

**DRAFT  
TOXICOLOGICAL PROFILE FOR  
COPPER**

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

September 2002

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## **UPDATE STATEMENT**

Toxicological profiles are revised and republished as necessary, but no less than once every three years. 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, E-29  
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.

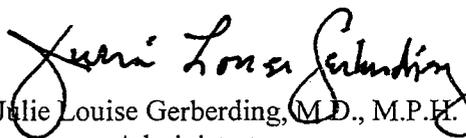
The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry  
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Atlanta, Georgia 30333

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 October 25, 2001 (66 FR 54014). 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); and October 21, 1999 (64 FR 56792). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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 is being 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

## 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.

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### *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:** (404) 498-0057  
**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.

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### ***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.

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### ***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](mailto:AOEC@AOEC.ORG) • Web Page: <http://www.aoc.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.

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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 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. The panel consisted of the following members:

1. Dr. Jonathan H. Freedman, Center for Environmental Genomes, Duke University, Durham, NC;
2. Dr. Paul Mushak, PB Associates, Durham, NC; and
3. Dr. Robert B. Ruckner, School of Medicine, Department of Nutrition, University of California at Davis, Davis, CA.

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.



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## 1. PUBLIC HEALTH STATEMENT

This public health statement tells you about copper and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Copper has been found in at least 884 of the 1,613 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which copper is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are 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 copper, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and the route of exposure (how you come in contact with it). You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

### 1.1 WHAT IS COPPER?

Copper is a reddish metal that occurs naturally in rock, soil, water, sediment, and, at low levels, air. Its average concentration in the earth's crust is about 50 parts copper per million parts soil (ppm) or, stated another way, 50 grams of copper per 1,000,000 grams of soil. Copper also occurs naturally in all plants and animals. It is an essential element for all known living organisms including humans and other animals at low levels of intake. At much higher levels, some toxic effects can occur.

## 1. PUBLIC HEALTH STATEMENT

Metallic copper can be easily molded or shaped. The reddish color of this element is most commonly seen in the U.S. penny, electrical wiring, and some water pipes. It is also found in many mixtures of metals, called alloys, such as brass and bronze. Many compounds (substances formed by joining two or more chemicals) of copper exist. These include naturally occurring minerals as well as manufactured chemicals. The most commonly used compound of copper is copper sulfate. Many copper compounds can be recognized by their blue-green color. When we speak of copper, we will not only be referring to copper metal, but also to compounds of copper that may be in the environment.

Copper is extensively mined and processed in the United States and is primarily used as the metal or alloy in the manufacture of wire, sheet metal, pipe, and other metal products. Copper compounds are most commonly used in agriculture to treat plant diseases, like mildew, or for water treatment and as preservatives for wood, leather, and fabrics. For more information on the properties and uses of copper, please see Chapters 4 and 5.

### **1.2 WHAT HAPPENS TO COPPER WHEN IT ENTERS THE ENVIRONMENT?**

Copper can enter the environment through releases from the mining of copper and other metals, and from factories that make or use copper metal or copper compounds. Copper can also enter the environment through domestic waste water, combustion of fossil fuels and wastes, wood production, phosphate fertilizer production, and natural sources (for example, windblown dust, from native soils, volcanoes, decaying vegetation, forest fires, and sea spray). Therefore, copper is widespread in the environment. About 1,400,000,000 pounds of copper were released into the environment by industries in 2000. Copper is often found near mines, smelters, industrial settings, landfills, and waste disposal sites.

When copper is released into soil, it typically becomes strongly attached to the organic material and minerals in the top layers of soil and does not move very far when it is released. When copper is released into water, the copper that dissolves can be carried in surface waters either as free copper or, more likely, bound to particles suspended in the water. Because copper binds so strongly to suspended particles and sediments, it typically does not enter groundwater. Copper

## 1. PUBLIC HEALTH STATEMENT

that enters water eventually collects in the sediments of rivers, lakes, and estuaries. Copper is carried on particles emitted from smelters and ore processing plants, and is then carried back to earth through gravity or in rain or snow. Copper is also carried into the air on windblown metallurgical dust. Indoor release of copper comes mainly from combustion processes (for example, kerosene heaters).

Copper does not break down in the environment. Copper can be found in plants and animals, and at high concentrations in mussels and oysters. Copper is also found in a range of concentrations in many foods and beverages that we eat and drink, including drinking water. You will find additional information on the fate of copper in the environment in Chapters 5 and 6.

