

# **TOXICOLOGICAL PROFILE FOR COPPER**

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

September 2004

## **DISCLAIMER**

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

## UPDATE STATEMENT

A Toxicological Profile for Copper, Draft for Public Comment was released in September 2002. 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/Toxicology Information Branch  
1600 Clifton Road NE,  
Mailstop F-32  
Atlanta, Georgia 30333



## 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 hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous 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 focus of the profiles is 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. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of 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 health professionals at the Federal, State, and local levels; 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 have also 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.

  
Julie Louise Gerberding, M.D., M.P.H.  
Administrator  
Agency for Toxic Substances and  
Disease Registry

### \*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare 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. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 7, 2003 (68 FR 63098). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792) and October 25, 2001 (66 FR 54014). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

## 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:** 1-888-42-ATSDR or (404) 498-0110    **Fax:** (770) 488-4178  
**E-mail:** [atsdric@cdc.gov](mailto:atsdric@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, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.



## CONTRIBUTORS

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

Alfred Dorsey, DVM  
ATSDR, Division of Toxicology, Atlanta, GA

Lisa Ingerman, Ph.D.  
Steven Swarts, Ph.D.  
Syracuse Research Corporation, 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 Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.



## PEER REVIEW

A peer review panel was assembled for copper (September 2002 profile). The panel consisted of the following members:

1. Dr. Jonathan H. Freedman, Center for Environmental Genomes, Duke University, Durham, North Carolina;
2. Dr. Paul Mushak, PB Associates, Durham, North Carolina; and
3. Dr. Robert B. Ruckner, School of Medicine, Department of Nutrition, University of California at Davis, Davis, California.
4. Dr. Edward Massaro, U.S. Environmental Protection Agency, Reproductive Toxicology Facility, Durham, North Carolina

These experts collectively have knowledge of copper'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. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

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.



## 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 COPPER?.....	1
1.2    WHAT HAPPENS TO COPPER WHEN IT ENTERS THE ENVIRONMENT?.....	2
1.3    HOW MIGHT I BE EXPOSED TO COPPER? .....	3
1.4    HOW CAN COPPER ENTER AND LEAVE MY BODY? .....	6
1.5    HOW CAN COPPER AFFECT MY HEALTH? .....	6
1.6    HOW CAN COPPER AFFECT CHILDREN? .....	7
1.7    HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO COPPER? .....	7
1.8    IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO COPPER? .....	8
1.9    WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?.....	8
1.10   WHERE CAN I GET MORE INFORMATION?.....	9
2. RELEVANCE TO PUBLIC HEALTH .....	11
2.1    BACKGROUND AND ENVIRONMENTAL EXPOSURES TO COPPER IN THE UNITED STATES.....	11
2.2    SUMMARY OF HEALTH EFFECTS .....	12
2.3    MINIMAL RISK LEVELS (MRLs) .....	15
3. HEALTH EFFECTS .....	21
3.1    INTRODUCTION .....	21
3.2    DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE .....	21
3.2.1  Inhalation Exposure .....	22
3.2.1.1  Death .....	22
3.2.1.2  Systemic Effects .....	22
3.2.1.3  Immunological and Lymphoreticular Effects .....	25
3.2.1.4  Neurological Effects .....	25
3.2.1.5  Reproductive Effects .....	25
3.2.1.6  Developmental Effects .....	31
3.2.1.7  Cancer.....	31
3.2.2  Oral Exposure.....	32
3.2.2.1  Death .....	32
3.2.2.2  Systemic Effects .....	32
3.2.2.3  Immunological and Lymphoreticular Effects .....	62
3.2.2.4  Neurological Effects .....	63
3.2.2.5  Reproductive Effects .....	63

3.2.2.6	Developmental Effects .....	63
3.2.2.7	Cancer .....	64
3.2.3	Dermal Exposure .....	64
3.2.3.1	Death .....	64
3.2.3.2	Systemic Effects .....	65
3.2.3.3	Immunological and Lymphoreticular Effects .....	65
3.2.3.4	Neurological Effects .....	65
3.2.3.5	Reproductive Effects .....	65
3.2.3.6	Developmental Effects .....	65
3.2.3.7	Cancer .....	65
3.2.4	Other Routes of Exposure .....	66
3.3	GENOTOXICITY .....	66
3.4	TOXICOKINETICS .....	68
3.4.1	Absorption .....	68
3.4.1.1	Inhalation Exposure .....	68
3.4.1.2	Oral Exposure .....	70
3.4.1.3	Dermal Exposure .....	72
3.4.2	Distribution .....	72
3.4.2.1	Inhalation Exposure .....	72
3.4.2.2	Oral Exposure .....	72
3.4.2.3	Dermal Exposure .....	73
3.4.3	Metabolism .....	73
3.4.4	Elimination and Excretion .....	74
3.4.4.1	Inhalation Exposure .....	74
3.4.4.2	Oral Exposure .....	74
3.4.4.3	Dermal Exposure .....	74
3.4.4.4	Other Routes of Exposure .....	74
3.4.5	Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models .....	74
3.5	MECHANISMS OF ACTION .....	76
3.5.1	Pharmacokinetic Mechanisms .....	76
3.5.2	Mechanisms of Toxicity .....	78
3.5.3	Animal-to-Human Extrapolations .....	79
3.6	TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS .....	80
3.7	CHILDREN'S SUSCEPTIBILITY .....	81
3.8	BIOMARKERS OF EXPOSURE AND EFFECT .....	85
3.8.1	Biomarkers Used to Identify or Quantify Exposure to Copper .....	86
3.8.2	Biomarkers Used to Characterize Effects Caused by Copper .....	87
3.9	INTERACTIONS WITH OTHER CHEMICALS .....	88
3.10	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE .....	89
3.11	METHODS FOR REDUCING TOXIC EFFECTS .....	91
3.11.1	Reducing Peak Absorption Following Exposure .....	91
3.11.2	Reducing Body Burden .....	92
3.11.3	Interfering with the Mechanism of Action for Toxic Effects .....	93
3.12	ADEQUACY OF THE DATABASE .....	93
3.12.1	Existing Information on Health Effects of Copper .....	93
3.12.2	Identification of Data Needs .....	95
3.12.3	Ongoing Studies .....	102
4.	CHEMICAL AND PHYSICAL INFORMATION .....	105
4.1	CHEMICAL IDENTITY .....	105
4.2	PHYSICAL AND CHEMICAL PROPERTIES .....	105

