Overview information for

Carbon monoxide

CARBON MONOXIDE REFERENCES					
Author Name	Title	Journal	Volume	Page number(s)	Year
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TOXICOLOGICAL PROFILE FOR CARBON MONOXIDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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UPDATE STATEMENT

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Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the toxic substances each profile describes. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The profiles focus on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. A health effects summary describes the adequacy of information to determine a substance's health effects. ATSDR identifies data needs that are significant to protection of public health.

Each profile:

(A) Examines, summarizes, and interprets available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) Determines whether adequate information on the health effects of each substance is available or being developed to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identifies toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are federal, state, and local health professionals; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other federal scientists also have reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Environmental Toxicology Branch (proposed) reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for carbon monoxide. The panel consisted of the following members:

1. Laurence Fechter, Ph.D., Senior Career Research Scientist, Jerry Pettis Memorial Veterans Medical Center, Loma Linda, California

2. Jerrold Leikin, M.D., Director of Medical Toxicology, NorthShore University Health System – OMEGA, Glenbrook Hospital, Glenview, Illinois

3. Stephen Thom, M.D., Ph.D., Professor, Emergency Medicine, University of Pennsylvania, Institute for Environmental Medicine, Philadelphia, Pennsylvania

These experts collectively have knowledge of carbon monoxide's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about carbon monoxide and the effects of exposure to it.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to carbon monoxide, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, pregnancy status, and state of health.

1.1 WHAT IS CARBON MONOXIDE?

Carbon monoxide is a gas	Carbon monoxide is a colorless, nonirritating, odorless, and tasteless gas. It is found in both outdoor and indoor air.
Sources of carbon monoxide in the atmosphere	Carbon monoxide is made when carbon in fuel is not burned completely. Carbon monoxide is produced from both human-made and natural sources. The most important human-made source of carbon monoxide arises from the exhaust of automobiles. Inside homes, improperly adjusted gas appliances, furnaces, wood burning stoves, and fireplaces are a potential source of carbon monoxide (see Section 1.3). Carbon monoxide is released from wood burning/volcanoes/forest fires.
Industrial uses	Carbon monoxide can be used in industry to synthesize many compounds such as acetic anhydride, polycarbonates, acetic acid, and polyketone.

1.2 WHAT HAPPENS TO CARBON MONOXIDE WHEN IT ENTERS THE ENVIRONMENT?

Converts to carbon dioxide	When carbon monoxide is released to the environment, it enters the air and remains in the atmosphere for an average of about 2 months. Eventually, carbon monoxide reacts with other compounds in the atmosphere and is converted to carbon dioxide. Microorganisms found in soil and water can also convert carbon monoxide to carbon dioxide.

1.3 HOW MIGHT I BE EXPOSED TO CARBON MONOXIDE?

Sources of exposure	All people are exposed to carbon monoxide at varying levels through inhalation of air. Places and times of the day that have a lot of vehicular traffic generally have higher levels of carbon monoxide as compared to areas of low traffic. You can be exposed to carbon monoxide from tobacco smoke whether as a smoker or from second-hand smoke. You can be exposed to carbon monoxide by using gas appliances or wood burning stoves and fireplaces. In emergency situations where power is lost, using an improperly vented generator inside a home or building or using gas grills, charcoal grills, or hibachis indoors can lead to dangerous levels of carbon monoxide. People are exposed to carbon monoxide inside of vehicles. High levels of carbon monoxide exposure have been observed when using recreational watercraft and boats. Gasoline-powered small engines and tools (e.g., gas-powered compressors or pressure washers) can emit high levels of carbon monoxide in a short period of time. See Chapter 6 for more information regarding these exposures.

1.4 HOW CAN CARBON MONOXIDE ENTER AND LEAVE MY BODY?

Carbon monoxide enters and leaves the body	Carbon monoxide in the air rapidly enters all parts of the body, including blood, brain, heart, and muscles when you breathe. The carbon monoxide in your body leaves through your lungs when you breathe out (exhale), but there is a delay in eliminating carbon monoxide. It takes about a full day for carbon monoxide to leave your body.

1.5 HOW CAN CARBON MONOXIDE AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

Carbon monoxide can harm the heart, brain, and lungs	Breathing high levels of carbon monoxide can kill you. Breathing lower levels of carbon monoxide can permanently harm your heart and brain. Carbon monoxide can be more harmful to you if you have heart or lung disease.

1.6 HOW CAN CARBON MONOXIDE AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Breathing carbon monoxide during pregnancy can harm your unborn child	Breathing high levels of carbon monoxide can lead to miscarriage. Breathing lower levels of carbon monoxide during pregnancy may harm the mental development of your child.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CARBON MONOXIDE?

Reduce indoor air levels of carbon monoxide	The most dangerous levels of carbon monoxide usually occur in indoor air. High levels occur as a result of improperly installed or unvented appliances that burn natural gas, kerosene, or other fuels. These include stoves, furnaces, heaters, and generators. Make sure that all of your appliances are installed properly and have periodic maintenance performed by professional installers. Always follow the manufacturer's recommendations on installing and using these devices. Make certain wood burning heaters and fireplaces are properly vented. Never use a gas-powered generator or burn charcoal indoors, as this can quickly lead to dangerous levels of carbon monoxide in your home. Do not use older portable propane heaters in enclosed indoor settings, including campers and tents, as dangerous levels of carbon monoxide can build up. Look for portable heaters that contain an oxygen depletion sensor (ODS) and are safer to use when camping. If oxygen levels start to fall, the sensor automatically shuts down the heater before it can produce dangerous levels of carbon monoxide. Older generation heaters without an ODS are intended for outdoor use only and should not be used indoors. Do not use gasoline-powered tools like pressure washers inside of homes. Substitute less hazardous equipment whenever possible. Use electric tools or tools with engines that are separate from the tools and can be located outside and away from air intakes. Do not let your car idle for long periods of time in your garage.
Avoid tobacco smoke	You can reduce your exposure to carbon monoxide by avoiding smoke from cigarettes and cigars since the smoke contains carbon monoxide.

Reduce outdoor exposure to carbon monoxide	You can reduce your exposure to carbon monoxide outdoors by avoiding running or exercising near busy roadways. Accidental carbon monoxide poisonings can occur from recreational water craft. Most new boats come with carbon monoxide detectors; however, the U.S. Coast Guard advises owners of boats built prior to 1998 to have the monitors inspected or replaced.
Install carbon monoxide detectors in your home	Carbon monoxide detectors can be purchased at home remodeling or hardware stores. It is important to understand that most smoke detectors do not detect carbon monoxide, so you should install carbon monoxide detectors in your home as well as smoke detectors.

If your doctor finds that you have been exposed to significant amounts of carbon monoxide, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CARBON MONOXIDE?

Carbon monoxide exposure can be measured with a blood test	Medical devices called carbon monoxide-oximeters can estimate the level of carbon monoxide in blood by using a simple test. These devices are found in clinical laboratories and hospitals.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but cannot be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels. These are levels of a toxic substance in air, water, soil, or food that do not exceed a critical value. This critical value is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it.

Some regulations and recommendations for carbon monoxide include the following:

Levels in air set by EPA	EPA established an environmental limit of 10 milligrams per cubic meter (mg/m^3) (9 parts per million by volume [ppmv]) of carbon monoxide in air averaged over 8 hours. This limit is not to be exceeded more than once per year.
Levels in workplace air set by OSHA	OSHA set a legal limit of 55 mg/m^3 (50 ppmv) for carbon monoxide in air averaged over an 8-hour work day.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences (proposed)
1600 Clifton Road NE
Mailstop F-62
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

1. PUBLIC HEALTH STATEMENT

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2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CARBON MONOXIDE IN THE UNITED STATES

Carbon monoxide is a colorless, odorless, non-irritating, and tasteless gas that is ubiquitous in the atmosphere. It arises from both natural and anthropogenic sources. It is produced as a primary pollutant during the incomplete combustion of fossil fuels and biomass. Carbon monoxide is also produced indirectly from the photochemical oxidation of methane and other volatile organic compounds (VOCs) in the atmosphere. Vegetation can emit carbon monoxide directly into the atmosphere as a metabolic byproduct, and the photooxidation of organic matter in surface waters (lakes, streams, rivers, oceans) and surface soils also results in the formation of carbon monoxide. Volcanic activity is an additional natural source of carbon monoxide in the atmosphere. The vast majority of anthropogenic carbon monoxide emissions arise from gasoline-powered automobile usage, although the total amount of carbon monoxide emitted to the environment from this source has declined significantly over the past several decades due to the use of catalytic converters and other emission control devices that are standard equipment on modern passenger vehicles.

The annual average outdoor carbon monoxide concentrations are roughly 0.12 parts per million by volume (ppmv) in the Northern Hemisphere and about 0.04 ppmv in the Southern Hemisphere. These levels are variable throughout the course of the year, with seasonal maximum levels occurring during late winter in both hemispheres and minimum levels being observed during late summer. Carbon monoxide concentrations are reported to range from a minimum of about 0.03 ppmv during summer in the Southern Hemisphere to a maximum of about 0.20 ppmv at high latitudes in the Northern Hemisphere during winter. Urban locations with high automobile usage or a high volume of stationary emission sources such as refineries or power plants typically have greater atmospheric levels of carbon monoxide as compared to rural or remote sites. Carbon monoxide levels in indoor air are strongly influenced by the presence of various appliances and whether or not the occupants of the residence smoke tobacco products. Unvented kerosene and gas space heaters; leaking chimneys and furnaces; back-drafting from furnaces, gas water heaters, wood stoves, and fireplaces; gas stoves, generators, and other gasoline-powered equipment; automobile exhaust from attached garages; and tobacco smoke all contribute to indoor air levels of carbon monoxide. Average levels in homes without gas stoves vary from 0.5 to 5 ppmv. Levels near properly adjusted gas stoves are often 5–15 ppmv and those near poorly adjusted stoves may be ≥30 ppmv.

Exposure of the general population to carbon monoxide occurs through inhalation of outdoor and indoor air. Populations living in urban areas with heavy vehicular traffic or stationary sources such as petroleum refineries, gas and coal burning power plants, petrochemical plants, and coke oven plants are more likely to be exposed to higher levels of carbon monoxide from ambient outdoor air. Occupational exposure for employees who work in these industries and other occupations that are subject to high levels of vehicular exhaust (such as taxi cab drivers, traffic or bicycle police, and toll booth workers) are also likely to be exposed to higher levels of carbon monoxide. Firefighters or other emergency response professionals can be exposed to high levels of carbon monoxide. Industrial or in-home use of methylene chloride paint strippers in poorly ventilated areas can lead to high levels of carbon monoxide in blood since carbon monoxide is a metabolic byproduct of methylene chloride. Members of the public who smoke or work in smoke-filled environments such as restaurants, bars, and casinos where smoking is allowed are also exposed to higher levels of carbon monoxide than members of the population who do not smoke and are not frequently exposed to second-hand tobacco smoke. Section 6.5 discusses exposures to the general population and occupational exposures in greater detail.

2.2 SUMMARY OF HEALTH EFFECTS

Health effects associated with acute carbon monoxide poisoning have been extensively documented. In the last decade, growing evidence has revealed endogenously produced carbon monoxide (produced from catabolism of heme and other endogenous precursors) to be a cell signaling agent that contributes to the regulation of numerous physiological systems, including brain and muscle oxygen storage and utilization (myoglobin, neuroglobin), relaxation of vascular and extra-vascular smooth muscle, modulation of synaptic neurotransmission, anti-inflammation, anti-apoptosis, anti-proliferation, and anti-thrombosis (see Section 3.5.2, Mechanisms of Toxicity). Endogenously produced carbon monoxide is not associated with toxicity; carbon monoxide toxicity occurs following exposure to exogenous carbon dioxide. Toxic effects of carbon monoxide are due to effects on cell metabolism through hypoxic and non-hypoxic modes of action. Both modes of action are thought to result from the ability of carbon monoxide to bind to heme and alter function and/or metabolism of heme proteins. Formation of carboxyhemoglobin (COHb) decreases the O_2 carrying capacity of blood and impairs release of O_2 from Hb for its utilization in tissues. Current toxicological and epidemiological research has focused on examining health effects of low-level carbon monoxide exposures that do not result in overt carbon monoxide poisoning and attempting to understand the connections between carbon monoxide toxicity and carbon monoxide *in vivo* production and metabolism. This research has revealed that the heart and cardiovascular system and the brain and developing nervous system are particularly sensitive to carbon monoxide. These studies have also shown

that people with ongoing cardiovascular and/or respiratory disease may be particularly vulnerable to carbon monoxide.

Modes of Action of Carbon Monoxide. Carbon monoxide exerts effects on cell metabolism through hypoxic and non-hypoxic modes of action. Both modes of action are thought to be largely (if not entirely) the result of the ability of carbon monoxide to bind to heme and alter function and/or metabolism of heme proteins. The binding affinity of carbon monoxide for hemoglobin is over 200 times greater than that of oxygen for hemoglobin. Formation of COHb decreases the O_2 carrying capacity of blood and impairs the release of O_2 from Hb for its utilization in tissues. Through similar mechanisms, carbon monoxide decreases O_2 storage in muscle cells by binding to, and displacing O_2 from, myoglobin. Although all tissues are vulnerable to carbon monoxide-induced hypoxic injury, those having the highest O_2 demand are particularly vulnerable, including the brain and heart.

Most of the non-hypoxic mechanisms of action of carbon monoxide have been attributed to binding of carbon monoxide to heme in proteins other than Hb. Notable targets of carbon monoxide include components of several important physiological regulatory systems, including brain and muscle oxygen storage and utilization (myoglobin, neuroglobin); nitric oxide cell signaling pathway (e.g., nitric oxide synthase, guanylyl cyclase); prostaglandin cell signaling pathway (cyclooxygenase, prostaglandin H synthase); energy metabolism and mitochondrial respiration (cytochrome c oxidase, cytochrome c, NADPH oxidase); steroid and drug metabolism (cytochrome P450); cellular redox balance and reactive oxygen species (ROS; catalase, peroxidases); and various transcription factors (e.g., neuronal PAS domain protein, NPAS2, implicated in regulation of circadian rhythm). Non-hypoxic modes of action are discussed in greater detail in Section 3.5.2.

Endogenous Carbon Monoxide. In addition to inhalation exposure to carbon monoxide in air, internal exposures to carbon monoxide occur as a result of production of carbon monoxide from endogenous precursors (e.g., heme degradation, auto-oxidation of phenols, photo-oxidation of organic compounds, and lipid peroxidation of cell membrane lipids) and from oxidative metabolism of exogenous precursors (e.g., carbon tetrachloride, dichloromethane, and other dihalomethanes). The latter two metabolic sources of carbon monoxide result in a carbon monoxide body burden in the absence of exposure to exogenous carbon monoxide in air. Endogenous carbon monoxide production rate has been estimated to be approximately 0.42 mL carbon monoxide at standard temperature and pressure, dry (STPD)/hour or 0.006 mL carbon monoxide/hour-kg body weight. However, numerous physiological and disease factors affect the rate of endogenous production of carbon monoxide, including the menstrual cycle, pregnancy,

diseases, and stimuli that increase catabolism of Hb or other heme proteins, including hemolysis, hematomas, hemolytic anemias, thalassemia, and Gilbert's syndrome.

Growing evidence has revealed endogenous carbon monoxide to be a cell signaling agent that contributes to the regulation of numerous physiological systems, including brain and muscle oxygen storage and utilization (myoglobin, neuroglobin), relaxation of vascular and extra-vascular smooth muscle, modulation of synaptic neurotransmission, anti-inflammation, anti-apoptosis, anti-proliferation, and anti-thrombosis. This has potentially important implications for the understanding of carbon monoxide toxicology and dose-response relationships for the following reasons: (1) carbon monoxide modulation of physiological processes may underlie some aspects of the toxicity of exogenous carbon monoxide; (2) exogenous carbon monoxide may disrupt physiological regulation of those systems that are responsive to endogenous carbon monoxide (e.g., vascular resistance); and (3) exposures to exogenous carbon monoxide may affect carbon monoxide-mediated physiological responses at levels that approach those resulting from endogenous production. One implication of this is that the dose threshold for effects of exogenous carbon monoxide on carbon monoxide-modulated physiological systems may lie near or below ambient air carbon monoxide concentrations.

Toxicokinetics. Inhaled carbon monoxide is rapidly and extensively absorbed into blood and distributes throughout the body. The distribution of carbon monoxide in the body largely reflects the binding of carbon monoxide to heme proteins (e.g., Hb, myoglobin). Measurements of total carbon monoxide concentrations in tissues obtained from human autopsies showed the highest concentrations in blood, spleen, lung, kidney, and skeletal muscle, with detectable levels also in brain and adipose tissue. However, as noted above (see *Modes of Action of Carbon Dioxide*), due to the high O_2 demand of the brain relative to other tissues, the brain is most sensitive organ to the effects of carbon monoxide. Higher concentrations of carbon monoxide in blood, heart, skeletal muscle, and spleen reflect the abundance of the major carbon monoxide binding proteins in these tissues. In blood, carbon monoxide rapidly distributes into erythrocytes where it exists primarily as a complex with Hb (COHb). Carbon monoxide in muscle exists primarily as a complex with myoglobin (COMb). Carbon monoxide in the maternal system distributes to fetal tissues where it binds to fetal Hb and other heme proteins. Steady-state fetal blood COHb concentrations are approximately 10–15% higher than maternal blood (fetal/maternal ratio=1.1–1.15) and fetal blood COHb elimination kinetics are slower than maternal blood. Carbon monoxide binding to fetal Hb is analogously similar to maternal Hb.

Absorbed carbon monoxide is eliminated from the body by exhalation and oxidative metabolism. Oxidative metabolism of carbon monoxide has been estimated to be a relatively small fraction (<10%) of endogenous carbon monoxide elimination. Under most conditions, the dominant route of elimination of absorbed carbon monoxide is exhalation. The decline in blood %COHb following cessation of an inhalation exposure to carbon monoxide exhibits at least two kinetic phases. The fast phase is thought to reflect a combination of exhalation of carbon monoxide along with slower distribution of blood carbon monoxide to tissues that continues after cessation of exposure. The elimination half-time for the slow phase is approximately 100–300 minutes. The carbon monoxide elimination half-time increases with age, with the most pronounced increase occurring from age 2 to 20 years and is approximately 6% longer in males compared to females. Exercise decreases carbon monoxide elimination half-time, although exercise and the increase in respiration would lead to increased CO exposure, if CO is still present in inspired air.

The importance of COHb as a potential biomarker of carbon monoxide exposure and hypoxia, particularly at low levels of exposure, has led to the development of a physiologically-based mechanistic model of carbon monoxide kinetics for predicting relationships between exposure and blood COHb levels. The model that has received the greatest attention and use in risk assessment and in clinical medicine is the Coburn-Forster-Kane (CFK) model. This model can be used to predict steady-state blood COHb levels that correspond to a given continuous inhalation exposure to carbon monoxide in a typical adult. The CFK model has been used to support discussions of the health effects of carbon monoxide in this Toxicological Profile, by providing a means for interconverting carbon monoxide exposure levels expressed in units of ppm or mg/m^3 and corresponding equivalent steady-state COHb% values (i.e., the COHb% that would be achieved with continuous exposure to the reported air carbon monoxide concentration). Predicted steady-state blood COHb levels corresponding to a range of carbon monoxide exposure concentrations are presented in the introduction to Section 3.2 (Table 3-1). Several other toxicokinetics models are described in Section 3.4.5.

Acute Carbon Monoxide Poisoning. Carbon monoxide poisoning is one of leading causes of morbidity and mortality due to poisoning in the United States. It has been estimated that carbon monoxide poisoning results in over 50,000 emergency room visits per year in the United States. The principal mechanism of many adverse effects of carbon monoxide exposure is COHb-induced tissue hypoxia; thus, tissues with high oxygen requirements (e.g., brain, heart) are the most sensitive to carbon monoxide-induced hypoxia. However, other non-hypoxic mechanisms (e.g., binding of carbon monoxide to other heme proteins, such as myoglobin and cytochrome c oxidase) and alterations in biological and

physiological functions of endogenous carbon monoxide, likely contribute to the adverse effects of acute carbon monoxide poisoning.

The extent of injury from acute carbon monoxide exposure depends upon the concentration and duration of exposure and the underlying health status of the exposed individual. The most commonly reported signs and symptoms associated with acute carbon monoxide poisoning are due to effects on the central nervous system and the cardiovascular system; however, because carbon monoxide exposure has the potential to affect nearly all tissues, the clinical presentation of acute carbon monoxide poisoning includes a wide range of symptoms. The severity of carbon monoxide poisoning is typically categorized as mild, moderate, or severe, based on clinical presentation. Signs and symptoms of mild carbon monoxide poisoning include headache, nausea, vomiting, dizziness, blurred vision, and occasionally cherry red lips and skin; headache and dizziness are the most commonly reported symptoms. Because these symptoms mimic flu-like viral illnesses, mild carbon monoxide poisoning can easily be misdiagnosed. Symptoms associated with moderate carbon monoxide poisoning may include confusion, syncope, chest pain, dyspnea, weakness, tachycardia, tachypnea, and rhabdomyolysis. Effects of severe poisoning may be life-threatening, including cardiac arrhythmias, myocardial ischemia, cardiac arrest, hypotension, respiratory arrest, noncardiogenic pulmonary edema, seizures, and coma. In addition to the immediate-onset effects of exposure, delayed-onset development of neuropsychiatric impairment typically occurs from several days to approximately 3–4 weeks of exposure, with symptoms including inappropriate euphoria, impaired judgment, poor concentration, memory loss, cognitive and personality changes, psychosis, and Parkinsonism Symptoms of acute carbon monoxide poisoning in children are the same as those in adults. Acute carbon monoxide poisoning during pregnancy has been associated with spontaneous abortion and fetal death; pregnancy outcome is likely to be dependent upon the severity of maternal poisoning and fetal age.

The relationship between the severity of clinical signs and symptoms of acute carbon monoxide poisoning and COHb levels is not well correlated. The poor correlation may be due to the length of time elapsed between cessation of exposure and measurement of COHb levels or to effects of supplemental oxygen treatment prior to COHb measurement. Generally, in healthy individuals, mild carbon monoxide poisoning that requires medical intervention are associated with COHb levels >20%. Fatalities due to carbon monoxide poisoning have been reported for a wide range of COHb levels (3–70%). Levels of COHb >50% are frequently fatal.

Primary Targets of Low-level Carbon Monoxide Exposure. The primary targets of low-level exposures to carbon monoxide (i.e., those that result in blood COHb levels <20%) appear to include the heart and cardiovascular system, the central nervous system, and the fetus and neonate. Adverse effects in the respiratory tract have been observed in human clinical studies and in animal studies at higher exposures than those associated with effects on the cardiovascular and central nervous systems and on development. A large body of epidemiologic studies has also provided evidence that ambient levels of carbon monoxide in air may contribute to respiratory morbidity and aggravation of ongoing respiratory disease (e.g., asthma; see Table 3-3). Epidemiologic studies have also examined possible associations between ambient air carbon monoxide concentrations and hematologic biomarkers of coagulation and inflammation. Although some studies have found significant associations, collectively, findings from these studies are inconclusive.

Cardiovascular System. Cardiovascular effects of inhalation exposures to carbon monoxide have been evaluated in controlled human clinical studies, epidemiology studies, and various animal models (monkeys, dogs, rats, and rabbits). In general, these studies provide convincing evidence for adverse cardiovascular effects in association with carbon monoxide exposures that result in blood COHb levels ≥2.4%, with effects occurring at the lowest levels in subjects with compromised cardiovascular function (e.g., coronary artery disease).

Results of controlled clinical studies in patients with coronary artery disease show that acute-duration exposure to carbon monoxide at levels producing blood COHb levels between 2.4 and 5.9% exacerbates underlying cardiovascular disease, including enhanced myocardial ischemia and increased cardiac arrhythmias. In patients with exertional angina, carbon monoxide exposure exacerbated exercise-induced myocardial ischemia, including decreased time-to-onset of angina symptoms, increased duration of angina symptoms, decreased time-to-onset of ST-segment depression (electrocardiogram [EKG or ECG] change indicative of myocardial ischemia), and decreased left ventricular ejection fraction. At the lowest blood COHb level evaluated in patients (i.e., COHb 2.4%), time-to-onset of angina symptoms and ST-segment depression were significantly decreased by 4.2 and 5.1%, respectively.

Epidemiological studies of exposure to carbon monoxide and cardiovascular outcomes have yielded mixed results. In general, the weight of evidence suggests that risks of certain specific outcomes (hospitalizations and emergency room visits related to congestive heart failure, ischemic heart disease, myocardial infarction, and stroke) are associated with increasing ambient carbon monoxide concentrations. The interpretation of these associations is complicated by the possibility that ambient air

carbon monoxide levels may be a surrogate measure for air pollution in general. However, the corroborated observations of associations between carbon monoxide exposure and outcomes related to ischemic heart disease is particularly provocative in the context of results of human clinical studies in which carbon monoxide-induced hypoxia exacerbated ischemia symptoms in patients with coronary artery disease. Mean ambient air carbon monoxide concentrations reported in studies that have found carbon monoxide-associated adverse cardiovascular outcomes ranged from 0.5 to 10 ppm, with maximum values ranging from 2 to 50 ppm. These values correspond to approximate steady-state blood COHb levels of <2% for the mean and <10% for the maximum.

Studies in animals have investigated adverse cardiovascular effects of carbon monoxide exposure over a much wider range of exposure conditions (e.g., exposure concentration and duration) and have evaluated additional outcome measures that are not possible to assess in humans. These studies provide further evidence of adverse cardiovascular effects of carbon monoxide exposure, including compensatory alterations in hemodynamics, cardiac hypertrophy, cardiac arrhythmias, and possibly atherosclerosis.

Based on studies described above, a blood COHb concentration of 2.4% is identified as the lowest-observed-adverse-effect level (LOAEL) for adverse cardiovascular outcomes in coronary artery disease patients. A no-observed-adverse-effect level (NOAEL) for this effect was not identified. The LOAEL for COHb can be converted to an equivalent human exposure concentration (for continuous exposure) that would yield the same steady-state blood COHb concentration (2.4%) by implementing the CFK model. The human equivalent exposure concentration is approximately 14 ppm.

Developmental Effects. Epidemiological studies have examined possible associations between exposure to ambient air carbon monoxide concentrations and various developmental outcomes, including pre-term birth, birth weight, congenital anomalies, neurodevelopment, and neonatal and infant death. Results of these studies have been mixed and collectively do not provide strong evidence for developmental effects in association with exposures to ambient levels of carbon monoxide. In general, these studies examined relatively low air carbon monoxide concentrations, typical of ambient levels (e.g., mean concentrations ranging from 0.5 to 3 ppm, with highest reported values ≤10 ppm; see Table 3-8). These studies typically relied on average ambient carbon monoxide concentrations (based on regional air monitoring) for estimating exposures and do not necessarily represent exposures that occurred to individuals during any particular period of gestation.

Numerous studies on developmental effects of gestational and early postnatal exposure to carbon monoxide have been conducted in animals. In general, most studies evaluated effects of relatively low carbon monoxide concentrations (i.e., ≤300 ppm), with exposure concentrations selected to produce maternal COHb levels typically associated with smoking (5–10%); however, studies did not consistently report maternal or fetal COHb levels. Studies in animals have examined effects of carbon monoxide exposure on numerous developmental outcomes, including several outcomes that have not been assessed in epidemiological studies (e.g., auditory and immune system development). Results of animal studies show adverse developmental effects of gestational and early postnatal carbon monoxide exposure, including decreased fetal weight, adverse central nervous system development, altered peripheral nervous system development, cardiac effects, altered sexual behavior, immunological effects, and hematological effects. In addition, some studies showed that developmental effects persisted beyond the postnatal period, although persistence of effects was not examined in all studies. The lowest LOAEL values for developmental effects were obtained in studies evaluating effects of carbon monoxide on the developing auditory system (i.e., LOAEL 12–25 ppm); however, since other developmental outcomes were not assessed at this range of low carbon monoxide concentrations, it is not possible to determine if the developing auditory system is more sensitive to carbon monoxide exposure than other systems. Gestational and/or early postnatal exposure of rats to 25 ppm carbon monoxide produced morphological changes in the developing auditory system, including swelling, cytoplasmic vacuolization, and atrophy of nerve terminals innervating inner hair cells; "distorted myelin" with vacuolization in the 8th cranial nerve at the level of the internal auditory canal; decreased immunoreactivity of the enzymes cytochrome oxidase, NADH-TR, and calcium-mediated myosin ATPase; and decreased immunostaining of neurofilament and myelin basic protein in the organ of corti. Exposure of rat pups during the early postnatal period decreased action potential amplitude of the 8th cranial nerve at ≥12 ppm carbon monoxide and decreased otoacoustic emissions at ≥50 ppm carbon monoxide, with effects on action potential amplitude of the 8th nerve persisting through age 73 days.

Based on studies described above, a maternal exposure concentration of 12 ppm is identified as a LOAEL for adverse neurodevelopmental outcomes in rats. This LOAEL can be converted to an equivalent blood COHb level in the rat by implementation of the CFK model, as adapted for the rat. The time-averaged blood COHb level predicted for the 16-day exposure (22 hours/day) is 1.8%. The equivalent human exposure concentration (for continuous exposure) that would yield the same steady-state blood COHb concentration (1.82%) is approximately 10 ppm.

Central Nervous System. As previously noted, acute exposure to high levels of carbon monoxide produces symptoms of central nervous system toxicity, including headache, dizziness, drowsiness, weakness, nausea, vomiting, confusion, disorientation, irritability, visual disturbances, convulsions, and coma. Lesions of the basal ganglia (primarily of the globus pallidus) and white matter have also been observed in magnetic resonance imaging (MRI) and computed tomography (CT) scans in association with acute carbon monoxide poisoning. Motor impairments consistent with damage to basal ganglia have been observed following carbon monoxide poisoning. Following acute-onset effects, delayed development of neuropsychiatric impairment may occur from several days to 3–4 weeks of exposure, with symptoms including inappropriate euphoria, impaired judgment, poor concentration, memory loss, cognitive and personality changes, psychosis, and Parkinsonism. Delayed neuropsychiatric impairment has been estimated to occur in up to 68% of patients with acute carbon monoxide poisoning. There is a poor correlation between initial symptom severity, and the likelihood of developing of delayed neuropsychiatric impairment. Exposures to carbon monoxide *in utero* have also been associated with decrements in neurodevelopment, as assessed later in childhood with neuropsychological tests.

Based on an extensive database of acute carbon monoxide poisoning, it is generally accepted that central nervous system symptoms are associated with acute exposures that result in blood COHb levels ≥20%. However, despite extensive clinical experience, general consensus on the dose-response relationship for carbon monoxide-induced nervous system effects at blood COHb levels between 5 and 20% has not been achieved.

Based on studies described above, a blood COHb concentration of 20% is identified as a LOAEL for adverse neurological outcomes, although the LOAEL range may extend below this level to 5%. These levels, 5 and 20%, can be converted to equivalent human exposure concentrations (for continuous exposure) that would yield the same steady-state blood COHb concentration by implementing the CFK model. The human equivalent exposure concentrations are approximately 32 ppm (COHb=5%) and 160 ppm (COHb=20%).

Respiratory Effects. Although cardiopulmonary arrest is an end point of fatal carbon monoxide poisoning, results of controlled clinical studies in healthy subjects indicate that the respiratory tract does not appear to be a primary target organ for carbon monoxide toxicity. Brief exposure to carbon monoxide at levels >1,000 ppm may decrease ventilatory performance, although conflicting results have been reported. Epidemiological studies have examined possible associations between ambient air carbon monoxide concentrations and mortality. These studies have examined relatively low carbon monoxide

concentrations (from a toxicological perspective) that are typical of ambient conditions of the study period (mean concentrations ranging from 0.3 to 10 ppm with the highest values ≤30 ppm; see Table 3-3). Collectively, these studies have yielded mixed results, with some studies finding significant associations between increasing ambient air carbon monoxide concentrations and respiratory outcomes (e.g., exacerbation of asthma symptoms, hospitalizations and emergency room visits related to asthma) and few studies finding associations that persist after accounting for exposures to other air pollutants that also have been shown to contribute to respiratory disease risk (e.g., NO_2, O_3, particulate matter [PM], and SO_2). The lack of strong evidence for associations between ambient air carbon monoxide concentrations at <30 ppm and pulmonary function is also consistent with the results of human clinical studies. Studies conducted in animals provide supporting evidence that the respiratory tract does not appear to be a primary target organ for carbon monoxide. Most of these studies evaluated carbon monoxide exposures that produced much higher COHb concentrations (i.e., COHb >50%) than those evaluated in controlled clinical studies in humans. In the studies that found effects on lung function (e.g., decreased compliance and increased airway resistance), animals had been exposed to carbon monoxide concentrations in the range of 8,000–28,400 ppm.

Hematological Effects. Hematological effects of carbon monoxide include compensatory responses to tissue hypoxia resulting from binding of carbon monoxide to Hb (e.g., increased blood volume, Hb, hematocrit, and erythrocyte count and volume). Possible associations between ambient air carbon monoxide concentrations and biomarkers of coagulation and inflammation have been examined in epidemiological studies. Biomarkers examined have included inflammation markers, C-reactive protein (CRP), serum amyloid A (SAA), and white blood cell (WBC) count; cell adhesion markers, E-selectin, von Willebrand factor, antigen (vWF), ICAM-1; and coagulation markers, fibrinogen, factor VII (FVII), prothrombin fragment 1+2, prothrombin time (PT), and activated partial thromboplastin time (APTT). Although some studies found significant associations between environmental carbon monoxide exposures and alteration in plasma proteins, these studies do not distinguish between possible direct effects of carbon monoxide and/or other air pollutants directly on coagulation and immune systems from indirect effects that result in changes in blood biomarkers. Furthermore, findings across studies are inconsistent. Environmental carbon monoxide exposures were shown to correlate with elevated C reactive protein in one trial, but not another by the same group. Plasma fibrinogen was increased in one study, decreased in one study, and unchanged in two studies. Other studies reported an elevation in soluble intercellular adhesion molecule-1, along with decreases in coagulation factor VII, serum albumin, and prothrombin time. Therefore, no conclusions can be drawn at this time on whether low-level environmental exposures may alter plasma inflammatory or coagulation markers. Nevertheless, direct effects are plausible, given

mechanistic studies that have revealed evidence that endogenous carbon monoxide may participate in the regulation of thrombosis and immune function (see Section 3.5.2, Mechanisms of Toxicity).

2.3 CARBON MONOXIDE DOSE-RESPONSE RELATIONSHIPS

Epidemiological and clinical studies provide evidence for a progression of some of the adverse health effects of carbon monoxide in humans with increasing blood levels of COHb (Figure 2-1). The relationship shown in Figure 2-1 does not necessarily mean that these effects result directly from the formation of COHb at the expense of decreasing O_2Hb levels in blood (i.e., hypoxic mechanisms). Other important mechanisms, previously mentioned and subsequently described in greater detail in Section 3.5.2, (Mechanisms of Toxicity), may also contribute to these effects. COHb may serve as a biomarker for carbon monoxide body burden or carbon monoxide burdens in specific target tissues where non-hypoxic modes of actions of carbon monoxide exert effects.

An alternative presentation of the relationship between blood COHb levels and adverse health effects is provided in Table 2-1. This table shows the predicted relationship between blood COHb levels that roughly correspond to adverse health effects and their corresponding equivalent human exposure concentrations that would result in the same steady-state blood COHb level. For example, in Table 2-1, a continuous exposure to approximately 14 ppm for a period exceeding 16 hours (i.e., sufficient to achieve steady state) would be expected to result in a blood COHb level of approximately 2.4%, the lower end of the range for cardiac effects in coronary artery disease patients. All predictions shown in Table 2-1 are based on the CFK model, described in Section 3.4.5 (Physiologically Based Pharmacokinetic/ Pharmacodynamic Models).

2.4 MINIMAL RISK LEVELS (MRLs)

Given the above considerations, MRLs for carbon monoxide are not proposed at this time. The rationale for this determination is as follows:

(1) Growing evidence suggests that endogenous carbon monoxide production is physiologically regulated and plays a role in regulating various important physiological processes, including processes that may underlie adverse effects on the cardiovascular, immune, blood coagulation, and nervous systems that have been observed in human clinical studies, epidemiological studies, or animal studies.

(2) Given the physiological role of endogenous carbon monoxide, it is likely that an exposure threshold for carbon monoxide actions, if one exists at all, would be at or near the endogenous

Figure 2-1. Blood Carboxyhemoglobin (COHb) Levels Corresponding to Adverse Health Effects of Carbon Monoxide in Humans

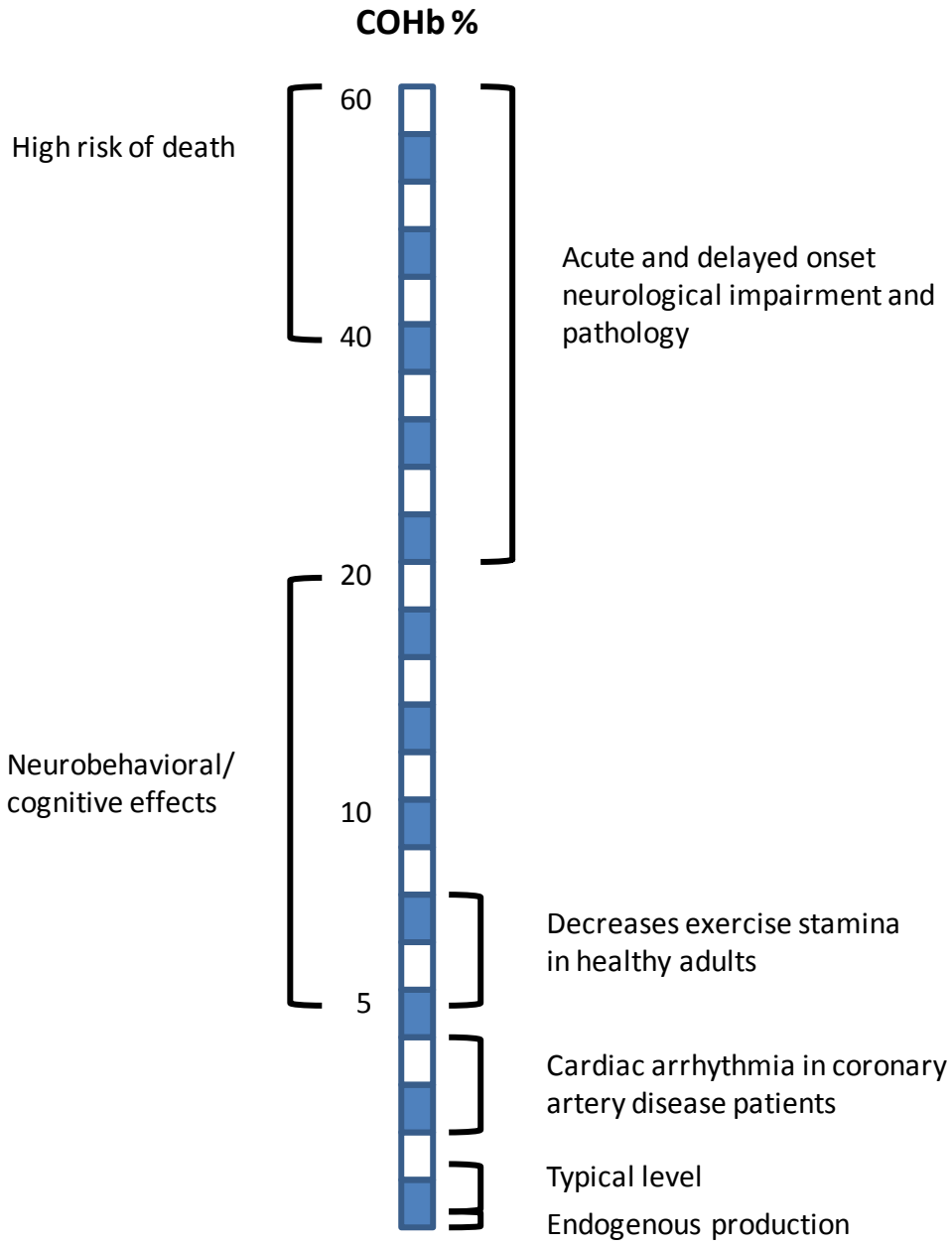

Table 2-1. Blood Carboxyhemoglobin (COHb) Levels Corresponding to Adverse Health Effects of Carbon Monoxide

Effect	COHb[a] (percent)	Exposure[b] (ppm)
Endogenous production	<0.5	0
Typical level in nonsmoker	0.5–1.5	1–8
Increased risk of arrhythmias in coronary artery disease patients and exacerbation of asthma (epidemiological studies)	0.3–2[b]	0.5–10[b]
Neurodevelopmental effects on the auditory system in rats	2–4[b]	12–25[b]
Enhanced myocardial ischemia and increased cardiac arrhythmias in coronary artery disease patients	2.4–6	14–40
Decreased exercise stamina in healthy adults	5–8	30–50
Neurobehavioral/cognitive changes, including visual and auditory sensory effects (decreased visual tracking, visual and auditory vigilance, visual perception), fine and sensorimotor performance, cognitive effects (altered time discrimination, learning, attention level, driving performance), and brain electrical activity	5–20	30–160
Acute and delayed onset of neurological impairment (headache, dizziness, drowsiness, weakness, nausea, vomiting, confusion, disorientation, irritability, visual disturbances, convulsions, and coma) and pathology (basal ganglia legions)	20–60	160–1,000
High risk of death	>50	>600

[a]Reported value, unless otherwise denoted as predicted.
[b]Predicted from the Coburn-Forster-Kane (CFK) model (unless otherwise denoted as reported), with a rate of endogenous carbon monoxide production assigned a value of 0.006 mL CO/kg body weight and all other parameter values as noted in Table 3-13.

production rate. Therefore, any exogenous source of carbon monoxide exposure would have the potential for exceeding the threshold and producing potentially adverse effects.

(3) Although there may be an exposure level that can be tolerated with minimal risk of adverse effects, the currently available toxicological and epidemiological data do not identify such minimal risk levels. Experimental clinical studies and animal toxicology studies that identify the lowest LOAELs do not identify NOAELs. These LOAELs are relatively low: COHb 2.4% for cardiovascular effects in humans and exposure concentrations of ≥12 ppm in rats for developmental effects. Converting these to human equivalent exposure concentrations (i.e., levels of continuous exposure that would result in steady-state COHb concentration in blood estimated from the CFK model) yield corresponding LOAELs of 14 and 10 ppm, respectively. Application of appropriate uncertainty factors to these LOAELs (e.g., for extrapolation from a LOAEL, for extrapolation from animals to humans, and for extrapolation to sensitive subpopulations) would result in MRLs that are 30–100 times lower than the corresponding LOAELs (e.g., approximately 0.1–0.5 ppm). These values are within the range of ambient carbon monoxide concentrations in the United States and would result, even for acute (e.g., 14-day) exposures, in internal doses that would be similar to endogenous production of carbon monoxide.

(4) Any exposure level determined to be of minimal risk at sea level would not necessarily be of minimal risk at higher altitudes (i.e., at lower O_2 partial pressures). This would apply, in particular, to modes of action of carbon monoxide that involve competition between carbon monoxide and O_2 for heme binding sites. The latter would include hypoxic mechanisms of actions that appear to underlie adverse cardiovascular effects of carbon monoxide (e.g., exacerbation of exercise-induced arrhythmias in patients who have coronary artery disease).

2. RELEVANCE TO PUBLIC HEALTH

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of carbon monoxide. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

Focus of the Health Effects Review. The literature on the toxicology of carbon monoxide is immense. Relatively recent reviews of the literature have been prepared by various organizations, including the World Health Organization (WHO 1999) and EPA (2000, 2009g), and numerous reviews have been compiled on the clinical toxicology and management of acute carbon monoxide poisoning. The review of the literature provided in this section is not intended to be comprehensive; rather, it is focused on the more important, recent developments in the toxicological and epidemiological assessment of carbon monoxide. Studies that have potential relevance to understanding the lower end of the dose-response relationship for carbon monoxide are emphasized. Typically, dose-response information is presented in Toxicological Profiles in Levels of Significant Exposure (LSE) tables and figures. However, this information on carbon monoxide has been represented in various types of units (e.g., exposure concentration, blood COHb), and end points are not easily assigned into categories of NOAELs or LOAELs (e.g., odds ratio from epidemiological studies). Therefore, in place of an LSE table, Table 3-1 provides an overview of exposures (ppm) and blood COHb levels (percent) that have been associated with specific categories of health effects. Table 3-2 can be used to convert the reported ambient air carbon monoxide concentrations into equivalent predicted blood COHb levels. However, considerable uncertainty attends to these dose interconversions as well as their relevance to a particular outcome. Predicted COHb levels and corresponding exposure concentrations may have greater relevance to outcomes mediated through hypoxic mechanisms than to those mediated through non-hypoxic mechanisms. Furthermore, steady-state requires exposure durations of approximately 16–24 hours. Exposures to lower levels of carbon monoxide for longer durations and exposures to higher levels for shorter durations that achieve similar blood COHb levels may not yield equivalent responses.

Table 3-1. Carbon Monoxide Exposures and Carboxyhemoglobin Levels Associated with Health Effects from Selected Studies Representing the Lowest Adverse Effect Levels

Study type	Subjects	Exposure (ppm)	COHb (%)	Effect	Comments	Reference
Respiratory						
Epidemiological	Asthmatic children	0.3–2	NR	Asthma	Exacerbation of asthma. Associations confounded by co-exposure to other air pollutants (NO_2, O_3, PM_{10}, $PM_{2.5}$, SO_2).	Park et al. 2005a; Rabinovitch et al. 2004; Rodriguez et al. 2007; Schildcrout et al. 2006; Silkoff et al. 2005; Slaughter et al. 2003; von Klot et al. 2002; Yu et al. 2000
Cardiovascular						
Clinical, acute exposure	Coronary artery disease patients (63 male adult nonsmokers)	117 (1 hour)	2.4	Myocardial ischemia	Decreased time-to-onset of angina and arrhythmia (ST-segment changes) during exercise.	Allred et al. 1989, 1991
Clinical, acute exposure	Healthy adults (15 male adult nonsmokers)	NR	5.1	Performance	Decreased maximal exercise duration and effort. No effect on heart rate or rhythm, cardiac perfusion, or blood pressure.	Adir et al. 1999
Epidemiological	General public	0.3–2	NR	Cardiovascular disease	Increased risk of congestive heart failure, ischemic heart disease, myocardial infarction, and stroke. Effect size more pronounced in elderly and people with ongoing respiratory or cardiovascular disease. Associations confounded by co-exposure to other air pollutants (NO_2, O_3, PM_{10}, $PM_{2.5}$, SO_2).	Berger et al. 2006; D'Ippoliti et al. 2003; Hosseinpoor et al. 2005; Lanki et al. 2006; Lee et al. 2003b; Mann et al. 2002; Szyszkowicz 2007; von Klot et al. 2005

Table 3-1. Carbon Monoxide Exposures and Carboxyhemoglobin Levels Associated with Health Effects from Selected Studies Representing the Lowest Adverse Effect Levels

Study type	Subjects	Exposure (ppm)	COHb (%)	Effect	Comments	Reference
Animal study, chronic exposure	Rats	200 (20 hours/ day, 72 weeks)	NR	Cardiomegaly	Left and right ventricle weights increased by 20% ($p<0.001$) and 14% ($p<0.001$).	Sørhaug et al. 2006
Neurological						
Clinical, acute exposure	Healthy adults	NR	5–20	Neurobehavioral/cognitive changes	Visual and auditory sensory effects (decreased visual tracking, visual and auditory vigilance, visual perception), fine and sensorimotor performance, cognitive effects (altered time discrimination, learning, attention level, driving performance), and brain electrical activity.	Beningnus et al. 1994
Clinical, acute exposure	Carbon monoxide-poisoned humans	NR	40–60	Neurological impairment and pathology	Acute and delayed onset neurological impairment (headache, dizziness, drowsiness, weakness, nausea, vomiting, confusion, disorientation, irritability, visual disturbances, convulsions, and coma) and pathology (basal ganglia legions).	Chambers et al. 2008; Dolan 1985; Ernst and Zibrak 1998; Hopkins et al. 2006; Kao and Nañagas 2006; Lo et al. 2007; Parkinson et al. 2002; Raub and Benignus 2002
Animal study, acute exposure	Rats	500–1,500		Neurosensory impairment	Potentiates noise-induced hearing loss, including noise-induced elevation of compound action potential threshold and auditory threshold shifts.	Chen and Fechter 1999; Fechter et al. 1988; Young et al. 1987

Table 3-1. Carbon Monoxide Exposures and Carboxyhemoglobin Levels Associated with Health Effects from Selected Studies Representing the Lowest Adverse Effect Levels

Study type	Subjects	Exposure (ppm)	COHb (%)	Effect	Comments	Reference
Developmental						
Animal study, acute exposure	Neonatal rats (exposed post-utero)	12–25	NR	Neurosensory development	Morphological changes in the developing auditory system, decreased 8th cranial nerve action potentials, and otoacoustic emissions in pups, which persisted to age 73 days.	Lopez et al. 2003, 2008; Stockard-Sullivan et al. 2003; Webber et al. 2003
Animal study, acute exposure	Neonatal rats or mice (exposed *in utero*)	60–150		Neurosensory/ neurobehavioral development	Decreased motor activity and response to stimulation, impaired righting reflexes, and impaired homing and memory acquisition behaviors.	De Salvia et al. 1995; Fechter and Annau 1977, 1980; Giustino et al. 1999; Mactutus and Fechter 1985; Singh 1986

COHb = blood carboxyhemoglobin; NR = not reported

Table 3-2. Predicted Steady-State Blood Carboxyhemoglobin (COHb) Levels[a]

Carbon monoxide exposure concentration (ppm)	Steady-state blood COHb (percent)
0.1	0.25
0.5	0.32
1	0.39
2	0.50
5	1.0
10	1.8
15	2.5
20	3.2
40	6.1
60	8.7
80	11
100	14
200	24
400	38
600	48
800	56
1,000	61

[a]Blood COHb levels are predicted from the Coburn-Forster-Kane (CFK) model (see Section 3.4.5 for a discussion of model and parameter values).

The discussion of health effects has been limited to the inhalation exposure pathway. Carbon monoxide exists in the environment as a gas (Henry's law constant >50,000 atm/mol fraction, 25 °C). As a result, humans can be exposed to carbon monoxide from breathing and/or contact with carbon monoxide in air. No information is available on the dermal absorption or toxicity of carbon monoxide resulting from exposures to gaseous carbon monoxide. However, as is the case for other gases that are avidly absorbed from the lung during inhalation (e.g., O_2), dermal absorption of carbon monoxide through intact skin would be expected to make a substantially minor contribution to absorbed carbon monoxide, relative to inhalation. No information is available on the absorption or toxicity of carbon monoxide resulting from oral exposures to gaseous carbon monoxide. Although carbon monoxide can dissolve in water (23 mL carbon monoxide/L water, 20 °C), appreciable concentrations in drinking water would occur only at very high partial pressures of carbon monoxide in air, conditions in which inhalation would be the dominant absorption pathway. Therefore, the only relevant pathway of exposure to humans is the inhalation pathway, and oral and dermal exposures are not considered further.

3.2 DISCUSSION OF HEALTH EFFECTS

This section of the Toxicological Profile summarizes results obtained from clinical cases of carbon monoxide poisoning, studies of controlled exposures conducted in humans, epidemiological studies of health outcomes associated with ambient air carbon monoxide concentrations, and experimental studies conducted in various animal models. Reported clinical studies are limited to exposures of acute duration. Animal studies have examined longer-duration exposures. Epidemiological studies have examined outcomes in the context of chronic exposures or acute variations in exposure concentrations that occur during chronic exposures. Some studies (e.g., clinical studies) have reported carbon monoxide doses in terms of blood COHb levels, while most epidemiological studies and some animal studies have reported exposure concentrations (e.g., ppm, mg/m^3). For comparability to human clinical studies, reported air carbon monoxide concentrations can be converted to corresponding equivalent steady-state COHb% values (i.e., the COHb% that would be achieved with continuous exposure to the reported air carbon monoxide concentration) through a model. This conversion has been made by application of the CFK model (see Section 3.4.5). Predicted steady-state blood COHb levels corresponding to a range of carbon monoxide exposure concentrations are presented in Table 3-2. This table can be used to convert the reported ambient air carbon monoxide concentrations into equivalent predicted blood COHb levels. Exposure concentrations are typically reported in units of ppm or mg/m^3; in the Toxicological Profile, exposure units are presented in units of ppmv (indicated as ppm). At standard temperature and pressure

(e.g., 25 °C, 760 Torr), the conversion factor is approximately 1 (i.e., 1 mg/m^3≈0.87 ppm, 1 ppm≈1.15 mg/m^3).

Overview of Acute Carbon Monoxide Toxicity and Modes of Action. Carbon monoxide exerts effects on cell metabolism through both hypoxic and non-hypoxic mechanisms. Both types of effects are thought to be largely (but not entirely) the result of the ability of carbon monoxide to bind to heme and alter function and/or metabolism of heme proteins. The binding affinity of carbon monoxide for hemoglobin is over 200 times greater than that of the affinity of oxygen for hemoglobin (Chakraborty et al. 2004). Formation of COHb decreases the O_2 carrying capacity of blood and impairs release of O_2 from Hb for its utilization in tissues. Through similar mechanisms, carbon monoxide decreases O_2 storage in muscle cells by binding to, and displacing O_2 from, myoglobin. Although all tissues are vulnerable to carbon monoxide-induced hypoxic injury, those having the highest O_2 demand are particularly vulnerable, including the brain and heart. The developing fetus may also be a sensitive target of carbon monoxide, through hypoxic and/or non-hypoxic mechanisms (Carratu et al. 1993, 2000a, 2000b; De Salvia et al. 1995; Lopez et al. 2003, 2008; Stockard-Sullivan et al. 2003; Webber et al. 2003).

Acute carbon monoxide poisoning is largely the result of tissue hypoxia. Signs and symptoms of carbon monoxide toxicity, in order of increasing severity include: (1) headache, nausea, dilation of cutaneous vasculature, vomiting, dizziness, and blurred vision; (2) confusion, syncope, chest pain, dyspnea, weakness, tachycardia, and tachypnea rhabdomyolysis; and (3) palpitations, cardiac dysrhythmias, hypotension, myocardial ischemia, cardiac arrest, respiratory arrest, pulmonary edema, seizures, and coma (Kao and Nañagas 2006). Although binding of carbon monoxide to blood Hb is a primary component of the hypoxic mode of action of carbon monoxide, blood COHb levels have not been shown to be a reliable predictor of severity of acute toxicity, in part due to time elapsed from removal from carbon monoxide exposure to COHb measurement and to the effects of emergency medical intervention (i.e., treatment with oxygen) on COHb levels prior to COHb measurement (Hampson and Hauff 2008). In general, typical levels of COHb in nonsmokers are <2% (Adams et al. 1988; Allred et al. 1991; Anderson et al. 1973; Hinderliter et al. 1989; Kleinman et al. 1989, 1998; Sheps et al. 1987, 1990). Of this, approximately 0.2–1.0% is derived from endogenous production of carbon monoxide (Coburn et al. 1963; Delivoria-Papadopoulos et al. 1974; Longo 1977). Levels ranging from 2 to 6% have been shown to exacerbate underlying cardiovascular disease, including enhanced myocardial ischemia and increased cardiac arrhythmias (Adams et al. 1988; Allred et al. 1989, 1991; Anderson et al. 1973; Kleinman et al. 1989, 1998; Leaf and Kleinman 1996b). In general, signs and symptoms of acute carbon monoxide poisoning can present at COHb levels ranging from 3 to 24% (Hampson and Hauff 2008; Kao and

Nañagas 2006). This level overlaps with levels found immediately following cigarette smoking, up to approximately 10% (Kao and Nañagas 2006). More severe signs of carbon monoxide poisoning are poorly correlated with blood COHb, with loss of consciousness occurring at a mean level of 24.3% (range: 2–70%; Hampson and Hauff 2008) and fatality at a mean level of 32.1% (range: 3.0–60%; Hampson and Hauff 2008). Exposures that result in COHb levels >50% are frequently fatal (Dolan 1985). Persistent neurologic sequelae, which can be delayed in onset, can also occur, including memory loss, impairments of concentration and language, affective disorders (e.g., depression), and Parkinsonism (Choi 2002; Klawans et al. 1982; Ringel and Klawans 1972), some of which may be related to pathologic changes in the brain (Gorman et al. 2003; Lo et al. 2007).

Most of the non-hypoxic mechanisms of action of carbon monoxide have been attributed to binding of carbon monoxide to heme in proteins other than Hb. Notable targets of carbon monoxide include components of several important physiological regulatory systems, such as brain and muscle oxygen storage and utilization (myoglobin, neuroglobin); nitric oxide cell signaling pathway (e.g., nitric oxide synthase, guanylyl cyclase); prostaglandin cell signaling pathway (cyclooxygenase, prostaglandin H synthase); energy metabolism and mitochondrial respiration (cytochrome c oxidase, cytochrome c, NADPH oxidase); steroid and drug metabolism (cytochrome P450), cellular redox balance, and ROS (catalase, peroxidases); and various transcription factors (e.g., neuronal PAS domain protein, NPAS2, implicated in regulation of circadian rhythm). Endogenously produced carbon monoxide may participate in the physiological regulation of some, if not all, of these systems. This has potentially important implications for the understanding of carbon monoxide toxicology and dose-response relationships for the following reasons: (1) carbon monoxide modulation of physiological processes may underlie some aspects of the toxicity of exogenous carbon monoxide; (2) exogenous carbon monoxide may disrupt physiological regulation of those systems that are responsive to endogenous carbon monoxide (e.g., vascular resistance); and (3) exposures to exogenous carbon monoxide may affect carbon monoxide-mediated physiological responses at levels that approach those resulting from endogenous production. One implication of this is that the dose threshold for effects of exogenous carbon monoxide on carbon monoxide-modulated physiological systems may lie near or below ambient air carbon monoxide concentrations.

Epidemiological Studies. Epidemiological studies of health outcomes associated with exposure to carbon monoxide fall into two major categories. Some studies have examined relationships between long-term average ambient air carbon monoxide concentrations and health outcomes, where the air carbon monoxide concentrations represent averages over years or decades. Other studies have examined

associations between outcomes and air concentrations measured over relatively narrow time slices (e.g., 1–24-hour average or maxima). These *short-term* studies are particularly suited to outcomes that might be related to short-term elevations in carbon monoxide exposure in close temporal proximity to the outcome of interest, which might otherwise be lost in longer-term average carbon monoxide concentrations (e.g., change in heart rate, heart rate variability, arrhythmia). End points that have been assessed in epidemiological studies include mortality, morbidly, and rates of medical assistance. Examples of the latter category include rates of hospital admissions or emergency room visits recorded to have been prompted by a given morbidity outcome, rates of activation of recorded activation of implantable cardioverter defibrillator (ICD) devices, and rates of rescue medication use by asthmatics. These studies are typically conducted using time-series analysis and Poisson regression models for estimated associations between carbon monoxide concentrations and outcome rates. Case-crossover designs have also been widely applied in air pollution epidemiology. This design offers many of the advantages of the case-control design (e.g., matching of individual cases and controls for potential co-variables and confounders), with the additional feature of each case serving as its own control, with each case assigned a *case exposure period*, usually within a few days of the outcome measurement, and a *control exposure period*, usually some time before or after the *case exposure period*. Another widely reported design in assessment of morbidity is the panel study in which members of the study cohort, usually a relatively small sample, are followed individually with respect to exposures and outcomes. Also reported are case-control studies, retrospective and cross-sectional cohort studies, and a few prospective studies of mortality.

Several important features of the epidemiological studies of ambient air carbon monoxide are of generic relevance to public health assessments. In particular, their utility for establishing dose-response relationships is limited by several factors:

(1) Nearly all studies have relied on area monitoring for estimating exposure levels; this has the potential to produce errors in assigning exposure levels to individuals.

(2) The temporal correspondence between monitored exposure levels and outcomes is highly uncertain. Outcomes that might be related to carbon monoxide exposure might occur in response to short-term elevations in carbon monoxide concentrations not captured in air monitoring data that are averaged over longer time periods (e.g., 24-hour average). Also, outcomes associated with a given exposure may have a latency period (e.g., myocardial infarction may occur days after the exposure that initiated the event). One approach to this problem has been to apply time-series techniques to quantify air concentration trends and to explore lag times between exposure concentration trends and the time of outcome.

(3) Ambient air carbon monoxide concentrations tend to be strongly correlated with other air quality variables that can affect cardiovascular function, either directly or indirectly (e.g., through effects on the respiratory tract). Typical variables that correlate with air carbon monoxide concentrations include particulate matter (e.g., total suspended particulates, PM_{10}, $PM_{2.5}$), NO_2, O_3, and SO_2. Ignoring co-variables that contribute to risk in regression models (e.g., single-pollutant models) can introduce upward bias in observed associations between air carbon monoxide concentrations and outcomes (e.g., inflate relative risk). On the other hand, assuming that strongly correlated co-variables are independent in multi-pollutant models can introduce downward bias in the carbon monoxide association. Although the strength of the carbon monoxide association may be underestimated in multi-pollutant models, for the reasons noted above, persistence of significant associations between the measured outcome and air carbon monoxide concentrations, when co-pollutants are accounted for in multivariate models, provides stronger support for a contribution of carbon monoxide to the outcome. Not all studies have explored multi-pollutant models; however, such models lend supporting evidence to the results of clinical studies that have shown carbon monoxide to exacerbate coronary vascular disease.

(4) Outcomes investigated have tended to be serious, life-threatening events (e.g., cardiac arrhythmia, myocardial infarction, stroke, heart failure); these outcomes reflect the "late-stage" consequences of contributing pathophysiology that might be associated with exposures to lower levels of carbon monoxide for longer durations than indicated in the epidemiological studies.

(5) Mean values of carbon monoxide exposure concentrations have ranged from 0.3 to 5 ppm, with the highest values ≤30 ppm. These values correspond to predicted steady-state COHb levels of <1% for the mean and <5% for the highest values (predicted from the CFK model). At these COHb levels, it is possible that only highly susceptible individuals exhibit the serious hypoxia-related outcomes. For these and other reasons, epidemiologic studies have typically focused on highly susceptible populations. A typical design has been to examine associations between temporal trends in ambient air carbon monoxide concentrations and hospital admissions or emergency department visits for which the reported diagnosis was some form of cardiovascular and/or respiratory disease of impairment.

3.2.1 Death

The Centers of Disease Control and Prevention (CDC) estimated that during the period 1999–2004, carbon monoxide was listed as a contributing cause of death on 16,447 death certificates in the United States, of which 2,631 deaths were categorized as unintentional and unrelated to fires (CDC 2007). Typically, fatal exposures to carbon monoxide produce coma, convulsions, and cardiorespiratory arrest (Raub et al. 2000; Wolf et al. 2008). Symptoms preceding death can include headache, dizziness, weakness, nausea, vomiting, mental confusion, visual disturbances, and loss of consciousness (Choi 2001; Raub et al. 2000). Clinical signs of life-threatening toxicity can include cardiac arrhythmia and myocardial ischemia, hypotension, pulmonary edema, and seizures (Kao and Nañagas 2006). Patients who have been resuscitated following carbon monoxide-induced cardiac arrest have a very low prognosis for survival (Hampson and Zmaeff 2001).

Although severe carbon monoxide toxicity is thought to primarily derive from hypoxia resulting from binding to, and displacement of, O_2 from heme proteins, including blood Hb, the relationship between blood COHb levels and signs indicative of life-threatening toxicity is highly uncertain (e.g., loss of consciousness, convulsions, coma, cardiopulmonary depression). In a survey of 1,407 cases of acute carbon monoxide poisoning patients (i.e., record of history of carbon monoxide exposure, signs and symptoms, blood COHb >2%, treatment with hyperbaric O_2), the mean blood COHb concentration was 22.3% (95% confidence interval [CI]: 22.7, 23.9, range: 2.1–72.3; Hampson and Hauff 2008). The group mean was only marginally lower than in patients who lost consciousness (24.3%, 95% CI: 23.3, 25.1, range: 2.1–73.3) or died (32.1%, 95% CI: 27.9, 36.4, range: 3.0–60.0). Although survivors had lower mean COHb levels (23.1, 95% CI: 22.5, 23.6) than that of fatalities, the upper end of the range exceeded that of fatalities (2.1–72.3%). The lower end of the range for COHb levels (2.1%) in this study reflects, at least in part, time delays between termination of exposure and measurement of blood COHb levels. However, that notwithstanding, this study suggests that blood COHb levels do not provide a reliable predictor of lethality. COHb levels can be converted to estimates of corresponding continuous air exposure levels by application of the CFK model. The mean for fatalities (32.1%) corresponds to a steady-state exposure (e.g., >500 minutes) to 300 ppm, or exposure to 1,000 ppm for approximately 80–90 minutes.

Epidemiological Studies. Epidemiological studies have examined possible associations between ambient air carbon monoxide concentrations and mortality. These studies have examined relatively low carbon monoxide concentrations (from a toxicological perspective) that are typical of ambient conditions of the study period. Mean air carbon monoxide concentrations in most of the studies were <2 ppm, with highest values ≤10 ppm. Epidemiologic studies of ambient carbon monoxide and mortality can be grouped into two categories: (1) studies that have examined the relationship between exposures to carbon monoxide estimated from short-term (e.g., daily or monthly average) ambient air carbon monoxide concentrations; and (2) studies that have based exposure estimates on long-term average air carbon monoxide concentrations. Although both types of studies have yielded mixed results, the larger, multi-city studies of long-term exposure have yielded estimates of carbon monoxide-associated mortality risk that are zero or less than zero (Jerrett et al. 2003; Lipfert et al. 2006b; Miller et al. 2007; Pope et al. 2002). Results from short-term exposure studies have been more varied, with some studies showing increased mortality risk when carbon monoxide is considered in single-pollutant models (percent increase in mortality: 0.2–0.6), which did not persist when the models were adjusted for co-pollutants (Burnett et al. 2004; Dominici et al. 2003a, 2003b; Samoli et al. 2007). This conclusion is supported by at least one meta-analysis of time-series published between 1985 and 2001 (Stieb et al. 2002), which estimated excess mortality risk

(pooled meta estimate) for a 1.1 ppm increment in air carbon monoxide concentration to be 1.6 (95% CI: 1.1, 2.1) based on a single-pollutant model and 0.7% (95% CI: -0.1, 1.5), based on a multi-pollutant model that included NO_2, O_3, PM_{10}, and SO_2 (both estimates from generalized additive model regression models). A study of survival among 1,073 carbon monoxide poisoning patients (followed from 1978 to 2005) found that survivors of carbon monoxide poisoning had an increased mortality (standardized mortality ratio [SMR]=1.9) (95% CI: 1.6, 2.2; NIOSH Life Table analysis as reference; Hampson et al. 2009; Leikin and Wills 2009).

While these studies provide some evidence in support of a mortality risk associated with inhalation exposures to carbon monoxide, as previously discussed in the introduction to Section 3.2, their utility for establishing dose-response relationships for these effects are limited by several factors: (1) reliance on area monitoring for estimating exposure levels; and (2) relatively strong correlations between ambient air carbon monoxide concentrations and other air quality variables that may contribute to mortality risk. The discussion presented below focuses on outcomes of the most recent follow-ups of larger (e.g., multi-city) studies. Numerous single-city studies have also been reported; however, results of these studies are, in general, consistent with findings of multi-city studies.

Three multi-city prospective mortality studies have examined possible associations between long-term average ambient air carbon monoxide concentrations and mortality. A prospective study examined mortality in a cohort of 552,138 adults in 151 U.S. metropolitan areas, enrolled in the study in 1982 and followed through 1998 (Pope et al. 1995, 2002). Based on estimated average ambient air carbon monoxide concentration during the period 1982–1998, relative risks for mortality per 1 ppm increase in carbon monoxide concentration (estimated from Figure 5 of Pope et al. 2002) were approximately 0.97 (95% CI: 0.93, 1.0) for all causes of death, 0.95 (95% CI: 0.88, 0.99) for cardiopulmonary death, and 0.90 (95% CI: 0.83, 0.96) for lung cancer death. A reanalysis of data from the same study included a more extensive treatment of covariables. The relative risk for death from all causes was estimated to be approximately 0.98 (95% CI: 0.92, 1.03) for an increase in ambient carbon monoxide concentration from 0.19 to 3.95 ppm (Jerrett et al. 2003). A smaller prospective study focused on cardiovascular deaths among postmenopausal women between the ages of 50 and 79 years (Miller et al. 2007). Women (n=65,893) without previous history of cardiovascular disease were enrolled in the study from 36 U.S. metropolitan areas during the period 1994–1998, and deaths were recorded up to mid-2003. Among the subset of the cohort that had complete data on ambient air pollutant levels from local monitoring stations (n=28,402), the hazard ratio for cardiovascular mortality was 0.92 (95% CI: 0.71, 1.21) per 1 ppm increase in ambient air carbon monoxide concentration based on a single-pollutant model and 0.93 (95%

CI: 0.67, 1.30) based on a multi-pollutant model that adjusted for air concentrations of NO_2, O_3, $PM_{2.5}$, PM_{10}, and SO_2. A prospective study of U.S. military veterans examined mortality outcomes in approximately 70,000 males who had been diagnosed with hypertension (Lipfert et al. 2000, 2006a, 2006b). Subjects were enrolled in the study in 1976 at the average age of 51 years and were followed through 2001 (Lipfert et al. 2006a). Mortality risk (all causes of death) was not significantly associated with ambient air carbon monoxide concentration. The relative risk was estimated to be 1.032 (95% CI: 0.954, 1.117) per 1 ppm increase in air carbon monoxide concentration based on a single-pollutant model and 1.023 (95% CI: 0.939, 1.115) after adjustment for NO_2 and O_3.

A multi-city, cross-sectional study examined mortality in all U.S. counties (excluding those of Alaska) for the period 1969–1997 (Lipfert and Morris 2002). Risk estimates were made for various exposure periods ranging from 2 to 9 years and for age categories. Estimates of mortality risk (all causes) attributable to average ambient air carbon monoxide concentrations for the exposure periods were mostly either not significant or significantly negative. Elevated risk was observed in some exposure periods for the age group 15–44 years; however, this outcome was not consistently observed across time periods.

Several multi-city studies have found significant associations between increasing short-term average ambient air carbon monoxide concentration and increasing mortality risk when carbon monoxide is considered in single-pollutant models, with the associations attenuated when models were adjusted for other co-pollutants. A time-series study examined mortality in 82 U.S. cities during the period 1987–1994 (Dominici et al. 2003b; HEI 2005; Samet et al. 2000). In the Dominici et al. (2003b) analysis of these data, a 1 ppm increase in ambient air carbon monoxide concentration (lag 1 day) was associated with increased mortality (from all causes) of 0.46% (95% CI: 0.18, 0.73). Mortality risk was not significant after adjustment for air concentration of PM_{10} alone or for PM_{10} and NO_2. A time-series study examined morality in 12 Canadian cities during the period 1987–1994 (Burnett et al. 2004). Mortality risk (all non-accidental causes) was significantly associated with ambient air carbon monoxide concentration (lag 1 day) in single-pollutant models, with an increase of 0.68% (t=3.12) per 1.02 ppm increases in air carbon monoxide concentration. However, the association did not persist when adjusted for NO_2 (0.07%, t=0.30). A time-series analysis examined mortality in 19 European cities during the period 1990–1997 (Samoli et al. 2007). This study found a significant association between carbon monoxide and total non-accidental and cardiovascular mortality in single-pollutant models. The estimated effect size varied depending on the model applied. The effect size for total mortality based on a single-pollutant model ranged from 0.59% increase (95% CI: 0.41, 1.79) to 1.20% (95% CI: 0.63, 1.77) per 1 mg/m^3 increase in carbon monoxide concentration (0–1-day lag). The effect on cardiovascular

mortality ranged from 0.8% increase (95% CI: 0.53, 1.07) to 1.25 (95% CI: 0.30, 2.21). Inclusion of black smoke or NO_2 in the models substantially decreased the estimated risk attributable to carbon monoxide, with the effect sizes no longer significant in some models.

3.2.2 Systemic Effects

Respiratory Effects. Although cardiopulmonary arrest is an end point of fatal carbon monoxide poisoning, results of controlled clinical studies in healthy subjects indicate that the respiratory tract does not appear to be a primary target organ for carbon monoxide toxicity. Brief exposure to carbon monoxide at levels >1,000 ppm may decrease ventilatory performance, although conflicting results have been reported (Chevalier et al. 1966; Fisher et al. 1969; Koike et al. 1991; Ren et al. 2001; Vesely et al. 2004). Epidemiological studies have examined possible associations between ambient air carbon monoxide concentrations and mortality. These studies have examined relatively low carbon monoxide concentrations (from a toxicological perspective) that are typical of ambient conditions of the study period (mean concentrations ranging from 0.3 to 10 ppm with the highest values ≤30 ppm). Collectively, these studies have yielded mixed results, with some studies finding significant associations between increasing ambient air carbon monoxide concentrations and respiratory outcomes (e.g., exacerbation of asthma symptoms, hospitalizations and emergency room visits related to asthma) and few studies finding associations that persist after accounting for exposures to other air pollutants that also have been shown to contribute to respiratory disease risk (e.g., NO_2, O_3, particulate matter, and SO_2). The lack of strong evidence for associations between ambient air carbon monoxide concentrations at <30 ppm and pulmonary function is also consistent with the results of human clinical and animal studies. Studies conducted in animals provide supporting evidence that the respiratory tract does not appear to be a primary target organ for carbon monoxide (EPA 1991, 2000; Sørhaug et al. 2006).

Clinical Studies. Few controlled clinical studies have evaluated adverse respiratory effects of carbon monoxide exposure. Available clinical studies have been conducted in small numbers (i.e., 4–12) of healthy subjects under acute exposure conditions (Chevalier et al. 1966; Fisher et al. 1969; Koike et al. 1991; Ren et al. 2001; Vesely et al. 2004). No controlled clinical studies evaluating respiratory effects of intermediate- or chronic-duration exposure in healthy subjects or of any duration exposure in patients with underlying respiratory diseases were identified.

Results of controlled clinical studies in healthy subjects indicate that brief exposure to carbon monoxide may decrease ventilatory performance, although conflicting results have been reported; however, based

on results of available clinical studies, the respiratory tract does not appear to be a major target organ for carbon monoxide. Exposure of 10 healthy subjects to 5,000 ppm carbon monoxide for 2–4 minutes (COHb 4%) decreased inspiratory capacity by 7.5% ($p<0.05$), total lung capacity by 2.1% ($p<0.02$), and mean resting diffusing capacity of lungs by 7.6% ($p<0.05$) (Chevalier et al. 1966). However, other studies have found no effects of acute carbon monoxide exposure on ventilatory function. No changes in ventilatory mechanics (vital capacity, functional residual capacity, airway conductance, lung volume, pulmonary resistance, dynamic lung compliance, diffusing capacity) were observed in four healthy subjects exposed to carbon monoxide producing blood COHb levels of 11–20% (Fisher et al. 1969). Exposure to 1,000 ppm carbon monoxide for 10–30 minutes (COHb ~10%; 10 subjects) (Ren et al. 2001) or 1,200 ppm carbon monoxide for 30–45 minutes (COHb 10.2%; 10 subjects) (Vesely et al. 2004) did not affect resting ventilation. During submaximal exercise challenge, acute exposure of 10 subjects to carbon monoxide producing blood COHb levels of 11–20% did not alter ventilation mechanics (Koike et al. 1991). The reason for these conflicting results is not apparent, although the small number of subjects evaluated in each study may have been a contributing factor.