### 1.3 HOW MIGHT I BE EXPOSED TO COPPER?

Copper is common in the environment. You may be exposed to copper by breathing air, drinking water, eating food, and by skin contact with soil, water, and other copper-containing substances. Most copper compounds found in air, water, sediment, soil, and rock are so strongly attached to dust and dirt or imbedded in minerals. However, you can still be exposed to copper upon ingestion of water or soil that contains copper or, to a lesser extent, by inhalation of copper-containing dust. Some copper in the environment is less tightly bound to particles and may be taken up by plants and animals. Soluble copper compounds (those that dissolve in water), which are most commonly used in agriculture, are more likely to threaten your health. When soluble copper compounds are released into lakes and rivers, they generally become attached to particles in the water within approximately 1 day. This could lessen your exposure to copper in water, depending on how strongly the copper is bound to the particles and how much of the particles settle into lake and river sediments.

The concentration of copper in air ranges from a few nanograms (1 nanogram equals 1/1,000,000,000 of a gram) in a cubic meter of air ( $\text{ng}/\text{m}^3$ ) to about 200  $\text{ng}/\text{m}^3$ . Near smelters, which process copper ore into metal, concentrations may reach 5,000  $\text{ng}/\text{m}^3$ . You may breathe

## 1. PUBLIC HEALTH STATEMENT

high levels of copper-containing dust if you live or work near copper mines or processing facilities.

You may be exposed to high levels of soluble copper in your drinking water, especially if your water is corrosive and you have copper plumbing and brass water fixtures. The average concentration of copper in tap water ranges from 20 to 75 parts copper per billion parts water (ppb). However, many households have copper concentrations of over 1,000 ppb. That is more than 1 milligram per liter of water. This is because copper is picked up from copper pipes and brass faucets when the water sits in the pipes overnight. After the water is allowed to run for 15–30 seconds, the concentration of copper in the water decreases.

The average concentration of copper in lakes and rivers is 4 ppb. The average copper concentration in groundwater is similar to that in lakes and rivers; however, monitoring data indicate that some groundwater contains higher levels of copper. This copper is generally strongly attached to particles in the water. Lakes and reservoirs recently treated with copper compounds to control algae or receive cooling water from a power plant may have high concentrations of dissolved copper. Once in natural water, much of this copper soon attaches to particles or converts to forms that can settle into sediments. This can limit exposure to copper unless the sediments are stirred; for example, by the resuspension and swallowing of sediments by swimmers in recreational waters.

Garden products containing copper that are used to control certain plant diseases are also a potential source of exposure. For example, you can find copper compounds in some fungicides.

Soil generally contains between 2 and 250 ppm copper, although concentrations close to 17,000 ppm have been found near copper and brass production facilities. High concentrations of copper may be found in soil because dust from these industries settles out of the air, or wastes from mining and other copper industries are disposed of on the soil. Another common source of copper in soil results from spreading sludge from sewage treatment plants. This copper generally stays strongly attached to the surface layer of soil. You may be exposed to this copper

## 1. PUBLIC HEALTH STATEMENT

by skin contact. Children may also be exposed to this copper by eating the dirt and dust generated therefrom.

Food naturally contains copper. You eat and drink about 1 milligram (1/1,000 of a gram) of copper every day. Copper is essential in your diet for good health.

While some hazardous waste sites on the NPL contain high levels of copper, we do not always know how high it is above natural levels. We also do not know what form it is in at most of these sites. However, evidence suggests that most copper at these sites is strongly attached to soil.

You may be exposed to copper in the workplace. If you work in the industry of mining copper or processing the ore, you are exposed to copper by breathing copper-containing dust or by skin contact. If you grind or weld copper metal, you may breathe high levels of copper dust and fumes. Occupational exposure to forms of copper that are soluble or not strongly attached to dust or dirt would most commonly occur in agriculture, water treatment, and industries such as electroplating, where soluble copper compounds are used.

For more information on the potential for exposure to copper, please refer to Chapter 6.

#### **1.4 HOW CAN COPPER ENTER AND LEAVE MY BODY?**

Copper can enter your body when you drink water or eat food, soil, or other substances that contain copper. Copper can also enter your body if you breathe air or dust containing copper. Copper may enter the lungs of workers exposed to copper dust or fumes.

Copper rapidly enters the bloodstream and is distributed throughout the body after you eat or drink it. Other foods eaten with copper can affect the amount of copper that enters the bloodstream. Your body is very good at blocking high levels of copper from entering the bloodstream. We do not know how much copper enters the body through the lungs or skin. Copper then leaves your body in feces and urine, mostly in feces. It takes several days for

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copper to leave your body. Generally, the amount of copper in your body remains constant (the amount that enters your body equals the amount that leaves). More information on how copper enters and leaves the body is presented in Chapter 3.

