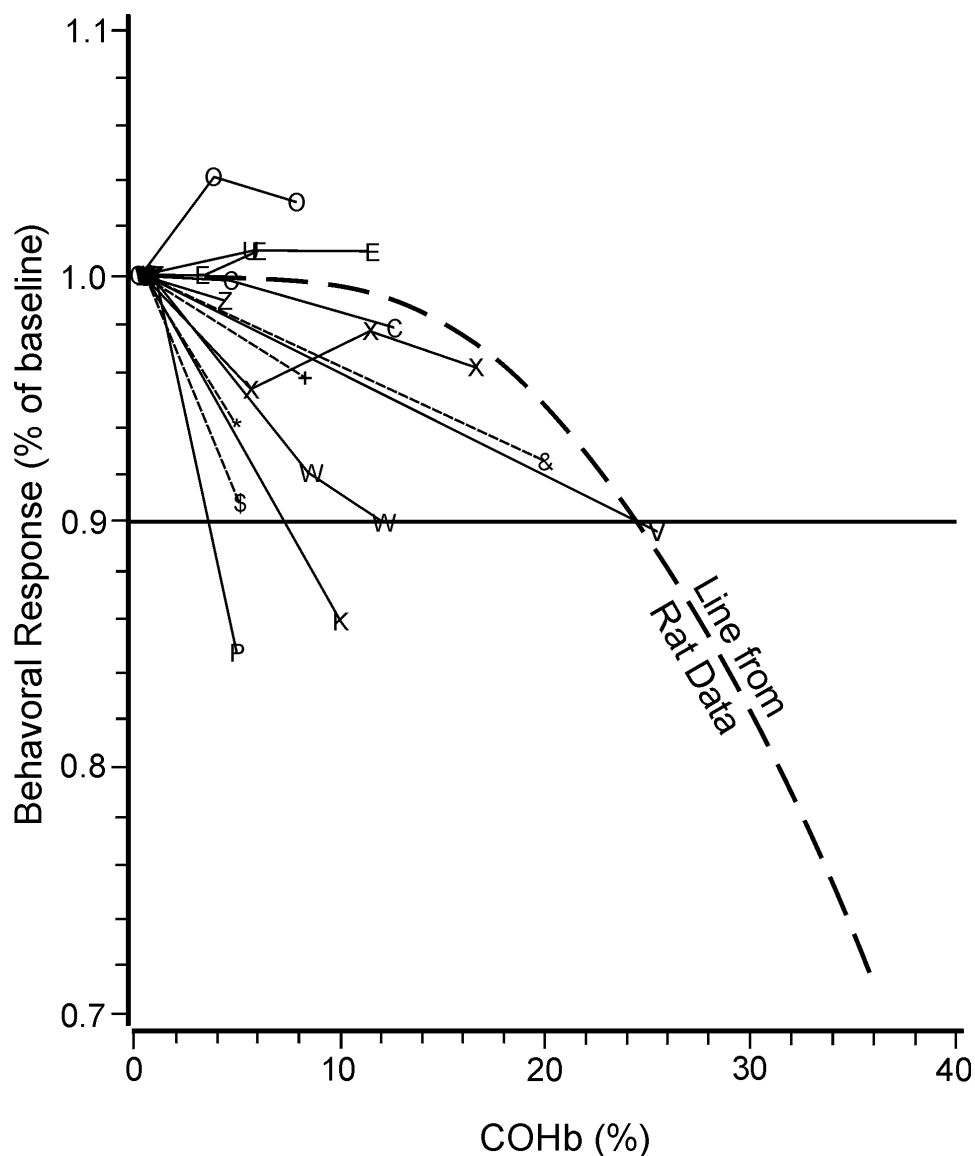


Figure 6-7. The relationship between COHb and behavior: effects in humans compared to rats. Points plotted are means from various human studies. The heavy dashed line is the line fitted to rat data as shown in Figure 6-6. The points for the human data are connected by thin lines to depict the dose-effect curve found in each study. Solid thin lines are from studies in which no significant effect was found; dashed lines 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), KC = 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), P = Weir et al. (1973), Z = Wright et al. (1973), + = Benignus et al. (1987), \$ = Putz et al. (1976), * = Putz et al. (1979), and = Ramsey (1973).

1 dose-related trend of decrements, and it could be argued reasonably that effects in humans cannot
2 be shown to differ from those in rats. Some of the human data, however, at low levels of COHb
3 (4 to 10%) do appear below baseline and were declared statistically significant (thin dashed lines)
4 by the authors of the original reports.

5 The low-COHb significant results plotted in Figure 6-3 were invariably reported in studies
6 in which only a few levels of COHb were evaluated. Studies in which more and higher COHb
7 levels were tested invariably did not find statistically significant effects, even at much higher
8 levels. Furthermore, for every study reporting low-COHb level impairments, other studies failed
9 to replicate the findings, or highly similar studies failed to find effects.

10 In summary, no reliable evidence demonstrating decrements in neural or behavioral
11 function in healthy young adult humans has been reported for COHb levels below 20%, and even
12 these studies are untested by replications. The low-COHb behavioral effects that have
13 sometimes been reported cannot be taken at face value because they are not reliably repeatable,
14 and they do not fit into a wider range, dose-effect pattern reported in other studies. It is more
15 reasonable to conclude that no statistically detectable behavioral impairments occur until COHb
16 exceeds 20 to 30%. The conclusion, based on behavioral evidence alone, is bolstered by the
17 findings that whole-brain CMRO₂ is not reduced by a similar amount until COHb rises to 21 to
18 32%. Because a dose-effect curve has been fitted, any level of effect may be considered
19 (e.g., ED-5 or ED-20). The interpolation of a curve to an ED-5 point would imply that the COHb
20 levels for such an effect size would be 15 to 26%. Such an interpolation is more speculative than
21 an ED-10, however, because the experimental verification would be difficult, requiring large
22 numbers of subjects and careful control of error variance. Additionally, as interpolation
23 approaches small effect sizes, the error possibility because of statistical model selection
24 (threshold versus continuous) increases dramatically.

25 Unless the effort is to find a behavioral paradigm that would yield replicable low-level
26 COHb decrements in behavior that were part of a wider range, dose-effect curve, it would seem
27 unfruitful to continue behavioral work. The lack of such dose-effect information within a study
28 has contributed to the problems of interpreting published literature. Behavioral work should be
29 encouraged, in an effort to determine whether reliable decrements in behavior are associated with
30 low levels of COHb. However, any new behavioral experiments should involve several CO
31 exposure levels, including a level high enough to produce changes. Failing that, inclusion of

1 some other procedure or a reference dose of some other active substance would be useful to
2 verify the sensitivity of the behaviors under study. In addition, other experiments should be
3 designed to contribute to our understanding of how CMRO₂ relates to COHb elevation and
4 behavioral changes.

5 Behaviors implicated by the research findings involve detection of infrequent events
6 (vigilance), hand-eye coordination (compensatory tracking), and other forms of continuous
7 performance (U.S. Environmental Protection Agency, 1991). Because of the unreliability of the
8 findings, however, it is questionable whether these behaviors should be cited as effects. Until
9 reliable behavioral effects are demonstrated in a dose-related manner, it is premature to speculate
10 about the kind of behavioral effects and, thus, to lend credence to unreliable findings.

11 Because COHb elevates brain blood flow, it has the possibility of altering the delivery of
12 other toxicants to the brain or altering the biotransformation or elimination of toxicants (e.g., Doi
13 and Tanaka, 1984; Kim and Carlson, 1983; Roth and Rubin, 1976a,b). In combination with
14 exercise or hypoxic hypoxia, the interactions would become even more complex. Disease and
15 ailments associated with aging concomitant with all of the above also could be important.
16 Interactions such as these are understood from physiological theory and could be given
17 quantitative estimates by the use of physiological simulation using whole-body physiological
18 models that are currently under development.