Epidemiological Studies. Epidemiological studies of exposure to carbon monoxide and respiratory outcomes fall into two major categories: (1) studies that have assessed respiratory morbidity in association with ambient air carbon monoxide concentrations; and (2) studies that have evaluated associations between ambient air carbon monoxide concentrations and the incidence of hospital admissions and/or emergency room visits related to respiratory disease (e.g., time-series studies, case-crossover). Collectively, these studies have yielded mixed results. Although some studies found significant associations between increasing ambient air carbon monoxide concentrations and respiratory outcomes (e.g., exacerbation of asthma symptoms, hospitalizations and emergency room visits related to asthma), few studies examined the robustness of the association in models that adjust for exposures to other air pollutants that also have been shown to contribute to respiratory disease risk (e.g., NO_2, O_3, particulate matter, and SO_2). While these studies provide some evidence in support of adverse respiratory effects of inhalation exposures to carbon monoxide, as previously discussed in the introduction to Section 3.2, their utility for establishing dose-response relationships for these effects are limited by several factors: (1) reliance on area monitoring for estimating exposure levels; (2) uncertainty in knowledge of temporal correspondence between monitored exposure levels and outcomes; (3) relatively strong correlations between ambient air carbon monoxide concentrations and other air quality variables that can affect respiratory function; and (4) relatively low carbon monoxide exposures studied. Mean values of carbon monoxide exposure concentrations have ranged from 0.3 to 10 ppm, with the highest values ≤30 ppm. These concentrations are well below those explored in experimental studies that found

minimal or no effects of carbon monoxide on pulmonary function in association with acute exposures to carbon monoxide (i.e., ≥1,000 ppm). The relatively low carbon monoxide concentrations studied in epidemiological studies, together with concurrent exposures to other air pollutants that may have more pronounced effects on respiratory function, may have contributed to the mixed results of these studies and relatively weak associations with carbon monoxide that have been observed (e.g., odds ratios and relative risks very close to 1). The lack of strong evidence for associations between ambient air carbon monoxide concentrations at <30 ppm and pulmonary function is also consistent with the results of human clinical and animal studies.

The presentation of epidemiology is organized by major categories of respiratory outcomes for which the studies were designed to evaluate, including pulmonary function, asthma and exacerbation of asthma symptoms, and hospital admissions and emergency room visits related to respiratory disease. Study conclusions are presented in the text, with selected supporting details presented in tabular form (Table 3-3). Although most studies explored various time lags between monitored air carbon monoxide concentrations and outcomes, as well as various sample strata, for the sake of brevity, only selected representative time lags (usually, those indicative of the strongest associations to carbon monoxide) are presented in the table. Where co-pollutant models have been explored, these results are also presented.

Studies of Pulmonary Function. Studies of possible associations between inhalation exposures to carbon monoxide and effects on pulmonary function have yielded mixed results (Chen et al. 1999; Fischer et al. 2002; Lagorio et al. 2006; Penttinen et al. 2001; Rabinovitch et al. 2004; Silkoff et al. 2005; Timonen et al. 2002). Several of these studies examined subjects who had ongoing lung disease (e.g., asthma, chronic obstructive lung disease) and who might be more sensitive to agents that affect pulmonary function (Canova et al. 2010; Rabinovitch et al. 2004; Silkoff et al. 2005; Timonen et al. 2002). Mean ambient air carbon monoxide concentrations in these studies ranged from 0.5 to 10 ppm, with the highest values ≤30 ppm (Lagorio et al. 2006). Studies that explored multi-pollutant models found that the association with carbon monoxide persisted (Canova et al. 2010) or was substantially weakened when adjustments were made for air particle matter (Penttinen et al. 2001). Therefore, is it difficult to sort out the effects of carbon monoxide from those of other urban air pollutants that have strong correlations with air carbon monoxide concentrations and that also could have affected pulmonary function.

Studies of children have yielded mixed results that are further complicated by lack of assessment of models in which correlated concentrations of other air pollutants were included (Chen et al. 1999; Fischer et al. 2002; Rabinovitch et al. 2004; Timonen et al. 2002). A study conducted in the San Joaquin Valley,

Table 3-3. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Respiratory Disease

Study	Design features	CO exposure	Effect size
Lung function			
Canova et al. 2010 Period: 2004–2005 Location: Padua, Italy	Outcome: Lung function (PEF, FEV_1) Design: Panel Sample: n=40 chronic asthmatics (n=19 followed for 2 years), age 15–44 years	Avg time: 8 hours Median: 1.72 mg/m^3 Range: 0.6–5.2 mg/m^3	Increment: 1 mg/m^3 β Coefficient (SE, p, % change); lag 1 day: Morning PEF deviations (L/minute) CO: -8.50 (3.54, 0.02, -2.60) $CO+SO_2$: -8.23 (3.41, 0.02, -2.52) $CO+NO_2$: -8.64 (3.52, 0.01, -2.64) $CO+PM_{10}$: -10.52 (4.18, 0.01, -3.22) $CO+SO_2+PM_{10}+NO_2$: -10.70 (4.15, 0.01, -3.27)
Chen et al. 1999 Period: 1995–1996 Location: Taiwan	Outcome: Lung function (FVC, FEV_1, FEV_1/FVC, $FEF_{25–75\%}$, PEF) Design: Cross-sectional Sample: n=941, age 8–13 years	Avg time: 1 hour maximum Range: 0.4–3.6 ppm	Increment: NR β Coefficient (SE), lag 2 days for 24 hours avg CO: FVC (mL) -147.71 (64.48) FEV_1 (mL) -82.42 (60.95)
Fischer et al. 2002 Period: NR Location: Utrecht, Netherlands	Outcome: Lung function (FVC, FEV_1, PEF, MMEF) Design: Panel study Sample: n=68, age 10–11 years	Avg time: 24 hours Mean: 0.80 ppm Range: 0.28–1,34 ppm	Increment: 100 $\mu g/m^3$ NO% increase (95% CI): 28.2 (6.9, 53.9) No significant associations with lung function end points
Lagorio et al. 2006 Period: 1999 Location: Rome, Italy	Outcome: Lung function (FVC, FEV_1) Design: Time-series panel study Sample: Patients (age 50–80 years) diagnosed with COPD n=11; asthma, n=11; IHD, n=7	Avg time: 24 hours Mean: 6.5 ppm Range: 1.4–25.2 ppm	Increment: 1 mg/m^3 No significant associations with lung function end points
Park et al. 2005a Period: 2002 Location: Incheon, Korea	Outcome: Lung function (PEF variability (>20%), mean PEF); Design: Panel Sample: n=64 bronchial asthmatics, age 16–75 years	Avg time: 24 hours Mean: 0.6 ppm SD range: 0.09–0.15 ppm	Increment: NR β Coefficient (SE): Mean PEF (L/minute): -10.103 (2.7146)

Table 3-3. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Respiratory Disease

Study	Design features	CO exposure	Effect size
Penttinen et al. 2001 Period: 1996–1997 Location: Helsinki, Finland	Outcome: Lung function (PEF) Design: Panel Sample: n=57 adult asthmatics	Avg time: 24 hours Median: 0.35 ppm Range: 0.09–0.96 ppm	Increment: 0.2 mg/m^3 β Coefficient (SE); lag 1 day: PEF deviations (L/minute) CO: -1.08 (0.36) CO+PNC: -0.67 (0.64); 1
Mortimer et al. 2008 Period: 1989–2000 Location: San Joaquin Valley, California	Outcome: Lung function (FVC, FEV_1, PEF, $FEF_{25–75}$, FEV_1/FVC, $FEF_{25–75}$/FVC, FEF_{25}, FEF_{75}) Design: Cohort Sample: n=232 asthmatic children, age 6–11 years	Avg time: 8 hours maximum Mean: 1–1.5 ppm Range: maximum ~6 ppm	Increment: ~1 ppm β Coefficient (SE); FEV_1/FVC: -0.0073 (0.0016) $FEF_{25–75}$/FVC: -0.2179 (0.0446) % Decrease: FEV_1/FVC: 2.5% $FEF_{25–75}$/FVC: 4.8%
Rabinovitch et al. 2004 Period: 1999–2002 Location: Denver, Colorado	Outcome: Lung function (FEV_1, PEF) Design: Panel study Sample: n=41–63 asthmatics, age 6–12 years	Avg time: 24 hours Mean 1.0 ppm Range: 0.3, 3.5 ppm	Increment: 0.4 ppm No significant associations with lung function end points
Silkoff et al. 2005 Period: 1999–2001 Location: Denver, Colorado	Outcome: Lung function (FEV_1, PEF) Design: Panel Sample: n=16–18, former smokers, age ≥40 years	Pollutant: CO Avg Time: 24 hours Mean: 1 ppm Range: 0.3–3.8 ppm	Increment: 1 ppm Significant association with decreasing FEV_1 in second winter season of study, but not in first (β coefficients reported graphically)
Timonen et al. 2002 Period: 1994 Location: Kuopio, Finland	Outcome: Lung function (FVC, FEV_1, MMEF, AEFV) Design: Panel Sample: n=33 with respiratory symptoms, age 7–12 years	Avg time: 24 hours Mean: 0.5 ppm Range: 0.09–2.4 ppm	Increment: 0.32 mg/m^3 β Coefficient (SE), lag 2 days: Baseline FEV_1 (mL): 11.7 (SE: 5.77, $p<0.05$) Exercise ΔFEV_1 (%): 0.087 (0.26)

Table 3-3. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Respiratory Disease

Study	Design features	CO exposure	Effect size
Asthma and exacerbation of asthma symptoms			
Clark et al. 2010 Period: 1999–2000 Location: British Columbia, Canada	Outcome: Asthma Design: Birth cohort case-control Sample: n=3,248 cases,16,240 controls, age birth–5 years	Avg time: 24 hours Mean: 0.62 mg/m^3 25^{th}–75^{th}%: 0.52–0.71 mg/m^3	Increment: 0.1 mg/m^3 Adjusted OR (95% CI) CO (*in utero* exposure): 1.07 (1.04, 1.11) CO (1^{st} year exposure): 1.10 (1.06, 1.13)
Hwang et al. 2005 Period: 2001 Location: Taiwan	Outcome: Asthma Design: Cross-sectional Sample: n=32,672, age 6–15 years	Avg time: 1 year Mean: 0.66 ppm Range: 0.42–0.96 ppm	Increment: 0.1 ppm Adjusted OR (95% CI) CO: 1.045 (1.017, 1.074) CO+SO_2: 1.066 (1.034, 1.099) CO+PM_{10}: 1.079 (1.047, 1.112) CO+O_3: 1.063 (1.1, 1.474) CO+SO_2+O_3: 1.111 (1.074, 1.15) CO+PM_{10}+ O_3: 1.119 (1.084, 1.155)
Park et al. 2005a Period: 2002 Location: Incheon, Korea	Outcome: Asthma symptoms Design: Panel Sample: n=64 bronchial asthmatics, age 16–75 years	Avg time: 24 hours Mean: 0.6 ppm SD range: 0.09–0.15 ppm	Increment: NR No significant association with asthma symptoms
Rabinovitch et al. 2004 Period: 1999–2002 Location: Denver, Colorado	Outcome: Asthma symptoms, rescue inhaler use Design: Panel study Sample: n=41–63 asthmatics, age 6–12 years	Avg time: 24 hours Mean 1.0 ppm Range: 0.3–3.5 ppm	Increment: 0.4 ppm β Coefficient (SE), 3-day moving avg: Asthma exacerbation: 1.012 (0.913, 1.123) Rescue inhaler: 1.065 (1.001, 1.133)
Rodriguez et al. 2007 Period: 1996–2003 Location: Perth, Australia	Outcome: Respiratory symptoms Design: Panel Population: n=263, age 0–5 years	Avg time: 8 hours Mean 1.4 ppm Range: 0.01–8.0 ppm	Increment: NR OR (95%CI), wheeze/chest rattle, lag 5 days: lag 0 days: 1.089 (0.968, 1.226) lag 5 days: 1.136 (1.016, 1.26) lag 0–5 days: 1.035 (1.005, 1.066)

Table 3-3. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Respiratory Disease

Study	Design features	CO exposure	Effect size
Schildcrout et al. 2006 Period: 1993–1995 Location: 8 North American cities	Outcome: Asthma symptoms; rescue inhaler use Design: Panel Sample: 990 asthmatics, age 5–12 years	Avg time: 24 hours 10th–90th%: 0.4–2.4 ppm	Increment: 1.0 ppm OR (95% CI), asthma symptoms, lag 0 days: CO: 1.08 (1.01, 1.14) CO+NO_2 1.07 (1, 1.14) CO+PM_{10}: 1.08 (1.01, 1.15) CO+SO_2 1.07 (0.99, 1.16)
Silkoff et al. 2005 Period: 1999–2001 Location: Denver, Colorado	Outcome: Asthma symptoms; rescue inhaler use Design: Panel Sample: n=16–18, former smokers, age ≥40 years	Avg time: 24 hours Mean: 1 ppm Range: 0.3–3.8 ppm	Increment: 1 ppm No significant associations with asthma symptoms or rescue medications
Slaughter et al. 2003 Period: 1993–1995 Location: Seattle, Washington	Outcome: Asthma severity; medication use Design: Panel Sample: n=133 asthmatics, age 5–13 years	Avg time: 24 hours Median: 1.47 ppm 25^{th}–75^{th}%: 0.23–1.87 ppm	Increment: 0.67 ppm OR (95% CI), asthma severity, lag 1 day: Asthma severity: 1.21 (1.08, 1.35) Rescue inhaler use: 1.09 (1.03, 1.16)
von Klot et al. 2002 Period 1996–1997 Location: Erfurt, Germany	Outcome: Asthma symptoms; medication use Design: Panel Sample: 53 asthmatics, age 37–77 years	Avg time: 24 hours Mean: 0.8 ppm Range: 0.3–2.3 ppm	Increment: 0.6 mg/m^3 OR (95% CI); wheezing prevalence, 5-day avg: CO: 0 1.13 (1.05, 1.22) CO+$MC_{0.01–2.5}$: 1.15 (1.04, 1.27) CO+$NC_{0.01–0.1}$: 1.09 (0.98, 1.22)
Yu et al. 2000 Period: 1993–1995 Location: Seattle, Washington	Outcome: Asthma symptoms Design: Panel Sample: n=133 asthmatics, age 5–13 years	Avg time: 24 hours Mean: 1.6 ppm Range: 0.65–4.18 ppm	Increment: 1.0 ppm OR (95% CI), lag=2 days: 1.26 (1.09, 1.46)

Table 3-3. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Respiratory Disease

Study	Design features	CO exposure	Effect size
Hospital admissions and emergency room visits related to respiratory disease			
Arbex et al. 2009 Period: 2001–2003 Location: São Paulo, Brazil	Outcome: COPD Design: Time series Sample: All ages	Avg time: 8 hours Mean: 2.71 ppm 25^{th}–75^{th}%: 1.9–3.2 ppm	Increment: 1.3 ppm % Increase (95% CI), lag 0–6 days: CO: 12.9% (1.3, 25.9)
Burnett et al. 2001 Period: 1980–1994 Location: Toronto, Canada	Outcome: Asthma, acute bronchitis/bronchiolitis; croup; pneumonia HAs Design: Time series Sample: <2 years	Avg time: 1 hour Mean: 1.18 ppm 25^{th}–75^{th}%: 1.3–2.3 ppm	Increment: 1.9 ppm % Increase (t value), lag 0–1 day: CO: 19.20% (3.48) CO+O_3: 14.30% (2.6)
Cakmak et al. 2006 Period: 1993–2000 Location: 10 Canadian cities	Outcome: Respiratory disease HAs Design: Time-series Sample: All ages	Avg time: 24 hours Mean: 0.8 ppm Range: 0.0–6.5 ppm	Increment: 0.8 ppm % Increase(95% CI), lag 2.8 days: CO: 0.60% (0.20, 1) CO+SO_2+NO_2+O_3: -0.20% (-0.70, 0.30)
Karr et al. 2006 Period: 1995–2000 Location: Southern California	Outcome: Acute bronchiolitis HAs Design: Case-crossover Sample: Age ≤1 year	Avg time: 24 hours Mean: 17 ppm Range: 0.004–9.6 ppm	Increment: 1.36 ppm OR (95% CI), lag 1 day: All: 0.99 (0.96, 1.02) Age 25–29 weeks: 0.86 (0.68, 1.1)
Linn et al. 2000 Period 1992–1995 Location: Los Angeles, California	Outcome: Asthma, COPD, pulmonary HAs Design: Time-series Sample: Age 0–29, ≥30 years	Avg time: 24 hours Mean: 1.0–2.1 ppm Range: 0.3–5.3 ppm	Increment: 1.0 ppm β (SE): Asthma, <30 years: 0.036 (0.016, p<0.05) Asthma ≥30 years: 0.028 (0.010, p<0.05) COPD, ≥30 years: 0.019 (0.007, p<0.05)
Lin et al. 2003 Period: 1981–1993 Location: Toronto, Canada	Outcome: Asthma HAs Design: Case-crossover Sample: Age 6–12 years	Avg time: 24 hours Mean: 1.18 ppm Range: 0–6.1 ppm	Increment: 0.5 ppm OR (95% CI), lag 1 day: Males CO: 1.05 (1, 1.11) Males CO+PM: 1.05 (0.99, 1.11) Females CO: 1.00 (0.93, 1.06) Females CO+PM: 1.00 (0.93, 1.07)
Lin et al. 2005 Period: 1998–2001 Location: Toronto, Canada	Outcome: Respiratory infection HAs Design: Case-crossover Sample: Age <15 years	Avg time: 24 hours Mean: 1.16 ppm Range: 0.38–2.45 ppm	Increment: 0.44 ppm OR (95% CI), lag 0–5 days: Males, CO: 1.13 (1.02, 1.25) Males, CO+PM: 1.08 (0.97, 1.20) Females, CO: 1.05 (0.93, 1.18) Females, CO+PM: 1.02 (0.90, 1.15)

Table 3-3. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Respiratory Disease

Study	Design features	CO exposure	Effect size
Peel et al. 2005 Period: 1993–2000 Location: Atlanta, Georgia	Outcome: Asthma; COPD, pneumonia EDVs Design: Time-series Sample: Ages all, 2–18 years	Avg time: 1 hour maximum Mean: 1.8 ppm 10^{th}–90^{th}%: 0.5–3.4 ppm	Increment: 1.0 ppm RR (95% CI); lag 0–13 days: All respiratory: 1.066 (1.045, 1.087) Asthma: 1.076 (1.047, 1.105) Pneumonia: 1.045 (1.011, 1.080) COPD: 1.032 (0.975, 1.092), 1.026 (1.004, 1.048; lag=0–2 days) No significant associations after adjustment for PM_{10}, NO_2, or O_3
Slaughter et al. 2005 Period: 1995–2001 Location: Spokane, Washington	Outcome: Respiratory, asthma; COPD, respiratory infection HAs and EDVs Design: Time-series Sample: All ages, adults	Avg time: 24 hours 5^{th}–95^{th}%: 1.25–3.05 ppm	Increment: 1.0 ppm RR (95% CI); lag 3 days: Respiratory EDV:1.03 (1.00, 1.06) Asthma EDV: 1.06 (1.00, 1.11) COPD EDV, Adults: 1.01 (0.93, 1.10) Respiratory HA: 0.99 (0.96, 1.03) Asthma HA: 1.00 (0.91, 1.11) COPD HA: Adults: 0.97 (0.88, 1.06)
Tolbert et al. 2007 Period: 1993–2004 Location: Atlanta, Georgia	Outcome: Asthma; COPD; URI, pneumonia; bronchiolitis EDVs Design: Time-series Sample: All ages	Avg time: 1 hour maximum Mean: 1.6 ppm Range: 0.1–7.7 ppm	Increment: 1.22 ppm RR (95% CI), lag 3 days: Respiratory diseases: 1.016 (1.009, 1.022) Not significant after adjustment for O_3, NO_2, or PM_{10}

Table 3-3. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Respiratory Disease

Study	Design features	CO exposure	Effect size
Yang et al. 2003 Period: 1986–1998 Location: Vancouver, Canada	Outcome: Respiratory disease HA Design: Case-crossover Sample: Ages <3; ≥65 years	Avg time: 24 hours Mean: 0.98 ppm 25^{th}–75^{th}%: 0.62–1.16 pm	Increment: 0.54 ppm OR (95% CI), lag 1 day: <3 years, CO: 1.04 (1.01, 1.07) <3 years, CO+O_3: 1.04 (1.01, 1.07) <3 years, CO+O_3+NO_2+SO_2: 1.02 (0.96, 1.08) ≥65 years, CO: 1.02 (1.00, 1.04) ≥65 years, CO+O_3: 1.02 (1.00, 1.04) ≥65 years, CO, O_3, NO_2, SO_2: 0.96 (0.93, 1.00)
Zanobetti and Schwartz 2006 Period: 1995–1999 Location: Boston, Massachusetts	Outcome: Pneumonia HAs Design: Case-crossover Sample: All ages	Avg time: 24 hours 25^{th}–75^{th}%: 0.39–0.60 ppm	Increment: 0.475 ppm % Increase (95% CI): 5.45 (1.10, 9.51; lag 0 days) 5.12 (0.83, 9.16; lag 0–1 day)

AEFV = area under the expiratory flow-volume curve; Avg = average; CI = confidence interval; CO = carbon monoxide; COPD = chronic obstructive pulmonary disease; EDV = emergency department visit; FEF = forced expiratory flow; $FEF_{25–75}$ = forced expiratory flow at 25–75% of vital capacity; FEV_1 = forced expiratory volume at 1 second; FVC = forced vital capacity; HA = hospital admission, IHD = ischemic heart disease; MC = particle mass concentration; MMEF = maximal midexpiratory flow; NC = particle number concentration; NR = not reported; OR = odds ratio; PEF = peak expiratory flow; PNC = particle number concentration/count; RR = relative risk; SD = standard deviation; SE = standard error; URI = upper respiratory infection

California examined lung function in a cohort of 232 asthmatic children (age 6–11 years) and found that long-term average exposures to carbon monoxide in infancy and childhood (age 0–6 years) was associated with significant decreasing forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) and forced midexpiratory flow rate ($FEF_{25–75}$)/FVC (Mortimer et al. 2008). Mean air carbon monoxide concentrations during the study period ranged from approximately 1 to 1.5 ppm, with the highest values ≤6 ppm. The effect sizes (per 1 ppm increase in air carbon monoxide concentration) were approximately 2.5% decrease in FEV_1/FVC and 4.8% decrease in $FEF_{25–75}$/FVC. A panel study conducted in Denver, Colorado (1999–2002) examined lung function in asthmatic children (n=41–63, age 6–12 years) and did not find a significant association between air carbon monoxide concentration and pulmonary function end points, FEV_1, and peak expiratory flow (PEF) (Rabinovitch et al. 2004). The mean air carbon monoxide concentration in the study was 1.0 ppm (range: 0.3–3.5 ppm). A similar panel study conducted in Kuopio, Finland examined lung function in children (n=33, age 7–12 years) who were diagnosed with chronic respiratory disease symptoms (Timonen et al. 2002). Increasing air carbon monoxide concentration was associated with decreasing FVC and FEV_1, when measured at rest, but not during exercise. Other air pollutants were also associated with decrements in baseline pulmonary function (particulate matter, NO_2); however, multi-pollutant models were not explored. The air carbon monoxide concentrations in this study were similar to that in the Rabinovitch et al. (2004) study (mean 0.6 mg/m^3 [0.5 ppm], range: 0.1–2.8 mg/m^3 [0.09–2.4 ppm]). A cross-sectional cohort study conducted in Taiwan (1995–1996) included asthmatic children (n=941, age 8–13 years; Chen et al. 1999). A significant association was found between increasing air carbon monoxide concentration and decreasing FVC; however, multi-pollutant models were not explored. Peak daily air carbon monoxide concentrations ranged from 0.4 to 3.6 ppm. Fischer et al. (2002) examined possible associations between carbon monoxide and pulmonary function in a panel of children (n=68, age 10–11 years) in The Netherlands. Increasing air carbon monoxide concentration was not associated with FVC, FEV_1, PEF, or maximal midexpiratory flow (MMEF); however, it was associated with increasing levels of expired endogenous nitric oxide radical (NO•). Here again, multi-pollutant models were not explored. The mean air carbon monoxide concentration in this study was 0.9 mg/m^3 (0.8 ppm) (range: 0.3–1.5 mg/m^3 [0.3–1.3 ppm]).

Results of studies of pulmonary function in adults have also been mixed and conflicting (Canova et al. 2010; Lagorio et al. 2006; Penttinen et al. 2001; Silkoff et al. 2005). A panel study of adult asthmatics (n=40, mean age 39 years) conducted in Padua, Italy (2004–2005) followed 19 subjects for 2 years. Increasing air carbon monoxide concentration was associated with decreasing morning and evening PEF, and the association persisted when adjusted for co-exposure to SO_2, NO_2, and particulate matter (Canova

et al. 2010). Another panel study of adult nonsmoking asthmatics (n=57, mean age 53 years) conducted in Helsinki, Finland (1996–1997) found that increasing air carbon monoxide concentration was associated with decreasing PEF; however, the association was not significant when adjusted for particulate matter (Penttinen et al. 2001). The mean air carbon monoxide concentration was 0.4 mg/m^3 (0.3 ppm) (range: 0.1–1.1 mg/m^3 [0.09–0.96 ppm]). A panel study of adult former smokers, diagnosed with chronic obstructive pulmonary disease (COPD), conducted in Denver, Colorado (1999–2001, n=16–18, age ≥40 years) found somewhat conflicting results. A significant association between increasing air carbon monoxide concentration and decreasing FEV_1 was found in the second winter season of the study, but not in the first winter season of the study (Silkoff et al. 2005). Air carbon monoxide concentrations were not significantly different in the two seasons (mean: 1.1–1.2 ppm; ranges: 0.3–3.8 and 0.4–2.8 ppm), although concentrations of other air pollutants (e.g., PM_{10}, $PM_{2.5}$, and NO_2) were higher in the second winter season, suggesting that other air pollutants may have contributed to the associations attributed to carbon monoxide in single-pollutant models. The study conducted by Lagorio et al. (2006) is notable because it included relatively high air carbon monoxide concentrations (mean range: 1.8 [spring]–10.6 [winter] ppm; range: 1.5–25.1 ppm). This panel study examined adults (n=29, age 18–80 years) in Rome, Italy (1999) who were diagnosed with asthma, COPD, or ischemic heart disease. Increasing air carbon monoxide concentration was not significantly associated with lung function parameters, and multi-pollutant models were not explored. A panel study conducted in Incheon, Korea that examined lung function in asthmatics (n=57, ages 16–75 years) found a significant association between air carbon monoxide concentrations and decreasing PEF; however, multi-pollutant models were not explored (Park et al. 2005a). The mean air carbon monoxide concentration was 0.6 ppm.

Studies of Asthma Incidence (or Prevalence) and Exacerbation of Asthma Symptoms. A birth cohort case-control study (n=3,248 cases, 16,240 controls) conducted in British Columbia, Canada, examined associations between exposures to carbon monoxide *in utero* or in the first year after birth and diagnoses of asthma up to ages 5 years (Clark et al. 2010). The odds ratio for asthma diagnosis was 1.07 (95% CI: 1.04, 1.11) for *in utero* exposure and 1.10 (95% CI: 1.06, 1.13) for exposure during the first year, both expressed per 0.1 mg/m^3 (0.09 ppm) increase in carbon monoxide concentration. A cross-sectional study examined asthma diagnoses among school-age children (n=32,672, age 6–15 years) in Taiwan (Hwang et al. 2005). The odds ratio for 0.1 ppm increases in air carbon monoxide concentration (annual average) was estimated to be 1.045 (95% CI: 1.017, 1.074) and persisted after adjustment for O_3, PM_{10}, and/or SO_2 in multi-pollutant models. The mean air carbon monoxide concentration was 0.6 ppm (range: 0.4–0.9 ppm). Several studies have examined possible associations between ambient air carbon monoxide concentrations and asthma symptoms (e.g., coughing, wheezing, chest tightness, shortness of breath,

inhaler use). Results of these studies have been mixed; however, collectively, these studies provide evidence for associations between increasing air carbon monoxide concentration and increasing severity of asthma (Park et al. 2005a; Rabinovitch et al. 2004; Rodriguez et al. 2007; Schildcrout et al. 2006; Silkoff et al. 2005; Slaughter et al. 2003; von Klot et al. 2002; Yu et al. 2000). One of the larger studies examined asthma symptoms in a panel of 990 children (ages 5–12 years) in eight North American cities (1993–1995, Schildcrout et al. 2006). A 1 ppm increase in air carbon monoxide concentration (lag=0 days) was associated with an odds ratio of 1.08 (95% CI: 1.01, 1.14) for asthma symptoms. The association remained significant after adjusting for NO_2, PM_{10}, or SO_2 in two-pollutant models. Air carbon monoxide concentrations ranged from approximately 0.4 to 2.4 ppm (10^{th}–90^{th} percentile range). Significant associations with increasing carbon monoxide concentration were also found when rescue medication use was evaluated as the asthma symptom end point.

The above results are consistent with those of several smaller panel studies. A study conducted in Seattle, Washington examined asthma symptoms (Yu et al. 2000) and asthma severity (Slaughter et al. 2003) in a panel of 133 asthmatic children (age 5–13 years). The mean air carbon monoxide concentration was 1.6 ppm (range: 0.6–4.8 ppm; Yu et al. 2000). Both studies found significant associations between ambient air carbon monoxide and asthma symptoms. In the Yu et al. (2000) study, a 1 ppm increase in air carbon monoxide (lag=2 days) was associated with an odds ratio of 1.26 (95% CI: 1.09, 1.46) for asthma symptoms. In the Slaughter et al. (2003) study, a 0.67 ppm increase in air carbon monoxide concentration was associated with an odds ratio of 1.21 (95% CI: 1.08, 1.35) for an increase in severity of asthma attack. A significant association with increasing carbon monoxide concentration was also found when rescue medication use was evaluated as the asthma severity end point (Slaughter et al. 2003). Rabinovitch et al. (2004) also found a significant association between increasing air carbon monoxide concentrations and increasing rescue medication use in a study of children in Denver, Colorado (1999–2002, n=41–63, age 6–12 years). A panel study of 263 children (age 0–5 years) in Perth, Australia, who were not diagnosed with asthma, also found a significant association between air carbon monoxide concentration and wheezing/chest rattle (Rodriguez et al. 2007).

Results of studies conducted in older asthmatic subjects have been mixed (Park et al. 2005a; Silkoff et al. 2005; von Klot et al. 2002). In a panel of 53 asthmatic adults (age 37–77 years) in Erfurt, Germany (1996–1997), a 0.6 mg/m^3 (0.5 ppm) increase in air carbon monoxide concentration (5-day average) was associated with an odds ratio of 1.13 (95% CI: 1.05, 1.22) for prevalence of wheezing; however, the association was attenuated when adjusted for ultrafine particle number concentration in air. Two other panel studies of asthmatics, one conducted in Incheon, Korea (2002, n=54, age 16–76 years; Park et al.

2005a) and one in Denver, Colorado (n=16 or 18, age ≥40 years, Silkoff et al. 2005), did not find significant associations between air carbon monoxide concentrations and asthma symptoms.

Studies of Hospital Admissions and Emergency Room Visits Related to Respiratory Symptoms. A large number of studies have examined associations between ambient carbon monoxide concentrations and rates of hospital admissions (e.g., Burnett et al. 2001; Cakmak et al. 2006; Karr et al. 2006; Lin et al. 2003, 2005; Linn et al. 2000; Slaughter et al. 2005; Yang et al. 2003; Zanobetti and Schwartz 2006) or emergency room visits related to respiratory disease (e.g., Arbex et al. 2009; Peel et al. 2005; Slaughter et al. 2005; Tolbert et al. 2007). Collectively, these studies provide evidence for associations between increasing carbon monoxide concentrations and increasing risk of respiratory symptoms that trigger the need for medical assistance. However, only a few studies have examined associations in multi-pollution models; therefore, relative contributions of other air pollutants to the reported outcomes are highly uncertain.

In studies that did evaluate multi-pollutant models, the associations between carbon monoxide concentrations and outcomes persisted in some studies (Burnett et al. 2001; Lin et al. 2003; Yang et al. 2003), but not in others (Lin et al. 2005; Peel et al. 2005; Tolbert et al. 2007). In a time-series analysis conducted in Toronto, Canada (1980–1994), Burnett et al. (2001) found a significant association between increasing air carbon monoxide concentrations and hospital admissions for asthma, acute bronchitis/ bronchiolitis, croup, and pneumonia in children (age <2 years). A 1.9 ppm increase in air carbon monoxide concentration (lag: 0–1 day) was associated with a 19.2% increase in hospital admissions, which remained elevated when adjusted for air O_3 concentration. A case-crossover study of hospital admissions of children (ages 6–12 years) for asthma in Toronto, Canada (1981–1993) found that a 0.5 ppm increase in air carbon monoxide concentration was associated with an odds ratio (lag: 1 day) of 1.05 (95% CI: 1.00, 1.11) in males but not in females (odds ratio: 1.00, 95% CI: 0.93, 1.06) and persisted in males after adjustment for particulate matter (Lin et al. 2003). Another case-crossover study directed at respiratory infections in children (age <15 years, males), also conducted in Toronto, Canada (1988–2001), estimated the odds ratios for a 0.44 ppm increase in air carbon monoxide concentration (lag: 0–5 days) to be 1.13 (95% CI: 1.01, 1.25) and 1.08 (95% CI: 0.97, 1.20) after adjustment for PM_{10} and $PM_{10-2.5}$ (Lin et al. 2005), respectively. Odds ratios for females were not significant. Yang et al. (2003) conducted a case-crossover study of hospital admissions for various respiratory disease categories in Vancouver, Canada (1986–1998) and found that an increase in carbon monoxide concentration of 0.5 ppm was associated with odds ratios of 1.04 (95% CI: 1.01, 1.07) for children (age <3 years) and 1.02 (95% CI: 1.00, 1.04) for elderly adults (age ≥65 years). The associations persisted when adjusted

for air O_3 concentration. In a time-series analysis of >400,000 emergency room visits for respiratory disease in Atlanta, Georgia (1993–2000), the estimated risk ratio for a 1 ppm increase in air carbon monoxide concentration (lag: 0–13 days) was 1.076 (95% CI: 1,047, 1.105) for all ages and 1.019 (95% CI: 1.004, 1.035) for asthma visits in children aged 2–18 years (Peel et al. 2005). The associations were not significant when adjusted for other air pollutants in two-pollutant models (e.g., PM_{10}, NO_2, or O_3). This study also found a significant risk ratio for emergency room visits related to pneumonia (risk ratio: 1.045, 95% CI: 1.011, 1.080; lag: 0–13 days). A revisit to the Atlanta, Georgia study, with the study period expended to 1993–2004 (Tolbert et al. 2007), found essentially similar results as reported in Peel et al. (2005). The risk ratio for all emergency room visits for all respiratory disease categories was 1.016 (95% CI: 1.009, 1.022) per 1.22 ppm increase in 1-hour maximum carbon monoxide concentration (lag: 3 days); however, the association was attenuated in models that adjusted for O_3, NO_2, or PM_{10}.

Studies that examined COPD admissions and emergency room visits yielded mixed results (Arbex et al. 2009; Peel et al. 2005; Slaughter et al. 2005; Yang et al. 2003). In the Yang et al. (2003) time-series study, conducted in Vancouver, Canada (1994–1998), the risk ratio for a 0.5 ppm increase in air carbon monoxide concentration (lag: 0–6 days) was 1.14 (95% CI: 1.03, 1.23) for COPD hospital admissions. A study conducted in São Paulo, Brazil found a 12.9% (95% CI: 1.3, 25.9) increase in COPD-related emergency room visits in association with a 1.9 ppm increase in air carbon monoxide concentration (lag: 0–6 days) (Arbex et al. 2009). On the other hand, significant associations between air carbon monoxide concentration and COPD hospital admissions or emergency room visits were not found in a time-series study conducted in Spokane, Washington (1995–2001; Slaughter et al. 2005). In the Peel et al. (2005) time-series study conducted in Atlanta, Georgia (1993–2000), relative risks for emergency room visits for COPD per 1 ppm increase in carbon monoxide concentration were 1.03 (95% CI: 1.00, 1.05) for lag 0–2 days and 1.03 (95% CI: 0.98, 1.09) for lag 0–13 days. The air carbon monoxide concentrations in these studies were similar (10^{th}–90^{th} percentile range: approximately 1.25–4.3 ppm)

Animal Studies. Most studies evaluating adverse respiratory effects of carbon monoxide in animals were conducted using carbon monoxide exposures that produced much higher COHb concentrations (i.e., COHb >50%) than those evaluated in controlled clinical studies in humans. Even at these high exposures, results of animal studies support those of controlled clinical studies indicating that the respiratory tract is not a major target organ for carbon monoxide. Animal studies published prior to 2000 have been reviewed in detail by the EPA (1991, 2000); therefore, these reviews largely form the basis of the following discussions for animals studies published prior to 2000.

Studies investigating adverse respiratory effects of carbon monoxide have evaluated the lung function and morphology, with most studies evaluating effects of brief exposure (i.e., a few minutes to <1 hour). In acute-duration studies, alterations in lung function (decreased compliance and increased airway resistance) were observed in rabbits and cats exposed to 8,000–28,400 ppm carbon monoxide for <1 hour (COHb >60%); however, no changes in lung function were observed in dogs exposed to 8,000–14,000 ppm carbon monoxide for 10–20 minutes (COHb 18–59%) (EPA 1991). In an intermediate-duration study, continuous exposure of rats to 50 ppm carbon monoxide for 21 days (COHb not reported) did not alter the pulmonary pressure-flow relationship (Carraway et al. 2002). Blood COHb concentrations were not reported for the Carraway et al. (2002) study; however, the CFK rat model predicts that COHb concentrations at the end of the 21-day exposure period would have been approximately 7%. Results of these studies suggest that carbon monoxide-induced changes in pulmonary function occur only following exposure to high carbon monoxide concentrations.

Studies evaluating effects of acute-duration carbon monoxide exposure on lung morphology have reported conflicting results (EPA 1991). Minimal changes in type 2 epithelial cells (fragmentation of lamellar bodies) and nonciliated bronchiolar cells (dilation of smooth endoplasmic reticulum and increased mitochondrial cristae) were reported in mice exposed to 50–90 ppm carbon monoxide for 1–5 days (COHb <10%) (Niden 1971). The study results were not presented in detail and the toxicological significance of these finding is not known; however, changes to the smooth endoplasmic reticulum and mitochondrial cristae are consistent with a compensatory response to altered electron transport due to possible carbon monoxide-induced interference with cytochromes involved in electron transport. In rabbits exposed to 8,000 ppm for 30 minutes (COHb 63%), examination of lung tissue by electron microscopy showed alveolar epithelial edema with detachment of the endothelium from the basement membrane (Fein et al. 1980). However, no morphological changes in lung tissue were observed following acute exposure (30 minute to 5 hours) of dogs and rabbits at carbon monoxide exposure producing blood COHb levels of 18–39% or following intermediate-duration exposure (6 weeks) of rabbits to 200 ppm carbon monoxide (COHb 11.9–19%) (Fisher et al. 1969; Hugod 1980). Results of a recent study in rats exposed chronically to 200 ppm carbon monoxide (COHb 14.7%) for 20 hours/day for 72 weeks showed no histopathological changes to lung tissue (Sørhaug et al. 2006).

Cardiovascular Effects. Cardiovascular effects of inhalation exposures to carbon monoxide have been evaluated in controlled human clinical studies, epidemiology studies, and various animal models (monkeys, dogs, rats, and rabbits). In general, these studies provide convincing evidence for adverse cardiovascular effects in association with carbon monoxide exposures that result in blood COHb levels

≥2.4%, with effects occurring at the lowest levels in subjects with compromised cardiovascular function (e.g., coronary artery disease). Results of controlled clinical studies in patients with coronary artery disease show that acute-duration exposure to carbon monoxide at levels producing blood COHb levels between 2.4 and 5.9% exacerbates underlying cardiovascular disease, including enhancing myocardial ischemia and increasing cardiac arrhythmias.

In healthy subjects, acute exposure to carbon monoxide at concentrations producing blood COHb levels of 3.35 and 20.5% resulted in compensatory cardiovascular responses and decreased exercise performance consistent with COHb-induced decreased O_2 carrying capacity of the blood; however, subjects did not exhibit exercise-induced adverse cardiovascular effects (e.g., evidence of myocardial ischemia or cardiac arrhythmias). Continuous exposure of healthy subjects, which included smokers, to carbon monoxide resulting in blood COHb levels of 2.4 and 5.1% produced several P-wave deviations (P-wave inversion, increased amplitude, decreased amplitude, and changes in P-wave direction) under resting conditions, although similar findings have not been reported in other studies.

Epidemiological studies of exposure to carbon monoxide and cardiovascular outcomes have yielded mixed results, although, in general, the weight of evidence suggests that risks of certain specific outcomes are associated with increasing ambient carbon monoxide concentrations (hospitalizations and emergency room visits related to congestive heart failure, ischemic heart disease, myocardial infarction, and stroke). The corroborated observations of associations between carbon monoxide exposure and outcomes related to ischemic heart disease are particularly provocative in the context of results of human clinical studies in which carbon monoxide-induced hypoxia exacerbated ischemia symptoms in patients with coronary artery disease. Mean ambient air carbon monoxide concentrations reported in studies that have found carbon monoxide-associated cardiovascular outcomes ranged from 0.5 to 10 ppm, with maximum values ranging from 2 to 50 ppm. These values correspond to approximate steady-state blood COHb levels of <2% for the mean and <10% for the maximum.

Studies in animals have investigated adverse cardiovascular effects of carbon monoxide exposure over a much wider range of exposure conditions (e.g., exposure concentration and duration) and have evaluated additional outcome measures that are not possible to assess in humans. These studies provide further evidence of adverse cardiovascular effects of carbon monoxide exposure, including compensatory alterations in hemodynamics, cardiac hypertrophy, cardiac arrhythmias, and possibly atherosclerosis.

Human Clinical Studies

Studies of Patients with Cardiovascular Disease. The effects of acute-duration carbon monoxide exposure on cardiovascular function have been evaluated in several controlled clinical studies in patients with underlying cardiovascular disease (Adams et al. 1988; Allred et al. 1989, 1991; Anderson et al. 1973; Dahms et al. 1993; Hinderliter et al. 1989; Kleinman et al. 1989, 1998; Leaf and Kleinman 1996b; Sheps et al. 1987, 1990) and in healthy subjects (Adir et al. 1999; Davies and Smith 1980; Hausberg and Somers 1997; Horvath et al. 1975; Kizakevich et al. 2000; Morse et al. 2008; Resch et al. 2005; Vogel and Gleser 1972; Zevin et al. 2001). In general, similar effects of acute-duration carbon monoxide exposure were not observed in studies on healthy study subjects, due to functional cardiovascular compensatory mechanisms (e.g., vasodilation and increased cardiovascular output) that protect against COHb-induced tissue hypoxia. Mechanisms contributing to cardiac effects of carbon monoxide in patients with coronary artery disease have not been conclusively established. Under conditions of cardiac ischemia, tissue hypoxia secondary to elevated COHb levels is thought to be a contributing factor. However, other direct cellular effects of carbon monoxide on cardiac muscle may also be important. These include modulation of coronary arteriole calcium-activated potassium channels. These channels are required for membrane hyperpolarization and flow-induced dilation and are reversibly activated by carbon monoxide under normoxic conditions, but they are inhibited when hypoxic/ischemic conditions prevail (Wang and Wu 1997; Wang et al. 1997a, 1997b).

Controlled clinical studies conducted in small numbers of patients with underlying coronary artery disease have evaluated effects of carbon monoxide exposure on myocardial ischemia. Patients evaluated had a diagnosis of coronary artery disease with exertional angina (i.e., exercise-induced angina or stable angina) and/or ventricular arrhythmia. Most studies were conducted using a randomized, double-blind, crossover design, with cardiovascular function assessments conducted during exercise challenge, either during or immediately following carbon monoxide exposure. Carbon monoxide exposures (concentration and duration) were designed to reach target blood COHb levels between 2 and 6%; exposure durations ranged from 1 to 4 hours via an environmental chamber, with carbon monoxide concentrations ranging from 42 to 357 ppm. Effects of carbon monoxide exposure were evaluated by comparison to assessments conducted during room air exposure and at corresponding COHb concentrations of <1%. Additional experimental details for each study are summarized in Table 3-4.

Results of controlled clinical studies in patients with coronary artery disease show that acute-duration exposure to carbon monoxide at levels producing blood COHb levels between 2.4 and 5.9% exacerbates

Table 3-4. Effects of Acute-Duration Exposure to Carbon Monoxide on Cardiovascular Function in Patients with Coronary Artery Disease

Reference	Study subjects	Design	Exposure	Outcomes assessed	Results
Adams et al. 1988	30 nonsmokers (22 men, 8 women; mean age: 58 years; age range 36–75 years) diagnosed with coronary artery disease with exertional angina pectoris	Randomized, cross-over, double-blind; exercise challenge tests (bicycle) administered immediately following each exposure.	Patients administered one of the following treatments (via environmental chamber) on 2 test days: 1-hour exposure to room air (measured COHb prior to exercise challenge: 1.6±0.1%[a]) or CO (measured COHb prior to exercise challenge: 5.9±0.1%[a]; mean CO concentration: 100–200 ppm). COHb measured by CO-Ox.	Duration of exercise, time-to-onset of exercise-induced angina symptoms and ischemic ST-segment changes (EKG), radionuclide ventriculograph (ventricular ejection fraction), systolic blood pressure. Results for CO exposure compared to room air exposure.	Mean duration of exercise: Decreased by 6.5% ($p<0.05$) following CO exposure, compared to air exposure. Time-to-onset of angina symptoms: Using actuarial analysis, subjects more likely to experience angina symptoms earlier in exercise following CO vs. air exposure ($p<0.05$). Time-to-onset of ischemic ST-segment changes: No effect of exposure. Systolic blood pressure: No effect of exposure. Ventricular ejection fraction: Left ventricular ejection fraction at submaximal exercise was decreased following CO exposure, compared to air exposure ($p<0.05$). NOAEL: Not established LOAEL: COHb 5.9%

Table 3-4. Effects of Acute-Duration Exposure to Carbon Monoxide on Cardiovascular Function in Patients with Coronary Artery Disease

Reference	Study subjects	Design	Exposure	Outcomes assessed	Results
Allred et al. 1989, 1991	63 male nonsmokers (age range: 41–75 years) diagnosed with coronary artery disease with exertional angina pectoris and ischemic ST-segment changes on EKG	Randomized, cross-over, double-blind; exercise challenge tests (treadmill) administered prior to and immediately following each exposure.	Patients administered one of the following treatments (via environmental chamber) on 3 test days: 1-hour exposure to room air (measured COHb prior to exercise challenge: 0.70±0.02%[a]), low CO (measured COHb prior to exercise challenge: 2.38±0.05%[a]; mean CO concentration: 117 ppm, range 42–202 ppm), or high CO (measured COHb: 4.66±0.09%[a]; mean CO concentration: 253 ppm, range 143–357 ppm). COHb measured by GC.	Time-to-onset of exercise-induced angina symptoms and ischemic ST-segment changes (EKG), total exercise duration, heart rate-systolic blood pressure double product. Effects determined based on comparison (percent change) for pre- and post-exposure exercise challenge outcomes on each test day. Results for each CO exposure compared to room air exposure.	Time-to-onset of angina symptoms: Decreased by 4.2% (p=0.027) for low CO exposure and 7.1% (p=0.002) for high CO exposure, compared to room air exposure. Time-to-onset of ischemic ST-segment changes: Decreased by 5.1% (p=0.01) for low CO exposure and 12.1% (p≤0.0001) for high CO exposure, compared to room air exposure. Mean duration of exercise: Decreased by 1.7% (p=0.29) for low CO exposure and 6.2% (p≤0.0001) for high CO exposure, compared to room air exposure. Heart rate-systolic blood pressure double product: No effect of CO exposure. NOAEL: Not established LOAEL: COHb 2.38%

Table 3-4. Effects of Acute-Duration Exposure to Carbon Monoxide on Cardiovascular Function in Patients with Coronary Artery Disease

Reference	Study subjects	Design	Exposure	Outcomes assessed	Results
Anderson et al. 1973	10 men (5 smokers, 5 nonsmokers; mean age: 49.9 years) diagnosed with coronary artery disease with exertional angina pectoris	Randomized, cross-over, double-blind; following COHb elevation to target levels, patients were administered exercise challenge test (treadmill) under maintenance CO exposure.	Patients administered one of the following treatments (via environmental chamber) on 3 test days: 4-hour exposure to room air (measured COHb, prior to exercise challenge: 1.3%), low CO (measured COHb: 2.9%; CO concentration: 50 ppm), or high CO (measured COHb: 4.5%; CO concentration: 100 ppm). COHb measured by spectrometry.	Time-to-onset and duration of angina symptoms.	Time-to-onset of angina symptoms: Decreased by 4.2% (p=0.027) for low CO exposure and 7.1% (p=0.002) for high CO exposure, compared to room air exposure. Duration of angina symptoms: No effect for low CO exposure; duration increased (p<0.01) for high CO exposure, compared to room air exposure. NOAEL: Not established LOAEL: COHb 2.9%
Dahms et al. 1993	33 nonsmokers (28 men, 5 women; mean age: 58 years; age range: 36–75 years) diagnosed with coronary artery disease with chronic ventricular arrhythmias	Randomized, cross-over, double-blind; following COHb elevation to target levels, patients were administered exercise challenge test (treadmill) under maintenance CO exposure.	Patients administered one of the following treatments (via environmental chamber) on 3 test days: 1-hour exposure to room air (measured COHb by CO-Ox, prior to exercise challenge: 0.7), low CO (measured COHb: 3.2%; mean CO concentration: 159 ppm), or high CO (measured COHb: 5.1%; mean CO concentration: 292 ppm). Maintenance exposure on the CO exposure days was to 19 and 31 ppm for the low and high COHb exposures, respectively. COHb measured by CO-Ox.	Frequency of ventricular arrhythmias evaluated during exposure, during exercise (under maintenance exposure), 1–6 hours after cessation of exposure, and 7–16 hours after cessation of exposure. Primary outcome was frequency of exercise-induced ventricular arrhythmias. Results for CO exposure compared to room air exposure.	No effect of CO, compared to room air, on frequency of ventricular arrhythmia under any conditions assessed. NOAEL: COHb 5.9% LOAEL: Not established

Table 3-4. Effects of Acute-Duration Exposure to Carbon Monoxide on Cardiovascular Function in Patients with Coronary Artery Disease

Reference	Study subjects	Design	Exposure	Outcomes assessed	Results
Hinderliter et al. 1989	10 nonsmokers (7 males, 3 females; mean age: 61 years) diagnosed with coronary artery disease with angina and low baseline ventricular ectopy	Randomized, cross-over, double-blind; exercise challenge tests (bicycle) administered immediately following each exposure.	Patients administered one of the following treatments (via environmental chamber) on 3 test days: 1-hour exposure to room air (measured COHb following exposure: 1.4±0.5%[b]), low CO (measured COHb following exposure: 4.0±0.4%[b]; CO concentration: 100 ppm), or high CO (measured COHb following exposure: 5.8±0.4%[b]; CO concentration: 200 ppm). COHb measured by CO-Ox.	Ventricular arrhythmia. Results for CO exposure compared to room air exposure.	No effect of CO, compared to room air, on frequency of ventricular arrhythmia. NOAEL: COHb 5.9% LOAEL: Not established

Table 3-4. Effects of Acute-Duration Exposure to Carbon Monoxide on Cardiovascular Function in Patients with Coronary Artery Disease

Reference	Study subjects	Design	Exposure	Outcomes assessed	Results
Kleinman et al. 1989	24 male nonsmokers (mean age: 59 years; age range: 49–66 years) diagnosed with coronary artery disease with stable angina pectoris	Randomized, cross-over, double-blind; exercise challenge tests (bicycle) administered immediately following each exposure.	Patients administered one of the following treatments (via environmental chamber) on 2 test days: 1-hour exposure to room air (measured COHb following exposure: 1.4±0.1%[c]) or CO (measured COHb following exposure: 3.0±0.1%[c]; mean CO concentration: 100 ppm). COHb measured by CO-Ox.	Time-to-onset and duration of angina symptoms, time-to-onset of ischemic ST-segment changes (EKG), heart rate, systolic blood pressure, oxygen update at angina. Results for CO exposure compared to room air exposure.	Time-to-onset of angina: Decreased by 5.89% ($p<0.046$) following CO exposure, compared to room air exposure. Duration of angina symptoms: Increased by 8.33% (not statistically significant) following CO exposure, compared to room air exposure. Time-to-onset of ischemic ST-segment changes: Decreased by 19.05% ($p<0.044$) following CO exposure, compared to room air exposure. Oxygen uptake at angina: Decreased by 2.15% ($p<0.04$) following CO exposure, compared to room air exposure. Systolic blood pressure: No effect of exposure. Heart rate: No effect of exposure. NOAEL: Not established LOAEL: COHb 3.0%

Table 3-4. Effects of Acute-Duration Exposure to Carbon Monoxide on Cardiovascular Function in Patients with Coronary Artery Disease

Reference	Study subjects	Design	Exposure	Outcomes assessed	Results
Kleinman et al. 1998; Leaf and Kleinman 1996b	17 male nonsmokers (mean age: 66 years; age range: 58–83 years) living at or near sea level, diagnosed with coronary artery disease with exertional angina pectoris	Randomized, cross-over, double-blind; exercise challenge tests (bicycle) administered immediately following each exposure at sea levels and under conditions simulating high altitude.	Patients administered one of the following treatments (via environmental chamber) on 4 test days: 2-hour exposure to room air at sea level (measured COHb following exposure: 0.6±0.3%[b]), room air at artificial high elevation (measured COHb following exposure: 0.6±0.3%[b]), CO at sea level (measured COHb: 3.9±0.5%[b]; mean CO concentration: 100 ppm), or CO at artificial high elevation (measured COHb: 4.0±0.6%[b]; mean CO concentration: 100 ppm), COHb measured by CO-Ox.	Time-to-onset and duration of angina symptoms, ST-segment depression and preventricular contractions (EKG), peak (end-exercise) heart rate, blood pressure, oxygen update, and carbon dioxide output. Results for CO exposure compared to room air exposure.	Time-to-onset of angina: Decreased by 9.1% ($p<0.05$) following CO exposure at sea level and by 7.6% ($p<0.05$) following CO exposure at high altitude, compared to matched room air exposure. Duration of angina symptoms: No effect of CO exposure. ST-segment changes: No effect of CO exposure. Preventricular contractions: No effect of CO exposure Peak heart rate: Increased ($p<0.05$) for CO at high altitude compared to CO at sea level and to room air at high altitude. Peak blood pressure: Increased ($p<0.05$) for CO at high altitude compared to room at CO at sea level. Oxygen uptake and carbon dioxide output: Decreased ($p<0.05$) by CO exposure at sea level and high altitude. NOAEL: Not established LOAEL: COHb 3.9–4.0%

Table 3-4. Effects of Acute-Duration Exposure to Carbon Monoxide on Cardiovascular Function in Patients with Coronary Artery Disease

Reference	Study subjects	Design	Exposure	Outcomes assessed	Results
Sheps et al. 1987	30 nonsmokers (age range: 38–75 years) diagnosed with coronary artery disease with exertional angina pectoris	Randomized, cross-over, double-blind; exercise challenge tests (bicycle) administered immediately following each exposure.	Patients administered one of the following treatments (via environmental chamber) on 2 test days: 1-hour exposure to room air (measured COHb following exposure: 1.5±0.05%[b]) or CO (measured COHb following exposure: 4.1±0.05%[b]; CO concentration: 100 ppm). COHb measured by CO-Ox.	Time-to-onset and duration of angina symptoms, ST-segment depression, cardiovascular function (heart rate, blood pressure, rate x pressure product, peak exercise workload, left ventricular ejection fraction), exercise duration. Results for CO exposure compared to room air exposure.	No statistically significant CO-induced changes for any outcomes, except for a small (0.5% decrease; p=0.049) in maximal ejection fraction. Study authors did not consider this change to be clinically significant. NOAEL: COHb 4.1% LOAEL: Not established

Table 3-4. Effects of Acute-Duration Exposure to Carbon Monoxide on Cardiovascular Function in Patients with Coronary Artery Disease

Reference	Study subjects	Design	Exposure	Outcomes assessed	Results
Sheps et al. 1990	41 nonsmokers (36 men, 5 women; mean age: 62.8 years; age range: 47–77 years) diagnosed with coronary artery disease	Randomized, cross-over, double-blind; exercise challenge tests (bicycle) administered immediately following each exposure.	Patients administered one of the following treatments (via environmental chamber) on 3 test days: 1-hour exposure to room air (measured COHb following exposure: 1.46±0.07%[a]), low CO (measured COHb following exposure: 4.01±0.06%[a]; CO concentration: 100 ppm), or high CO (measured COHb following exposure: 5.91±0.08%[a]; CO concentration: 200 ppm). COHb measured by CO-Ox.	Ventricular arrhythmia (EKG) and ventricular ejection fraction (radionuclide ventriculography), blood pressure, heart rate, exercise duration. Results for CO exposure compared to room air exposure.	For COHb 4.01%: No effects on any parameter evaluated. For COHb 5.91%: During exercise, statistically significant changes in single premature ventricular depolarizations (36% increase; p=0.03), complex premature ventricular depolarizations (6.3% increase; p=0.02), heart rate (3.2% increase; p=0.01). NOAEL: COHb 4.01% LOAEL: COHb 5.91%

[a]Mean±standard error (SE).
[b]Mean±standard deviation (SD).
[c]Means; report does not indicate if SD or SE.

CO = carbon monoxide; COHb = carboxyhemoglobin; CO-Ox = CO oximetry; EKG = electrocardiogram; GC = gas chromatography; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

underlying cardiovascular disease, including enhanced myocardial ischemia and increased cardiac arrhythmias. In patients with exertional angina, carbon monoxide exposure exacerbated exercise-induced myocardial ischemia, including decreased time-to-onset of angina symptoms (Adams et al. 1988; Allred et al. 1989, 1991; Anderson et al. 1973; Kleinman et al. 1989, 1998; Leaf and Kleinman 1996b), increased duration of angina symptoms (Anderson et al. 1973; Kleinman et al. 1989), decreased time-to-onset of ST-segment depression (EKG change indicative of myocardial ischemia) (Allred et al. 1989, 1991; Kleinman et al. 1989), and decreased left ventricular ejection fraction (Adams et al. 1988). At the lowest blood COHb level evaluated in patients (i.e., COHb 2.4%), time-to-onset of angina symptoms and of ST-segment depression were significantly decreased by 4.2 and 5.1%, respectively (Allred et al. 1989, 1991). In contrast, no carbon monoxide-induced exacerbation of exertional angina, based on time-to-onset of angina symptoms and ST-segment depression and duration of angina symptoms, were observed at a blood COHb level of 4.1% (Sheps et al. 1987). Clinical evaluations in angina patients with ventricular arrhythmias have yielded mixed results on the effects of carbon monoxide-induced ventricular arrhythmias (Dahms et al. 1993; Hinderliter et al. 1989; Sheps et al. 1990). At a blood COHb level of 5.9%, but not 4.0%, single and complex premature ventricular depolarizations were significantly increased by 36 and 6.3%, respectively (Sheps et al. 1990). However, at this same blood COHb level, carbon monoxide exposure did not increase ventricular arrhythmias in other studies (Dahms et al. 1993; Hinderliter et al. 1989). Reasons for conflicting results in these studies are not readily apparent, although numbers of patients evaluated were small and the severity of underlying coronary artery disease may have varied in each study.

Studies of Healthy Subjects. Several controlled clinical studies in small numbers of healthy subjects have evaluated effects of acute-duration exposure to carbon monoxide on exercise performance, including cardiovascular function. In general, study protocols were similar to those used in clinical studies on patients with coronary artery disease, although typical carbon monoxide exposures were for shorter durations (a few minutes to ≤1 hour) to higher carbon monoxide concentrations (50–3,000 ppm) and produced slightly higher blood COHb levels (2.4–20.5%). However, one study exposed subjects continuously for 7 days (Davies and Smith 1980). Additional experimental details for each study are summarized in Table 3-5.

Results of several controlled clinical studies in healthy subjects show that carbon monoxide exposures that resulted in blood COHb levels between 3.35 and 20.5% decreased exercise performance, including decreased exercise duration (Adir et al. 1999); decreased maximal exercise effort or maximal aerobic capacity (Adir et al. 1999; Horvath et al. 1975; Vogel and Gleser 1972); decreased resistance to muscle

Table 3-5. Effects of Acute-Duration Carbon Monoxide Exposure on Cardiovascular Function in Healthy Subjects

Reference	Study subjects	Design	Exposure	Outcomes assessed	Results
Adir et al. 1999	15 healthy nonsmoking men (mean age: 26 years; age range: 18–35 years)	Randomized, cross-over, double-blind; exercise challenge tests (bicycle) administered immediately following each exposure.	Subjects administered one of the following treatments (via closed breathing circuit) on 2 test days: 3–4-minute exposure to room air (COHb: 0.59±0.08%[a]) or CO (measured COHb: 5.1±0.65%[a]; CO concentration not reported). COHb measured by CO-Ox.	Level of anaerobic respiration (plasma lactate/pyruvate ratio), cardiac arrhythmia (EKG), heart rate and blood pressure (resting and peak), cardiac perfusion (thallium heart scintigraphy), exercise duration, maximal effort (metabolic equivalent units).	Anaerobic respiration: No effect of CO exposure. Cardiac arrhythmia: No effect of CO exposure. Cardiac perfusion: No effect of CO exposure. Heart rate and blood pressure: No effect of CO exposure. Exercise duration: Decreased by 10.4% (p=0.0012) for CO exposure compared to air exposure. Maximal effort: Decreased by 12.4% (p=0.001) for CO exposure compared to air exposure. NOAEL: Not established LOAEL: COHb 5.1%
Davies and Smith 1980	Groups (14–15/group) of matched healthy (information on sex not reported; age range: 17–27 years)	Randomized, parallel group.	Continuous exposure to room air (COHb 0.5%), low CO (15 ppm CO; COHb 2.4%), or high CO (50 ppm CO; COHb 7.2%) for 7 days.	EKG; no statistical analysis conducted.	P-wave changes: P-wave deviations of ≥0.1 mV observed in 3/15 subjects at low CO and 6/15 at high CO, compared to 0/14 for room air. Marked ST-segment depression: 1/15 subject (a heavy smoker) at low CO exposure. NOAEL: Not established LOAEL: COHb 2.4%

Table 3-5. Effects of Acute-Duration Carbon Monoxide Exposure on Cardiovascular Function in Healthy Subjects

Reference	Study subjects	Design	Exposure	Outcomes assessed	Results
Hausberg and Somers 1997	10 healthy subjects (8 men, 2 women; mean age: 27 years); 9/10 were nonsmokers	Randomized, double-blind, vehicle (air) controlled.	Subjects were assessed under vehicle control (room air), then administered CO (1,000 ppm for 30 minutes, followed by 100 ppm for 30 minutes); COHb increased from 0.2±0.1%[b] for room air exposure to 8.3±0.5%[b] during the first 30 minutes of exposure; COHb levels were maintained during the second 30 minutes of CO exposure. COHb measured by CO-Ox.	Forearm blood flow (plethysmography), blood pressure, heart rate, minute ventilation, muscle sympathetic nerve activity (microneurography).	No effects of CO treatment on any parameter evaluated. NOAEL: COHb 8.3% LOAEL: Not established

Table 3-5. Effects of Acute-Duration Carbon Monoxide Exposure on Cardiovascular Function in Healthy Subjects

Reference	Study subjects	Design	Exposure	Outcomes assessed	Results
Horvath et al. 1975	4 healthy men (mean age: 24.6 years; age range: 23–33 years); 3/4 were nonsmokers	Randomized, single-blind, cross-over; exercise challenge tests (treadmill) to exhaustion administered immediately following each exposure.	Subjects administered one of the following treatments (via environmental chamber) on 3 test days (exposure duration not reported): Vehicle exposure to room air (measured COHb following exposure: 0.33±0.06%[b]), low CO (measured COHb following exposure: 3.35±0.14%[b]; CO concentration: 75 ppm), or high CO (measured COHb following exposure: 4.30±0.30%[b]; CO concentration: 100 ppm). Method for measuring COHb not reported.	EKG, maximal aerobic capacity (maximal oxygen consumption), work time, ventilatory volume.	EKG: No effect of CO exposure. Maximal aerobic capacity: Decreased at high CO exposure ($p<0.05$). Ventilatory volume and work times: Decreased at low and high CO exposure ($p<0.05$). NOAEL: Not established LOAEL: COHb 3.35%

Table 3-5. Effects of Acute-Duration Carbon Monoxide Exposure on Cardiovascular Function in Healthy Subjects

Reference	Study subjects	Design	Exposure	Outcomes assessed	Results
Kizakevich et al. 2000	16 healthy nonsmoking men (age range: 18–29 years)	Randomized, cross-over (no details on blinding reported); upper (handcrank) and lower body (treadmill) exercise challenges at submaximal effort administered following exposure.	Subjects exposed to CO (concentrations 1,000–3,000 ppm) for 4–6 minutes, followed by maintenance CO exposure (27–100 ppm) on separate test days: Room air (COHb 1.8%); CO-1 (COHb 5.0%); CO-2 (COHb 9.8%); CO-3 (COHb 14.8%); or CO-4 (COHb 19.2%). COHb measured by CO-Ox.	Cardiac rhythm, output, stoke volume, heart rate, and contractility, time-to-peak ejection time, blood pressure.	Cardiac rhythm: No effects of CO exposure, compared to room air exposure; no arrhythmias or ST-segment depression. Compensatory changes associated with reduced oxygen carrying capacity: Significant increases in heart rate at all CO exposures and cardiac contractility at COHb 9.8%. NOAEL: Not established LOAEL: COHb 5.0%
Morse et al. 2008	12 healthy nonsmoking men (mean age: 25 years)	Cross-over; skeletal muscle fatigue challenge administered following exposure.	Room air or 3,000 ppm for 6 minutes (COHb 6.2%).	Leg strength, muscle fatigue assessed during voluntary and electrically evoked muscle contractions.	Resistance to muscle fatigue decreased under voluntary (13% decrease; $p<0.05$) and electrically evoked stimulation (12.5% decrease; $p<0.05$). No effect on leg strength. NOAEL: Not established LOAEL: COHb 6.2%
Resch et al. 2005	6 healthy nonsmoking men (mean age: 26 years)	Randomized, cross-over, double-blind.	Subjects administered the following treatments: Room air (COHb 1.2%), 500 ppm for 30 minutes (COHb 8.5%, or 500 ppm for 30 minutes (COHb 9.4%).	Retinal and submacular choroidal blood flow.	Significant increases in retinal and choroidal blood flow and retinal vessel diameter at COHb ≥8.5%. Study authors state that the relationship of this finding to tissue hypoxia is unknown. NOAEL: Not established LOAEL: COHb 8.5%

Table 3-5. Effects of Acute-Duration Carbon Monoxide Exposure on Cardiovascular Function in Healthy Subjects

Reference	Study subjects	Design	Exposure	Outcomes assessed	Results
Vogel and Gleser 1972	8 men, including 3 smokers (age range: 20–23 years)	Randomized, cross-over (no details on blinding reported); exercise challenges administered during exposure.	1-hour exposure to air (COHb 1.0–1.7%) or 225 ppm CO (COHb 18.6–20.5%).	Maximal oxygen uptake assessed at rest and at submaximal and maximal exercise.	At rest, no effect of CO exposure. At submaximal exercise, no change in oxygen uptake due to compensatory increase in cardiac output. At maximal exercise, oxygen uptake decreased by 23% ($p<0.001$). NOAEL: Not established LOAEL: COHb 18.6–20.5%
Zevin et al. 2001	12 healthy men (smokers; age range: 27–47)	Single-blind, cross-over.	Subjects exposed to three treatments for durations of 7 days each: Room air (COHb 0.4%), 1,200 ppm CO inhalation 20 times/day (~every 45 minutes, 20 times/day to simulate smoking (COHb 6%), or 20 cigarettes/day (COHb 5%).	Heart rate, blood pressure, catecholamine release, platelet activation, white blood cell count, C-reactive protein (inflammation marker).	CO exposure: No effect on serum levels of c-reactive protein or platelet factor 4, heart rate, blood pressure, or catecholamine release, compared to room air. Smoking: Significant elevation in serum levels of CRP and platelet factor 4, increased heart rate, or catecholamine release, compared to room air. No effect on blood pressure. NOAEL (CO): COHb 6% LOAEL (CO): Not established

[a]Mean± standard deviation (SD).
[b]Mean± standard error (SE).
[c]Means; report does not indicate if SD or SE.

CO = carbon monoxide; COHb = carboxyhemoglobin; CO-Ox = CO oximetry; EKG = electrocardiogram; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

fatigue (Morse et al. 2008); and induced compensatory increases in heart rate and cardiac output (Kizakevich et al. 2000; Vogel and Gleser 1972). The above effects of exercise performance are consistent with COHb-induced decreased O_2 carrying capacity of the blood and normal physiological compensatory mechanisms. Evaluations on the potential for carbon monoxide exposure to produce exercise-induced cardiac arrhythmias similar to those observed in patients with coronary artery disease (i.e., ST-segment depression and premature ventricular contractions) have yielded negative results at blood COHb levels up to 5.1% (Adir et al. 1999; Horvath et al. 1975; Kizakevich et al. 2000), although the potential for carbon monoxide-induced cardiac arrhythmias during exercise challenge was not evaluated at higher blood COHb levels. In subjects (including smokers and nonsmokers) exposed continuously for 7 days and evaluated at rest, EKG showed several P-wave deviations (P-wave inversion, increased amplitude, decreased amplitude, and changes in P-wave direction) in 3/15 subjects exposed to 15 ppm carbon monoxide (COHb 2.4%) and in 6/15 subjects exposed to 50 ppm carbon monoxide (COHb 5.1%), compared to 0/14 in subjects exposed to room air (Davies and Smith 1980). In one subject, a heavy smoker, marked ST-depression also was observed. However, interpretation of these findings is limited due to lack of statistical analyses and of evaluation for potential confounding factors (e.g., smoking, medication use). Other studies evaluating effects of a single 1-hour exposure to carbon monoxide (Hausberg and Somers 1997) or repeated brief exposures to carbon monoxide (approximately once every 45 minutes to simulate smoking; Zevin et al. 2001) on cardiovascular function (blood pressure, heart rate, forearm blood flow) under resting conditions showed no effects at blood COHb levels up to 8.3%.

In conclusion, results of controlled clinical studies in patients with cardiovascular disease provide compelling evidence that acute-duration exposure to carbon monoxide resulting in COHb levels of 2.4–5.8% exacerbates cardiovascular morbidity (myocardial ischemia and cardiac arrhythmias). Effects at lower blood COHb levels have not been evaluated. However, it should be noted that patients with more severe cardiovascular disease may be more sensitive than patients evaluated in these clinical studies. In healthy subjects, acute exposure to carbon monoxide at concentrations producing blood COHb levels of 3.35 and 20.5% resulted in compensatory cardiovascular responses and decreased exercise performance consistent with COHb-induced decreased O_2 carrying capacity of the blood; however, subjects did not exhibit exercise-induced adverse cardiovascular effects (e.g., evidence of myocardial ischemia or cardiac arrhythmias). Continuous exposure of healthy subjects, which included smokers, to carbon monoxide resulting in blood COHb levels of 2.4 and 5.1% produced P-wave deviations under resting conditions, although similar findings have not been reported in other studies.

Epidemiological Studies. Epidemiological studies of exposure to carbon monoxide and cardiovascular outcomes fall into two major categories: (1) studies that have assessed cardiovascular morbidity in cohorts or individuals (e.g., case-crossover, case-control) in association with ambient air carbon monoxide concentrations; and (2) studies that have evaluated associations between air carbon monoxide concentrations and the incidence of hospital admissions and/or emergency room visits related to cardiovascular disease (e.g., time-series studies, case-crossover). Collectively, these studies have yielded mixed results, although, in general, the weight of evidence suggests that risks of certain specific outcomes are associated with increasing ambient carbon monoxide concentrations (hospitalizations and emergency room visits related to congestive heart failure, ischemic heart disease, myocardial infarction, and stroke). Corroborated observations of association between carbon monoxide exposure and outcomes related to ischemic heart disease are consistent with results of human clinical studies that have shown that carbon monoxide-induced hypoxia exacerbates symptoms of coronary artery disease. Therefore, it is plausible that in certain susceptible populations, such as individuals who have ongoing cardiac impairment that would make them vulnerable to ischemia, exposure to carbon monoxide could contribute to triggering ischemic episodes and cardiac sequelae. While these studies provide some evidence in support of adverse cardiovascular effects of inhalation exposures to carbon monoxide, their utility for establishing dose-response relationships for these effects are limited by several factors: (1) reliance on area monitoring for estimating exposure levels; (2) uncertainty in knowledge of temporal correspondence between monitored exposure levels and outcomes; (3) relatively strong correlations between ambient air carbon monoxide concentrations and other air quality variables that can affect respiratory function; (4) tendency of outcomes investigated to be serious, life-threatening events (e.g., cardiac arrhythmia, myocardial, infarction, stroke, heart failure) and reflect the "late-stage" consequences of contributing pathophysiology that might be associated with exposures to lower levels of carbon monoxide for longer durations than indicated in the epidemiological studies; and (5) relatively low carbon monoxide exposures studied. Mean values of carbon monoxide exposure concentrations have ranged from 0.3 to 4.6 ppm, with the highest values ≤30 ppm. These values correspond to predicted steady-state COHb levels of <1% for the mean and <5% for the highest values (predicted from the CFK model). The latter range is consistent with COHb levels observed in a study of emergency department admissions for cardiopulmonary complaints (Leikin and Vogel 1986). At these COHb levels, it is possible that only highly susceptible individuals exhibit the serious cardiovascular outcomes that have been studied. Clinical studies described previously in this section of the Toxicological Profile have found that exposures to carbon monoxide that produce COHb levels of 2.4–5% can exacerbate underlying cardiovascular disease, including exercise-induced angina and cardiac arrhythmia; however, higher levels (3–20%) can be tolerated without producing such effects, even under exertion, in healthy individuals. For these and other reasons, epidemiologic studies

have typically focused on highly susceptible populations. A typical design has been to examine associations between temporal trends in ambient air carbon monoxide concentrations and hospital admissions or emergency department visits for which the reported diagnosis was some form of cardiovascular disease of impairment.