**1.5 HOW CAN COPPER AFFECT MY HEALTH?**

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Copper is essential for good health. However, exposure to higher doses can be harmful. Long-term exposure to copper dust can irritate your nose, mouth, and eyes, and cause headaches, dizziness, nausea, and diarrhea. If you drink water that contains higher than normal levels of copper, you may experience vomiting, diarrhea, stomach cramps, and nausea. Intentionally high intakes of copper can cause liver and kidney damage and even death. We do not know if copper can cause cancer in humans. EPA has determined that copper is not classifiable as to human carcinogenicity.

More detailed information on the health effects of copper in animals and humans can be found in Chapter 3.

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**1.6 HOW CAN COPPER AFFECT CHILDREN?**

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

Exposure to high levels of copper will result in the same types of effects in children and adults. We do not know if children are more susceptible to the toxicity of copper than adults. Studies in animals suggest that children may have more severe effects than adults; we do not know if this would also be true in humans. There is a very small percentage of infants and children who are unusually sensitive to copper. We do not know if copper can cause birth defects or other developmental effects in humans. Studies in animals suggest that ingestion of high levels of copper may cause a decrease in fetal growth.

**1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO COPPER?**

If your doctor finds that you have been exposed to significant amounts of copper, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate. The greatest potential source of copper exposure is through drinking water, especially in water that is first drawn in the morning after sitting in copper piping and brass faucets overnight. To reduce copper in drinking water, run the water for at least 15–30 seconds before using it.

**1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO COPPER?**

Copper is normally found in all tissues of the body, blood, urine, feces, hair, and nails. High levels of copper in the blood, urine, hair, and nails can show that you have been exposed to higher than normal levels of copper. Tests to measure copper levels in the body are not usually available at a doctor's office because they require special equipment. Although these tests can show that you have been exposed to higher than normal copper levels, they can not be used to

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predict the extent of exposure or potential health effects. More detailed information on the measurement of copper is provided in Chapters 3 and 7.

### **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. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA).

Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated 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 copper include the following:

EPA has determined that drinking water should not contain more than 1.3 mg copper per liter of water (1.3 mg/L). EPA has developed regulations on the amount of copper released by industry.

OSHA has set a limit of 0.1 milligrams/cubic meter (mg/m<sup>3</sup>) of copper fumes (vapor generated from heating copper) and 1.0 mg/m<sup>3</sup> of copper dusts (fine metallic copper particles) and mists

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(aerosol of soluble copper) in workroom air to protect workers during an 8-hour work shift (40-hour workweek).

The Food and Nutrition Board of the Institute of Medicine has developed recommended dietary allowances (RDAs) of 340 micrograms ( $\mu\text{g}$ ) of copper per day for children aged 1–3 years, 440  $\mu\text{g}/\text{day}$  for children aged 4–8 years, 700  $\mu\text{g}/\text{day}$  for children aged 9–13 years, 890  $\mu\text{g}/\text{day}$  for children aged 14–18 years, and 900  $\mu\text{g}/\text{day}$  for adults. This provides enough copper to maintain health. Further information on regulations and guidelines pertaining to copper is provided in Chapter 8.

### 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

Agency for Toxic Substances and Disease Registry  
Division of Toxicology  
1600 Clifton Road NE, Mailstop E-29  
Atlanta, GA 30333  
Web site: <http://www.atsdr.cdc.gov>

\* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)  
Fax: 1-404-498-0057

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

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\* To order toxicological profiles, contact

National Technical Information Service  
5285 Port Royal Road  
Springfield, VA 22161  
Phone: 1-800-553-6847 or 1-703-605-6000

## 2. RELEVANCE TO PUBLIC HEALTH

The primary purpose of this chapter is to provide a summary of the health effects of copper based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for the primary health effects of copper. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

For a more detailed discussion of the toxicity of copper and the potential for human exposure, please see Chapters 3 and 6, respectively.

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO COPPER IN THE UNITED STATES

Copper is a metallic element that occurs naturally as the free metal. Most copper compounds occur in +1 Cu(I) and +2 Cu(II) valence states. Copper is primarily used as a metal or an alloy (e.g., brass, bronze, gun metal). Copper sulfate is used as a fungicide, algicide, and nutritional supplement. Copper particulates are released into the atmosphere by windblown dust; volcanic eruptions; and anthropogenic sources, primarily copper smelters and ore processing facilities. Copper particles in the atmosphere will settle out or be removed by precipitation. The mean concentration of copper in ambient air in the United States is 5–200 ng/m<sup>3</sup>. Copper is released into waterways by natural weathering of soil and rocks, disturbances in soil, or anthropogenic sources (e.g., effluent from sewage treatment plants). Copper concentrations in drinking water vary widely as a result of variations in pH and hardness of the water supply; the levels range from a few ppbs to 10 ppm. The mean concentration of copper in soil in the United States ranges from 14 to 41 mg/kg. The daily intake of copper from food is 1.0–1.3 mg/day for adults.

