

**TOXICOLOGICAL PROFILE FOR  
CARBON MONOXIDE**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Agency for Toxic Substances and Disease Registry

June 2012

## **DISCLAIMER**

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

## UPDATE STATEMENT

A Toxicological Profile for Carbon Monoxide, Draft for Public Comment was released in September 2009. This edition supersedes any previously released draft or final profile.

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

Agency for Toxic Substances and Disease Registry  
Division of Toxicology and Human Health Sciences (proposed)/  
Environmental Toxicology Branch (proposed)  
1600 Clifton Road NE  
Mailstop F-62  
Atlanta, Georgia 30333

This page is intentionally blank.

## 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.



Christopher J. Portier, Ph.D.  
Assistant Administrator

Agency for Toxic Substances and Disease Registry

### \*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](mailto: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.



## CONTRIBUTORS

### CHEMICAL MANAGER(S)/AUTHOR(S):

Sharon Wilbur, M.A.  
Malcolm Williams, DVM, Ph.D.  
Robert Williams, Ph.D.  
Franco Scinicariello, M.D., M.P.H.  
ATSDR, Division of Toxicology and Human Health Sciences (proposed), Atlanta, GA

Julie M. Klotzbach, Ph.D.  
Gary L. Diamond, Ph.D.  
Mario Citra, Ph.D.  
SRC, Inc., North Syracuse, NY

### 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.

This page is intentionally blank.

## 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.

This page is intentionally blank.

## CONTENTS

DISCLAIMER .....	ii
UPDATE STATEMENT .....	iii
FOREWORD .....	v
QUICK REFERENCE FOR HEALTH CARE PROVIDERS.....	vii
CONTRIBUTORS .....	ix
PEER REVIEW .....	xi
CONTENTS.....	xiii
LIST OF FIGURES .....	xvii
LIST OF TABLES.....	xix
1. PUBLIC HEALTH STATEMENT.....	1
1.1 WHAT IS CARBON MONOXIDE? .....	1
1.2 WHAT HAPPENS TO CARBON MONOXIDE WHEN IT ENTERS THE ENVIRONMENT?.....	2
1.3 HOW MIGHT I BE EXPOSED TO CARBON MONOXIDE?.....	2
1.4 HOW CAN CARBON MONOXIDE ENTER AND LEAVE MY BODY?.....	3
1.5 HOW CAN CARBON MONOXIDE AFFECT MY HEALTH?.....	3
1.6 HOW CAN CARBON MONOXIDE AFFECT CHILDREN?.....	3
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CARBON MONOXIDE? .....	4
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CARBON MONOXIDE? .....	5
1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? .....	5
1.10 WHERE CAN I GET MORE INFORMATION? .....	6
2. RELEVANCE TO PUBLIC HEALTH .....	9
2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CARBON MONOXIDE IN THE UNITED STATES .....	9
2.2 SUMMARY OF HEALTH EFFECTS.....	10
2.3 CARBON MONOXIDE DOSE-RESPONSE RELATIONSHIPS .....	20
2.4 MINIMAL RISK LEVELS (MRLs) .....	20
3. HEALTH EFFECTS.....	25
3.1 INTRODUCTION.....	25
3.2 DISCUSSION OF HEALTH EFFECTS.....	30
3.2.1 Death.....	34
3.2.2 Systemic Effects .....	38
3.2.3 Immunological and Lymphoreticular Effects.....	97
3.2.4 Neurological Effects.....	98
3.2.5 Reproductive Effects .....	104
3.2.6 Developmental Effects .....	105
3.2.7 Cancer.....	139
3.3 GENOTOXICITY.....	139
3.4 TOXICOKINETICS.....	141
3.4.1 Absorption.....	141
3.4.2 Distribution .....	143
3.4.3 Metabolism.....	148