The presentation of the epidemiology is organized by major categories of cardiovascular outcomes for which the studies were designed to evaluate, including studies of heart rate and heart rate variability, cardiac arrhythmia, ischemic heart disease and related subcategories (e.g., myocardial infarction), heart failure, stroke, and blood pressure. Study conclusions are presented in the text, with selected supporting details presented in tabular form. Although most of the studies explored various time lags between monitored air carbon monoxide concentrations and outcomes, as well as various sample strata, for the sake of brevity, only those indicative of the strongest associations to carbon monoxide are presented in the tables. Where co-pollutant models have been explored, these results are also presented.

Studies of Heart Rate (HR) and Heart Rate Variability (HRV). Studies of associations between exposure to carbon monoxide and various measures of HR and HRV have yielded mixed results (Table 3-6). Carbon monoxide exposure concentrations in these studies represent relatively narrow time periods (e.g., averages over 1–5 days prior to the end point assessment). Mean values of carbon monoxide exposure concentrations ranged from 0.3 to 4.6 ppm, with the highest values ≤30 ppm (predicted steady-state COHb%: <5). Significant associations between increasing carbon monoxide exposure and increasing HR were found in some studies (Liao et al. 2004; Peters et al. 1999) and not in others (Gold et al. 2000). Assessments of HRV found significant associations with increasing carbon monoxide exposure in some studies (Dales 2004; Riojas-Rodriguez et al. 2006; Schwartz et al. 2005; Tarkiainen et al. 2003; Timonen et al. 2006) and no associations with HRV in other studies (Chan et al. 2005; Gold et al. 2000; Holguin et al. 2003; Liao et al. 2004; Park et al. 2005b). In general, associations for HRV end points were not robust for various measures of HRV across studies. For example, assessments of standard deviation of the normal-to-normal interval (SDNN) yielded significant associations in some studies (Dales 2004; Schwartz et al. 2005; Timonen et al. 2006) and not in others (Chan et al. 2005; Gold et al. 2000; Liao et al. 2004; Park et al. 2005b; Tarkiainen et al. 2003).

Three studies are particularly notable for their relatively large size. Park et al. (2005b) assessed HRV in 497 male subjects (age range: 21–82 years) of the Boston Normative Aging Study and linked these data to local measurements of air pollutant concentrations (carbon monoxide, $PM_{2.5}$, O_3, NO_2, SO_2). The mean carbon monoxide exposure concentration was 0.50 ppm (24-hour average, range: 0.13–18 ppm). The

Table 3-6. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Cardiovascular Disease

Study	Design features	CO exposure	Effect size
Heart rate and heart rate variability			
Chan et al. 2005 Period: 2001–2002 Location: Taipei, Taiwan	Outcome: HRV Design: Panel Sample: 83 patients, age 43–75 years	Avg time: 1 hour Mean 1.1 ppm Range: 0.1–7.7 ppm	No statistically significant effect on SDNN, rMSSD, LFV, or HFV
Dales 2004 Period: NR Location: Toronto, Canada	Outcome: HRV Design: Panel Sample: 36 subjects with preexisting CAD, age 51–88 years	Avg time: 24 hours Mean 95th%: 2.40 ppm Range: 0.4–16.5 ppm	Increment: NR Regression coefficient (95% CI): SDNN (not taking β-blockers): 0.0111 (0.002, 0.020, p=0.02) No statistically significant effect on HRV among those taking β-blockers
Gold et al. 2000 Period: 1997 Location: Boston, Massachusetts	Outcome: HR and HRV Design: Panel/cohort Sample: n=21, age 53–87 years	Avg time: 24 hours Mean: 0.47 ppm Range: 0.12–0.82 ppm	Increment: 0.6 ppm % Change (lag 2 days): No significant effect of CO on HR or HRV
Holguin et al. 2003 Period: 2000 Location: Mexico City, Mexico	Outcome: HRV Design: Panel Sample: n=34, age 60–90 years	Avg time: 24 hours Mean: 3.3 ppm Range: 1.8–4.8 ppm	Increment: 10 ppm Regression coefficients (95% CI), lag 0 days: HFV: 0.003 (-0.004, 0.001) LFV: 0.001 (-0.006, 0.008) LFV/HFV: 0.001 (-0.005, 0.002)
Liao et al. 2004 Period: 1996–1998 Location: Various U.S. cities	Outcome: HR HRV. Design: Cohort Sample: n=6,784, age 45–64 years	Avg time: 24 hours Mean: 0.65 ppm SD: 0.44 ppm	Increment: 0.44 ppm Regression coefficient, lag 1 day: HR (bpm): 0.404 (p<0.05) HFV (log transformed): -0.033 LFV (log transformed): 0.006 SDNN: -0.274
Park et al. 2005b Period: 2000–2003 Location: Boston, Massachusetts	Outcome: HRV Design: Panel/cohort Sample: n=497 males, age 21–81 years	Avg time: 24 hours Mean: 0.50 ppm Range: 0.13–1.8 ppm	Increment: 0.24 ppm % Change in HRV (95% CI), 4-hour moving avg: SDNN (log10): 2.0 (-2.9, 7.3) HFV (log10): 8.8 (-4.6, 24.1) LFV(log10): 3.2 (-7.0, 14.6) LFV:HFV(log10): -5.1 (-13.5, 4.1)

Table 3-6. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Cardiovascular Disease

Study	Design features	CO exposure	Effect size
Peters et al. 1999 Study: 1984–1985 Location: Augsburg, Germany	Outcome: HR Design: Cohort Sample: n=2,681, age 25–64 years	Avg time: 24 hours Mean: 3.9 ppm Range: 0.8–10.0 ppm	Increment: 6.6 mg/m^3 Mean change in HR, bpm (95% CI), lag 0 days: All: 0.97 (0.02, 1.91) Male: 0.95 (-0.37, 2.27) Female: 0.98 (-0.37, 2.34)
Riojas-Rodriguez et al. 2006 Period: 2001–2002 Location: Mexico City, Mexico	Outcome: HRV Design: Panel Sample: n=30, age 25–76 years	Avg time: 24 hours Mean: 2.9 ppm Range: 0.1–18.0 ppm	Increment: 1 ppm Regression coefficients (95% CI), lag 5 minutes: HFV: -0.006 (-0.023, 0.010) LFV: -0.024 (-0.041, -0.007) VLFV: -0.034 (-0.061, -0.007)
Schwartz et al. 2005 Period: 1999 Location: Boston, Massachusetts	Outcome: HRV Design: Panel Sample: n=28, age 61–89 years	Avg time: 24 hours Median: 0.45 ppm 25^{th}–75^{th}%: 0.38–0.54 ppm	Increment: 0.16 ppm % Change in HRV (95% CI), lag 1 day: SDNN: -4.2 (-0.6, -7.7) rMSSD: -10.2 (-2.4, -17.4) PNN50: -14.8 (-3.0, -25.2) LFV/HFV: 6.2 (-0.6, 13.4)
Tarkiainen et al. 2003 Period: 1997–1998 Location: Kuopio, Finland	Outcome: HRV Design: Panel Sample: n=6 males, age 55–68 years	Avg time: 24 hours Mean: 4.6 ppm Range: 0.5–27.4 ppm	Increment: NR RR (95% CI), lag 5 minutes: CO >2.7 ppm: Significant increase in rMSSD (2.4 ms, p=0.034) CO <27 ppm: No significant association between CO and NN, SDNN, or rMSSD
Timonen et al. 2006 Period: 1998–1999 Location: Amsterdam, Netherlands; Erfert, Germany; Helsinki, Finland	Outcome: HRV Design: Panel Sample: n=131, age 64–72 years	Avg time: 24 hours Mean: 0.3–0.5 ppm Range: 0.1–2.2 ppm	Increment: 1 mg/m^3 β coefficient (95% CI), lag 2 days SDNN: -5.96 (-10.7, -0.72) HFV: -30.7 (-59.8, -1.5) LHV/HFV: -10.1 (-36.9, 16.7)

Table 3-6. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Cardiovascular Disease

Study	Design features	CO exposure	Effect size
Cardiac arrhythmia			
Berger et al. 2006 Period: 2000–2001 Location: Erfurt, Germany	Outcome: SVT and VT 24-hour EKG Design: Panel Sample: 57 males with CHD, age 52–76 years	Avg time: 24 hours Mean: 0.45 ppm Range: 0.10–1.68 ppm	Increment: 0.22 mg/m^3 RR for SVT (95% CI), 5-day avg: 1.18 (1.04, 1.35)
Dockery et al. 2005 Period: 1995–2002 Location: Boston, Massachusetts	Outcome: Tachycardia Design: Panel Sample: n=203 with ICDs, age 19–90 years	Avg time: 24 hours Median: 0.8 ppm 25^{th}–75^{th}%: 0.53–1.02 ppm	Increment: 0.48 ppm OR for VT (95% CI), lag 2 days: All: 1.14 (0.95, 1.29) AR ≤3 days prior: 1.65 (1.17, 2.33)
Gold et al. 2005 Period: 1999 Location: Boston, Massachusetts	Outcome: ST-segment Design: Panel Sample: n=24, age 61–68 years	Avg time: 5 hours Median: 0.52 ppm 10^{th}–90^{th}%: 0.20–1.08 ppm	Significant association between CO and ST-segment depression did not persist in multiple pollutant models
Metzger et al. 2007 Period: 1993–2002 Location: Atlanta, Georgia	Outcome: CAR, VT Design: Panel Sample: n=518 with ICDs, with ≥1 VT event, age 15–88 years	Avg time: 1 hour Mean: 1.7 ppm Range: 0.1–7.7 ppm	Increment: 1 ppm OR for VT (95% CI), lag 0 days: All: 0.999 (0.970, 1.028)
Peters et al. 2000b Period: 1995–1997 Location: Eastern Massachusetts	Outcome: VT or fibrillation Design: Panel Sample: n=100 with ICDs, mean age 62 years	Avg time: 24 hours Mean: 0.58 ppm 25^{th}–75^{th}%: 0.66 ppm	Increment: 0.65 ppm OR for ≥10 defibrillated discharges (95% CI): Lag 3: 1.98 (1.05, 3.72) Lag 5-day avg: 1.94 (1.01, 0.75)
Rich et al. 2004 Period: 2000 Location: Vancouver, Canada	Outcome: CAR Design: Case-crossover Sample: n=34 with ≥1 ICD discharge, age 15–85 years	Avg time: 24 hours Mean: 0.553 ppm Interquartile range: 0.162 ppm	No significant effect of CO (quantitative results not reported)
Rich et al. 2005 Period: 1995–1999 Location: Boston, Massachusetts	Outcome: VAR Design: Panel/case-crossover Sample: n=203 with implanted ICDs	Avg time: 24 hours Median: 0.78 ppm 25^{th}–75^{th}%: 0.52–1.03	Increment: 0.5 ppm OR: (95% CI), lag 0–2 days: 1.11 (0.88, 1.40) (also not significant at other lags)

Table 3-6. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Cardiovascular Disease

Study	Design features	CO exposure	Effect size
Rich et al. 2006b Period: 2001 and 2002 Location: St. Louis, Missouri	Outcome: VAR Design: Case-crossover Sample: n=60 with ≥1 ICD CAR recorded	Avg time: 24 hours Median: 0.5 ppm 25th–75th%: 0.6 ppm	Increment: 0.2 ppm OR for VAR (95% CI), lag 0–1 day: 0.99 (0.80, 1.21)
Rich et al. 2006a Period: 1995–1999 Location: Boston, Massachusetts	Outcome: AF Design: Panel/case-crossover Sample: n=203 with ICDs	Avg time: 24 hours Median: 0.78 ppm 25th–75th%: 0.52–1.03 ppm	Increment: 0: 0.58 ppm OR for AF (95% CI): Lag 0: 0.87 (0.56, 1.37) Lag 0–23 hours: 0.71 (0.39, 1.28)
Sarnat et al. 2006 Period: 2000 Location: Steubenville, Ohio	Outcome: CAR Design: Panel Sample: 32 nonsmoking, age 53–90 years	Avg time: 24 hours Mean: 0.02 ppm Range 0–1.5 ppm	Increment: 0.2 ppm RR (95% CI), 5-day moving avg: SVE: 0.99 (0.76, 1.29) VE: 1.05 (0.75, 1.46)
Vedal et al. 2004 Period: 1997–2000 Location: Vancouver, Canada	Outcome: CAR Design: Panel Sample: n=50 with ICDs and ≥1 CAR event/4 years, age 12–77 years	Avg time: 24 hours Mean: 0.6 ppm Range: 0.3–1.6 ppm	Increment: 0.2 ppm No significant effect for CO (results shown in plots)
Cardiac arrest			
Dennekamp et al. 2010 Period: 2003–2006 Location: Melbourne, Australia	Outcome: Cardiac arrest Design: Case-crossover Sample: 8,434 cases, age >35–103 years	Avg time: 24 hours Mean: 0.44 ppm 25th–75th%: 0.27–0.52 ppm	Increment: 0.25 ppm RR % change (95% CI): Lag 0–1: 3.09 (0.25, 4.58) Lag 0: 2.09 (-0.33, 4.58) Lag 1: 2.38 (-0.54, 5.39) Lag 2: -0.09 (-2.96, 2.86) Lag 3: 1.61 (-1.31, 4.62)
Levy et al. 2001 Period: 1988–1994 Location: Seattle, Washington	Outcome: Cardiac arrest Design: Case-crossover Sample: 362 cases, age 25–75 years	Avg time: 24 hours Mean: 1.79 ppm Range: 0.52–5.92 ppm	RR (95% CI), lag 1 day: 0.99 (0.83, 1.18)

Table 3-6. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Cardiovascular Disease

Study	Design features	CO exposure	Effect size
Silverman et al. 2010 Period: 2002–2006 Location: New York, New York	Outcome: Cardiac arrest Design: Case-crossover Sample: 8,216 cases, mean age >65.6 years	Avg time: 24 hours Median: 0.9 ppm 5^{th}–95^{th}%: 0.6–1.5 ppm	Increment: 0.3 ppm RR (95% CI): Lag 0–1: ~0.99 (0.96, 1.03) (estimated from Figure 2)
Sullivan et al. 2003 Period: 1985–1994 Location: Washington State	Outcome: Cardiac arrest Design: Case-crossover Sample: 1,542 cases, median age 69 years	Avg time: 24 hours Mean: 1.92 ppm Range: 0.52–7.21 ppm	Increment: 1.02 ppm OR (95% CI): Lag 0: 0.95 (0.85, 1.05) Lag 1: 0.97 (0.87, 1.08) Lag 2: 0.99 (0.89, 1.11)
Myocardial infarction			
Peters et al. 2001 Period: 1995–1996 Location: Boston, Massachusetts	Outcome: Onset of MI Design: Case-crossover Sample: 772 cases	Avg time: 24 hours Mean: 1.09 ppm 5^{th}–95^{th}%: 0.49–1.78 ppm	Increment: 1 or 0.6 ppm OR (95% CI): 2 hours: 1.22 (0.89, 1.67) per 1 ppm 24 hours: 0.98 (0.70, 1.36) per 0.6 ppm
Rosenlund et al. 2006 Period: 1992–1994 Location: Stockholm, Sweden	Outcome: MI Design: Case-control Sample: 1,397 cases, 1,870 controls, age range 45–70 years	Avg time: 30 years Mean: 0.058 ppm 5^{th}–95^{th}%: 0.012–0.258 ppm	Increment: 300 µg/m^3 OR: (95% CI): All cases: 1.04 (0.89, 1.21) Nonfatal: 0.98 (0.82, 1.16) Fatal: 1.22 (0.98, 1.52) Fatal, in-hospital: 1.16 (0.89, 1.51) Fatal, out-hospital: 1.36 (1.01, 1.84)

Table 3-6. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Cardiovascular Disease

Study	Design features	CO exposure	Effect size
Blood pressure			
Ibald-Mulli et al. 2001 Period: 1984–1985 Location: Augsburg, Germany	Outcome: SBP Design: Cohort Sample: n=2,607 men and women age 25–64 years	Avg time: 24 hours Mean: 3.6 ppm Range: 1.5–7.2 ppm	Increment: 5.6 mg/m^3 Mean change in SBP, mmHg (95% CI): All: 0.53 (-0.66, 1.72) Males: 0.68 (-0.94, 2.31) Females: 0.51 (-1.31, 2.19)
Zanobetti et al. 2004b Period: 1999–2001 Location: Boston, Massachusetts	Outcome: BP Design: Cohort/panel Sample description: n=62, age 39–90 years	Avg time: 120 hours Mean: 0.66 ppm 10^{th}–90^{th}%: 0.48–0.86 ppm	Increment: NR RR: No significant effect of CO on BP

AF = atrial fibrillation; AR = arrhythmia; Avg = average; BP = blood pressure; CAD = coronary artery disease; CAR = cardiac arrhythmia; CHD = coronary heart disease; CI = confidence interval; CO = carbon monoxide; EKG = electrocardiogram; HFV = high frequency (HR) variability; HR = heart rate; HRV = heart rate variability; ICD = implantable cardioverter defibrillator; LFV = low frequency (HR) variability; MI = myocardial infarction; NR = not reported; OR = odds ratio; PNN50 = proportion of interval differences of successive normal-beat intervals >50 ms in EKG; rMSSD = root mean squared differences between adjacent RR intervals; RR = relative risk; SBP = systolic blood pressure; SD = standard deviation; SDNN = standard deviation normal-to-normal (NN or RR) time interval between each QRS complex in the EKG; SVE = supraventricular ectopy; SVT = supraventricular tachycardia; VAR = ventricular arrhythmia; VLFV = very low frequency (HR) variability; VE = ventricular ectopy; VT = ventricular tachycardia

study did not find significance between carbon monoxide exposure levels and HRV end points assessed (SDNN, low frequency [LF], high frequency [HF], LF/HF). A study conducted in Augsburg, Germany evaluated possible associations between exposures to total suspended particles (TSP), SO_2, and carbon monoxide (mean: 4.5 mg/m^3 [3.9 ppm], range: 2.4–6.8 mg/m^3 [2.1–5.9 ppm) and HR in 2,681 adults (age range: 25–64 years; Peters et al. 1999). A 6.6 mg/m^3 (5.8 ppm) increase in 24-hour average carbon monoxide concentration was associated with a small but significant increase in HR of approximately 1 beat per minute (0.97 beats/minute, 95% CI: 0.02, 1.91); however, carbon monoxide exposure was not significantly associated with HR when based on a 5-day average exposure concentration (0.7 per 3.3 mg/m^3 [2.9 ppm], 95% CI: -0.09, 1.58). A subsample of 6,232 adults (age range: 45–64 years) from the *Atherosclerosis Risk in Communities* study (Washington County, Maryland; Forsyth County, North Carolina; and selected suburbs of Minneapolis, Minnesota and Jackson, Mississippi) examined possible associations between exposure to carbon monoxide (mean: 0.65 ppm, standard deviation [SD]: 0.44) and HR and HRV, as well as to other air pollutants (PM_{10}, O_3, NO_2, SO_2; Liao et al. 2004). An increase in carbon monoxide exposure concentration of 0.44 ppm was associated with a small but significant increase in HR of 0.4 beats per minute (standard error [SE]: 0.16, 95% CI: 0.09, 0.7 [calculated from SE]). Carbon monoxide exposure was not significantly associated with HRV.

Studies of Arrhythmia. Studies of associations between exposure to carbon monoxide and cardiac arrhythmia (e.g., fibrillation, tachycardia) have yielded mixed results (Table 3-6). Mean values of carbon monoxide exposure concentrations (i.e., averages over 1–5 days prior to the end point assessment) ranged from 0.2 to 1.7 ppm, with the highest values ≤8 ppm. Significant associations between increasing carbon monoxide exposure and arrhythmia episode incidence were found in some studies, particularly when the analysis was restricted to subjects with prior recent arrhythmia (Berger et al. 2006; Dockery et al. 2005; Peters et al. 2000a), but not in other studies (Metzger et al. 2007; Rich et al. 2004, 2005; Sarnat et al. 2006; Vedal et al. 2004). One of the larger studies examined associations between exposures to carbon monoxide (median: 0.8 ppm; 95th percentile: 1.37 ppm) and other air pollutants (e.g., PM_{10}, $PM_{2.5}$, O_3, NO_2, SO_2) and ventricular arrhythmia episodes in 203 patients who were monitored with implanted defibrillators (ICDs) and who had prior episodes of ventricular tachycardia (Dockery et al. 2005; Rich et al. 2005). In the total sample, exposure to carbon monoxide was not significantly associated with ventricular arrhythmia; however, when restricted to patients who had experienced arrhythmias within the 3 days of the exposure assessment, increasing carbon monoxide exposure of 0.48 ppm was significantly associated ventricular arrhythmia (odds ratio: 1.65; 96% CI: 1.17, 2.33). A larger study examined 512 patients (age range: 15–88 years) exposed to a mean carbon monoxide concentration of 1.7 ppm

(range: 0.1–7.7 ppm) and did not find a significant association with defibrillator discharges and carbon monoxide exposure concentration (Metzger et al. 2007).

Studies that have assessed arrhythmias from EKG measurements have also yielded mixed results (Berger et al. 2006; Sarnat et al. 2006). A study of 57 coronary heart disease patients (age range: 52–76 years) found a significant association between increasing carbon monoxide exposure and risk of supraventricular tachycardia (Berger et al. 2006). Mean carbon monoxide exposure concentration was 0.52 mg/m^3 (0.45 ppm; range: 0.11–1.93 mg/m^3 [0.10–1.68 ppm]). The relative risk for a 0.27 mg/m^3 (0.24 ppm) increase in carbon monoxide was 1.18 (95% CI: 1.04, 1.35). A significant association between carbon monoxide exposure and ventricular tachycardia was not evident. Sarnat et al. (2006) did not find a significant association between carbon monoxide exposure concentrations (mean: 0.2 ppm, range: 0.1–1.5) and arrhythmia in a sample of 32 adults (age range: 53–90 years). The study did find significant associations between increased blood pressure and other air pollutants (e.g., $PM_{2.5}$, SO_2, O_3, back carbon).

Studies of Ischemic Heart Disease. Numerous studies have examined possible associations between carbon monoxide exposure and ischemic heart disease (Tables 3-6 and 3-7). Although results have been mixed, most studies, in particular those that examined hospital admissions or emergency room visits as the health outcome, have found increased risk association with increased ambient air carbon monoxide concentrations. A case-control study of myocardial infarction (1,397 cases, 1,870 controls) conducted in Sweden did not find a significant association with carbon monoxide exposure (Rosenlund et al. 2006). Exposure concentrations were estimated from emissions data and air dispersion modeling; the mean was 61.8 $\mu g/m^3$ (0.067 ppm; 5^{th}–95^{th} percentile range: 14–296 $\mu g/m^3$; predicted steady-state COHb%: <0.3). The odds ratio for myocardial infarct for a 300 $\mu g/m^3$ (0.3 ppm) increase in 30-year average carbon monoxide concentration was 1.04 (95% CI: 0.89, 1.21). When restricted to out-of-hospital deaths, the odds ratio was 1.36 (95% CI: 1.01, 1.84). A smaller case-crossover study (772 cases) conducted in Boston, Massachusetts did not find a significant association between carbon monoxide exposure and myocardial infarction (Peters et al. 2001). The odds ratio for a 1 ppm increment in carbon monoxide exposure concentration, for a 2-hour period prior to infarct, was 1.22 (95% CI: 0.89, 1.67); the mean carbon monoxide exposure concentration was 1.09 (5^{th}–95^{th} percentile range: 0.49–1.78 ppm, predicted steady-state COHb%: ≤0.55).

Possible associations between carbon monoxide exposure (and other air pollutants; e.g., PM, NO_2, O_3) and ischemic heart disease have also been explored in studies of hospital admissions and/or hospital emergency department visits (D'Ippoliti et al. 2003; Hosseinpoor et al. 2005; Lanki et al. 2006; Lee et al.

Table 3-7. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Hospital Admissions and Emergency Department Visits Related to Cardiovascular Disease

Study	Design features	CO exposure	Effect size
Ischemic heart disease			
D'Ippoliti et al. 2003 Period: 1995–1997 Location: Rome, Italy	Outcome: MI HAs Design: Case-crossover Sample: n=6,531, age ≥18 years	Avg time: 24 hours Mean: 3.8 ppm 25^{th}–75^{th}%: 2.4–3.8 ppm	Increment: 1 mg/m^3 OR (95% CI), lag 0–2 days: CO alone: 1.044 (1.000, 0.089) CO with TSP: not significant
Hosseinpoor et al. 2005 Period: 1996–2001 Location: Tehran, Iran	Outcome: AP HAs Design: Time series Sample: n=1,826	Avg time: 24 hours Mean: 9.4 ppm Range: 1.4–50.5 ppm	Increment: 1 mg/m^3 (0.87 ppm) RR (95% CI), lag 1 day: CO alone: 1.0096 (1.0060, 1.0132) CO with NO_2, O_3, and PM_{10}: 1.0093 (1.0036, 1.0151)
Lanki et al. 2006 Period: 1994–2000 Location: Helsinki, Rome, Stockholm	Outcome: MI HAs Design: Time series Sample: 26,854 admissions, age ≥35 years	Avg time: 24 hours Median: 0.4–2.3 ppm 75^{th}% Range: 0.5–2.9 ppm	Increment: 0.2 mg/m^3 RR (95% CI), lag 0 days: All: 1.007 (1.001, 1.012) Fatal (≤75 years): 1.027 (1.006, 1.048)
Lee et al. 2003b Period: 1997–1999 Location: Seoul, Korea	Outcome: IHD, MI, AP HAs Design: Time series Sample: ~10,000 HAs	Avg time: Daily maximum Mean: 1.8 ppm 25^{th}–75^{th}%: 1.2–2.2 ppm	Increment: 1 ppm RR (95% CI), lag 5 days: All year, all ages: 0.94 (0.91, 0.98) All year, ≥64 years: 1.07 (1.01, 1.13) Summer, all ages: 1.19 (1.02, 1.38) Summer, ≥64 years: 1.60 (1.27, 2.03) All year, ≥64 years (with PM_{10}): 1.04 (0.98, 1.11)
Maheswaran et al. 2005b Period: 1994–1998 Location: Sheffield, United Kingdom	Outcome: IHD HAs Design: Ecological Subjects: 11,407 admissions, age ≥45 years	Avg time: NR 20^{th}–80^{th}%: 0.34–0.40 ppm	Increment: 5^{th} vs. 1^{st} quintile RR, adjusted for sex, age, deprivation, smoking (95% CI): 0.88 (0.79, 0.98)
Mann et al. 2002 Period: 1988–1995 Location: California	Outcome: IHD, MI HAs Design: Time series Sample: 54,863 HAs	Avg time: 8 hours Mean: 2.07 ppm Range: 0.30–11.8 ppm	Increment: 1 ppm % Change (95% CI), lag 0 days: with arrhythmia: 2.99 (1.80, 4.99) with CHF: 3.60 (1.620, 5.63) without secondary diagnosis: 1.62 (0.65, 2.59)

Table 3-7. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Hospital Admissions and Emergency Department Visits Related to Cardiovascular Disease

Study	Design features	CO exposure	Effect size
Szyszkowicz 2007 Period: 1997–2003 Location: Montreal	Outcome: IHD EDVs Design: Time series Sample: 4,979 EDVs	Avg time: 24 hours Mean: 0.5 ppm Range: 0.1–3.1 ppm	Increment: 0.2 ppm % Change (95% CI), lag 0 days: All: 5.4 (2.3, 8.5) Males: 7.5 (3.6, 11.6) Females: 2.7 (-2.0, 7.6) All: ≥64 years: 4.9 (1.3, 8.7) Males: ≥64 years: 7.5 (2.6, 12.6) Females: ≥64 years: 0: 2.4 (-3.0, 0.0)
von Klot et al. 2005 Period: 1992–2001 Location: 5 European cities	Outcome: MI, AP, CAR, HF, HAs Design: Prospective cohort Sample: 22,006 survivors of first MI	Avg time: 24 hours Mean: 0.37–0.87 ppm	Increment: 0.2 mg/m^3 RR (95% CI), lag 0 days: MI: 1.022 (0.998, 0.047) AP: 1.009 (0.992, 0.02) Any cardiac: 1.014 (1.001, 0.026)
Stroke			
Chan et al. 2006 Period: 1997–2002 Location: Taipei, Taiwan	Outcome: Stroke EDVs Design: Time series Sample: 7,341 EDVs, age 50–100 years	Avg time: 8 hours Mean: 1.7 ppm Range: 0.6–4.4 ppm	Increment: 0.8 ppm OR (95% CI), lag 2 days: All: 1.03 (1.01, 1.06) Stroke: 1.03 (1.01, 1.05) Significant after adjustment for O_3, $PM_{2.5}$, PM_{10}
Henrotin et al. 2007 Period: 1994–2004 Location: Dijon, France	Outcome: Stroke HAs Design: Case-crossover Sample: 1,707 cases, age: ≥40 years	Avg time: 24 hours Mean: 0.60 ppm Range: 0–3.5 ppm	Increment: 10 $\mu g/m^3$ OR (95% CI), lag 0 days: Ischemic: 0.999 (0.997, 1.001) Hemorrhagic: 1.000 (0.996, 1.004) Other lags not significant
Maheswaran et al. 2005b Period: 1994–1998 Location: Sheffield, United Kingdom	Outcome Stroke HAs Design: Ecological Sample: 11,407 HAs, age ≥45 years	Avg time: NR 20^{th}–80^{th}%: 0.34–0.40 ppm	Increment: 5^{th} vs. 1^{st} quintile RR (95% CI) adjusted for sex, age, deprivation, smoking: 1.11 (0.99, 1.25)

Table 3-7. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Hospital Admissions and Emergency Department Visits Related to Cardiovascular Disease

Study	Design features	CO exposure	Effect size
Tsai et al. 2003 Period: 1997–2000 Location: Kaohsiung, Taiwan	Outcome: Stroke HAs Design: Case-crossover Statistical analyses: NR Sample: 23,192 HAs	Avg time: 24 hours Mean 0.79 ppm Range: 0.24–1.72 ppm	Increment: 0.8 ppm OR (95% CI), lag 0–2 days: >20 °C: 1.21 (1.14, 1.28) <20 °C: 1.77 (1.31, 2.39) Significant OR when adjusted for PM_{10}, SO_2, or O_3
Villeneuve et al. 2006a Period: 1992–2002 Location: Edmonton, Canada	Outcome: Stroke EDVs Design: Case-crossover Sample: 12,422 EDVs, age ≥65 years	Avg time: 24 hours Mean: 0.8 ppm 25^{th}–75^{th}%: 0.5–1.0 ppm	Increment: 0.5 ppm OR (95% CI), lag 0–2 days: April–September: 1.32 (1.09, 1.60) (not significant for all seasons)
Wellenius et al. 2005a Period: NR Location: 9 U.S. cities	Outcome: Stroke EDVs Design: Time series Sample: 155,503 EDVs, age ≥65 years	Avg time: NR Median: 1.02 ppm 25^{th}–75^{th}%: 0.73–1.44 ppm	Increment: 0.71 ppm % Change (95% CI) lag 0 days: Ischemic: 2.83 (1.23, 4.46) Hemorrhagic: -1.61 (-4.79, 1.68)
Heart failure			
Lee et al. 2007a Period: 1996–2004 Location: Kaohsiung, Taiwan	Outcome: CHF HAs Design: Case-crossover Sample description: 13,475 HAs	Avg time: 24 hours Mean: 0.76 ppm Range: 0.14–1.72 ppm	Increment: 0.31 ppm OR (lag 0–2 days): ≥25 °C: 1.19 (1.09–1.31) <25 °C: 1.39 (1.24–1.54) Significant when adjusted for PM_{10}, NO_2, SO_2, or O_3
Symons et al. 2006 Period: 2002 Location: Baltimore, Maryland	Outcome: CHF HAs, symptom exacerbation Design: Case-crossover Sample: 125 cases, median age 70 years	Avg time: 24 hours Mean: 0.4 ppm Range: 0.1–1.0 ppm	Increment: 0.2 ppm OR (95% CI), lag 1 day: Avg: 0.90 (0.70, 1.17) Cumulative: 0.82 (0.60, 1.13) Other lags not significant
Wellenius et al. 2005b Period: 1987–1999 Location: Pennsylvania	Outcome: CHF HAs Design: Case-crossover Sample: 54,019 HAs, age ≥65 years	Avg time: 24 hours Mean: 1.03 ppm 25^{th}–75^{th}%: 0.68–1.23 ppm	Increment: 0.55 ppm % Change (85% CI), lag 0 days: 4.55 (3.33, 5.79) Significant when adjusted for NO_2 PM_{10}, NO_2, SO_2, or O_3

Table 3-7. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Hospital Admissions and Emergency Department Visits Related to Cardiovascular Disease

Study	Design features	CO exposure	Effect size
Miscellaneous cardiovascular disease			
Ballester et al. 2001 Period: 1994–1996 Location: Valencia, Spain	Outcome: HD, CBVD EDVs Design: Time series Sample: >9,000 EDVs	Avg time: 1 hour Mean: 5.4 ppm Range: 0.5–15.5 ppm	Increment: 1 mg/m^3 RR (95% CI): All, lag 2: 1.0077 (0.9912, 1.0138) HD, lag 1: 1.0092 (0.9945, 1.0242) CBVD, lag 1: 0.9874 (0.9646, 1.0107)
Ballester et al. 2006 Period: 1995–1999 Location: 14 cities in Spain	Outcome: HD, CVD HAs Design: Time series Sample: >250,000 HAs	Avg time: 8 hours Mean: 1.2–2.4 ppm 10^{th}% Range: 0.3–1.5 ppm 90^{th}% Range: 1.7–3.4 ppm	Increment: 1 mg/m^3 % Change (95% CI), lag 0–1 day: CVD: 2.06 (0.65, 3.48) HD: 4.15 (1.31, 7.08)
Barnett et al. 2006 Period: 1998–2001 Location: Australia, Auckland, New Zealand	Outcome: CVD HAs Design: Case-crossover Sample: age ≥15 years	Avg time: 8 hours Mean: 0.5–2.1 ppm Range: 0.0–7.9 ppm	Increment: 0.9 ppm % Change (95% CI) lag 0–1 day: Lags examined (days): 0–1 15–64 years CVD, <65 years: 1.2 (0.3, 2.1) CVD, ≥65 years: 2.2 (0.9, 3.4) Significant when adjusted for NO_2 or PM_{10}
Bell et al. 2009 Period: 1999–2005 Location: 126 urban U.S. counties	Outcome: CVD HAs Design: Time series Sample: >9.3 million HAs, age >65 years	Avg time: 1 hour Median (daily maximum): 1.3 ppm 25^{th}–75^{th}%: 0.9–1.9 ppm	Increment: 1 ppm RR % Change (95% CI) lag 0 days: CO: 0.96 (0.79, 1.12) CO+NO_2: 0.55 (0.36, 0.74) CO+$PM_{2.5}$: 0.76 (0.57, 0.96) CO+NO_2+$PM_{2.5}$: 0.52 (0.29, 0.75)
Chang et al. 2005 Period: 1997–2001 Location: Taipei, Taiwan	Outcome: CVD HAs Design: Case-crossover Sample 74,509 HAs	Avg time: 24 hours Mean: 1.37 ppm Range: 0.37–3.66 ppm	Increment: 0.49 ppm OR (95% CI) lag 0–2 days: ≥20 °C: 1.090 (1.064, 1.118) <20 °C: 0.984 (0.927, 1.044) Significant when adjusted for PM_{10}, NO_2, SO_2, or O_3

Table 3-7. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Hospital Admissions and Emergency Department Visits Related to Cardiovascular Disease

Study	Design features	CO exposure	Effect size
Fung et al. 2005 Period: 1995–2000 Location: Windsor, Ontario, Canada	Outcome: CVD HAs Design: Time series Sample: 11,632 HAs	Avg time: 24 hours Mean: 1.3 ppm Range: 0.0–11.8 ppm	Increment: 1.2 ppm % Change (95% CI), lag 0–2 days: <65 years: -0.5 (-6.7, 6.0) ≥65 years: 2.8 (-1.1, 7.0)
Jalaludin et al. 2006 Period: 1997–2001 Location: Sydney, Australia	Outcome: CVD EDVs Design: Time series Sample: >100,000 EDVs, age ≥65 years	Avg time: 8 hours Mean 0.82 ppm Range: 0.02–4.63 ppm	Increment: 0.69 ppm % Change (95% CI), lag 0–1 days: 2.35 (1.39, 3.32) Significant when adjusted for PM_{10}, NO_2, SO_2, or O_3
Koken et al. 2003 Period: 1993–1997 Location: Denver, Colorado	Outcome: CVD HAs Design: Time series Sample: >4,000 HAs, age 65 years	Avg time: 24 hours Mean: 0.9 ppm Range: 0.3, 1.6 ppm	Increment: 0.3 ppm % Change (95% CI) lag 3 days: CHF: 10.5 (0.1, 22.0) CO not significantly associated with other CVD categories.
Linn et al. 2000 Period: 1992–1995 Location: Los Angeles, California	Outcome: CVD, CBVD HAs Design: Time series Sample: >500,000 HAs, age >30 years	Avg time: 24 hours Mean 1.0–2.0 ppm Range: 0.2–5.3 ppm	Increment: 1 ppm Poisson regression coefficient (SE), lag 0 days: CVD, all: 0.032 (0.003) ($p<0.05$) Significant for AR, CBVD, CHF, MI, stroke $p<0.05$
Metzger et al. 2004 Study: 1993–2000 Location: Atlanta, Georgia	Outcome: Cardiovascular: CVD EDVs Design: Time series Sample: 4,407,535 EDVs	Avg time: 1 hour Median: 1.5 ppm 10^{th}–90^{th}%: 0.5–3.4 ppm	Increment: 1 ppm RR (95% CI), lag 0–2 days: All CVD: 1.017 (1.008, 1.027) PVD/CBVD: 1.031 (1.010, 1.052) Not significant for AR, CHF, IHD categories
Peel et al. 2007 Period: 1993–2000 Location: Atlanta, Georgia	Outcome: CVD EDVs Design: Case-crossover Sample: 4,407,535 EDVs	Avg time: 1 hour Mean: 1.8 ppm SD: 1.2 ppm	Increment: 1.2 ppm OR (95% CI), lag 0–2 days: 1.020 (1.010, 10.030) ORs for specific CVD categories tended to increase with co-diagnoses of HT, AR, CHF, COPD

Table 3-7. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Hospital Admissions and Emergency Department Visits Related to Cardiovascular Disease

Study	Design features	CO exposure	Effect size
Yang et al. 2004a Period: 1997–2000 Location: Kaohsiung, Taiwan	Outcome: CVD HAs Design: Case-crossover Sample: 29,661 HAs	Avg time: 24 hours Mean: 0.79 ppm Range 0.24–1.72 ppm	Increment: 0.28 ppm OR (95% CI), lag 0–2 days: ≥25 °C: 1.264 (1.205, 1.326) <25 °C: 1.448 (1.357, 1.545) Significant when adjusted for PM_{10}, NO_2, SO_2, or O_3

AP = angina pectoris; AR = arrhythmia; Avg = average; CAR = cardiac arrhythmia; CBVD = cerebrovascular disease; CHF = congestive heart failure; CI = confidence interval; CO = carbon monoxide; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; EDV = emergency department visit; HA = hospital admission; HD = heart disease; HF = heart failure; HT = hypertension; IHD = ischemic heart disease; MI = myocardial infarction; NR = not reported; OR = odds ratio; PVD = peripheral vascular disease; RR = relative risk; SD = standard deviation; SE = standard error; TSP = total suspended particles

2003b; Maheswaran et al. 2005b; Mann et al. 2002; Szyszkowicz 2007; von Klot et al. 2005). Although results have been mixed, most studies found significant associations between increasing carbon monoxide exposure concentration and ischemic heart disease-related admissions or emergency room visits (Table 3-7). These included increased odds (or relative risk) for hospital admissions for angina pectoris, myocardial infarction, and aggregated ischemic heart disease categories (D'Ippoliti et al. 2003; Hosseinpoor et al. 2005; Lanki et al. 2006; Lee et al. 2003b; Mann et al. 2002; Szyszkowicz 2007; von Klot et al. 2005). Mean air carbon monoxide concentrations in these studies ranged from approximately 0.4 to 2 ppm, with the upper percentiles (i.e., $\geq 75^{th}$) ranging from approximately 1 to 5 ppm, although one study reported a mean of 10.8 mg/m^3 (9.40 ppm) and a maximum of 57.9 mg/m^3 (approximately 50 ppm; Hosseinpoor et al. 2005). Associations with carbon monoxide tended to be stronger for more elderly males than for females or other age strata (e.g., Lee et al. 2003b; Szyszkowicz 2007). Risks were higher when ischemic heart disease was accompanied by a diagnosis of arrhythmia or congestive heart failure (Mann et al. 2002; see further discussion of carbon monoxide associations with congestive heart failure, below). Lee et al. (2003b) found a significant association (1997–1999) between ischemic heart disease-related hospital admissions in Seoul, Korea and carbon monoxide exposure concentrations among males ≥64 years of age, but not for females or other age strata. A 1 ppm increase in carbon monoxide concentration was associated with a relative risk of 1.07 (95% CI: 1.01, 1.1) for hospital admission. The mean daily 1-hour maximum carbon monoxide concentration was 1.8 ppm (25^{th}–75^{th} percentile range: 1.2–2.2 ppm). The association with carbon monoxide exposure was not significant after adjustment for exposure to PM_{10} in a two-pollutant model (1.04. 95% CI: 0.98, 1.11). Two-pollutant models with carbon monoxide and other gaseous pollutants were not reported, although significant associations were found when NO_2, O_3, or SO_2 were considered alone. Szyszkowicz (2007) examined records of 4,979 emergency room visits in Montreal, Canada for the period 1997–2002. The percent increase in visits related to ischemic heart disease for a 0.2 ppm increase in carbon monoxide concentration was 5.4% (95% CI: 2.3, 8.5) for all patients, 7.5% (2.6–12.6) for males ≥64 years, and 2.4% (-3.0–0.0) for females ≥64 years. The mean carbon monoxide exposure concentration was 0.5 ppm (range: 0.1–3.1 ppm). Two other studies examined ischemic heart disease end points in multiple-pollutant models. Hosseinpoor et al. (2005) found that the relative risk for hospital admissions for angina pectoris (1,826 cases; Tehran, Iran; 1996–2001) was 1.044 (95% CI: 1.000, 0.089) when air carbon monoxide concentrations were considered in a carbon monoxide model and 1.0093 (95% CI: 1.0036, 1.0151) when the model was adjusted for PM_{10}, O_3, and NO_2. Air carbon monoxide concentrations examined in this study were relatively high compared to other studies (mean: 10.8 ppm; range: 1.6–58 ppm). A study conducted in Rome, Italy examined records of 6,351 hospital admissions (1995–1997) for myocardial infarction and found a significant association between increasing air carbon monoxide concentration and increasing odds

of hospital admission (odds ratio: 1.004, 95% CI: 1.000, 0.089), which did not persist when adjusted for total suspended solids (D'Ippoliti et al. 2003). The mean air carbon monoxide concentration was 3.8 ppm (25^{th}–75^{th} percentile range: 2.4–3.7 ppm).

Studies of Stroke. Possible associations between ambient air carbon monoxide concentrations and stroke have been examined in studies of hospital admissions and emergency room visits (Chan et al. 2006; Henrotin et al. 2007; Maheswaran et al. 2005b; Tsai et al. 2003b; Villeneuve et al. 2006a; Wellenius et al. 2005a; Table 3-7). Although results of these studies have been mixed, several studies have found significant associations between stroke admissions and/or emergency room visits and increasing air carbon monoxide concentrations (Chan et al. 2006; Tsai et al. 2003b; Villeneuve et al. 2006a; Wellenius et al. 2005a). Studies that explored two-pollutant models found that the associations persisted after adjustment for PM_{10}, SO_2, or O_3 (Chan et al. 2006; Tsai et al. 2003b). Mean air carbon monoxide concentrations in these studies ranged from 0.4 to 1.7 ppm, and the highest reported values were ≤5 ppm. The largest study was a time-series analysis of ambient air carbon monoxide concentrations and 155,503 records of stroke-related emergency room visits in nine U.S. cities (Wellenius et al. 2005a). The study found that a 0.71 ppm increase in ambient air carbon monoxide concentration was associated with a 2.83% (95% CI: 1.23, 4.46) increase in daily rate of emergency room visits for ischemic stroke. Chan et al. (2006) conducted a time-series analysis of ambient air carbon monoxide concentrations in Taipei, Taiwan (1997–2002) and emergency room visits related to cerebrovascular disease, including stroke (n=7,341) and found a significant odds ratio for a 0.8 ppm increase in air carbon monoxide concentration for all cerebrovascular disease (1.03, 95% CI: 1.01, 1.06) and stroke (1.03, 95% CI: 1.01, 1.05), which remained significant after adjusting for O_3, $PM_{2.5}$ and PM_{10}, or $PM_{2.5}$ (1.034, 95% CI: 1.001, 1.067). A larger study conducted in Kaohsiung, Taiwan (1997–2000) examined records of 23,192 hospital visits for stroke in a case-crossover design and found significant odds ratios for a 0.8 ppm increase in carbon monoxide concentration (1.77, 95% CI: 1.31, 2.39), which also persisted after adjustment for SO_2, O_3, or PM_{10} (Tsai et al. 2003b).

Studies of Other Cardiovascular Outcomes. Case-crossover studies examining possible associations between ambient carbon monoxide concentrations and cardiac arrest have either not found significant associations or found associations that were relatively small in magnitude (Dennekamp et al. 2010; Levy et al. 2001; Silverman et al. 2010; Sullivan et al. 2003; Table 3-6). In two studies that were conducted in Seattle, Washington, the mean carbon monoxide exposure concentration (both studies) was 1.7 ppm, with the highest value reported as 5.9 ppm. The study reported by Levy et al. (2001) included 362 cases out-of-hospital cardiac arrests (1988–1994); the relative risk for a 1-day lag between exposure estimate and

outcome was 0.88 (95% CI: 0.83, 1.18). The Sullivan et al. (2003) study examined 1,542 cases of out-of-hospital cardiac arrest cases (1985–1994); the odds ratio for a 1.02 ppm increase in carbon monoxide concentration (1-day lag) was 0.97 (95% CI: 0.87, 1.08). The Silverman et al. (2010) study examined 8,216 cases of out-of-hospital cardiac arrests in New York City (2002–2006) and did not find a significant association; the relative risk for a 0.3-ppm increment in carbon monoxide was approximately 0.99 (95% CI: 0.96, 1.03). The Dennekamp et al. (2010) study examined 8,434 cases of out-of-hospital cardiac arrests in Melbourne, Australia (2003–2006) and found a small association; the relative risk was 1.031 (95% CI: 1.002, 1.046) per 0.25-ppm increase in carbon monoxide concentration.

Possible associations between air carbon monoxide concentrations and cardiac failure (primarily, congestive heart failure) have also been examined in studies of hospital admissions (Lee et al. 2007a; Symons et al. 2006; Wellenius et al. 2005b; Table 3-6). The larger of the these studies (Lee et al. 2007a) examined 13,475 hospital admissions for congestive heart failure in Kaohsiung, Taiwan (1996–2004) and found a significant odds ratios for hospital admission associated with a 0.31 ppm increase in air carbon monoxide concentration (odds ratio: 1.39, 95% CI: 1.24, 1.54). The odds ratio remained significant in two-pollutant models that adjusted for PM_{10}, NO_2, SO_2, or O_3.

Studies of possible associations between carbon monoxide exposure and abnormal blood pressure have not found significant associations (Ibald-Mulli et al. 2001; Zanobetti et al. 2004b; Table 3-6). The Ibald-Mulli et al. (2001) study included 2,607 men and women (age range 25–64 years) in the Augsburg, Germany area; the mean carbon monoxide exposure concentration was approximately 3.6 ppm and the upper end of the range was 7.2 ppm. The estimated increment in systolic blood pressure for a 4.9 ppm increase in carbon monoxide concentration was 1.06 (95% CI: -0.17, 2.29). The Zanobetti et al. (2004b) study measured blood pressure in repeated examinations of 62 subjects, and found no association between blood pressure and carbon monoxide exposure concentrations (90^{th} percentile concentration <1.2 ppm).

Several studies have evaluated more generic cardiovascular disease outcomes, for example, hospital admissions or emergency room visits for any cardiovascular disease (Ballester et al. 2001, 2006; Barnett et al. 2006; Bell et al. 2009; Chang et al. 2005; Fung et al. 2005; Jalaludin et al. 2006; Koken et al. 2003; Linn et al. 2000; Metzger et al. 2004; Peel et al. 2007; Yang et al. 2004a; Table 3-7). Here again, although results have been mixed, most studies found significant associations between increased rate of hospital admissions or emergency room visits and increased air carbon monoxide concentrations. The association was stronger for older subjects (e.g., ≥64 years, Barnett et al. 2006), and in several studies that examined multi-pollutant models, the association persisted after adjustment for PM_{10}, NO_2, SO_2, or O_3

(Bell et al. 2009; Chang et al. 2005; Jalaludin et al. 2006; Yang et al. 2004a). The mean air carbon monoxide concentrations in these studies ranged from 0.8 to 6 ppm, with the highest values ≤18 ppm.

Animal Studies. Although clinical studies in patients with coronary artery disease provide compelling evidence of adverse cardiovascular effects of acute-duration exposure to carbon monoxide, these studies are limited with respect to exposure conditions and outcomes assessed. Studies in animals, however, have investigated adverse cardiovascular effects of carbon monoxide exposure over a much wider range of exposure conditions (e.g., exposure concentration and duration) and have evaluated additional outcome measures that are not possible to assess in humans. In general, animal studies evaluated carbon monoxide exposures resulting in higher COHb levels than those evaluated in clinical studies in patients and healthy volunteers. Results of animal studies provide evidence of adverse cardiovascular effects of carbon monoxide exposure, including compensatory alterations in hemodynamics, cardiac hypertrophy, cardiac arrhythmias, and possibly atherosclerosis (EPA 1991, 2000). For most outcomes evaluated in animal studies, conflicting evidence has been reported. Although the reasons for different results have not been established, differences in species sensitivity, exposure regimens, and experimental protocols are possible factors. Animal studies published prior to 2000 have been reviewed in detail by EPA (1991, 2000); therefore, these reviews largely form the basis of the following discussions for animals studies published prior to 2000.

Studies investigating the effects of acute-duration carbon monoxide exposure on hemodynamics have been conducted in several animal species, including monkeys, dogs, rats, and rabbits, under exposure conditions producing blood COHb levels ranging from 6.2 to 70% (EPA 1991, 2000). Results show that brief exposure (from a few minutes to approximately 3 hours) to carbon monoxide at concentrations of 80–20,000 ppm produces alterations in hemodynamics that are consistent with COHb-induced hypoxia and responsive compensatory mechanisms (e.g., vasodilation and increased cardiovascular output), including increased coronary blood flow, decreased myocardial O_2 consumption, increased heart rate, and alterations in blood flow to various vascular beds (e.g., cerebral, limb muscular). Generally, carbon monoxide-induced effects on hemodynamics were observed at blood COHb levels ≥7.5%. With longer exposure durations at these same concentrations, COHb-induced tissue hypoxia and subsequent compensatory increases in heart rate and cardiac workload lead to the development of cardiomyopathy. Several studies confirm carbon monoxide-induced cardiomegaly in rats and rabbits exposed to 160–11,000 ppm carbon monoxide (COHb 12–58%) for intermediate durations (14 days to ~6 months) (EPA 1991, 2000). Cardiac remodeling, including left ventricular fibrosis of interstitial and perivascular tissue, was observed in rats exposed to 30 ppm, with five daily spikes of 100 ppm, for 12 hours/day for 4 weeks

(Andre et al. 2010). Under these same exposure conditions, carbon monoxide reduced myocardial perfusion reserved under β-adrenergic stress and alterations in contractile function (Meyer et al. 2011). In rats exposed chronically to 200 ppm carbon monoxide (COHb 14.7%) for 20 hours/day for 72 weeks, left and right ventricle weights increased by 20% ($p<0.001$) and 14% ($p<0.001$), respectively (Sørhaug et al. 2006). Studies evaluating developmental cardiovascular effects are reviewed in Section 3.2.6 (Developmental Effects).

Alterations in cardiac rhythm, possibly due to disturbances in cardiac conduction, have been observed in animals exposed to carbon monoxide for acute to intermediate durations (EPA 1991, 2000). Under conditions of simulated myocardial ischemia (i.e., coronary artery ligation), acute exposure (up to 15 minutes) of dogs to up to 5,000 ppm carbon monoxide (COHb 4.9–15%) enhanced myocardial ischemia, as indicated by ST-segment alterations, and severity of myocardial injury. Results of a recent study in rats exposed to 50 ppm carbon monoxide (COHb not reported) for 1 week indicate that rats with pulmonary hypertension may be more sensitive to carbon monoxide-induced myocardial ischemia (Gautier et al. 2007). However, in other studies simulating myocardial injury in dogs exposed to 100–500 ppm carbon monoxide for 6–120 minutes (COHb 5.1–20%), cardiac arrhythmias or alterations in cardiac conduction speed were not observed. In studies evaluating intermediate-duration (6–24 weeks) exposure of dogs and monkeys, 100 ppm carbon monoxide (COHb 2.6–12%) induced cardiac arrhythmias, including R-wave depression, ST-segment elevation, increased T-wave, preventricular contractions, and reduced threshold for stimulus-induced ventricular fibrillation. In contrast, no evidence of cardiac arrhythmias was observed in dogs exposed continuously to 50 ppm carbon monoxide (COHb 7.3%) for 3 months or in monkeys exposed intermittently to 500 ppm (COHb 21.6%) for 14 months.

Conflicting evidence has been reported regarding the potential for carbon monoxide exposure to induce or enhance atherosclerosis (EPA 1991, 2000). Results of most studies in animals (monkeys, baboons, rabbits, and pigs) fed normal diets were negative for inducing or enhancing atherosclerosis at carbon monoxide concentrations of 50–400 ppm (COHb ~20%) for exposure durations up to 14 months. However, atherosclerosis was increased in monkeys continuously exposed to 200 ppm carbon monoxide (COHb 20.6%) for 2 weeks (Thomsen 1974) and in rabbits and monkeys fed high cholesterol diets exposed to 100–300 ppm carbon monoxide (COHb 9–33%) for 2–7 months. Based on the weight of evidence, EPA (1991, 2000) concluded that the available data do not strongly support a relationship between atherogenic effects and carbon monoxide exposure.

Gastrointestinal Effects. Studies evaluating gastrointestinal effects of exposure to low levels of carbon monoxide (i.e., producing blood COHb levels <20%) were not identified. Although the gastrointestinal tract has not been identified as a specific target organ for carbon monoxide-induced toxicity, exposure to carbon monoxide at levels producing hypoxia would be expected to affect any tissue, in particular those tissues with high O_2 utilization requirements (e.g., brain, liver, kidney, heart, small intestine).

Hematological Effects. Hematological effects of carbon monoxide include compensatory responses to tissue hypoxia resulting from binding of carbon monoxide to Hb (e.g., increased blood volume, Hb, hematocrit, and erythrocyte count and volume). Possible associations between ambient air carbon monoxide concentrations and hematologic biomarkers of coagulation and inflammation have been examined in epidemiological studies. Collectively, these studies provide some evidence for associations that may reflect effects of carbon monoxide in modulating these systems.

Hypoxia and Related Compensatory Responses. Inhalation exposure to carbon monoxide results in the formation of COHb, a stable complex between carbon monoxide and Hb. Because carbon monoxide has a much higher affinity for Hb than O_2 (equilibrium constant for carbon monoxide is >200 times that of O_2), O_2 is displaced from Hb by relatively low partial pressures of carbon monoxide. Binding of carbon monoxide to Hb has two effects that contribute to impaired O_2 delivery to tissues: (1) in the presence to carbon monoxide, the amount of O_2 that can be stored on Hb for delivery to tissues decreases; and (2) binding of carbon monoxide to Hb impairs release of O_2 from Hb for its diffusion into tissues (see Section 3.4.3 for further discussion of effects of carbon monoxide on O_2 dissociation from Hb). At sufficient levels of COHb, the combined effects of impaired O_2 storage and transport results in tissue hypoxia, the principal mechanism of many adverse effects of carbon monoxide exposure.

To maintain O_2 delivery to tissues under conditions of hypoxia, compensatory hematological responses (e.g., increased erythrocyte count, hematocrit, and Hb) occur. The dose-response relationship for carbon monoxide-induced compensatory hematological responses in humans has not been established. Studies in animals show that compensatory hematological effects occur in response to the COHb-induced reduction in O_2 delivery to tissues. Compensatory hematological effects, including increased blood volume, Hb, hematocrit, and erythrocyte count and volume, have been observed following acute- and intermediate-duration carbon monoxide exposure (Davidson and Penney 1988; Penney 1988; Penney et al. 1974a, 1974b; WHO 1999). Continuous exposure of rats to 500 ppm carbon monoxide (COHb 40%) for 5–42 days produced duration-dependent increases in hematocrit, blood Hb, erythrocyte count, and mean cell

Hb concentration; mean cell volume was increased after 42 days of exposure (Davidson and Penney 1988). The largest increases (approximately 45–55%) were observed for hematocrit, blood Hb, and erythrocyte count, with increases reaching maximum levels after 30 and 42 days of exposure. Similarly, blood Hb concentration increased by 70% in rats exposed continuously to 500 ppm carbon monoxide (COHb approximately 12% after 42 days) for up to 42 days, with the most rapid increase occurring within the first 21 days of exposure (Penney et al. 1974b). A small, but statistically significant increase in Hb concentration (6.0%; $p<0.001$) was observed in rats exposed to 100 ppm carbon monoxide (COHb 9.25%) for 30 days (Penney et al. 1974b). In rats exposed to 200–1,300 ppm carbon monoxide (COHb not reported) for 10–17 days, dose-related increases in hematocrit and blood volume were observed (Penney et al. 1988).

Epidemiological Studies of Blood Markers Related to Coagulation. Studies of carbon monoxide mechanisms of action have provided evidence that carbon monoxide may participate in the regulation of vascular thrombi formation and inflammation (see Section 3.5.2, Mechanisms of Toxicity). Possible associations between ambient air carbon monoxide concentrations and biomarkers of coagulation and inflammation have been examined in epidemiological studies (Baccarelli et al. 2007; Liao et al. 2005; Pekkanen et al. 2000; Rückerl et al. 2006, 2007; Steinvil et al. 2008). Biomarkers that have been examined include inflammation markers, C-reactive protein (CRP), serum amyloid A (SAA), and WBC count; cell adhesion markers, E-selectin, von Willebrand factor, antigen (vWF), ICAM-1; and coagulation markers, fibrinogen, factor VII (FVII), prothrombin fragment 1+2, prothrombin time (PT), and activated partial thromboplastin time (APTT). Collectively, these studies provide some evidence for associations between ambient air carbon monoxide concentration and changes in hematological indicators of inflammation and coagulation. However, interpretation of the results of these studies, in particular quantitative estimates of the effect magnitudes on outcomes, is limited by several factors: (1) reliance on area monitoring for estimating exposure levels; (2) uncertainty in knowledge of temporal correspondence between monitored exposure levels and outcomes; (3) relatively strong correlations between ambient air carbon monoxide concentrations and other air quality variables that can affect respiratory function; and (4) relatively low carbon monoxide exposures studied. The mean values of carbon monoxide exposure concentrations have ranged from 0.3 to 3 ppm, with the highest values $\leq$12 ppm.

Major findings from the body of reported epidemiological studies of hematological outcomes are summarized below. Although most of the studies explored various time lags between monitored air carbon monoxide concentrations and outcomes, as well as various sample strata, for the sake of brevity,

only those indicative of the strongest associations to carbon monoxide are presented. Where co-pollutant models have been explored, these results are also presented.

A cohort study conducted in London, United Kingdom (1991–1993) examined plasma fibrinogen concentrations in adult office workers (n=7,205) and found a significant association between increasing air carbon monoxide concentrations (mean 1.4 mg/m^3 [1.2 ppm], maximum: 9 mg/m^3 [8 ppm]) and increasing plasma fibrinogen concentrations (Pekkanen et al. 2000). For a 3-day lag between measured carbon monoxide concentration and fibrinogen assessment, the odds ratio for a plasma fibrinogen exceeding 3.19 g/L was 1.22 ($p<0.02$) per 1.6 mg/m^3 (1.4 ppm) increase in air carbon monoxide concentration. Increasing air concentration of NO_2 was also associated with increasing plasma fibrinogen concentration (odds ratio: 1.22, $p<0.01$), and when both were considered in two-pollutant models, the associations were no longer significant, reflecting the relative high correlation between air carbon monoxide and NO_2 concentrations ($r=0.81$). When stratified by gender, the carbon monoxide association for a 1-day lag (3-day lag data not reported) was significant in males, but not in females.

In contrast to the Pekkanen et al. (2000) study, a smaller cohort study conducted in Tel-Aviv, Israel (2003–2006, n=3,659, mean age: 46 years) found a significant association between increases in air carbon monoxide concentration and decreasing plasma fibrinogen concentration among males, but not among females (Steinvil et al. 2008). The largest effect was estimated for the 1-week air carbon monoxide average (mean: 0.8 ppm, 75^{th} percentile: 1 ppm), for which a 0.3 ppm increase in air carbon monoxide concentration was associated with a 7.7 mg/dL (95% CI: -12.1, -3.3) decrease in plasma fibrinogen in males, with no association among females (-1.6 mg/dL, 95% CI: -7.3, 4.1). Increasing air carbon monoxide concentration was also associated with a significant decrease in WBCs among males (-158 cell/µL, 95% CI: -298, -18), but not females (-182 cell/µL, 95% CI: -281, 61). However, as in the Pekkanen et al. (2000) study, the association between air NO_2 and fibrinogen was stronger than that of carbon monoxide and when included in two-pollutant models, the association with carbon monoxide was no longer significant. Significant associations with air carbon monoxide concentrations were not found for CRP.

A cohort study conducted in three U.S. locations (1996–1998) examined various blood biomarkers of coagulation and inflammation (i.e., fibrinogen, factor VIII-C, von Willebrand factor, serum albumin, WBC) in subjects enrolled in an *Atherosclerosis Risk in Communities* study (n=10,208) and found a significant association between increasing air carbon monoxide concentrations (mean 1.4 ppm, SD: 0.6) and decreasing serum albumin concentrations (Liao et al. 2005). A 0.6 ppm increase in air carbon

monoxide concentration corresponded to a 0.018 g/dL (SE: 0.003, $p<0.01$) decrease in serum albumin concentration. Other blood biomarkers evaluated were not significantly associated with air carbon monoxide concentration; results of multi-pollutant models were not reported.

A panel study conducted in Efert, German (2000–2001) examined air carbon monoxide concentrations (mean: 0.52 mg/m^3 [0.45 ppm], range: 0.11–1.93 [0.10–1.68 ppm]) and several blood biomarkers of coagulation and inflammation in 57 nonsmoking male coronary heart disease patients (age range: 51–7 years; Rückerl et al. 2006). Biomarkers evaluated included inflammation markers, CRP and SAA; cell adhesion markers, E-selectin, vWF, ICAM-1; and coagulation markers, fibrinogen, FVII, and prothrombin fragment 1+2. Odds ratios for increase in air carbon monoxide concentration of 0.27 mg/m^3 (0.23 ppm) (2-day lag) were: increasing CRP, 1.5 (95% CI: 1.1, 2.1); increasing ICAM-1, 1.7 (95% CI: 1.3, 2.3); and decreasing FVII, 2.8 (95% CI: 5.1, 0.4). Significant associations were not found for other blood biomarkers, including fibrinogen. A larger cohort study did not find significant associations between ambient air carbon monoxide concentrations (mean range: 0.3–1.48 mg/m^3 [0.3–1.29 ppm]) and plasma interleukin-6 (IL-6), CRP, or fibrinogen among myocardial infarction survivors (n=1,003, age range: 31–87 years) in six European cities (2003–2004, Rückerl et al. 2007).

A panel study conducted in Milan, Italy (1995–2005) evaluated associations (mean range: 1.14–3.11 ppm; highest value: 11.4 ppm) between air carbon monoxide concentrations and several blood coagulation parameters, using prothrombin time (PT) and activated partial thromboplastin time (APTT) as outcome measures in 1,218 healthy adolescents and adults (age 11–84 years; Baccarelli et al. 2007). Increasing ambient air carbon monoxide concentration was associated with a decrease in PT (β coefficient: -0.11; 95% CI: -0.18, -0.05). Associations were also significant for PM_{10} and NO_2; however, results from multi-pollutant models were not reported. Significant associations with carbon monoxide were not found for other blood biomarkers evaluated in the study, including carbon monoxide had no effect on fibrinogen, functional antithrombin, functional protein C, protein C antigen, functional protein S, or free protein S.

Musculoskeletal Effects. Studies evaluating effects of exposure to low levels of carbon monoxide (i.e., producing blood COHb levels <20%) on bone in humans or animals were not identified. A 26-year-old woman who attempted suicide by inhalation of charcoal smoke developed heterotopic ossification (formation of mature lamellar bone within soft tissue) of the femoral joints and proximal thighs within 3 months of exposure (Chen et al. 2010). Exposure levels of carbon monoxide were not reported; blood COHb level at the time of admission to the emergency room was 23.5%, although the time from exposure

to emergency room admission was not reported. The study authors suggested that development of heterotopic ossification was secondary to ischemic reperfusion. In mice continuously exposed to 2,400 ppm for 180 days, increased bone mass was observed in parietal bone, sternum, lumbar vertebrae, and ribs (but not femur), and the marrow cavities of ribs, parietal bone, and femurs were expanded (Zebro et al. 1983).

A study of 25 patients with delayed sequelae following exposure to carbon monoxide reported persistent muscle weakness, lasting from 1 to 60 months following exposure (Huang et al. 2011). Evaluation by computed tomography (CT) imaging showed decreased technetium (^{99m}Tc) sestamibi in skeletal muscle. ^{99m}Tc sestamibi, a lipophilic cation used in nuclear medicine imaging, is retained within mitochondria of skeletal muscle. Decreased uptake of ^{99m}Tc sestamibi is indicative of muscle damage due to altered mitochondrial metabolism. Carbon monoxide exposure levels were not reported; blood COHb levels for the study cohort were reported as >10%, although COHb range was not reported. Rhabdomyolysis and myonecrosis have been reported in cases of carbon monoxide poisoning (Florkowski et al. 1992; Herman et al. 1988; Kuska et al. 1980; Wolff 1994). Damage to muscle tissue is consistent with hypoxia due to binding of carbon monoxide to Hb and myoglobin and with inhibition of cellular aerobic metabolism due to binding of carbon monoxide to intracellular cytochrome oxidases (Wolff 1994).

Hepatic Effects. Studies evaluating hepatic effects of exposure to low levels of carbon monoxide (i.e., producing blood COHb levels <20%) were not identified. Although the liver has not been identified as a specific target organ for carbon monoxide-induced toxicity, exposure to carbon monoxide at levels producing hypoxia would be expected to affect any tissue, in particular those tissues with high O_2 utilization requirements (e.g., brain, liver, kidney, heart, small intestine).

Renal Effects. Studies evaluating renal effects of exposure to low levels of carbon monoxide (i.e., producing blood COHb levels <20%) were not identified. Although the kidney has not been identified as a specific target organ for carbon monoxide-induced toxicity, exposure to carbon monoxide at levels producing hypoxia would be expected to affect any tissue, in particular those tissues with high O_2 utilization requirements (e.g., brain, liver, kidney, heart, small intestine). The kidney is the site of active transport processes involved in maintaining blood homeostasis and, next to the brain, is the greatest contributor to basal metabolic rate due to use of ATP-dependent active transport processes. Carbon monoxide-induced hypoxia would decrease the availability of oxygen to produce ATP in renal mitochondria, which would produce adverse effects to the kidneys. Acute renal failure secondary to

rhabdomyolysis has been observed in cases of acute carbon monoxide poisoning (Florkowski et al. 1992; Kuska et al. 1980; WHO 1999; Wolff 1994).

Endocrine Effects. Studies evaluating endocrine effects of exposure to low levels of carbon monoxide (i.e., producing blood COHb levels <20%) were not identified. Although the endocrine system has not been identified as a specific target for carbon monoxide-induced toxicity, exposure to carbon monoxide at levels producing hypoxia would be expected to affect any tissue.

Dermal Effects. Studies evaluating dermal effects of exposure to low levels of carbon monoxide (i.e., producing blood COHb levels <20%) were not identified. Skin lesions have been observed in patients with severe carbon monoxide poisoning (Myers et al. 1985; Torne et al. 1991). Lesions are primarily observed in pressure areas and are characterized by blisters, subepidermal vesicles, and sweat gland necrosis.

Ocular Effects. Visual field deficits, temporary or permanent blindness, retinal venous congestion, retinal hemorrhage, papilledema, and optic atrophy have been associated with severe carbon monoxide poisoning in humans (Choi 2001). Numerous clinical studies have investigated the potential for carbon monoxide to induce visual effects (decreased visual tracking, visual vigilance, visual perception) at COHb levels <20% (Benignus et al. 1990; EPA 1991, 2000; Raub and Benignus 2002; Raub et al. 2000). Interpretation of results from most of these clinical studies is complicated by poor study design (single-blind or unblinded designs, small number of study subjects), inadequate reporting, inconsistent results, and inability to duplicate positive findings (Benignus et al. 1990; EPA 1991, 2000; Raub and Benignus 2002; Raub et al. 2000). No information was identified to indicate that carbon monoxide is an ocular irritant in humans or animals.

3.2.3 Immunological and Lymphoreticular Effects

Little information is available regarding the potential of carbon monoxide exposure to produce adverse immunological effects. Epidemiological studies regarding blood biomarkers of immunological status are summarized in the section on Hematologic Effects. Immunological biomarkers examined in these studies have included CRP, SAA, and WBC; however, other markers that can be influenced by the immune system have also been evaluated, including cell adhesion markers such as E-selectin, vWF, and ICAM-1; and coagulation markers such as fibrinogen, FVII, prothrombin fragment 1+2, PT, and APTT. Although results of these studies have been mixed, collectively, they provide some evidence for associations

between ambient air carbon monoxide concentration and changes in hematological indicators of inflammation and coagulation. However, these studies do not distinguish between possible effects of carbon monoxide and/or other air pollutants on the immune system from indirect effects of carbon monoxide on blood biomarkers. Mechanistic studies have revealed evidence that carbon monoxide may participate in the regulation of immune function (see Section 3.5.2, Mechanisms of Toxicity).

Exposure of male Sprague-Dawley rats to 2,000 ppm carbon monoxide for 40 minutes followed by exposure to 3,000 ppm for 20 minutes activated and induced proliferation of microglia, immune effector cells, in the brain (Wang et al. 2011). In addition, expression of several immune makers, including MHCII, CD-4, VCAM-1, INF-γ, and OC-42, were increased in the hippocampus and cortex of the brain. Results of a study in guinea pigs investigating the effects of repeated brief bursts of carbon monoxide on systemic immune function were equivocal (Snella and Rylander 1979). Exposure of guinea pigs to 3-minute bursts of 10,000 ppm carbon monoxide 12 times/day for 4 weeks resulted in an 88% reduction in the number of splenic plaque-forming cells, compared to unexposed controls; however, the reduction did not reach statistical significance. Studies evaluating effects of gestational exposure on the developing immune system function are reviewed in Section 3.2.6 (Developmental Effects) (Giustino et al. 1993, 1994).

3.2.4 Neurological Effects

The literature reporting adverse nervous system effects, specifically central nervous system effects, of acute exposure of humans to carbon monoxide is extensive. This literature includes case studies of carbon monoxide poisoning, clinical studies of neurobehavioral effects of controlled exposures in humans, and experimental studies in a variety of animal models (e.g., dogs, rodents, nonhuman primates). Much of this literature has been summarized and analyzed in recent reviews and meta-analyses (Benignus et al. 1990; EPA 1991, 2000; Kao and Nañagas 2006; Raub and Benignus 2002; Raub et al. 2000; WHO 1999). This section summarizes the major findings from these analyses. Although the literature on central nervous system effects of acute experimental and accidental exposures of humans to carbon monoxide is extensive, reports of effects of longer-duration exposure of humans are not available. Effects of gestational and perinatal exposure on the developing nervous system are discussed in Section 3.2.6 (Developmental Effects).

Acute exposure to high levels of carbon monoxide produces symptoms of central nervous system toxicity (EPA 1991, 2000; Ernst and Zibrak 1998; Raub and Benignus 2002; WHO 1999). Symptoms of central

nervous system toxicity include headache, dizziness, drowsiness, weakness, nausea, vomiting, confusion, disorientation, irritability, visual disturbances, convulsions, and coma. Symptoms vary depending upon the degree of exposure; headache and dizziness are the most commonly reported symptoms (Dolan 1985; Ernst and Zibrak 1998). Neuroimaging evaluations of patients with acute carbon monoxide poisoning show lesions of the basal ganglia (primarily of the globus pallidus) and white matter (Hopkins et al. 2006; Kao and Nañagas 2006; Lo et al. 2007; Parkinson et al. 2002). Following acute-onset effects, delayed development of neuropsychiatric impairment may occur within 1–4 weeks of exposure, with symptoms including inappropriate euphoria, impaired judgment, poor concentration, memory loss, cognitive and personality changes, and psychosis. Delayed neuropsychiatric impairment has been estimated to occur in up to 68% of patients with acute carbon monoxide poisoning (Ernst and Zibrak 1998; Kao and Nañagas 2006; Raub and Benignus 2002; Raub et al. 2000; WHO 1999; Wolf et al. 2008). The relationship between initial symptom severity and the likelihood of developing delayed neuropsychiatric impairment has not been established. A cohort analysis of 256 patients with carbon monoxide poisoning suggests that initial symptom severity does not correlate to delayed-onset effects (Chambers et al. 2008). However, based on a review of available data, Kao and Nañagas (2006) concluded that patients with more severe initial symptoms are more likely to develop delayed neuropsychiatric impairment.

Mechanisms of acute and delayed adverse nervous system effects produced by carbon monoxide have not been conclusively established. Tissue hypoxia secondary to COHb formation may be a contributing factor, particularly in association with high levels of blood COHb (>60%); however, direct cellular effects of carbon monoxide (e.g., ATP depletion, excitotoxicity, oxidative stress, immunological responses) and postischemic reperfusion injury may also contribute to neurotoxicity (see Section 3.5.2, Mechanisms of Toxicity) (Ernst and Zibrak 1998; Gorman et al. 2003; Kao and Nañagas 2006). Under conditions of hypoxia, including that induced by COHb formation, cerebrovascular vasodilation and increased cardiac output occur as compensatory mechanisms to maintain O_2 delivery to the brain (Gorman et al. 2003; Helfaer and Traystman 1996; Raub and Benignus 2002; WHO 1999). In healthy individuals, cardiovascular compensation effectively maintains whole brain O_2 delivery up to COHb levels of approximately 60% (EPA 2000). However, based on studies conducted in animals, the elevated cerebral blood flow during carbon monoxide exposure is heterogeneous among different brain regions and may not be sufficient to satisfy O_2 demand in all brain regions (Okeda et al. 1987; Sinha et al. 1991). However, despite these compensatory cardiovascular actions, cerebral O_2 consumption declines as blood COHb levels increase, with statistically significant decreases at COHb levels of 30–50% (Raub and Benignus 2002). Results of an analysis conducted by EPA (2000) of data obtained in goats (Doblar et al. 1977) and sheep (Langston et al. 1996) show that the cerebral metabolic rate for O_2 ($CMRO_2$) decreased

10% at a blood COHb of approximately 23%. These results are consistent with data obtained from humans showing no statistically significant decline in $CMRO_2$ at COHb levels up to 20% (Paulson et al. 1973).