The general population is exposed to copper through inhalation, consumption of food and water, and dermal contact with air, water, or soil that contains copper. The primary source of copper is the diet; however, the amount of copper in the diet does not usually exceed the dietary requirements for copper. Drinking water is the primary source of excess copper. Populations living near sources of copper emissions, such as copper smelters and refineries and workers in these and other industries may also be exposed to high levels of copper in dust by inhalation. Copper has been identified in at least 884 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA NPL.

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**2.2 SUMMARY OF HEALTH EFFECTS**

Copper is an essential nutrient that is incorporated into a number of metalloenzymes involved in hemoglobin formation, carbohydrate metabolism, catecholamine biosynthesis, and cross-linking of collagen, elastin, and hair keratin. The copper-dependent enzymes, some of which are cytochrome c oxidase, superoxide dismutase, ferroxidases, monoamine oxidase, and dopamine  $\beta$ -monooxygenase, function to reduce molecular oxygen. Symptoms associated with copper deficiency in humans include normocytic, hypochromic anemia, leukopenia, and osteoporosis; copper deficiency is rarely observed in the U.S. general population. In the United States, the median intake of copper from food is 0.93–1.3 mg/day for adults (0.013–0.019 mg Cu/kg/day using a 70-kg reference body weight). A recommended dietary allowance (RDA) of 0.9 mg/day (0.013 mg/kg/day) has recently been established .

Copper is readily absorbed from the stomach and small intestine; after nutritional requirements are met, there are several mechanisms that prevent copper overload. Excess copper absorbed into gastrointestinal mucosal cells is bound to the metal binding protein metallothionein. This bound copper is excreted when the cell is sloughed off. Copper that eludes the intestinal barrier can be stored in the liver or incorporated into bile and excreted in the feces. Although copper homeostasis plays an important role in the prevention of copper toxicity, exposure to excessive levels of copper can result in a number of adverse health effects including liver and kidney damage, anemia, immunotoxicity, and developmental toxicity. Many of these effects are consistent with oxidative damage to membranes or macromolecules. Copper can bind to the sulfhydryl groups of several enzymes, such as glucose-6-phosphatase and glutathione reductase, thus interfering with their protection of cells from free radical damage.

One of the most commonly reported adverse health effect of copper is gastrointestinal distress. Vomiting, nausea, and abdominal pain, usually occurring shortly after drinking beverages that were stored in a copper or untinned brass container or first draw water (water that sat in the pipe overnight) . The observed effects are not usually persistent or associated with other health effects. Animal studies have also reported gastrointestinal effects (hyperplasia of forestomach mucosa) following ingestion of copper sulfate in the diet. Copper is also irritating to the respiratory tract. Coughing, sneezing, runny nose, pulmonary fibrosis, and increased vascularity of the nasal mucosa have been reported in workers exposed to copper dust.

The liver is also a sensitive target of toxicity. Liver damage (necrosis, fibrosis, abnormal biomarkers of liver damage) have been reported in individuals ingesting lethal doses of copper sulfate. Liver effects

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have also been observed in individuals diagnosed with Wilson's disease, Indian childhood cirrhosis, or idiopathic copper toxicosis. These syndromes are genetic disorders that result in an accumulation of copper in the liver; the latter two syndromes are associated with excessive copper exposure.

Inflammation, necrosis, and altered serum marker of liver damage have been observed in rats fed diets with copper sulfate levels that are at least 100 times higher than the nutritional requirement. Damage to the proximal convoluted tubules of the kidney have also been observed in rats. The liver and kidney effects usually occur at similar dose levels; however, the latency period for the kidney effects is longer than for the liver effects.

There is some evidence from animal studies to suggest that exposure to airborne copper or high levels of copper in drinking water can damage the immune system. Impaired cell-mediated and humoral-mediated immune function have been observed in mice. Studies in rats, mice, and mink suggest that exposure to high level of copper in the diet can result in decreased embryo and fetal growth.

The carcinogenicity of copper has not been adequately studied. An increase in cancer risk has been found among copper smelters; however, the increased risk has been attributed to concomitant exposure to arsenic. Increased lung and stomach cancer risks have also been found in copper miners. However, a high occurrence of smoking and exposure to radioactivity, silica, iron, and arsenic preclude associating the risk with copper exposure. Animal studies have not found increased cancer risks in orally exposed rats or mice. IARC has classified copper 8-hydroxyquinoline in Group 3, unclassifiable as to carcinogenicity in humans and EPA has classified copper in Group D, not classifiable as to human carcinogenicity

A more detailed discussion of the critical targets of copper toxicity, the gastrointestinal tract and the liver, follows.