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL .....	111
5.1 PRODUCTION .....	111
5.2 IMPORT/EXPORT .....	117
5.3 USE.....	117
5.4 DISPOSAL .....	118
6. POTENTIAL FOR HUMAN EXPOSURE .....	121
6.1 OVERVIEW .....	121
6.2 RELEASES TO THE ENVIRONMENT .....	124
6.2.1 Air .....	129
6.2.2 Water.....	135
6.2.3 Soil .....	141
6.3 ENVIRONMENTAL FATE.....	142
6.3.1 Transport and Partitioning.....	143
6.3.1.1 Ambient Air.....	143
6.3.1.2 Ambient Waters.....	144
6.3.1.3 Ambient Soils .....	146
6.3.1.4 Bioconcentration and Biomagnification .....	149
6.3.2 Transformation and Degradation .....	151
6.3.2.1 Air.....	151
6.3.2.2 Water .....	151
6.3.2.3 Sediment and Soil.....	155
6.3.2.4 Other Media.....	158
6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT .....	158
6.4.1 Air .....	158
6.4.2 Water.....	163
6.4.3 Sediment and Soil .....	167
6.4.4 Other Environmental Media.....	171
6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE .....	182
6.6 EXPOSURES OF CHILDREN .....	183
6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES .....	184
6.8 ADEQUACY OF THE DATABASE.....	185
6.8.1 Identification of Data Needs .....	185
6.8.2 Ongoing Studies .....	189
7. ANALYTICAL METHODS .....	193
7.1 BIOLOGICAL MATERIALS .....	193
7.2 ENVIRONMENTAL SAMPLES.....	193
7.3 ADEQUACY OF THE DATABASE.....	197
7.3.1 Identification of Data Needs .....	198
7.3.2 Ongoing Studies .....	198
8. REGULATIONS AND ADVISORIES .....	201
9. REFERENCES .....	207
10. GLOSSARY .....	267

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



## LIST OF FIGURES

3-1. Levels of Significant Exposure to Copper – Inhalation.....	28
3-2. Levels of Significant Exposure to Copper – Oral.....	50
3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance .....	77
3-4. Existing Information on Health Effects of Copper.....	94
6-1. Frequency of NPL Sites with Copper Contamination .....	122



## LIST OF TABLES

3-1. Levels of Significant Exposure to Copper – Inhalation.....	26
3-2. Levels of Significant Exposure to Copper – Oral.....	28
3-3. Genotoxicity of Copper <i>In Vivo</i> .....	67
3-4. Genotoxicity of Copper <i>In Vitro</i> .....	69
3-5. Ongoing Studies on Copper.....	103
4-1. Chemical Identity of Copper .....	106
4-2. Chemical Identity of Copper Sulfate .....	107
4-3. Physical and Chemical Properties of Copper and Copper Sulfate.....	109
5-1. Facilities that Produce, Process, or Use Copper .....	112
5-2. Facilities that Produce, Process, or Use Copper Compounds.....	114
6-1. Releases to the Environment from Facilities that Produce, Process, or Use Copper.....	125
6-2. Releases to the Environment from Facilities that Produce, Process, or Use Copper Compounds ...	127
6-3. Summary of Copper Concentrations in Environmental Media .....	130
6-4. Global Emissions of Copper from Natural Sources ( $\times 10^6$ kg/year).....	131
6-5. Global Emissions of Copper from Anthropogenic Sources ( $\times 10^6$ kg/year).....	132
6-6. Concentrations of Copper in Particulate Matter (<10 $\mu$ m) Generated from Various Sources.....	134
6-7. Concentrations of Copper in Water .....	139
6-8. Concentrations of Copper in Air.....	160
6-9. Particle Size Distributions and Total Copper Concentrations in Dust Collected at Four Mine Waste Pump Sites in Butte, Montana .....	162
6-10. Concentration of Copper in Surface Soils of the United States (in ppm-Dry Weight [dw], Equivalent to mg/kg-dw).....	168
6-11. Geometric Means of Selected Soil Elements and Associated Soil Parameters in U.S. Surface Soils by Land Resource Regions.....	169
6-12. Copper Content of Selected Foods (mg/kg) .....	173
6-13. Copper Content of Human Tissues and Body Fluids .....	178

6-14. Agricultural Sources of Copper Contamination in Soils .....	181
6-15. Ongoing Studies on Environmental Fate and the Potential for Human Exposure to Copper .....	190
7-1. Analytical Methods for Determining Copper in Biological Materials .....	194
7-2. Analytical Methods for Determining Copper in Environmental Samples .....	195
8-1. Regulations and Guidelines Applicable to Copper .....	202