Based on an extensive database of acute carbon monoxide poisoning, it is generally accepted that central nervous system symptoms are associated with acute exposures that produce blood COHb levels ≥20% (EPA 1991, 2000; Raub and Benignus 2002; Raub et al. 2000; WHO 1999). However, results of clinical studies of associations between carbon monoxide exposure and carbon monoxide-induced nervous system effects at blood COHb levels between 5 and 20% are more difficult to interpret (EPA 1991, 2000; Raub and Benignus 2002; Raub et al. 2000; WHO 1999). Numerous clinical studies have investigated the potential for carbon monoxide to induce adverse nervous system effects at COHb levels <20%, including visual and auditory sensory effects (decreased visual tracking, visual and auditory vigilance, visual perception), fine and sensorimotor performance, cognitive effects (altered time discrimination, learning, attention level, driving performance), and brain electrical activity (Benignus et al. 1990; EPA 1991, 2000; Raub and Benignus 2002; Raub et al. 2000). Interpretation of results from most of these clinical studies is complicated by poor study design (single-blind or unblinded designs, small number of study subjects), inadequate reporting, inconsistent results, and inability to duplicate positive findings (Benignus et al. 1990; EPA 1991, 2000; Raub and Benignus 2002; Raub et al. 2000). Therefore, although evidence has been provided for central nervous system effects in humans in association with carbon monoxide exposures that result in COHb levels <20%, dose-response relationships for these effects have not been firmly established. Effects of exposure to ambient environmental levels of carbon monoxide on neurological function and behavior have not been investigated in epidemiological studies.

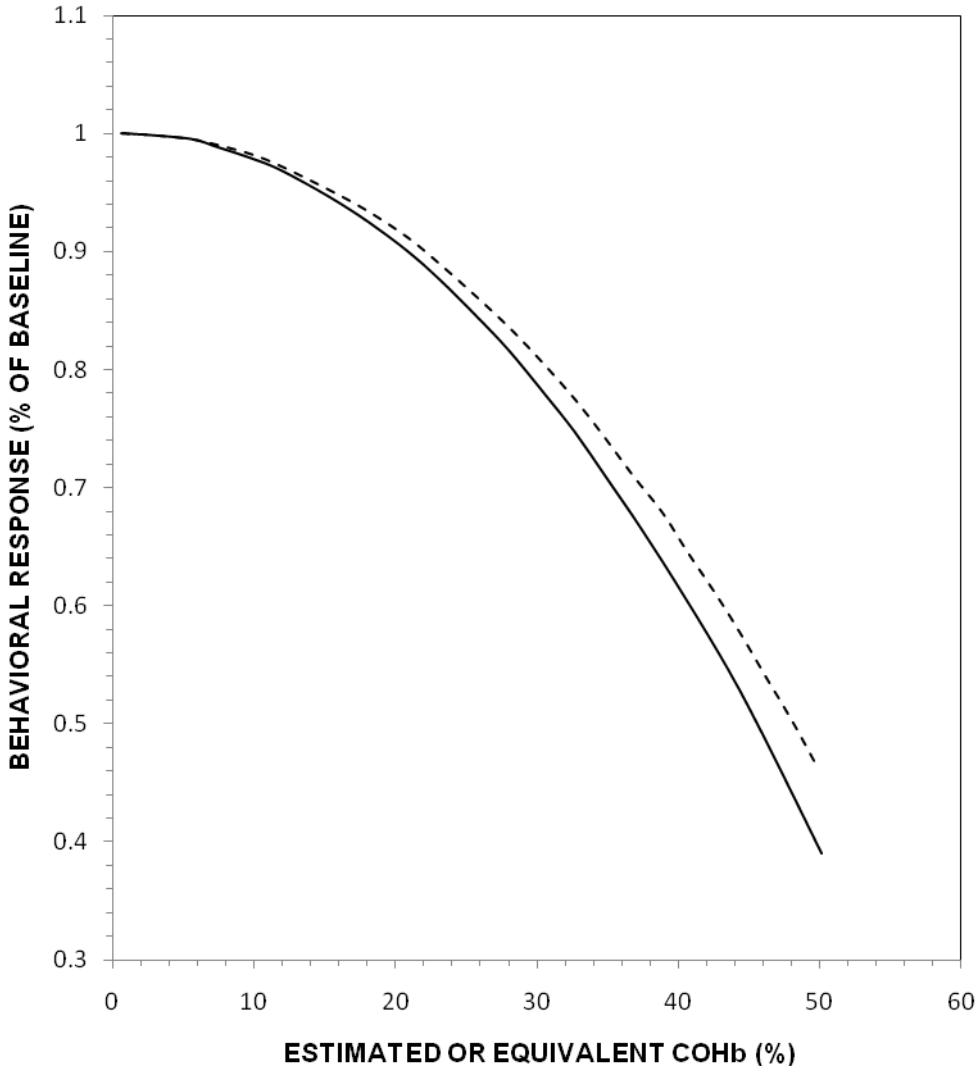
Benignus (1994) conducted a meta-analysis of the clinical literature on carbon monoxide-induced behavioral effects (also see Benignus et al. 1990; EPA 2000; Raub and Benignus 2002). To minimize the introduction of bias from poorly designed studies, the Benignus analysis included only studies conducted using a double-blind design. The primary goal of these analyses was to compare the dose-response relationship of carbon monoxide-induced effects in humans to other extrapolated data, specifically, the dose-response functions for COHb-induced behavioral effects in rats and hypoxic hypoxia (HH)-induced behavioral effects in humans. Rat COHb dose-response data were converted to human COHb equivalents using a modification of the CFK human model, adjusted to predict exposure-COHb relationships in rats (Benignus and Annau 1994). Data on behavioral effects were also adjusted to account for carbon monoxide-Hb-related hypothermia that occurs in rats (Gordon 1990), but not in humans, assuming response additivity of hypothermia and hypoxia (Benignus 1994). Dose-response data for HH-induced

behavioral effects were converted to COHb equivalents (COHb% that yields the equivalent arterial O_2 content as a given level of HH) and were corrected for hyperventilation that occurs in HH and resulting changes in alveolar ventilation rate, based on estimates of blood CO_2 (i.e., hypocapnia-induced by HH). For all data sets (i.e., carbon monoxide human, carbon monoxide rat, HH human), behavioral responses were transformed to percent of baseline response. Dose-response curves were fit to the extrapolated carbon monoxide rat and HH human data; curve-fitting was not conducted for carbon monoxide human data, due to the small effect level and low COHb levels. Comparison of the extrapolated carbon monoxide rat and HH human data showed very close agreement, with nearly superimposable dose-response curves (Figure 3-1); comparison of dose-response data from carbon monoxide in humans to extrapolated data from HH humans is shown in Figure 3-2. The dose-response relationship from this meta-analysis predicts a 10% decrement in behavioral outcomes in humans in association with COHb levels of approximately ≥20% (range: approximately 18–25%, based on 90% confidence limits) in healthy, sedentary individuals. As discussed by Benignus (1994) and others (Benignus et al. 1990; EPA 1991; Raub and Benignus 2002), the magnitude of behavioral effects that may occur at blood COHb levels ≤20% is expected to be small. Although most task performances are not likely to be affected, it is possible that even small effects (i.e., <10% decrement) could interfere with successful task performance for more difficult or demanding tasks. Therefore, potential minimal behavioral changes occurring at COHb levels ≤20% may be important under certain conditions or in sensitive individuals (e.g., individuals with compromised cardiovascular or central nervous system function).

Clinical studies evaluating exposure to low levels of carbon monoxide (i.e., producing blood COHb levels <20%) have focused on the potential for carbon monoxide to induce behavioral effects; however, very little information is available on the effects of carbon monoxide on sensory system function in humans.

Results of clinical studies in evaluating the effects of low carbon monoxide exposures on alterations in sensory perception (i.e., visual and auditory) are equivocal (EPA 1991, 2000). Epidemiological studies have not assessed the potential for carbon monoxide to produce alterations in sensory system function. Studies conducted in mature rats provide evidence that acute exposure (<10 hours) to higher levels of carbon monoxide (500–1,500 ppm) potentiates noise-induced hearing loss, including noise-induced elevation of compound action potential threshold (Chen and Fechter 1999) and auditory threshold shifts (Fechter et al. 1988; Young et al. 1987). In mature rabbits, exposure to 700 ppm for 9.5 hours/day for 5 days potentiated noise-induced increases in the auditory brainstem response threshold (Mortazavi et al. 2010). In these studies, exposure to carbon monoxide alone did not produce changes in auditory function. Noise-induced hearing loss was partially reversed within 4 weeks following exposure to noise alone, but

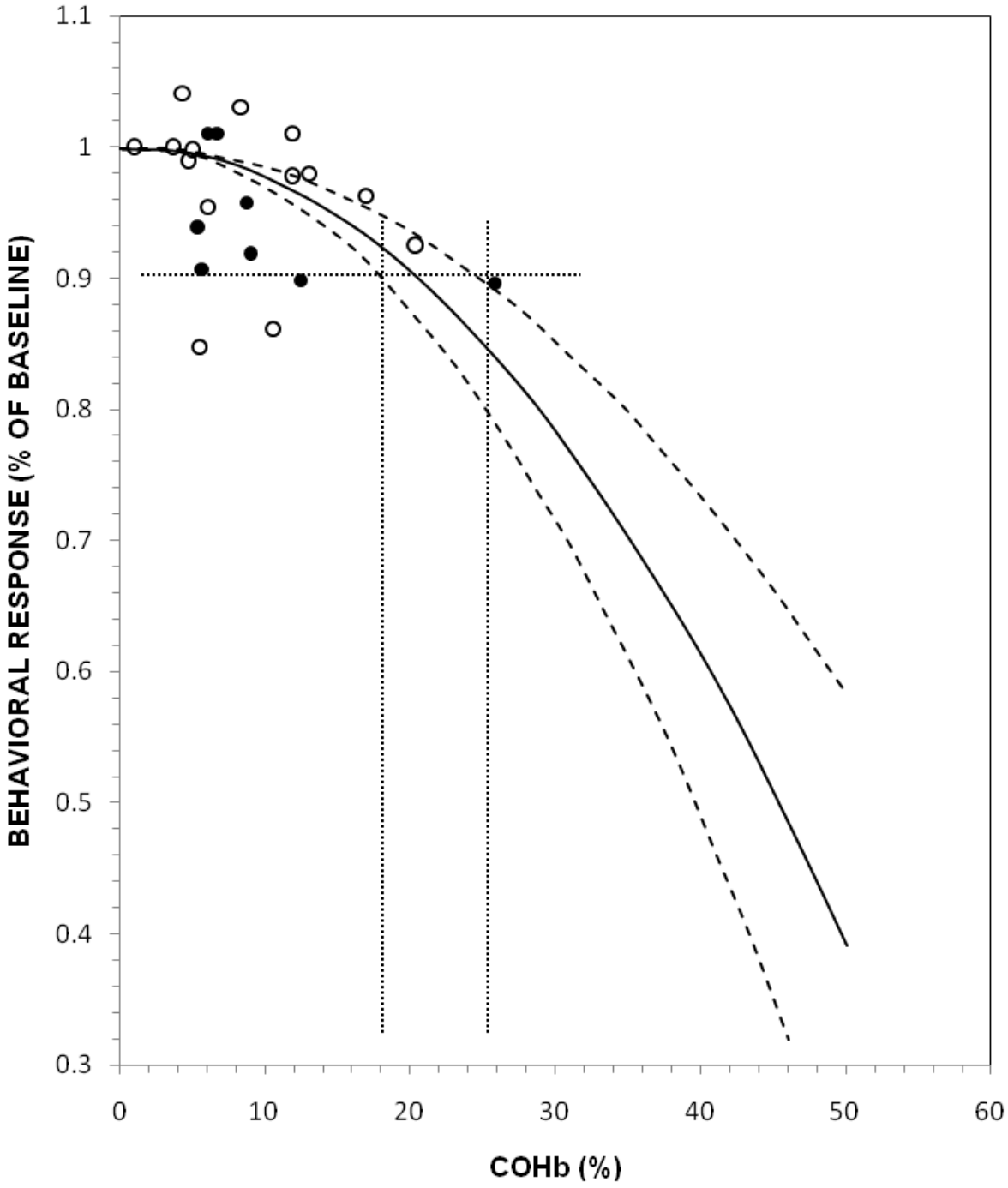
Figure 3-1. Hypoxic Hypoxia Human and Carbon Monoxide Rat Curves*



*Behavioral decrements in rats with elevated carboxyhemoglobin (COHb; dashed line) compared to behavioral effects in hypoxic humans (solid line) in which hypoxia has been expressed in equivalence to COHb.

Source: Raub and Benignus 2002

Figure 3-2. Hypoxic Hypoxia Human and Carbon Monoxide Human Curves*



*Behavioral decrements in humans (circles) with elevated carboxyhemoglobin (COHb) compared to behavioral effects in hypoxic humans (solid and dotted lines) in which hypoxia has been expressed in equivalence to COHb. Closed and open circles were the mean values for studies reporting statistically and non-significant results, respectively.

Source: Raub and Benignus 2002

not following exposure to noise and carbon monoxide (Chen and Fechter 1999). Results are consistent with carbon monoxide-induced impairment of mechanisms that repair noise-induced damage to outer hair cells. In marked contrast to results observed in adult rats, developmental studies in animals show that gestational and early postnatal exposure to low levels of carbon monoxide (i.e., 12–25 ppm carbon monoxide) may lead to altered development of the auditory system (Beltran-Parrazal et al. 2010; Lopez et al. 2003, 2008, 2010; Stockard-Sullivan et al. 2003; Webber et al. 2003). These data are discussed in Section 3.2.6.

Additional evidence for effects of carbon monoxide on depressed auditory thresholds and increased cochlear blood flow have been provided from studies in which adult rats received parenteral doses of carbon monoxide (Fechter et al. 1987b). However, in these studies, auditory thresholds assessed by measurement of the compound action potential recorded at the round window remained stable up to COHb levels of at least 30%. Transient impairments of the compound action potential threshold were observed among subjects that attained COHb levels of approximately 50%. Cochlear blood flow measured using laser Doppler flowmetry also increased following carbon monoxide exposure, reaching a maximum of 140% of control values at approximately 50% COHb. In those instances of high COHb production that did produce impairment of auditory threshold, recovery of function was observed as COHb levels declined.

3.2.5 Reproductive Effects

Fetal death in humans has been reported in cases of maternal carbon monoxide poisoning during pregnancy. Epidemiological studies have examined possible relationships between exposures to ambient air concentrations of carbon monoxide and fetal mortality (see Section 3.2.6). Studies in animals provide further evidence that maternal exposure during pregnancy can result in fetal death.

Case Reports. Several case reports have evaluated pregnancy outcomes following acute carbon monoxide poisoning (Brown et al. 1992; Caravati et al. 1988; Cramer 1982; Elkharrat et al. 1991; Farrow et al. 1990; Greingor et al. 2001; Hollander et al. 1987; Margulies 1986; Norman and Halton 1990; Silverman and Montano 1997; Yildiz et al. 2010). In all cases, the severity of carbon monoxide poisoning required emergency room treatment or hospitalization, suggesting that maternal COHb levels exceeded 20%. Pregnancy outcomes varied widely, from delivery of healthy infants at term to fetal death within first few days of exposure. Pregnancy outcome is most likely related to fetal age at time of exposure, with sensitivity increasing with fetal age, and severity of maternal poisoning, although maternal

COHb levels are not a good indicator of fetal outcome (Greingor et al. 2001). Fetal death may be secondary to maternal hypoxia and/or fetal hypoxia. The available information from these cases is not adequate to define dose-response relationships for acute carbon monoxide exposure and pregnancy outcomes.

Animal Studies. Few animal studies have assessed the effects of carbon monoxide exposure on reproductive function. Continuous exposure of male mice to 50 ppm carbon monoxide for 2 weeks prior to mating with unexposed females or of male and female mice to 50 ppm carbon monoxide for 2 weeks prior to mating had no effect on pregnancy rate or live or dead fetuses/dam (Stupfel and Bouley 1970). Exposure of pregnant rats to carbon monoxide concentrations up to 200 ppm over the entire gestational period had no effect on number of liters, fetuses per litter, or number of live/dead pups per litter (Fechter and Annau 1977; Penney et al. 1983). In contrast, increased fetal death during the first 24 hours of the postnatal period was observed in rabbits following maternal exposure to 90 and 180 ppm carbon monoxide during pregnancy (9.9 and 35% mortality) (Astrup et al. 1972).

3.2.6 Developmental Effects

Epidemiological studies have examined possible associations between exposure to ambient air carbon monoxide concentrations and various developmental outcomes, including pre-term birth, birth weight, congenital anomalies, neonatal and infant death, and neurodevelopment. Results of these studies have been mixed and, collectively, do not provide strong evidence for developmental effects in association with exposures to ambient levels of carbon monoxide. Studies conducted in animals provide evidence of adverse developmental effects of gestational and early postnatal carbon monoxide exposure, including decreased fetal weight, adverse central nervous system development, altered peripheral nervous system development, cardiac effects, altered sexual behavior, immunological effects, and hematological effects. In addition, some studies showed that developmental effects persisted beyond the postnatal period.

Epidemiological Studies. Interpretation of the results of epidemiological studies of developmental effects of carbon monoxide, and in particular, quantitative estimates of the effect magnitudes on outcomes, is limited by several factors: (1) reliance on area monitoring for estimating exposure level that may not represent exposures that occurred in individuals during any particular period of gestation; (2) uncertainty in knowledge of temporal correspondence between monitored exposure levels and outcomes; (3) relatively strong correlations between ambient air carbon monoxide concentrations and other air quality variables that may affect developmental outcomes; and (4) relatively low carbon monoxide

exposures studied. In general, these studies examined relatively low air carbon monoxide concentrations, typical of ambient levels (e.g., mean concentrations ranging from 0.5 to 3 ppm, with the highest reported values ≤10 ppm). The presentation of the epidemiological studies is organized by major categories of birth and neonatal outcomes. Study conclusions are presented in the text, with selected supporting details presented in tabular form (Table 3-8). Although most studies explored various time lags between monitored air carbon monoxide concentrations and outcomes, as well as various sample strata, for the sake of brevity, only selected representative time lags (usually those indicative of the strongest associations to carbon monoxide) are presented in the tables. Where co-pollutant models have been explored, these results are also presented.

Studies of Neurodevelopment. A prospective birth cohort study conducted in Guatemala (2002–2010), where exposure to wood smoke is common, examined cognitive development in a sample of 39 children (Dix-Cooper et al. 2011). Various cognitive and motor function tests were performed at age 6–7 years, and associations between test scores and maternal exposures to carbon monoxide during the third trimester were evaluated. Carbon monoxide exposures were measured with passive personal air monitors worn at the breathing zone during pregnancy. The weekly mean concentration during the third trimester was 3.8 ppm (range: 0.62–12.52 ppm). Cognitive and motor function tests performed at age 6–7 years included assessments of information processing speed, visual-spatial integration, short- and long-term memory, attention, fine motor speed, and coordination. In 4 of 11 tests administered, decreasing performance was associated with increasing third trimester maternal exposures. These included visual-spatial integration (β: -4.4 per $\log_{10}$ ppm, 95% CI: -9.5, 0.07), immediate recall (β: -0.3 per $\log_{10}$ ppm, 95% CI: -0.6, 0.01), delayed recall (β: -4.48 per $\log_{10}$ ppm, 95% CI: -9.8, 0.1), and finger tapping (β: -5.7 per $\log_{10}$ ppm, 95% CI: -9.7, -1.7). Significant associations were not found for carbon monoxide exposure measured with passive personal monitors worn by the infants during the first 9 postnatal months.

Studies of Pre-term Birth. Several epidemiological studies have examined possible associations between ambient air carbon monoxide concentrations and risk of pre-term birth (Huynh et al. 2006; Jalaludin et al. 2007; Leem et al. 2006; Liu et al. 2003; Ritz et al. 2000, 2007; Rudra et al. 2011; Wilhelm and Ritz 2005). Results of these studies have been mixed and have included estimates of significantly elevated risk or lower risks of pre-term birth (Jalaludin et al. 2007). Mean air carbon monoxide concentrations evaluated in these studies ranged from 0.8 to 2.7 ppm, with the highest values ≤10 ppm (Ritz et al. 2000).

Table 3-8. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Developmental Outcomes

Study	Design features	CO exposure	Effect size
Bell et al. 2007 Period: 1999–2002 Location: Connecticut and Massachusetts	Outcome: BW, LBW Design: Retrospective cohort Sample: n=358,504 live full-term singleton births	Avg time: 24 hours Mean: 0.65 ppm SD: 0.2 ppm	Increment: 0.30 ppm β coefficient (95% CI) BW (g), total gestation: CO: -16.2 (-19.7, -12.6) Significant negative β persisted after adjustment for NO_2, SO_2, $PM_{2.5}$, or PM_{10} OR (90% CI) LBW, total gestation: CO: 1.028 (0.983, 1.074)
Brauer et al. 2008 Period: 1999–2004 Location: Vancouver, Canada	Outcome: PTB, LBW, SGA Design: Retrospective cohort Sample: n=70,249 live singleton births	Avg time: 24 hours Mean: 0.55 ppm Range: 0.11–1.23 ppm	Increment: 0.1 mg/m^3 OR (95% CI), total gestation: SGA: 1.06 (1.03, 1.08) LBW: 1.02 (0.96, 1.09) PTB: 1.16 (1.01, 1.33)
Chen et al. 2002 Period: 1991–1999 Location: Nevada	Outcome: BW, LBW Design: Retrospective cohort Sample: n=39,338 live singleton births	Avg time: 8 hours Mean: 0.86 ppm Range: 0.42–4.25 ppm	Increment: 1 ppm β coefficient (SE), BW (g): TM 1: -1.02 (6.68) TM 2: -0.07 (6.58) TM 3: -3.95 (6.76) Not significant when adjusted for PM_{10} or O_3 ORs not significant for LBW
Dadvand et al. 2011 Period: 1993–2003 Location: England	Outcome: CA (heart) Design: Case-control Sample: n=2,769 cases, 14,256 controls	Avg time: 1 week Mean: 0.48 ppm Range: 0.37–1.21 ppm	Increment: 1 mg/m^3 OR (95% CI) Cardiac septa: 2.330 (1.748, 3.102) Pulmonary valve stenosis: 2.682 (1.298, 5.534) Ventricular septa: 2.634 (1.871, 3.707) CO not associated with other cardiac malformations
Dix-Cooper et al. 2011 Period: 2002–2010 Location: San Marcos, Guatemala.	Outcome: Cognitive development Design: Prospective birth cohort Sample: n=39 children, assessed at age 6–7 years	Avg time: 48 hours (personal monitor) Maternal (3^{rd} TM) Mean: 3.83 ppm Range: 0.62–12.52 ppm	Increment: log_{10} ppm β coefficient (95% CI) Visual-spatial integration: -4.4 (-9.5, 0.07) Immediate recall: -0.3 (-0.6, 0.01) Delayed recall: -4.8 (-9.8, 0.1) Finger tapping: -5.7 (-9.7, -1.7)

Table 3-8. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Developmental Outcomes

Study	Design features	CO exposure	Effect size
Gilboa et al. 2005 Period: 1997–2000 Location: Texas	Outcome: CA (heart, orofacial) Design: Case-control Sample: n=4,594 cases	Avg time: 24 hours Mean: NR 25^{th}–75^{th}%: 0.4–0.7 ppm	Increment: <0.4 ppm (reference), 0.4–0.5 (L), 0.5–0.7 (M), >0.7 (H) OR (95% CI), 3–8 weeks of gestation: Conotruncal defect: (L) 1.38 (0.97, 1.97); (M) 1.17 (0.81, 1.70); (H) 1.46 (1.03, 2.08) Teratology of Fallot: (L) 0.92 (0.52, 1.62); (M) 1.17 (0.75, 2.14); (H) 2.04 (1.16, 3.29) CO not associated with other heart defects or orofacial defects
Gouveia et al. 2004 Period: 1997 Location: San Paulo, Brazil	Outcome: BW, LBW Design: Retrospective cohort Sample: n=179,460 live full-term singleton births	Avg time: 8 hours Mean: 3.7 ppm Range: 1.1–11.4	Increment: 1 ppm β coefficient (95% CI), BW (g): TM 1: -23.1 (-41.3, -4.9) TM 2: 3.2 (-18.2, 24.5) TM 3: 1.9 (-18.2, 22.0) Significant negative β did not persist after adjustment for SO_2 or PM_{10} OR (95% CI), LBW: 4^{th} vs. 1^{st} quartile exposure: TM 1: 1.02 (0.82, 1.27); TM 2: 1.07 (0.88, 1.30) TM 3: 0.93 (0.76, 1.12)
Ha et al. 2001 Period: 1996–1997 Location: Seoul, South Korea	Outcome: LBW Design: Retrospective cohort Sample: n=276,763 live full-term singleton births	Avg time: 8 hours Median: 1.7 ppm 25^{th}–75^{th}%: 0.99–1.41	Increment: 0.42 ppm RR (95% CI): TM 1: 1.08 (1.04, 1.12) TM 3: 0.91 (0.87, 0.96)
Ha et al. 2003 Period: 1995–1999 Location: Seoul, South Korea	Outcome: Post-neonatal mortality (1–12 months) Design: Time series Sample: n=1,045 deaths	Avg time: 24 hours Median: 1.2 ppm Range: 0.39–3.38 ppm	Increment: 0.57 ppm RR (95% CI), lag 0 days: All causes: 1.020 (0.976, 1.067) Respiratory: 1.388 (1.009, 1.911)

Table 3-8. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Developmental Outcomes

Study	Design features	CO exposure	Effect size
Huynh et al. 2006 Period: 1999–2000 Location: California	Outcome: PTB Design: Case-control Sample: n=10,673 cases (24–36 weeks), 32,119 controls (39–44 weeks)	Avg time: 24 hours Mean: 0.8 ppm SD: 0.2 ppm	Increment: 1 ppm OR (95% CI) Month 1 (of gestation): CO: 1.10 (0.999, 1.20) $CO+PM_{2.5}$: 1.03 (0.93, 1.13) Last 2 weeks: CO: 1.00 (0.93, 1.09) $CO+PM_{2.5}$: 0.97 (0.90, 1.06) Total gestation: CO: 1.06 (0.95, 1.18) $CO+PM_{2.4}$: 0.98 (0.87, 1.10) No significant trend in OR with exposure quartile
Hwang and Jaakkola 2008 Period: 2001–2003 Location: Taiwan	Outcome: CA (oral cleft) Design: Case-control Sample: n=653 cases	Avg time: 8 hours Mean: 0.69 ppm Range: 0.25–2.7 ppm	Increment: 0.1 ppm RR (95% CI), oral cleft Cleft lip: Month 1: 1.00 (0.96, 1.04) Month 2: 1.00 (0.96, 1.03) Month 3: 1.00 (0.96, 1.03) Cleft lip with or without cleft palate: Month 1: 1.00 (0.97, 1.04) Month 2: 1.00 (0.97, 1.05) Month 3: 1.00 (0.96, 1.04) No significant ORs after adjustment for NO_2, O_3, or PM_{10}

Table 3-8. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Developmental Outcomes

Study	Design features	CO exposure	Effect size
Jalaludin et al. 2007 Period: 1998–2000 Location: Sydney, Australia	Outcome: PTB (<37 or <42 weeks) Design: Retrospective cohort Sample: n=721,289 full-term singleton births	Avg time: 8 hours Mean: 0.9 ppm SD: 0.68 ppm	Increment: 1 ppm RR (95% CI) <5 km of monitoring site or city-wide: Month 1, <5 km: 1.03 (0.68, 1.54) Month 1, city-wide: 0.89 (0.84, 0.95) TM 1, <5 km): 1.24 (0.81, 1.91) TM 1, city-wide: 0.77 (0.71, 0.83) Last month, <5 km: 1.00 (0.86, 1.15) Last month, city-wide: 0.96 (0.88, 1.04) TM 3, <5 km: 1.11 (0.94, 1.31) TM 3, city-wide: 0.99 (0.90, 1.09)
Lee et al. 2003a Period: 1996–1998 Location: Seoul, Korea	Outcome: LBW Design: Retrospective cohort Sample: n=388,105 live full-term singleton births	Avg time: 24 hours Mean: 1.2 ppm Range: 0.4–3.4 ppm	Increment: 0.5 ppm OR (95% CI): TM 1: 1.04 (1.01, 1.07) TM 2: 1.03 (1.00, 1.06) TM 3: 0.96 (0.93, 0.99) Total gestation: 1.05 (1.01, 1.09)
Leem et al. 2006 Period: 2001–2002 Location: Incheon, Korea	Outcome: PTB Design: Retrospective cohort Sample: n=52,113 live singleton births	Avg time: 24 hours Mean: NR Range: 0.3–1.4 ppm	Increment: quartiles (mg/m^3): 1^{st} 0.47–0.63; 2^{nd} 0.6–0.77, 3^{rd} 0.78-0.90, 4^{th} 0.91–1.27 OR (95% CI): TM 1: 2^{nd}, 0.92 (0.81, 1.05); 3^{rd}, 1.14 (1.01, 1.29); 4^{th}, 1.26 (1.11, 1.44) TM 3: 2^{nd} , 1.07 (0.95, 1.21); 3^{rd}, 1.07 (0.94, 1.22); 4^{th}, 1.16 (1.01, 1.34)
Lin et al. 2004a Period: 1998–2000 Location: Sao Paulo, Brazil	Outcome: Neonatal mortality (<28 days) Design: Time series Sample: n=6,700 deaths	Avg time: 24 hours Median: 2.83 ppm Range: 0.54–10.25 ppm	Increment: 0.57 ppm β coefficient (SE), deaths/day, lag 0 days: 0.0061 (0.0110)

Table 3-8. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Developmental Outcomes

Study	Design features	CO exposure	Effect size
Lin et al. 2004b Period: 1995–1997 Location: Taiwan	Outcome: LBW Design: Retrospective cohort Sample: n=92,288 live full-term singleton births	Avg time: 24 hours Mean: Taipei, 0.84–1.31 ppm; Kaohsiun, 5.56–10.05 ppm Range: NR	Increment: <1.1 (reference),1.1–14.2 (L) vs. >14.2 (H) ppm OR (95% CI): TM 1: (L) 1.01 (0.89, 1.16); (H) 0.90 (0.75, 1.09) TM 2: (L) 1.02 (0.90, 1.16); (H) 1.00 (0.82, 1.22) TM 3: (L) 0.88 (0.77, 1.00); (H) 0.86 (0.71, 1.03) Total gestation: (L) 0.89 (0.77, 1.01); (H) 0.77 (0.63–0.94)
Liu et al. 2003 Period: 1985–1998 Location: Vancouver, Canada	Outcome: PTB, LBW, IUGR Design: Retrospective cohort Sample: n=386,202 live singleton births	Avg time: 24 hours Mean: 1.0 ppm 25^{th}–75^{th}%: 0.7–1.2 ppm	Increment: 1 ppm OR (95% CI): PTB, first month: 0.95 (0.89, 1.01) PTB, last month: 1.08 (1.01, 1.15) LBW, first month: 1.01 (0.93, 1.09) LBW, last month: 0.96 (0.88, 1.04) IUGR, first month:1.06 (1.01, 1.10) IUGR, last month: 0.98 (0.94, 1.03) IUGR, TM 1: 1.05 (1.00, 1.10) IUGR, TM 2: 0.97 (0.92, 1.01) IUGR, TM 3: 0.97 (0.93, 1.02)
Liu et al. 2007 Period: 1995–2007 Location: Canada	Outcome: IUGR Design: Retrospective cohort Sample: n=386,202 live singleton births	Avg time: 24 hours Mean: 1.1 ppm 25^{th}–75^{th}%: 0.6–1.3 ppm	Increment: 1 ppm RR (95% CI): TM 1: CO:1.18 (1.14, 1.23) CO+NO_2+O_3: 1.18 (1.12, 1.24) TM 2: CO:1.14 (1.10, 1.18) CO+NO_2+O_3: 1.15 (1.08, 1.21) TM 3: CO:1.09 (1.24, 1.14) CO+NO_2+O_3: 1.20 (1.14, 1.26)

Table 3-8. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Developmental Outcomes

Study	Design features	CO exposure	Effect size
Maisonet et al. 2001 Period: 1994–1996 Location: Northeast United States	Outcome: BW Design: Retrospective cohort Sample: n=89,557 live full-term singleton births	Avg time: 24 hours Mean: 1.1 ppm 25^{th}–75^{th}%: 0.9–1.5 ppm	Increment: 1 ppm OR (95% CI): TM 1: 1.08 (0.91, 1.28) TM 2: 1.14 (0.83, 1.58) TM 3: 1.31 (1.06, 1.62) African-Americans: TM 1: 1.43 (1.18, 1.74) TM 2: 1.27 (0.87, 1.86) TM 3: 1.75 (1.50, 2.04) CO had no effect on strata for whites or Hispanics
Mannes et al. 2005 Period: 1998–2000 Location: Sydney, Australia	Outcome: BW, SGA Design: Retrospective cohort Sample: n=136,056 live full-term singleton births	Avg time: 8 hours Mean: 0.8 ppm 25^{th}–75^{th}%: 0–4.6 ppm	Increment: 1 ppm β coefficient (95% CI) BW (g), TM 2, <5 km from monitoring site: CO: -29.87 (-50.98, -6.76) $CO+NO_2$: -20.17 (-43.12, 2.78) $CO+ PM_{10}$: -27.31 (-55.30, 0.68) OR (95% CI) SGA <5 km from monitoring site: TM 1: 0.99 (0.86, 1.14) TM 2: 1.06 (0.90, 1.25) TM 3: 1.05 (0.90, 1.23) One month prior to birth: 1.10 (9.96, 1.27)
Medeiros and Gouveia 2005 Period: 1998–2000 Location: Sao Paulo, Brazil	Outcome: BW, LBW Design: Retrospective cohort Sample: n=311,735 live full-term singleton births (37–41 weeks)	Avg time: 24 hours Mean: ~2–3 ppm Range: ~1–12 ppm	Increment: 1 ppm β coefficient (95% CI) BW: TM 1: -11.9 (-15.5, -8.2) TM 2 4.9 (0.5, 9.3) TM 3: 12.1 (7.6, 16.6) OR (95% CI) LBW (75^{th} % vs. 25^{th} %): TM 1: 0.98 (0.91, 1.06); TM 2: 0.97 (0.90, 1.05) TM 3: 1.03 (0.96, 1.11

Table 3-8. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Developmental Outcomes

Study	Design features	CO exposure	Effect size
Morello-Frosch et al. 2010 Period: 1996–2006 Location: California	Outcome: BW, LBW Design: Retrospective cohort Sample: n=3.5 million live full-term singleton births (37–44 weeks)	Avg time: 24 hours Mean: 0.87 ppm 25^{th}–95^{th}%: 0.56–1.09 ppm	Increment: 1 ppm β coefficient (95% CI) BW: CO, TM 1–3: -5.4 (-6.8, -4.1) (remained significant when adjusted for O_3 and SO_2, but not when adjusted for PM_{10} or $PM_{2.5}$) OR (95% CI) LBW: CO, TM 1–3: 1.04 (1.02, 1.06)
Parker et al. 2005 Period: 2000 Location: California	Outcome: BW, SGA Design: Retrospective cohort Sample: n=18,247 live full-term singleton births	Avg time: 24 hours Mean: 0.78 ppm 25^{th}–95^{th}%: 0.57–0.93 ppm	Increment (ppm): <0.57 (reference), 0.57–0.76 (L), 0.76–0.93 (M), >0.93 (H) OR (95% CI) for total gestation: CO, L: 0.93 (0.80, 1.09) CO, M: 0.91 (0.78, 1.06) CO, H: 0.95 (0.81, 1.12) CO (L)+$PM_{2.5}$: 0.90 (0.77, 1.06) CO (M)+$PM_{2.5}$: 0.91 (0.77, 1.07) CO (H)+$PM_{2.5}$: 0.82 (0.68, 0.99)
Ritz and Yu 1999 Period: 1989–1993 Location: California	Outcome: LBW Design: Retrospective cohort Sample: n=125,275 live full-term singleton births	Avg time: 6–9 AM Mean: 2.59 ppm 95^{th}%: 5.5 ppm	Increment (ppm): <2.2 (reference), 2.2–<5.5 (L), >5.5 (H) OR (95% CI): CO (L): 1.04 (0.96, 1.13) CO, (H): 1.22 (1.03, 1.44) CO (L)+NO_2+O_3_PM_{10}: 1.10 (0.91, 1.32) CO (H)+NO_2+O_3_PM_{10}: 1.38 (0.86, 2.22)

Table 3-8. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Developmental Outcomes

Study	Design features	CO exposure	Effect size
Ritz et al. 2000 Period: 1989–1993 Location: California	Outcome: PTB Design: Retrospective cohort Sample: n=97,518 live singleton births	Avg time: 6–9 AM Mean: 2.70 ppm Range: 0.36–9,12 ppm	Increment: 3 ppm RR (95% CI): Adjusted for risk factors: Last 6 weeks: 1.06 (1.02, 1.10) First month: 1.01 (0.97, 1.04) Adjusted for risk factors and season of birth and conception: Last 6 weeks: 1.04 (0.99, 1.10) First month: 1.04 (0.99, 1.09) Adjusted for risk factors, NO_2, O_3, and PM_{10}: Last 6 weeks: 1.05 (0.97, 1.12) First month: 1.03 (0.96, 1.10)
Ritz et al. 2002 Period: 1987–1993 Location: California	Outcome: CA (heart, orofacial) Design: Case-control Sample: n=3,549 cases	Avg time: 24 hours Mean: NR 25^{th}–75^{th}%: 1.4–2.46 ppm	Increment: <1.4 ppm (reference), 1.14–1.57 (L), 1.57–2.39 (M), >2.39 (H) OR (95% CI), month 2 of gestation: Ventricular septal: CO: (L) 1.62 (1.05, 2.48); (M) 2.09 (1.19, 3.67); (H) 2.95 (1.44, 6.05) $CO+NO_2+O_3+PM_{10}$: (L) 1.63 (1.00, 2.66); (M) 1.97 (1.0, 3.91); (H) 2.84 (1.15, 6.99) CO not associated with conotruncal, aortic artery and valve, or pulmonary artery and valve defects
Ritz et al. 2006 Period: 1989–2000 Location: California	Outcome: Post-neonatal mortality (28 days–1 year) Design: Case-control Sample: n=13,146 cases	Avg time: 24 hours Mean: 1.63 ppm Range: 0.38–3.44 ppm	Increment: 1 ppm OR (95% CI), exposure period 2 months prior to death: All causes: 1.11 (1.06, 1.16) SIDS: 1/19 (1.10, 1.28) OR not significant after adjustment for NO_2, O_3, and PM_{10}

Table 3-8. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Developmental Outcomes

Study	Design features	CO exposure	Effect size
Ritz et al. 2007 Period: 2003 Location: California	Outcome: PTB Design: Nested case-control Sample: n=2,543 cases, 2,543 controls from 58,316 births in registry	Avg time: 24 hours Mean: NR Range: NR	Increment (ppm): <0.58 (reference), 0.59–0.91 (L), 0.92–1.25 (M), >1.25 (H) OR (95% CI), adjusted for risk factors: TM 1: L: 1.17 (1.08, 1.26); M: 1.15 (1.05, 1.26); H: 1.25 (1.12, 1.38) Last 6 weeks: L: 1.00 (0.93, 1.08); M: 1.08 (0.98, 120); H: 1.03 (0.93, 1.14) Total gestation: L: 0.76 (0.70, 0.82); M: 0.84 (0.77, 0.91); H: 1.03 (0.91, 1.17)
Rudra et al. 2011 Period: 1996–2006\ Location: Seattle and Tacoma, Washington	Outcome: PTB, PEC Design: Prospective cohort Sample: n=3,509 pregnant women	Avg time: 1 month Median: 1.08 ppm 25^{th}–75^{th}%: 0.80–1.38 ppm	Increment (ppm): 0.1 ppm OR (95% CI), adjusted for risk factors: PTB: 0.98 (0.94, 1.01) PEC: 1.07 (1.02, 1.13) PEC: 0.98 (0.91, 1.06) (adjusted for year of birth)
Salam et al. 2005 Period: 1975–1987 Location: California	Outcome: BW, LBW, IUGR Design: Retrospective cohort Sample: n=3,901 births (37–44 weeks)	Avg time: 24 hours Mean: 1.8 ppm SD: 0.9 ppm	Increment: 1.4 ppm OR (95% CI): TM 1: LBW, CO: 1.0 (0.7, 1.5) IUGR, CO: 1.2 (1.0, 1.4) β coefficient (95% CI) for IUGR TM 1: CO: -21.7 (-42,3, -1.1) CO + O_3: -28.6 (-50.4, -6.9)
Tsai et al. 2006a Period: 1994–2000 Location: Taiwan	Outcome: Post-neonatal mortality (27 days–1 year) Design: Case-crossover Sample: n=206 cases	Avg time: 24 hours Mean: 0.83 ppm Range: 0.23–1.77 ppm	Increment: 0.31 ppm OR (95% CI), lag 0–2 days: All causes: 1.051 (0.304, 3.630)

Table 3-8. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Developmental Outcomes

Study	Design features	CO exposure	Effect size
Wilhelm and Ritz 2005 Period: 1994–2000 Location: California	Outcome: LBW, PTB Design: Retrospective cohort Sample: n=106,483 births for PTB outcome, 136,134 births for LBW outcome	Avg time: 24 hours Mean: 1.2–1.4 ppm Range: 0.2–5.9 ppm	Increment: 1 ppm (≤1 mile from monitoring station) RR (95% CI), adjusted for risk factors: PTB, TM 1: CO: 1.06 (1.00, 1.12) $CO+NO_3+O_3$: 1.10 (1.01, 1.20) $CO+NO_3+O_3+PM_{10}$: 0.99 (0.83, 1.18) PTB, last 6 weeks: CO: 1.04 (0.98, 1.09) $CO+NO_3+O_3$: 1.10 (1.03, 1.18) $CO+NO_3+O_3+PM_{10}$: 0.98 (0.83, 1.16) LBW, TM 3: CO: 1.10 (0.98, 1.23) $CO+NO_3+O_3$: 1.15 (0.98, 1.35) $CO+NO_3+O_3+PM_{10}$: 1.21 (0.85, 1.74)
Woodruff et al. 2008 Period: 1999–2002 Location: U.S. counties with >250,000 residents	Outcome: Post-neonatal mortality (28 days–1 year) Design: Retrospective cohort Sample: n=6,639 deaths of 3,583,495 births	Avg time: 24 hours Median: 0.70 ppm 25^{th}–75^{th}%: 0.48–0.87 ppm	Increment: 0.39 ppm OR (95% CI), exposure during age 0–2 months: All causes: 1.01 (0.95, 1.07) Respiratory: CO: 1.14 (0.93, 1.40) $CO+O_3+PM_{10}+SO_2$: 1.02 (0.89, 1.15) SIDS: CO: 0.88 (0.76, 1.03) SIDS, $CO+O_3+PM_{10}+SO_2$:.0.96 (0.87, 1.06)
Yang et al. 2006 Period: 1994–2000 Location: Taiwan	Outcome: Post-neonatal mortality (27 days–1 year) Design: Case-crossover Sample: n=471 cases	Avg time: 24 hours Mean: 1.158 ppm Range: 0.32–4.84 ppm	Increment: 0.55 ppm OR (95% CI), lag 0–2 days: All causes: 1.038 (0.663, 1.624)

Avg = average; BW = birth weight; CA = congenital anomalies; CI = confidence interval; CO = carbon monoxide; IUGR = intrauterine growth rate (BW <10^{th} percentile of birth cohort when adjusted for gestational age); LBW = low birth weight (<2,500 g); OR = odds ratio; PTB = pre-term birth (<37 weeks); PEC = preeclampsia; RR = relative risk; SD = standard deviation; SE = standard error; SGA = small for gestational age (BW <10^{th} percentile of birth cohort when adjusted for gestational age); SIDS = sudden infant death syndrome; TM = trimester

A prospective cohort study conducted in the Seattle and Tacoma areas of Washington (1996–2006) examined possible associations between air carbon monoxide concentrations and pre-term birth and preeclampsia in 3,509 pregnancies (Rudra et al. 2011). Pre-term birth was not significantly associated with air carbon monoxide concentrations; the odds ratio was 0.98 (95% CI: 0.94, 1.01) per 0.1 ppm increase in carbon monoxide concentration. This study did find an association between carbon monoxide and preeclampsia (odds ratio: 1.07, 95% CI: 1.02, 1.13). However, the association was not significant when year of pregnancy was included in the model (0.98, 95% CI: 0.91, 1.06). A retrospective cohort study (n=97,158 births) conducted in southern California (1989–1993) found a significant association between increasing air carbon monoxide concentration (mean: 2.7 ppm, range: 0.6–9.12) and pre-term birth (Ritz et al. 2000). After adjustment for other risk factors as well as ambient air concentrations of NO_2, O_3, and PM_{10}, the relative risk of pre-term birth was estimated to be 1.12 (95% CI: 1.04, 1.21) per 3 ppm increase in air carbon monoxide concentration during the last 6 weeks of pregnancy. Subjects were matched to ambient carbon monoxide measurements made at monitors that were <2 miles from the residence. In a follow-up study (1994–2000) that included 106,483 births, relative risk (adjusted for NO_2 and O_3) was estimated to be 1.10 (95% CI: 1.03, 1.08) per 1 ppm increment in air carbon monoxide concentration during the last 6 weeks of pregnancy (Wilhelm and Ritz 2005). The association was not significant when PM_{10} was included in the model along with NO_2 and O_3 (relative risk: 0.98; 95% CI: 0.83, 1.18). A subsequent analysis of southern California data included a nested case-control study consisting of a subset of 2,543 cases of pre-term birth (<37 weeks of gestation) or low birth weight (<2,500 g) and an equal number of randomly selected controls for a larger cohort of 58,316 births (Ritz et al. 2007). Detailed individual data on potential co-variables were obtained, including maternal age, race, education, marriage status, birth season, parity, active and passive smoking, and alcohol use during pregnancy. The adjusted odds ratio in the case-control study for pre-term birth (exposure to >1.25 ppm in first trimester compared to <0.58 ppm) was 1.21 (95% CI: 0.88, 1.65; adjusted for co-variables other than co-pollutants). The odds ratio in the larger cohort (n=58,316) was similar (odds ratio: 1.25, 95% CI: 1.12, 1.38; adjusted for maternal age, race, education, birth season, and parity). Results of multi-pollutant models were not reported. A larger case-control study, also conducted in southern California (1999–2000), did not find a significant association between ambient air carbon monoxide concentration and pre-term birth (Huynh et al. 2006). This study examined 10,673 cases of pre-term births (<37 weeks of gestation) and 32,119 full-term controls (matched for last menstrual period date within 2 weeks of cases). The adjusted odds ratios for pre-term birth were not significant when adjusted for maternal age, maternal race/ethnicity, maternal education, marital status, and parity (with or without inclusion of $PM_{2.5}$ exposure). A 1 ppm increase in ambient carbon monoxide concentration during the first month of pregnancy was associated with an odds ratio of 1.10 (95% CI: 0.99, 1.20) when CO was considered alone,

and 1.03 (95% CI: 0.83, 1.13) after adjustment for PM_{10}. This study matched ambient carbon monoxide measurements to subjects whose residence was <5 miles of the monitoring station, whereas the Ritz et al. (2000, 2007) and Wilhelm and Ritz (2005) studies matched subjects to <2 miles from the monitoring station.

Other large retrospective cohort studies have examined pre-term births in association with ambient air carbon monoxide concentrations. Liu et al. (2003) examined a cohort of 229,085 births in Vancouver, Canada (1985–1998). The odds ratio for pre-term birth for a 1 ppm increase in ambient air carbon monoxide concentration measured during the first month of pregnancy was 1.08 (95% CI: 1.01, 1.15; adjusted for maternal age, parity, infant sex, birth weight, and season of birth) and remained elevated after adjustment for NO_2 and O_3 (1.08, 95% CI: 1.00, 1.20). The mean air carbon monoxide concentration in the study was 1 ppm, and the highest value was 12.8 ppm. A cohort study of 52,113 births in Incheon, Korea (2001–2002) also estimated elevated risks of pre-term birth in association with increasing ambient air carbon monoxide concentrations during the first trimester. The relative risk increased with increasing estimated exposure concentration and was 1.26 (95% CI: 1.11, 1.44) for the strata 0.91–1.27 mg/m^3 (0.79–1.10 ppm) compared to the reference, >0.47–0.63 mg/m^3 (0.40–0.55 ppm) (adjusted for maternal age, parity, sex, season of birth, and education level of father and mother; Leem et al. 2006). Results of multi-pollutant models were not reported. The ambient air carbon monoxide concentrations ranged from approximately 0.35 to 1.4 ppm and were matched to subjects by spatial kriging (a spatial statistical method for interpolating exposure levels between sampling locations), with spatial averaging on a scale of approximately 3.5 km^2. A cohort study of 123,840 births in Sydney, Australia (1998–2000) did not find a significant association between ambient air carbon monoxide concentration and pre-term birth (Jalaludin et al. 2007). The highest odds ratio estimated was 1.24 (95% CI: 0.81, 1.91) or a 1 ppm increase in 8-hour maximum carbon monoxide concentration measured during first trimester, based on residence <5 km of the monitoring station. When exposure estimates were based on city-wide monitoring, the odds ratio was significantly less than 1 (0.89, 95% CI: 0.84, 0.95), suggesting that risk of pre-term birth decreased with a 1 ppm increase in air carbon monoxide concentration. The city-wide mean 8-hour maximum air carbon monoxide concentration was 0.9 ppm (SD: 0.68).

Studies of Low Birth Weight. Results of studies of low birth weight (i.e., <2,500 g or <10^{th} percentile weight for gestation age) have been mixed, with most studies finding associations between increasing ambient air carbon monoxide concentrations and decreasing birth weight (Bell et al. 2007; Gouveia et al. 2004; Ha et al. 2001; Lee et al. 2003a; Liu et al. 2003, 2007; Maisonet et al. 2001; Mannes et al. 2005; Medeiros and Gouveia 2005; Morello-Frosch et al. 2010; Parker et al. 2005; Ritz and Yu 1999; Salam et

al. 2005; Wilhelm and Ritz 2005). In some studies that found significant regression coefficients (i.e., β coefficients) relating air carbon monoxide concentration to birth weight (g), magnitudes of the changes in birth weight were not sufficient to produce elevated risk of low birth weight, where low birth weight is defined categorically as a birth weight <2,500 g. Furthermore, the relative contribution of co-exposures to other air pollutants has not been completely elucidated in epidemiology studies. In many, but not all, studies showing significant associations with birth weight, these associations were not significant after adjustments for exposures to other co-pollutants (e.g., NO_2, O_3, PM_{10}). All of these studies described below estimated risks after adjustment for typical co-variables that are thought to affect birth weight (e.g., infant sex, maternal age, race/ethnicity, and education, interval since previous live birth, previous low birth weight or preterm infant, level of prenatal care, birth season, parity, and gestational age). Collectively, the reported studies of birth weight outcomes provide supportive evidence for an association between ambient air carbon monoxide concentrations and low birth weight.

A series of studies conducted in California found that such associations were stronger when carbon monoxide was the only pollutant considered in the model and attenuated when adjustments were made for co-pollutants (Morello-Frosch et al. 2010; Parker et al. 2005; Ritz and Yu 1999; Salam et al. 2005; Wilhelm and Ritz 2005). Mean air carbon monoxide concentrations in these studies ranged from 0.75 to 2.4 ppm and the highest value reported was 6.70 ppm (Wilhelm and Ritz 2005). Morello-Frosch et al. (2010) found significant associations between increasing carbon monoxide concentrations and decreasing birth weight and elevated risk of low birth weight in a sample of 3.5 million births (1996–2006). The β coefficient for birth weight was -5.4 g (95% CI: -6.8, -4.1) per 1 ppm increase in carbon monoxide concentration for the entire period of pregnancy and was also significant for exposures during the first or third trimesters. The odds ratio for low birth weight was 1.04 (95% CI: 1.02, 1.06). The association between exposure to carbon monoxide and birth weight persisted when adjusted for exposures to ozone and SO_2, but was no longer significant when adjusted for PM_{10} or $PM_{2.5}$. The Ritz and Yu (1999) study found elevated risk of low birth weight in a sample of 125,573 births (1989–1993). The odds ratio (>5.5 vs. <2.2 ppm during third trimester) was 1.22 (95% CI: 1.03, 1.44) when carbon monoxide alone was the only air pollutant considered and 1.38 (95% CI: 0.86, 2.22) when NO_2, O_3, and PM_{10} were included in the model. The odds ratios remained significant after adjustment for NO_2, O_3, and PM_{10}, when the analysis was restricted to women <20 years of age (multi-pollutant model: 5.08, 95% CI: 1.77, 16.63; carbon monoxide alone: 1.54, 95% CI: 1.07, 2.22). In a follow-up study (Wilhelm and Ritz 2005; 1994–2000) that included 136,134 births, the odds ratio (>1.84 vs. <0.96 ppm) was estimated to be 1.36 (95% CI: 1.04, 1.76) for women who resided ≤1 mile from an air monitoring station; however, risk was no longer significant when NO_2 and O_3 (1.29, 95% CI: 0.92, 1.81) or NO_2, O_3, and PM_{10} (1.39, 95%

CI: 0.77, 2.49) were included in the model. A smaller cohort study (1975–1987) of 3,901 births found significant associations between ambient air carbon monoxide concentrations and low birth weight and intrauterine growth retardation (IUGR, <15th percentile of weight at gestational age; Salam et al. 2005). The estimated odds ratio for IUGR was 1.2 (95% CI: 1.0, 1.4) for a 1.4 ppm increase in air carbon monoxide concentration in the first trimester (carbon monoxide considered alone). Although the odds ratio for low birth weight was not significant (1.0, 95% CI: 0.7, 1.5), a significant association between increasing air carbon monoxide concentration and lower birth weight was observed when birth weight was treated as a continuous variable (β coefficient: -21.7 g, 95% CI: -42.3, -1.1), which persisted when O_3 was included in the model (-28.6, 95% CI: -50.4, -6.9). A cohort study of 18,247 full-term births in California (2000) did not find a significant association between ambient air carbon monoxide concentration and risk of SGA (i.e., small for gestational age, <10th percentile of weight for gestational age; Parker et al. 2005). The SGA odds ratio (>0.97 vs. <0.57 ppm for entire pregnancy) was 0.95 (95% CI: 0.81, 1.12) when carbon monoxide was considered alone and 0.82 (95% CI: 0.68, 0.99) when adjusted for $PM_{2.5.}$ When treated as a continuous variable, a significant association between increasing air carbon monoxide concentration and lower birth weight was found when carbon monoxide was modeled alone (β coefficient: -20.5 g, 95% CI: -40.1, -0.8); however, the association was not significant when adjusted for $PM_{2.5}$ (2.6, 95% CI: -20.6, 25.8).

Other studies of low birth weight conducted in the United States have yielded mixed results. A cohort study of 89,557 full-term births conducted in five northeastern cities (1994–1996) estimated the odds ratio for low birth weight to be 1.31 (95% CI: 1.06, 1.62) for a 1 ppm increase in air carbon monoxide concentration during the third trimester (Maisonet et al. 2001). When stratified by race, the effect was only significant among African Americans for the first trimester (odds ratio: 1.43, 95% CI: 1.18, 1.74) and third trimester (odds ratio: 1.75, 95% CI: 1.50, 2.04). Results of multi-pollutant models were not reported. A cohort study of 358,504 births in Connecticut and Massachusetts found a significant association between increasing ambient air carbon monoxide concentration (for entire pregnancy) and reduced birth weight (β coefficient: -16.2, 95% CI: -19.7, -12.6), which persisted when adjusted for NO_2, O_3, PM_{10}, $PM_{2.5}$, or SO_2 (Bell et al. 2007). However, the magnitude of the change in birth weight did not result in a significant odds ratio (odds ratio: 1.028, 95% CI: 0.983, 1.074). Mean air carbon monoxide concentrations in the above studies ranged from 0.65 to 0.95 ppm.

Two studies examined low birth weight or IUGR in Canada (Liu et al. 2003, 2007). The Liu et al. (2003) study included 229,085 births in the Vancouver area (1985–1998) and found a significant association between ambient air carbon monoxide concentration (during fist month of pregnancy) and IUGR risk per

1 ppm increase in carbon monoxide (odds ratio: 1.06, 95% CI: 1.01, 1.10), which persisted when adjusted for NO_2, O_3, or SO_2 (OR estimates not reported). In a larger area study (Liu et al. 2007) that included 386,202 births (1995–2000), odds ratios were significant for IUGR when ambient air carbon monoxide concentrations were considered during the first trimester (1.18, 95% CI: 1.14, 1.22), second trimester(1.14, 95% CI: 1.10, 1.18), or third trimester (1.19, 95% CI: 1.14, 1.24). The odd ratios remained significant after adjustment for exposures to NO_2 and $PM_{2.5}$. The mean air carbon monoxide concentration in both studies was 1 ppm and the highest value reported was 5.6 ppm.

Two studies conducted in Seoul, South Korea (1996–1997, 1996–1998) found significantly increased risk of low birth weight in cohorts of 276,763 births (Ha et al. 2001) and 388,105 births (Lee et al. 2003a). In the Ha et al. (2001) study, the relative risk of low birth weight for a 0.42 ppm increase in ambient air carbon monoxide concentration during the first trimesters was 1.08 (95% CI: 1.04, 1.12). In the Lee et al. (2003a) study, the odds ratios for a 0.5 ppm increase in carbon monoxide concentration were 1.04 (95% CI: 1.01, 1.07) for the first trimester, 1.03 (1.00–1.06) for the second trimester carbon monoxide, 0.96 (0.93–0.99) for the third trimester carbon monoxide, and 1.05 (1.01–1.09) for carbon monoxide concentration during the entire pregnancy. Results of multi-pollutant models were not reported. The mean air carbon monoxide concentration was 1.2 ppm (range: 0.4–3.4 ppm).

A cohort study conducted in Sydney, Australia (1998–2000) included 138,056 births and found a significant association between increasing ambient air carbon monoxide concentration and decreasing birth weight (Mannes et al. 2005). For carbon monoxide exposure during the second trimester, an increase of 1 ppm was associated with a 28.7 g reduction birth weight (95% CI: 7.76, 50.98). The association did not persist when the regression models were adjusted for exposure to NO_2 or PM_{10} in two-pollutant models. Furthermore, the magnitude of the effect did not result in a significant risk of SGA (<2 SD of mean weight for gestational age). The mean ambient carbon monoxide concentration was 0.8 ppm (range: 0–4.6).

Two cohort studies conducted in Sao Paulo, Brazil also found a significant association between increasing ambient air carbon monoxide concentration and decreasing birth weight (Gouveia et al. 2004; Medeiros and Gouveia 2005). In the Gouveia et al. (2004) study, in a cohort of 179,460 births (1997), a 1 ppm increase in ambient air carbon monoxide concentration during the first trimester was associated with a 23.1 g reduction in birth weight (95% CI: 4.9, 41.3); however, the effect was not of sufficient magnitude to result in elevated risk of low birth weight. The Medeiros and Gouveia (2005) study included 311,735 births (1998–2000) and estimated a reduction in birth weight of 11.9 g (95% CI: 8.2, 15.5) per

1 ppm increase in first trimester carbon monoxide concentration. Here again, odds ratios for low birth weight were not significant. The ambient carbon monoxide concentrations in these studies ranged from approximately 1 to 11 ppm.

Studies of Congenital Anomalies. Possible associations between exposures to carbon monoxide and developmental anomalies have been evaluated in four case-control studies (Dadvand et al. 2011; Gilboa et al. 2005; Hwang and Jaakkola 2008; Ritz et al. 2002). Three of the studies found significant associations between carbon monoxide and heart anomalies (i.e., ventricular septic defect (Ritz et al. 2002), conotruncal defects (Gilboa et al. 2005), malformation of cardiac septa (Dadvand et al. 2011), and pulmonary valve stenosis (Dadvand et al. 2011). The evaluation in the Hwang and Jaakkola (2008) study was limited to cleft lip and palate and found no association with carbon monoxide, consistent with the Ritz et al. (2002) study. Collectively, these studies do not provide convincing evidence for associations between exposure to carbon monoxide and congenital anomalies.

The Dadvand et al. (2011) study included 2,769 cases and 14,256 controls born during the period 1993–2003 in northeast England. The study examined heart anomalies, including malformations of the cardiac chambers and connections, cardiac septa, aortic and mitral valves, and great arteries and vein; atrial septal defect; coarctation of aorta; congenital pulmonary stenosis; tetralogy of Fallot; and ventricular septal defect. Of these, significant associations with carbon monoxide concentrations (odds ratio per 1 mg/m^3 [0.87 ppm] increase in carbon monoxide concentration) were observed for malformation of cardiac septa (2.330, 95% CI: 1.748, 3.102), pulmonary valve stenosis (2.682, 95% CI: 2.682, 5.534), and ventricular septal defect (2.634, 95% CI: 1.871, 3.707). The Ritz et al. (2002) study included 3,549 cases and 10,649 controls born during the period 1987–1993 in southern California. The study included various categories of anomalies including heart and pulmonary, conotruncal, cleft lip and palate, and chromosomal defects. Of these, significant odds ratios were found for ventricular septal defects with increasing ambient air carbon monoxide concentration during the second month of pregnancy. Odds ratios increased with increasing ambient air carbon monoxide concentration during the second month of pregnancy (<1.14 ppm reference): 1.14–1.60 ppm, odds ratio 1.62 (95% CI: 1.05, 2.48); 1.60–<2.47 ppm, odds ratio 2.09 (95% CI: 1.19, 3.67); and ≥2.47 ppm, odds ratio 2.95 (95% CI: 1.44, 6.05). Significant odds ratios for ventricular septal defects persisted in multi-pollutant models.

A case-control study conducted in Texas (1996–2000) included 4,594 cases and 3,667 controls (Gilboa et al. 2005). Anomalies considered in the study included heart and pulmonary, conotruncal, and cleft lip and palate. Of these, a significant dose trend was evident for tetralogy of Fallot (a conotruncal anomaly of the

heart), with a significant odds ratio (>0.7 vs. <0.4 ppm) for ambient air carbon monoxide concentration during the 3rd–8th week of pregnancy (2.04, 95% CI: 1.26, 3.29). The odds ratio for any conotruncal anomaly was also significant at the highest exposure category (>0.7 vs. <0.4 ppm) (1.46, 95% CI: 1.03, 2.08). Results of multi-pollutant models were not reported.

A case-control study conducted in Taiwan (2001–2003) included 653 cases of cleft lip and/or palate and 6,530 controls and examined associations with ambient air carbon monoxide concentrations measured during the first trimester of pregnancy (Hwang and Jaakkola 2008). Air carbon monoxide concentration was not associated with odds ratio for either anomaly in single- or multiple-pollutant models (O_3, PM_{10}, or SO_2).

Studies of Neonatal and Infant Mortality. Studies of possible associations between ambient air carbon monoxide concentrations and neonatal and infant mortality have yielded mixed results (Ha et al. 2003; Lin et al. 2004a; Ritz et al. 2006; Tsai et al. 2006a; Woodruff et al. 2008; Yang et al. 2006). Although increased risk of infant mortality in association with increasing ambient air carbon monoxide concentrations has been reported (Ha et al. 2003; Ritz et al. 2006), these outcomes have not been rigorously examined for the possible confounding by birth weight and/or gestational age, two relatively influential variables in predicting infant mortality. In one study that did examine the effect of stratification by gestational age or birth weight, the association between air carbon monoxide concentration and mortality from all causes or sudden infant death syndrome (SIDS) persisted in single-pollutant models, but not in models that adjusted for NO_2, PM_{10}, and O_3 (Ritz et al. 2006). Collectively, these studies do not provide convincing evidence for an association between ambient air carbon monoxide concentrations and neonatal or infant mortality.

A time-series analysis conducted in Sao Paulo, Brazil (1998–2000) did not find a significant association between ambient air carbon monoxide concentrations and neonatal mortality (age 1–28 days; Lin et al. 2004a). The mean air carbon monoxide concentration was 2.8 ppm (range: 0.5–10 ppm). A case-control study conducted in California (1989–2000) included 13,146 cases of infant death (age 28 days–1 year) and 151,015 controls (Ritz et al. 2006). Results varied depending on the temporal window for averaging air carbon monoxide concentration. The odds ratio for infant death for a 1 ppm increase in ambient air carbon monoxide concentration, averaged for 2 months prior to death, was 1.11 (95% CI: 1.06, 1.16), with higher risk for deaths attributable to SIDS (odds ratio: 1.19; 95% CI: 1.10, 1.28). However, risks were not significant after adjustment for co-pollutants (NO_2, PM_{10}, and O_3). For an averaging period of 2 weeks prior to death, risks were significant for all respiratory-related deaths that occurred between

28 days and 1 year (odds ratio: 1.14, 95% CI: 1.03, 1.25) or from age 28 days to 3 months (odds ratio: 1.20, 95% CI: 1.02, 1.40). Significant respiratory deaths persisted in multi-pollutant models. The association between air carbon monoxide concentration and SIDS mortality risk was persistent when the data were stratified by gestational age and birth weight; however, in these strata, the associations were not significant after adjustment for exposure to NO_2, PM_{10}, and O_3. The mean air carbon monoxide concentration in the study was 1.6 ppm (range: 0.4–3.4 ppm).

A retrospective cohort study analyzed deaths that occurred between age 28 days and 1 year in a cohort of 3,590,134 births (6,939 deaths) across U.S. counties having a population >250,000 residents (1989–2000; Woodruff et al. 2008). Ambient air carbon monoxide concentration (median: 0.70 ppm, 25^{th}–75^{th} percentile range: 0.48–0.87 ppm) during the first 2 months postpartum was not associated with infant death of any category, including all causes (odds ratio: 1.01, 95% CI: 0.95, 1.07), respiratory (odds ratio: 1.14, 95% CI: 0.93, 1.40), or SIDS (odds ratio: 0.88, 95% CI: 0.76, 1.03). The latter values were estimated from single-pollutant models; however, similar results were obtained in multi-pollutant models that adjusted for O_3 and SO_2.

A time-series study conducted in Seoul, South Korea (1995–1999) found a significant risk of respiratory-related mortality (age 1 month–1 year) in association with increasing ambient air carbon monoxide concentration measured on the day of death (odds ratio: 1.388, 95% CI: 1.009, 1.911, per 0.57 ppm increase in carbon monoxide concentration), but not for deaths from all causes (Ha et al. 2003). Two case-crossover studies conducted in Taiwan (1994–2000) did not find a significant association between ambient air carbon monoxide concentration and infant mortality (Tsai et al. 2006a; Yang et al. 2006). The Tsai et al. (2006a) study included 206 cases (age 28 days–1 year), and the mean ambient air carbon monoxide concentration was 0.83 ppm (range: 0.23–1.77 ppm). The Yang et al. (2006) study included 471 cases (age 27 days–1 year); the mean ambient air carbon monoxide concentration was 1.58 ppm (range: 0.3–4.8 ppm).