**Gastrointestinal Effects.** The available human and animal data suggest that the gastrointestinal tract is a sensitive target of toxicity. There are numerous reports of nausea, vomiting, and abdominal pain immediately after ingesting beverages contaminated with copper; these effects are not usually persistent. Nausea, vomiting, and/or abdominal pain have been observed following exposure to a single dose of copper sulfate of 4 mg/L and higher, which is equivalent to a dose of 0.011 mg/kg. These symptoms were also reported in adults drinking water containing >3 mg/L copper sulfate (0.0731 mg Cu/kg/day) for 1–2 weeks. Similar gastrointestinal effects were observed in adults ingesting copper oxide. Although gastrointestinal irritation may play a role in the observed gastrointestinal effects, data from ferrets and

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monkeys suggest that vagal afferent fibers and 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors are involved in copper-induced emesis.

**Hepatic Effects.** In humans, copper-induced hepatic damage is dependent on several factors including genetics, age, and copper intake. Liver damage is rarely reported in adults; the few reported cases of liver damage (centrilobular necrosis, jaundice, and increased aspartate aminotransferase activity) have been associated with intentional ingestion of a lethal dose of copper sulfate. In infants and children, reported liver effects are usually manifested in one of three syndromes: Wilson's disease, Indian childhood cirrhosis, and idiopathic copper toxicosis. Wilson's disease is an autosomal recessive genetic disorder associated with impaired copper metabolism. Although very high levels of copper are found in the liver, dietary exposure to higher than normal levels of copper does not appear to be necessary for the manifestation of liver damage. There is strong evidence that Indian childhood cirrhosis and idiopathic copper toxicosis are also caused by a genetic defect that is transmitted in an autosomal recessive mode. However, unlike Wilson's disease, manifestation of the disease is associated with exposure to unusually high levels of dietary copper from milk stored in copper or brass containers or from drinking water. The clinical age of onset is usually between 6 months and 5 years, and the observed liver effects include pericellular fibrosis, abnormal biochemical markers of liver damage (e.g., increased serum aspartate aminotransferase and alkaline phosphatase activities and serum bilirubin levels), and very high levels of copper in the liver. In general, the potential hepatotoxicity of copper has not been extensively investigated in healthy humans. Two studies have established no effect levels of 0.14 and 0.315 mg Cu/kg/day in adults and infants, respectively; both studies used serum chemistry biomarkers (e.g., alanine aminotransferase, aspartate aminotransferase) to assess liver damage.

Adverse liver effects have been observed in rats exposed to dietary copper levels that were more than 100 times higher than the nutritional requirement. The liver effects included inflammation, necrosis, and abnormal serum chemistry markers of liver damage. Rats appear to develop a tolerance to copper doses of 180–<550 mg Cu/kg/day. Tolerance is defined as “the ability to endure the continued or increasing administration of a toxicant and the capacity to exhibit less response to a test dose than previous”. As the levels of hepatic copper increase, so does the severity of the damage until peak copper levels are reached. After about 3–5 weeks of exposure, the copper levels begin to decline and are maintained at a steady level for the remainder of the exposure period. When the hepatic levels decline, regeneration of hepatic tissue is observed, and continued exposure or exposure to higher doses does not result in more tissue damage. The decline in hepatic copper levels and regeneration of damaged tissue occurs early at higher doses. At

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doses >550 mg Cu/kg/day, the liver becomes permanently overloaded and chronic hepatitis develops. Regeneration was also not seen at doses of 140 mg Cu/kg/day and lower.