3.4.4	Elimination and Excretion.....	154
3.4.5	Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models .....	155
3.5	MECHANISMS OF ACTION .....	174
3.5.1	Pharmacokinetic Mechanisms.....	174
3.5.2	Mechanisms of Toxicity.....	176
3.5.3	Animal-to-Human Extrapolations .....	182
3.6	TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS .....	183
3.7	CHILDREN’S SUSCEPTIBILITY .....	184
3.8	BIOMARKERS OF EXPOSURE AND EFFECT .....	187
3.8.1	Biomarkers Used to Identify or Quantify Exposure to Carbon Monoxide .....	188
3.8.2	Biomarkers Used to Characterize Effects Caused by Carbon Monoxide.....	188
3.9	INTERACTIONS WITH OTHER CHEMICALS .....	189
3.10	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE .....	192
3.11	METHODS FOR REDUCING TOXIC EFFECTS.....	193
3.11.1	Reducing Peak Absorption Following Exposure.....	194
3.11.2	Reducing Body Burden .....	194
3.11.3	Interfering with the Mechanism of Action for Toxic Effects .....	195
3.12	ADEQUACY OF THE DATABASE .....	195
3.12.1	Existing Information on Health Effects of Carbon Monoxide .....	196
3.12.2	Identification of Data Needs.....	196
3.12.3	Ongoing Studies .....	203
4.	CHEMICAL AND PHYSICAL INFORMATION.....	207
4.1	CHEMICAL IDENTITY.....	207
4.2	PHYSICAL AND CHEMICAL PROPERTIES.....	207
5.	PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL .....	211
5.1	PRODUCTION .....	211
5.2	IMPORT/EXPORT .....	211
5.3	USE .....	211
5.4.	DISPOSAL.....	212
6.	POTENTIAL FOR HUMAN EXPOSURE .....	213
6.1	OVERVIEW.....	213
6.2	RELEASES TO THE ENVIRONMENT .....	215
6.2.1	Air .....	215
6.2.2	Water.....	217
6.2.3	Soil .....	217
6.3	ENVIRONMENTAL FATE .....	218
6.3.1	Transport and Partitioning.....	218
6.3.2	Transformation and Degradation .....	219
6.3.2.1	Air.....	219
6.3.2.2	Water.....	219
6.3.2.3	Sediment and Soil .....	219
6.4	LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT .....	220
6.4.1	Air .....	220
6.4.2	Water.....	234
6.4.3	Sediment and Soil .....	234
6.4.4	Other Environmental Media.....	234
6.5	GENERAL POPULATION AND OCCUPATIONAL EXPOSURE .....	235
6.6	EXPOSURES OF CHILDREN.....	240

6.7	POPULATIONS WITH POTENTIALLY HIGH EXPOSURES .....	241
6.8	ADEQUACY OF THE DATABASE .....	241
6.8.1	Identification of Data Needs .....	242
6.8.2	Ongoing Studies .....	244
7.	ANALYTICAL METHODS.....	245
7.1	BIOLOGICAL MATERIALS.....	245
7.2	ENVIRONMENTAL SAMPLES .....	246
7.3	ADEQUACY OF THE DATABASE .....	252
7.3.1	Identification of Data Needs .....	252
7.3.2	Ongoing Studies.....	253
8.	REGULATIONS, ADVISORIES, AND GUIDELINES.....	255
9.	REFERENCES .....	259
10.	GLOSSARY .....	303
APPENDICES		
A.	ATSDR MINIMAL RISK LEVELS AND WORKSHEETS .....	A-1
B.	USER'S GUIDE.....	B-1
C.	ACRONYMS, ABBREVIATIONS, AND SYMBOLS.....	C-1
D.	INDEX .....	D-1

This page is intentionally blank.