Animal Studies. Numerous studies on developmental effects of gestational and early postnatal exposure to carbon monoxide have been conducted in animals. Study details are summarized in Table 3-9. In general, most studies evaluated effects of relatively low carbon monoxide concentrations (i.e., ≤300 ppm), with exposure concentrations selected to produce maternal COHb levels typically associated with smoking; however, studies did not consistently report maternal or fetal COHb levels. Studies in animals have examined effects of carbon monoxide exposure on numerous developmental outcomes, including several outcomes that have not been assessed in epidemiological studies (e.g., auditory and immune

Table 3-9. Effects of Gestational or Perinatal Exposure on Developmental Outcomes in Animals

Reference	Species	Exposure	COHb	Results
Effects on birth weight				
Astrup et al. 1972	Rabbits	Continuous exposure to 0, 90, or 180 ppm CO throughout gestation	mCOHb: 8–9% in 90 ppm CO group; 16–18% in 180 ppm CO group fCOHb: NR	Birth weight: Fetal weight decreased by 11 and 20% in the 90 and 180 ppm CO groups, respectively. NOAEL (birth weight): Not established LOAEL (birth weight): 90 ppm CO (mCOHb 8–9%)
Carmines and Rajendran 2008	Rats	2 hours/day to 600 ppm CO on GDs 6–19 (nose-only exposure)	mCOHb: ~30% (measured on GD 20) fCOHb: NR	Birth weight: Significantly decreased by 11%, compared to control. NOAEL (birth weight): Not established LOAEL (birth weight): 600 ppm CO (mCOHb ~30%)
Fechter and Annau 1977	Rats	Continuous exposure to 0 or 150 ppm CO on GDs 0–21	mCOHb: 15% fCOHb: NR	Birth weight: Decreased by 4.8%, compared to controls (not statistically significant). Pre-weanling weight: Pre-weanling weight significantly decreased, compared to control, on PNDs 4–21 (decreased by 16 and 27% on PNDs 4 and 21, respectively). NOAEL (pre-weanling weight): Not established LOAEL (pre-weanling weight): 60 ppm CO (mCOHb 15%)
Fechter and Annau 1980	Rats	Continuous exposure to 0 or 150 ppm CO on GDs 0–20	mCOHb: NR fCOHb: NR	Birth weight: Decreased by 7.6%, compared to controls. NOAEL (pre-weanling weight): Not established LOAEL (pre-weanling weight): 150 ppm CO
Fechter et al. 1987a	Rats	Continuous exposure to 0, 75, 150, or 300 ppm CO from GD 0 through PND 10	mCOHb: 11, 18, and 27% in the 75, 150, or 300 ppm CO, respectively fCOHb: NR	Birth weight: Fetal weight decreased by 8.9 and 13.8% in 150 and 300 ppm CO groups, respectively, compared to control; by PND 21, no effects of CO treatment on pup weight. NOAEL (birth weight): 75 ppm CO (mCOHb 11%) LOAEL (birth weight): 150 ppm CO (mCOHb 18%)

Table 3-9. Effects of Gestational or Perinatal Exposure on Developmental Outcomes in Animals

Reference	Species	Exposure	COHb	Results
Penney et al. 1983	Rats	Continuous exposure to 0, 157, 166, or 200 ppm CO on GDs 5–22	mCOHb: 24.9% (in dams exposed to 200 CO, measured over period of PNDs 1–6) fCOHb: 21.8, 24.9, and 3.10–33.5% at 157, 166, and 200 ppm CO, respectively (at birth)	Birth weight: Statistically significant decrease (~10%) in all CO groups, compared to control. NOAEL (birth weight): Not established LOAEL (birth weight): 157 ppm CO (fCOHb 21.8%)
Prigge and Hochrainer 1977	Rats	Continuous exposure to 0, 60, 125, 250, or 500 ppm CO on GDs 0–21	mCOHb: NR fCOHb: NR	Birth weight: Dose-related, statistically significant decrease (7.5–36.7%) in fetal weight at ≥125 ppm, compared to control. NOAEL (birth weight): 60 ppm CO LOAEL (birth weight): 125 ppm CO
Storm and Fechter 1985b	Rats	Continuous exposure to 0, 75, 150, or 300 ppm CO for entire gestational period	mCOHb: 11.5, 18.5, and 26.8% in the 75, 150, and 300 ppm CO groups, respectively fCOHb: NR	Birth weight: Fetal weight decreased by 12.5% in 300 ppm CO group, compared to control. NOAEL (birth weight): 150 ppm CO (mCOHb 18.5%) LOAEL (birth weight): 300 ppm CO (mCOHb 27%)
Tolcos et al. 2000b	Guinea pigs	10 hours/day 0 or 200 ppm CO from GDs 23 or 25 to GD 68	mCOHb: 8.5% fCOHb: 13%	Birth weight: Fetal weight decreased by 9.6% in CO group, compared to control. NOAEL (birth weight): Not established LOAEL (birth weight): 200 ppm CO (mCOHb 8.5%)
Effects on CNS (central control of respiratory function)				
McGregor et al. 1998	Guinea pigs	10 hours/day 0 or 200 ppm CO from GDs 23 or 25 to GD 68	mCOHb: 8.5% fCOHb: 13%	CNS development (function): On PND 4, pups from CO-exposed dams exhibited abnormal respiratory responses to asphyxia and hypercapnia; responses consistent with developmental alterations in brain stem. NOAEL (CNS function): Not established LOAEL (CNS function): 200 ppm CO (mCOHb 8.5%)

Table 3-9. Effects of Gestational or Perinatal Exposure on Developmental Outcomes in Animals

Reference	Species	Exposure	COHb	Results
Effects on CNS (behavioral)				
De Salvia et al. 1995	Rats	0, 75, or 150 ppm CO on GDs 0–20	mCOHb: ~15% for 150 ppm CO (NR for 75 ppm CO) fCOHb: NR	CNS development (behavioral effects): Significant impairment of acquisition (at 3 and 18 months) and reacquisition (at 18 months) of conditioned avoidance behavior following gestational exposure of pups to 150 ppm CO. NOAEL (CNS behavioral): 75 ppm CO LOAEL (CNS behavioral): 150 ppm CO
Fechter and Annau 1977	Rats	Continuous exposure to 0 or 150 ppm CO on GDs 0–21	mCOHb: 15% fCOHb: NR	CNS development (behavioral effects): During the preweaning period, CO pups were less active and showed decreased response to L-DOPA-induced movement stimulation. NOAEL (CNS behavioral): Not established LOAEL (CNS behavioral): 60 ppm CO (mCOHb 15%)
Fechter and Annau 1980	Rats	Continuous exposure to 0 or 150 ppm CO on GDs 0–20	mCOHb: NR fCOHb: NR	CNS development (behavioral effects): Pups of exposed dams showed impaired righting reflexes, impaired negative geotaxis, and delayed homing behavior. NOAEL (CNS behavioral): Not established LOAEL (CNS behavioral): 150 ppm CO
Giustino et al. 1999	Rats	Continuous exposure to 75 and 150 ppm CO on GDs 0–20	mCOHb: 7.3 and 16.1% in 75 and 150 ppm CO groups, respectively fCOHb: NR	CNS development (behavioral effects): Alterations in habituation and working memory in young adult male offspring at PND 40, including decreased time of exploration of novel objects (75 and 150 ppm CO) and lack of habituation after the second exposure to a previously viewed object (150 ppm CO); decreased spontaneous motor activity in open field test (75 and 150 ppm CO). NOAEL (CNS behavioral): Not established LOAEL (CNS behavioral): 75 ppm CO

Table 3-9. Effects of Gestational or Perinatal Exposure on Developmental Outcomes in Animals

Reference	Species	Exposure	COHb	Results
Mactutus and Fechter 1985	Rats	Continuous exposure to 150 ppm CO over entire gestational period	mCOHb: 15.6% fCOHb: NR	CNS development (behavioral effects): Prenatal CO exposure induced learning and memory deficits in male and female offspring, as indicated by impairments in reacquisition performance, an index of retention, on PND 31 and decrements in two-way conditioned avoidance behavior (flashing light warnings followed by mild foot shock) on PND 120. NOAEL (CNS behavioral): Not established LOAEL (CNS behavioral): 150 ppm CO (mCOHb 15.6%)
Singh 1986	Mice	Continuous exposure to 0, 65, or 135 ppm CO on GDs 7–18	mCOHb: NR fCOHb: NR	CNS development (behavioral effects): On PNDs 1–10, pups of exposed dams showed impaired righting reflexes (125 ppm CO), geotaxis (125 ppm CO), and aerial righting reflex (65 and 125 ppm CO). NOAEL (CNS behavioral): Not established LOAEL (CNS behavioral): 65 ppm CO
Tattoli et al. 1999	Rats	Continuous exposure to 0, 75, or 150 ppm CO on PNDs 1–10	COHb in pups: NR	CNS development (behavioral effects): Assessed at 3 and 18 months of age, no effects of early postnatal exposure on acquisition and reacquisition of an active avoidance task in either adult or aged rats. NOAEL: 150 ppm CO LOAEL: Not established

Table 3-9. Effects of Gestational or Perinatal Exposure on Developmental Outcomes in Animals

Reference	Species	Exposure	COHb	Results
Effects on CNS (neurotransmitter)				
Cagiano et al. 1998	Rats	Continuous exposure to 0 or 150 ppm CO on GDs 0–20	mCOHb: ~16% fCOHb: NR	CNS development (neurotransmitter changes): On PND 80, no CO effect on basal extracellular levels of dopamine in the nucleus accumbens; however, the amphetamine-induced dopamine release was decreased in pups of CO-exposed dams. NOAEL (CNS neurotransmitter): Not established LOAEL (CNS neurotransmitter): 150 ppm CO (mCOHb 16%)
Fechter and Annau 1977	Rats	Continuous exposure to 0 or 150 ppm CO on GDs 0–21	mCOHb: 15% fCOHb: NR	CNS development (neurotransmitter changes): Brain dopamine content decreased by 45 and 25% on PNDs 1 and 4, respectively. NOAEL (CNS neurotransmitter): Not established LOAEL (CNS neurotransmitter): 60 ppm CO (mCOHb 15%)
Fechter and Annau 1980	Rats	Continuous exposure to 0 or 150 ppm CO on GDs 0–20	mCOHb: NR fCOHb: NR	CNS development (neurotransmitter changes): On PND 1, no effect of CO exposure on forebrain and hindbrain levels of dopamine or norepinephrine. NOAEL (CNS neurotransmitter): 150 ppm CO LOAEL (CNS neurotransmitter): Not established
Fechter et al. 1987a	Rats	Continuous exposure to 0, 75, 150, or 300 ppm CO from GD 0 through PND 10	mCOHb: 11, 18, and 27% In the 75, 150, or 300 ppm CO, respectively fCOHb: NR	CNS development (neurotransmitter changes): On PND 21, pups of CO-exposed dams showed elevated dopamine levels in neostriatum (150 and 300 ppm CO). NOAEL (CNS neurotransmitter): 75 ppm CO (mCOHb 11%) LOAEL (CNS neurotransmitter): 150 ppm CO (mCOHb 18%)
Storm and Fechter 1985a	Rats	Continuous exposure to 0 or 150 ppm for entire gestational period	mCOHb: NR fCOHb: NR	CNS development (neurotransmitter changes): Norepinephrine levels (amount and concentration) in cerebellum (but not cortex) elevated from PND 14 to 42, compared to controls. NOAEL (CNS neurotransmitter): Not established LOAEL (CNS neurotransmitter): 150 ppm CO

Table 3-9. Effects of Gestational or Perinatal Exposure on Developmental Outcomes in Animals

Reference	Species	Exposure	COHb	Results
Storm and Fechter 1985b	Rats	Continuous exposure to 0, 75, 150, or 300 ppm CO for entire gestational period	mCOHb: 11.5, 18.5, and 26.8% in the 75, 150, and 300 ppm CO groups, respectively fCOHb: NR	CNS development (neurotransmitter changes): On PND 21, weight of cerebellum decreased by 8.5 and 11.4% in 150 and 300 ppm CO groups, respectively; dose-related trend for decreased norepinephrine concentration in pons/medulla (but not neocortex, hippocampus, or cerebellum; decreased serotonin concentration in pons/medulla in 150 and 300 ppm CO groups. On PND 42, weight of cerebellum decreased by 8.3% in 300 ppm CO group; dose-related trend for increased norepinephrine concentration neocortex and hippocampus (but not pons/medulla or cerebellum). NOAEL (CNS neurotransmitter): 75 ppm CO (mCOHb 11.5%) LOAEL (CNS neurotransmitter): 150 ppm CO (mCOHb 18.5%)
Tolcos et al. 2000b	Guinea pigs	10 hours/day 0 or 200 ppm CO from GDs 23 or 25 to GD 68	mCOHb: 8.5% fCOHb: 13%	CNS development (neurotransmitter changes): Effects on cholinergic and catecholaminergic pathways in the medulla, including significant decrease in tyrosine hydroxylase-immunoreactivity in the nucleus tractus solitarius, dorsal motor nucleus of the vagus, area postrema, intermediate reticular nucleus, and ventrolateral medulla; significant increase in choline acetyltransferase-immunoreactivity in the dorsal motor nucleus of the vagus and hypoglossal nucleus, compared with controls. NOAEL (CNS neurotransmitter): Not established LOAEL (CNS neurotransmitter): 200 ppm CO (mCOHb 8.5%)

Table 3-9. Effects of Gestational or Perinatal Exposure on Developmental Outcomes in Animals

Reference	Species	Exposure	COHb	Results
Effects on CNS (auditory system)				
Lopez et al. 2003	Rats	Continuous exposure to 0, 12, or 25 ppm CO on PNDs 8–22	mCOHb: NR fCOHb: NR	CNS development (auditory system): Pups examined on PND 27, nerve terminals innervating inner hair cells were swollen, with cytoplasmic vacuolization and atrophy (25 ppm CO); in the 8th cranial nerve at the level of the internal auditory canal, fibers showed "distorted myelin" with vacuolization (25 ppm CO); in spiral ganglion neurons of the organ of corti, decreased immunoreactivity of enzymes cytochrome oxidase, NADH-TR, and calcium-mediated myosin ATPase (25 ppm CO); in organ of corti, decreased immunostaining of neurofilament and myelin basic protein (25 ppm CO). NOAEL (CNS auditory): 12 ppm CO LOAEL (CNS auditory): 25 ppm CO
Lopez et al. 2008	Rats	10–18 hours/day to 25 ppm CO on GDs 5–20 or on GDs 5–20 plus PNDs 5–20	mCOHb: NR fCOHb: NR	CNS development (auditory system): Similar effects in pups exposed during gestation only and during gestation and PNDs 5–20. On PND 3, no morphological deterioration or loss of inner or outer hair cells; on PND 20, vacuolization on the afferent terminals at the basal portion of the cochlea; type I spiral ganglia neurons and afferent nerve fibers showed decreased neurofilament-immunoreactivity. NOAEL (CNS auditory): Not established LOAEL (CNS auditory): 25 ppm CO

Table 3-9. Effects of Gestational or Perinatal Exposure on Developmental Outcomes in Animals

Reference	Species	Exposure	COHb	Results
Stockard-Sullivan 2003	Rats	22 hour/day to 12, 25, 50, or 100 ppm CO on PNDs 6–22	COHb in pups: 5–7% in 100 ppm CO group (not measured in other groups)	CNS development (auditory system): Decreased in otoacoustic emissions at 50 and 100 ppm CO, measured at age 22–24 days; attenuation of the amplitude of the 8th nerve action potential in all CO groups, measured at age 22–24 days, with effects persisting though age 73 days in the 50 and 100 ppm CO group (not examined at later ages in other groups); no effect on auditory brain stem conduction times in any CO group, measured at ages 22, 30, or 51–52 days. NOAEL (CNS auditory): Not established LOAEL (CNS auditory): 12 ppm CO
Webber et al. 2003	Rats	Continuous exposure to 0, 12.5, 25, or 50 ppm CO on GDs 8 through 20–22	mCOHb: NR fCOHb: NR	CNS development (auditory system): Examined effects of CO exposed on central inferior colliculus (an area of the mid-brain with auditory integrative functions) during period of synaptogenesis/auditory development. Immunostaining of c-Fos (marker of neuronal activation in the nervous system) showed significant decrease in C-Fos immunoreactivity in the central inferior colliculus on PNDs 27 and 75–77 in all CO groups. Results indicate that gestational exposure to CO can produce changes in the auditory system of rats that persist into adulthood. NOAEL (CNS auditory): Not established LOAEL (CNS auditory): 12.5 ppm CO

Table 3-9. Effects of Gestational or Perinatal Exposure on Developmental Outcomes in Animals

Reference	Species	Exposure	COHb	Results
Effect on peripheral nervous system				
Carratu et al. 1993	Rats	Continuous exposure to 0, 75, or 100 ppm CO on GDs 0–20	mCOHb: ~15% for 150 ppm CO (NR for 75 ppm CO) fCOHb: NR	PNS development (electrophysiological changes): In sciatic nerves isolated on PND 40, inactivation kinetics of inactive sodium channels were significantly slowed and negative shift in sodium equilibrium potential was observed in both CO groups; on PND 270, sciatic nerves showed negative shift in sodium equilibrium potential both CO groups. NOAEL (PNS development): Not established LOAEL (PNS development): 75 ppm CO
Carratu et al. 2000a	Rats	Continuous exposure to 0 or 150 ppm CO on GDs 0–20	mCOHb: 16.02% fCOHb: NR	PNS development (neuronal development): Altered sphingomyelin composition of sciatic nerve, but no effect on motor activity in pups at PND 90. NOAEL (PNS development): Not established LOAEL (PNS development): 150 ppm CO
Carratu et al. 2000b	Rats	Continuous exposure to 0, 75, or 100 ppm CO on GDs 0–20	mCOHb: 7.34 and 16.08% in the 75 and 150 ppm CO groups, respectively fCOHb: NR	PNS development (neuronal development): Exposure of dams produced decreased myelin sheath thickness of nerve fibers (75 and 100 ppm CO) but not axon diameter or motor activity in pups at PNDs 40 and 90. NOAEL (PNS development): Not established LOAEL (PNS development): 75 ppm CO
Effects on cardiovascular system				
Penney et al. 1982	Rats	Continuous exposure to 0 or 500 ppm CO on PNDs 1–32	COHb in pups: 38–42%	CVS (heart weight): Relative heart weight increased on PND 14 and remained above normal through PND 104. NOAEL (developmental heart weight): Not established LOAEL (developmental heart weight): 500 ppm CO (COHb 38–42%)

Table 3-9. Effects of Gestational or Perinatal Exposure on Developmental Outcomes in Animals

Reference	Species	Exposure	COHb	Results
Penney et al. 1983	Rats	Continuous exposure to 0, 157, 166, or 200 ppm CO on GDs 5–22	mCOHb: 24.9% (in dams exposed to 200 CO, measured over period of PNDs 1–6) fCOHb: 21.8, 24.9, and 3.10–33.5% at 157, 166, and 200 ppm CO, respectively (at birth)	CVS (heart weight): Dose-related, statistically significant increased in relative heart weight (10–108%) in all CO groups, compared to control. NOAEL (developmental heart weight): Not established LOAEL (developmental heart weight): 157 ppm CO (fCOHb 21.8%)
Prigge and Hochrainer 1977	Rats	Continuous exposure to 0, 60, 125, 250, or 500 ppm CO on GDs 0–21	mCOHb: NR fCOHb: NR	CVS (heart weight): Dose-related, statistically significant increase in relative heart weight (10–52%) in all CO groups, compared to control. NOAEL (developmental heart weight): Not established LOAEL (developmental heart weight): 60 ppm CO
Sartiani et al. 2004	Rats	Continuous exposure to 0 or 150 ppm CO on GDs 0–20	mCOHb: NR fCOHb: NR	CVS (myocardial electrophysiological changes): In ventricular cardiocytes isolated from pups on PNDs 1–60, delayed development of age-related action potential duration shortening was observed. Delay was maximum at 4 weeks of age. NOAEL (CVS function): Not established LOAEL (CVS function): 150 ppm CO
Effects on sexual behavior				
Cagiano et al. 1998	Rats	Continuous exposure to 0, 75, or 150 ppm CO on GDs 0–20	mCOHb: ~7.5 and ~16% in 75 and 150 ppm CO groups, respectively fCOHb: NR	Development of sexual behavior: On PND 80, in pups of dams exposed to 150 ppm CO (but not 75 ppm CO), alterations in sexual behavior, including increase in mount to intromission latency, decrease in mount to intromission frequency, and decrease in ejaculation frequency. NOAEL (developmental sexual behavior): 75 ppm CO LOAEL (developmental sexual behavior): 150 ppm CO

Table 3-9. Effects of Gestational or Perinatal Exposure on Developmental Outcomes in Animals

Reference	Species	Exposure	COHb	Results
Effects on immunological system				
Giustino et al. 1993	Rats	Continuous exposure to 75 and 150 ppm CO on GDs 0–20	mCOHb: ~15% in 150 ppm CO group (NR in 75 ppm CO group) fCOHb: NR	Immunological effects: On PNDs 15 and 21, decreased splenic macrophage phagocytosis of *Candida albicans* (150 ppm CO); on PND 15, decreased splenic macrophage killing (75 and 150 ppm CO); no effects observed on PND 60. NOAEL (immunological): Not established LOAEL (immunological): 75 ppm CO
Giustino et al. 1994	Rats	Continuous exposure to 75 and 150 ppm CO on GDs 0–20	mCOHb: ~15% in 150 ppm CO group (NR in 75 ppm CO group) fCOHb: NR	Immunological effects: On PND 21, significant decreased in number of leukocyte common antigen cells in 150 ppm CO group; no effects observed on PND 540. NOAEL (immunological): 75 ppm CO LOAEL (immunological): 150 ppm CO (mCOHb ~15%)
Effects on hematological system				
Prigge and Hochrainer 1977	Rats	Continuous exposure to 0, 60, 125, 250, or 500 ppm CO on GDs 0–21	mCOHb: NR fCOHb: NR	Hematological effects: Dose-related, statistically significant decrease in hematocrit (14.8–34.2%) and hemoglobin (12.5–28.4%) at ≥250 ppm, compared to control. NOAEL (hematological): 125 ppm CO LOAEL (hematological): 250 ppm CO

CNS = central nervous system; CO = carbon monoxide; COHb = carboxyhemoglobin; CVS = cardiovascular system; fCOHb = fetal COHb; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; mCOHb = maternal COHb; NOAEL = no-observed-adverse-effect level; NR = not reported; PND = postnatal day

system development). Results of animal studies show adverse developmental effects of gestational and early postnatal carbon monoxide exposure, including decreased fetal weight, adverse central nervous system development, altered peripheral nervous system development, cardiac effects, altered sexual behavior, immunological effects, and hematological effects. In addition, some studies showed that developmental effects persisted beyond the postnatal period (Carratu et al. 1993, 2000a, 2000b; De Salvia et al. 1995; Mactutus and Fechter 1985; Stockard-Sullivan et al. 2003; Webber et al. 2003), although persistence of effects was not examined in all studies. The lowest LOAEL values for developmental effects were obtained in studies evaluating effects of carbon monoxide on the developing auditory system (i.e., LOAEL 12–25 ppm carbon monoxide); however, since other developmental outcomes were not assessed at this range of low carbon monoxide concentrations, it is not possible to determine if the developing auditory system is more sensitive to carbon monoxide exposure than other systems, or to identify a biological basis for such susceptibility.

Birth Weight. Several studies have evaluated effects of gestational exposure to carbon monoxide on birth weight in rats (Carmines and Rajendran 2008; Fechter and Annau 1977, 1980; Fechter et al. 1980, 1987a; Penney et al. 1983; Prigge and Hochrainer 1977; Singh 2008; Storm and Fechter 1985b), rabbits (Astrup et al. 1972), and guinea pigs (Tolcos et al. 2000b). Results consistently show that gestational exposure to carbon monoxide significantly decreased birth weight and/or pre-weanling weight, with LOAEL values ranging from 60 ppm carbon monoxide (maternal COHb 15%) for continuous exposure during gestation (Fechter and Annau 1977) to 600 ppm (maternal COHb approximately 30%) for intermittent (2 hours/day) exposure (Carmines and Rajendran 2008). Decreases in birth weight exhibited exposure concentration-dependence (Astrup et al. 1972; Fechter et al. 1987a; Prigge and Hochrainer 1977) and were exacerbated when dams were fed protein-deficient diets (Singh 2008).

Central Nervous System Development. Several studies have observed adverse effects on the developing central nervous system, including altered control of respiratory function, behavioral effects, changes in brain neurotransmitters levels, alteration of the cerebellum, and auditory development. Gestational exposure of guinea pigs to 200 ppm carbon monoxide produced abnormal respiratory responses to asphyxia and hypercapnia, indicative of altered brain stem development (McGregor et al. 1998). In rat or mouse pups exposed to 60–150 ppm carbon monoxide during gestation, behavioral changes included decreased motor activity and response to stimulation (Fechter and Annau 1977, 1980), impaired righting reflexes (Fechter and Annau 1980; Singh 1986), and impaired homing and memory acquisition behaviors (Giustino et al. 1999; Mactutus and Fechter 1985). Effects on acquisition and reacquisition behavior persisted up to 18 months of age in rats exposed to 150 ppm carbon monoxide during gestation (De Salvia

et al. 1995; Mactutus and Fechter 1985), although similar effects were not observed in pups exposed to 150 ppm carbon monoxide during the early postnatal period (Tattoli et al. 1999). Gestational exposure of rats or guinea pigs to 60–300 ppm carbon monoxide produced altered levels of dopamine and norepinephrine in several regions of the brain (Cagiano et al. 1998; Fechter and Annau 1977; Fechter et al. 1987a; Storm and Fechter 1985a, 1985b; Tolcos et al. 2000b). Gestational and postnatal exposure of rat pups to low levels of carbon monoxide (25 ppm) produced changes consistent with oxidative stress in the cerebellum, including increased expression of neuroglobin and cytoglobin and up-regulation of genes related to generation of ROS and lipid metabolism; changes were more pronounced in pups exposed during gestation compared to those exposed only during the postnatal period (Beltran-Parrazal et al. 2010; Lopez et al. 2009). Gestational or postnatal exposure to low levels of carbon monoxide (i.e., 12–25 ppm) has been shown to have effects on the developing auditory system. Gestational and/or early postnatal exposure of artificially-reared rat pups (i.e., reared on formula to allow exposure to the pups without exposure to the dams during nursing) to 25 ppm carbon monoxide produced morphological changes in the developing auditory system, including swelling, cytoplasmic vacuolization and atrophy of nerve terminals innervating inner hair cells, "distorted myelin" with vacuolization in the 8th cranial nerve at the level of the internal auditory canal, decreased immunoreactivity of the enzymes cytochrome oxidase, NADH-TR, and calcium-mediated myosin ATPase, and decreased immunostaining of neurofilament and myelin basic protein in the organ of corti (Lopez et al. 2003, 2008). Limited physiological and acoustic testing of pups suggested potential functional impairment in the auditory system. Neuroglobin was decreased in spiral ligament cells and spiral ganglia neuron of the cochlea of rat pups exposed to 25 ppm carbon monoxide during gestation (Lopez et al. 2010). The study authors suggested that decreased cochlear neuroglobin could result in development of auditory deficits. Exposure of artificially-reared rat pups during the early postnatal period decreased action potential amplitude of the 8th cranial nerve at ≥12 ppm carbon monoxide, although the magnitude of the effect was not dose-dependent. Otoacoustic emissions showed a small reduction in amplitude (3 dB at two of three frequencies tested and one loudness level) at ≥50 ppm carbon monoxide, with effects on action potential amplitude of the 8th nerve persisting through age 73 days (Stockard-Sullivan et al. 2003). The reduction in amplitude of otoacoustic emissions observed in this study was relatively small. Larger effects are more typically associated with hearing loss (e.g., 10–29 dB across five or more frequencies). Gestational exposure on gestation days (GDs) 8–20 of dam-reared rat pups to ≥12.5 ppm carbon monoxide significantly decreased neuronal activation of the central inferior colliculus (the area or the brain with auditory integrative function), with effects observed through postnatal days 75–77 (Webber et al. 2003). Results indicate that carbon monoxide-induced effects on brain auditory integrative neurons can persist into adulthood.

Peripheral Nervous System Development. Gestational exposure to carbon monoxide produced effects on peripheral nervous system development. In sciatic nerves of pups exposed during gestation, myelin sheath thickness was decreased and sphingomyelin composition was altered at 75–150 ppm carbon monoxide, with changes persisting through age 90 days (Carratu et al. 2000a, 2000b). Altered nerve transmission, indicative of slowed inactivation kinetics of inactive sodium channels, was observed in sciatic nerves from pups exposed to 75 ppm carbon monoxide during gestation, with changes persisting to age 270 days (Carratu et al. 1993).

Cardiac Effects. Dose-related increases in heart weight were observed in rat pups exposed to 60–157 ppm carbon monoxide during gestation (Penney et al. 1983; Prigge and Hochrainer 1977) or to 500 ppm carbon monoxide during the early postnatal period (Penney et al. 1982). The development of cardiomyopathy is consistent with a pathophysiological compensatory response to hypoxia. In ventricular cells isolated from pups exposed to 150 ppm carbon monoxide (but not 75 ppm) during gestation, age-related decreases in action potential duration were seen (Sartiani et al. 2004). Maturation of cardiac cells was impaired, as indicated by decreased expression of sarcomeric proteins (actin, myosin, and troponin I), Ca^{2+} transporters (Ca^{2+} transporting ATPase), and enzymes (aldolase), in rat pups exposed to 150 ppm carbon monoxide during gestation (Sartiani et al. 2010)

Sexual Behavior. In male pups exposed to 150 ppm carbon monoxide during gestation, altered development of sexual behavior was observed at age 80 days (Cagiano et al. 1998). Effects included increased mount to intromission latency, decreased mount to intromission frequency, and decreased ejaculation frequency.

Immune System Effects. In studies conducted by Giustino et al. (1993, 1994), gestational exposure produced reversible alterations in immune system function. Decreases in splenic macrophage phagocytosis of *Candida albicans* was observed in pups exposed to 150 ppm carbon monoxide, and decreased splenic macrophage killing was observed in pups exposed to 75 and 150 ppm carbon monoxide (Giustino et al. 1993); effects did not persist at age 60 days. Rats exposed to 150 ppm carbon monoxide, but not 75 ppm, showed an alteration in splenic immune cell populations, with a significant decrease in leukocyte common antigen cells; effects did not persist to age 540 days (Giustino et al. 1994).

Hematological Effects. Dose-related decreases in hematocrit and Hb were observed in pups exposed to 250 and 500 ppm carbon monoxide during gestation (Prigge and Hochrainer 1977). Effects are consistent with physiological compensatory responses to COHb-induced hypoxia.

3.2.7 Cancer

Epidemiological studies have examined possible associations between exposure to ambient air concentration of carbon monoxide and cancer mortality (described in Section 3.2.1, Death). A prospective study examined mortality in a cohort of 552,138 adults in 151 U.S. metropolitan areas enrolled in the study in 1982 and followed through 1998 (Jerrett et al. 2003; Pope et al. 1995, 2002). Based on estimates of average ambient air carbon monoxide concentration during the period 1982–1998, relative risk for mortality from lung cancer was approximately 0.90 (95% CI: 0.83, 0.96) per 1 ppm increase in carbon monoxide concentration (estimated from Figure 5 of Pope et al. 2002). A time-series analysis conducted in New York City, New York (1985–1994) evaluated data on cancer deaths with or without contributing respiratory diseases (De Leon et al. 2003). Estimates of cancer mortality risk were significant only in the strata with contributing respiratory disease (risk ratio was approximately 1.18, the 95% lower confidence limit >1) and did not persist when estimates were adjusted for ambient concentrations of PM_{10} (risk ratio approximately 1.06, 95% CI: ~0.97, 1.17). Collectively, the epidemiological data do not show an increase in cancer risk in association with exposure to carbon monoxide.

Carbon monoxide has not been assessed for carcinogenicity using animal models.

3.3 GENOTOXICITY

Few studies have evaluated the genotoxic effects of carbon monoxide exposure. Results of available studies are summarized in Table 3-10. An *in vitro* bacterial replication assay in *Escherichia coli* reported that exposure to carbon monoxide inhibited deoxyribonucleic acid (DNA) synthesis (Cairns and Denhardt 1968); however, interpretation of study results is compromised by poor reporting of experimental and analytical methods (e.g., carbon monoxide concentration, exposure conditions, and statistical analyses). Exposure of pregnant mice to carbon monoxide during gestation produced dose-related increases in micronuclei and sister chromatid exchanges in maternal bone marrow and fetal blood (Kwak et al. 1986).

Pregnant mice were exposed to 0, 1,500, 2,500, or 3,500 ppm carbon monoxide for 10 minutes on GDs 5, 11, or 15 or to 0 or 500 ppm carbon monoxide for 1 hour on GDs 0–6, 7–13, or 14–20; maternal bone marrow and fetal blood were examined for micronuclei formation and sister chromatid exchanges on GD 21. Increases in micronuclei and sister chromatid exchanges in maternal bone marrow and fetal blood were observed under all carbon monoxide exposure conditions, compared to unexposed controls.

Table 3-10. Genotoxicity of Carbon Monoxide

Species (test system)	Exposure	End point	Results	Reference
Prokaryotic organisms:				
Escherichia coli, TAMT	CO concentration not reported	DNA replication	+	Cairns and Denhardt 1968
Mammalian cells:				
Mice (ICR strain, pregnant females, 64/dose)	0, 1,500, 2,500, or 3,500 ppm CO for 10 minutes on GD 5, 11, or 16; fetal blood and maternal bone marrow examined on GD 21	Sister chromatid exchange	Maternal bone marrow: + Fetal blood: +	Kwak et al. 1986
Mice (ICR strain, pregnant females, 50/dose)	0 or 500 ppm CO for 1 hour on GDs 0–6, 7–13, or 14–20; fetal blood and maternal bone marrow examined on GD 21	Sister chromatid exchange	Maternal bone marrow: + Fetal blood: +	Kwak et al. 1986
Mice (ICR strain, pregnant females, 64/dose)	0, 1,500, 2,500, or 3,500 ppm CO for 10 minutes on GD 5, 11, or 16; fetal blood and maternal bone marrow examined on GD 21	Chromosomal aberrations, micronucleus assay	Maternal bone marrow: + Fetal blood: +	Kwak et al. 1986
Mice (ICR strain, pregnant females, 50/dose)	0 or 500 ppm CO for 1 hour on GDs 0–6, 7–13, or 14–20; fetal blood and maternal bone marrow examined on GD 21	Chromosomal aberrations, micronucleus assay	Maternal bone marrow: + Fetal blood: +	Kwak et al. 1986

+ = positive result; CO = carbon monoxide; DNA = deoxyribonucleic acid; GD = gestation day

The magnitude of effect was similar in dams and fetuses. Although blood COHb levels were not measured in this study, a 1-hour exposure to 500 ppm carbon monoxide would be expected to produce a maternal blood COHb concentration of approximately 20–25% (based on CFK model prediction for rats).

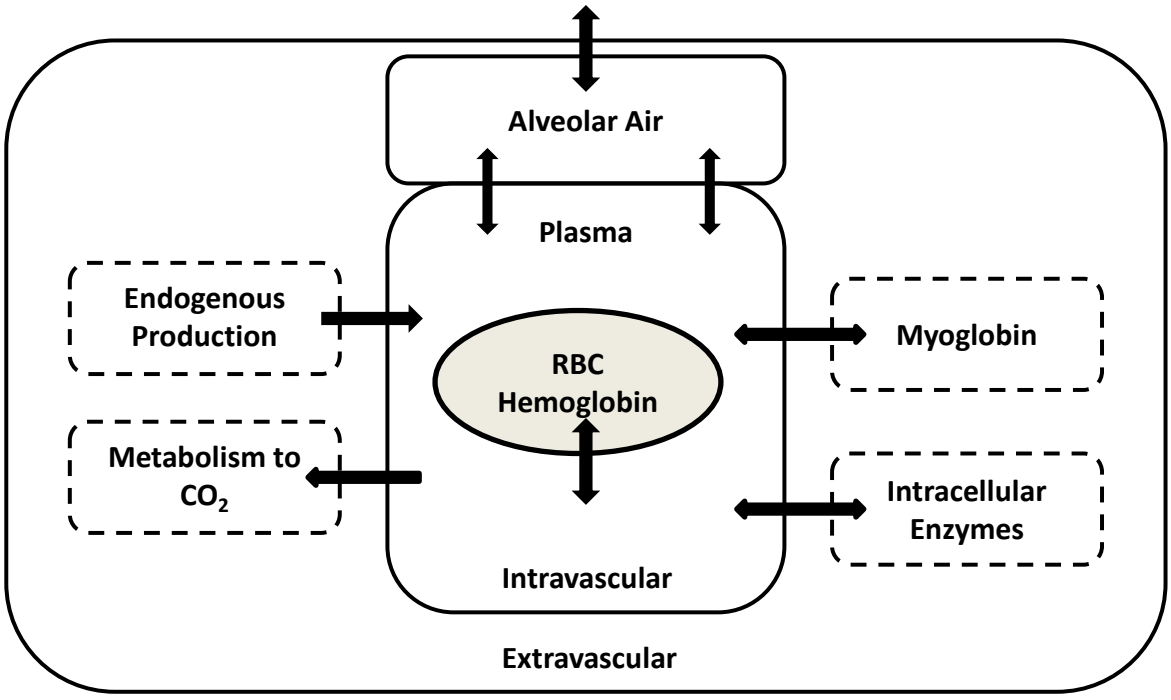
3.4 TOXICOKINETICS

Carbon monoxide exists in the environment as a gas (Henry's law constant >50,000 atm/mol fraction, 25 °C, see Table 4-2). As a result, humans can be exposed to carbon monoxide from breathing and/or skin contact with carbon monoxide in air. No information is available on the dermal absorption of carbon monoxide resulting from exposures to gaseous carbon monoxide. However, as is the case for other gases that are avidly absorbed from the lung (e.g., O_2), dermal absorption of carbon monoxide through intact skin would be expected to make a minor contribution to absorbed carbon monoxide, relative to inhalation. Although carbon monoxide can dissolve in water (23 mL CO/L water, 20 °C), appreciable concentrations in drinking water would occur only at very high partial pressures of carbon monoxide in air, conditions in which inhalation would be the dominant absorption pathway. Since the only relevant pathway of exposure to humans is the inhalation pathway, oral and dermal exposures are not considered further in the discussion of the toxicokinetics of carbon monoxide,

3.4.1 Absorption

Inhaled carbon monoxide is rapidly and extensively absorbed into blood (Benignus et al. 1994; Burge and Skinner 1995; Peterson and Stewart 1970, 1975; Tikuisis et al. 1987b). Inhaled carbon monoxide is transported to lung alveoli as a result of convective forces in the respiratory tract and diffusion. At the alveolar gas-blood interface, carbon monoxide dissolves into pulmonary capillary plasma and, from plasma, diffuses into erythrocytes and other tissues (Figure 3-3). Binding of carbon monoxide by erythrocyte Hb (to form COHb) contributes to maintaining relatively low concentrations of dissolved carbon monoxide in erythrocyte cytosol and a partial pressure gradient to drive carbon monoxide transfer from alveolar air to blood. Diffusion of carbon monoxide into erythrocytes and binding of carbon monoxide to Hb is sufficiently rapid that near equilibrium is achieved between carbon monoxide partial pressures in alveolar air and alveolar end capillary (arterial) blood (Chakraborty et al. 2004). Continued uptake of carbon monoxide results from systemic elimination processes that lower mixed venous blood carbon monoxide concentrations returned to alveolar capillaries (Benignus et al. 1994). The primary elimination processes include diffusive transfer of carbon monoxide to extravascular tissues and binding of carbon monoxide to intracellular heme proteins (e.g., muscle myoglobin), and oxidative metabolism of carbon monoxide to CO_2. Seconds after initiating inhalation exposures to carbon monoxide, COHb is

Figure 3-3. Summary of Carbon Monoxide Uptake, Distribution, and Elimination Pathways



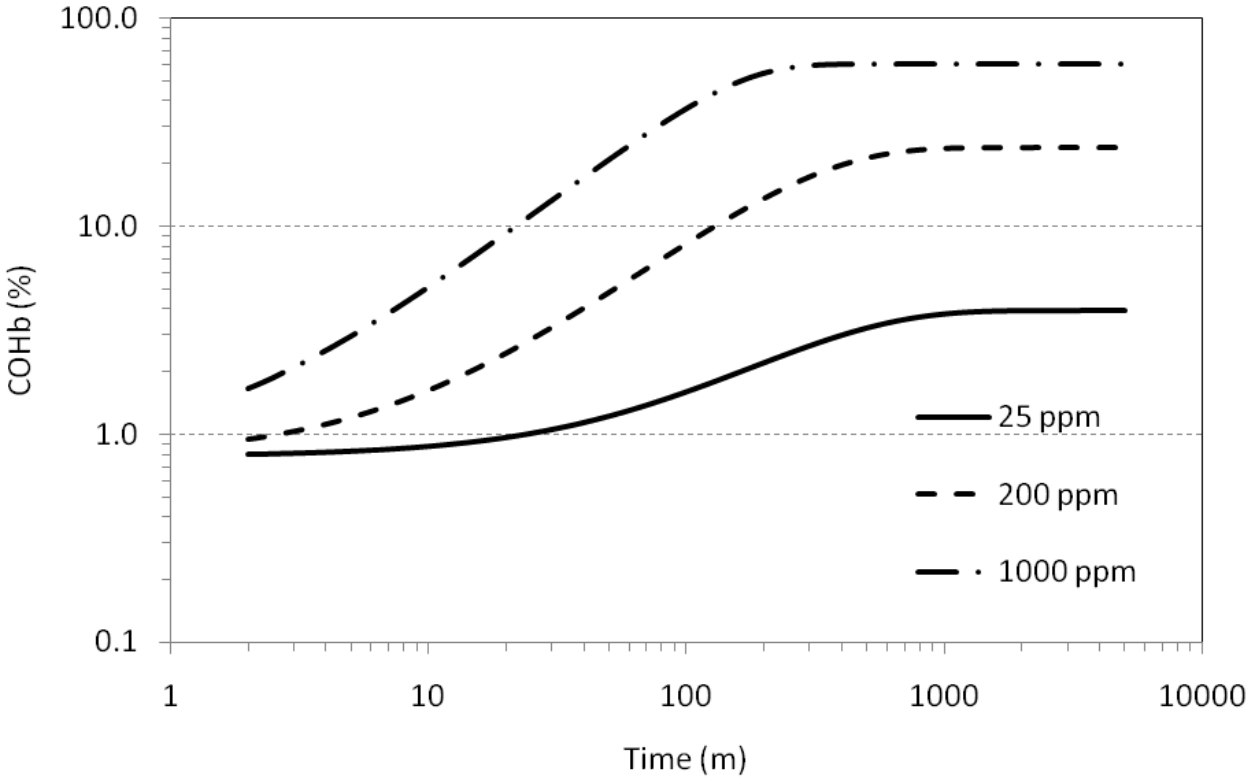
detected in arterial blood. During 2–6 minutes of exposure, arterial COHb concentrations were approximately twice venous COHb concentrations and approached unity within 3–5 minutes of cessation of exposure (Benignus et al. 1994). With continued exposure to a constant air carbon monoxide concentration, a steady-state would be achieved within 200–500 minutes (Figure 3-4; Bruce and Bruce 2003; Peterson and Stewart 1970, 1975). At that point, net absorption diminishes to a value determined primarily by metabolic elimination of carbon monoxide (see Section 3.4.3, Metabolism).

Major factors that control absorption of carbon monoxide include those that affect delivery of inhaled air to the alveolar region of the lung and those that affect lung carbon monoxide diffusion capacity. Lung diffusion capacity refers to the driving force for diffusion of carbon monoxide across the alveolar air-blood interface and is reflected in the carbon monoxide partial pressure difference between inspired and exhaled air. In general, factors that increase alveolar ventilation, cardiac output, and gas diffusing capacity of the lung, while maintaining alveolar ventilation perfusion matching (i.e., proportional increases in alveolar ventilation rate and cardiac output) tend to increase absorption of inhaled carbon monoxide. Factors that may increase net carbon monoxide absorption include exercise, supine position, age (increased in infancy and childhood and declines in adults with age), altitude, increasing blood Hb concentration, and decreasing partial pressure of O_2 in inhaled air or blood (Castillo et al. 2006; Horvath et al. 1988; Joumard et al. 1991; McGrath et al. 1993; Peterson and Stewart 1975; Tikuisis et al. 1992).

3.4.2 Distribution

Inhaled carbon monoxide distributes to blood and extravascular tissues. In blood, carbon monoxide rapidly distributes into erythrocytes where is exists primarily as a complex with Hb (COHb). The binding equilibrium constant for COHb is approximately 750 μM^{-1} (Chakraborty et al. 2004; see further discussion in Section 3.4.3, Metabolism). At a blood Hb concentration of 150 g/L (approximately 2.3 mM), the molar concentration ratio of COHb would be approximately $1.7x10^6$ times greater than the molar concentration of dissolved carbon monoxide. The relative affinity of Hb for carbon monoxide and O_2 greatly favors binding of carbon monoxide to Hb over O_2. The CO/O_2 affinity ratio (Haldane constant) is approximately 234 (Chakraborty et al. 2004). This means that a partial pressure of O_2 (pO_2) approximately 234 times that of pCO is needed to achieve an equilibrium in which equal amounts of O_2 and carbon monoxide are bound to Hb (i.e., %COHb = % oxyhemoglobin [O_2Hb]; Engel et al. 1969; Rodkey et al. 1969; Roughton 1970). In general, typical levels of COHb in nonsmokers are <2% (Adams et al. 1988; Allred et al. 1991; Anderson et al. 1973; Hinderliter et al. 1989; Kleinman et al. 1989, 1998; Sheps et al. 1987, 1990). Of this, COHb levels of approximately 0.2–1.0% are thought to be derived from

Figure 3-4. Temporal Profile of Blood Carboxyhemoglobin (%) for Hypothetical Continuous Exposures to Air Carbon Monoxide at Concentrations of 25, 200, or 1,000 ppm



Source: Peterson and Stewart 1975

endogenous production of carbon monoxide (Coburn et al. 1963; Delivoria-Papadopoulos et al. 1974; Longo 1977). Levels of COHb can (rarely) achieve 10% immediately following cigarette smoking (Kao and Nañagas 2006; Landaw 1973).

Although bound extensively to Hb in blood, distribution of dissolved carbon monoxide out of the vasculature can occur in response to diffusion gradients for carbon monoxide created by binding of carbon monoxide to Hb, myoglobin, and other heme proteins in extravascular tissues (e.g., muscle, spleen), as well as removal of carbon monoxide from extravascular tissues by oxidative metabolism (Bruce and Bruce 2006; Bruce et al. 2008; Luomanmäki and Coburn 1969). Myoglobin, the dominant binding protein for carbon monoxide in cardiac and skeletal muscle, has a lower affinity for carbon monoxide than Hb (COMb equilibrium constant of ≈20 μM^{-1} and Haldane constant of approximately 23) and a single binding site for carbon monoxide (Gibson et al. 1986); however, its abundance in muscle can result in transfer of substantial amounts of inhaled carbon monoxide into muscle tissue. At a skeletal muscle myoglobin concentration of 4.7 g/kg muscle (approximately 0.26 mmole/kg; Moller and Sylven 1981), the molar concentration ratio of COMb would be approximately $7.4x10^3$ times greater than the molar concentration of dissolved carbon monoxide. Binding of carbon monoxide to Hb in blood and myoglobin in muscle decreases the concentrations of dissolved carbon monoxide in both tissues and limits the concentration gradient for diffusion of carbon monoxide into muscle (Bruce and Bruce 2006; Bruce et al. 2008). Exercise can increase the rate of transfer of carbon monoxide from blood to skeletal muscle (Richardson et al. 2002; Werner and Lindahl 1980). The effect of exercise is thought to be related, in part, to increased O_2 consumption and lower pO_2 in muscle, which favors binding of carbon monoxide to myoglobin, and increased muscle blood flow. These effects a more pronounced at low COHb concentrations (≤2%) than at higher concentrations (20% COHb; Richardson et al. 2002). Hypoxia appears to increase transfer of carbon monoxide from blood to muscle (Coburn and Mayers 1971; Richardson et al. 2002).

Binding of carbon monoxide to intracellular proteins, in particular, heme proteins, contributes to maintaining a favorable gradient for carbon monoxide diffusion from plasma into cells. Measurements of total carbon monoxide concentrations in tissues obtained from human autopsies showed the highest concentrations in blood, spleen, lung, kidney, and skeletal muscle, with detectable levels also in brain and adipose tissue (Table 3-11, Vreman et al. 2006). Higher concentrations of carbon monoxide in blood, heart, skeletal muscle, and spleen observed in human autopsy studies reflect the abundance of the major carbon monoxide binding proteins in these tissue, Hb in erythrocytes and spleen (site of destruction and storage of erythrocytes), and myoglobin in cardiac and skeletal muscle. If the values presented in

Table 3-11. Post-Mortem Tissue Distribution of Carbon Monoxide in Humans[a]

Exposure	Adipose	Brain	Muscle	Heart	Kidney	Lung	Spleen	Blood
Concentration (pmol/100 g)								
Background	2	3	15	31	23	57	79	165
Fire	5	7	24	54	27	131	95	286
Fire + carbon monoxide	18	17	168	128	721	1,097	2,290	3,623
Carbon monoxide asphyxiation	25	72	265	527	885	2,694	3,455	5,196
Tissue/blood carbon monoxide concentration ratio								
Background	0.012	0.018	0.091	0.188	0.139	0.345	0.479	1.000
Fire	0.017	0.024	0.084	0.189	0.094	0.458	0.332	1.000
Fire + carbon monoxide	0.005	0.005	0.046	0.035	0.199	0.303	0.632	1.000
Carbon monoxide asphyxiation	0.005	0.014	0.051	0.101	0.170	0.518	0.665	1.000
Body weight (kg)	70	70	70	70	70	70	70	70
Tissue mass (percent)	200	2.0	40.0	0.5	0.4	1.4	0.3	7.4
Tissue carbon monoxide burden (nmol)								
Background	0.28	0.04	4.20	0.10	0.07	0.57	0.14	8.55
Fire	0.70	0.10	6.72	0.18	0.08	1.31	0.17	14.81
Fire + carbon monoxide	2.52	0.24	47.04	0.42	2.22	10.97	4.12	187.67
Carbon monoxide asphyxiation	3.50	1.01	74.20	1.73	2.73	26.95	6.22	269.15
Tissue carbon monoxide burden (percent of total)								
Background	2.0	0.3	30.1	0.7	0.5	4.1	1.0	61.3
Fire	2.9	0.4	27.9	0.7	0.3	5.4	0.7	61.5
Fire + carbon monoxide	1.0	0.1	18.4	0.2	0.9	4.3	1.6	73.5
Carbon monoxide asphyxiation	0.9	0.3	19.2	0.4	0.7	7.0	1.6	69.8

[a]Carbon monoxide concentrations based on Vreman et al. (2006). Tissue masses based on Davies and Morris (1993) and ILSI (1994).

Table 3-11 are converted to tissue carbon monoxide mass (pmol), based on assumed tissue masses for a 70-kg adult (Davies and Morris 1993; ILSI 1994), carbon monoxide in blood and muscle accounted for approximately 60–70 and 20–30% of total body carbon monoxide burden, respectively. Relatively large contributions of blood and skeletal muscle to total body carbon monoxide content is consistent with the contributions that these tissues make to total body Hb and muscle myoglobin (Bruce and Bruce 2003). In a typical adult, blood contains approximately 12 mmoles of Hb with a total binding capacity of approximately 48 mmole carbon monoxide when completely saturated and muscle contains approximately 8 mmoles of myoglobin with a total binding capacity of 8 mmole carbon monoxide when completely saturated.

The distribution of carbon monoxide residues observed in human autopsy studies is similar to that observed in rodents. In mice and rats that had not been intentionally exposed to air carbon monoxide (i.e., sacrificed during steady-state conditions), blood and muscle accounted for most the total body carbon monoxide burden (Vreman et al. 2005). Following 30-minute exposures to carbon monoxide (5,000 ppm), blood made a much larger contribution (approximately 90%) to carbon monoxide body burden, reflecting the longer period needed for carbon monoxide to distribute from blood to extravascular tissues (Vreman et al. 2005).

Carbon monoxide in the maternal system distributes to fetal tissues. Measurements of steady-state COHb concentrations in fetal and maternal blood of nonsmoking women have found fetal COHb concentrations to be approximately 10–15% higher than maternal blood (fetal/maternal ratio=1.1–1.15; Longo 1977). Carbon monoxide binding to fetal Hb is analogously similar to maternal Hb. Both Hbs have the same binding capacity of 4 moles CO/mole Hb and both exhibit cooperative binding of carbon monoxide, whereby binding affinity increases as carbon monoxide molecules are successively added to Hb (see Section 3.4.3, Metabolism). However, the binding affinity of fetal Hb is approximately twice that of maternal Hb (Di Cera et al. 1989). The Haldane coefficient, reflecting the relative affinities of carbon monoxide and O_2 (CO/O_2) for fetal Hb, appears to be approximately 20% lower than adult Hb (Di Cera et al. 1989; Engel et al. 1969; Hill et al. 1977). The higher binding affinity of fetal Hb as well as the relatively small diffusion gradients for carbon monoxide between maternal and fetal blood contribute to slower kinetics of COHb in fetal blood compared to maternal blood. This has been experimentally verified in studies conducted in pregnant sheep (Longo and Hill 1977). The half-time for approach to steady-state in the human fetus has been predicted (from modeling) to be approximately 7.5 hours in the fetus, compared to approximately 4 hours in maternal blood (Hill et al. 1977). As a result, with continuous exposure to a constant level of carbon monoxide in air, fetal blood COHb concentration would

be expected to lag behind maternal levels and reach a steady-state that is approximately 10–15% higher than maternal (Longo 1977). Similarly, following cessation of exposure, elimination kinetics of carbon monoxide from fetal blood would be expected to lag behind that of maternal blood (Hill et al. 1977).

3.4.3 Metabolism

Metabolism of carbon monoxide consists of three major processes: (1) metabolic production of carbon monoxide from endogenous and exogenous precursors; (2) binding of carbon monoxide to heme proteins (e.g., Hb, myoglobin, cytochromes); and (3) oxidative metabolism of carbon monoxide to CO_2.

Metabolic Production of Carbon Monoxide. Carbon monoxide is produced from the enzymatic degradation of endogenous and exogenous precursors. The major endogenous source of carbon monoxide production is the oxidative metabolism of heme by the enzyme heme oxygenase (HO). The net rate of endogenous production of carbon monoxide (i.e., total production minus metabolism) has been estimated in healthy adults to be approximately 0.42 mL CO/hour (16.4 µmole/hour) or approximately 400 µmole/day (Coburn et al. 1963). Of this, approximately 75–80% is thought to be derived from Hb metabolism, and the remaining portion from metabolism of other heme proteins, such as myoglobin, cytochromes, peroxidases, and catalase (Berk et al. 1976). Endogenous carbon monoxide production contributes to a blood COHb concentration of approximately 0.4–0.7% (Benignus 1995; Coburn et al. 1965). Carbon monoxide is produced in all tissues that express HO; however, the major tissues contributing to carbon monoxide production are also major sites of heme metabolism, including liver, spleen, and reticuloendothelial system (Berk et al. 1974).

Numerous physiological and disease factors affect the rate of endogenous production of carbon monoxide. Carbon monoxide production increases by approximately 2-fold during the post-ovulatory (progesterone) phase of the menstrual cycle (Delivoria-Papadopoulos et al. 1974; Mercke and Lundh 1976). Carbon monoxide production also increases during pregnancy, reaching values that are 2–5 times that of the estrogen phase of the menstrual cycle at partum and returning to pre-pregnancy levels within 4 days following delivery (Longo 1977). Contributing factors to the increase in carbon monoxide production during pregnancy include the contribution of the growing fetus to carbon monoxide production, as well as the increase in maternal erythrocyte production and related changes in Hb metabolism (Longo 1977). The rate of production of carbon monoxide is accelerated in conditions that increase catabolism of Hb or other heme proteins, including hemolysis, hematomas, hemolytic anemias, thalassemia, and Gilbert's syndrome (Berk et al. 1974; Coburn et al. 1964, 1965; Hampson 2007; Meyer

et al. 1998; Solanki et al. 1988). Carbon monoxide production was estimated to be 2–3 times higher in patients with hemolytic anemia compared with healthy individuals (Coburn et al. 1965).

HO is the rate-limiting step in heme degradation, and its expression and activity are modulated by numerous factors. The HO-1 isozyme (one of three isozymes) and expression of the enzyme is induced by heme and heme derivatives, oxidative stress, hypoxia (including altitude-induced hypoxia), various metals, various cytokines, and exogenous carbon monoxide (Wu and Wang 2005). These factors would tend to promote endogenous carbon monoxide production.

In addition to endogenous carbon monoxide production from metabolism of heme, carbon monoxide is produced from oxidative metabolism of certain exogenous hydrocarbons, including dichloromethane (DCM) and other dihalomethanes, and carbon tetrachloride (Agency for Toxic Substances and Disease Registry 2000, 2005; Stevens et al. 1980). The oxidative metabolism of DCM by isoform CYP2E1 of cytochrome P450 results in the production of carbon monoxide and increased blood COHb concentrations in blood (Andersen et al. 1991). Elevated blood COHb levels have been observed following DCM poisoning (Leikin et al. 1990). Other sources of exogenous carbon monoxide production include the heme oxidase catalysis of products of auto-oxidation of phenols, photo-oxidation of organic compounds, and lipid peroxidation of cell membrane lipids (Rodgers et al. 1994).

Binding of Carbon Monoxide to Heme Proteins. Carbon monoxide binds to heme and competes for binding of O_2. Binding of carbon monoxide to heme proteins (e.g., blood Hb, muscle myoglobin) has profound effects on the kinetics of distribution and elimination kinetics of both carbon monoxide and O_2. Affinities of heme for carbon monoxide for Hb and myoglobin are sufficiently high to result in concentrations of dissolved carbon monoxide being 10^3–10^6 times lower than the concentrations of COHb or COMb. This substantially lowers the concentration of dissolved carbon monoxide in blood and tissues, decreases the diffusion gradients for carbon monoxide movement of carbon monoxide from tissues and blood to the lungs, and substantially prolongs the elimination time for carbon monoxide than would otherwise occur in the absence of binding. Furthermore, the rates of dissociation of carbon monoxide from Hb and myoglobin are substantially slower than that of O_2 and sufficiently slow, relative to erythrocyte capillary transit times, to limit rates of exchange of carbon monoxide between tissues and capillary blood. Binding of carbon monoxide to Hb also increases the affinity of Hb for O_2, decreasing the availability of O_2 to tissues.

Although carbon monoxide binds to many different heme proteins (see Section 3.5.2), the affinities and abundance of Hb and myoglobin in the body results in most of the body stores of carbon monoxide being associated with these two heme proteins. Estimated kinetics and equilibrium parameters for carbon monoxide and O_2 binding to Hb and myoglobin are presented in Table 3-12. Each of the four heme moieties in Hb can bind O_2 or carbon monoxide. The overall affinity (i.e., equilibrium constant, K_{eq}) is substantially higher for carbon monoxide (≈750 μM^{-1}) compared to that of O_2 (≈3.2 μM^{-1}). As a result, at similar partial pressures of the two gases ($pCO=PO_2$), binding of carbon monoxide will occur at the expense of binding of O_2, and the O_2 carrying capacity of blood will be compromised. The ratio of the K_{eq} values (CO/O_2) is referred to as the Haldane constant (≈234). This value gives the partial pressure ratio (pO_2/pCO) needed to achieve equal amounts of bound COHb and O_2Hb (i.e., %COHb = %O_2Hb).

At an ambient air pO_2 of approximately 160 Torr (21% O_2), the equilibrium condition of equal %COHb = %O_2Hb would be achieved at a carbon monoxide exposure concentration of approximately 900 ppm. The affinity of Hb for carbon monoxide results in an equilibrium condition in which nearly all carbon monoxide in blood is bound to Hb. For example, based on the value of K_{eq} of 750 μM^{-1}, at a blood Hb concentration of 150 g/L (≈2.3 mM), the equilibrium ratio of bound carbon monoxide to dissolved carbon monoxide in blood would be approximately $1.7x10^6$ (i.e., > 10^6 times as much carbon monoxide is bound to Hb than is circulating in blood as dissolved carbon monoxide). The carbon monoxide dissociation rate from Hb (k_d≈0.008 s^{-1}; $t_{1/2}$≈87 s) is slower than from O_2 (k_e≈20 s^{-1}, $t_{1/2}$≈0.035 s). As a result, exchange of O_2 bound to Hb in blood with alveolar air and tissues is much more efficient than carbon monoxide exchange (i.e., fast vs. slow dissociation relative to erythrocyte transit times in capillaries). These two characteristics (high affinity and slow dissociation) contribute to relatively long retention times of carbon monoxide in blood following exposures to carbon monoxide.

Binding of O_2 to the four heme moieties of Hb is cooperative (Alcantara et al. 2007; Roughton 1970). The associative reaction rate (k_a) becomes faster with successive additions of O_2, increasing the affinity (K_{eq}) of Hb for O_2 (values for k_a shown in Table 3-12 are for the high affinity, R, state of fully loaded Hb). Cooperative binding of O_2 to Hb serves an important physiological function. Under conditions of relatively high pO_2 in arterial blood entering the lung (pO_2=100 mmHg), cooperative binding promotes the loading of Hb with O_2; with successive binding of O_2 molecules, the associative rate and affinity increases, promoting binding of a subsequent molecule of O_2. Conversely, at lower pO_2 in venous blood (pO_2≈20 mmHg), cooperative binding promotes unloading of O_2 for utilization; dissociation of a molecule of O_2 decreases the affinity of Hb for O_2, promoting the dissociation of a subsequent molecule

Table 3-12. Hemoglobin and Myoglobin Binding Kinetics and Equilibrium Constants for Oxygen and Carbon Monoxide

Ligand	k_a ($\mu M^{-1} \cdot s^{-1}$)	k_d (s^{-1})	K_{Eq} (μM^{-1})	M
Hemoglobin[a]				
Oxygen	66	20	3.2	1
Carbon monoxide	6	0.008	750	234
Myoglobin[b]				
Oxygen	14	12	1.2	1
Carbon monoxide	0.51	0.019	26.8	23

[a]Based on Chakraborty et al. 2004
[b]Based on Gibson et al. 1986

k_a = association rate constant; k_b = dissociation rate constant; K_{Eq} = equilibrium constant; M = Haldane constant (K_{Eq} CO/K_{Eq} O_2)

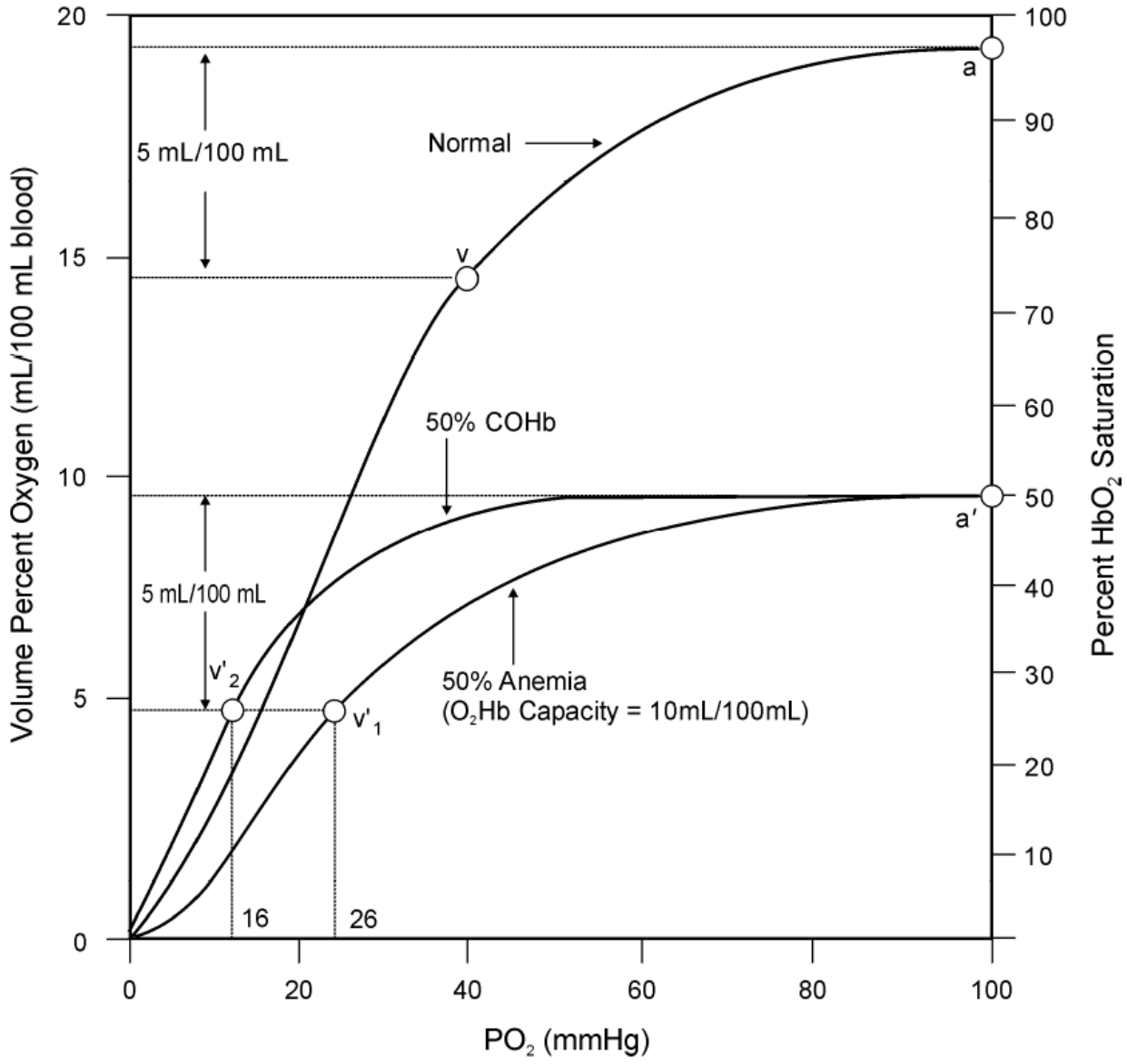
of O_2. Cooperative binding contributes to the sigmoid shape of the O_2 dissociation curve for Hb (Figure 3-5).

Binding of carbon monoxide to Hb is also cooperative. Binding of carbon monoxide increases the associative rate of binding and affinity of both carbon monoxide and O_2. As a result, the presence of carbon monoxide has several effects on the dissociation curve for O_2 (Figure 3-5): (1) decreases the partial pressure of O_2 in blood and tissues (i.e., by an amount equal to pCO), shifting the pO_2 axis downscale at each point in the arterial-venous circuit; (2) displaces O_2 from Hb, decreasing the maximum %COHb achieved in arterial blood; and (3) shifts the O_2 dissociation curve downscale so that less O_2 dissociates O_2 from Hb (more will remain bound, $\%O_2Hb$ will be higher) at the lower pO_2 values in venous blood. The combined result of these changes is that less O_2 in blood is available for utilization in tissues.

The binding affinities of carbon monoxide and O_2 to myoglobin are lower than that for Hb; however, the higher affinity for carbon monoxide (Haldane constant ≈23), results in preferential binding of carbon monoxide over O_2 and displacement of O_2 of myoglobin at similar partial pressures of both gasses (Table 3-12). In addition to displacing O_2 from myoglobin, binding of carbon monoxide to myoglobin has a pronounced effect on the distribution of carbon monoxide in the body by limiting the dissolved carbon monoxide concentration in muscle and, thereby, the rates of diffusion of carbon monoxide from muscle to blood. The affinity of myoglobin (K_{eq}≈27) results in an equilibrium condition in which dissolved carbon monoxide concentrations in muscle are very low relative to COMb concentrations. For example, based on a value for K_{eq} of 27 μM^{-1}, at a muscle myoglobin content of approximately 4.7 g/kg (≈0.28 mM), the equilibrium ratio of bound carbon monoxide to dissolved carbon monoxide in muscle would be approximately $7.4x10^3$ (approximately 10^4 times as much carbon monoxide is bound to myoglobin than is dissolved muscle tissue). Furthermore, the carbon monoxide dissociation rate from myoglobin (k_d≈0.019 s^{-1}; $t_{1/2}$≈36 s) is slower than O_2 (k_e≈12 s^{-1}, $t_{1/2}$≈0.06 s). As a result exchange of carbon monoxide bound to myoglobin in muscle with blood is much less efficient than O_2 exchange (i.e., slow vs. fast dissociation relative to erythrocyte transit times in capillaries). These two characteristics (high affinity and slow dissociation) contribute to relatively long retention times of carbon monoxide in muscle following exposures to carbon monoxide.

Oxidative Metabolism of Carbon Monoxide. Carbon monoxide can be oxidized to CO_2. The rate of oxidation has been estimated in human subjects who inhaled ^{14}CO to be approximately 0.015 mL CO/hour, which corresponds to approximately 0.6 µmol/hour; 14 µmol/day, and approximately 3% of

Figure 3-5. Oxyhemoglobin Dissociation Curve for Normal Human Blood Containing 50% Carboxyhemoglobin and for Blood of an Anemic Human



Source: EPA 2000

endogenous carbon monoxide production (Luomanmaki and Coburn 1969). Similar measurements made in dogs yielded estimates for carbon monoxide metabolism that were approximately 8% of endogenous production (Luomanmaki and Coburn 1969). The major pathway for metabolism of carbon monoxide to CO_2 is oxidation by mitochondrial cytochrome oxidase (Fenn 1970; Young and Caughey 1986).

3.4.4 Elimination and Excretion

Absorbed carbon monoxide is eliminated from the body by exhalation and oxidative metabolism. Oxidative metabolism of carbon monoxide has been estimated to be a relatively small fraction (<10%) of endogenous carbon monoxide production (Luomanmaki and Coburn 1969). Under most conditions, the dominant route of elimination of absorbed carbon monoxide is exhalation. Rates of elimination of carbon monoxide in humans who have experienced inhalation exposures to carbon monoxide have been estimated from kinetic analyses of the time course of blood %COHb (Bruce and Bruce 2006; Joumard et al. 1991; Landaw 1973; Levasseur et al. 1996; Peterson and Stewart 1970; Shimazu et al. 2000; Weaver et al. 2000). The decline in blood %COHb following cessation of an inhalation exposure to carbon monoxide exhibits at least two kinetic phases (Bruce and Bruce 2006; Shimazu et al. 2000). The fast phase is thought to reflect a combination of exhalation of carbon monoxide along with slower distribution of blood carbon monoxide to tissues that continues after cessation of exposure (Bruce and Bruce 2006). The elimination half-times for both phases appear to increase with exposure intensity and/or duration; a contributing factor to this effect may be the amount of carbon monoxide accumulated in extravascular stores. In human subjects exposed to 2% carbon monoxide for 1–3 minutes (peak COHb%=30–40), values for elimination half-lives were 5.7±1.5 and 103±20.5 minutes for the fast and slow phases, respectively (Shimazu et al. 2000). The fast phase rate increased when subjects were exposed to 500 ppm for 5–10 hours (peak %COHb=34–37): 21.5±2.1 and 118±11.2 minutes, respectively (Shimazu et al. 2000). Rates have been reported for the slow phase of elimination. In subjects whose peak %COHb ranged from 2 to 15, the half-life was 320 minutes (range: 128–409 minutes, Peterson and Stewart 1970). Bruce and Bruce (2006) measured the time to achieve one-half of peak %COHb in subjects whose peak %COHb values ranged from 15 to 20 and estimated a half-life of 248 minutes (range: 206–328). Clinical studies conducted on healthy individuals exposed to ambient air carbon monoxide concentrations have found that elimination half-time increases with age, with the most pronounced increase occurring from age 2 to 20 years, and is approximately 6% longer in males compared to females (Joumard et al. 1991). The gender effect may be related to relative differences in body size and/or muscle mass. Exercise decreases carbon monoxide elimination half-time (Joumard et al. 1991).

The rate of elimination of absorbed carbon monoxide is accelerated by inhaling high concentrations of O_2 (Landaw 1973; Peterson and Stewart 1970; Weaver et al. 2000). Elimination half-lives of approximately 20 minutes have been observed in subjects who inhaled 100% O_2 following cessation of exposure to carbon monoxide. An analysis of elimination rates observed in 93 acute carbon monoxide poisoning patients who were treated with 100% O_2 did not find significant associations between elimination half-lives and age, gender (<40 years, ≥40 years), smoke inhalation, history of loss of consciousness, concurrent tobacco smoking, degree of initial metabolic acidosis (base excess), or initial %COHb level (Weaver et al. 2000).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-

specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

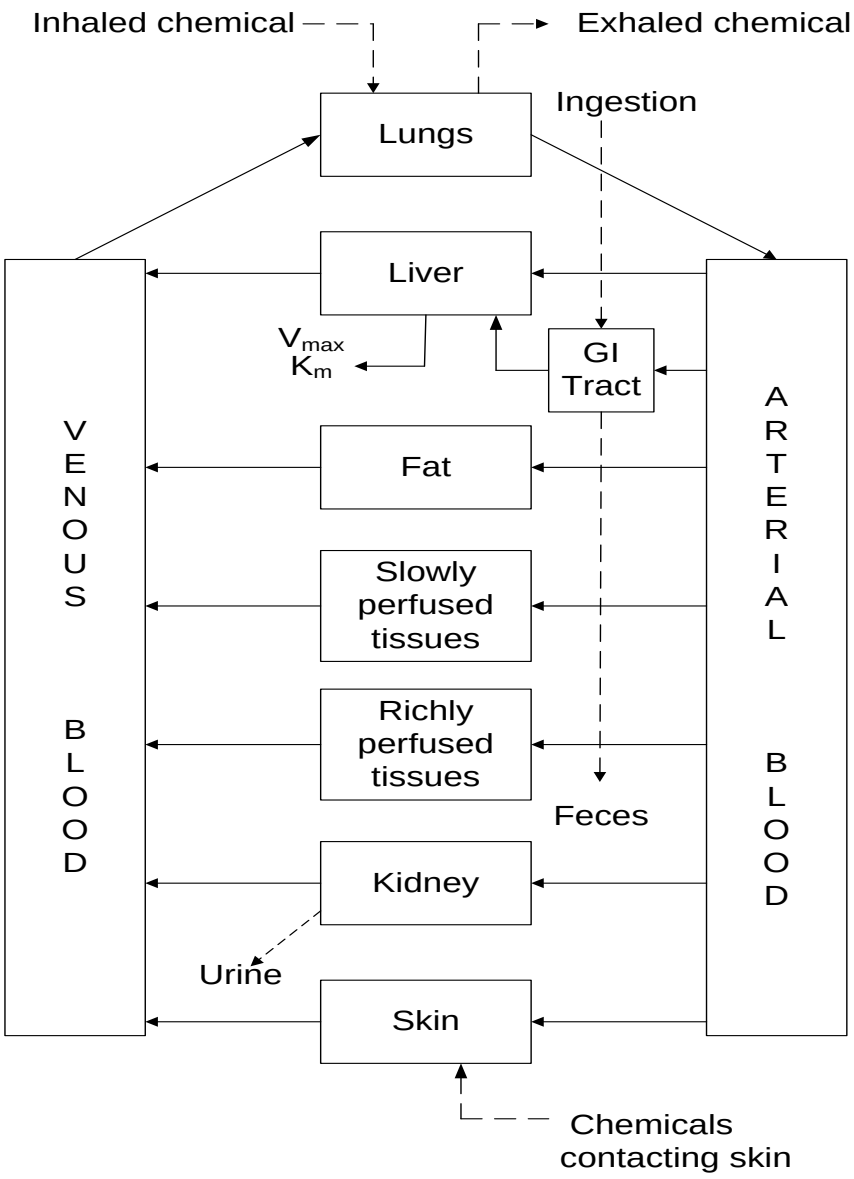
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-6 shows a conceptualized representation of a PBPK model.

If PBPK models for carbon monoxide exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

The first physiologically-based mechanistic model of carbon monoxide kinetics was reported in Coburn et al. (1965). This model, which subsequently became known as the Coburn-Forster-Kane (CFK) model, was developed to predict relationships between inhalation exposures to carbon monoxide and blood COHb levels in humans. Numerous modifications and extensions of the original CFK model have been reported that more rigorously address nonlinearities resulting from interdependence of COHb and O_2Hb levels in blood (Tikuisis et al. 1987b), simulation of arterial and venous blood compartments (Smith et al. 1994), simulation of maternal-fetal transfer of carbon monoxide (Hill et al. 1977), extrapolation to nonhuman species (Benignus and Annau 1994; Hill et al. 1977; Longo and Hill 1977), linkage of the CFK model to more complex respiratory gas exchange models (Abram et al. 2007; Benignus 1995), and use in simulating the elimination kinetics of carbon monoxide produced from exogenous precursors (Andersen

Figure 3-6. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

et al. 1991). A multi-compartment model was also developed that simulates carbon monoxide absorption and distribution kinetics in muscle (Bruce and Bruce 2003; Bruce et al. 2008).

Coburn-Forster-Kane Model

The CFK model, as originally described in Coburn et al. (1965), is a single-compartment model of instantaneous equilibrium between carbon monoxide, O_2, and blood Hb, and assumes that blood O_2Hb concentration is constant (i.e., independent of COHb concentration). This linear form of the CFK model is expressed in the following differential equation which is integrated over time to solve for COHb concentration (Equation 1):

$$V_b \cdot \frac{d[COHb]_t}{d_t} = V_{CO} - \frac{[COHb]_{t-1} \cdot P_cO_2}{[O_2Hb] \cdot M} \cdot \left(\frac{1}{\frac{1}{D_LCO} + \frac{1}{V_A}} \right) + \left(\frac{P_ICO}{\frac{1}{D_LCO} + \frac{1}{V_A}} \right) \quad \text{Eq. (1)}$$

where *t* represents time at the end of the integration time step and *t-1* represents the time at the beginning of the time step; V_b is blood volume in mL; *[COHb]* is the COHb concentration in mL carbon monoxide per mL blood (STPD); V_{CO} is the endogenous carbon monoxide production rate in mL/minute (STPD); *[O_2Hb]* is the oxyhemoglobin concentration in mL O_2 per mL blood (STPD); P_cO_2 is the average partial pressure of O_2 in lung capillaries in Torr; *M* is the Haldane constant; V_A is the alveolar ventilation in mL/minute (STPD); D_LCO is the lung diffusing capacity of carbon monoxide in mL/minute-Torr (STPD); and P_ICO is the carbon monoxide partial pressure in inhaled air in Torr.

The linear form of the CFK model is acceptable for simulating low COHb concentrations (<6%; Smith 1990). However, at higher COHb levels, appreciable errors are introduced into the simulation by ignoring the interdependence of COHb and O_2Hb levels that result from limited binding capacity of Hb. This interdependence can be introduced into the CFK model by replacing the constant term for *[O_2Hb]* with the following expression relating COHb and O_2Hb (Tikuisis et al. 1987b; Equation 2):

$$[O_2Hb] = 1.38 \cdot Hb - [COHb] \quad \text{Eq. (2)}$$

where 1.38·Hb represents the maximum binding capacity of Hb for O_2 or carbon monoxide in mL O_2/mL blood (STPD). The resulting nonlinear form of the CFK model is expressed in Equations 3 and 4:

$$\frac{d[COHb]_t}{d_t} = \frac{V_{CO}}{V_b} + \frac{1}{V_b \cdot \beta} \cdot \left(P_I CO - \frac{[COHb]_{t-1} \cdot P_c O_2}{[O_2 Hb]_{t-1} \cdot M} \right) \quad \text{Eq. (3)}$$

$$\beta = \frac{1}{D_L CO} + \frac{P_B - 47}{V_A} \quad \text{Eq. (4)}$$

where P_B is the barometric pressure (Torr) and the value 47 represents the partial pressure of water in water saturated air (Torr). Typical parameters values used in the CFK model are presented in Table 3-13. Parameter values for application of the nonlinear CFK model for predicting COHb levels in rats were reported by Benignus and Annau (1994) and are also shown in Table 3-13.

Validation of the model. Numerous studies have examined the accuracy of exposure-blood COHb relationships predicted from the CFK model (Benignus et al. 1994; Coburn et al. 1965; Hauck and Neuberger 1984; Joumard et al. 1991; Peterson and Stewart 1970, 1975; Stewart et al. 1970, 1973; Tikuisis et al. 1987a, 1987b). In general, the model performs well for predicting near equilibrium conditions; however, it performs less well in predicting the early uptake phase of carbon monoxide kinetics and COHb levels associated with rapidly changing exposures (Benignus et al. 1994; Tikuisis et al. 1987a, 1987b). The model also underestimates the arterial blood COHb level and overestimates the venous blood COHb level, an expected outcome of the simplistic assumption of a single well-mixed blood compartment. Nevertheless, the model predicts quasi-steady-state blood COHb levels that agree closely with observations (Benignus et al. 1994; Bruce and Bruce 2003; Tikuisis et al. 1987a, 1987b).

McCartney (1990) reported a sensitivity analysis of the CFK model and found that parameter value sensitivities varied considerably in magnitude at different points in the exposure simulation (Figure 3-7). At steady-state, the model is most sensitive to the values assigned to the parameters representing the input value, the inhaled carbon monoxide concentration (P_ICO), as well as the total Hb level (Hb) and the Haldane coefficient (M). Increases in values for any of these parameters result in higher predicted COHb levels. However, during the accumulation phase of the simulation, the predicted COHb level is also highly sensitive to alveolar ventilation rate (V_A) and the lung carbon monoxide diffusing capacity (D_LCO), with increases in these parameters resulting in higher COHb levels, and to the value assigned to the blood volume (V_b), with increases in the parameter value resulting in lower predicted COHb levels.