21 **6.4 DEVELOPMENTAL TOXICITY**

22 An issue directly relevant to the protection of public health is the potential effect of CO on
23 growth and function of the developing fetus, infant, and child. Results obtained from new
24 research on this specific outcome of CO exposure (e.g., Carratù et al., 1993, 1996; Di Giovanni
25 et al., 1993; De Salvia et al., 1995; De Luca et al., 1996) have not changed the conclusions
26 presented in Section 10.5 of the previous criteria document (U.S. Environmental Protection
27 Agency, 1991). From all of the laboratory animal studies, it is clear that severe, acute CO
28 poisoning can be fetotoxic, although specification of maternal and fetal COHb levels is difficult
29 because such exposures rarely involve the achievement of steady-state COHb levels or permit
30 careful and rapid determination of COHb levels. Available data (reviewed in U.S.
31 Environmental Protection Agency, 1991; Annau and Fechter, 1994; Carratù et al., 1995; Penney,

1996b) provide strong evidence that maternal CO exposures of 150 to 200 ppm, leading to approximately 15 to 25% COHb, produce reductions in birth weight, cardiomegaly, delays in behavioral development, and disruption of cognitive function in laboratory animals of several species. Isolated experiments (Prigge and Hochrainer, 1977; Abbatiello and Mohrmann, 1979; Singh, 1986) suggest that some of these effects may be present at concentrations as low as 60 to 65 ppm (approximately 6 to 11% COHb) maintained throughout gestation (see Table 6-6). 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 very unlikely that ambient levels of CO typically encountered by pregnant women would cause increased fetal risk. It is necessary, however, to consider the combined effects of CO with the other common risk factors that may cause adverse fetal outcome (e.g., tobacco and alcohol consumption, genetic background, maternal general health, 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

1 weights, and increased fetal malformations were reported at CO concentrations as low as 65 ppm
2 maintained between 6 and 23 h per day during the first trimester of pregnancy (gestational
3 days 8 through 18). Previous evidence of the fetotoxic and teratogenic effects of CO in
4 laboratory animals (U.S. Environmental Protection Agency, 1991) came largely from high levels
5 of exposure (i.e., in the range of 500 ppm for rodents).

6 There are studies (e.g., Schoendorf and Kiely, 1992; Scragg et al., 1993; Mitchell et al.,
7 1993; Klonoff-Cohen et al., 1995; Blair et al., 1996; Hutter and Blair, 1996; MacDorman et al.,
8 1997) linking maternal cigarette smoking with sudden infant death syndrome (SIDS), but the role
9 of CO is uncertain, especially in relation to other known risk factors for SIDS, such as
10 developmental abnormalities (Schwartz et al., 1998), prone sleeping (Kahn et al., 1993; Franco
11 et al., 1996), overheating (Douglas et al., 1996), and soft bedding (Ponsonby et al., 1993; Kemp
12 et al., 1998). Data from human populations (Hoppenbrouwers et al., 1981) suggesting a link
13 between ambient CO exposures and SIDS are weak, but further study should be encouraged.
14 Children may experience neurological symptoms such as dizziness or fainting after an acute
15 episode of CO poisoning (>15% COHb) or, in some cases, neurological impairment may develop
16 days to weeks after very high exposures (Crocker and Walker, 1985). Human data from these
17 cases of accidental high CO exposures are difficult to use in identifying a LOEL for CO because
18 of the small number of cases reviewed and problems in documenting exposure levels. However,
19 such data, if systematically gathered and reported, could be useful in identifying possible ages of
20 special sensitivity to CO and co-factors or other risk factors that might identify sensitive
21 subpopulations.

24 **6.5 ACUTE PULMONARY EFFECTS**

25 It is unlikely that CO has any direct effects on lung tissue, except for extremely high
26 concentrations that can cause cell damage and edema (Niden and Schulz, 1965; Fein et al., 1980;
27 Burns et al., 1986). No new information has been published in the literature to change this
28 conclusion drawn from Section 10.2 of the previous criteria document (U.S. Environmental
29 Protection Agency, 1991). Experimental studies on the effects of CO exposures producing
30 COHb saturations up to 56% failed to find any consistent effects on pulmonary cells and tissue or
31 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 not found strong relationships with pulmonary function, symptomatology, and disease (Lutz, 1983; Robertson and Lebowitz, 1984; Lebowitz et al., 1987).

6.6 OTHER SYSTEMIC EFFECTS OF CARBON MONOXIDE

Laboratory animal studies (reviewed in Section 10.6 of U.S. Environmental Protection Agency, 1991) suggest that enzyme metabolism and the P-450-mediated metabolism of xenobiotic compounds may be affected by CO exposure (e.g., Montgomery and Rubin, 1971; Pankow et al., 1974; Roth and Rubin, 1976a,b,c). Most of the authors of these studies have concluded, however, that effects on metabolism at low COHb levels ($\leq 15\%$) are attributable entirely to tissue hypoxia produced by increased levels of COHb because the effects are no greater than those produced by comparable levels of hypoxia produced by insufficient oxygen delivery. 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 (Zebro et al., 1983), and immune capacity in the lung and spleen (Snella and Rylander, 1979). It generally is agreed that these effects are caused by the severe tissue damage occurring during acute CO poisoning resulting from one or more of the following: ischemia resulting from the formation of COHb, inhibition of oxygen release from oxyhemoglobin, inhibition of cellular cytochrome function (e.g., cytochrome oxidases), and metabolic acidosis.

6.7 PHYSIOLOGIC RESPONSES TO CARBON MONOXIDE EXPOSURE

The only evidence for short- or long-term compensation to increased COHb levels in the blood is indirect. Experimental animal data (reviewed in Section 10.7 of U.S. Environmental Protection Agency, 1991) indicate that incremental increases in COHb produce physiological responses that tend to offset the deleterious effects of CO exposure on oxygen delivery to the tissues. Experimental human data (presented in a report by Kizakevich et al., 1994) indicate that compensatory cardiovascular responses to submaximal upper- and lower-body exercise (e.g., increased heart rate, cardiac contractility, cardiac output) occur after CO exposures. These changes were highly significant for exposures attaining 20% COHb. Other compensatory responses are increased coronary blood flow, cerebral blood flow, hemoglobin (through increased hemopoiesis), and oxygen consumption in muscle.

Short-term compensatory responses in blood flow or oxygen consumption may not be complete or may even be absent in certain persons. For example, from the laboratory animal studies, it is known that coronary blood flow is increased with COHb, and, from human clinical studies, it is known that subjects with ischemic heart disease respond to the lowest levels of COHb (6% or less). The implication is that, in some cases of cardiac impairment, the short-term compensatory mechanism is impaired.

From neurobehavioral 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 be only hypothesized.

The mechanism by which long-term adaptation may occur, if it can be demonstrated in humans, is assumed to be increased hemoglobin concentration via an increase in hemopoiesis. This alteration in hemoglobin production has been demonstrated repeatedly in laboratory animal studies, but no recent studies have been conducted that indicate the occurrence of some adaptational benefit. Even if the hemoglobin increase is a signature of adaptation, it has not been demonstrated at low ambient concentrations of CO.

6.8 COMBINED EXPOSURE OF CARBON MONOXIDE WITH OTHER POLLUTANTS, DRUGS, AND ENVIRONMENTAL FACTORS

6.8.1 High-Altitude Effects

Although there are many studies comparing and contrasting the effects of inhaling CO with those produced by short-term, high-altitude exposure, there are relatively few reports on the combined effects of inhaling CO at high altitudes. There are data (reviewed in Section 11.1 of U.S. Environmental Protection Agency, 1991) to support the possibility that the effects of these two hypoxic factor episodes are at least additive. Most of these early data were obtained at CO concentrations too high to have much meaning for regulating the amount of CO in ambient air. More recent studies by Kleinman et al. (1998) evaluated the combined effects of lower levels of CO at high altitude. In general, the results confirm the additivity of hypoxic effects at a simulated altitude of 2.1 km and CO exposures resulting in 4% COHb.

There are even fewer studies of the long-term effects of CO at high altitude. These studies, identified in Table 11-2 of the previous criteria document (U.S. Environmental Protection Agency, 1991), indicate few changes at CO concentrations below 100 ppm and altitudes below 4,572 m (15,000 ft). The fetus may be particularly sensitive to the effects of CO at altitude (Longo, 1976), as is especially true with the high levels of CO associated with maternal smoking (Moore et al., 1982).