### 2.3 MINIMAL RISK LEVELS (MRLs)

#### *Inhalation MRLs*

The available data on the toxicity of inhaled copper were considered inadequate for derivation of acute-, intermediate-, or chronic-duration inhalation MRLs. Data on the inhaled toxicity of copper in humans following acute-duration exposure are limited to a report of workers developing metal fume fever while cutting brass pipe with an electric cutting tool in a poorly ventilated area (Armstrong et al. 1983); exposure levels were not reported. Respiratory effects and impaired immune function have been observed in mice following a single exposure to 3.3 mg Cu/m<sup>3</sup> as copper sulfate or repeated exposure to 0.12–0.13 mg Cu/m<sup>3</sup> as copper sulfate (Drummond et al. 1986). The Drummond et al. (1986) study was not used to derive an acute-duration inhalation MRL because a small number of animals was tested (four per group) and a limited number of end points (respiratory tract and immune function) were examined. Intermediate-duration data are limited to studies by Johansson et al. (1983, 1984), which did not find any histological alterations in the lungs or functional or morphological alterations in alveolar macrophages of rabbits exposed to copper chloride. As with the acute-duration data, the limited number of end points examined preclude deriving an intermediate-duration inhalation MRL. The chronic-duration database for copper consists of two occupational exposure studies reporting respiratory (Askergren and Mellgren 1975; Suciú et al. 1981) and gastrointestinal (Suciú et al. 1981) irritation, hepatic effects (Suciú et al. 1981), and possible neurological and reproductive effects (Suciú et al. 1981). Chronic-duration inhalation MRLs cannot be derived from these studies due to poor exposure characterization and/or lack of controls.

#### *Oral MRLs*

C An MRL of 0.02 mg/kg/day has been derived for acute-duration oral exposure (1–14 days) to copper.

The available human and animal acute-duration studies strongly suggest that the gastrointestinal tract is the most sensitive target of copper toxicity. Numerous studies have reported nausea, vomiting, and abdominal pain immediately following ingestion of copper-contaminated water or other beverages. In studies involving a single exposure to copper, adverse gastrointestinal effects (nausea, vomiting, abdominal pain, and/or diarrhea) have been observed at doses of 0.011–0.08 mg Cu/kg (Araya et al. 2001;

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Gotteland et al. 2001; Nicholas and Brist 1968; Olivares et al. 2001); the study by Olivares et al. (2001) reported a no effect level of 0.0057 mg/kg. Several studies have examined the gastrointestinal tract effects following repeated exposure to elevated levels of copper in drinking water. In a 2-week study, 60 women were given copper sulfate containing water to be used for drinking and cooking purposes. An increased occurrence of nausea, vomiting, and/or abdominal pain was observed when the women were given 5 mg/L copper sulfate (0.0731 mg Cu/kg/day) (Pizarro et al. 1999). No adverse effects were noted at copper concentrations of 1 or 3 mg/L (0.0006 or 0.0272 mg Cu/kg/day). Nausea, vomiting, and/or abdominal pain were also reported by women ingesting water containing 5 mg/L (0.1 mg Cu/kg/day) as copper sulfate or copper oxide for 1 week (Pizarro et al. 2001). Animal studies support the identification of the gastrointestinal tract as a sensitive target of toxicity. Hyperplasia of the forestomach mucosa was observed in rats exposed to 44 mg Cu/kg/day as copper sulfate in the diet (NTP 1993) and in mice exposed to 197 mg Cu/kg/day as copper sulfate in the diet (NTP 1993). At higher doses, liver and kidney damage have been observed (Haywood 1980; Haywood and Comerford 1980; Haywood et al. 1985b; NTP 1993).

An acute-duration oral MRL of 0.02 mg Cu/kg/day was derived for copper based on gastrointestinal effects using the data from the Pizarro et al. (1999) study. To estimate total copper exposure, the concentration of copper in the drinking water (0.0272 mg Cu/kg/day) was added to the reported average dietary copper intake (0.0266 mg Cu/kg/day). The total copper exposure level of 0.0538 mg Cu/kg/day was considered a no-observed-adverse-effect-level (NOAEL) for gastrointestinal effects. The NOAEL was divided by an uncertainty factor of 3 (to account for human variability) to yield an acute-duration oral MRL of 0.02 mg Cu/kg/day. The acute-duration MRL, which accounts for dietary exposure as well as environmental contamination, is approximately 2 times higher than the RDA and is slightly higher than the upper end of the range of typical dietary intakes.

- C The acute-duration oral MRL of 0.02 mg Cu/kg/day has been adopted as the intermediate-duration oral MRL.

There are limited data on the intermediate-duration toxicity of copper in humans. In a study by Pratt et al. (1985), a group of seven adults were administered 10 mg Cu/day (0.14 mg Cu/kg/day) as copper gluconate in a capsule for 12 weeks. No significant alterations in serum markers of liver damage (cholesterol and triglyceride levels and aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, and lactate dehydrogenase activities) were found. Similarly, no alterations in total bilirubin, serum alanine aminotransferase, serum aspartate aminotransferase, or gamma glutamyl transferase were observed in infants exposed to 0.315 mg Cu/kg/day for 9 months (Olivares et al. 1998). Neither study