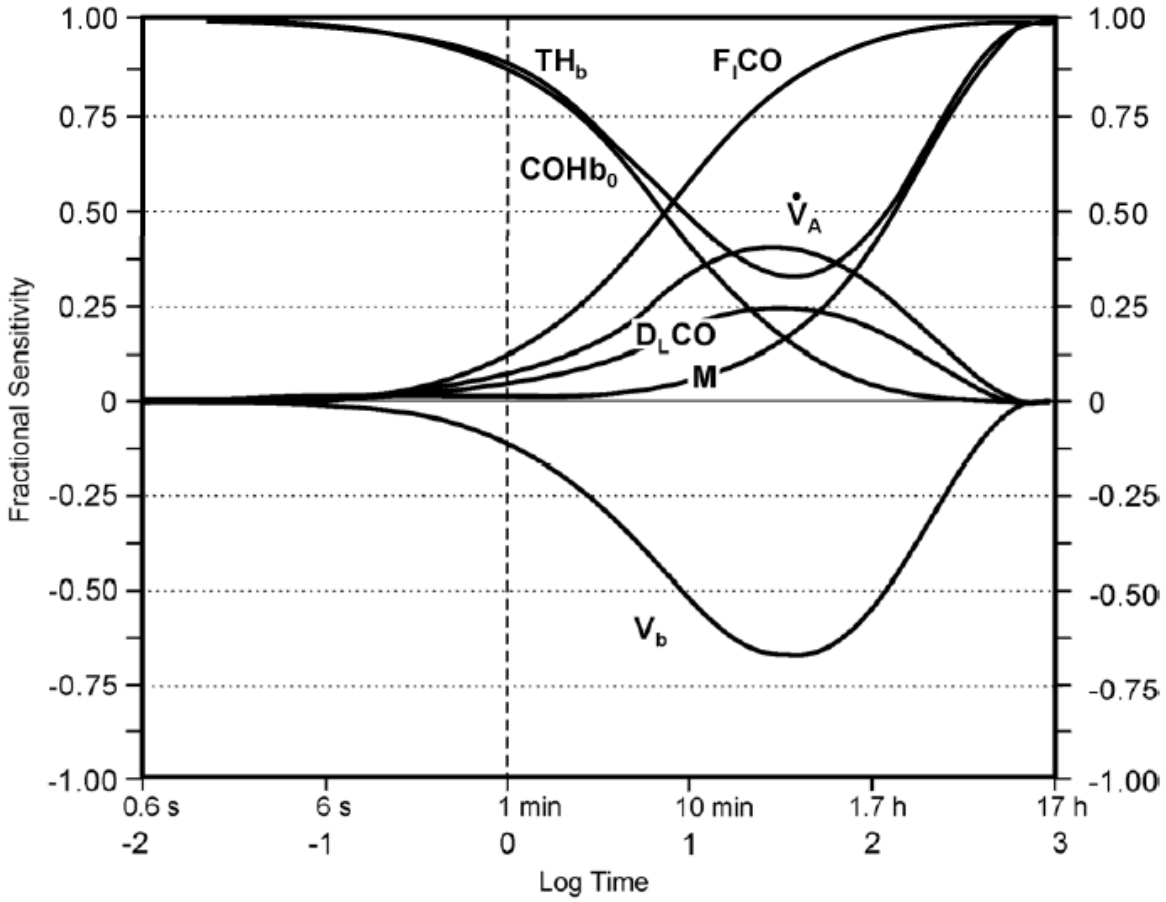
Table 3-13. Parameter Values for the Coburn-Forster-Kane (CFK) Model

Parameter	Definition	Unit	Value	
			Human[a]	Rat[b]
BW	Body weight	kg	70	0.250
$COHb_0$	Blood COHb level at start of simulation	mL CO/mL blood (STPD)	0.00155	0.00155
D_LCO	Lung CO diffusing capacity	mL CO/minute-Torr (STPD)	30	0.027·0.563·BW
Hb	Blood Hb concentration	g/mL	0.144	0.158
M	Haldane coefficient	unitless	218	207
O_2HbMAX	Maximum blood O_2Hb concentration	mL O_2/mL blood (STPD)	1.38	1.38
P_CO_2	Average partial pressure of O_2 in alveolar air	Torr (STPD)	49	49
P_ICO	Partial pressure of inhaled CO	Torr (STPD)	Input	Input
V_A	Alveolar ventilation rate	L/hour[c]	$(15 \cdot BW^{0.74})$	$(15 \cdot BW^{0.74})$
V_B	Blood volume	L[d]	0.074·BW	0.074·BW
V_{CO}	Endogenous CO production rate	mL/minute (STPD)	0.007	0.000333·BW

[a]Based on Tikuisis et al. (1992)
[b]Based on Benignus and Annau (1994)
[c]Must be converted to mL/minute by multiplying 1,000/60
[d]Must be converted to mL by multiplying by 1,000

BW = body weight; CO = carbon monoxide; COHb = carboxyhemoglobin; Hb = hemoglobin; STPD = standard temperature and pressure, dry (i.e., adjusted for partial pressure of water vapor in saturated air [47 Torr STP])

Figure 3-7. Plot of Standardized Sensitivity Coefficients for Carboxyhemoglobin (COHb) Levels Predicted from the Coburn-Forster-Kane (CFK) Model for a 100 ppm Exposure to an Individual Engaged in Vigorous Exercise (Alveolar Ventilation Rate=30 L/Minute)*



*Each curve represents the time trend of sensitivity coefficients for a given parameter during the simulation. Time trends for six model parameters are shown: D_LCO, lung carbon monoxide diffusion capacity; F_ICO, fractional air carbon monoxide concentration (ppm); M, Haldane coefficient; THb, blood hemoglobin concentration; V_A, alveolar ventilation rate; and V_B, blood volume. Sensitivity coefficients and central coefficients are for 1% upward and downward perturbation of each parameter. Coefficients >0 indicate an increase in predicted COHb in association with an increase in the parameter value; coefficients that are <0 indicate that COHb decreased in association with an increase in the parameter value.

Source: EPA (2009g) based on McCartney (1990)

Risk assessment. The CFK model has been used in establishing the National Ambient Air Quality Standard for carbon monoxide (EPA 2000) and has been used in analyses that have supported development of Threshold Limit Values for occupational safety (Tikuisis et al. 1987b).

Target tissues. The CFK model predicts COHb levels in blood.

Species extrapolation. Although originally developed to simulate blood COHb levels in humans, the model can be used to predict COHb levels in other mammalian species if physiological and chemical-specific parameter values are available for the species of interest. The latter include the Haldane coefficient (*M)*, the binding capacity of Hb, and the lung carbon monoxide diffusing capacity (D_LCO). Parameter values for the rat have been reported by Benignus and Annau (1994; Table 3-13).

Interroute extrapolation. The CFK model simulates inhalation exposures.

Smith et al. (1994) Multi-compartment Model

The nonlinear CFK model, described above, represents blood as a well-mixed compartment, an acceptable assumption for simulating near equilibrium conditions. However, during uptake and elimination phases of carbon monoxide kinetics, appreciable differences have been observed between arterial and venous blood (Benignus et al. 1994). Improved prediction of arterial COHb levels was achieved with an expansion of the CFK model to include slowly and rapidly perfused compartments and an arm compartment (representing vascular sampling sites) that includes compartments representing the major arterial and venous vasculature (Smith et al. 1994, Table 3-14; Figure 3-8).

Validation of the model. The Smith et al. (1994) models was evaluated with data collected from 15 healthy adults subjects who inhaled carbon monoxide under controlled conditions (Benignus et al. 1994). Each subject (15 adult males) inhaled for approximately 5 minutes from a bag that had an initial carbon monoxide concentration of approximately 7,000 ppm. The exposures achieved end exposure blood COHb concentrations ranging from 10 to 15%. The Smith et al. (1994) model provided improved predictions of COHb levels in samples taken from radial artery and antecubital vein.

Risk assessment. Risk assessment applications of the Smith et al. (1994) were not identified in the available literature.

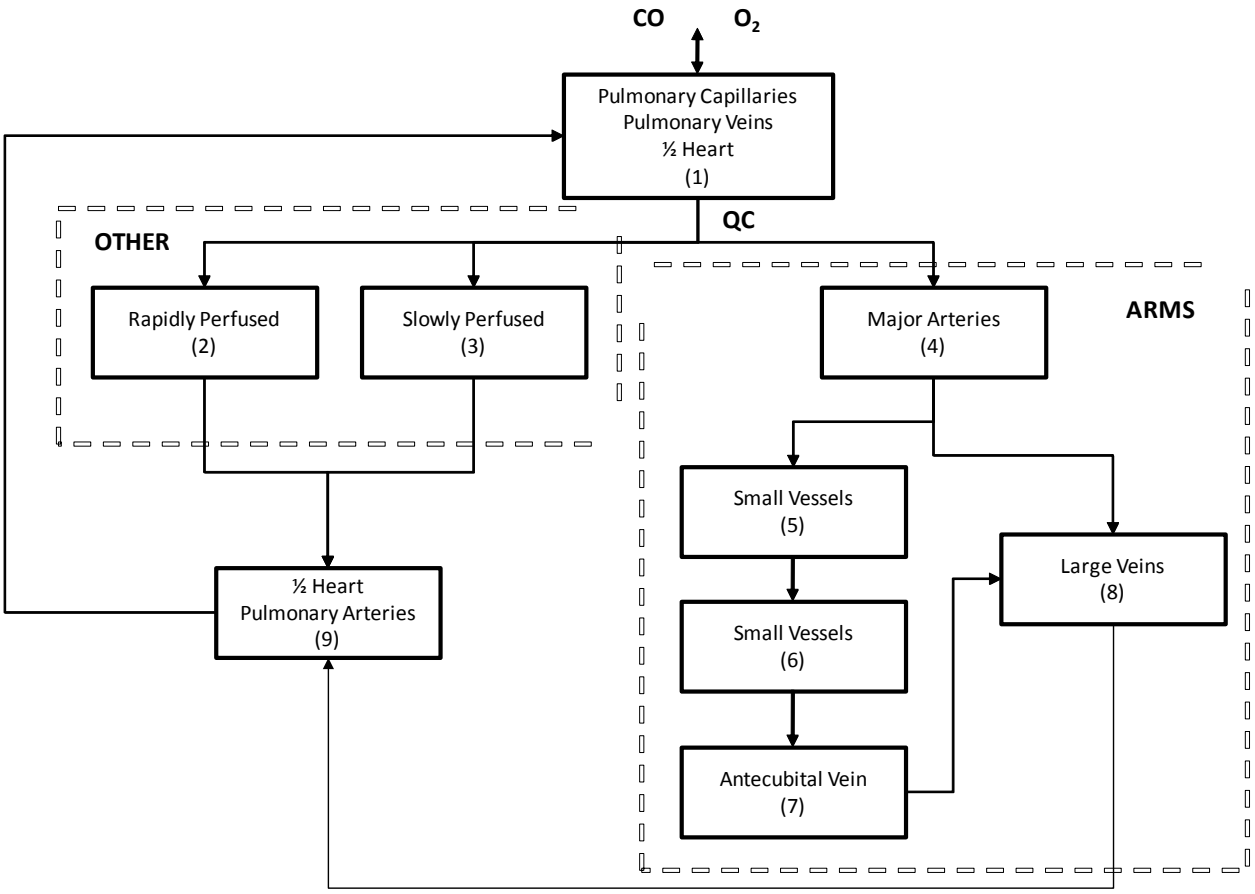
Table 3-14. Parameter Values for the Smith et al. (1994) Model

Parameter	Definition	Unit	Value
Chemical parameters[a]			
$COHb_0$	Blood COHb level at start of simulation	mL CO/mL blood (STPD)	0.00155
D_LCO	Lung CO diffusing capacity	mL CO/minute-Torr (STPD)	30
Hb	Blood Hb concentration	g/mL	0.144
M	Haldane coefficient	unitless	218
O_2HbMAX	Maximum blood O_2Hb concentration	mL O_2/mL blood (STPD)	1.38
P_CO_2	Average partial pressure of O_2 in alveolar air	Torr (STPD)	49
P_ICO	Partial pressure of inhaled CO	Torr (STPD)	Input
V_{CO}	Endogenous CO production rate	mL/minute (STPD)	0.007
Compartment volumes[b]			
BW	Body weight	kg	70
V_B	Blood volume	L	$0.074 \cdot BW$
V_1	Volumes of pulmonary capillaries and veins and ½ heart	L	$0.1 \cdot V_B$
V_2	Volume of rapidly perfused compartment	L	$0.11 \cdot V_B$
V_3	volume of slowly perfused compartment	L	$0.652 \cdot V_B$
V_4	Volume of major arteries in arms	L	$0.0069 \cdot V_B$
V_5, V_6	Volume of small vessels in arms	L	$0.0076 \cdot V_B$
V_7	Volume of intermediate veins in arms	L	$0.0025 \cdot V_B$
V_8	Volume of large veins in arms	L	$0.0361 \cdot V_B$
V_9	Volume of ½ heart and pulmonary arteries	L	$0.085 \cdot V_B$
Compartment flows[c]			
V_A	Alveolar ventilation rate	L/hour	$(15 \cdot BW^{0.74})$
QC	Cardiac output	L/hour	$(15 \cdot BW^{0.74})$
Q_{12}	Flow to rapidly perfused tissue	L/hour	$0.6 \cdot QC$
Q_{13}	Flow to slowly perfused tissue	L/hour	$0.35 \cdot QC$
Q_{14}	Flow to arteries of arms	L/hour	$0.05 \cdot QC$
Q_{45}	Flow to small vessels in arms	L/hour	$0.005 \cdot QC$

[a]Based on Tikuisis et al. (1992)
[b]Must be converted to mL/minute by multiplying 1,000/60
[c]Must be converted to mL by multiplying by 1,000

BW = body weight; CO = carbon monoxide; COHb = carboxyhemoglobin; Hb = hemoglobin; STPD = standard temperature and pressure, dry (i.e., adjusted for partial pressure of water vapor in saturated air [47 Torr STP])

Figure 3-8. Structure of the Smith et al. (1994) Model*



*Diffusive exchange carbon monoxide (CO) and oxygen (O_2) occurs between lung alveolar space alveolar capillary blood. Instantaneous equilibrium is assumed between gases and blood hemoglobin, governed by the Haldane coefficient. Blood carboxyhemoglobin (COHb) is apportioned to various blood subcompartments according to subcompartment blood flows and volumes.

Target tissues. The Smith et al. (1994) model predicts COHb levels in arterial and venous blood.

Species extrapolation. Although originally developed to simulate blood COHb levels in humans, the model could be used to predict COHb levels in other mammalian species provided that physiological and chemical-specific parameter values are available for the species of interest.

Interroute extrapolation. The Smith et al. (1994) model simulates inhalation exposures.

Hill et al. (1977) Maternal-Fetal Model

Hill et al. (1977) developed a multi-compartment model for simulating maternal-fetal transfer of carbon monoxide. This model includes simulations of maternal, placental, and fetal compartments, as well as maternal and fetal contributions to endogenous production of carbon monoxide (Table 3-15; Figure 3-9).

The model assumes instantaneous equilibrium of O_2 and carbon monoxide with Hb in maternal, placental, and fetal tissues, with delivery to placental and fetal tissues governed by blood flow rates.

Validation of the model. The Hill et al. (1977) model was evaluated with data collected in experiments conducted in pregnant sheep (Longo 1977; Longo and Hill 1977). Pregnant sheep were exposed to 30, 50, or 100 ppm carbon monoxide for 24 hours or to 300 ppm for 4 hours, and maternal and fetal arterial blood was sampled from indwelling catheters for measurement of COHb levels. These exposures achieved maternal blood COHb levels ranging from approximately 4 to 24% (300 ppm). Steady-state blood COHb levels in the fetus, achieved during the exposures to 30–100 ppm, were approximately 70% higher than maternal levels. The model predicted maternal and fetal arterial blood COHb levels that agreed with observations (e.g., were within ±1 SD of observations). The model predicts slower accumulation and elimination of COHb in the human fetus compared to the maternal system, with steady-state values in fetal blood that are approximately 10–12% higher in than maternal blood. The latter prediction agrees with observations made in cord blood (Longo 1977).

Risk assessment. Risk assessment applications of the Hill et al. (1977) model were not identified in the available literature. However, Hill et al. (1977) present and discuss predictions made with the model regarding effects of various factors on maternal and fetal blood COHb levels, including air carbon monoxide concentration, air O_2 concentration, altitude, exercise, fetal O_2 utilization, and fetal blood flow.

Table 3-15. Parameter Values for the Hill et al. (1977) Model

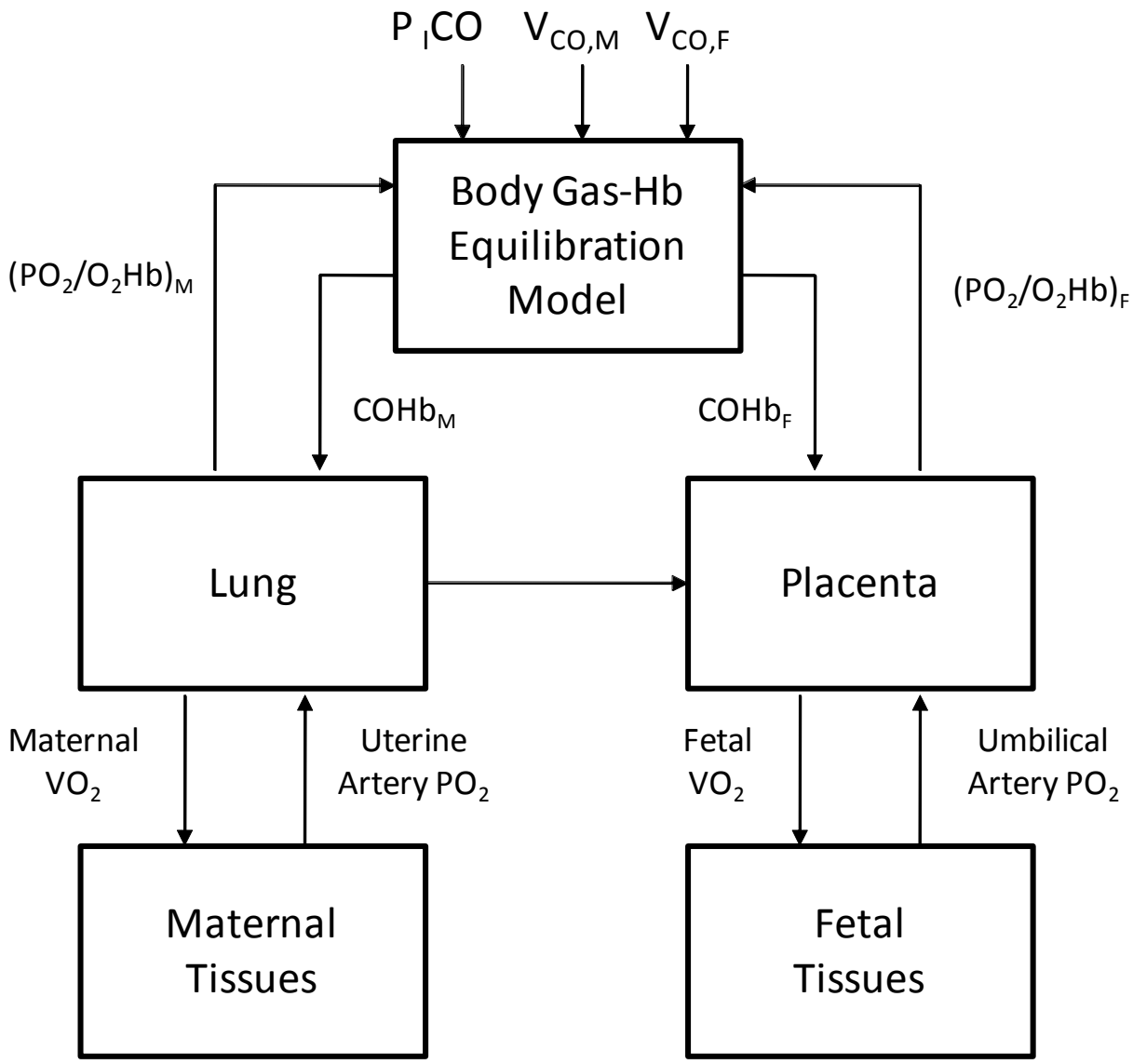
Parameter	Definition	Unit	Value
Chemical parameters			
D_MCO	Lung membrane diffusing capacity	mL CO/minute-Torr	50, 60
D_LCO	Lung CO diffusing capacity	mL CO/minute-Torr	30, 28
D_PCO	Placental CO diffusing capacity	mL CO/minute-Torr	1.5, 2.7
Hb_M	Maternal blood Hb concentration	g/mL	0.125
Hb_F	Fetal blood Hb concentration	g/mL	0.155
cap_M	Maternal blood O_2 capacity	mL O_2/mL	0.168
cap_F	Fetal blood O_2 capacity	mL O_2/mL	0.208
M_M	Haldane coefficient for maternal Hb	unitless	223
M_F	Haldane coefficient for fetal Hb	unitless	181
P_B	Atmospheric pressure	Torr	760
P_{HOH}	Partial pressure of water vapor (STP)	Torr	47
$(PO_2/O_2Hb)_L$	Average ratio of partial pressure of O_2 to O_2Hb concentration in lung capillaries	Torr/%	1.029 (at P_ICO=0)
$(PO_2/O_2Hb)_M$	Average ratio of partial pressure of O_2 to O_2Hb concentration in maternal placental capillaries	Torr/%	0.5609 (at P_ICO=0)
$(PO_2/O_2Hb)_F$	Average ratio of partial pressure of O_2 to O_2Hb concentration in fetal placental capillaries	Torr/%	0.4128 (at P_ICO=0)
P_AO_2	Partial pressure of O_2 in alveolar air	Torr	108
P_ACO_2	Partial pressure of CO_2 in alveolar air	Torr	32
P_VO_2	Partial pressure of O_2 in mixed venous blood in pulmonary artery	Torr	38
P_VCO_2	Partial pressure of CO_2 in mixed venous blood in pulmonary artery	Torr	38
P_FO_2	Partial pressure of O_2 in umbilical artery	Torr	20
P_FCO_2	Partial pressure of CO_2 in umbilical artery	Torr	48
P_MO_2	Partial pressure of O_2 in uterine artery	Torr	95
P_MCO_2	Partial pressure of CO_2 in uterine artery	Torr	32
$P_{50,M}$	Partial pressure of O_2 at half O_2 saturation in maternal blood	Torr	26.4
$P_{50,F}$	Partial pressure of O_2 at half O_2 saturation in fetal blood	Torr	20.0
pH_M	pH of uterine artery blood	M	7.40
pH_F	pH of umbilical artery blood	M	7.34
pH_M	pH of mixed venous blood	M	7.37
P_ICO	Partial pressure of inhaled CO	Torr	Input
$V_{CO,M}$	Maternal endogenous CO production rate	mL/minute	0.0153
$V_{CO,F}$	Fetal endogenous CO production rate	mL/minute	0.0006
VO_{2M}	Total maternal O_2 consumption rate	mL/minute	271
VO_{2F}	Fetal O_2 consumption rate	mL/minute	22

Table 3-15. Parameter Values for the Hill et al. (1977) Model

Parameter	Definition	Unit	Value
Compartment volumes			
vol_M	Maternal blood volume	mL	5,000
vol_F	Fetal blood volume	mL	400
Compartment flows			
V_A	Alveolar ventilation rate	mL/minute	6,000
Q_M	Maternal placental blood flow	mL/minute	350
Q_F	Fetal placental blood flow	mL/minute	350
Q_L	Lung blood flow	mL/minute	5,600

CO = carbon monoxide; Hb = hemoglobin; STP = standard temperature and pressure

Figure 3-9. Structure of the Hill et al. (1977) Maternal-Fetal Model*



*Average blood carboxyhemoglobin (COHb) levels in maternal and fetal tissues are calculated in the Body Gas Equilibration Model, based on inputs of PO_2/O_2Hb from lung, maternal tissue, placental tissue, and fetal placental capillary models.

P_ICO = inhaled carbon monoxide partial pressure; $V_{CO,M}$ = maternal endogenous carbon monoxide production; $V_{CO,F}$ = fetal endogenous carbon monoxide production; VO_2 = oxygen consumption

Of particular relevance to risk assessment is the prediction of slower accumulation and elimination of COHb in the human fetus compared to the maternal system. Based on model predictions, the elimination half-times were approximately 4 hours for maternal and 7.5 hours for fetal. Furthermore, the model predicted a more pronounced effect of breathing 100% O_2 on carbon monoxide elimination from the maternal system (5-fold decrease in half-time) compared to the effect on fetal half-time (2-fold decrease).

Target tissues. The Hill et al. (1977) model predicts COHb levels in maternal and fetal blood.

Species extrapolation. The Hill et al. (1977) model has been applied to predicting maternal and fetal blood COHb levels in humans and sheep (Hill et al. 1977; Longo 1977; Longo and Hill 1977).

Interroute extrapolation. The Hill et al. (1977) model simulates inhalation exposures.

Bruce et al. (2008) Blood-Muscle Model

Bruce et al. (Bruce and Bruce 2003; Bruce et al. 2008) developed a multi-compartment model that simulates kinetics of carbon monoxide, blood COHb, and muscle COMb (Table 3-16; Figure 3-10). The model includes compartments for blood, muscle, and other non-vascular tissues. In blood, carbon monoxide exists as dissolved carbon monoxide in equilibrium with COHb. Binding of carbon monoxide and O_2 to Hb is assumed to achieve instantaneous equilibrium of carbon monoxide with Hb, defined by the Haldane equation, with adjustment for cooperative binding of carbon monoxide and O_2 to Hb and myoglobin. Simulation of arterial and venous blood includes a time delay to account for the time required to achieve mixing of arterial blood leaving the lung and mixed venous blood. The muscle compartment consists of two subcompartments, between which dissolved carbon monoxide exchanges by diffusion. Subcompartment 1 represents tissue that exchanges dissolved carbon monoxide with the arterial and venous vasculature (representing arterial-venous shunting). Subcompartment 2 represents tissue that exchanges with capillary blood. Dissolved carbon monoxide in muscle is in equilibrium with myoglobin, with the equilibrium defined by the Haldane equation adjusted for cooperative binding of O_2. Carbon monoxide in the other tissue compartment is assumed to consist entirely of dissolved carbon monoxide.

Validation of the model. The Bruce et al. (2008) model was evaluated with data collected in experiments various experiments conducted in volunteers (Benignus et al. 1994; Burge and Skinner 1995; Peterson and Stewart 1975; Tikuisis et al. 1987a). The evaluations are reported in Bruce and Bruce (2003, 2006) and Bruce et al. (2008). The model predicted observed arterial and venous blood COHb

Table 3-16. Parameter Values for the Bruce et al. (2008) Model[a]

Parameter	Definition	Unit	Value
Chemical parameters			
D_LCO	Lung CO diffusion capacity	mL CO/minute-Torr	30
D_MCO	Muscle CO diffusion capacity	mL CO/minute-Torr	1.75
D_TO_2	Within tissue diffusion coefficient for O_2	mL/minute-Torr	0.00060
D_TCO	Within tissue diffusion coefficient for O_2	mL/minute-Torr	0.00045
Hb	Blood Hb concentration	g/mL	0.14
Hb_F	Fetal blood Hb concentration	g/mL	0.155
M_{Hb}	Haldane coefficient for Hb	unitless	218
M_{Mb}	Haldane coefficient for Mb	unitless	36
n	Hill equation exponent	unitless	variable[a]
O_2Hb_{Max}	O_2 capacity of Hb	mL O_2/g Hb	1.381
P_B	Barometric pressure	Torr	760
P_AO_2	Partial pressure of O_2 in arterial blood	Torr	100
P_MO_2	Partial pressure of O_2 in muscle	Torr	20
$P_{50}Hb$	Partial pressure at 50% Hb saturation	Torr	variable[a]
$P_{50}Mb$	Partial pressure at 50% Mb saturation	Torr	2.32
$MRO_{2\ B}$	Whole body O_2 consumption	mL/minute/g	0.0032
$MRO_{2\ M}$	Muscle O_2 consumption	mL/minute/g	0.021–0.03
SO_2	Solubility of O_2 in plasma	mL/Torr	$3.14 \cdot 10^{-5}$
SCO	Solubility of CO in plasma	mL/Torr	$2.35 \cdot 10^{-5}$
VO_2	Total body O_2 consumption	mL/minute	225
VCO	Endogenous CO production	ml/minute	0.007
Volumes			
V_M	Volume of muscle	L	29.1
$V_{M1}F$	Volume of muscle subcompartment 1	L	$0.4 \cdot V_M$
$V_{M2}F$	Volume of muscle subcompartment 1	L	$0.6 \cdot V_M$
V_{OT}	Volume of other tissue	L	9.6

Table 3-16. Parameter Values for the Bruce et al. (2008) Model[a]

Parameter	Definition	Unit	Value
Flows			
Q_C	Cardiac output	mL/minute	5,800
$Q_M f$	Blood flow fraction to muscles	unitless	0.40
$Q_{OT} f$	Blood flow fraction to other tissue	unitless	0.25
V_A	Alveolar ventilation rate	mL/minute	5,500

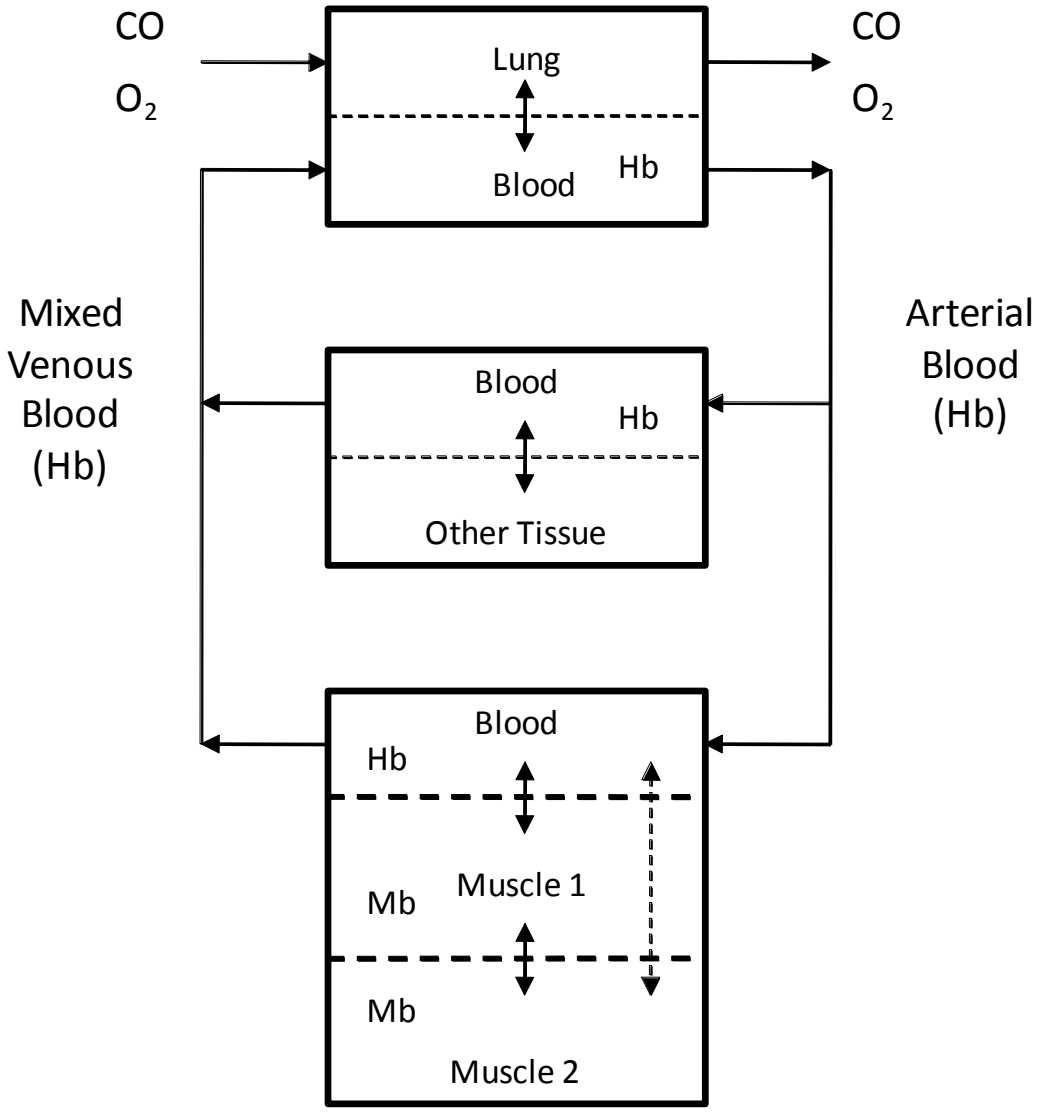
[a]Estimated from Hill equation:

$$O_2Hb = O_2Hb_{max} \cdot \frac{(PO_2 / P_{50})^n}{1 + (PO_2 / P_{50})^n}$$

Values for *n* ranged from approximately 2.34 at COHb=0% to 1.8 at COHb=100%. Values for P_{50}Hb ranged from 25 at COHb=0% to 0 at COHb=100%

CO = carbon monoxide; COHb = carboxyhemoglobin; Hb = hemoglobin

Figure 3-10. Structure of the Bruce et al. (2008) Model*



*The model simulates diffusive exchange of carbon monoxide (CO) and oxygen (O_2) between alveolar space and capillaries and tissue capillary blood and tissues. Competitive cooperative binding of carbon monoxide and O_2 with hemoglobin (Hb) occurs in blood and to myoglobin (Mb) in muscle. No binding is assumed in the other tissue compartments. In muscle, diffusive exchange is assumed to occur between blood and both muscle subcompartments, as well as between muscle compartments.

Sources: Adapted from Bruce and Bruce (2003); Bruce et al. (2008)

differences and kinetics during and following single or multiple brief exposures to carbon monoxide (Benignus et al. 1994). The model predicted continued uptake of carbon monoxide into muscle during the first 300 minutes following cessation of exposure, with subsequent return of muscle carbon monoxide to blood (Bruce and Bruce 2006). Blood-muscle carbon monoxide exchange, in combination with elimination of carbon monoxide from blood to exhaled air, resulted in multi-phase blood elimination kinetics, with the early faster phase dominated by transfer of carbon monoxide from blood to muscle, and the later slower phase contributed by return of carbon monoxide from muscle to blood and elimination from blood to exhaled air. The multi-phase kinetics predicted from the model agreed with post-exposure elimination kinetics of carbon monoxide from blood observed in Benignus et al. (1994). The model also predicted blood COHb kinetics observed in 1- and 5-minute exposures observed in Tikuisis et al. (1987a).

Model predictions match the CFK model when muscle diffusion is set to zero, and the model predicts lower blood COHb levels than the CFK model when the muscle carbon monoxide diffusion is enabled. This difference reflects the blood-muscle kinetics and storage of carbon monoxide in muscle myoglobin that is not accounted for in the CFK model.

Risk assessment. Risk assessment applications of the Bruce et al. (2008) model were not identified in the available literature. However, the model has been applied to predicting the outcome of breathing 100% O_2 on blood COHb and muscle COMb kinetics (Bruce and Bruce 2006). The model predicted a decrease in blood and muscle elimination half-times. Of particular relevance to risk assessment is the prediction of continued uptake of carbon monoxide from blood to muscle that occurs for several hours after cessation of exposure, which contributes to slowing the elimination kinetics of carbon monoxide from the body.

Target tissues. The Bruce et al. (2008) model predicts blood COHb and muscle COMb levels and can also be used to predict blood and muscle carbon monoxide burden.

Species extrapolation. The Bruce et al. (2008) model has been applied only to predicting blood COHb and muscle COMb levels in humans. The model could be applied to other mammalian species providing that physiological and chemical-specific parameter values are available for species of interest.

Interroute extrapolation. The Bruce et al. (2008) model simulates inhalation exposures.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Pharmacokinetic mechanisms of carbon monoxide action are related to its binding to heme proteins. Kinetics and equilibria of binding to the major heme proteins that have the greatest influence on carbon monoxide pharmacokinetics (Hb and myoglobin) are discussed in the Section 3.4, Toxicokinetics.

Absorption. Inhaled carbon monoxide is rapidly and extensively absorbed into blood (Benignus et al. 1994; Burge and Skinner 1995; Peterson and Stewart 1970, 1975; Tikuisis et al. 1987b). Inhaled carbon monoxide is transported to lung alveoli as result of convective forces in the respiratory tract and diffusion. At the alveolar gas-blood interface, carbon monoxide dissolves into pulmonary capillary plasma and, from plasma, diffuses into erythrocytes and other tissues. Binding of carbon monoxide by erythrocyte Hb (to form COHb) contributes to maintaining relatively low concentrations of dissolved carbon monoxide in erythrocyte cytosol and a partial pressure gradient to drive carbon monoxide transfer from alveolar air to blood. Diffusion of carbon monoxide into erythrocytes and binding of carbon monoxide to Hb is sufficiently rapid that near-equilibrium is achieved between carbon monoxide partial pressures in alveolar air and alveolar end capillary (arterial) blood (Chakraborty et al. 2004). Continued uptake of carbon monoxide results from systemic elimination processes that lower mixed venous blood carbon monoxide concentrations returned to alveolar capillaries (Benignus et al. 1994).

Distribution. The distribution of absorbed carbon monoxide is determined, in large part, by its affinity for binding to heme. Binding of carbon monoxide to intracellular heme proteins contributes to maintaining gradients for carbon monoxide diffusion from plasma into erythrocytes and extravascular tissues. The dominant heme proteins that influence carbon monoxide distribution are erythrocyte Hb and muscle myoglobin. The distribution of carbon monoxide in the body is largely a reflection of the distribution of Hb and myoglobin, with the largest carbon monoxide burden found in blood, heart, skeletal muscle, and spleen (Vreman et al. 2005, 2006). Relatively large contributions of blood and skeletal muscle to total body carbon monoxide content is consistent with the contributions that these tissues make to total body Hb and muscle myoglobin (Bruce and Bruce 2003). In a typical adult, blood contains approximately 12 mmoles of Hb, with a total binding capacity of approximately 48 mmole carbon monoxide when completely saturated, and muscle contains approximately 8 mmoles of myoglobin, with a total binding capacity of 8 mmole carbon monoxide when completely saturated.

Metabolism. Metabolism of carbon monoxide consists of three major processes: (1) metabolic production of carbon monoxide from endogenous and exogenous precursors; (2) binding of carbon monoxide to heme proteins; and (3) oxidative metabolism of carbon monoxide to CO_2.

Metabolic Production of Carbon Monoxide. Endogenous carbon monoxide is produced primarily from the enzymatic degradation of heme by the enzyme HO. Carbon monoxide is produced in all tissues that express HO; however, the major tissues contributing to carbon monoxide production are also major sites of heme metabolism, including liver, spleen, and reticuloendothelial system (Berk et al. 1974). Three isoforms of HO have been identified, of which HO-1 is inducible, whereas HO-2 and HO-3 are constitutive. In general, factors that induce HO-1 increase carbon monoxide production, whereas inhibition of HO activity or expression of HO decreases carbon monoxide production. Numerous stimuli have been shown to up-regulate HO-1 expression (Wu and Wang 2005): (1) those related to heme metabolism (e.g., heme and heme derivatives, endogenous carbon monoxide); (2) stimuli that produce or are associated with physiological or oxidative stress such as hyperoxia, heat shock factors, oxidized lipids, lipopolysaccharides, hydrogen peroxide, radiation (including ultraviolet light), endotoxin, heavy metals and arsenite, and various cytokines (e.g., interleukins, TNF-α); (3) substances that are mediators of vascular resistance (NO, angiotensin II); and (4) mitogens and other factors that regulate cell growth (e.g., growth factors, phorbol ester). Expression of the constitutive isoform, HO-2, is increased by estrogen, glucocorticoids, stimuli that inhibit HO, and stimuli that down-regulate NO production (e.g., inhibition of NO synthase). In human cells (e.g., grown in culture), expression of HO-1 is down-regulated during hypoxia, heat shock factors, and interferon-γ. The response to the above factors is not uniform across species. For example, hypoxia and heat shock have been shown to induce HO in rodents, whereas the dominant effect in human tissues is down-regulation (Nakayama et al. 2000; Shibahara et al. 2003; Wu and Wang 2005).

Carbon monoxide can be produced from oxidative metabolism of certain exogenous hydrocarbons (e.g., DCM) by isoform CYP2E1 of cytochrome P450 (Andersen et al. 1991) and from heme oxidase catalysis of products of auto-oxidation of phenols, photo-oxidation of organic compounds, and lipid peroxidation of cell membrane lipids (Rodgers et al. 1994).

Carbon Monoxide Binding to Heme Proteins. Carbon monoxide competes for O_2 for binding to the iron site in heme. Kinetic constants and equilibrium constants for the binding of O_2 and carbon monoxide to Hb and myoglobin are provided in Table 3-12.

Oxidative Metabolism of Carbon Monoxide. The mechanism of oxidative metabolism of carbon monoxide to CO_2 is thought involve catalysis by cytrochrome c oxidase (Fenn 1970; Young and Caughey 1986).

Excretion. Absorbed carbon monoxide is eliminated from the body by exhalation and oxidative metabolism. Oxidative metabolism of carbon monoxide has been estimated to be a relatively small fraction (<10%) of endogenous carbon monoxide production (Luomanmaki and Coburn 1969). Under most conditions, the dominant route of elimination of absorbed carbon monoxide is exhalation. The mechanism of elimination of carbon monoxide by exhalation is diffusion, with the driving forces at the alveolar interface being the partial pressure difference between carbon monoxide in alveolar air and in alveolar capillary blood. The latter is maintained at a relatively low level by binding of carbon monoxide to Hb. Diffusion is also the mechanism of release of carbon monoxide from intracellular stores to blood, with the driving forces influenced by binding of carbon monoxide to extravascular heme proteins (e.g., myoglobin) and blood Hb.

3.5.2 Mechanisms of Toxicity

Carbon monoxide exerts effects on cell metabolism through both hypoxic and non-hypoxic mechanisms. Both types of effects are thought to be largely (if not entirely) the result of the ability of carbon monoxide to bind to heme and alter function and/or metabolism of heme proteins. Carbon monoxide may also act through mechanisms unrelated to heme binding, although evidence for this is currently more contentious.

Hypoxic Mechanisms. Carbon monoxide produces tissue hypoxia by binding to, and displacing O_2 from, Hb. The formation of COHb decreases the O_2 carrying capacity of blood and impairs release of O_2 from Hb for its utilization in tissues (see Section 3.4.3, Metabolism for further discussion of kinetics of binding of carbon monoxide and O_2 to Hb). Through similar mechanisms, carbon monoxide decreases O_2 storage in muscle cells by binding to, and displacing O_2 from, myoglobin. The principal mechanisms underlying the hypoxic mechanism of carbon monoxide are: (1) higher affinity of carbon monoxide for Hb than O_2 and (2) increased binding affinity for O_2 from COHb. The overall affinity of Hb for carbon monoxide is approximately 230 times greater than that for O_2 (Chakraborty et al. 2004). As a result, at a partial pressure of carbon monoxide that is approximately 230-fold lower than ambient O_2 concentration (21%/230≈900 ppm), O_2 and carbon monoxide will bind to Hb in an equimolar ratio (i.e., COHb≈50%). Binding of carbon monoxide and O_2 to the four heme moieties of Hb is cooperative (Alcantara et al. 2007; Perrella and Di Cera 1999; Roughton 1970). The associative reaction rate (ka) becomes faster with

successive additions of carbon monoxide or O_2, increasing the affinity (Ka) of Hb for O_2 and impairing the release of O_2 from Hb for utilization in tissues. Overall, the affinity increase is 588-fold due to cooperative events as more carbon monoxide binds to hemoglobin; however, this is not a monotonic function with each ligation. Once the first hemoglobin chain binds a carbon monoxide molecule, the affinity increases 16.5-fold when the second carbon monoxide molecule binds, 4.6-fold at the third ligation step, and 7.7-fold in the fourth ligation step (Perrella and Di Cera 1999).

Although all tissues are vulnerable to carbon monoxide-induced hypoxic injury, those having the highest O_2 demand are particularly vulnerable, including the brain and heart. Carbon monoxide-induced hypoxia triggers compensatory cardiovascular responses that include increased cardiac output (heart rate and stroke volume) and dilation of cardiac and cerebral vasculature. During exercise, cardiac work and O_2 consumption increase and the vulnerability of the heart to carbon monoxide-induced hypoxic injury increases. In patients who have underlying coronary artery or myocardial disease, the increased O_2 demand of exercise, in combination with decreased O_2 carrying capacity of blood and impaired release of O_2 from Hb, can produce cardiac toxicity (e.g., myocardial ischemia, exertional angina, arrhythmia) at lower carbon monoxide exposure levels than experienced in healthy individuals (Adams et al. 1988; Allred et al. 1989, 1991; Anderson et al. 1973; Kleinman et al. 1989, 1998; Leaf and Kleinman 1996b).

Brain hypoxia induced by carbon monoxide can result in various symptoms of impaired central nervous system function, including headache, dizziness, drowsiness, weakness, nausea, vomiting, confusion, disorientation, irritability, visual disturbances, convulsions, and coma (Dolan 1985; Ernst and Zibrak 1998). Delayed development of neuropsychiatric and neurological impairment may occur within 1–4 weeks of exposure, with symptoms including inappropriate euphoria, impaired judgment, poor concentration, memory loss, cognitive and personality changes, psychosis, and Parkinsonism (Choi 2002; Ernst and Zibrak 1998; Kao and Nañagas 2006; Klawans et al. 1982; Raub and Benignus 2002; Raub et al. 2000; Ringel and Klawans 1972; WHO 1999; Wolf et al. 2008).

Non-Hypoxic Mechanisms. Most of the non-hypoxic mechanisms of action of carbon monoxide have been attributed to binding of carbon monoxide to heme in proteins other than Hb. A list of heme proteins that have been shown to undergo functional modification in response to carbon monoxide is presented in Table 3-17. Notable targets of carbon monoxide include components of several important physiological regulatory systems, including brain and muscle O_2 storage and utilization (myoglobin, neuroglobin), nitric oxide NO cell signaling pathway (e.g., nitric oxide synthase [NOS], guanylyl cyclase [GC]), prostaglandin cell signaling pathway (cyclooxygenase, prostaglandin H synthase), energy metabolism and

Table 3-17. Heme Proteins Modulated by Carbon Monoxide

Name of protein	Effects or carbon monoxide or heme oxygenase up-regulation	Reference
Catalase	Inhibition	Hu and Kincaid 1992
Cyclooxygenase	Inhibition	Alcaraz et al. 2003
	Activation	Lee et al. 2001
Cytochrome *c*	Binding	Bhuyan and Kumar 2002
Cytochrome P450	Inhibition	Estabrook et al. 1980
Cytochrome *c* oxidase	Inhibition	Wohlrab and Ogunmola 1971
Guanylyl cyclase	Activation	Stone and Marletta 1994
Hemoglobin	Inhibition	Forster 1970
Neuroglobin	Inhibition	Burmester et al. 2000
Myoglobin	Inhibition	Coburn and Mayers 1971
Cytoglobin	Inhibition	Geuens et al. 2003; Sawai et al. 2003
NADPH oxidase	Inhibition	Taille et al. 2004
NO synthases	Inhibition	Thorup et al. 1999; Willis et al. 1995
Peroxidases	Binding	Carlsson et al. 2005
Prostaglandin H synthase	Binding	Lou et al. 2000
Tryptophan dioxygenase	Inhibition	Piantadosi 2002
NPAS2	Inhibition	Dioum et al. 2002

Source: Wu and Wang 2005

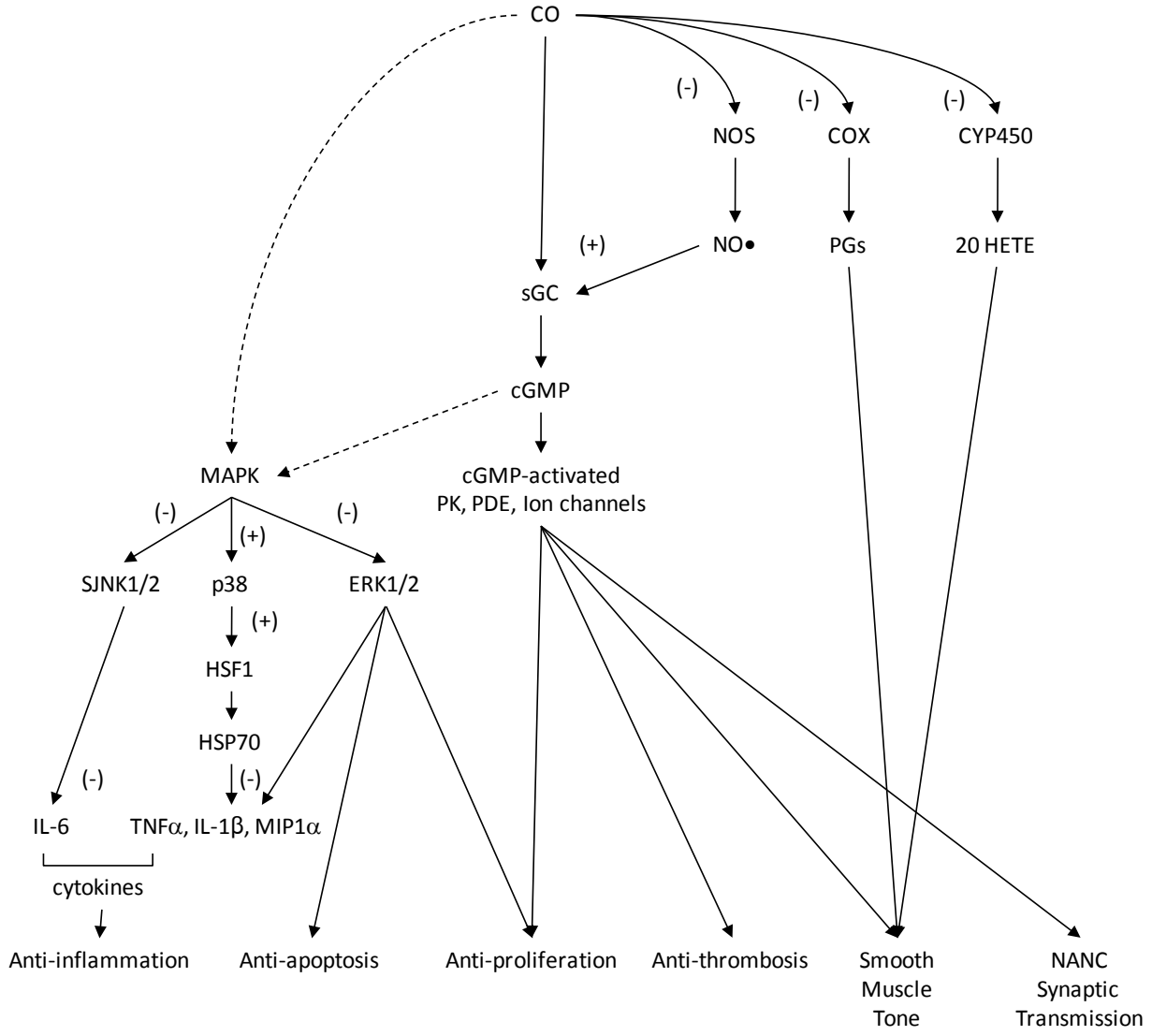
mitochondrial respiration (cytochrome c oxidase, cytochrome c, NADPH oxidase), steroid and drug metabolism (cytochrome P450), cellular redox balance and ROS (catalase, peroxidases), and various transcription factors (e.g., neuronal PAS domain protein, NPAS2, implicated in regulation of circadian rhythm).

Endogenously produced carbon monoxide may participate in the physiological regulation of some, if not all, of these systems. This has potentially important implications for the understanding of carbon monoxide toxicology and dose-response relationships for the following reasons: (1) carbon monoxide modulation of physiological processes may underlie some aspects of the toxicity of exogenous carbon monoxide; (2) exogenous carbon monoxide may disrupt physiological regulation of those systems that are responsive to endogenous carbon monoxide (e.g., vascular resistance); and (3) exposures to exogenous carbon monoxide may affect carbon monoxide-mediated physiological responses at levels that approach those resulting from endogenous production. Whole-body endogenous carbon monoxide production rate has been estimated to be approximately 16.4 μmol/hour (0.007 mL/minute STPD; Coburn 1970a). Local rates of production of carbon monoxide in tissues are influenced by many tissue-specific factors, including those that regulate intracellular heme oxygenase activity (e.g., some areas of brain have relatively high HO-2 activities). A similar whole-body rate of delivery of carbon monoxide to the alveolar region of the lung would be achieved by inhaling air at a carbon monoxide concentration of approximately 1–2 ppm (i.e., assuming that alveolar ventilation rate is approximately 4,000 mL/minute; 0.007 mL/minute/4,000 mL/minute=1.75·10–6 mL CO/mL air, STPD=1.75 ppm). Such levels are only modestly above national average ambient air carbon monoxide concentrations in the United States (approximately 0.5 ppm, see Chapter 6) and well within variability observed in measurements made with personnel air monitors (Chang et al. 2000). One implication of this is that, if a dose threshold for effects of exogenous carbon monoxide exists at all, it may lie near or below ambient air carbon monoxide concentrations. Although currently available toxicology and epidemiological studies provide evidence for increasing severity of adverse carbon monoxide effects in association with increasing levels of exposure, these studies do not provide strong evidence supporting or refuting a dose threshold for adverse effects.

Of the many physiological systems that may contribute to non-hypoxic mechanisms of carbon monoxide action, the following are thought to be particularly important and are the subject on ongoing intense research interests: modulation of cell signaling pathways and generation of ROS.

Carbon Monoxide Modulation of Cell Signaling and Ion Channel Activity. Cell signaling pathways that are thought to be modulated by carbon monoxide are depicted in Figure 3-11. These pathways

Figure 3-11. Potential Signaling Pathways Modulated by Carbon Monoxide



+ = stimulates pathway; – = inhibits pathway; cGMP = cyclic guanosine monophosphate; CO = carbon monoxide; COX = cylcooxygenase; CRF = corticotropin releasing factor; CNS = central nervous system; CYPP40 = cytochrome P450; ERK = extracellular signal regulated kinase; 20-HETE = 20-hydroxyeicostetraenoic acid; HSF = heat shock factor; HSP = heat shock protein; IL = interleukin; JNK = a stress activate protein kinase; MAPK = mitogen activate protein kinase; MIP = macrophage inflammatory protein; NANC = non-noradrenergic non-cholinergic; NO• = nitric oxide radical; NOS = nitrogen oxide synthase; PDE = phosphodiesterase; PG = prostaglandins; PK = protein kinase; sGC = soluble guanylate cyclase; TNF = tumor necrosis factor

Adapted from Ryter et al. 2006; Volti et al. 2008

contribute to the regulation of various physiological process, including inflammatory responses, apoptosis, cell proliferation, thrombosis (i.e., platelet aggregation), smooth muscle tone (including vasodilation and relaxation of extravascular smooth muscle), and synaptic neurotransmission in the central and peripheral nervous systems (e.g., glutamate). The nitric oxide radical (NO•) plays an important signal transduction role in regulating smooth muscle relaxation, synaptic neurotransmission (e.g., glutamate), platelet function, and other physiological processes (Denninger and Marletta 1999). One of the major transduction pathways mediated by NO• is the NO•-cGMP pathway, in which NO• produced by the enzyme NOS binds to the heme moiety of soluble guanylate cyclase (sGC), which catalyzes conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). The latter (cGMP) activates various downstream signaling cascades that regulate cell function (e.g., cGMP-dependent protein kinase, cGMP-regulated cation channels, and cGMP-regulated phosphodiesterase). Carbon monoxide binds to the heme moieties of both NOS and sGC, and in doing so, inhibits NOS activity and activates sGC activity (Stone and Marletta 1994; Thorup et al. 1999). The potency of carbon monoxide for activating sGC is approximately 20-fold less than that of NO•; as a result, in the presence of NO•, carbon monoxide may modulate sGC activity downward by displacing NO• from sGC (Stone and Marletta 1994). The NO•-cGMP signaling pathway has been implicated in the mechanism by which carbon monoxide produces relaxation of smooth muscle (Ny et al. 1996) and inhibition of platelet homotypic aggregation (Brune and Ullrich 1987). Carbon monoxide increases platelet-neutrophil interactions (heterotypic aggregation) through a free-radical mechanism (Thom et al. 2006).

Carbon monoxide modulates mitogen activated protein kinase (MAPK) signaling pathways, either through its interaction with sGC (Ryter et al. 2006) or through secondary effects on ROS generation (see below). MAPK pathways are important regulators of cytokine production and release in inflammatory responses and in regulating apoptosis and proliferation.

Carbon monoxide exposure can perturb heme protein binding by nitric oxide; induce a variety of proteins including heme oxygenase (HO), superoxide dismutase, and nitric oxide synthase; alter mitochondrial function; and modify production of ATP and ROS (Brown and Piantadosi 1992; Davutoglu et al. 2006; Kim et al. 2007; Lee et al. 2006; Maulik et al. 1996; Nakao et al. 2008; Piantadosi et al.1997; Thom et al. 1994, 1997, 2000; Zuckerbraun et al. 2003). Carbon monoxide increases production of ROS from mitochondria and also some non-mitochondrial sources, which can activate one or more protein kinases (e.g., p38 MAPK, c-Jun N-terminal kinase, ERK), signal transducers (e.g., peroxisome proliferator-activated receptor-γ), and transcriptional regulators (e.g., nuclear factor-κB, AP-1), as well as guanylate

cyclase, and lead to secondary events such as vasodilation and fibrinolysis (Arruda et al. 2004; Fujita et al. 2001; Mishra et al. 2006; Ryter and Otterbein 2004; Soares et al. 2004; Wijayanti et al. 2004).

Carbon monoxide also binds to the heme moieties and inhibits cytochrome P450 and cyclooxygenase (COX) and, thereby, can modify physiological processes regulated by products of these enzyme systems. Inhibition of cytochrome P450 catalyzed production of eciosanoids (e.g., 20-hydroxyeicostetraenoic acid, [20-HETE]) and COX-mediated production of prostaglandins have been postulated as a potential mechanisms by which carbon monoxide may contribute to the regulation of vascular smooth muscle tone and vasodilation (Botros et al. 2002; Volti et al. 2008).

Carbon monoxide has been shown to modulate activity of several ion channels, including calcium-sensitive and voltage-gated K^+ channels, cardiac L-type and intestinal smooth muscle L-type Ca^{2+} channels, and epithelial Na^+ channels (Peers 2011; Peers and Steel 2011; Peers et al. 2009). Carbon monoxide may augment or inhibit channel activity, depending on ion channel type and carbon monoxide concentration. Several mechanisms for ion channel modulation have been proposed, including increased production of ROS (cardiac L-type Ca^{2+} channels and voltage-gated K^+ channels), protein kinase G activation (K^+ channels), and increased nitric oxide and cGMP (intestinal smooth muscle L-type Ca^{2+} channels).

Carbon Monoxide Modulation of ROS Generation. Carbon monoxide may promote and/or modify ROS generation through several different mechanisms. Binding to the heme moiety and inhibition of mitochondrial cytochrome c oxidase disrupts mitochondrial respiration and promotes ROS generation (Alonso et al. 2003; D'Amico et al. 2006; Favory et al. 2006a; Iheagwara et al. 2007; Zuckerbraun et al. 2007). Carbon monoxide also appears to promote a more general disruption of the regulation of iron and ferritin levels, at least in part through promotion of heme protein degradation (Cronje et al. 2004; Ghio et al. 2008; Iheagwara et al. 2007).

3.5.3 Animal-to-Human Extrapolations

Studies conducted in nonhuman primates, dogs, and various rodent species have demonstrated the major health effects of carbon monoxide that have been observed in humans, including COHb-related hypoxia, cardiovascular responses, and neurological effects (Benignus 1994; Benignus et al. 1990; EPA 1991, 2000; Raub and Benignus 2002). These studies also provide support for the concept of non-hypoxic modes of action of carbon monoxide that operate on a variety of physiological systems (e.g., Wu and

Wang 2005; also, see Section 3.5.2 for discussion and relevant references). These systems include physiological regulatory systems that function in all mammalian species, such as brain and muscle oxygen storage and utilization; nitric oxide cell signaling pathway; prostaglandin cell signaling pathway; energy metabolism and mitochondrial respiration; steroid and drug metabolism; cellular redox balance and ROS; and various transcription factors. Therefore, results from mechanistic studies conducted in typical laboratory animal models are likely to be directly relevant to understanding mechanisms of action of carbon monoxide in humans. Manifestations of these various modes of action may differ qualitatively and quantitatively across species. For example, rats exhibit pronounced hypothermia in response to exposures to carbon monoxide, whereas at low levels of exposure (e.g., COHb <20%), this response is not evident in humans (Benignus 1994; Gordon 1990). Differences in dose-response relationships between humans and animal models can also be expected, in part due to differences in physiological and chemical determinants of carbon monoxide uptake, elimination, and binding kinetics with major heme proteins, (Benignus and Annau 1994; Longo and Hill 1977) as well as interspecies differences in physiological regulation of systems that are non-hypoxic targets of carbon monoxide.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are

similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans and/or animals after exposure to carbon monoxide. Several cell signaling pathways that are thought to be modulated by endogenous carbon monoxide that could play a role in the regulation of activity of the hypothalamic-pituitary-adrenal (HPA) axis include cGMP and NO• signaling (Mancuso et al. 1997, 2010; Snyder et al. 1998; Wu and Wang 2005). Modulation of endogenous carbon monoxide levels and/or production has been shown to modify various HPA axis processes, including release of arginine vasopressin (AVP), gonadotropin, and corticotropin releasing hormone from the hypothalamus, release of adrenocorticotropic hormone (ACTH) from the pituitary, and response of the adrenal gland to ACTH (Wu and Wang 2005). The toxicological significance of these various actions of carbon monoxide has not been established.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less

susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

The fetus may be particularly vulnerable to maternal carbon monoxide exposure. Carbon monoxide in the maternal system distributes to fetal tissues. Measurements of steady-state fetal COHb concentrations in fetal and maternal blood of nonsmoking women have found fetal COHb concentrations to be

approximately 10–15% higher than maternal blood (fetal/maternal ratio=1.1–1.15; Longo 1977). Binding affinity of fetal Hb is approximately twice that of maternal Hb (Di Cera et al. 1989). The higher binding affinity of fetal Hb, as well as the relatively small diffusion gradients for carbon monoxide between maternal and fetal blood, contribute to slower kinetics of COHb in fetal blood compared to maternal blood. As a result, with continuous exposure to a constant level of carbon monoxide in air, the kinetics of fetal blood COHb concentration would be expected to lag behind maternal kinetics and to reach a steady-state that is approximately 10–15% higher than maternal (Longo 1977). Similarly, following cessation of exposure, elimination kinetics of carbon monoxide from fetal blood would be expected to lag behind that of maternal blood (Hill et al. 1977).

Epidemiological studies have examined possible associations between exposure to ambient air carbon monoxide concentrations and various developmental outcomes, including pre-term birth, reduced birth weight, congenital anomalies, and neonatal and infant death (see Section 3.2.6, Table 3-8). Results of these studies have been mixed and, collectively, do not provide strong evidence for developmental effects, including neonatal or infant mortality in association with exposures to ambient levels of carbon monoxide (<10 ppm). However, studies conducted in animals provide evidence of adverse developmental effects of gestational and early postnatal carbon monoxide in association with maternal exposure concentrations as low as 12–25 ppm. Observed effects have included decreased fetal weight, adverse central nervous system development, altered peripheral nervous system development, cardiac effects, altered sexual behavior, immunological effects, and hematological effects (see Table 3-9). In addition, some studies showed that developmental effects persisted beyond the postnatal period (Carratu et al. 1993, 2000a, 2000b; De Salvia et al. 1995; Lopez et al. 2003, 2008; Stockard-Sullivan et al. 2003; Webber et al. 2003).

Although no studies have directly compared the sensitivity of adults and children to the effects of carbon monoxide, several epidemiological studies have examined pulmonary function, asthma morbidity, and exacerbation of asthma symptoms in children (Chen et al. 1999; Fischer et al. 2002; Mortimer et al. 2008; Yu et al. 2000). Although results have been mixed, these studies provide some evidence for increased vulnerability of asthmatic children to carbon monoxide-associated respiratory effects (see Section 3.2.2, Respiratory Effects).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring. This report is available at http://www.cdc.gov/exposurereport/. The biomonitoring data for carbon monoxide from this report is discussed in Section 6.5. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to carbon monoxide are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by carbon monoxide are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or

other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Carbon Monoxide

Measurement of blood COHb is the principal biomarker for identifying exposure to carbon monoxide. Nearly all carbon monoxide in the body exists as complexes with Hb and other heme proteins. Approximately 60–70% of the body burden exists as blood COHb (Bruce and Bruce 2003; Vreman et al. 2006). Therefore, measurement of COHb provides a useful indicator of the elevated carbon monoxide body burden, although the utility for blood COHb measurements for large-scale screening for elevated exposures or poisoning is questionable (Heckerling et al. 1990). The relationship between COHb levels and exposure is more complex because of the numerous physiological factors that influence carbon monoxide uptake and elimination. The elimination half-time of absorbed carbon monoxide has been estimated to be approximately 300 minutes (Bruce and Bruce 2006; Peterson and Stewart 1970); therefore, a value for COHb measured at a given time following exposure will reflect both the exposure and elimination rate of carbon monoxide. Several pharmacokinetic models have been developed that can be used to predict blood COHb levels that would correspond to a given exposure concentration and duration in a typical adult and in the fetus resulting from maternal exposures (see Section 3.4.5). These models can be used to reconstruct possible carbon monoxide exposure scenarios (e.g., concentrations, duration and gap between measurement of COHb and cessation of exposure) that could result in a given measured COHb level.

3.8.2 Biomarkers Used to Characterize Effects Caused by Carbon Monoxide

Although blood COHb reflects current carbon monoxide body burden, measurement of blood COHb has not been shown to be a reliable predictor of severity of acute toxicity (Hampson and Hauff 2008). Furthermore, due to the time elapsed between cessation of CO exposure to measurement of COHb, coupled with effects of medical intervention (see Section 3.11, Methods Reducing Toxic Effects), blood COHb does not provide reliable estimates of the level of CO exposure. Typical levels of COHb in nonsmokers are <2% (Adams et al. 1988; Allred et al. 1991; Anderson et al. 1973; Hinderliter et al. 1989; Kleinman et al. 1989, 1998; Sheps et al. 1987, 1990). Levels of ≥10% can be observed immediately after smoking a cigarette (Kao and Nañagas 2006). In general, signs and symptoms of acute carbon monoxide poisoning can present at COHb levels ranging from 3 to 24% (Hampson and Hauff 2008; Kao and Nañagas 2006). Levels ranging from 2 to 6% have been shown to exacerbate underlying cardiovascular

disease, including enhanced myocardial ischemia and increased cardiac arrhythmias (Adams et al. 1988; Allred et al. 1989, 1991; Anderson et al. 1973; Kleinman et al. 1989, 1998; Leaf and Kleinman 1996b). More severe signs of carbon monoxide poisoning are poorly correlated with blood COHb, with loss of consciousness occurring at mean levels of 24.3% (range: 2–70%) and fatality at mean levels of 32.1% (range: 3.0–60%; Hampson and Hauff 2008). Exposures that result in COHb levels >50% are usually fatal (Kao and Nañagas 2006).

Diagnosis and characterization of carbon monoxide toxicity include both the measurement of blood COHb and assessment of signs. In order of increasing severity, these include: (1) headache, nausea, dilation of cutaneous vasculature, vomiting, dizziness, and blurred vision; (2) confusion, syncope, chest pain, dyspnea, weakness, tachycardia, and tachynea rhabdomyolysis; and (3) palpitations, cardiac dysrhythmias, hypotension, myocardial ischemia, cardiac arrest, respiratory arrest, pulmonary edema, seizures, and coma (Kao and Nañagas 2006). Neuropsychological testing and neuroimaging have been considered for evaluating central nervous system effects (Tomaszewski 2006).

Cardiac enzyme markers are associated with myocardial dysfunction and an elevated risk for long-term cardiac mortality following carbon monoxide poisoning; biochemical markers for brain injury, such as neuron-specific enolase and S-100 beta protein, have not been found to reliably correlate with severity of poisoning or clinical outcome (Brvar et al. 2004; Davutoglu et al. 2006; Kalay et al. 2007; Rasmussen et al. 2004; Satran et al. 2005).

3.9 INTERACTIONS WITH OTHER CHEMICALS

The effects of combined exposure of carbon monoxide with other chemicals (e.g., pollutants, drugs) were reviewed by the EPA (1991, 2000). In general, research has mainly focused on effects of combined chemical exposures on the cardiovascular, respiratory, and central nervous systems. As discussed in Section 3.10 (Populations that Are Unusually Susceptible), in addition to interactions with other chemicals, exposure to carbon monoxide at a higher altitude may result in higher body burdens of carbon monoxide and, therefore, there may be higher vulnerability to carbon monoxide at higher altitudes than at lower altitudes (McGrath et al. 1993), in particular for people who have not physiologically adapted to higher altitudes (Horvath et al. 1988; Hsia 2002).

Oxygen. The chemical interaction of highest toxicological and clinical significance is that between carbon monoxide and O_2. Carbon monoxide and O_2 compete for binding to heme (Chakraborty et al.

2004; Gibson et al. 1986). Binding to, and displacing O_2 from, heme proteins, including blood Hb and muscle myoglobin, has profound effects on the kinetics of distribution and elimination kinetics of both carbon monoxide and O_2, and is also the principal mechanism underling the hypoxic effects of carbon monoxide (Bruce and Bruce 2006; Bruce et al. 2008; Vreman et al. 2005, 2006). Decreasing levels of O_2 in inspired air facilitates carbon monoxide binding to Hb and myoglobin and exacerbates carbon monoxide-induced hypoxia. This interaction can contribute to a higher vulnerability to carbon monoxide toxicity at lower O_2 pressures that occur at higher altitudes (Horvath et al. 1988; Hsia 2002; McGrath et al. 1993). Increasing levels of O_2 in inspired air facilitates displacement of carbon monoxide from Hb and myoglobin, increases the rate of carbon monoxide elimination from the body, and increases O_2 availability to tissues (Landaw 1973; Peterson and Stewart 1970; Weaver et al. 2000). These actions of O_2 form the basis for the use of 100% O_2 and hyperbaric O_2 therapy in the treatment of carbon monoxide poisoning (Lavonas 2007; Tomaszewki 2006).

Chemicals that Bind to Hemoglobin. Several nitrate compounds, including dinitrotoluenes (Ellis et al. 1985; U.S. Army 1979) and nitroanilines (NTP 1993), bind to hemoglobin and induce anemia. Although studies evaluating the interaction between CO and other chemicals that bind hemoglobin were not identified, any chemical that binds to hemoglobin, and thereby reduces the oxygen carrying capacity of the blood, could potentiate the effects of CO.

Cyanide. Carbon monoxide and cyanide poisonings can occur concomitantly in victims of smoke inhalation (Lundquist et al. 1989; Shusterman et al. 1996; Wetherell 1966). Experimental studies conducted in animal models provide evidence that carbon monoxide and cyanide can produce synergistic toxicity (Moore et al. 1987; Norris et al. 1986; Pitt et al. 1979).

Drugs Affecting the Central Nervous System. Due to effects of carbon monoxide on the central nervous system, it is anticipated that combined exposure to drugs with activity in the central nervous system, including therapeutic agents and drugs of abuse, could enhance the central nervous system toxicity of carbon monoxide (EPA 1991, 2000). However, the available data are not sufficient to determine if effects of combined exposures are additive or exhibit other types of interaction relationships (e.g., synergistic). Enhanced carbon monoxide-induced central nervous system toxicity has been reported to occur with concomitant exposures to alcohol, barbiturates, amphetamine, chlorpromazine, nicotine, diazepam, and morphine (EPA 1991).

Drugs Affecting the Cardiovascular System. In response to carbon monoxide-induced tissue hypoxia, alterations in hemodynamics and responsive compensatory mechanisms (e.g., vasodilation and increased cardiovascular output) occur, including increased coronary blood flow, decreased myocardial O_2 consumption, increased heart rate, and alterations in blood flow to various vascular beds (e.g., cerebral, limb muscular). Thus, drugs used to treat patients with coronary artery disease (e.g., beta-blockers, calcium-channel blockers, nitrates) potentially may affect susceptibility to carbon monoxide. This is of particular concern, as patients with cardiovascular disease are more susceptible to carbon monoxide-induced cardiovascular toxicity than are healthy individuals. However, little data evaluating potential interactions with therapeutic agents used to treat cardiovascular disease are available (EPA 1991, 2000).

Air Pollution. Numerous epidemiological studies have examined associations between exposure to carbon monoxide and other air pollutants (e.g., NO_2, O_3, particular matter, SO_2). In general, these studies have found evidence for multiple air pollutant contributors to outcomes observed, including cardiovascular, respiratory, and mortality end points (see discussion of epidemiology in Section 3.2). The interactive aspects of these associations have not been fully explored or elucidated. However, evidence is provided from several studies of increased risks of adverse cardiovascular and respiratory outcomes in the context of ongoing cardiovascular disease (e.g., ischemic heart disease) and respiratory diseases (e.g., asthma). These studies suggest that it is both plausible and likely that interactions contribute to outcomes observed in populations that experience co-exposures to carbon monoxide, NO_2, O_3, particular matter, and SO_2.

Tobacco Smoke. In addition to exposures to carbon monoxide, tobacco smoking results in exposures to a variety of agents that act directly on the heart to increase cardiac O_2 demand (e.g., nicotine) (Benowitz 1997) and that contribute to respiratory and coronary vascular disease, both of which can render people more vulnerable to carbon monoxide toxicity (see Section 3.10, Populations that are Unusually Susceptible).

Noise. Studies conducted in animals provide evidence that acute exposure to carbon monoxide potentiates noise-induced hearing loss, including noise-induced elevation of compound action potential threshold (Chen and Fechter 1999; Mortazavi et al. 2010) and auditory threshold shifts (Fechter et al. 1988; Young et al. 1987). However, in these studies, exposure to carbon monoxide alone did not produce changes in auditory function. Additional details are provided in Section 3.2.4.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to carbon monoxide than will most persons exposed to the same level of carbon monoxide in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of carbon monoxide, or compromised function of organs affected by carbon monoxide. Populations who are at greater risk due to their unusually high exposure to carbon monoxide are discussed in Section 6.7, Populations with Potentially High Exposures.

Cardiovascular Disease. Studies of the cardiovascular effects of inhalation exposures to carbon monoxide conducted in controlled human clinical studies, epidemiology studies, and various animal models (monkeys, dogs, rats, and rabbits) provide convincing evidence for adverse cardiovascular effects in association with carbon monoxide exposures that result in blood COHb levels of ≥2.4%, with effects occurring at the lowest levels in subjects who have compromised cardiovascular function (e.g., coronary artery disease). Therefore, exposure to carbon monoxide appears to exacerbate underlying cardiovascular disease, and people with cardiovascular disease that renders them vulnerable to myocardial ischemia (e.g., coronary artery disease) represent a population that would be unusually susceptible to carbon monoxide. Epidemiological studies of exposure to ambient concentrations of carbon monoxide and cardiovascular outcomes also provide supporting evidence for higher vulnerability of people with pre-existing heart conditions, such as ischemic heart disease, people with a history of cardiac arrhythmia, and the elderly (Barnett et al. 2006; D'Ippoliti et al. 2003; Dockery et al. 2005; Hosseinpoor et al. 2005; Lanki et al. 2006; Lee et al. 2003b; Mann et al. 2002; Rich et al. 2005; Szyszkowicz 2007; von Klot et al. 2005).