The potential effects on human health of inhaling CO at high altitudes are complex (see Section 5.4.1) Whenever CO binds to hemoglobin (Hb), it reduces the amount of Hb available to carry oxygen. People visiting high altitudes (where the partial pressure of oxygen in the

1 atmosphere is lower) will experience reduced levels of oxygen in the blood (hypoxemia) because
2 of a relative hypoventilation that occurs, particularly during sleep. Carbon monoxide, by binding
3 to Hb, intensifies the hypoxemia existing at high altitudes by further reducing transport of oxygen
4 to the tissues. In addition, COHb saturations are higher at altitude than at sea level because,
5 in part, of changes in elimination of endogenous CO and of more rapid uptake of exogenous CO
6 (McGrath, 1992; McGrath et al., 1991, 1993). However, within hours of arrival at high altitude,
7 certain physiological adjustments begin to take place (Grover et al., 1986), and, over several
8 days, these mechanisms will operate to lessen the initial impact of atmospheric hypoxia.
9 Hemoconcentration occurs, and the increased Hb concentration offsets the decreased blood
10 oxygen saturation and restores oxygen concentrations to former levels. Consequently, the simple
11 additive model of COHb and altitude hypoxemia may be valid only during early altitude
12 exposure. The new visitor to higher altitudes, especially the elderly and those with CAD
13 (Kleinman et al., 1998; Leaf and Kleinman, 1996a), may be at greater risk from the added effects
14 of ambient CO than the adapted resident. The period of increased risk probably is prolonged in
15 the elderly because adaptation to high altitude proceeds more slowly with increasing age (Dill
16 et al., 1985).

18 **6.8.2 Interaction with Drugs**

19 There remains little direct information on the possible enhancement of CO toxicity by
20 concomitant drug use or abuse; however, there are some data suggesting cause for concern.
21 There is some evidence that interactions of drug effects with CO exposure can occur in both
22 directions, that is, CO toxicity may be enhanced by drug use, and the toxic or other effects of
23 drugs may be altered by CO exposure. Nearly all published data available on CO combinations
24 with drugs concern psychoactive drugs (Montgomery and Rubin, 1971, 1973; McMillan and
25 Miller, 1974; Medical College of Wisconsin, 1974; Pankow et al., 1974; Rockwell and
26 Weir, 1975; Roth and Rubin, 1976a,b,c; Mitchell et al., 1978; Topping et al., 1981; Kim and
27 Carlson, 1983; Engen, 1986; Knisely et al., 1987, 1989). Descriptions of these studies were
28 provided in Section 11.2 of the previous criteria document (U.S. Environmental Protection
29 Agency, 1991). The following summary, excerpted from the last review, still applies because
30 nothing significant has appeared in the recently published literature.

1 The use and abuse of psychoactive drugs and alcohol are widespread. Because of the effect
2 of CO on brain function, interactions between CO and psychoactive drugs could be anticipated.
3 However, very little systematic research has addressed this question. In addition, very little of
4 the research that has been done has utilized models for expected effects from treatment
5 combinations. Thus, often it is not possible to assess whether the combined effects of drugs and
6 CO exposure are additive or differ from additivity. It is important to recognize that even additive
7 effects of combinations can be of clinical significance, especially when the individual is unaware
8 of the combined hazard. The greatest evidence for a potentially important interaction of CO
9 comes from studies with alcohol in both laboratory animals and humans, where at least additive
10 effects have been obtained (Mitchell et al., 1978; Knisely et al., 1987, 1989). The significance of
11 these effects is augmented by the probable high incidence of combined alcohol use and CO
12 exposure in the population.

13 Besides interaction with psychoactive drugs, there is growing concern that prescribed
14 medications, especially nitric oxide blockers and calcium channel blockers, could interact with
15 CO. There are no known published data available, however, on CO combinations with these
16 drugs.

18 **6.8.3 Interaction with Other Air Pollutants and Environmental Factors**

19 Much of the data concerning the combined effects of CO and other pollutants found in
20 ambient air are based on laboratory animal experiments that were discussed in Section 11.3 of
21 the previous criteria document (U.S. Environmental Protection Agency, 1991). More recent
22 studies published since then have confirmed the conclusions made at that time and are included
23 here for completeness. Only a few controlled-exposure studies of humans are available, and the
24 results were discussed in more detail in the previous document. These early studies in healthy
25 human subjects (Drinkwater et al., 1974; Raven et al., 1974a,b; Gliner et al., 1975; Hackney
26 et al., 1975a,b; DeLucia et al., 1983) on relevant concentrations of common air pollutants such as
27 CO, NO₂, O₃, and peroxyacetylnitrate failed to show any interaction from combined exposure.
28 The more recent epidemiology studies (e.g., Morris et al., 1995; Schwartz and Morris, 1995;
29 Schwartz, 1997, 1999; Burnett et al., 1997a,b; Morris and Naumova, 1998; Burnett et al., 1999)
30 suggest an association between hospital admissions for cardiovascular disease and ambient
31 exposure to multiple pollutants, including CO and PM. In animal studies, no interaction was

1 observed following combined exposure of CO and common air pollutants such as NO₂ and SO₂
2 (Busey, 1972; Murray et al., 1978; Hugod, 1979). However, an additive effect on learning
3 behavior was observed following combined exposure of high levels (>100 ppm) of CO and NO
4 (Groll-Knapp et al., 1988), and a synergistic dose effect (increased COHb) was observed after
5 combined exposure to CO and O₃ (Murphy, 1964).

6 Toxicological interactions of combustion products, primarily CO, carbon dioxide, NO₂, and
7 hydrogen cyanide (HCN), at levels typically produced by indoor and outdoor fires, have shown a
8 synergistic effect on mortality following CO plus CO₂ exposure (Rodkey and Collison, 1979;
9 Levin et al., 1987a) and CO plus NO₂ exposure (Levin, 1996), and an additive effect with HCN
10 (Levin et al., 1987b). Additive effects on mortality also were observed when CO, HCN, and low
11 oxygen were combined; adding CO₂ to this combination was synergistic (Levin et al., 1988).

12 Finally, laboratory animal studies (Young et al., 1987; Yang et al., 1988; Fechter et al.,
13 1988, 1997; Fechter, 1995; Cary et al., 1997) suggest that combinations of environmental factors
14 such as heat stress and noise may be important determinants of health effects occurring in
15 combination with CO exposure. Of the effects described, one potentially most relevant to typical
16 human exposures is a greater decrement in the exercise performance seen when heat stress is
17 combined with 50 ppm CO (Drinkwater et al., 1974; Raven et al., 1974a,b; Gliner et al., 1975).

18 All of studies discussed above involve interactions with exogenous exposure to CO. There
19 are endogenous sources of CO (e.g., heme degradation, peroxidative degradation of unsaturated
20 fatty acids, xenobiotic metabolism) that also can lead to increased COHb saturation. They are
21 discussed in more detail in Section 5.3 of this document. Possibly one of the greatest concerns
22 regarding potential risk in the population comes from inhalation exposure to the halogenated
23 hydrocarbons widely used as solvents, especially the dihalomethanes (e.g., methylene chloride
24 [dichloromethane], dibromomethane, diiodomethane, and bromochloromethane). There is some
25 indication from the older literature (Fodor and Roscovanu, 1976) that oral exposure to
26 trihalogenated methane derivatives also will lead to increased COHb. Other volatile solvents
27 (e.g., carbon tetrachloride, chloroform, methanol) were tested in laboratory animals, but none
28 produced increased levels of COHb (Pankow, 1996).

29 Methylene chloride provides the greatest potential exposure to the population because it has
30 been widely used as a paint remover, degreaser, and aerosol propellant (Wilcosky and Simonsen,
31 1991). When inhaled, it will undergo metabolic breakdown by cytochrome P-450 in liver to

form CO, chloride, and CO₂. 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). Also, 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, NO₂, 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 $\leq 5\%$, because of the large variability and potential high bias of the optical methods such as CO-Ox. The key human health effects most clearly demonstrated to be associated with exposure to ambient CO are summarized in Table 6-7.

Maximal exercise duration and performance in healthy individuals have been shown to be reduced at COHb levels of $\geq 2.3\%$ and $\geq 4.3\%$ (GC), respectively. The decrements in performance at these levels are small and likely to affect only competing athletes rather than people engaged in everyday activities. In fact, no effects were observed during submaximal exercise in healthy individuals at COHb levels as high as 15 to 20%.