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reported significant alterations in the occurrence of gastrointestinal disturbances, although the high dropout rate observed in the copper-exposed infants may have been related to gastrointestinal effects. Severe liver damage (pericellular fibrosis, increased serum aminotransferase and alkaline phosphatase activities) has been observed in children with a genetic susceptibility to high levels of copper in the liver. Numerous studies in rats support the identification of the liver as a critical target of toxicity following intermediate-duration oral exposure. Inflammation, necrosis, and increased alanine and aspartate aminotransferases activities have been reported at exposure levels of 16 mg Cu/kg/day as copper sulfate in the diet (Haywood 1980, 1985; Haywood and Comerford 1980; Haywood and Loughran 1985; Haywood et al. 1985a; NTP 1993). No liver effects were observed at 8 mg Cu/kg/day (NTP 1993). The Pratt et al. (1985) and Olivares et al. (1998) studies provide suggestive evidence that liver effects are not likely to occur at lower doses than gastrointestinal effects following intermediate-duration oral exposure.

The database on the chronic oral toxicity of copper is inadequate for derivation of a MRL. Massie and Aiello (1984) reported a 15% decrease in the lifespan in mice exposed to 4.2 mg Cu/kg/day as copper gluconate in drinking water.



### 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 copper. 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.

#### 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not

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the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for copper. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. 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 within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

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**3.2.1 Inhalation Exposure****3.2.1.1 Death**

No studies were located regarding death of humans or animals following inhalation exposure to copper.

**3.2.1.2 Systemic Effects**

No studies were located regarding cardiovascular, musculoskeletal, renal, dermal, or body weight effects in humans or animals following inhalation exposure to copper.

Respiratory, gastrointestinal, hematological, hepatic, endocrine, and ocular effects were observed in humans. Respiratory effects have also been observed in animals exposed to copper sulfate aerosols.

**Respiratory Effects.** In humans, copper is a respiratory irritant. Workers exposed to copper dust report a number of symptoms that are suggestive of respiratory irritation, including coughing, sneezing, thoracic pain, and runny nose (Askergren and Mellgren 1975; Suciú et al. 1981). In the Suciú et al. (1981) study of 75–100 workers involved in sieving copper, lung radiographs revealed linear pulmonary fibrosis, and in some cases, nodulation. During the first year of operation, the workers were exposed to 434 mg Cu/m<sup>3</sup>; the exposure levels declined each year, and by year 3, the levels were 111 mg Cu/m<sup>3</sup>. In sheet metal workers exposed to patina dust (copper-hydroxide-nitrate, copper-hydroxide-sulfate, copper silicate, copper oxide), 6 of the 11 examined workers had increased vascularity and superficial epistatic vessels in the nasal mucosa (Askergren and Mellgren 1975); no exposure levels were reported.

Copper is considered the etiologic agent in the occupational disease referred to as “vineyard sprayer’s lung”. This disease, which is observed in vineyard workers spraying an antimildew agent containing 1–2.5% copper sulfate neutralized with hydrated lime, was first described in humans by Cortez Pimentel and Marques (1969). In most cases, published information on this disease comes from case reports (Cortez Pimentel and Marques 1969; Cortez Pimentel and Menezes 1975; Stark 1981; Villar 1974; Villar and Nogueira 1980) with no concentration-response information. Common findings include intraalveolar desquamation of macrophages, formation of histiocytic and noncaseating granulomas containing inclusions of copper, and healing of lesions in the form of fibrohyaline nodules, very similar to those found in silicosis (Cortez Pimentel and Marques 1969; Plamenac et al. 1985). Higher incidences of abnormal columnar cells, squamous metaplasia without atypia, copper containing macrophages,

### 3. HEALTH EFFECTS

eosinophilia, and respiratory spirals were found in the sputa of smoking and nonsmoking vineyard sprayers, as compared to rural workers from the same geographic region who did not work in the vineyards (Plamenac et al. 1985).

Mild respiratory effects have been observed in hamsters and mice exposed to airborne copper sulfate. Decreased cilia beating was also observed in hamsters, but not in mice, exposed to 3.3 mg Cu/m<sup>3</sup> as copper sulfate for 3 hours (Drummond et al. 1986). Alveolar thickening was observed in mice exposed to 0.12 mg Cu/m<sup>3</sup> as copper sulfate for 3 hours/day, 5 days/week for 1–2 weeks (Drummond et al. 1986); the severity of the effect increased with the duration of exposure. In rabbits exposed to 0.6 mg Cu/m<sup>3</sup> as copper chloride for 6 hours/day, 5 days/week for 4–6 weeks, the only histological alteration in the lungs was a slight increase in alveolar type II cell volume density (Johansson et al. 1984); this effect was not considered adverse. No functional or morphological alterations were observed in the alveolar macrophages of similarly exposed rabbits (Johansson et al. 1983).