Asthma and COPD. Several studies have examined possible associations between ambient air carbon monoxide concentrations and pulmonary function in subjects who had ongoing lung disease (e.g., asthma, chronic obstructive lung disease) and who might be more sensitive to agents that affect pulmonary function (Rabinovitch et al. 2004; Silkoff et al. 2005; Timonen et al. 2002), as well as asthma morbidity and exacerbation of asthma symptoms (Park et al. 2005a; Rabinovitch et al. 2004; Schildcrout et al. 2006; Silkoff et al. 2005; Slaughter et al. 2003; von Klot et al. 2002; Yu et al. 2000). Results of these studies have been mixed; however, collectively, these studies provide evidence for higher vulnerability of people who have ongoing respiratory disease, including asthma and COPD. This subpopulation may also include a subpopulation of former tobacco smokers (Silkoff et al. 2005). As noted in Section 3.7,

Children's Susceptibility, the fetus may be particularly vulnerable to exposures that occur during pregnancy.

Anemia. Conditions that produce anemia (e.g., hemolysis, hemorrhage, reduced hematopoiesis, or iron, vitamin B-6, folate, and/or vitamin B-12 deficiency) decrease the oxygen carrying capacity of blood. Hemolytic anemia increases heme metabolism and endogenous carbon monoxide production. These factors would be expected to render individuals more vulnerable to hypoxic effects of carbon monoxide.

Environmental and Behavioral Factors. In addition to ongoing diseases, other environmental and/or behavior factors may increase vulnerability to carbon monoxide toxicity. In general, factors that increase alveolar ventilation and cardiac output, while maintaining alveolar ventilation perfusion matching (i.e., proportional increases in alveolar ventilation rate and cardiac output), tend to increase absorption of inhaled carbon monoxide. Factors that increase carbon monoxide absorption include moderate exercise, supine position, age (increased in infancy and childhood and declines in adults with age), altitude, increasing blood Hb concentration, and decreasing partial pressure of O_2 in inhaled air or blood.

These factors could contribute to higher body burdens of carbon monoxide and, therefore, higher vulnerability to carbon monoxide at higher altitudes than at lower altitudes (McGrath et al. 1993), in particular for people who have not physiologically adapted to higher altitudes (Horvath et al. 1988; Hsia 2002). Exercise increases oxygen demand, absorption of carbon monoxide, and transfer of carbon monoxide from blood to muscle, and decreases elimination of carbon monoxide (Joumard et al. 1991; Richardson et al. 2002; Werner and Lindahl 1980); these factors may contribute to higher vulnerability during strenuous exercise.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section describes clinical practice and research concerning methods for reducing toxic effects of exposure to carbon monoxide. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to carbon monoxide. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to carbon monoxide:

Dart RC, ed. 2004. Medical toxicology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1208.

Lavonas EJ. 2007. Carbon monoxide poisoning. In: Haddad and Winchester's clinical management of poisoning and drug overdose. 4th ed. Philadelphia, PA: Saunders, 1297-1307

Tomaszewski C. 2006. Carbon monoxide. In: Goldfrank's toxicologic emergencies. New York, NY: McGraw-Hill, 1689-1704.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to carbon monoxide occurs by the inhalation route. General recommendations for reducing absorption of carbon monoxide following acute high-level inhalation exposure have included immediate removal of the exposed individual from the contaminated area and administering 100% oxygen through a face mask that does not allow rebreathing of expired air or by endotracheal tube for a minimum of 4 hours. For patients with life-threatening carbon monoxide exposure, hyperbaric oxygen therapy has also been suggested, although this remains a controversial method for treatment (Buckley et al. 2011; Dart 2004; Lavonas 2007; Tomaszewski 2002; Weaver et al. 2000, 2009; Wolf et al. 2008). Hyperbaric oxygen treatment is optimal within 6 hours of exposure, as patients treated after 6 hours have displayed a higher percent of delayed sequelae (30 vs. 19%) and mortality (30 vs. 14%) compared with patients treated within 6 hours of carbon monoxide exposure (Tomaszewski 2006).

Studies conducted in animal models have provided evidence for a potential influence of isocapnia or hypercapnia (i.e., normal or elevated CO_2 levels) in the effect of O_2 therapy in promoting the reduction in carbon monoxide body burden. Studies utilizing laboratory animals (dogs and sheep) exposed to carbon monoxide have demonstrated that the carbon monoxide washout time can be significantly reduced if the subjects receive a mixture of oxygen and carbon dioxide gas designed to maintain normal PCO_2 values (Fisher et al. 1999; Kreck et al. 2001). This outcome has been replicated in experimental trials using volunteers exposed to carbon monoxide concentrations producing COHb levels of 10–12%. As compared to the subjects treated with hyperoxia alone, those treated with hyperoxia and carbon dioxide who maintained isocapnia showed accelerated clearance of carbon monoxide (Rucker et al. 2002; Takeuchi et al. 2000). These studies identify a potential means to enhance the treatment of acute carbon monoxide poisoning.

3.11.2 Reducing Body Burden

Absorbed carbon monoxide binds to, and displaces oxygen (O_2) from, blood Hb and other heme proteins (e.g., muscle myoglobin). Nearly all of carbon monoxide in the body exists as complexes with Hb or other heme proteins. Binding to heme proteins limits diffusion of carbon monoxide from tissues to blood

and elimination of carbon monoxide from blood to exhaled air. At ambient oxygen pressures of approximately 0.2 atm, elimination of carbon monoxide occurs with a half-time of approximately 100–300 minutes (Bruce and Bruce 2006; Peterson and Stewart 1970). However, the elimination rate can be increased substantially by administering 100% oxygen (Tomaszewski 2006; Weaver et al. 2000). As noted above, the general recommendation for reducing the body burden of carbon monoxide is administration of 100% oxygen through a face mask that does not allow rebreathing of expired air, at ambient pressure, and/or hyperbaric oxygen therapy. The longer time period required for the elimination of carbon monoxide in the fetus (Hill et al. 1977; Longo 1977) has prompted a concern about the premature cessation of oxygen therapy to a pregnant woman based upon her COHb level.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Binding of carbon monoxide to Hb impairs transfer of oxygen to tissues and can produce tissue hypoxia. Tissues that have a high oxygen utilization rate, including brain and heart, are particularly vulnerable to hypoxia. Carbon monoxide-induced hypoxia is treated by administering 100% oxygen, which increases the dissolved concentration of oxygen in blood, facilitates displacement of carbon monoxide from Hb, and increases the rate of elimination of carbon monoxide from the body. Hyperbaric oxygen therapy may further reduce the risk of brain and heart injury from hypoxia. Intravenous fluids and inotropic agents may be administered to alleviate hypotension and myocardial depression (Lavonas 2007; Tomaszewski 2006).

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of carbon monoxide is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of carbon monoxide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Carbon Monoxide

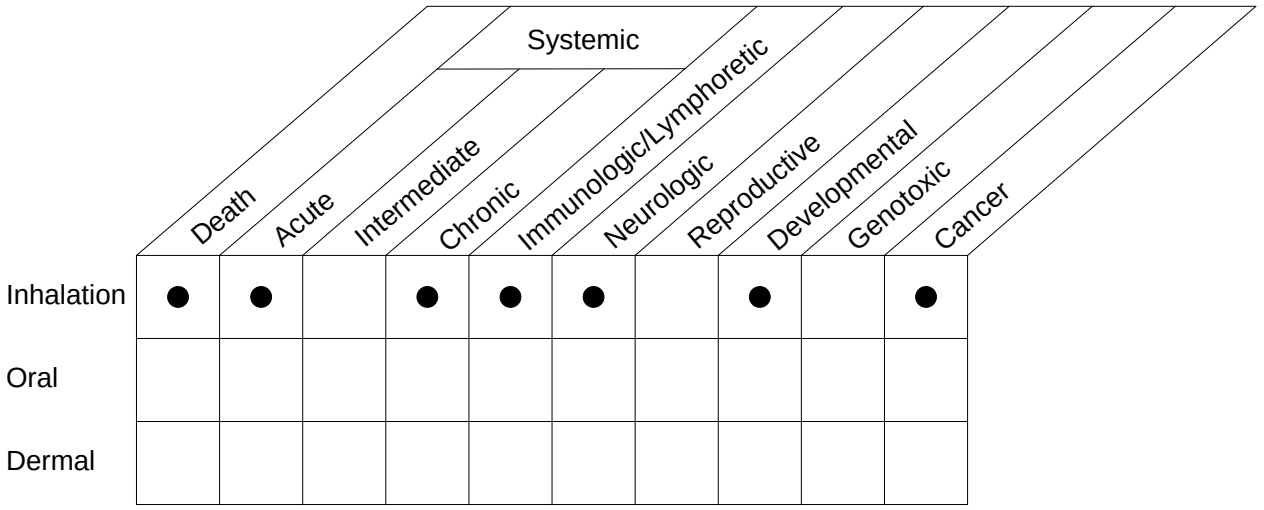
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to carbon monoxide are summarized in Figure 3-12. The purpose of this figure is to illustrate the existing information concerning the health effects of carbon monoxide. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Human clinical studies of acute exposures have investigated cardiovascular, respiratory, and neurobehavioral end points. Human epidemiology studies have examined possible associations between ambient air carbon monoxide concentrations and various health end points, including mortality, cardiovascular, respiratory, blood biomarkers of coagulation and inflammation, and developmental (pre-term birth, birth weight, congenital anomalies, neonatal and infant mortality). Studies conducted in animals have included acute, intermediate, and chronic exposures that have largely focused on cardiovascular, respiratory, and reproductive (e.g., fetal mortality) end points. Bioassays of carcinogenicity of carbon monoxide have not been reported. Carbon monoxide has been assessed for genotoxicity in an *in vivo* mouse model of micronuclei formation and sister chromatid exchange.

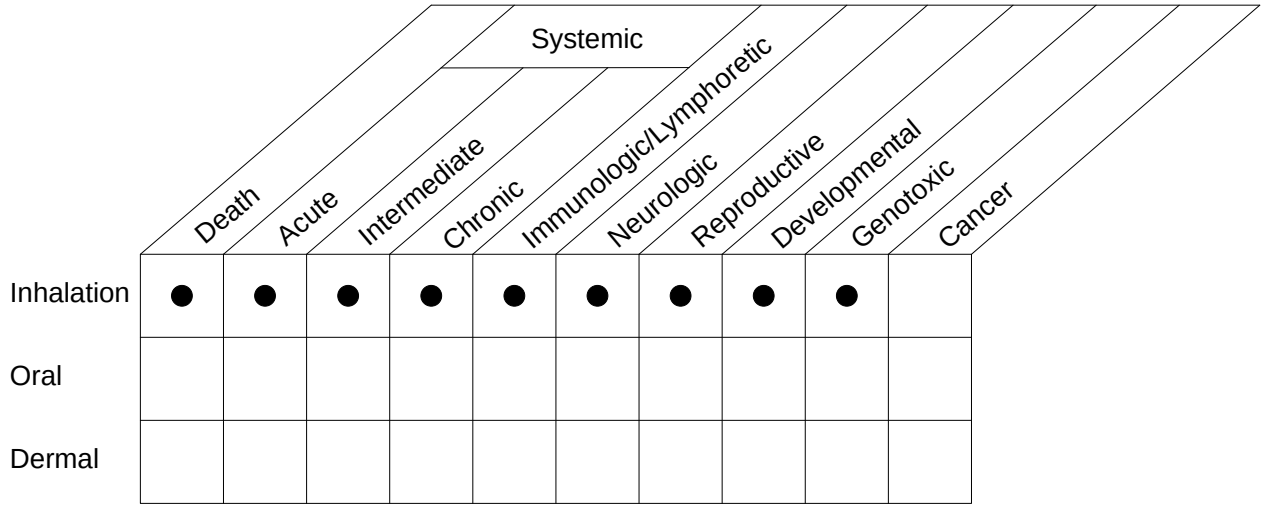
3.12.2 Identification of Data Needs

Acute-Duration Exposure. Most information on effects of acute exposures to carbon monoxide derive from clinical case studies of carbon monoxide poisoning, in which blood COHb levels were >20%. Although these studies provide information on effects resulting from severe carbon monoxide-induced toxicity, they do not provide information on low dose-response relationships for carbon monoxide. Experimental clinical studies providing low dose-response information have focused on evaluating organ systems that are expected to be vulnerable to or contribute to hypoxia (e.g., brain, heart, respiratory tract). Effects of acute exposures to carbon monoxide on other organ systems have been studied far less thoroughly. Studies of low-dose carbon monoxide exposure in humans or animals have not identified NOAELs for sensitive organ systems and have not provided data that would enable low-dose response

Figure 3-12. Existing Information on Health Effects of Carbon Monoxide



Human



Animal

● Existing Studies

modeling (e.g., benchmark dose). Such studies would be beneficial for analyses in support of deriving MRLs.

Experimental clinical studies have examined cardiovascular effects in humans, including a major vulnerable subpopulation, people with ongoing heart disease; however, these studies have not identified NOAELs in cardiovascular disease patients (Adams et al. 1988; Allred et al. 1989, 1991; Anderson et al. 1973; Kleinman et al. 1989, 1998; Leaf and Kleinman 1996b). Studies investigating the effects of acute-duration carbon monoxide exposure on hemodynamics have been conducted in several animal species, including monkeys, dogs, rats, and rabbits, under exposure conditions producing blood COHb levels ranging from 6.2 to 70% (EPA 1991, 2000). These studies have shown that brief exposure (from a few minutes to approximately 3 hours) to carbon monoxide at concentrations of 80–20,000 ppm produces alterations in hemodynamics that are consistent with COHb-induced hypoxia and responsive compensatory mechanisms (e.g., vasodilation and increased cardiovascular output), including increased coronary blood flow, decreased myocardial O_2 consumption, increased heart rate, and alterations in blood flow to various vascular beds (e.g., cerebral, limb muscular).

A few clinical experimental studies have evaluated adverse respiratory effects of carbon monoxide exposure in relatively small numbers of healthy subjects (Chevalier et al. 1966; Fisher et al. 1969; Koike et al. 1991; Ren et al. 2001; Vesely et al. 2004). Results of these studies indicate that brief exposure to relatively higher levels (e.g., ≥500 ppm) of carbon monoxide may decrease ventilatory performance. No studies were identified that examined effects of carbon monoxide on respiratory function in patients with underlying respiratory diseases, who would be expected to have a higher sensitivity to hypoxic effects of carbon monoxide. Studies of dose-response relationships of respiratory function at low levels of carbon monoxide exposure (e.g., COHb <20%) in patients with respiratory disease (e.g., asthma) would be beneficial for quantifying vulnerability of this subpopulation to carbon monoxide toxicity.

Intermediate-Duration Exposure. Controlled experimental studies in humans of effects of intermediate-duration exposures to carbon monoxide were not identified. Intermediate-duration studies have examined cardiovascular and respiratory effects of exposure to carbon monoxide in various animal models, including monkeys, dogs, and rodents (EPA 2000). The observation of cardiomegaly in rats exposed chronically to carbon monoxide (Sørhaug et al. 2006) suggests that prolonged exposure to carbon monoxide may produce effects on the heart that might not be observed with acute exposures. Additional intermediate-duration exposure studies in animals that provide dose-response relationships for

cardiovascular effects and other end points (e.g., respiratory, neurological) would be beneficial for analyses in support of deriving MRLs.

Chronic-Duration Exposure and Cancer. Epidemiological studies have examined health outcomes in the context of chronic exposures or acute variations in exposure concentrations that occur during chronic exposures. Outcomes that have been assessed include mortality, including cancer mortality, cardiovascular effects, respiratory effects, effects on blood biomarkers of coagulation and inflammation, and developmental effects (pre-term birth, birth weight, congenital anomalies, neonatal and infant mortality). A chronic study conducted in rats found cardiomegaly, which may have represented long-term adaptive changes to carbon monoxide-induced hypoxia (Sørhaug et al. 2006). This finding suggests that prolonged exposure to carbon monoxide may produce effects on the heart that might not be evident from acute- or intermediate-duration studies. Additional chronic-duration exposure studies in animals would that provide dose-response relationships for cardiovascular effects and other end points (e.g., respiratory, neurological) would be beneficial for analyses in support of deriving MRLs.

Carbon monoxide has not been assessed for carcinogenicity using animal models. Cancer bioassays in animals would provide a more confident basis for establishing whether or not carbon monoxide has carcinogenic potential in humans.

Genotoxicity. In a bacterial replication assay with *Escherichia coli*, exposure to carbon monoxide inhibited DNA synthesis (Cairns and Denhardt 1968). Gestational exposure of mice to carbon monoxide increased micronuclei formation and sister chromatid exchange in dams (bone marrow) and fetuses (blood) (Kwak et al. 1986). Additional studies conducted on the mechanisms of genotoxicity in mammalian cells would provide a more confident basis for establishing whether or not carbon monoxide has carcinogenic potential in humans.

Reproductive Toxicity. Pregnancy outcomes, including fetal death in humans, have been reported in cases of maternal carbon monoxide poisoning during pregnancy (Brown et al. 1992; Caravati et al. 1988; Cramer 1982; Elkharrat et al. 1991; Farrow et al. 1990; Greingor et al. 2001; Hollander et al. 1987; Margulies 1986; Norman and Halton 1990; Silverman and Montano 1997). Epidemiological studies have examined possible relationships between exposures to ambient air concentrations of carbon monoxide and fetal mortality (see Table 3-8). Few studies of reproductive effects in animals were identified, and these have been limited to assessments of effects of maternal exposure during pregnancy on fetal mortality (Astrup et al. 1972; Fechter and Annau 1977; Penney et al. 1983; Stupfel and Bouley 1970). The

available data do not allow a confident determination of the relative sensitivity of reproductive systems to carbon monoxide. Greater confidence would be achieved from studies that examine more comprehensive end points of reproductive toxicity in females and males, in association with exposures prior to mating and pregnancy and during pregnancy.

Developmental Toxicity. Epidemiological studies have examined developmental outcomes in the context of chronic exposures or acute variations in exposure concentrations that occur during chronic exposures (see Table 3-8). Outcomes that have been assessed include pre-term birth, birth weight, congenital anomalies, neonatal, infant mortality, and neurodevelopment. Studies conducted in animals provide evidence of adverse developmental effects of gestational and early postnatal carbon monoxide exposure, including decreased fetal weight, adverse central nervous system development, altered peripheral nervous system development, cardiac effects, altered sexual behavior, immunological effects, and hematological effects. In addition, some studies showed that developmental effects persisted beyond the postnatal period (see Table 3-9). Two studies found functional impairments in the auditory system of rats in association with exposures to ≥12 ppm carbon monoxide during the neonatal periods or during gestation (Stockard-Sullivan et al. 2003; Webber et al. 2003). These values are the lowest LOAELs for external exposure that have been reported and, as a result, have a substantial impact on analyses conducted to derive MRLs. Additional studies to establish greater confidence in the dose-response relationship for neurodevelopmental effects on the auditory system would be beneficial for establishing MRLs for carbon monoxide based on this end point. Studies conducted to understand the mechanism for this effect would provide additional information about the relevance of these effects to humans exposed at similar levels.

Immunotoxicity. Epidemiological studies have examined effects on blood biomarkers of inflammation. Biomarkers examined have included been inflammation markers (CRP, SAA, and WBC) and cell adhesion markers (E-selectin, vWF, and ICAM-1) (Baccarelli et al. 2007; Liao et al. 2005; Pekkanen et al. 2000; Rückerl et al. 2006, 2007; Steinvil et al. 2008). A study conducted in guinea pigs examined effects of carbon monoxide exposure on plaque forming cells in spleen (Snella and Rylander 1979). Effects of gestational exposure on the developing immune system have been studied in rats (Giustino et al. 1993, 1994). Studies conducted in cell culture and *in vivo* models of sepsis have examined effects of endogenous and exogenous carbon monoxide on inflammatory responses and cytokine and signaling pathways involved in inflammation (Ryter et al. 2006). These studies suggest a potential for carbon monoxide to exert effects on the immune system. Additional studies to establish

modes of action and dose-response relationships would be beneficial for determining the sensitivity of the immune system to carbon monoxide, relative to other targets of toxicity, and for establishing MRLs.

Neurotoxicity. Experimental clinical studies (Benignus et al. 1994), clinical case studies (Chambers et al. 2008; Dolan 1985; Ernst and Zibrak 1998; Hopkins et al. 2006; Kao and Nañagas 2006; Lo et al. 2007; Parkinson et al. 2002; Raub and Benignus 2002), and studies conducted in animals (Benignus et al. 1994; Chambers et al. 2008; Chen and Fechter 1999; Dolan 1985; Ernst and Zibrak 1998; Fechter et al. 1988; Hopkins et al. 2006; Kao and Nañagas 2006; Lo et al. 2007; Parkinson et al. 2002; Raub and Benignus 2002; Young et al. 1987) have examined effects of acute carbon monoxide exposures on behavior cognitive function. Although these studies provided strong evidence for impairments in association with exposures that result in blood COHb levels >20%, dose-response relationships for lower levels remain controversial (Benignus 1994; Benignus et al. 1990; Raub and Benignus 2002). Further research on dose-response relationships of neurobehavioral and neurosensory effects at low levels of carbon monoxide exposure (e.g., COHb<20%) utilizing double-blind designs would be beneficial for analyses in support of deriving MRLs.

Epidemiological and Human Dosimetry Studies. Epidemiological studies have examined health outcomes in the context of chronic exposures or acute variations in exposure concentrations that occur during chronic exposures (see Tables 3-3, 3-6, 3-7, and 3-8). Outcomes that have been assessed include mortality, including cancer mortality, cardiovascular effects, respiratory effects, blood biomarkers of coagulation and inflammation, and developmental effects (pre-term birth, birth weight, congenital anomalies, neonatal and infant mortality). Human dosimetry studies have examined relationships between carbon monoxide exposure levels and durations and blood COHb levels in resting subjects, during exercise, and at various altitudes (see Tables 3-4 and 3-5). Studies of elimination kinetics of carbon monoxide in humans have explored effects of exercise, age, gender, and oxygen therapy on elimination half-time (Bruce and Bruce 2006; Joumard et al. 1991; Landaw 1973; Levasseur et al. 1996; Peterson and Stewart 1970; Shimazu et al. 2000; Weaver et al. 2000).

Biomarkers of Exposure and Effect.

Exposure. Measurement of blood COHb is the principal biomarker for identifying exposure to carbon monoxide. Several pharmacokinetics models have been developed that can be used to predict blood COHb levels that would correspond to a given exposure concentration and duration in a typical adult and in the fetus resulting from maternal exposures. These models can be used to reconstruct possible carbon

monoxide exposure scenarios (e.g., concentrations, duration, and gap between measurement of COHb and cessation of exposure) that could result in a given measured COHb level.

Effect. Although blood COHb reflects current carbon monoxide body burden, measurement of blood COHb has not been shown to be a reliable predictor of severity of acute toxicity (Hampson and Hauff 2008). Therefore, diagnoses and characterization of toxic effects of carbon monoxide relies on both the measurement of blood COHb and the assessment of signs and symptoms of carbon monoxide toxicity. Studies conducted to identify biomarkers of non-hypoxic mechanisms of carbon monoxide (those unrelated to blood COHb levels) would be beneficial for internal dosimetry in epidemiological and clinical experimental studies, for development of PBPK/PD models of non-hypoxic effects of carbon monoxide, and for improving diagnosis of carbon monoxide poisoning.

Absorption, Distribution, Metabolism, and Excretion. Pharmacokinetics of carbon monoxide has been extensively studied in humans and in animal models, including nonhuman primates (see Section 3.4). Studies conducted in humans have provided information on absorption, metabolism, distribution, and elimination kinetics, as well as physiological factors (e.g., age, gender) and environmental factors (e.g., altitude, exercise) that affect carbon monoxide kinetics. These studies have provided the bases for pharmacokinetic models that simulate carbon monoxide absorption and elimination kinetics and blood COHb and muscle COMb levels in humans (see Section 3.4.5). Several studies have provided estimates of rates of whole-body endogenous production of carbon monoxide in adult males and females during and following pregnancy (Coburn et al. 1963; Delivoria-Papadopoulos et al. 1974; Longo 1977; Mercke and Lundh 1976). However, measurement of local tissue production rates would also be valuable for studying mechanisms by which endogenously produced carbon monoxide modulates cellular metabolism and cell signaling pathways, as well as the relative contributions of exogenous carbon monoxide and endogenously produced carbon monoxide contribute to these processes.

Comparative Toxicokinetics. Major physiological and biochemical determinants of blood and skeletal muscle carbon monoxide kinetics that would be expected to contribute to interspecies differences in carbon monoxide toxicokinetics have been identified. This information provides a basis for extrapolating pharmacokinetics models across mammalian species, for which physiological (e.g., ventilation rates, blood Hb levels) and chemical-specific parameters are known (e.g., binding affinities and capacities of Hb and myoglobin, long carbon monoxide diffusion capacity). Models developed to simulate carbon monoxide kinetics in humans have been adapted for applications to animal models (e.g., rats; Benignus and Annau 1994) and to simulate maternal-fetal transfer of carbon monoxide during

pregnancy in sheep (Longo and Hill 1977). Adaptation of these models to a wider range of species would be facilitated by studies that provide estimates of model parameters in these species (e.g., Haldane coefficient, binding coefficients of Hb and Mb, and the lung carbon monoxide diffusing capacity).

Methods for Reducing Toxic Effects. Efficacies of normobaric and hyperbaric oxygen therapy for hastening the elimination of carbon monoxide from the body and for treating carbon monoxide-induced hypoxia have been studied. Although hyperbaric oxygen therapy is considered to be a therapeutic option, its efficacy, over normobaric therapy, remains controversial (Wolf et al. 2008). Further research regarding benefits and limitations of hyperbaric oxygen therapy would improve the clinical management of treatment of carbon monoxide poisoning.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

Mechanisms of Toxicity. Although hypoxic mechanisms of action of carbon monoxide are well established (i.e., those related to formation of COHb), a better understanding is needed of non-hypoxic mechanisms, their contribution to observed adverse health effects of carbon monoxide, and related dose-response relationships.

3.12.3 Ongoing Studies

Ongoing studies pertinent to information of health effects and/or mechanisms of action of carbon monoxide are listed in Table 3-18.

Table 3-18. Ongoing Studies on the Health Effects of Carbon Monoxide

Investigator	Affiliation	Research description	Sponsor
Abraham NG	New York Medical College	Heme oxygenase regulation of eicosanoid biosynthesis	National Institute of Diabetes and Digestive and Kidney Diseases
Bauer AJ	University of Pittsburgh at Pittsburgh Office of Research	Protective mechanisms of carbon monoxide in intestinal inflammation	National Institute of Diabetes and Digestive and Kidney Diseases
Bauer PM	University of Pittsburgh at Pittsburgh Office of Research	Role of caveolin-1 and eNOS in mediating the therapeutic effects of carbon monoxide in polycyclic aromatic hydrocarbons	National Heart, Lung, and Blood Institute
Choi AM	Brigham and Women's Hospital Research Administration	Role of heme oxygenase in hyperoxic lung injury	National Heart, Lung, and Blood Institute
Durante W	University of Missouri-Columbia	Carbon monoxide and vascular cell function	National Heart, Lung, and Blood Institute
Fallon MB	University of Texas	Mediators of pulmonary vasodilatation in liver disease	National Institute of Diabetes and Digestive and Kidney Diseases
Fowler AA	Virginia Commonwealth University	Role of hypotoxia inducible factor-1 in inflammation	National Heart, Lung, and Blood Institute
Kibbe MR	Northwestern University	Nitric oxide eluting therapies for vascular surgery	National Heart, Lung, and Blood Institute
Lefer DJ	Yeshiva University	Mechanism of myocardial reperfusion injury in diabetes	National Heart, Lung, and Blood Institute
Leffler CW	University of Tennessee Health Science Center	Carbon monoxide in newborn cerebral circulation	National Heart, Lung, and Blood Institute
Leffler CQ	University of Tennessee Health Science Center	Control of neonatal circulation	National Heart, Lung, and Blood Institute
Lindahl PA	Texas A&M University System	Bioinorganic chemistry of carbon monoxide dehydrogenase	National Institute of General Medical Sciences
Machado RF	Clinical Center	Effects of inhaled carbon monoxide on human lung inflammation	Not applicable
Mapes JP	Rules-Based Medicine, Inc.	Biomarker profiles for carbon monoxide poisoning	National Institute of Environmental Health Sciences
McCurry KR	University of Pittsburgh at Pittsburgh Office of Research	Cytoprotective effect of carbon monoxide in lung ischemia/ reperfusion	National Heart, Lung, and Blood Institute
Morse ED	University of Pittsburgh at Pittsburgh Office of Research	Inhibitor of differentiation-1 mediates antifibrotic effects of carbon monoxide	National Heart, Lung, and Blood Institute
Murase N	University of Pittsburgh at Pittsburgh Office of Research	Protective role of carbon monoxide in hepatic I/R injury	National Institute of Diabetes and Digestive and Kidney Diseases

Table 3-18. Ongoing Studies on the Health Effects of Carbon Monoxide

Investigator	Affiliation	Research description	Sponsor
O'Neill MS	University of Michigan at Ann Arbor	Air pollution, inflammation, and preterm birth: a mechanistic study in Mexico City	National Institute of Environmental Health Sciences
Parfenova H	University of Tennessee Health Science Center	Heme oxygenase and cerebral vascular injury	National Institute of Neurological Disorders and Stroke
Raman CS	University of Texas Health Science Center, Houston	Structural biology of gaseous messenger signaling	National Institute of General Medical Sciences
Roberts GP	University of Wisconsin Madison	Sensing mechanisms for carbon monoxide and other small molecules	National Institute of General Medical Sciences
Tolbert PE	Emory University	Air pollution and birth defects in Atlanta, 1968–2002	National Institute of Environmental Health Sciences
Tulis DA	North Carolina Central University	NO-independent cGMP regulation of vascular remodeling	National Heart, Lung, and Blood Institute
Vitali SH	Children's Hospital Boston	Hypoxic inflammation, pulmonary hypertension, and HO-1	National Heart, Lung, and Blood Institute
Williams MA	Swedish Medical Center, First Hill	Ambient air pollution, preeclampsia, and preterm delivery	National Institute of Environmental Health Sciences
Xuan U	University of Louisville	Delayed cardioprotection induced by NO and carbon monoxide	National Heart, Lung, and Blood Institute

Source: FEDRIP 2009

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

The chemical identity of carbon monoxide is shown in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Carbon monoxide is a highly poisonous, odorless, colorless, and tasteless gas. It is very flammable in air over a wide range of concentrations (George 2001) and burns in air with a bright blue flame (O'Neil et al. 2006). It becomes a liquid at 81.62 K (-191.53 °C) and is insoluble in water above 70 °C (George 2001). The physical and chemical properties of carbon monoxide are shown in Table 4-2.

Table 4-1. Chemical Identity of Carbon Monoxide

Characteristic	Carbon monoxide[a]
Synonym(s)	Carbon oxide, flue gas, monoxide
Registered trade name(s)	
Chemical formula	CO[b]
Chemical structure	:C≡≡≡O:
Identification numbers:	
CAS registry	630-08-0[b]
NIOSH RTECS	FG350000
EPA hazardous waste	No data
OHM/TADS	No data
DOT/UN/NA/IMDG shipping	1016[c]; 9202[d,e]
HSDB	903
NCI	No data

[a]All information obtained from HSDB 2009, except where noted.
[b]O'Neil 2006
[c]Compressed
[d]NIOSH 2005
[e]Cryogenic liquid

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Carbon Monoxide

Property	Carbon monoxide[a]
Molecular weight	28.01
Color	Colorless
Physical state	Gas
Melting point	-205 °C
Boiling point	-191.5 °C
Density at 25 °C	1.145 g/L at 25 °C and 1 atm[3b]
Odor	Odorless
Odor threshold:	
Water	No data
Air	No data
Solubility:	
Water at 20 °C	2.3 mL/100 mL
Organic solvents	Appreciably soluble in ethyl acetate, chloroform, and acetic acid; freely absorbed by a concentrated solution of cuprous chloride in hydrochloric acid or ammonium hydroxide; solubility in methanol and ethanol about 7 times as great as in water; soluble in benzene
Partition coefficients:	
Log K_{ow}	Not applicable
Log K_{oc}	Not applicable
Henry's law constant at 25 °C	57,978.5 atm/mol fraction (~1.04 atm-m^3/mole)[c]
Autoignition temperature	605 °C[d]
Flashpoint	Flammable gas[d]
Flammability limits	Upper limit 74.2%; lower limit 12.5%[e]
Conversion factors	1 ppm=1.16 mg/m^3 at 20 °C and 1 atm
Explosive limits	No data

[a]All information obtained from HSDB 2009, except where noted.
[c]Yaws et al. 1999
[b]Lide 2008
[d]IPCS 2008
[e]George 2001

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Carbon monoxide is produced by the incomplete combustion of carbon in liquid, solid, and gaseous fuels (George 2001). Commercially, it is produced on an industrial scale by the partial oxidation of hydrocarbon gases from natural gas or by the gasification of coal and coke. Laboratory-scale production of carbon monoxide is accomplished by heating calcium carbonate with zinc dust (O'Neil et al. 2006). Carbon monoxide is also obtained from the dehydration of formic acid (Lewis 2007). The majority of carbon monoxide produced is used immediately downstream and at the plant site for chemical synthesis or steel manufacturing; consequently, quantitative production volumes are not available (George 2001).

Carbon monoxide is a co-product along with hydrogen in syn gas (synthetic gas) production, gases are then separated and purified by pressure swing adsorption and/or cryogenic distillation.

Carbon monoxide is a major air pollutant (Lewis 2007). It is a byproduct of highway vehicle exhaust, of industrial processes and fuel combustion in boilers and incinerators, and of household appliances fueled with gas, oil, kerosene, or wood, and fires. The largest contribution comes from highway motor vehicles. Carbon monoxide exceeds all other atmospheric pollutants, combined with the exception of CO_2 (George 2001).

The major facility within the United States that manufactures or processes carbon monoxide (produced in commercial quantities exceeding 5,000 pounds or $10,000 in value annually) is Air Liquide America L.P. in Freeport, Texas (SRI 2008).

5.2 IMPORT/EXPORT

No data were located on the import or export of carbon monoxide.

5.3 USE

Carbon monoxide is used by the chemical industry for the synthesis of many compounds such as acetic anhydride, polycarbonates, acetic acid, and polyketones (George 2001). It finds application as a reducing agent in metallurgical operations, specifically the Mond process for the recovery of nickel, in the manufacture of metal carbonyls, and in organic synthesis, especially for the Fischer-Tropsch process for

petroleum-related products and in the oxo reaction (O'Neil et al. 2006). Carbon monoxide is also used in the manufacture of zinc white pigments (Lewis 2007).

5.4. DISPOSAL

EPA considers a waste to be hazardous if it exhibits any of the following characteristics: ignitability, corrosivity, reactivity, or toxicity as defined in 40 CFR 261.21–261.24. Under the Resource Conservation and Recovery Act (RCRA) (40 USC 6901 et seq.), EPA has specifically listed many chemical wastes as hazardous. Although carbon monoxide is not specifically listed as a hazardous waste under RCRA, EPA requires employers to treat waste as hazardous if it exhibits any of the characteristics discussed above (OSHA 2000).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Carbon monoxide is a colorless, odorless, and tasteless gas that is ubiquitous in the atmosphere (George 2001). It arises from both natural and anthropogenic (human-made) sources. It is produced as a primary pollutant during the incomplete combustion of fossil fuels and biomass, including internal combustion engines, wildfires, and controlled burns. Carbon monoxide is also produced indirectly from the photochemical oxidation of methane and other VOCs in the atmosphere. Vegetation can emit carbon monoxide into the atmosphere as a metabolic byproduct. Photooxidation of organic matter in surface waters (lakes, streams, rivers, oceans) and surface soils also results in the formation of carbon monoxide. Volcanic activity is another natural source of carbon monoxide in the atmosphere. Carbon monoxide is also produced endogenously in humans during the normal catabolism of hemoglobin (Hb). The amount of anthropogenic carbon monoxide emissions versus that from natural sources is difficult to quantify since both sources of carbon monoxide vary over time. The EPA estimated that 84% of all carbon monoxide emissions in 2005 arose as a result of human activity, with biogenic emissions accounting for 16% of the total emissions (EPA 2012). However, an analysis of the carbon monoxide budget over North America concluded that during the summer months, when natural sources of carbon monoxide precursors such as biogenic VOCs and forest fires are high, natural sources of carbon monoxide in the atmosphere are far greater than anthropogenic contributions (Miller et al. 2008). Data from the EPA National Emissions Inventory (NEI) suggest that as much as 75% of the total point and non-point emissions of carbon monoxide are historically associated with on-road automobile use (EPA 2010).

The background levels of carbon monoxide have changed significantly in the past several decades. Concentrations have decreased appreciably due to reduced emissions from automobiles as a consequence of advancements in automotive design. The development of catalytic converters for passenger vehicles, beginning in the 1970s, resulted in a substantial decrease in carbon monoxide emissions, despite large increases in miles traveled (George 2001). In the early 1980s, automakers equipped vehicles with more sophisticated catalytic converters and added on-board computers and O_2 sensors in order to help optimize the efficiency of the converter. The end result is that modern passenger automobiles emit about 90% less carbon monoxide over their lifetimes as compared to vehicles designed in previous decades (George 2001).

The annual average outdoor carbon monoxide concentrations are roughly 0.12 parts per million by volume (ppmv) in the Northern Hemisphere and about 0.04 ppmv in the Southern Hemisphere (EPA

2000). These levels are variable throughout the course of the year, with seasonal maximum levels occurring during late winter in both hemispheres when inversion conditions (in which air pollutants are trapped near the ground beneath a layer of warm air) are more frequent. Minimum levels are generally observed during late summer. Carbon monoxide concentrations are reported to range from a minimum of about 0.03 ppmv during summer in the Southern Hemisphere to about 0.20 ppmv at high latitudes in the Northern Hemisphere during winter (EPA 2000). Urban locations with high automobile usage or a high volume of stationary emission sources, such as refineries or power plants, typically have greater atmospheric levels of carbon monoxide as compared to rural or remote sites. In metropolitan areas in the United States, as much as 95% of all carbon monoxide emissions result from on-road vehicle exhaust (EPA 2008). The majority of these on-road emissions are derived from gasoline-powered vehicles, since diesel vehicles emit less carbon monoxide. There is also a diurnal pattern of atmospheric carbon monoxide concentrations in urban areas, with the highest levels occurring during hours with heavy vehicular usage (rush hours) and the lowest levels occurring at times that correlate with lower commuting activity (Campbell et al. 1995; EPA 2000). Maximum carbon monoxide levels frequently exceed 5 ppmv at these locations during the high commute hours.

Carbon monoxide levels in indoor air are greatly dependent upon the presence of combustion-based appliances and whether occupants smoke tobacco products. Unvented kerosene and gas space heaters; leaking chimneys and furnaces; back-drafting from furnaces, gas water heaters, wood stoves, and fireplaces; gas stoves, generators, and other gasoline-powered equipment; automobile exhaust from attached garages; and tobacco smoke all contribute to indoor air levels of carbon monoxide (EPA 2009a). Average levels in homes without gas stoves vary from 0.5 to 5 ppmv. Levels near properly adjusted gas stoves are often 5–15 ppmv, and those near poorly adjusted stoves may be ≥30 ppmv (EPA 2009a). Dangerous levels of carbon monoxide can occur inside boat cabins, partially enclosed cockpits, and beneath swim platforms or other enclosed areas (USCG 2008). Most new boats are equipped with carbon monoxide monitors; however, the U.S. Coast Guard advises owners of boats built prior to 1998 to have the monitors inspected or replaced (USCG 2008).

The primary degradation pathway of carbon monoxide in the environment occurs through its reaction with photochemically-produced hydroxyl radicals. (It should be noted that the production of hydroxyl radicals requires ultraviolet [UV] radiation that does not penetrate windows and therefore, photooxidation is likely negligible indoors.) In addition, soils and coastal waters may also act as a sink for carbon monoxide, since various forms of microorganisms are capable of utilizing carbon monoxide as an energy source (Tolli et al. 2006).

Exposure of the general population to carbon monoxide occurs through inhalation. Populations living in urban areas with heavy vehicular traffic or stationary sources such as petroleum refineries, gas and coal burning power plants, petrochemical plants, and coke oven plants are more likely to be exposed to higher levels of carbon monoxide from ambient outdoor air. Employees in these refineries and plants and workers who are subject to high levels of vehicular exhaust (such as taxi cab drivers and toll booth workers) may be occupationally exposed to higher levels of carbon monoxide. Members of the public who smoke or work in smoke-filled environments such as restaurants, bars, and casinos where smoking is allowed are exposed to higher levels of carbon monoxide than members of the population who do not smoke and are not frequently exposed to second-hand tobacco smoke.

6.2 RELEASES TO THE ENVIRONMENT

6.2.1 Air

Title I of the Clean Air Act of 1970 establishes carbon monoxide as one of six criteria pollutants and sets national air quality standards for carbon monoxide and the other criteria pollutants (EPA 2000). Two databases developed by the EPA are particularly useful for monitoring carbon monoxide levels and emissions throughout the United States. EPA's National Emission Inventory (NEI) database contains detailed information about sources that emit criteria air pollutants and their precursors and hazardous air pollutants for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. The Air Quality System (AQS) database is EPA's repository of criteria air pollutant monitoring data since the 1970s. Table 6-1 contains data for carbon monoxide emissions from 1970 to 2008 from the NEI database for 13 major emission categories. Detailed carbon monoxide emissions from these sources for individual years are available as zipped Microsoft Access® database files that may be accessed directly from the EPA website; however, these data are subject to occasional revisions by EPA as emission estimates for a specific time period are amended. As indicated in Table 6-1, on-road vehicle use has historically accounted for the largest percentage of emissions in the United States as compared to the other emission sources; however, the quantity of carbon monoxide emitted from automobiles has been declining significantly over the past 4 decades due to the use of emission control devices and catalytic converters.

Indoor air levels of carbon monoxide are highly dependent upon the smoking habits, the types of appliances and heating units that are used in the home or building, and whether or not the home or building has an attached garage for automobiles. Carbon monoxide levels from the use of appliances will

Table 6-1. Anthropogenic Carbon Monoxide Emissions (Thousands of Short Tons) from 1970 to 2008

	Emissions by category[a]													
Year[b]	1	2	3	4	5	6	7	8	9	10	11	12	13	Total
1970	237	770	3,625	3,397	3,644	2,179	620	NA	NA	7,059	163,231	11,371	7,909	204,042
1975	276	763	3,441	2,204	2,496	2,211	630	NA	NA	3,230	153,555	14,329	5,263	188,398
1980	322	750	6,230	2,151	2,246	1,723	830	NA	NA	2,300	143,827	16,685	8,344	185,408
1985	291	670	7,525	1,845	2,223	462	694	2	49	1,941	134,187	19,029	7,927	176,845
1990	363	879	4,269	1,183	2,640	333	537	5	76	1,079	110,255	21,447	11,122	154,188
1991	349	920	4,587	1,127	2,571	345	548	5	28	1,116	104,980	21,934	8,618	147,128
1992	350	955	4,849	1,112	2,496	371	544	5	17	1,138	99,705	22,419	6,934	140,895
1993	363	1,043	4,181	1,093	2,536	371	594	5	51	1,248	94,431	22,904	7,082	135,902
1994	370	1,041	4,108	1,171	2,475	338	600	5	24	1,225	89,156	23,389	9,656	133,558
1995	372	1,056	4,506	1,223	2,380	348	624	6	25	1,185	83,881	23,874	7,298	126,778
1996	408	1,188	2,741	1,053	1,599	354	561	1	70	2,904	78,606	24,358	15,016	128,859
1997	423	1,162	2,742	1,071	1,710	367	582	2	71	2,948	75,849	23,668	7,316	117,911
1998	451	1,151	2,727	1,081	1,702	366	590	2	72	3,121	73,244	23,689	7,184	115,380
1999	496	1,213	3,829	350	1,255	159	571	52	163	3,019	68,708	23,316	11,410	114,541
2000	484	1,219	3,081	361	1,295	161	592	51	169	1,849	68,061	24,178	12,964	114,465
2001	485	1,253	3,088	372	1,380	162	615	50	178	1,851	63,476	24,677	8,676	106,263
2002	657	1,267	3,550	284	987	357	490	2	118	1,594	60,596	22,662	18,493	111,057
2003	652	1,229	3,477	259	934	355	504	2	114	1,580	56,579	21,999	17,364	105,078
2004	647	1,190	3,404	233	882	353	519	2	111	1,567	52,562	21,336	16,235	99,041
2005	643	1,152	3,331	208	829	351	534	2	107	1,554	48,544	20,672	15,106	93,034
2006	661	1,173	3,343	227	869	352	522	2	110	1,564	45,318	19,793	13,981	87,915
2007	680	1,195	3,352	246	908	353	511	2	113	1,574	42,092	18,915	12,856	82,801
2008	699	1,216	3,369	265	947	355	500	2	115	1,584	38,866	18,036	11,731	77,685

[a]Categories
1. Fuel combustion electric utilities
2. Fuel combustion industrial utilities
3. Fuel combustion other
4. Chemical allied manufacturing
5. Metal processing
6. Petroleum and related categories
7. Other industrial processes
8. Solvent utilization
9. Storage and transport
10. Waste disposal and recycling
11. Highway vehicles
12. Off-highway
13. Miscellaneous

[b]Emission estimates are subject to updates for subsequent revised versions of the National Emissions Inventory (NEI) database. These numbers may be different than values published for previous versions of the data and may also be different than values for subsequent revisions of the data as generated by the Environmental Protection Agency.

NA = not available

Source: EPA 2009h

depend on several factors, such as the type of fuel used, ventilation, appliance design, fuel consumption rate, use pattern, and operating condition (EPA 1991, 2000, 2010). As reported in the EPA Air Quality Criteria Reports (1991, 2000), carbon monoxide emissions from ranges, ovens, and pilot lights using natural gas were typically greater under yellow tipping flame conditions (characteristic of an improper air-fuel ratio) than blue tipping flame conditions (characteristic of properly adjusted stoves). The average emission rate (mass of carbon monoxide emitted per energy unit produced) for top burning ovens and broilers was 11.9–87.7 micrograms per kilojoule (μg/kJ) under blue flame conditions, as opposed to 53.5–156.6 μg/kJ for improperly adjusted ovens and broilers. In separate tests using three different gas ranges deliberately adjusted to produce blue tipping or yellow tipping flames, the average emission rate ranged from 34.3–70.9 μg/kJ under properly adjusted operation to 108.4–196.9 μg/kJ under improperly adjusted conditions (EPA 1991, 2000).

Quantitative estimates have been made regarding emissions of carbon monoxide from wood-burning stoves and fireplaces under normal operating conditions (Houck et al. 2006). Carbon monoxide emission factor data were based on 277 tests on 70 fireplace models. The mean emission factor was 64.1 g carbon monoxide emitted per kg dry wood (SD of 40.7 g/kg dry wood) (Houck et al. 2006). It has been reported that emission rates of carbon monoxide for well-tuned unvented gas appliances range from 0.15 to 3.2 g/hour, while rates for poorly tuned unvented ones range from 1.5 to 22 g/hour (Dutton et al. 2001).

6.2.2 Water

Direct anthropogenic releases of carbon monoxide to water are not expected; however, natural processes occur that result in carbon monoxide formation in waters. The photodegradation of dissolved organic matter is primarily responsible for producing carbon monoxide in sunlit surface waters (Tolli et al. 2006). Emissions from oceans are a minor source of carbon monoxide with estimated ranges from about 10 to 100 teragrams (Tg) annually (EPA 2000; Liss and Slater 1974).

6.2.3 Soil

The formation of carbon monoxide in soils appears to occur by abiotic processes, such as thermal decomposition or photodecomposition of organic matter. In general, warm and moist conditions found in most soils favor carbon monoxide uptake, whereas hot and dry conditions as found in deserts and some savannas favor the release of carbon monoxide from soil to the atmosphere with estimated annual emissions of about 30 Tg per year (EPA 2000).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Carbon monoxide is a gas that will partition to the atmosphere and is distributed globally by the horizontal movement of the wind. Wind direction determines the horizontal transport of carbon monoxide and what impact emissions from one location will have upon another site (EPA 1991). Carbon monoxide levels may be high around local sources, and locations downwind from the source may also be elevated. The transport of carbon monoxide in urban locations is complex and can be influenced by the geometry of street canyons, topography around roadways, and presence of noise barriers, vegetation, and buildings, as well as local meteorological factors. A field study was designed to characterize the air quality and flow of pollutants near a highway with and without noise barriers (Baldauf et al. 2008). The site also contained an open field and a residential neighborhood with mature vegetation. Time-series carbon monoxide levels were collected in an open field with no barrier and an area behind the noise barrier. Levels of carbon monoxide were reduced as much as 50% behind the noise barrier as compared to measurements taken at the open field, depending upon the direction of the wind. However, when wind direction was directly toward the road, carbon monoxide levels behind the barrier were slightly higher than in the open field indicating that pollutants can be trapped behind noise barriers depending upon meteorological conditions (Baldauf et al. 2008).

In most urban areas during the winter months, there is often enhanced stability in the atmospheric boundary layer, which reduces the vertical mixing of emissions from the ground. This effectively traps carbon monoxide at street levels during these periods. Unreacted carbon monoxide in the troposphere is slowly transported to the mesosphere and stratosphere, where it reacts with atomic oxygen generated by the photodissociation of O_2 (Fabian et al. 1979; Pressman and Warneck 1970).

The surface waters of the world's oceans are saturated with carbon monoxide with respect to the atmosphere and are therefore a net source of atmospheric carbon monoxide. Using a mean atmospheric carbon monoxide concentration over the ocean surface of 0.13 ppmv and a surface water concentration of $6x10^{-8}$ cm^3 carbon monoxide per cm^3 water, the total annual flux of carbon monoxide to the atmosphere from seawater was estimated at approximately $4.3x10^{13}$ g/year (43 teragrams (Tg)) (Liss and Slater 1974). Other reported estimates based on computed carbon monoxide concentrations in surface waters were reported to range from 13 to 165 Tg/year (Ohta 1997). Differences in microbial activity in surface water account for the variations in surface water levels and the flux into the atmosphere (Conrad and Seiler 1988).

6.3.2 Transformation and Degradation

6.3.2.1 Air

Carbon monoxide is generally stable under environmental conditions. Reactions with molecular oxygen (O_2) or water vapor are very slow at ambient temperatures and pressure. Carbon monoxide reacts with ground-state triplet oxygen atoms, $O(^3P)$, produced by the atmospheric photodegradation of nitrogen dioxide and ozone, or atomic oxygen, formed by the photodissociation of molecular O_2 in the stratosphere, to form CO_2 (NRC 1977). However, the primary degradation pathway of carbon monoxide in the troposphere is through its reaction with photochemically-produced hydroxyl radicals. This results in the formation of CO_2 and atomic hydrogen, which rapidly reacts with O_2 to form peroxy radicals (EPA 2000, 2010). The second-order rate constant for the gas-phase reaction of carbon monoxide with hydroxyl radicals at atmospheric pressure has been measured as $2.4x10^{-13}$ cm^3/molecule-second (EPA 1991). This corresponds to an estimated tropospheric half-life of approximately 22–67 days, assuming a hydroxyl radical concentration of $5.0x10^5$–$1.5x10^6$ hydroxyl radicals per cm^3 air. No estimates of the half-life of carbon monoxide in indoor air were located. Hydroxyl radicals are formed photochemically by sunlight; therefore, their levels in indoor air will be negligible.

6.3.2.2 Water

Although oceans and other water bodies are considered a net source of carbon monoxide in the environment, evidence suggests that various microorganisms may degrade carbon monoxide in the water (Conrad and Seiler 1988). Taxonomically diverse microorganisms isolated from surface waters collected off the New England coast readily oxidized carbon monoxide (Tolli et al. 2006). Microbial oxidation rate constants for carbon monoxide in coastal waters were reported to range from 0.01 to 0.11 $hours^{-1}$, corresponding to half-lives on the order of several hours (Tolli et al. 2006). These rates were reported to be approximately an order of magnitude greater than in oligotrophic environments, suggesting the presence of an active carbon monoxide oxidizing microbial community near shore.

6.3.2.3 Sediment and Soil

Soils may act as a source or a sink for carbon monoxide, depending on soil moisture, intensity of sunlight reaching the soil surface, and soil temperature (Conrad and Seiler 1985). In general, warm and moist conditions found in most soils favor uptake, whereas hot and dry conditions as found in deserts and some

savannas favor the release of carbon monoxide (EPA 2000). Global estimates of carbon monoxide consumption by soil microorganisms ranged from 15 to 640 Tg (from $1.5x10^{13}$ to $6.4x10^{14}$ g) per year (King 1999a). Carbon monoxide oxidation to CO_2 has been demonstrated for both aerobic and anaerobic microorganisms.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to carbon monoxide depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of carbon monoxide in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on carbon monoxide levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring carbon monoxide in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

The concentration of carbon monoxide in air can be represented using various concentration units. Air monitoring data for carbon monoxide are usually expressed or reported as either parts per million by volume (ppmv) or parts per billion by volume (ppbv). A concentration of 1 ppmv implies that for every million molecules of gas in the measured volume, one of them is a carbon monoxide molecule. In order to express these concentrations in mass units, the following conversion factors may be used: 1.00 ppmv=1.16 mg/m^3 (1.00 mg/m^3=0.86 ppmv) and 1.00 ppbv=1.16 $\mu g/m^3$ at 20 °C.

Annual average outdoor carbon monoxide concentrations are about 0.12 ppmv in the Northern Hemisphere and about 0.04 ppmv in the Southern Hemisphere (EPA 2000). In general, the concentration of carbon monoxide decreases with altitude in the Northern Hemisphere, but this vertical gradient may be reversed in the Southern Hemisphere due to the transport of carbon monoxide from the Northern to the Southern Hemisphere (EPA 1991). Annual 24-hour average carbon monoxide concentrations obtained at monitoring locations at rural sites in the United States are typically about 0.2 ppmv, compared with an annual 24-hour average of 1.2 ppmv across all monitoring sites (EPA 2000). Carbon monoxide levels (1- and 8-hour maximum levels) from various cities in the United States for 2008 are provided in Table 6-2. These data are derived from measurements submitted to the EPA AQS database, which collects data from EPA, state, local, and tribal air pollution control agencies. As indicated by the data presented in the table, only one measurement exceeded the EPA 8-hour carbon monoxide level of 9 ppm,

Table 6-2. 1-Hour and 8-Hour Maximum Carbon Monoxide Levels at Monitoring Stations Throughout the United States

	1-Hour carbon monoxide level			8-Hour carbon monoxide level				
Number of measure-ments	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	City	State[a]
2,169	8.1	6.7	0	3.6	3.5	0	Fairbanks	AK
2,176	6.1	6	0	4.1	3.8	0	Anchorage	AK
1,988	5.1	4.5	0	2.5	2.3	0	Not provided	AK
2,176	5.6	5.5	0	3.1	2.8	0	Anchorage	AK
2,173	5.7	4.5	0	3.3	2.2	0	Fairbanks	AK
2,173	8.3	8	0	4.8	4.7	0	Anchorage	AK
7,500	19.6	15.9	0	10.7	8.1	1	Birmingham	AL
7,563	8	6.1	0	2.3	2.2	0	Fairfield	AL
8,012	3.4	3	0	2.4	2.3	0	Birmingham	AL
8,750	6.8	2.5	0	1.8	1.5	0	North Little Rock	AR
5,049	1.5	1.4	0	1	1	0	Surprise	AZ
4,584	0.7	0.7	0	0.5	0.5	0	Not provided	AZ
7,947	3.1	3.1	0	2.5	2.4	0	Phoenix	AZ
8,720	2.2	1.8	0	1.3	1	0	Tucson	AZ
8,736	2.6	2.1	0	1.1	1.1	0	Tucson	AZ
8,696	2.9	2.5	0	1.4	1.3	0	Tucson	AZ
4,369	2.5	2.5	0	1.9	1.5	0	Tucson	AZ
8,157	1.5	1.3	0	1	0.9	0	Tucson	AZ
4,315	2	1.8	0	1.3	1.2	0	Tucson	AZ
5,027	2.4	2.3	0	1.8	1.4	0	Tempe	AZ
5,043	1.8	1.7	0	1.4	1.4	0	Chandler	AZ
5,057	3.7	3.2	0	2.2	2	0	Phoenix	AZ
8,654	3	3	0	2.7	2.4	0	Phoenix	AZ
4,933	2	2	0	1.5	1.4	0	Scottsdale	AZ
5,060	2.1	2	0	1.6	1.5	0	Glendale	AZ
5,038	2.1	2	0	1.3	1.3	0	Phoenix	AZ
5,012	1.7	1.7	0	1.4	1.3	0	Mesa	AZ
8,575	4.7	4.5	0	3.1	3	0	Phoenix	AZ
8,307	3.9	3.6	0	2.8	2.8	0	Phoenix	AZ
8,397	3.6	3.5	0	2.6	2.2	0	Phoenix	AZ
6,905	2.1	1.9	0	1.1	1	0	Lompoc	CA
6,893	1.4	1.2	0	0.6	0.6	0	Goleta	CA
6,097	1.6	1.3	0	0.7	0.6	0	Vandenberg Air Force Base	CA
6,177	3.3	3	0	2.1	1.9	0	San Jose	CA
7,046	7.6	3.7	0	1.3	1.1	0	Davenport	CA
6,230	2.7	2.5	0	1.9	1.7	0	Vallejo	CA

Table 6-2. 1-Hour and 8-Hour Maximum Carbon Monoxide Levels at Monitoring Stations Throughout the United States

	1-Hour carbon monoxide level			8-Hour carbon monoxide level				
Number of measure-ments	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	City	State[a]
6,251	0.9	0.9	0	0.7	0.6	0	Benicia	CA
6,244	3.5	1.9	0	1.3	1.1	0	Santa Rosa	CA
5,550	2.8	2.3	0	1.8	1.7	0	Modesto	CA
6,035	1.9	1.9	0	1.2	1.2	0	Turlock	CA
6,270	2.2	2.2	0	1.4	1.4	0	Livermore	CA
6,227	2.9	2.4	0	1.6	1.4	0	Oakland	CA
6,202	1.9	1.8	0	1.3	1.3	0	Fremont (Centerville)	CA
6,175	2.1	2	0	1.5	1.5	0	Berkeley	CA
5,576	3.1	3	0	2.4	2.1	0	Chico	CA
6,240	1.5	1.5	0	1	1	0	Concord	CA
6,274	1	0.9	0	0.8	0.8	0	Bethel Island	CA
6,225	2.5	2.1	0	1.3	0.9	0	San Pablo	CA
6,266	2.8	2.2	0	1.4	1.3	0	Pittsburg	CA
5,430	2.6	2.6	0	1.8	1.7	0	Fresno	CA
5,563	3.1	2.8	0	2.3	2.1	0	Fresno	CA
5,519	1.6	1.5	0	1	1	0	Fresno	CA
4,785	2.3	2.2	0	1.5	1.3	0	Clovis	CA
5,768	1.9	1.9	0	1.6	1.4	0	Eureka	CA
5,543	8.2	7	0	5.3	4.1	0	Calexico	CA
5,262	7.3	6.8	0	3.2	3.1	0	Calexico	CA
6,270	2.5	2.3	0	1.7	1.7	0	El Centro	CA
4,139	3.5	2.7	0	2.2	2.1	0	Bakersfield	CA
5,554	2.3	2.1	0	1.4	1.3	0	Azusa	CA
5,552	2.7	2.3	0	1.8	1.7	0	West Los Angeles	CA
5,555	3	2.8	0	2.5	2	0	Burbank	CA
5,560	2.9	2.8	0	2	1.9	0	Los Angeles	CA
5,594	3.4	3.3	0	2.3	2.1	0	Reseda	CA
5,579	5.8	5.7	0	4.3	4.1	0	Lynwood	CA
5,281	2.9	2.5	0	1.9	1.8	0	Pico Rivera	CA
5,557	2.6	2.6	0	1.7	1.7	0	Pomona	CA
5,550	2.4	2.4	0	2	1.9	0	Pasadena	CA
5,567	3.3	3	0	2.5	2.4	0	Long Beach	CA
5,315	3.1	2.6	0	1.9	1.8	0	Los Angeles	CA
5,495	1.6	1.5	0	0.9	0.8	0	Santa Clarita	CA
5,538	2.2	1.7	0	0.9	0.8	0	Lancaster	CA
6,208	1.7	1.7	0	1	1	0	San Rafael	CA

Table 6-2. 1-Hour and 8-Hour Maximum Carbon Monoxide Levels at Monitoring Stations Throughout the United States

	1-Hour carbon monoxide level			8-Hour carbon monoxide level				
Number of measure-ments	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	City	State[a]
7,224	4.5	3.9	0	3.4	3.3	0	Ukiah	CA
3,282	1.5	1.4	0	1	0.9	0	Willits	CA
7,177	2.2	1.6	0	0.9	0.8	0	Salinas	CA
6,255	3.2	3.1	0	1.8	1.6	0	Napa	CA
5,560	3.3	3	0	2.4	2.1	0	Anaheim	CA
5,571	3	2.8	0	2	2	0	Costa Mesa	CA
5,524	1.5	1.5	0	1.1	1	0	Mission Viejo	CA
5,567	4.7	4.6	0	2.5	2.4	0	La Habra	CA
5,605	4.7	4.5	0	1.9	1.9	0	Riverside	CA
5,574	1	0.9	0	0.5	0.5	0	Palm Springs	CA
5,546	2.7	2.5	0	1.9	1.7	0	Rubidoux (West Riverside)	CA
5,564	1.1	1.1	0	0.8	0.8	0	Lake Elsinore	CA
6,390	2.3	2.3	0	1.8	1.8	0	North Highlands	CA
7,292	2.9	2.7	0	2.5	1.8	0	Sacramento	CA
8,036	3.1	3.1	0	2.8	2.4	0	Sacramento	CA
4,812	2.7	2.5	0	1.8	1.7	0	Sacramento	CA
5,519	1.4	1.3	0	1.2	1.1	0	Barstow	CA
5,587	1.4	1.4	0	0.9	0.9	0	Victorville	CA
5,491	2.1	1.9	0	1.4	1.2	0	Upland	CA
1,388	1.3	1.1	0	0.8	0.8	0	Fontana	CA
5,556	2.2	2.1	0	1.4	1.4	0	San Bernardino	CA
6,212	2	2	0	1.5	1.5	0	Chula Vista	CA
706	2.4	2.2	0	1.8	1.5	0	San Diego	CA
6,006	4.6	4	0	2.8	2.5	0	Escondido	CA
6,130	3.1	3.1	0	2.5	2.5	0	San Diego	CA
5,119	4.3	3.9	0	2.7	2.5	0	Otay Mesa	CA
6,247	2.1	1.9	0	1.5	1.4	0	San Francisco	CA
5,546	2.6	2.5	0	1.6	1.6	0	Stockton	CA
6,214	4.3	3.8	0	1.9	1.8	0	Redwood City	CA
4,811	5.2	3.4	0	1.2	1.2	0	Santa Barbara	CA
5,462	1.5	1.5	0	0.8	0.8	0	Santa Maria	CA
6,182	3.5	2.5	0	1.7	0.9	0	Capitan	CA
6,190	3.1	3.1	0	2.4	1.7	0	Welby	CO
6,505	3.5	3.3	0	2.7	2.4	0	Longmont	CO

Table 6-2. 1-Hour and 8-Hour Maximum Carbon Monoxide Levels at Monitoring Stations Throughout the United States

	1-Hour carbon monoxide level			8-Hour carbon monoxide level				
Number of measure-ments	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	City	State[a]
6,507	3.4	3.2	0	2.3	2.2	0	Greeley	CO
6,481	2.2	2.1	0	1.4	1.3	0	Grand Junction	CO
6,487	5.1	4.6	0	3	2.2	0	Fort Collins	CO
4,249	0.8	0.8	0	0.7	0.7	0	Not provided	CO
6,420	4	3.5	0	2.6	2.3	0	Colorado Springs	CO
6,203	7.1	7	0	3.1	2.3	0	Denver	CO
6,488	4.8	4.5	0	2.4	1.9	0	Denver	CO
6,499	6	5.9	0	3.7	3.1	0	Hartford	CT
6,319	1.6	1.6	0	1.4	1.1	0	Westport	CT
6,305	3.3	3.2	0	2.2	2	0	Bridgeport	CT
6,491	1.2	1.1	0	0.9	0.9	0	Thomaston	CT
6,511	1.8	1.6	0	1.3	1.2	0	East Hartford	CT
3,314	2.2	2.1	0	1.9	1.6	0	New Haven	CT
6,525	6	4	0	2.6	1.8	0	Washington	DC
6,513	3	2.7	0	2.6	2.1	0	Washington	DC
7,030	1.4	1	0	0.9	0.8	0	Not provided	DE
7,171	2	2	0	1.3	1.1	0	Wilmington	DE
6,500	2.1	2	0	1.6	1.6	0	Fort Lauderdale	FL
6,513	1.6	1.5	0	1	0.9	0	Clearwater	FL
6,499	2.4	2.1	0	1.6	1.5	0	Hollywood	FL
6,269	8.7	6.2	0	3.3	2.8	0	Jacksonville	FL
6,318	2.5	2.1	0	1.4	1.2	0	Jacksonville	FL
6,250	2.3	2.2	0	1.1	1.1	0	Jacksonville	FL
6,551	2.6	2.5	0	2	1.8	0	Tampa	FL
6,511	1.2	1	0	0.5	0.4	0	Plant City	FL
6,506	2.2	2	0	1.2	1.1	0	Miami	FL
6,515	2.4	2	0	1.7	1.4	0	Not provided	FL
6,329	3.9	3.9	0	2.4	2.1	0	Miami	FL
6,550	2.8	2.6	0	2.1	1.6	0	Miami	FL
6,449	1.1	1	0	1	1	0	Winter Park	FL
2,167	1.5	1.4	0	1.1	1.1	0	Palm Beach	FL
6,280	1.5	1.4	0	1.2	1.1	0	Pompano Beach	FL
5,747	2.8	2.1	0	1.8	1.8	0	Decatur	GA
6,435	0.5	0.5	0	0.5	0.5	0	Not provided	GA
5,918	2.2	2.1	0	1.4	1.2	0	Atlanta	GA

Table 6-2. 1-Hour and 8-Hour Maximum Carbon Monoxide Levels at Monitoring Stations Throughout the United States

	1-Hour carbon monoxide level			8-Hour carbon monoxide level				
Number of measure-ments	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	City	State[a]
6,554	2.1	1.7	0	1	1	0	Honolulu	HI
5,268	1.7	1.3	0	0.7	0.7	0	Ewa Beach	HI
2,050	1.5	1.1	0	0.7	0.6	0	Cedar Rapids	IA
5,017	1.6	1.5	0	1.3	1.2	0	Cedar Rapids	IA
7,396	1.9	1.6	0	1	1	0	Des Moines	IA
8,199	1.2	1.2	0	0.7	0.7	0	Davenport	IA
4,609	4.1	3.6	0	1.6	1.5	0	Boise	ID
7,797	2.9	2.7	0	2.3	2.2	0	East Saint Louis	IL
7,977	2.5	2.2	0	1.5	1.3	0	Springfield	IL
7,965	5.6	3	0	1.9	1.7	0	Rockford	IL
7,917	3.6	3.2	0	2.9	2.1	0	Peoria	IL
7,960	2.5	2.5	0	2.3	2.2	0	Maywood	IL
8,007	1.9	1.3	0	1.2	0.9	0	Northbrook	IL
7,926	2.4	2.3	0	1.7	1.5	0	Cicero	IL
7,783	2.3	2	0	1.8	1.5	0	Schiller Park	IL
7,982	7.3	4.4	0	2	1.5	0	Chicago	IL
6,380	1.9	1.7	0	1.2	1.2	0	Indianapolis (Remainder)	IN
5,972	2	1.8	0	1.5	1.1	0	Evansville	IN
6,538	9.1	7.1	0	3.3	3	0	East Chicago	IN
3,984	0.8	0.8	0	0.7	0.7	0	Pittsboro	IN
6,445	3.9	3.8	0	2.9	2.3	0	Fort Wayne	IN
8,710	3.6	3.5	0	3.2	2.1	0	Indianapolis	IN
6,520	2.8	2.7	0	2	1.2	0	Wichita	KS
6,394	2.7	2.4	0	1.6	1.5	0	Wichita	KS
6,389	2.2	2.2	0	1.8	1.4	0	Kansas City	KS
7,113	6.9	3.4	0	2.8	2.2	0	Louisville	KY
6,937	3.1	3.1	0	2.7	2.1	0	Louisville	KY
7,723	2.9	2.5	0	1.9	1.8	0	Baton Rouge	LA
5,769	0.9	0.7	0	0.4	0.4	0	Lynn	MA
6,586	3.4	3.4	0	3	2.5	0	Springfield	MA
6,835	3.7	3.2	0	2.6	2.1	0	Lowell	MA
6,830	1.7	1.6	0	1.3	1	0	Boston	MA
6,875	1.5	1.5	0	1.1	0.9	0	Boston	MA
6,831	2.8	2.7	0	1.7	1.3	0	Worcester	MA
6,022	2.6	2.4	0	1.6	1.5	0	Essex	MD
6,407	0.4	0.4	0	0.3	0.3	0	Not provided	MD

Table 6-2. 1-Hour and 8-Hour Maximum Carbon Monoxide Levels at Monitoring Stations Throughout the United States

	1-Hour carbon monoxide level			8-Hour carbon monoxide level				
Number of measure-ments	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	City	State[a]
6,104	2.4	2.2	0	2.1	2	0	Baltimore	MD
6,439	1.4	1	0	0.9	0.8	0	Beltsville	MD
1,211	0.6	0.6	0	0.4	0.4	0	Presque Isle	ME
5,816	1.6	1.4	0	1.3	1	0	Portland	ME
6,351	0.4	0.4	0	0.4	0.3	0	Not provided	ME
4,569	2	1.6	0	1.2	1.1	0	Allen Park	MI
4,218	2	1.8	0	1.1	1	0	Grand Rapids	MI
7,278	2	2	0	0.8	0.7	0	Minneapolis	MN
7,262	0.5	0.5	0	0.3	0.3	0	Inver Grove Heights	MN
5,712	0.6	0.6	0	0.4	0.3	0	Rosemount	MN
2,169	1.8	1.5	0	1.2	1.2	0	Fridley	MN
7,022	3.2	3.1	0	2.4	2.4	0	St. Paul	MN
6,975	1.8	1.7	0	1.2	1.2	0	St. Cloud	MN
7,122	4.1	2.2	0	1.8	1.5	0	Duluth	MN
6,533	1.1	1	0	0.7	0.7	0	Sunset Hills	MO
6,536	1.9	1.8	0	1.2	1	0	Springfield	MO
6,528	3.3	2.9	0	2.2	1.6	0	St. Louis	MO
6,469	2.4	2.1	0	1.8	1.4	0	St. Louis	MO
2,083	3.4	3.4	0	2.9	2.7	0	Missoula	MT
2,104	2	1.9	0	0.7	0.7	0	Not provided	MT
6,916	6.7	5.7	0	2.4	2.2	0	West Yellowstone	MT
1,542	6.1	4.2	0	1.6	1.1	0	Not provided	MT
7,130	4.8	3.7	0	2.3	2	0	Billings	MT
7,244	7.7	3	0	1.8	1.5	0	Great Falls	MT
5,578	7.2	3.4	0	2.4	1.9	0	Kalispell	MT
2,819	1.5	1.5	0	1.3	1.1	0	Not provided	NC
7,811	1.9	1.8	0	1.5	1.4	0	Charlotte	NC
3,664	3.5	3.1	0	2.2	2.2	0	Raleigh	NC
7,081	4	2.8	0	2.4	1.8	0	Raleigh	NC
7,384	1.6	1.5	0	0.9	0.7	0	Rockwell	NC
2,044	2.2	2.2	0	1.7	1.7	0	Fayetteville	NC
7,927	2.3	2.1	0	1.9	1.6	0	Charlotte	NC
1,985	1.9	1.9	0	1.6	1.5	0	Greensboro	NC
6,531	2.7	2.5	0	2.3	1.9	0	Winston-Salem	NC
2,754	1.9	1.9	0	1.5	1.2	0	Durham	NC
7,930	6.5	1.7	0	1.2	0.7	0	Not provided	ND

Table 6-2. 1-Hour and 8-Hour Maximum Carbon Monoxide Levels at Monitoring Stations Throughout the United States

	1-Hour carbon monoxide level			8-Hour carbon monoxide level				
Number of measure-ments	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	City	State[a]
6,365	3.1	2.9	0	2.5	2	0	Omaha	NE
7,252	6.5	4.5	0	1.8	1.8	0	Lincoln	NE
6,464	9.4	6	0	4.4	3.5	0	Manchester	NH
6,285	1.5	1.4	0	1.1	1.1	0	Fort Lee	NJ
2,188	1.8	1.6	0	1.1	1	0	Elizabeth	NJ
6,544	2.3	1.9	0	1.5	1.3	0	Morristown	NJ
6,508	3.4	3.4	0	2	1.6	0	Freehold	NJ
6,373	2.2	2.1	0	1.2	1.2	0	Camden	NJ
6,522	1	0.9	0	0.7	0.6	0	Not provided	NJ
6,498	2.1	2.1	0	1.7	1.5	0	Jersey City	NJ
6,318	2	1.6	0	1.2	0.9	0	Perth Amboy	NJ
6,484	2.2	2.2	0	1.8	1.6	0	Hackensack	NJ
6,326	3.7	2.7	0	1.8	1.4	0	Burlington	NJ
3,065	3.6	2.8	0	1.8	1.5	0	Albuquerque	NM
6,140	2.6	2.2	0	1.7	1.1	0	Albuquerque	NM
3,130	2.6	2.5	0	1.8	1.7	0	Albuquerque	NM
5,792	6.5	3	0	2.4	2.3	0	Albuquerque	NM
3,057	4.9	3.7	0	1.6	1.3	0	Albuquerque	NM
806	2.4	2.4	0	1.9	1.8	0	South Valley	NM
6,377	4.2	3.9	0	2.1	2	0	Sparks	NV
6,463	2.2	1.9	0	1.5	1.5	0	Lemmon Valley-Golden Valley	NV
4,243	2.9	2.7	0	2.2	1.7	0	Carson City	NV
5,033	3.5	2.9	0	2.3	2.1	0	Las Vegas	NV
6,217	5.1	4.7	0	4.2	3.7	0	Las Vegas	NV
6,275	4.1	3.9	0	3.1	2.8	0	Las Vegas	NV
6,190	3.2	2.9	0	2.1	2.1	0	Las Vegas	NV
6,271	4.2	3.6	0	2.5	2.4	0	Las Vegas	NV
6,178	5.8	5.3	0	2.6	2.4	0	Stateline	NV
6,476	2.1	2.1	0	1.5	1.5	0	Reno	NV
6,515	1.8	1.7	0	1.3	1.3	0	Reno	NV
6,400	3	2.9	0	2.3	2.2	0	Reno	NV
6,512	1.8	1.7	0	0.8	0.8	0	Reno	NV
6,466	1.8	1.8	0	1.2	0.9	0	Holtsville	NY
7,922	3	2.7	0	1.8	1.8	0	Schenectady	NY
7,445	8.6	2.3	0	1.7	1.6	0	New York	NY
7,956	2	1.9	0	1.7	1.4	0	Syracuse	NY

Table 6-2. 1-Hour and 8-Hour Maximum Carbon Monoxide Levels at Monitoring Stations Throughout the United States

	1-Hour carbon monoxide level			8-Hour carbon monoxide level				
Number of measure-ments	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	City	State[a]
7,957	1.4	1.3	0	1.2	1	0	Niagara Falls	NY
7,769	1.5	1.2	0	1	0.9	0	Albany	NY
4,245	1.6	1.5	0	1.2	1.2	0	New York	NY
7,429	1.3	1.2	0	1.1	1	0	Rochester	NY
5,757	1.3	1	0	0.7	0.7	0	Tonawanda	NY
7,452	1.6	1.6	0	1.1	1	0	Buffalo	NY
7,962	2.3	2.1	0	1.8	1.7	0	New York	NY
3,419	1.7	1.6	0	1.3	1.2	0	New York	NY
6,967	4.8	4.8	0	2.1	1.5	0	Cleveland	OH
7,023	7.8	6.3	0	3.3	2.4	0	Cleveland	OH
6,948	2	1.5	0	0.9	0.8	0	Akron	OH
7,003	1.7	1.6	0	1.3	1.1	0	Akron	OH
6,158	2.9	2.9	0	2.6	2.5	0	Canton	OH
8,739	2.3	2.3	0	1.6	1.5	0	Dayton	OH
8,720	1.5	1.4	0	1.1	1	0	Dayton	OH
7,259	2.6	2.6	0	2.6	2.3	0	Mentor	OH
6,358	5.9	5.1	0	3.6	2.7	0	Cincinnati	OH
7,183	2.7	2.3	0	1.6	1.4	0	Columbus	OH
7,232	2	1.8	0	1.5	1.3	0	Cleveland	OH
7,252	2	2	0	1.2	1.2	0	Cleveland	OH
7,752	2.5	2.1	0	1.1	1.1	0	Oklahoma City	OK
1,382	0.4	0.4	0	0.3	0.3	0	Cherry Tree	OK
3,185	1.7	0.5	0	0.4	0.3	0	Park Hill	OK
4,625	1.7	0.3	0	0.5	0.3	0	Not provided	OK
2,278	1.7	1.6	0	1.4	1.3	0	Tulsa	OK
7,991	2.1	1.9	0	1.3	1.2	0	Tulsa	OK
5,933	2.7	2.6	0	2.3	2.2	0	Portland	OR
6,541	2.7	2.7	0	1.8	1.6	0	Portland	OR
6,437	3.4	3.4	0	2.6	2.2	0	Medford	OR
6,530	2.2	2.1	0	1.7	1.6	0	Eugene	OR
5,023	0.8	0.8	0	0.5	0.4	0	Not provided	PA
7,048	1.9	1.8	0	1.6	1.5	0	Pittsburgh	PA
7,243	2	2	0	1.3	1.2	0	York	PA
7,211	1.4	1	0	0.8	0.5	0	Greensburg	PA
6,517	1.6	1.6	0	1.3	1.1	0	Pittsburgh	PA
6,523	2.3	2.1	0	1.7	1.4	0	Pittsburgh	PA
7,054	2.6	2	0	1.6	1.3	0	Beaver Falls	PA

Table 6-2. 1-Hour and 8-Hour Maximum Carbon Monoxide Levels at Monitoring Stations Throughout the United States

	1-Hour carbon monoxide level			8-Hour carbon monoxide level				
Number of measure-ments	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	City	State[a]
7,197	1.5	1.3	0	0.9	0.9	0	Not provided	PA
7,206	1.4	1.2	0	0.8	0.7	0	Altoona	PA
7,009	4.3	2.9	0	2	1.9	0	Bristol	PA
7,215	1.7	1.4	0	1.2	1.1	0	Johnstown	PA
7,174	1.4	1.4	0	1.1	1.1	0	Harrisburg	PA
7,152	2.8	1.6	0	1	1	0	Erie	PA
4,958	0.5	0.5	0	0.3	0.3	0	Not provided	PA
7,212	1.8	1.4	0	1.2	1	0	Scranton	PA
6,694	2.6	1.9	0	1.6	1.4	0	Lancaster	PA
7,162	1.2	1.2	0	0.7	0.7	0	New Castle	PA
7,200	2.6	2.4	0	1.9	1.5	0	Wilkes-Barre	PA
7,306	1.1	1.1	0	0.8	0.8	0	Norristown	PA
7,308	2.1	2	0	1.6	1.6	0	Freemansburg	PA
6,160	3.7	2.7	0	1.7	1.3	0	Philadelphia	PA
1,764	1.3	1.1	0	0.7	0.7	0	Philadelphia	PA
7,094	1.3	1.2	0	1.2	1.1	0	Charleroi	PA
3,795	4.2	2.8	0	2.3	2.3	0	Bayamon	PR
5,854	3.8	3.7	0	2.4	2.3	0	San Juan	PR
6,421	3.9	3.3	0	1.7	1.4	0	San Juan	PR
6,420	1.5	1.4	0	1	0.9	0	East Providence	RI
8,714	2.3	2	0	1.4	1.3	0	Greenville	SC
8,561	0.9	0.8	0	0.5	0.5	0	Not provided	SC
8,747	3.2	3.2	0	2.4	1.9	0	Nashville	TN
6,248	1.7	1.5	0	1	1	0	Kingsport	TN
8,514	3.2	2.5	0	1.5	1.4	0	Memphis	TN
6,824	1.6	1.5	0	0.8	0.7	0	Brownsville	TX
5,201	1.7	1.7	0	1.4	1.3	0	Dallas	TX
7,170	7	6.1	0	4.9	3.2	0	El Paso	TX
6,895	2.9	2.7	0	1.5	1.5	0	El Paso	TX
7,198	5	4.8	0	3	1.8	0	El Paso	TX
6,712	7.3	6	0	4.2	2.4	0	El Paso	TX
7,202	6.7	6.6	0	4.8	3.9	0	El Paso	TX
6,985	4.3	4	0	3	2.8	0	El Paso	TX
7,040	3.5	3.4	0	1.7	1.7	0	Laredo	TX
7,176	2.5	2.1	0	1.4	1.3	0	El Paso	TX
6,875	2.9	2.7	0	1.7	1.5	0	Not provided	TX
6,310	3.8	3.7	0	2.7	2.3	0	Houston	TX

Table 6-2. 1-Hour and 8-Hour Maximum Carbon Monoxide Levels at Monitoring Stations Throughout the United States

	1-Hour carbon monoxide level			8-Hour carbon monoxide level				
Number of measure-ments	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	City	State[a]
6,258	2.1	1.9	0	1.6	1.3	0	Houston	TX
6,322	8.9	8.1	0	5.9	5.2	0	Houston	TX
5,662	1.4	1.4	0	1	0.8	0	Houston	TX
6,863	1.7	1.5	0	0.9	0.6	0	Deer Park	TX
5,594	1.8	1.7	0	1	0.7	0	Nederland	TX
7,105	0.8	0.3	0	0.3	0.3	0	Waco	TX
7,080	1.7	1.7	0	1.1	1	0	Fort Worth	TX
7,205	1.8	1.4	0	1	0.9	0	Arlington	TX
7,241	0.7	0.6	0	0.4	0.4	0	Austin	TX
6,942	3.2	2.9	0	1.4	1.3	0	Laredo	TX
6,154	0.9	0.9	0	0.5	0.5	0	Not provided	TX
6,309	2.5	2.4	0	1.9	1.4	0	San Antonio	TX
7,199	7.8	4.7	0	2.7	2.6	0	San Antonio	TX
7,235	3.2	2.9	0	1.6	1.6	0	Socorro	TX
6,469	3	2.9	0	2.2	2.1	0	Not provided	UT
6,297	4.1	3.6	0	2.4	2.3	0	Salt Lake City	UT
5,776	27.9	24.2	0	8.8	6.4	0	Ogden	UT
6,333	5	3.9	0	1.6	1.5	0	Provo	UT
5,744	3.3	3.3	0	2	2	0	Ogden	UT
2,125	3.7	3.3	0	1.8	1.8	0	West Valley	UT
5,996	1.1	1	0	0.9	0.8	0	Annandale	VA
6,479	1.3	1.2	0	1	0.8	0	Richmond	VA
6,469	1.7	1.6	0	1.2	1.1	0	Not provided	VA
7,175	1.4	1.4	0	1.2	1	0	Not provided	VA
7,133	1.9	1.9	0	1.9	1.8	0	Franconia	VA
6,489	2	2	0	1.5	1.4	0	Roanoke	VA
7,097	2	2	0	1.5	1.5	0	Mclean	VA
6,365	1.9	1.9	0	1.2	1.2	0	Alexandria	VA
6,439	4.2	4.1	0	1.6	1.3	0	Hampton	VA
6,487	4.7	4.5	0	2.2	1.9	0	Norfolk	VA
6,218	3.1	2.7	0	2.1	1.8	0	Rutland	VT
6,194	1.9	1.8	0	1.2	1.1	0	Burlington	VT
7,232	3.4	3.1	0	2.3	1.9	0	Bellevue	WA
5,468	0.3	0.3	0	0.3	0.3	0	Not provided	WA
6,885	1.4	1.2	0	0.9	0.9	0	Seattle	WA
7,140	4.3	4.1	0	2.4	2.4	0	Spokane	WA
7,674	0.5	0.5	0	0.4	0.4	0	Not provided	WI

Table 6-2. 1-Hour and 8-Hour Maximum Carbon Monoxide Levels at Monitoring Stations Throughout the United States

	1-Hour carbon monoxide level			8-Hour carbon monoxide level				
Number of measure-ments	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	First maximum (ppmv)	Second maximum (ppmv)	Number exceeding average	City	State[a]
6,541	3.9	3.5	0	2.3	2.2	0	Weirton	WV
6,532	2.7	2.7	0	1.8	1.7	0	Weirton	WV
6,449	4.5	4.3	0	2.9	2.3	0	Weirton	WV
6,984	0.9	0.8	0	0.6	0.4	0	Not provided	WY
6,361	0.9	0.9	0	0.7	0.7	0	Not provided	WY

[a]Post office state abbreviations are used.