Adverse effects have been observed in individuals with CAD at 3 to 6% COHb by optical methods of measurement. At these levels, individuals with reproducible exercise-induced angina (chest pain) are likely to experience a reduced capacity to exercise because of decreased time to onset of angina. The indicators of myocardial ischemia during exercise, which is detectable by

TABLE 6-7. KEY HEALTH EFFECTS OF EXPOSURE TO AMBIENT CARBON MONOXIDE

Target Organ	Health Effects ^{a,b}	Tested Population ^c	References
Lungs	Reduced maximal exercise duration with 1-h peak CO exposures resulting in $\geq 2.3\%$ 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 $\geq 2.4\%$ COHb (GC)	Individuals with coronary artery disease	Allred et al. (1989a,b; 1991)
Heart	Reduced exercise duration because of increased chest pain (angina) with peak CO exposures resulting in $\geq 3\%$ COHb (CO-Ox)	Individuals with coronary artery disease	Anderson et al. (1973) Sheps et al. (1987) Adams et al. (1988) Kleinman et al. (1989, 1998) Allred et al. (1989a,b; 1991)
Heart	Increased number and complexity of arrhythmias (abnormal heart rhythm) with peak CO exposures resulting in $\geq 6\%$ COHb (CO-Ox)	Individuals with coronary artery disease and high baseline ectopy (chronic arrhythmia)	Sheps et al. (1990)
Heart	Increased hospital admissions associated with ambient pollutant exposures	Individuals >65 years old with cardiovascular disease	Schwartz and Morris (1995) Morris et al. (1995) Schwartz (1997) Burnett et al. (1997a)
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)

^aThe 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.

^bMeasured blood COHb level after CO exposure.

^cFetuses, infants, pregnant women, elderly people, and people with anemia or with a history of cardiac or respiratory disease may be particularly sensitive to CO.

1 electrocardiographic (ECG) changes (ST depression) and associated angina, were statistically
2 significant in one study at $\geq 2.4\%$ COHb (GC) and showed a dose-response relationship with
3 increasing COHb. An increase in the number and complexity of exercise-related arrhythmias

1 also has been observed at $\geq 6\%$ COHb (CO-Ox) in some people with CAD and high levels of
2 baseline ectopy (a chronic arrhythmia) that may present an increased risk of sudden death.

3 In community epidemiologic studies, short-term fluctuations in ambient CO concentration
4 have been associated quite frequently with heart disease exacerbation, especially in the elderly.
5 Short-term ambient CO concentrations have been associated somewhat less frequently with daily
6 mortality. Results from experimental laboratory studies, and reports of increased morbidity and
7 mortality in workers routinely exposed to combustion products, provide some qualitative support
8 for these community-level studies. However, the available epidemiologic database is
9 inconclusive as to whether observed statistical associations reflect actual and specific effects of
10 ambient CO exposure. Further research is needed on short-term and long-term exposure to
11 ambient CO and other combustion-related air pollutants, and on the relative influence of
12 exposure to pollutants from non-ambient sources.

13 Central nervous system effects, including reductions in hand-eye coordination (driving or
14 tracking) and in attention or vigilance, have been reported at peak COHb levels of 5% and
15 higher, but later work indicates that significant behavioral impairments in healthy individuals
16 should not be expected until COHb levels exceed 20%. It must be emphasized, however, that
17 even a 5% COHb level is associated with 1-h CO concentrations of 100 ppm or higher. Thus, at
18 typical ambient air levels of CO, no observable central nervous system effects would be expected
19 to occur in the healthy population.

20 The current ambient air quality standards for CO (9 ppm for 8 h and 35 ppm for 1 h) are
21 intended to keep COHb levels below 2.1% to protect the most sensitive members of the general
22 population (i.e., individuals with CAD). Individuals in motor vehicles are at the greatest risk
23 from ambient CO exposure, followed by pedestrians, bicyclists, and joggers in the proximity of
24 roadways and the rest of the general urban population exposed to vehicle exhaust. Several hours
25 of exposure to peak ambient CO concentrations found occasionally at downtown urban sites
26 during periods of heavy traffic would be required to produce COHb levels of concern in the most
27 sensitive nonsmokers. Carbon monoxide levels occurring outside the downtown urban locations
28 are expected to be lower and are probably more representative of levels found in residential areas
29 where most people live. Significant health effects from ambient CO exposure are not likely
30 under these latter exposure conditions. Active cigarette smoking increases the risk for
31 developing cardiovascular and pulmonary disease, and passive smoking also can elevate COHb

1 levels in nonsmokers under conditions of poor ventilation, putting nonsmoking co-workers and
2 family members at increased risk. Carbon monoxide poisoning from indoor exposures to higher
3 than ambient CO levels occurs frequently, has more severe consequences and often is
4 overlooked.
5

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7. INTEGRATIVE SUMMARY AND CONCLUSIONS

7.1 INTRODUCTION

Carbon monoxide (CO) is a colorless, tasteless, odorless, and nonirritating gas that is a product of incomplete combustion of carbon-containing fuels. It also is produced within living organisms by the natural degradation of hemoproteins (e.g., hemoglobin, myoglobin, cytochromes) or as a by-product of xenobiotic metabolism, especially the breakdown of inhaled organic solvents containing halomethanes (e.g., methylene bromide, iodide, or chloride). With external exposure to additional CO, subtle health effects can begin to occur, and exposure to very high levels can result in death.

The health significance of CO in the air largely results from CO being absorbed readily from the lungs into the bloodstream, there forming a slowly reversible complex with hemoglobin (Hb), known as carboxyhemoglobin (COHb). The presence of significant levels of COHb in the blood causes hypoxia (i.e., reduced availability of oxygen to body tissues). The blood COHb level, therefore, represents a useful physiological marker to predict the potential health effects of CO exposure. The amount of COHb formed is dependent on the CO concentration and duration of exposure, exercise (which increases both the amount of air inhaled and exhaled per unit of time), 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 and cerebrovascular disease) limit blood flow to the tissues, obstructive lung disease (e.g., bronchitis, emphysema, asthma) causes

1 gas-exchange abnormalities that limit the amount of oxygen that diffuses into the blood, and
2 anemia reduces the oxygen-carrying capacity of the blood. Under any of these conditions,
3 exposure to CO could reduce further the amount of oxygen available to the affected body tissues.
4 A reduction in oxygen delivery due to elevated COHb levels, combined with impaired air or
5 blood flow to the diseased tissues, will further reduce organ system function and limit exercise
6 capacity.

7 The existing national ambient air quality standards (NAAQS) for CO of 9 ppm for 8 h and
8 35 ppm for 1 h (Federal Register, 1994) have been established to reduce the risk of adverse
9 health effects in the population groups most sensitive to the presence of CO in the ambient air.
10 The term “ambient air” is interpreted to mean outdoor air at ground level where people live and
11 breathe. A great majority of people, however, spend most of their time indoors. A realistic
12 assessment of the health effects from exposure to ambient CO, therefore, must be set in the
13 context of total exposure, a major component of which is indoor exposure.

14 This chapter provides a summary of the key factors discussed in Chapters 2 through 6 of
15 the present document that determine what risk ambient CO poses to public health. An effort also
16 is made to qualitatively delineate key factors that contribute to anticipated health risks from
17 ambient CO in special subpopulations that form a significant proportion of the population at
18 large. Risk factors such as age, gender, and pregnancy are discussed, as well as preexisting heart,
19 lung, vascular, and hematologic diseases. Subpopulations at risk because of exposure to ambient
20 CO alone, or combined with other environmental factors, are identified. This information will be
21 used by the U.S. Environmental Protection Agency’s Office of Air Quality Planning and
22 Standards for development of their staff paper and associated assessments that will help to
23 determine the adequacy of the existing CO NAAQS.

26 **7.2 ENVIRONMENTAL SOURCES**

27 Carbon monoxide comes from both natural and anthropogenic processes. About half of the
28 atmospheric CO is released at the earth’s surface from fossil fuel and biomass burning, and the
29 rest is produced as the result of photochemical reactions in the atmosphere. About two-thirds of
30 the CO in the atmosphere arises from human activities; natural processes account for the
31 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 (from both on- or nonroad vehicles) 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.