## LIST OF FIGURES

2-1. Blood Carboxyhemoglobin (COHb) Levels Corresponding to Adverse Health Effects of Carbon Monoxide in Humans .....	21
3-1. Hypoxic Hypoxia Human and Carbon Monoxide Rat Curves .....	102
3-2. Hypoxic Hypoxia Human and Carbon Monoxide Human Curves .....	103
3-3. Summary of Carbon Monoxide Uptake, Distribution, and Elimination Pathways.....	142
3-4. Temporal Profile of Blood Carboxyhemoglobin (%) for Hypothetical Continuous Exposures to Air Carbon Monoxide at Concentrations of 25, 200, or 1,000 ppm .....	144
3-5. Oxyhemoglobin Dissociation Curve for Normal Human Blood Containing 50% Carboxyhemoglobin and for Blood of an Anemic Human.....	153
3-6. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance .....	157
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) .....	161
3-8. Structure of the Smith et al. (1994) Model.....	164
3-9. Structure of the Hill et al. (1977) Maternal-Fetal Model.....	168
3-10. Structure of the Bruce et al. (2008) Model.....	172
3-11. Potential Signaling Pathways Modulated by Carbon Monoxide .....	180
3-12. Existing Information on Health Effects of Carbon Monoxide .....	197

This page is intentionally blank.

## LIST OF TABLES

2-1. Blood Carboxyhemoglobin Levels Corresponding to Adverse Health Effects of Carbon Monoxide.....	22
3-1. Carbon Monoxide Exposures and Carboxyhemoglobin Levels Associated with Health Effects from Selected Studies Representing the Lowest Adverse Effect Levels.....	26
3-2. Predicted Steady-State Blood Carboxyhemoglobin (COHb) Levels.....	29
3-3. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Respiratory Disease .....	41
3-4. Effects of Acute-duration Exposure to Carbon Monoxide on Cardiovascular Function in Patients with Coronary Artery Disease .....	56
3-5. Effects of Acute-Duration Carbon Monoxide Exposure on Cardiovascular Function in Healthy Subjects.....	65
3-6. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Cardiovascular Disease.....	73
3-7. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Hospital Admissions and Emergency Department Visits Related to Cardiovascular Disease.....	81
3-8. Selected Epidemiological Studies of Associations Between Ambient Carbon Monoxide Concentrations and Developmental Outcomes.....	107
3-9. Effects of Gestational or Perinatal Exposure on Developmental Outcomes in Animals.....	125
3-10. Genotoxicity of Carbon Monoxide.....	140
3-11. Post-Mortem Tissue Distribution of Carbon Monoxide in Humans.....	146
3-12. Hemoglobin and Myoglobin Binding Kinetics and Equilibrium Constants for Oxygen and Carbon Monoxide.....	151
3-13. Parameter Values for Coburn-Forster-Kane (CFK) Model .....	160
3-14. Parameter Values for the Smith et al. (1994) Model.....	163
3-15. Parameter Values for the Hill et al. (1977) Model .....	166
3-16. Parameter Values for the Bruce et al. (2008) Model.....	170
3-17. Heme Proteins Modulated by Carbon Monoxide .....	178
3-18. Ongoing Studies on the Health Effects of Carbon Monoxide .....	204

4-1. Chemical Identity of Carbon Monoxide.....	208
4-2. Physical and Chemical Properties of Carbon Monoxide.....	209
6-1. Carbon Monoxide Emissions (Thousands of Short Tons) from 1970 to 2008.....	216
6-2. 1-Hour and 8-Hour Maximum Carbon Monoxide Levels at Monitoring Stations Throughout the United States.....	221
6-3. Average Annual Estimated Non Fatal Carbon Monoxide Exposure Cases in the United States Emergency Room Visits (2004–2006) .....	236
6-4. Carboxyhemoglobin Levels in the U.S. Population Based Upon Smoking Status.....	238
7-1. Analytical Methods for Determining Carbon Monoxide in Biological Samples .....	247
7-2. Analytical Methods for Determining Carbon Monoxide in Environmental Samples .....	248
8-1. Regulations, Advisories, and Guidelines Applicable to Carbon Monoxide .....	256