Source: EPA 2009i

and no measurements exceeded the 1-hour average level of 35 ppm at the 365 different monitoring sites. Using data from this nationwide network of monitoring sites, EPA estimated that there has been a 75% decrease in the ambient levels of carbon monoxide in the United States from 1980 to 2006 (EPA 2008).

The EPA Integrated Science Assessment (ISA) on carbon monoxide (2010), used monitoring data from 2005 to 2007 at 12 remote locations in the United States to estimate policy-relevant background (PRB) concentrations of carbon monoxide. These concentrations are defined as levels that would be expected to occur in the United States in the absence of anthropogenic emissions in continental North America. These remote-site baseline measurements were obtained from The National Oceanic and Atmospheric Administration's (NOAA) Earth System Research Laboratory (ESRL), Global Monitoring Division (GMD). The 3-year average carbon monoxide PRBs at remote locations outside the continental United States (OCONUS) were 0.13 ppmv (Alaska sites) and 0.0992 ppmv (Hawaii sites). Over the continental United States (CONUS) region, the 3-year average carbon monoxide PRB concentration was 0.132 ppmv (EPA 2010). The seasonal variability of carbon monoxide levels was observed at each monitoring location with minima achieved during the summer and fall months and maxima observed during the winter and spring seasons.

Urban areas with heavy vehicular traffic congestion tend to have high levels of carbon monoxide in ambient air. These levels follow a predictable diurnal pattern, which reaches maximum concentrations at times of heavy commuting and then decreases during periods of low vehicular traffic. The apex of these profiles corresponds to the morning and evening rush hour commutes when vehicle density is at its highest. For many locations, the morning peak yields higher carbon monoxide levels than the evening peak, because the height of the mixed layer is much lower during the morning, thereby inhibiting vertical mixing that helps dissipate the carbon monoxide. In the late afternoon and into early evening, increased atmospheric turbulence resulting from solar activity raises the height of the mixed layer, resulting in generally lower carbon monoxide concentrations compared with those of the morning (EPA 2000). A study conducted by the Toronto (Canada) Public Health Department examined the level of carbon monoxide at four sites in Toronto as a function of traffic density (Campbell et al. 1995). The four areas of the study were categorized as low, medium, or high in terms of traffic density. Mean hourly carbon monoxide levels ranged from 0.63 ppmv at a low traffic density site (average daily vehicle count of 2,000 vehicles) to 1.54 ppmv at a site in which the vehicular count was about 45,000 per day (Campbell et al. 1995). Chen et al. (2008) measured carbon monoxide levels at 10 roadside pollution monitoring sites in the city of Leicester, England. A diurnal carbon monoxide concentration pattern was observed in this study; however, the carbon monoxide levels during the evening rush hour period generally exceeded the

levels than the morning commute. Maximum carbon monoxide levels at these sites ranged from 0.8 to 3.1 ppmv during the morning commute, while maximum levels were 1.0–4.0 ppmv during the evening rush hour (Chen et al. 2008).

High levels of carbon monoxide inside vehicles and other transportation sources that use gasoline powered engines are frequently observed. Duci et al. (2003) studied the concentration of carbon monoxide in vehicles along heavy traffic routes in Athens, Greece. The mean carbon monoxide exposure level for trips greater than 30 minutes in duration were 21.4 ppmv for private car versus 10.4, 9.6, 4, and 11.5 ppmv for bus, trolley, electric train, and pedestrians, respectively, during the winter season (Duci et al. 2003). Besides the mode of transportation, the route travelled, the monitoring period, and the season of year had significant influences on the measured carbon monoxide concentrations. In-vehicle carbon monoxide levels were monitored in a passenger vehicle driven along a heavily traveled route of a commercial/residential area of Beirut, Lebanon under several ventilation modes (Abi Esper et al. 2007a). Trips were conducted during morning rush hours in spring and summer months. The highest mean carbon monoxide levels were observed within vehicles driven with the windows and vents closed (37.4 ppmv) and windows closed and air conditioning on recirculation ventilation settings (30.8 ppmv) (Abi Esper et al. 2007a). Opening a window or setting the air conditioning unit to fresh air intake generally resulted in a reduction of carbon monoxide levels within the vehicle.

Indoor air levels of carbon monoxide are greatly dependent upon the presence of indoor combustion sources such as wood burning stoves, fireplaces, gas space heaters, and gas stoves, as well as the operating condition and usage patterns of these appliances or whether the occupants smoke. Dutton et al. (2001) studied carbon monoxide levels in two residences located in Boulder, Colorado using unvented natural gas fireplaces. Time-averaged carbon monoxide levels were1.5–78 ppmv at one residence and 1.6–30 ppmv at the other residence while the fireplace operated uninterrupted; however, levels >100 ppm were observed at one of the residences on several occasions. Background carbon monoxide levels were 0–7 ppmv in the homes when the fireplaces were not operating. Attached garages may also be a significant source of carbon monoxide to the indoor air of residences. The net increase of carbon monoxide levels in 16 homes with attached garages ranged from <1 to 30 ppmv following the cold start of an automobile enclosed within the attached garage (Graham et al. 2004).

6.4.2 Water

The levels of carbon monoxide in the surface waters of the world's oceans are supersaturated with respect to the partial pressure of carbon monoxide in the atmosphere and are subject to diurnal cycling. Levels have been reported to vary from $2x10^{-8}$ to $1.3x10^{-7}$ cm^3 carbon monoxide per cm^3 of water (20–130 nanoliters per liter [nL/L]) based on measurements in the Pacific Ocean and from $2x10^{-8}$ to $1x10^{-7}$ cm^3 carbon monoxide per cm^3 of water (20–100 nL/L) in the North Atlantic (Liss and Slater 1974). Carbon monoxide concentrations in seawater measured in the upwelling region of the equatorial Pacific Ocean were reported to range from 42 to 173 nL/L on two consecutive sampling dates and reached a maximum value of 246 nL/L on subsequent sampling at a later date (Ohta 1997). These levels showed a marked diurnal variation with a maximum and minimum occurring early in the afternoon and morning, respectively. The concentrations in the water column decreased as a function of depth from the water surface to approximately 10 nL/L at a depth of 70 meters. Tolli et al. (2006) reported a carbon monoxide level of 12 nanomoles/L at a coastal sampling location in Vineyard Sound, Massachusetts.

6.4.3 Sediment and Soil

In-situ soil-gas carbon monoxide levels were studied in a pine forest soil and cultivated soil as a function of depth from the surface (King 1999b). In the pine forest soil, the carbon monoxide concentrations remained elevated (250–320 ppbv) and greater than the atmospheric levels through the upper surface soil (O-horizon, 0–2 cm depth), but declined to values less than the atmospheric level in the lower depths of the soil (A-horizon 2–10 cm depth). In the cultivated soil, carbon monoxide levels decreased rapidly from approximately 250 ppbv in the upper 1 cm of the O-horizon to approximately 50 ppbv at a depth of 3 cm, which was roughly 5-fold less than ambient atmospheric levels.

6.4.4 Other Environmental Media

Carbon monoxide is released from tobacco smoke; however, the amount released is a function of the type of tobacco product (e.g., cigarette, cigar) and the degree to which tobacco is actively smoked. Moir et al. (2008) examined the emissions of carbon monoxide and other compounds under two smoking conditions from marijuana and tobacco cigarettes using a mechanical rotary smoking machine. The standard conditions employed a puff volume of 35 mL, puff duration of 2 seconds, and a puff interval of 60 seconds. Conditions more consistent with marijuana smoking employed a puff volume of 70 mL, puff duration of 2 seconds, and a 30-second interval between puffs. These conditions were referred to as extreme conditions. Under standard conditions, the average±standard deviation (SD) emission of carbon

monoxide in mainstream smoke (n=20) was 20.8±1.9 mg carbon monoxide per tobacco cigarette and 13.4±1.6 mg carbon monoxide per marijuana cigarette. Under extreme smoking conditions, the levels were 41.5±4.0 mg carbon monoxide per tobacco cigarette and 35.3±2.9 mg carbon monoxide per marijuana cigarette. These results predict that typical use of marijuana (70 mL puff volume) would result in more carbon monoxide being inhaled than during typical cigarette smoking (30 mL puff volume). The carbon monoxide emissions in sidestream smoke were 61.7±2.0 and 54.0±3.7 mg carbon monoxide per tobacco cigarette and marijuana cigarette, respectively, using the standard conditions. Under extreme smoking conditions, the levels were 61.6±2.9 and 50.6±3.9 mg carbon monoxide per cigarette for tobacco and marijuana cigarettes, respectively.

Emissions from plants and biomass burning are reported to contribute approximately $1x10^{14}$ g/year to the global environment (Khalil and Rasmussen 1990). The direct emission of carbon monoxide from living plants increases as a function of solar irradiance. The source of the carbon monoxide likely occurs as a result of direct photooxidation of the plant material followed by transport to the stomata; however, the exact mechanism is not fully understood (Sanderson 2002).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is exposed to carbon monoxide through the inhalation of indoor and outdoor air. Since carbon monoxide is ubiquitous in the environment, all humans are exposed to some level of carbon monoxide. The CDC estimated that during 2004–2006, an estimated average of 20,636 emergency room visits occurred for nonfatal, unintentional, non-fire-related carbon monoxide exposures annually (CDC 2008). Approximately 73% of these exposures occurred in residences, 13% occurred in workplace settings, and the rest were in other or unknown settings. The greatest number of incidences (8,538 incidences representing approximately 41% of the cases) occurred during the winter months of December through February. Nearly 70% of the incidences were diagnosed as carbon monoxide poisoning. Table 6-3 displays the estimated number of exposure cases categorized by age and gender.

Weather-related disasters in which large segments of the population have lost power for extended periods of time often result in carbon monoxide-related accidents through the improper use of gasoline-powered devices. Two major hurricanes struck the Gulf Coast of the United States in 2005 (hurricanes Katrina and Rita) resulting in sustained power outages for many residents of the affected states. Multiple carbon monoxide poisonings were reported over the period of disrupted power, primarily due to the use of improperly vented generators (CDC 2006). Twenty-seven separate incidents of carbon monoxide

Table 6-3. Average Annual Estimated Non-Fatal Carbon Monoxide Exposure Cases in the United States Emergency Room Visits (2004–2006)

Age (years)	Number of cases[a]	Percentage of the total
0–4	2,344	11.4
5–9	1,407	6.8
10–14	1,577	7.6
15–24	3,341	16.2
25–34	4,183	20.3
35–44	2,775	13.5
45–54	2,229	10.8
55–64	1,444	7.0
≥65	1,328	6.4
Gender		
Male	9,770	47.3
Female	10,866	52.7

[a]Age data were unavailable for eight cases.

Source: CDC 2008

poisoning were reported during the dates of August 29–October 19, 2005, in Texas and Alabama, resulting in 78 nonfatal cases and 10 deaths. A portable generator was involved in 25 (93%) of the 27 incidents. Regarding the other two incidents, one involved a fixed generator and one involved a portable gas stove (CDC 2006).

Recreational water craft are a source of accidental carbon monoxide exposures (USCG 2008). A study conducted by the National Institute for Occupational Safety and Health (NIOSH) confirmed 176 acute boating-related carbon monoxide poisonings over a 15-year period at a lake on the Arizona/Utah border (CDC 2005). The findings of this study indicated that occupancy near carbon monoxide sources, failed carbon monoxide detectors, water level exhaust from generators on houseboats or cabin cruisers, and carbon monoxide from generators or propulsion engines within the airspace formed by an extended rear houseboat deck contributed to these accidents (CDC 2005).

NIOSH (1996) issued a report describing carbon monoxide poisonings that occurred through the use of small gasoline-powered engines and tools such as pressure washers, gas-powered saws, and compressors. In many cases, dangerous levels of carbon monoxide built up rapidly when using these tools, even in relatively open spaces with some ventilation like parking garages or open barns.

Blood carboxyhemoglobin (COHb) levels were measured on a cross-sectional national probability sample of persons representative of the civilian population in the United States aged 3–74 years in the second National Health and Nutrition Examination Survey (NHANES II) conducted from February 1976 to February 1980 (Radford and Drizd 1982). The statistical analysis of COHb levels in blood of the population based on smoking status and age is provided in Table 6-4. Four principal inhalation exposure routes were examined (outdoor air, indoor air, occupational exposure, and smoking). Of these four exposure routes, it was concluded that COHb levels in the population were most influenced by smoking status. Close examination of the data also indicated that COHb levels in the population tended to be greater during the winter months as opposed to the summer months, presumably due to the amount of time spent indoors where carbon monoxide levels are assumed to be higher than outdoor air. A slightly higher proportion of ex-smokers had COHb levels over 2% versus people who never smoked (5.5% versus 3.6%). This accounts for the higher mean and standard deviation for ex-smokers than for never-smokers, because the two medians are nearly identical (0.77% COHb versus 0.74% COHb, respectively). This difference may be accounted for in part or wholly by the inclusion in the ex-smoking group of people who incorrectly reported a history of having stopped smoking (Radford and Drizd 1982).

Table 6-4. Carboxyhemoglobin (COHb) Levels in the U.S. Population Based Upon Smoking Status

Age (years)	N[2a]	N[3b]	Mean COHb percent	Standard deviation	Standard error	50th percentile	75th percentile	90th percentile	95th percentile
All smoking status									
3–74	9,365	195,877	1.93	2.236	0.037	0.91	2.38	5.49	6.83
3–11	2,055	30,066	0.73	0.502	0.019	0.67	0.87	1.12	1.42
12–74	7,310	165,812	2.14	2.358	0.044	1.01	3.17	5.79	7.05
Never smoked[c]									
3–74	5,459	106,042	0.83	0.671	0.021	0.72	0.97	1.33	1.65
3–11	2,055	30,066	0.73	0.502	0.019	0.67	0.87	1.12	1.42
12–74	3,404	75,976	0.87	0.726	0.025	0.74	1.01	1.38	1.77
Ex-smokers[c]									
12–74	1,366	28,655	0.97	0.999	0.031	0.77	1.04	1.58	2.08
Current smokers[c]									
12–74	2,533	61.015	4.30	2.533	0.072	4.15	5.89	7.56	8.68

[a]N^2 = unweighted population size
[b]N^3 = population estimate in thousands
[c]Never-smokers were defined as persons who self-reported that they had smoked fewer than 100 cigarettes in their lifetimes and were not current smokers. Ex-smokers were persons who reported that they had smoked more than 100 cigarettes but were not current smokers. Current smokers were persons reporting that they were current cigarette, cigar, or pipe smokers.

Source: Radford and Drizd 1982

Additional studies have shown that COHb levels do not differ in ex-smokers versus those who never smoked (Yasuda et al. 2004).

Carbon monoxide exposure to European populations residing in five cities have been investigated through the EXPOLIS research project conducted from 1996 to 1998, and the results of this study have been summarized in several publications (Bruinen de Bruin et al. 2004a, 2004b; Hanninen et al. 2004). The geometric mean 48-hour exposure levels of nonsmoking subjects were 1.68, 0.82, 0.45, 2.17, and 1.50 mg/m^3 (1.45, 0.71, 0.39, 1.87, and 1.29 ppmv) in Athens, Basle, Helsinki, Milan, and Prague, respectively (Hanninen et al. 2004). Bruinen de Bruin et al. (2004a) used data for 50 office workers residing in Milan, Italy over a 1-year period to assess the contribution of local sources to exposure and microenvironment concentrations. This study examined the time that the subjects spent in 11 different microenvironments and three exposure-influencing activities: gas cooking, smoking, and commuting. The results of this study indicated that exposures from indoor environments contributed approximately 82% of the total carbon monoxide exposures, because this is where the study population spent over 90% of their time; however, approximately 16% of the total exposure to carbon monoxide occurred from commuting activities, even though these activities only accounted for about 7.5% of the population's time.

Occupations such as toll both workers, gas station attendants, taxi drivers, and traffic or bicycle police are potentially exposed to high levels of carbon monoxide due to emissions from automobile exhaust. Carbon monoxide levels were monitored continuously during both morning (9 AM–12 PM) and afternoon (2–4 PM) hours at seven gas stations located in New York, New Jersey, and Connecticut (API 1994). Mean (arithmetic) concentrations of carbon monoxide at the pumping islands ranged from 1.15 to 5.44 ppmv, with a maximum 1-minute level of 144 ppmv observed at one station. Firefighters and rescue/response personnel are potentially exposed to carbon monoxide levels near or exceeding recommended occupational exposure limits. A study conducted from 1986 to 1989 in northern California was performed to estimate the level of carbon monoxide that wildland firefighters are exposed to during various job tasks associated with that profession (Materna et al. 1992). Following a series of prescribed burns, the instantaneous fireline carbon monoxide levels ranged from 3 to 80 ppmv; however, firefighters who tended gasoline powered pumping engines were exposed to levels as high as 300 ppmv. The mean time-weighted average (TWA) exposure level obtained from 46 personal measurements was 14.4 ppmv, but one employee had a TWA exposure of 38 ppmv and five firefighters had TWAs >25 ppmv. Industrial or in-home use of methylene chloride paint strippers in poorly ventilated areas can lead to high levels of carbon monoxide in blood, since carbon monoxide is a metabolic byproduct of methylene chloride.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

As with adults, children are exposed to carbon monoxide through the inhalation of indoor and outdoor air. The NHANES II survey (see Table 6-4) includes COHb levels of children. Several activities may influence the levels of carbon monoxide to which children or infants are exposed. Time spent indoors versus outdoors, riding in automobiles, and exposure to second-hand tobacco smoke influence the total carbon monoxide exposure that children receive. COHb levels in children were significantly greater when measured during the winter months of November–March, as opposed to levels obtained in May–September. The average COHb level for all children in the NHANES study aged 3–11 years was 0.87% for samples collected during the winter months and 0.58% during the summer months. The location where the children in the population resided also influenced the COHb levels observed in the study. Children residing in central cities with populations over 1 million tended to have the highest mean COHb levels (1.01% in winter months and 0.77% in summer months), while children living in rural areas had mean COHb levels of 0.79% in the winter months and 0.49% during the summer months (Radford and Drizd 1982).

Pregnant females who smoke potentially expose their unborn fetus to carbon monoxide, and the health consequences of this activity have been discussed in Chapter 3. Carbon monoxide crosses the placenta and can accumulate in the fetus to a greater extent than in the mother.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Populations that are exposed to high levels of vehicular traffic are expected to have greater exposure to carbon monoxide, as compared to individuals in low traffic density areas. As discussed in Section 6.5, certain occupations such as toll workers, gas station attendants, firefighters, and other professions exposed to combustion sources may have high levels of exposure.

Members of the general population who smoke or live with smokers are exposed to higher levels of carbon monoxide than nonsmoking members of the general population. COHb levels typically average about 5% in regular smokers, but may be as high as 10% in heavy smokers (Benowitz 2003). Data from the NHANES II study indicate that mean COHb levels in the blood of smokers are approximately 4 times greater than levels for members of the nonsmoking population (Radford and Drizd 1982). More recent data support these conclusions. In a study of 11,403 men aged 35–64 years, the mean COHb level for nonsmokers was 0.79%, but rose to 6.54% for those who smoked >40 cigarettes/day (Law et al. 1997). COHb levels were measured as part of pulmonary function testing in 100 subjects in one pulmonary laboratory located in a Virginia hospital outpatient setting (Mahoney et al. 2007). COHb levels for the entire group averaged 1.9%, with a range of 1–8%. The average COHb level for nonsmokers (n=85) was 1.6%, while the level for smokers (n=15) was 3.5%. COHb levels were measured for smokers versus nonsmokers at four commercial establishments where cigarette smoking was not prohibited and COHb levels were also obtained in a control group of 50 college students and professors in a well-ventilated, nonsmoking environment (Light et al. 2007). The average COHb concentration of 33 smokers from the commercial establishments was 5.04%, while the average value for the 27 nonsmokers was 2.49%. COHb levels ranged from 1 to 6% in the nonsmokers and from 1 to 14% in the smoking group. The COHb levels in the control group were 1%.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5)(A) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of carbon monoxide is available. Where adequate information is not available, ATSDR, in conjunction with National Institute of Environmental Health Sciences (NIEHS), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of carbon monoxide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. Information is available on the physical and chemical properties of carbon monoxide (George 2001; Lide 2008; O'Neil et al. 2006; Verschueren 2001). These data are captured in Chapter 4. No data needs are identified.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2007, became available in February of 2009. This database is updated yearly and should provide a list of industrial production facilities and emissions. Adequate information on the production and use of carbon monoxide was located (George 2001); no information on the import/export of carbon monoxide was found, but these volumes are assumed to be low. Since carbon monoxide is not required to be reported under the TRI, the production and emissions from U.S. industrial facilities is not reported to the EPA. The EPA continuously updates the NEI database, which contains detailed information about sources that emit carbon monoxide. No data needs are identified.

Environmental Fate. The environmental fate of carbon monoxide is well understood. When released to the atmosphere, carbon monoxide eventually reacts with photochemically produced hydroxyl radicals and is oxidized to CO_2 (EPA 2000, 2010). Microorganisms have also been shown to oxidize carbon monoxide to CO_2 (Tolli et al. 2006). Data on the half-life of carbon monoxide in indoor environments would be desirable.

Bioavailability from Environmental Media. Carbon monoxide is a gas and is not considered bioavailable from environmental media other than air. No data needs are identified.

Food Chain Bioaccumulation. Carbon monoxide is a gas and does not bioaccumulate in the food chain. No data needs are identified.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of carbon monoxide in contaminated media at hazardous waste sites are needed so that the information obtained on levels of carbon monoxide in the environment can be used in combination with the known body burden of carbon monoxide to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

The EPA continuously monitors carbon monoxide levels throughout the United States. The EPA's NEI database contains detailed information about sources that emit criteria air pollutants, including carbon monoxide for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. The AQS database is EPA's repository of criteria air pollutant monitoring data since the 1970s. These databases are updated regularly.

Exposure Levels in Humans. All humans are exposed to carbon monoxide through the inhalation of ambient air. Indoor air levels of carbon monoxide are highly variable and depend upon the type, condition, and venting procedures of appliances. The NHANES II survey, conducted from February 1976 to February 1980, provided an analysis of COHb levels in blood of the population based on smoking status, age, race, and other factors (Radford and Drizd 1982). These data are not current; therefore, a data need exists to update these data with new monitoring results.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children are exposed to carbon monoxide by the same pathway as adults (inhalation of air). While the levels of COHb in children's blood from the NHANES II study is comprehensive, these surveys are over 2 decades old. Therefore, a data need exists to update this study with new monitoring results.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for carbon monoxide were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry

facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2009) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. A study being conducted by Ohio State University (Ross Kauffman, principal investigator) seeks to study tobacco use in two Ohio prisons. One objective of this study is to examine the influence of an indoor tobacco ban on smoking behaviors among low-security prisoners. A second objective is to provide prison administrators with the information needed to develop successful policies by gathering information on prisoner attitudes toward tobacco control policies and cessation programs in correctional settings. The study is also intended to lay the groundwork for future studies of tobacco use in prison facilities. It is anticipated that this study will address COHb levels in the prison facilities.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring carbon monoxide, its metabolites, and other biomarkers of exposure and effect to carbon monoxide. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Carbon monoxide forms a strong coordination bond with the iron atom complex of Hb forming COHb, which is a unique biomarker for carbon monoxide exposure for humans. COHb absorbs radiation in the blue wavelength region of the visible spectrum known as the Soret region (390–440 nm) and COHb levels in blood can be analyzed spectrophotometrically (Rodkey et al. 1979). Carbon monoxide-oximeters are specialized medical instruments that are employed in clinical and hospital settings to rapidly determine COHb, O_2Hb, and methemoglobin (MetHb) levels in blood by taking the difference between the light absorption at each of these Hb derivatives and the total light absorption for all Hb derivatives that are present in the blood sample (Mahoney et al. 1993). This instrument is particularly useful for measuring high levels of COHb. Fetal Hb and bilirubin have the potential to interfere with spectrophotometric determination of COHb if present in sufficient quantities. Methylene blue cardiac dye and sulfhemoglobin can also adversely affect these measurements. In addition, some carbon monoxide-oximeters have been shown to overestimate low concentrations of COHb as compared to gas chromatography (GC) methods (Mahoney et al. 1993).

GC with reduction gas detectors is a selective and sensitive method to measure the amount of carbon monoxide bound to Hb in the blood and is considered a highly reliable method for measuring exposure to carbon monoxide, especially at low levels. The addition of potassium ferricyanide to Hb-bound carbon monoxide oxidizes Hb to MetHb and releases carbon monoxide, which is injected in the gas chromatograph (Vreman et al. 1984). Carbon monoxide eluted from the GC column reacts with mercuric

oxide (HgO) to form gaseous mercury vapor; the mercury released and measured spectrophotometrically at 254 nm is proportional to the amount of carbon monoxide gas released. The detection limits for this method were reported as 0.05 nL of carbon monoxide per µL of blood, corresponding to a saturation of approximately 0.005% COHb in blood (Vreman et al. 1984).

Carbon monoxide levels in humans can be estimated by the analysis of exhaled breath using GC and electrochemical devices. In many measurement techniques, the subject performs an inhalation-breathhold maneuver and exhales through a mouthpiece into the instrument inlet. The alveolar air is retained for analysis, and the reading in ppm of carbon monoxide can be converted to COHb using a calibration curve (EPA 2000). A rapid and sensitive technique for the analysis of carbon monoxide in a single exhaled breath sample has been described (Fritsch et al. 2007). This analysis requires the subject to exhale into a mouthpiece that is attached to a Nafion® dryer and cooling trap to remove water, CO_2, and other possible interfering species. Detection is by high resolution infrared cavity ring-down laser spectroscopy in a multipath absorption cell. Amperometric electrochemical sensors have also been used for the analysis of carbon monoxide in exhaled breath and ambient air (Vreman et al. 1994). These sensors typically consist of a series of electrodes (working, reference, and counter electrodes) immersed in an electrolyte solution. Carbon monoxide diffuses through a porous Teflon membrane and is oxidized at the working electrode. The transfer of electrons that accompanies the redox reaction yields the output signal of the sensor. A reference electrode measures the potential of the electrolyte. The current flowing through the working electrode is compensated by the third electrode, a counterelectrode through which an equal and opposite current flows (Vreman et al. 1994).

The analytical methods used for the detection of carbon monoxide in biological samples are summarized in Table 7-1.

7.2 ENVIRONMENTAL SAMPLES

Analytical methods for the detection of carbon monoxide in environmental samples have been thoroughly discussed in several review articles (EPA 1991, 2000; Novelli 1999). Table 7-2 provides a summary of many of these analytical methods that are commonly employed in environmental monitoring studies of carbon monoxide. Analytical methods used to measure carbon monoxide in environmental samples require the use of high purity standard reference gas in order to frequently calibrate the instrument and ensure consistent measurements between different laboratories.

Table 7-1. Analytical Methods for Determining Carbon Monoxide in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Collect sample and transfer to a 5 mL heparinized syringe and shake for 1 minute before analysis.	Spectro-photometric determination using CO-oximeters	<5% COHb		Mahoney et al. 1993
Blood	Blood placed into 2 mL CO-free GC vial containing 100 g/L $K_3Fe(CN)_6$ in 0.1 mol/L potassium phosphate buffer, pH 6.0, containing 10 g of saponin/L.	GC with mercury reduction gas detector	0.005% COHb		Mahoney et al. 1993
Blood	Obtain blood by heel stick (infant) or fingerstick (adult) and venipuncture. Mix with $K_3Fe(CN)_6$ containing solution to liberate carbon monoxide to a headspace.	GC with mercury reduction gas detector	0.005% COHb		Vreman et al. 1984
Breath	Breath samples collected with a reverse syringe pump and analyzed within 30 minutes or kept on ice until analysis within 3 hours.	EC sensor or GC with mercury reduction gas detector	EC: 0.1 µL carbon monoxide/L air GC: 50% of the noise level of 0.01 µL carbon monoxide/L air		Vreman et al. 1994

COHb = carboxyhemoglobin; EC = electrochemical; GC = gas chromatography; $K_3Fe(CN)_6$ = potassium ferricyanide

Table 7-2. Analytical Methods for Determining Carbon Monoxide in Environmental Samples

Sample matrix	Preparation method[a]	Analytical method	Sample detection limit[b]	Percent recovery	Reference
Air	Atmospheric constituents separated using two-column isothermic chromatography in a temperature-controlled oven, followed by analysis using FID, HgO/UV absorbance, or ECD.	GC-FID GC-HgO/UV GC-ECD	25–50 ppbv GC-FID 10 ppb GC-ECD 1–2 ppb GC-HgO/UV	NR	Novelli 1999
Air	Air samples passed through reference and measurement optical cells. An optical filter is used to transmit only a small band width of infrared radiation.	NDIR-GFC	22–70 ppbv	NR	Novelli 1999
Air	Air samples introduced into commercial instruments over a wide spectral bandwidth or the use of optical filters can be employed to narrow the spectral wavelength.	FTIR	1 ppbv	NR	Novelli 1999
Air	Tune laser to 4.7 µm and measure absorption by carbon monoxide gas.	TDLS	<1 ppbv	NR	Novelli 1999
Air	Measure in fluorescence chambers operated at low pressure to avoid O_2 absorption.	RF	5 ppbv	NR	Novelli 1999
Workplace air	Each sample collected by drawing a known volume of air into a five-layer aluminized gas sampling bag. A portion of the gas sample is introduced into a gas sampling loop, injected into a gas chromatograph, and analyzed using a discharge ionization detector.	GC-DID	0.12 ppmv; (0.400 ppmv quantitative)		OSHA 1991 (Method 210)

Table 7-2. Analytical Methods for Determining Carbon Monoxide in Environmental Samples

Sample matrix	Preparation method[a]	Analytical method	Sample detection limit[b]	Percent recovery	Reference
Sea water	Water samples siphoned into a glass stopcock and a portion of the water replaced with carbon monoxide free synthetic air to create a headspace. The flask was shaken vigorously by hand for 1 minute and kept standing at room temperature for 5 minutes in the dark.	GC-FID	6 nL of carbon monoxide/L of water		Ohta 1997
Soil gas	Samples collected using a 1-cm^3 syringe fitted with a 50-mm-long 26-gauge side port needle. A 1-cm^3 sample was obtained (sampling time, about 60 seconds); the syringe was then raised, and its contents were rapidly analyzed in the field by using GC.	GC-HgO/UV	<5 ppbv	NR	King 1999b

[a]Hydrogen-rich carrier gas is used to reduce carbon monoxide to methane prior to analysis by FID and N_2O is added to a nitrogen rich carrier gas for analysis by ECD. Helium gas is used as the carrier gas for analysis by DID.
[b]Measurements of atmospheric carbon monoxide levels are relative to high purity reference gas used to calibrate the instruments.

DID = discharge ionization detector; ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; FTIR = Fourier transform spectroscopy; GFC = gas filter correlation; HgO = mercuric oxide; NDIR = non-dispersive infrared; NR = not reported; RF = resonance fluorescence; TDLS = tunable diode laser spectroscopy; UV = ultraviolet

Most techniques used for the measurement of carbon monoxide in the environment employ spectroscopic methods or GC. Non-dispersive infrared (NDIR) spectroscopy and GC using flame ionization detection (FID) are the two most common methods used to analyze carbon monoxide in environmental samples. Commercial instruments are capable of detection limits in the ppb range. For analysis by NDIR spectroscopy, air is pumped into samples cells and the absorption is measured at a carbon monoxide vibrational band at 2,174 cm^{-1} (4.7 μm). An optical filter is employed before the sample to remove light of other frequencies. Most NDIR spectrometers use gas filter correlation (GFC) methodology to improve sensitivity and reduce interferences by other gasses. In this method, the sample is simultaneously passed through both a reference cell containing a high concentration of carbon monoxide and a sample cell containing nitrogen gas. Gas species other than carbon monoxide will attenuate radiation equally in both cells; however, when carbon monoxide is present, the amount of light passing through the reference cell is unchanged, but that passing through the sample cell is absorbed at the characteristic carbon monoxide frequency. This difference in absorption between the light passing through the cells is linearly related to carbon monoxide concentrations in the air sample (EPA 2000).

In GC analysis of carbon monoxide, air samples are pumped through a silica gel or alumina pre-column followed by an analytical column composed of a molecular sieve. The pre-column captures CO_2, non-methane hydrocarbons, and water, and the molecular sieve effectively separates carbon monoxide from hydrogen gas and methane. Since the sensitivity for carbon monoxide by FID is low, a hydrogen-rich carrier gas is used to reduce carbon monoxide to methane using heated nickel as a catalyst prior to FID analysis. Minimum detection limits of 0.05 ppmv or better have been achieved (Novelli 1999). With the development of the discharge ionization detector (DID) for use with GC analysis, it is possible to measure carbon monoxide concentrations directly at low levels in occupational settings (OSHA 1991). Helium is generally used as the sample carrier gas and as the ionized species. Helium passes through a chamber where a glow discharge is generated and high-energy photons are produced. The high-energy photons pass through an aperture to a second chamber and ionize the carbon monoxide in the sample stream. The resulting ions produce an electrical current, which is measured with a standard electrometer (OSHA 1991). The greater the concentration of carbon monoxide in the sample, the more ions will be produced, resulting in a greater current. OSHA method 210 discusses the GC-DID analysis for carbon monoxide and reports a detection limit of 0.12 ppmv and quantification limit of 0.40 ppmv.

As discussed in Novelli (1999), electron capture detection (ECD) can also be used in conjunction with GC to measure atmospheric levels of carbon monoxide. Carbon monoxide does not elicit a strong

response from the ECD because it does not easily capture electrons; however, the addition of N_2O to a N_2 carrier gas improves sensitivity. In addition, GC/mass spectrometry, GC with mercury reduction gas detection, Fourier transform infrared (FTIR) spectroscopy, tunable diode laser spectroscopy (TDLS), and resonance fluorescence spectroscopy have also been used to measure carbon monoxide levels in air (Novelli 1999).

Commercially available electrochemical carbon monoxide detectors for home use can be purchased at most hardware or home improvement stores. These detectors use electrodes that reside in an electrolyte solution such as dilute sulfuric acid. Carbon monoxide is oxidized at one electrode to CO_2 and O_2 is consumed at the other electrode (Vreman et al. 1994). Measurement of the current in the cell provides a measure of the concentration of carbon monoxide in the atmosphere. Metal oxide semiconductor detectors such as tin oxide sensors operate on the principle that the resistance of a tin oxide layer decreases as carbon monoxide adsorbs to the surface of the sensor and is oxidized to CO_2 (Dobos and Zimmer 1985). When the conductance exceeds a preset threshold level, an 85 dB alarm is sounded (the same loudness as a smoke alarm). Biomimetic detectors use a gel-coated disc containing synthetic Hb that turns black when carbon monoxide is present at high levels. Reduction in the amount of transmitted light through the disc alerts the sensor to possible carbon monoxide contamination and sets off the alarm. Early carbon monoxide detectors were designed to provide an audible warning at relatively low levels of exposure and were often difficult to reset (Leikin 1996). Furthermore, the general public's knowledge regarding the use and placement of these alarms in the residence was limited. Recent changes to the design and standards of these alarms have made them more user friendly to the general population and helped to eliminate low-level activations, which can be caused by a variety of common occurrences. The use and effectiveness of these home-based alarms, including guideline standards from Underwriters Laboratory, have been reviewed by Rhee and Leikin (2007).

Ohta (1997) discussed a GC-FID method for the detection of carbon monoxide in seawater. Water samples were collected in a glass stopcock and a portion of the water was replaced with carbon monoxide free synthetic air to create a headspace. The flask was shaken vigorously by hand for 1 minute and kept standing at room temperature for 5 minutes in the absence of sunlight in order to complete the equilibration between aqueous and gaseous phases. A small portion of air (1–2 mL) was injected into the GC for analysis. Carbon monoxide concentrations were corrected based on equilibrium constants of carbon monoxide between the aqueous and gaseous phases in the flask for headspace preparation. The concentrations were further corrected for water vapor contained in the headspace gas at concentrations of

3.8–4.1% in volume at 26–27 °C. The detection limit was reported as 6 nanoliters of carbon monoxide per liter of water.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of carbon monoxide is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of carbon monoxide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. COHb is a unique biomarker of exposure for humans to carbon monoxide and accurate, sensitive methods exist for its measurement (Mahoney et al. 1993). GC methods are also available for measuring Hb-bound carbon monoxide (Vreman et al. 1984).

Effect. No specific biomarkers of effect for carbon monoxide were identified. Effects and symptoms of carbon monoxide poisoning are generally related to tissue hypoxia and are not specific for carbon monoxide exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Sensitive analytical methods are available for determining the levels of carbon monoxide in air samples. Thorough reviews on this subject are available from the EPA (1991, 2000) and Novelli (1999). Analytical methods are also available for the determination of carbon monoxide in water samples (Ohta 1997).

7.3.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2009) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified. Platypus Technologies LLC located in Madison, Wisconsin is developing a liquid crystal-based sensor for real-time detection of ozone, carbon monoxide, and CO_2. Kestrel Labs Inc. located in Boulder, Colorado is developing a new carbon monoxide-oximeter that can use laser light sources for accurate photoplethysmographic measurements of COHb.

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8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

MRLs were not derived for carbon monoxide, as discussed in Section 2.3.

EPA (IRIS 2009) has not established an oral reference dose (RfD) or an inhalation reference concentration (RfC) for carbon monoxide.

The International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), and EPA have not classified carbon monoxide for human carcinogenicity (IARC 2009; IRIS 2009; NTP 2005).

OSHA has required employers of workers who are occupationally exposed to carbon monoxide to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs) (OSHA 2009). The employer must use engineering and work practice controls to reduce exposures to not exceed 55 mg/m^3 (50 ppmv) for carbon monoxide at any time (OSHA 2009).

EPA has designated carbon monoxide as a hazardous air pollutant (HAP) under the Clean Air Act (CAA) (EPA 2009c). Additionally, under the National Ambient Air Quality Standards (NAAQS), EPA is required to set limits to protect public health, including the health of "sensitive" populations, such as asthmatics, children, and the elderly. Carbon monoxide is required to not to exceed levels of 10 and 40 mg/m^3 (9 and 35 ppmv) for 8- and 1-hour averaging times, respectively, and not to be exceeded more than once per year (EPA 2009d).

The international and national regulations, advisories, and guidelines regarding carbon monoxide in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Carbon Monoxide

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2009
WHO	Air quality guidelines		WHO 2000
	TWA based on effects other than cancer or odor/annoyance using an averaging time of:		
	15 minutes	100 mg/m^3 (87 ppm)	
	30 minutes	60 mg/m^3 (52 ppm)	
	1 hour	30 mg/m^3 (26 ppm)	
	8 hours	10 mg/m^3 (9 ppm)	
	Drinking water quality guidelines	No data	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	29 mg/m^3 (25 ppm)	ACGIH 2008
	TLV-basis (critical effect)	Carboxyhemoglobinemia	
AIHA	ERPG-1[a]	229 mg/m^3 (200 ppm)	AIHA 2008
	ERPG-2[a]	401 mg/m^3 (350 ppm)	
	ERPG-3[a]	573 mg/m^3 (500 ppm)	
EPA	AEGL-1[b]	Not recommended due to insufficient data	EPA 2009b
	AEGL-2[b]		
	10 minutes	481 mg/m^3 (420 ppm)	
	30 minutes	172 mg/m^3 (150 ppm)	
	60 minutes	95 mg/m^3 (83 ppm)	
	4 hours	38 mg/m^3 (33 ppm)	
	8 hours	31 mg/m^3 (27 ppm)	
	AEGL-3[b]		
	10 minutes	1,948 mg/m^3 (1,700 ppm)	
	30 minutes	687 mg/m^3 (600 ppm)	
	60 minutes	378 mg/m^3 (330 ppm)	
	4 hours	172 mg/m^3 (150 ppm)	
	8 hours	149 mg/m^3 (130 ppm)	
	Hazardous air pollutant	No	EPA 2009c 42 USC 7412

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Carbon Monoxide

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	National Ambient Air Quality Standards		EPA 2009d
	8-hour averaging time[c]	10 mg/m^3 (9 ppm)	
	1-hour averaging time[c]	40 mg/m^3 (35 ppm)	
NIOSH	REL (10-hour TWA)	40 mg/m^3 (35 ppm)	NIOSH 2005
	Ceiling	229 mg/m^3 (200 ppm)	
	IDLH	1,375 mg/m^3 (1,200 ppm)	
	Target organs	Cardiovascular system, lungs, blood, and central nervous system	
OSHA	PEL (8-hour TWA) for general industry	55 mg/m^3 (50 ppm)	OSHA 2009 29 CFR 1910.1000, Table Z-1
b. Water			
EPA	Drinking water standards and health advisories	No	EPA 2006a
	National primary drinking water standards	No	EPA 2003
	National recommended water quality criteria	No	EPA 2006b
c. Food			
FDA	EAFUS[d]	No	FDA 2008
d. Other			
ACGIH	Carcinogenicity classification	No	ACGIH 2008
	Biological exposure indices (end of shift)		
	Carboxyhemoglobin in blood	3.5% hemoglobin	
	Carbon monoxide in end-exhaled air	23 mg/m^3 (20 ppm)	
EPA	Carcinogenicity classification	No	IRIS 2009
	RfC	No	
	RfD	No	
	Superfund, emergency planning, and community right-to-know		

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Carbon Monoxide

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	Designated CERCLA hazardous substance	No	EPA 2009e 40 CFR 302.4
	Effective date of toxic chemical release reporting	No	EPA 2009f 40 CFR 372.65
NTP	Carcinogenicity classification	No	NTP 2005

[a]ERPG-1 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing other than mild, transient health effects. ERPG-2 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing irreversible or other serious adverse effects. ERPG-3 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without life-threatening health effects (AIHA 2008).
[b]AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects; however, the effects are not disabling and are transient and reversible upon cessation of exposure. AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death (EPA 2009b).
[c]Not to be exceeded more than once per year.
[d]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences (proposed), expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences (proposed), Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

MRLs were not derived for carbon monoxide, as discussed in Section 2.3.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

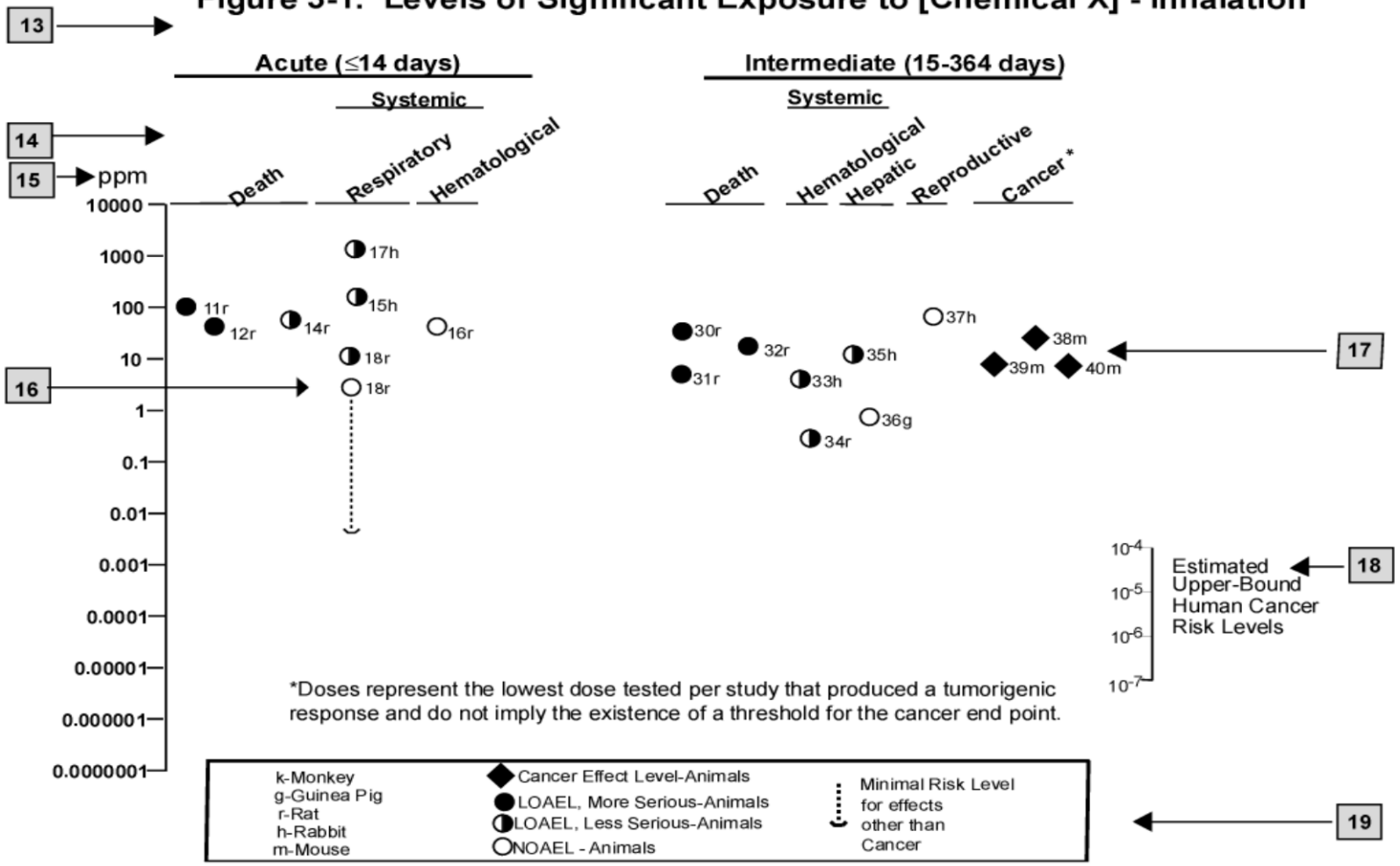
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX

Public Health England

Protecting and improving the nation's health

Carbon Monoxide

Toxicological Overview

Key Points

Kinetics and metabolism

- following inhalation, carbon monoxide binds with haemoglobin to form carboxyhaemoglobin
- when bound, it reduces the rate at which oxygen is delivered to the tissues, thereby causing hypoxia
- once exposure has ceased, oxygen competes with carbon monoxide to bind with haemoglobin; the displaced carbon monoxide is predominantly eliminated unchanged via the lungs

Health effects of acute exposure

- the most common symptoms following acute exposure are headache, nausea, vomiting, vertigo, alteration in consciousness and subjective weakness
- symptoms of severe poisoning include confusion, myocardial infarction, respiratory failure, loss of consciousness and death
- long-term neurological effects may occur following an acute exposure, including cognitive and behavioural changes

Health effects of chronic exposure

- chronic exposure to low concentrations of carbon monoxide may lead to lethargy, headaches, nausea, flu-like symptoms and neuropsychological and cardiovascular issues
- adverse outcomes including fetal and neonatal death, congenital malformations and neurological effects have been reported following acute exposure to high levels of carbon monoxide during pregnancy

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Summary of Health Effects

The signs and symptoms of carbon monoxide exposure are often non-specific, therefore poisoning can be difficult to diagnose.

The most common symptoms following acute exposure are headache, nausea and vomiting, vertigo, alteration in consciousness and subjective weakness. Severe symptoms include confusion, myocardial infarction, respiratory failure, loss of consciousness and death. The cardiovascular system and the central nervous system (CNS) are the most sensitive target organs for carbon monoxide toxicity. Following an acute exposure, neuropsychiatric features may develop in some individuals; these have been observed up to 40 days after initial exposure.

Blood carboxyhaemoglobin levels are not a reliable indicator of poisoning severity and/or clinical outcome. No significant adverse health effects have been reliably demonstrated in the literature where carbon monoxide exposure resulted in carboxyhaemoglobin levels of below 6% in healthy individuals. A carboxyhaemoglobin level of 30% indicates severe exposure, however significant poisoning effects cannot be excluded at lower concentrations.

Like acute poisoning, chronic carbon monoxide exposure can result in non-specific symptoms (headache, lethargy, syncope, nausea and flu-like symptoms), which may be misdiagnosed. Neurophysiological symptoms including anxiety, psychomotor dysfunction, loss of balance and changes in sleep, memory, vision and smell have also been reported. Epidemiological studies have linked rises in ambient air carbon monoxide and cardiovascular endpoints.

Several adverse outcomes have been reported following acute exposure to high levels of carbon monoxide during pregnancy. These include fetal and neonatal death, congenital malformations and neurological effects and are associated with moderate to severe maternal toxicity. Some studies have reported effects following chronic low level exposure to carbon monoxide during pregnancy, without maternal toxicity.

Kinetics and Metabolism

Following inhalation, carbon monoxide diffuses rapidly across the alveolar and capillary membranes of the lungs, into the blood [1]. Once absorbed, it diffuses through the plasma and enters the red blood cells, where approximately 80 – 90 % binds with haemoglobin, to form carboxyhaemoglobin. Carbon monoxide is also produced endogenously, however this alone is not associated with toxicity [2]. In non-smokers, the baseline carboxyhaemoglobin is around 1-2% while in smokers it is around 5-10% [3].

As exposure to a constant concentration of carbon monoxide continues, the blood carboxyhaemoglobin concentration increases until it reaches equilibrium with the ambient air. For example, exposure to 100 ppm carbon monoxide would result in an equilibrium concentration of carboxyhaemoglobin of 14 % (table 1). As carboxyhaemoglobin levels rise to meet equilibrium, the level is determined by the duration of exposure, pulmonary ventilation and baseline carboxyhaemoglobin levels [1]. When in equilibrium, the level of carboxyhaemoglobin is mainly dependent upon the concentrations of carbon monoxide and oxygen inhaled [1, 4].

Absorbed carbon monoxide is distributed throughout the body. Although it predominantly binds to haemoglobin, carbon monoxide also binds to other haem proteins such as myoglobin, cytochrome P450, dopamine hydroxylase and cytochrome oxidase, leading to a wide distribution [1]. Following autopsies in humans, the highest concentrations of carbon monoxide have been found in the blood, spleen, lung, kidney and skeletal muscle (and detected in the brain and adipose tissue) [2].

Carbon monoxide does not accumulate in the body as carboxyhaemoglobin is fully dissociable. Once exposure has ceased, oxygen competes with carbon monoxide for binding sites and the displaced carbon monoxide is mainly eliminated unchanged via the lungs or undergoes oxidative metabolism [1]. Conversion of carbon monoxide to carbon dioxide by oxidative metabolism is a minor route of elimination. The elimination half-life of carbon monoxide increases with age (with the greatest increase occurring from ages 2 to 20) and is approximately 6% longer in males than females [2]. The half-time elimination of carbon monoxide is 320 minutes when breathing air, 80 minutes when breathing 100% oxygen and 23 minutes with hyperbaric oxygen (at 304 kPa) [1].

Pregnant women produce more endogenous carbon monoxide, typically having carboxyhaemoglobin levels which are 20% higher than non-pregnant values [5]. Carbon monoxide may be transferred across the placenta and into fetal circulation. The elimination half-life of carbon monoxide in the fetus is up to 4 to 5 times longer than in the mother, this is due to fetal haemoglobins greater binding affinity and the relatively small diffusion gradient between maternal and fetal blood [2, 6]. At steady state this may result in fetal concentrations being up to 10-15% higher than maternal concentrations; therefore maternal levels may not accurately represent fetal levels [5, 6].

Table 1: Correlation between carbon monoxide concentration in air and blood carboxyhaemoglobin concentration

Carbon monoxide concentration (ppm)	Equilibrium carboxyhaemoglobin concentration (%)
10	1.6
15	2.4
20	3.2
25	3.9
30	4.7
40	6.1
50	7.6
100	14.0

Reference

Committee on the Medical Effects of Air Pollutants (COMEAP), Guidance on the Effects on Health of Indoor Air Pollutants, 2004.

Mechanism

The main mechanism of carbon monoxide toxicity is carboxyhaemoglobin induced hypoxia. The affinity of haemoglobin for carbon monoxide is 245-fold higher than that for oxygen [7]. Therefore haemoglobin will preferentially bind carbon monoxide over oxygen following an exposure. This decreases the oxygen carrying capacity of the blood and alters the dissociation curve of oxyhaemoglobin. As a result, the rate at which oxygen is delivered to cells is reduced, interfering with cellular respiration and causing tissue hypoxia [1].

Non-hypoxic mechanisms may also contribute to the adverse health effects associated with carbon monoxide poisoning. This is thought to be due to the ability of carbon monoxide to bind to other haem proteins that are involved in important physiological regulatory systems [2, 7, 8].

Sources and Route of Human Exposure

Inhalation is the major route of exposure to exogenous carbon monoxide [7]. Therefore, exposure by inhalation will be the focus of this entry. Dermal or ocular exposure to the liquefied gas may occur but the risk is considered to be very low.

Carbon monoxide is released into the atmosphere from both natural and anthropogenic sources [2]. It is formed following the incomplete combustion of carbonaceous fuels/materials such as diesel oils, petroleum products, domestic gas or solid fuels including charcoal [3, 4]. Natural sources of carbon monoxide in the atmosphere include volcanoes, photochemical reactions and natural fires [2]. Small amounts of carbon monoxide are also endogenously produced in the human body [7].

Global background concentrations of carbon monoxide have been recorded between 0.06-0.14 mg/m^3. 8 hour averages of ambient carbon monoxide in European cities are typically below 20 mg/m^3 with short peaks below 60 mg/m^3 [5].

The most important source of exposure to carbon monoxide for the general population is from fuel burning appliances which are poorly installed, faulty or used inappropriately (including inadequate ventilation) [4, 7]. Carbon monoxide poisonings have been reported following the use of barbeques in enclosed areas such as tents and caravans. Carbon monoxide poisoning has been reported following prolonged smoking of shisha/hooka pipes without proper ventilation [3, 4]. Neighbouring premises may also be affected by the carbon monoxide produced by an appliance in an adjoining property [4]. Inhalation of smoke from house fires can result in carbon monoxide exposure and related toxicity [3, 9].

Of 479 suspected or confirmed incidents of carbon monoxide poisoning reported to the UK National Poisons Information Service (NPIS) between 2014-2015, 84% involved exposure at home and 6% in the workplace. A faulty boiler was suspected as the cause of exposure in 62% of those occurring at home (where the source was known) [3].

Other sources of exposure to carbon monoxide include tobacco smoke, from active and passive smoking, car exhausts and incense burning. Tobacco smoke and car engines run in an integral garage may significantly contribute to indoor carbon monoxide exposure [7].

In the absence of indoor sources, outdoor concentration is the main parameter affecting indoor CO concentration, which is generally low in UK houses. Under these conditions, the indoor/outdoor (I/O) ratio of CO concentrations is almost 1.0. With gas cooking and smoking, peak CO concentrations may be increased from background levels (typically <1 mg/m^3) and I/O ratios of 1.4 and 1.2 have been reported, respectively [10]. This indicates that gas cooking should not be an issue of concern, under normal ventilation conditions. However, high peaks (>100 mg/m^3) can occur with malfunctioning or inappropriately used flued and unflued domestic appliances (boilers, heaters, fires, stoves and ovens), which burn carbon containing fuels (coal, coke, gas, kerosene and wood) [7, 11-13]. Increasing airtightness of dwellings may increase concentrations of CO to levels that could cause poisoning or lead to chronic exposure with subclinical adverse health effects [14].

Monitoring in the kitchens of UK homes have shown weekly averages of 0.3-2.7 mg/m^3, 1-hour averages of 1.9-24.5 mg/m^3 and 15-minute averages of around 180 mg/m^3 carbon monoxide [8, 11]. Measurements in the living rooms of 168 subjects in the UK yielded carbon monoxide levels of 0-48.1 mg/m^3, with the highest being in homes with fuel burning appliances [11]. In a study of 37 newly built homes, two-week mean CO concentrations did not exceed the WHO 8-hour average guideline of 10 mg/m^3 (8.6 ppm) in any home, but exceeded the 1-hour and 8-hour WHO guidelines in one home with gas cooking, in the winter peak level study [10].

A range of 0.05-0.6 mg/m^3 was measured in offices near a busy street in London. The WHO quotes peak exposures of 60-115 mg/m^3 carbon monoxide for non-accidental situations including underground car parks, enclosed ice rinks and homes with gas appliances. Experimental use of a kerosene stove in a tent lead to levels of 200-550 mg/m^3 carbon monoxide (and a mean carboxyhaemoglobin concentration of 21.5% in those exposed to it) [7].

Occupational situations in which (construction) workers may encounter significant levels of carbon monoxide include using LPG (e.g. heaters, cookers) or petrol (e.g. generators, cut off saws) powered equipment in enclosed spaces, disruption of gas flues or ventilation during building refurbishment and inadequately installing new gas appliances [15]. Workplace exposure limits (WELs) are enforced to protect workers from the harmful effects of carbon monoxide; in the UK the long term work place exposure limit (WEL) is 35 mg/m^3 (30 ppm) and the short term WEL is 232 mg/m^3 (200 ppm) [16].

Health Effects of Acute/Single Exposure

Human data

General toxicity

The cardiovascular system and the central nervous system (CNS) are particularly sensitive to carbon monoxide induced hypoxia, due to their high oxygen requirements [2].

The symptoms of carbon monoxide exposure often mimic those of more common illnesses, such as viral infections or food poisoning, resulting in cases of poisoning being difficult to diagnose and often mistaken for infections [4]. Mild exposures are associated with headache, flushing, nausea, dizziness, myalgia or neuropsychological impairment. Moderate toxicity may be associated with dizziness, ataxia and weakness while severe symptoms include confusion, myocardial infarction, respiratory failure, loss of consciousness and death [3, 6]. Skin blisters, rhabdomyolysis, compartment syndrome, acute renal failure, pulmonary oedema, dysrhythmias, retinal haemorrhages, cortical blindness, choreoathetosis, and mutism are less common features [3].

The most common symptom of carbon monoxide positioning is a headache, with nausea and vomiting, vertigo, alteration in consciousness and subjective weakness, in descending order of frequency reported (see table 2) [4].

Blood carboxyhaemoglobin levels are not a reliable indicator of poisoning severity and/or clinical outcome [3]. This may be due to other non-hypoxic mechanisms contributing to carbon monoxide toxicity, differences in individual sensitivities to carbon monoxide exposures and differences in subjective reporting of symptom type [8].

In non-smokers the baseline carboxyhaemoglobin is around 1-2% while in smokers it is around 5-10% [3]. Beyond a reduction in maximum exercise capacity, no adverse health effects have been reliably demonstrated in the literature where carbon monoxide exposure resulted in carboxyhaemoglobin levels of below 6% in healthy people [7]. Exacerbation of pre-existing cardiovascular disease has been reported in individuals with carboxyhaemoglobin levels ranging from 2-6% [2]. A carboxyhaemoglobin level of 30% or more indicates severe exposure however, significant poisoning cannot be excluded at lower concentrations [3].

Age, anaemia, existing cardio pulmonary diseases and prior exposure to carbon monoxide may determine an individual’s susceptibility to carbon monoxide toxicity as well as altitude and activity level [7].

Table 2: The frequency of the most commonly reported symptoms in carbon monoxide poisoning

Symptoms	Frequency of reporting (%)
Headache	90%
Nausea and vomiting	50%
Vertigo	50%
Alteration in consciousness	30%
Subjective weakness	20%

Reference
National Poisons Information Service (NPIS), TOXBASE. Carbon Monoxide. 2013.

Neurotoxicity

Acute exposure to carbon monoxide causes symptoms of CNS toxicity, as described in the general toxicity section.

Compensatory mechanisms act to protect the brain from carbon monoxide induced hypoxia. As carboxyhaemoglobin levels increase there is a proportional compensatory increase in arterial blood flow to the brain to prevent hypoxia. Studies have demonstrated that brain tissue metabolism remains constant up to carboxyhaemoglobin levels of 20%, suggesting hypoxia does not occur at CO lower levels [7].

Lesions of the basal ganglia and white matter have been observed in patients with acute carbon monoxide poisoning [2].

Cardiovascular toxicity

Similarly to the brain, compensatory mechanisms act against cellular hypoxia, by increasing blood flow rate to the heart to ensure a constant delivery of oxygen. At the point where blood flow cannot meet oxygen demand, the myocardium becomes ischaemic resulting in chest pain and reduced myocardial functioning [8].

In clinical studies, acute controlled low-level exposures to carbon monoxide sufficient to cause carboxyhaemoglobin levels of 2.4-5.9% exacerbated existing cardiovascular disease. Carbon monoxide exposure exacerbated exercise induced myocardial ischemia including reduced time to angina, increased duration of angina symptoms and in some cases time to ST-depression (indication of myocardial ischemia) in individuals with exertional angina. In healthy subjects, acute controlled exposure to carbon monoxide has resulted in reduced exercise performance (but not adverse cardiovascular effects) [2].

Delayed effects following an acute exposure

In some cases of severe poisoning, symptoms persist when carboxyhaemoglobin levels have returned to normal [17, 18]. Some individuals may develop neuropsychiatric features; this is more likely following, severe poisoning, loss of consciousness during exposure or in those aged over 40 [3]. Reported features include headache, memory and language impairment, disorientation, visual changes, apathy, irritability, inappropriate euphoria, inability to concentrate, personality change, neuropathy, incontinence, chorea, apraxia, psychosis, dementia and parkinsonism [3, 7].

Delayed features following acute high level exposure to carbon monoxide may develop up to 40 days after exposure [3]. The cause of such delayed neurological symptoms are largely unknown, although it has been speculated that free radical production and lipid peroxidation during the reperfusion phase, when oxygen becomes available, may contribute [18].

Cardiac damage during poisoning increases the risk of mortality for the 10 years following exposure [19].

Health Effects of Chronic/Repeated Exposure

Human data

General toxicity

Long-term low level exposure to carbon monoxide is frequently associated with faulty domestic heating appliances. Chronic carbon monoxide poisoning is often misdiagnosed or in some cases undiagnosed because the symptoms are non-specific. Features include headache, lethargy, nausea and flu-like symptoms [3].

Epidemiological studies indicate that environmental exposure to ambient levels of carbon monoxide in air may be associated with respiratory and cardiovascular morbidity [2, 7].

Respiratory

There is inconclusive evidence for an association between increasing ambient air concentrations of carbon monoxide and respiratory outcomes (e.g. exacerbation of asthma, hospitalisations and emergency room visits related to respiratory complaints) [2, 7].

Neurotoxicity

Chronic exposure to carbon monoxide has been reported to cause neurological impairments [3]. However, it has not been fully elucidated whether chronic exposure to low concentrations of carbon monoxide produces long lasting effects on the brain. Individuals may often experience short periods of acute carbon monoxide poisoning in addition to long-term low level exposure. Therefore, it can be difficult to determine the type of exposure responsible for the adverse health effects. Neuropsychological symptoms reported include anxiety, psychomotor dysfunction, loss of balance and changes in sleep, memory, vision and smell [17].

Cardiovascular toxicity

Chronic epidemiology studies have demonstrated a positive association between ambient air carbon monoxide exposure and cardiovascular morbidity (emergency department visits and hospitalisation for ischemic heart disease, congestive heart failure and cardiovascular disease) in several locations where carbon monoxide levels ranged from 0.6 to 10.9 mg/m^3 [7].

There is some evidence that chronic exposure to carbon monoxide may lead to the onset of atherosclerosis [18].

Genotoxicity

There are inadequate data available to assess the genotoxicity of carbon monoxide [2]. It would not be expected, from its structure, to have any significant mutagenic properties.

Carcinogenicity

There are limited data available on the carcinogenicity of carbon monoxide in humans. Epidemiological studies of populations exposed to ambient air concentrations of carbon monoxide have failed to show an association with increased cancer risk [2].

Reproductive and developmental toxicity

Several adverse birth outcomes have been reported following acute exposure to high levels of carbon monoxide poisoning during pregnancy. These include fetal and neonatal death, congenital malformations and neurological effects and are associated with moderate to severe (loss of consciousness/coma) maternal toxicity [6].

The risk of adverse outcomes following carbon monoxide exposure is greater in the presence of maternal toxicity; however risk to the fetus cannot be ruled out following less severe maternal toxicity or low level exposures with no maternal toxicity. Adverse outcomes following in-utero exposure to chronic low levels (e.g. smoking, ambient air pollution) of carbon monoxide, without maternal toxicity have also been investigated. Some studies have reported an association between environmental carbon monoxide exposure and pre-term delivery, low birthweight, congenital malformations (including heart defects), sudden infant death and neurodevelopmental problems [6].

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This document from the PHE Centre for Radiation, Chemical and Environmental Hazards reflects understanding and evaluation of the current scientific evidence as presented and referenced here.

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