1 Indoor and in-transit concentrations of CO can be significantly different from the typically
2 low ambient CO concentrations. The CO levels in homes without combustion sources are
3 usually lower than 5 ppm. The highest residential concentrations of CO that have been reported
4 are associated with vehicle startup and idling in attached garages and the use of unvented gas or
5 kerosene space heaters where peak concentrations of CO as high or higher than 50 ppm have
6 been reported. Carbon monoxide concentrations also have exceeded 9 ppm for 8 h in several
7 homes with gas stoves and, in one case, 35 ppm for 1 h; however, these higher CO
8 concentrations were in homes with older gas ranges that had pilot lights that burn continuously.
9 Newer or remodeled homes have gas ranges with electronic pilot lights. Also, the availability of
10 other cooking appliances (e.g., microwaves, heating plates) has decreased the use of gas ranges in
11 meal preparation.

12 Average CO concentrations as high as 10 to 12 ppm have been reported in human exposure
13 studies for in-vehicle compartments of moving automobiles. Carbon monoxide concentrations
14 will depend, however, on the season and traffic pattern, and the findings of more recent studies
15 suggest that pre-1990 study results are no longer applicable. For example, commuter exposure to
16 motor vehicle exhaust fell from a high of 37 ppm CO for a Los Angeles, CA, study in 1965 to a
17 low of 3 ppm CO for a New Jersey Turnpike study in 1992. For San Francisco, CA, using the
18 same data collection protocol, typical commuter exposures fell about 50% in the 11-year period
19 from 1980 to 1991, despite a 19% increase in average daily traffic. Carbon monoxide levels in
20 other indoor environments affected by engine exhaust (e.g., parking garages, tunnels) follow
21 similar trends but tend to be higher than in other indoor environments.

22 Because indoor and outdoor air quality differ substantially, and because people spend much
23 of their time indoors, ambient air quality measurements alone do not provide accurate estimates
24 of personal or population exposure to CO from ambient and nonambient sources. Whereas the
25 ambient monitoring data reflect exposure to ambient sources of CO only, the measurement of
26 CO from personal monitors reflects more accurately the actual total human population exposure
27 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 hemoglobin 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).

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.

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

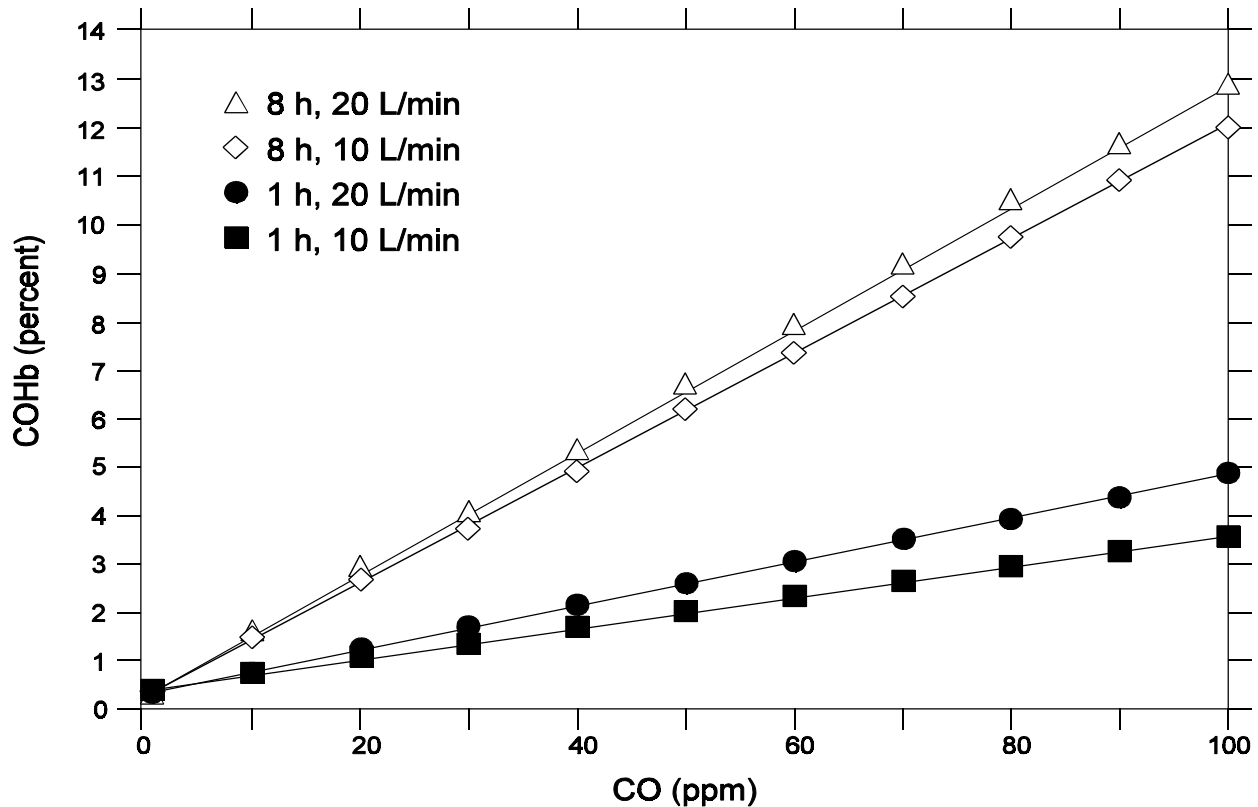


Figure 7-1. Predicted COHb levels resulting from 1- and 8-h exposures to CO at rest (minute ventilation rate of 10 L/min) and with light exercise (20 L/min) are based on the Coburn-Forster-Kane equation, using the following assumed parameters for nonsmoking adults: altitude = 0 ft, initial COHb level = 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.

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.

**TABLE 7-1. PREDICTED CARBON MONOXIDE EXPOSURES
IN THE POPULATION**

Exposure Conditions ^c	Predicted COHb Response ^{a,b}	
	1 h, Light Exercise	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.

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 myoglobin (Mb), cytochrome oxidase, mixed-function oxidases (e.g., cytochrome P-450), tryptophan oxygenase, and dopamine hydroxylase. Hemoprotein binding to CO would be favored under conditions of low intracellular partial pressure of oxygen (PO₂), particularly in brain and myocardial tissue when intracellular PO₂ 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 large variability in response across studies that tested the same concentrations of CO, and work 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

1 until COHb levels exceed 20% (CO-Ox). At 6% COHb (CO-Ox) or higher, some people with
2 CAD and high levels of baseline ectopy (chronic arrhythmia) may experience an increase in the
3 number and complexity of exercise-related arrhythmias.

4 Epidemiologic studies have associated elevated ambient CO levels with increased
5 exacerbation of heart disease in the population, but overall findings are not conclusive, possibly
6 because personal exposures may not be represented adequately by the CO concentrations
7 measured by fixed-site monitors. For example, exposure to cigarette smoke or to combustion
8 exhaust gases from small engines and recreational vehicles typically raises COHb levels much
9 higher than levels resulting from mean ambient CO exposures, and, for most people, exposures
10 to indoor sources of CO will exceed controllable outdoor exposures.

11 Health effects are more likely to occur, therefore, in individuals who are physiologically
12 stressed, either by exercise or by medical conditions that can make them more susceptible to low
13 levels of CO. The specific subpopulations potentially at risk from exposure to ambient CO are
14 discussed next.

17 **7.7 SUBPOPULATIONS POTENTIALLY AT RISK FROM EXPOSURE** 18 **TO AMBIENT CARBON MONOXIDE**

19 Most of the known quantifiable concentration-response relationships regarding the human
20 health effects of CO come from two carefully defined population groups: (1) healthy,
21 predominantly male, young adults and (2) patients with diagnosed CAD. On the basis of the
22 effects described, patients with reproducible exercise-induced angina appear to be best
23 established as a sensitive group within the general population that is at increased risk of
24 experiencing the health effects (i.e., decreased exercise duration because of exacerbation of
25 cardiovascular symptoms) of concern at ambient or near-ambient CO-exposure concentrations
26 that result in COHb levels as low as 2.4% (GC). A smaller sensitive group of healthy individuals
27 experience decreased exercise duration at similar levels of CO exposure, but only during
28 short-term maximal exercise. Decrements in exercise duration in the healthy population,
29 therefore, primarily would be a concern for athletes, rather than for people performing everyday
30 activities.

1 It can be hypothesized, however, from both clinical and theoretical work and from
2 experimental research in laboratory animals, that certain other groups in the population are at
3 potential risk to exposure from CO. Probable risk groups that have not been studied adequately,
4 but that could be expected to be susceptible to CO because of gender differences, aging, or
5 preexisting disease or because of the use of medications or alterations in their environment
6 include fetuses and young infants; pregnant women; the elderly, especially those with
7 compromised cardiovascular function; individuals with partially obstructed coronary arteries, but
8 not yet manifesting overt symptomatology of CAD; those with heart failure; people with
9 peripheral vascular or cerebrovascular disease; individuals with hematologic diseases (e.g.,
10 anemia) that affect oxygen-carrying capacity or transport in the blood; individuals with
11 genetically unusual forms of hemoglobin associated with reduced oxygen-carrying capacity;
12 those with chronic obstructive pulmonary disease; people using medicinal or recreational drugs
13 with central nervous system depressant properties; individuals exposed to other chemical
14 substances (e.g., methylene chloride) that increase endogenous formation of CO; and individuals
15 who have not adapted to high altitude and are exposed to a combination of high altitude and CO.
16 Little empirical evidence is available by which to specify health effects associated with ambient
17 or near-ambient CO exposures in these probable risk groups.

19 **7.7.1 Age, Gender, and Pregnancy as Risk Factors**

20 The fetus and newborn infant are theoretically susceptible to CO exposure for several
21 reasons. Fetal circulation is likely to have a higher COHb level than the maternal circulation
22 because of differences in uptake and elimination of CO from fetal Hb. Because the fetus
23 normally has a lower oxygen tension in the blood than does the mother, a drop in fetal oxygen
24 tension resulting from the presence of COHb could have potentially serious effects. The
25 newborn infant, with a comparatively high rate of oxygen consumption and lower
26 oxygen-transport capacity for Hb than those of most adults, also would be potentially susceptible
27 to the hypoxic effects of increased COHb. Data from laboratory animal studies on the
28 developmental toxicity of CO suggest that prolonged exposure to high levels (>60 ppm) of
29 CO during gestation may produce a reduction in birth weight, cardiomegaly, and delayed
30 behavioral development. Limited epidemiologic findings suggest some association of subchronic
31 ambient CO exposure with low birth weight, but 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. 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 introduced in Chapter 6, heart disease is a smaller and more specific subcategory of cardiovascular disease that comprises, besides heart disease, other disorders such as cerebrovascular disease (including stroke), hypertension (high blood pressure), and diseases of the blood vessels. At the present time, short-term variations in ambient CO have been more strongly associated with heart disease exacerbation than exacerbation of other cardiovascular diseases. Heart disease, in turn, has other diagnostic subcategories, such as ischemic heart disease (including CAD, myocardial infarction, and angina), heart failure, and disturbances of heart rhythm (arrhythmia). Patients with heart disease have a markedly reduced circulatory capacity and, therefore, may be very sensitive to limitations in oxygen-carrying capacity. Thus, exposure to CO will reduce their exercise capacity and could have more serious consequences.

Coronary heart disease (CHD) remains the major cause of death and disability in industrialized societies. In the United States, CHD is the single largest killer of males and females, causing a total of 481,000 deaths in 1995 (American Heart Association, 1997), two-thirds of all deaths from heart disease (U.S. Centers for Disease Control and Prevention,

1 1997) and about half of all deaths from cardiovascular disease (see Figure 7-2). Almost
2 14 million Americans have a history of this disease, with much greater prevalence in both males
3 and females at increasing ages (see Figure 7-3). Individuals with CHD have myocardial
4 ischemia, which occurs when the heart muscle receives insufficient oxygen delivered by the
5 blood. For some, exercise-induced angina pectoris (chest pain) can occur. In all patients with
6 diagnosed CAD, however, the predominant type of ischemia, as identified by ST segment
7 depression, is asymptomatic (i.e., silent). Thus, patients who experience angina typically have
8 additional ischemic episodes that are asymptomatic. Unfortunately, some individuals in the
9 population have CAD but are totally asymptomatic and, therefore, do not know they are
10 potentially at risk. It has been estimated that 5% of middle-aged men show signs of ischemia
11 during an exercise stress test; a significant number of these men will have angiographic evidence
12 of CAD. Persons with both asymptomatic and symptomatic CAD have a limited coronary flow
13 reserve and, therefore, will be sensitive to a decrease in oxygen-carrying capacity induced by CO
14 exposure.

15 Heart failure is a major and growing public health problem. Almost 5 million Americans
16 have heart failure, and about 400,000 new cases occur each year (American Heart Association,
17 1997). Because the prevalence of heart failure is known to increase with age, improvements in
18 the average life expectancy of the general population would be expected to increase the
19 magnitude of the problem over the next few decades. The etiology of heart failure is diverse, but
20 the most common secondary conditions observed in hospitalized patients are CHD, hypertension,
21 chronic obstructive pulmonary disease (COPD), diabetes, and cardiomyopathy (Croft et al.,
22 1997). The exacerbation of some of these secondary conditions by CO are not well known;
23 however, any heart failure patients with CAD, for example, might be even more sensitive to CO
24 exposure.

25 26 **7.7.2.2 Subjects with Other Vascular Diseases**

27 Vascular disease, including cerebrovascular disease, is present in both males and females
28 and is more prevalent above 65 years of age because of the increasing likelihood of adverse
29 effects from atherosclerosis or thickening of the artery walls. Atherosclerosis is a leading cause
30 of many deaths from heart attack and stroke (American Heart Association, 1997). In fact, when
31 considered separately from other cardiovascular diseases, stroke ranks as the third leading cause

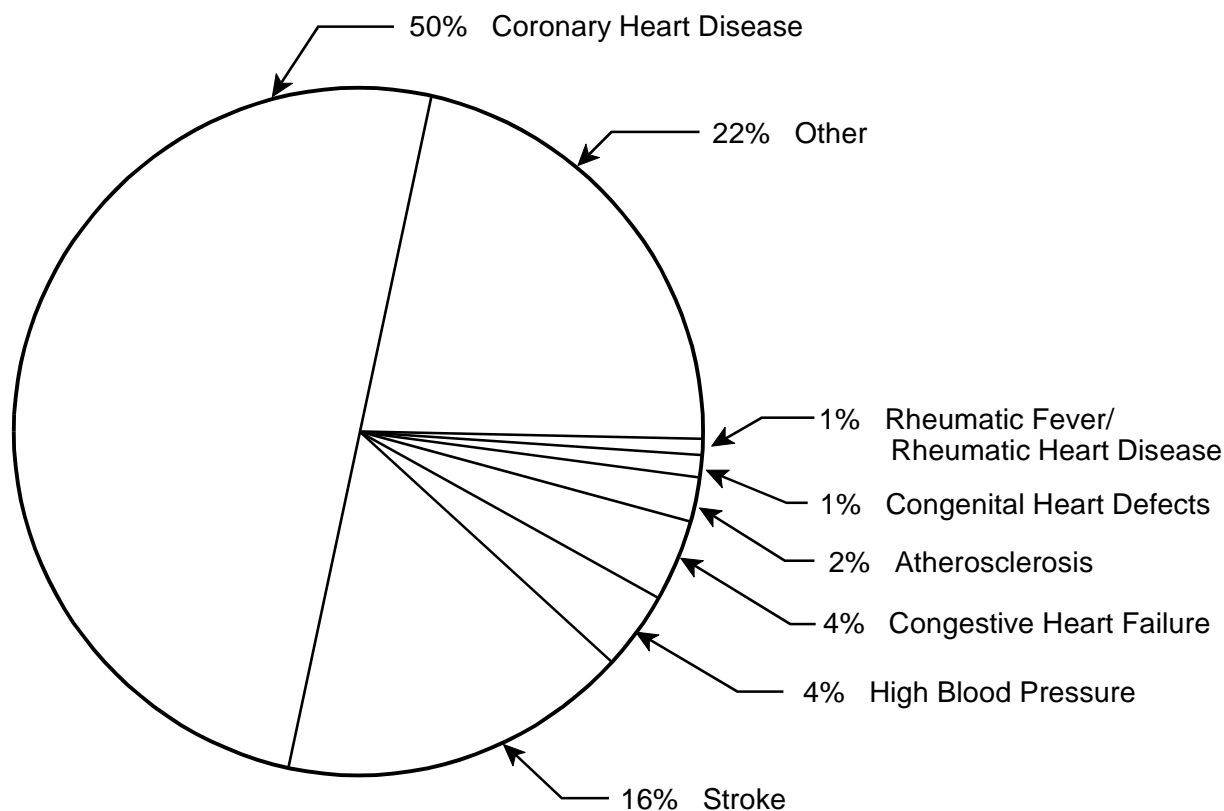


Figure 7-2. Percentage breakdown of deaths from cardiovascular diseases in the United States (1996 mortality statistics).

Source: American Heart Association (1997); National Center for Health Statistics (1995).

1 of death behind heart disease and cancer (U.S. Centers for Disease Control and Prevention,
 2 1997). Vascular diseases are associated with a limited blood flow capacity and, therefore,
 3 patients with these diseases should be sensitive to CO exposure. It is not clear, however, how
 4 low levels of exposure to CO will affect these individuals. For example, only one study,
 5 reviewed in the previous criteria document (U.S. Environmental Protection Agency, 1991), has
 6 been reported on patients with peripheral vascular disease. Ten men with diagnosed intermittent
 7 claudication (lameness) experienced a significant decrease in time to onset of leg pain when
 8 exercising on a bicycle ergometer after breathing 50 ppm CO for 2 h (2.8% COHb). Further
 9 research is needed, therefore, to better determine the sensitivity of individuals with vascular
 10 disease to CO.

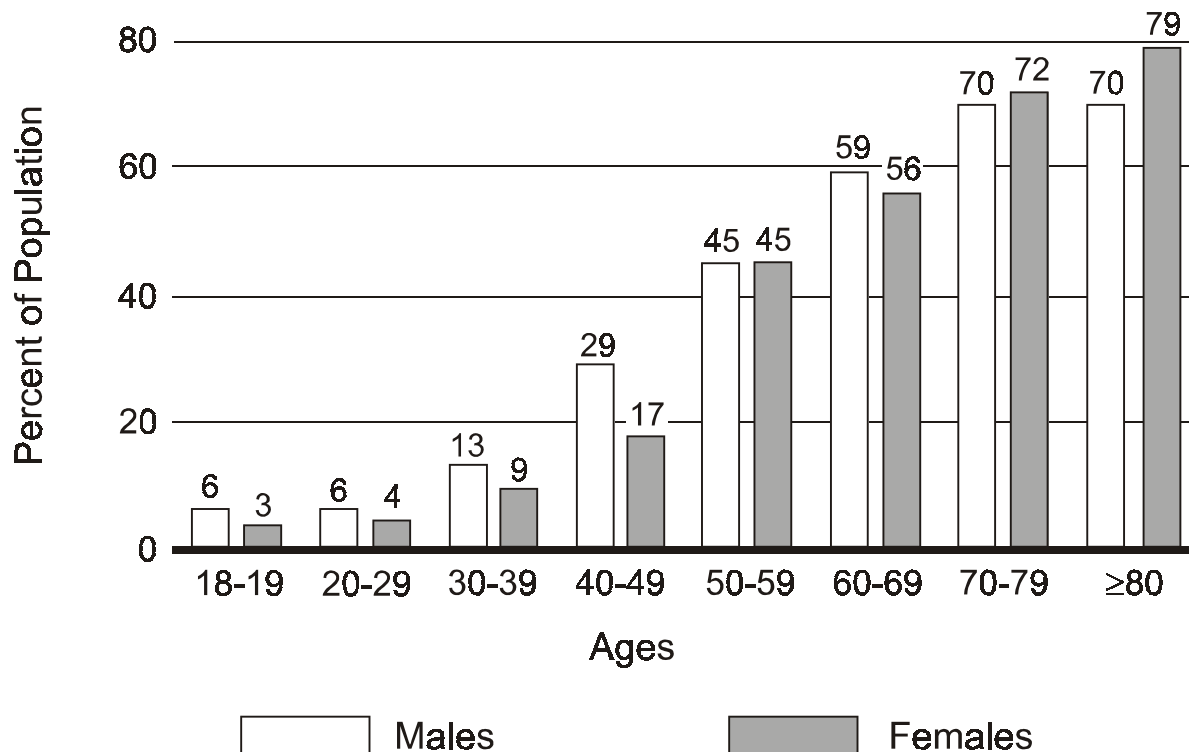


Figure 7-3. Estimated prevalence of cardiovascular disease by age and sex for the United States, 1988 to 1991.

Source: American Heart Association (1997); Collins (1997); Adams and Marano (1995).

7.7.2.3 Subjects with 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

1 average lifespan of red blood cells with abnormal hemoglobin S is 12 days compared to an
2 average of 120 days in healthy individuals with normal Hb. As a result, baseline COHb levels
3 can be as high as 4%. In subjects with Hb Zurich, where affinity for CO is 65 times that of
4 normal Hb, COHb levels range from 4 to 7%. Presumably, exogenous exposure to CO, in
5 conjunction with higher endogenous CO levels, could result in critical levels of COHb.
6 However, it is not known how ambient or near-ambient levels of CO would affect individuals
7 with these disorders.

9 **7.7.2.4 Subjects with Obstructive Lung Disease**

10 Chronic obstructive pulmonary disease (COPD) is a prevalent disease especially among
11 smokers, and a large number (>50%) of these individuals have limitations in their exercise
12 performance demonstrated by a decrease in oxygen saturation during mild to moderate exercise.
13 As a consequence, individuals with hypoxia resulting from COPD such as bronchitis and
14 emphysema may be susceptible to CO during submaximal exercise typical of normal daily
15 activity. In spite of their symptoms, many of them ($\approx 30\%$) continue to smoke and already may
16 have COHb levels of 4 to 8%. The COPD patients with hypoxia are also more likely to have a
17 progression of the disease resulting in severe pulmonary insufficiency, pulmonary hypertension,
18 and right heart failure.

19 Hospital admissions for asthma have increased considerably in the past few years,
20 particularly among individuals less than 18 years of age. Because asthmatics also can experience
21 exercise-induced airflow limitation, it is likely that they also would experience hypoxia during
22 attacks and be susceptible to CO. It is not known, however, how exposure to CO actually would
23 affect these individuals. Observed epidemiologic associations of short-term ambient CO levels
24 with respiratory disease frequency cannot yet be interpreted with confidence.

26 **7.7.3 Subpopulations at Risk from Combined Exposure to Carbon Monoxide** 27 **and Other Chemical Substances**

28 **7.7.3.1 Interactions with Drugs**

29 There is an almost complete absence of data on the possible toxic consequences of
30 combined CO exposure and drug use. Because of the diverse classes of both cardiovascular and
31 psychoactive drugs, and the many other classes of drugs that have not been examined at all, it

1 must be concluded that this is an area of concern that is difficult to address meaningfully at the
2 present time.

4 **7.7.3.2 Interactions with Other Chemical Substances in the Environment**

5 Besides direct exposure to ambient CO, there are other chemical substances in the
6 environment that can lead to increased COHb saturation when inhaled. Halogenated
7 hydrocarbons used as organic solvents undergo metabolic breakdown by cytochrome P-450 to
8 form CO and inorganic halide. Possibly the greatest concern regarding potential risk in the
9 population comes from exposure to one of these halogenated hydrocarbons, methylene chloride,
10 and some of its derivatives that could result in potentially harmful levels of COHb in individuals
11 at risk.

13 **7.7.4 Subpopulations Exposed to Carbon Monoxide at High Altitudes**

14 For patients with CAD, restricted coronary blood flow limits oxygen delivery to the
15 myocardium. Carbon monoxide also has the potential for compromising oxygen transport to the
16 heart. For this reason, such patients have been identified as the subpopulation most sensitive to
17 the effects of CO. A reduction in PO₂ in the atmosphere, as at high altitude, also has the
18 potential for compromising oxygen transport. Therefore, patients with coronary artery disease
19 who visit higher elevations may be unusually sensitive to the added effects of atmospheric CO.

20 It is important to distinguish between the long-term resident of high altitude and the newly
21 arrived visitor from low altitude. Specifically, the visitor will be more hypoxemic than the fully
22 adapted resident. The combination of high altitude with CO will pose the greatest risk to persons
23 newly arrived at high altitude who have underlying cardiopulmonary disease, particularly because
24 they are usually older individuals.

25 It is known that low birth weights occur both in infants born at altitudes above 6,000 ft and
26 in infants born near sea level, whose mothers had elevated COHb levels because of cigarette
27 smoking. It also has been shown that COHb levels in smokers at high altitude are higher than
28 those in smokers at sea level. Although it is probable that the combination of hypoxic hypoxia
29 and hypoxia resulting from ambient exposure to CO could reduce birth weight further at high
30 altitude and possibly modify future development, no data are available to evaluate this
31 hypothesis.

7.8 CONCLUSIONS

Ambient CO concentrations measured at central, fixed-site monitors in metropolitan areas of the United States have decreased significantly since the late 1980s, when air quality was reviewed in the previous criteria document (U.S. Environmental Protection Agency, 1991). The decline in ambient CO follows approximately the decline in motor vehicle emissions. Exposure to tobacco smoke, to CO indoors from unvented or partially vented combustion 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 raised the level of scientific concern regarding ambient CO as a potential risk factor for heart disease exacerbation, mortality, and low birth weight. Results of these studies make a strong scientific case for further research on the health effects of ambient CO exposure. This research should address CO alone and as a component of the overall ambient air pollution mix. 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.

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APPENDIX A

Abbreviations and Acronyms

1		
2		
3		
4		
5	AC	Alternating current
6	AER	Air exchange rate
7	AIRS	Aerometric Information Retrieval System
8	AQCD	Air quality criteria document
9	BTPS	Body temperature and pressure, saturated with water vapor at 37 °C
10	C	Carbon
11	CAA	Clean Air Act
12	CAD	Coronary artery disease
13	CaO ₂	Arterial oxygen content
14	CARB	California Air Resources Board
15	CAS	Children's Activity Survey
16	CASAC	Clean Air Scientific Advisory Committee
17	CFD	Cumulative frequency distribution
18	CFK	Coburn-Forster-Kane
19	cGMP	Cyclic guanosine monophosphate
20	CH ₃	Methyl radical
21	CH ₄	Methane
22	CH ₃ Br	Methyl bromide
23	CH ₃ CCl ₃	Methyl chloroform
24	CH ₃ CHO	Acetaldehyde
25	CH ₃ Cl	Methyl chloride
26	CH ₃ CO	Acetyl radical
27	CH ₂ O	Formaldehyde
28	CH ₃ O ₂	Methyl peroxy radical
29	CH ₃ OOH	Methyl hydroperoxide

1	CHD	Coronary heart disease
2	CHF	Congestive heart failure
3	CI	Confidence interval
4	CMAQ	Congestion Management and Air Quality
5	CMRO ₂	Cerebral metabolic rate for oxygen
6	CMSA	Consolidated metropolitan statistical area
7	CO	Carbon monoxide
8	CO ₂	Carbon dioxide
9	COH	Coefficient of haze
10	COHb	Carboxyhemoglobin
11	COMb	Carboxymyoglobin
12	CO-Ox	CO-Oximetry or CO-Oximeter
13	COPD	Chronic obstructive pulmonary disease
14	CPSC	Consumer Product Safety Commission
15	CRM	Certified Reference Material
16	CTM	Chemical Transport Model
17	CVD	Cardiovascular disease
18	D _L CO	Diffusing capacity for carbon monoxide
19	ECG	Electrocardiogram
20	ED	Effective dose for a specific decrement in function
21	EMFAC7	Emissions Factor 7
22	EPA	U.S. Environmental Protection Agency
23	ETS	Environmental tobacco smoke
24	FAF	Forced-air furnace
25	F _I CO	Fractional concentration of carbon monoxide in inhaled air
26	FDA	Food and Drug Administration
27	FID	Flame ionization detection or detector
28	GAM	General additive model

1	GC	Gas chromatography or gas chromatograph
2	GFC	Gas filter correlation
3	GLM	General linear model
4	h ν	Photon
5	H	Atomic hydrogen
6	H ₂	Molecular hydrogen
7	Hb	Hemoglobin
8	HCN	Hydrogen cyanide
9	HCO	Formyl radical
10	HO	Heme oxygenase
11	HO ₂	Hydroperoxy radical
12	H ₂ O ₂	Hydrogen peroxide
13	HOCO	Carboxyl radical
14	IR	Infrared
15	LOEL	Lowest-observed-effect level
16	M	Haldane coefficient
17	M	Mediator
18	Mb	Myoglobin
19	MDL	Minimum detection limit
20	MI	Myocardial infarction
21	MSA	Metropolitan Statistical Area
22	n	Number
23	N	North
24	N ₂	Molecular nitrogen
25	NAAQS	National Ambient Air Quality Standards
26	NAMS	National Air Monitoring Station
27	NASA	National Aeronautics and Space Administration
28	Ni(CO) ₄	Nickel tetracarbonyl

1	NDIR	Nondispersive infrared
2	NEM	National Ambient Air Quality Standards Exposure Model
3	NHANES	National Health and Nutrition Examination Survey
4	NIST	National Institute of Standards and Technology
5	NMDA	N-methyl-D-aspartate
6	NMHC	Non-methane hydrocarbon
7	NMi	Nederland Meetinstituut (i.e., Dutch Bureau of Standards)
8	NMOC	Non-methane organic compounds
9	NO	Nitric oxide
10	•NO	Nitric oxide free radical
11	NO ₂	Nitrogen dioxide
12	NO _x	Nitrogen oxides
13	NOAA/CMDL	National Oceanic and Atmospheric Administration Climate Monitoring Diagnostics Laboratory
14	NTRM	National Institute of Standards and Technology Traceable Reference Material
15	O	Atomic oxygen
16	O ₂	Molecular oxygen
17	O ₃	Ozone
18	OGI	Oregon Graduate Institute
19	OH	Hydroxyl radical
20	O ₂ Hb	Oxyhemoglobin
21	p	Probability
22	P _{atm}	Pressure in atmospheres
23	P _B	Barometric pressure
24	PAH	Polycyclic aromatic hydrocarbon
25	PAN	Peroxyacetyl nitrate
26	PCO	Partial pressure of carbon monoxide
27	PEM	Personal exposure monitor

1	PM	Particulate matter
2	PM _{2.5}	Particulate matter with an aerodynamic diameter $\leq 2.5 \mu\text{m}$
3	PM ₁₀	Particulate matter with an aerodynamic diameter $\leq 10 \mu\text{m}$
4	pNEM	Probabilistic National Ambient Air Quality Standards Exposure Model
5	P _I O ₂	Partial pressure of oxygen in humidified inspired air
6	PO ₂	Partial pressure of oxygen
7	PRM	Primary Reference Material
8	\dot{Q}	Perfusion
9	r	Linear regression correlation coefficient
10	R ²	Multiple correlation coefficient
11	RBC	Red blood cell
12	RER	Respiratory exchange ratio
13	RR	Relative risk
14	S	South
15	SD	Standard deviation
16	SHAPE	Simulation of Human Activity and Pollutant Exposure
17	SIDS	Sudden infant death syndrome
18	SLAMS	State and Local Air Monitoring Station
19	SO ₂	Sulfur dioxide
20	SRM	Standard Reference Materials
21	ST	Segment of the electrocardiogram
22	STPD	Standard temperature and pressure, dry
23	TCM	Transportation Control Measure
24	TDL	Tunable diode laser
25	TDLS	Tunable diode laser spectroscopy
26	T _g	Teragram
27	TSP	Total suspended particulate
28	TWA	Time-weighted average

1	UHC	Unburned hydrocarbon
2	UV	Ultraviolet
3	UVGSH	Unvented gas space heater
4	\dot{V}_A	Alveolar ventilation
5	V_D	Volume of physiological dead space
6	VMT	Vehicle miles of travel
7	W/F	Wall or floor furnace
8		