**Gastrointestinal Effects.** In workers involved in grinding and sieving copper dust, anorexia, nausea, and occasional diarrhea were reported (Suciu et al. 1981); exposure levels ranged from 111 to 434 mg Cu/m<sup>3</sup> over a 3-year period. It is likely that the observed gastrointestinal effects were due to oral exposure to copper. Ingestion probably resulted from mucociliary clearance of copper particles deposited in the nasopharyngeal and tracheobronchial regions of the respiratory tract.

No studies were located regarding gastrointestinal effects in animals following inhalation exposure to copper.

**Hematological Effects.** Decreased hemoglobin and erythrocyte levels have been observed in workers exposed to airborne copper levels of 0.64–1.05 mg/m<sup>3</sup>. Results of hair analysis reveal that the workers were also exposed to iron, lead, and cadmium (Finelli et al. 1981).

No studies were located regarding hematological effects in animals following inhalation exposure to copper.

**Hepatic Effects.** Hepatomegaly was observed in workers involved in grinding and sieving copper dust (Suciu et al. 1981); the exposure levels ranged from 111 to 434 mg Cu/m<sup>3</sup>.

No studies were located regarding hepatic effects in animals following inhalation exposure to copper.

### 3. HEALTH EFFECTS

**Endocrine Effects.** Seven cases of enlargement of the sella turcica, nonsecretive hypophyseal adenoma, accompanied by obesity, arterial hypertension, and "red facies" were observed in 75–111 workers exposed to 111–434 mg Cu/m<sup>3</sup> as copper dust (Suciu et al. 1981). The study authors noted that there was a possibility that the clinical manifestations of hypophyseal adenoma or of Cushing's syndrome may have been the result of a disturbance of copper metabolism. The significance of this effect and its relationship to copper exposure cannot be determined.

**Ocular Effects.** Eye irritation has been reported by workers exposed to copper dust (Askergren and Mellgren 1975). The irritation is likely due to direct contact with the copper rather than a systemic effect resulting from inhalation exposure.

**Other Systemic Effects.** A few studies have reported metal fume fever, a 24–48-hour illness characterized by chills, fever, aching muscles, dryness in the mouth and throat, and headache, in workers exposed to copper dust or fumes (Armstrong et al. 1983; Gleason 1968). Gleason (1968) reported airborne copper dust concentrations of 0.075–0.12 mg/m<sup>3</sup>. It has been suggested that other metals present in the workplace may have been the causative agent for the metal fume fever, rather than copper. This is supported by the small number of reports of metal fume fever despite the extensive use of copper in many industries (Borak et al. 2000).

#### 3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans following inhalation exposure to copper.

Data on the immunotoxicity of copper are limited to an acute-duration exposure study in which mice were exposed to copper sulfate (Drummond et al. 1986). Increased mortality and decreased survival time were observed in mice challenged by an aerosol of *Streptococcus zooepidemicus* following 0.56 mg Cu/m<sup>3</sup> for 3 hours or 0.13 mg Cu/m<sup>3</sup> for 3 hours/day, 5 days/week for 2 weeks (Drummond et al. 1986). Decreased bactericidal activity was also observed in mice exposed to 3.3 mg Cu/m<sup>3</sup> for 3 hours or 0.12 mg Cu/m<sup>3</sup> for 3 hours/day, 5 days/week for 2 weeks following exposure to an aerosol of *Klebsiella pneumonia* (Drummond et al. 1986).

These LOAEL values for immunological effects are recorded in Table 3-1 and plotted in Figure 3-1.

### 3. HEALTH EFFECTS

#### 3.2.1.4 Neurological Effects

Only one study examining neurological effects was located. Headache, vertigo, and drowsiness were reported in factory workers exposed to 111–434 mg/m<sup>3</sup> copper dust (Suciu et al. 1981).

#### 3.2.1.5 Reproductive Effects

Sexual impotence was reported in 16% of 75–100 workers exposed to 111–434 mg/m<sup>3</sup> copper dust during grinding and sieving operations (Suciu et al. 1981). The significance of this finding is difficult to assess because a control group was not used.

No studies were located regarding reproductive effects in animals following inhalation exposure to copper.

#### 3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans and animals following inhalation exposure to copper.

#### 3.2.1.7 Cancer

There are limited data for humans and no data for animals on the carcinogenicity of inhaled copper. Although a number of studies have examined cancer risk among copper smelters, these papers are not discussed because the cancer risk has been attributed to exposure to arsenic rather than to copper. In a study of over 6,700 male workers at a Chinese copper mine, significant increases in the risk of cancer (all sites combined) (standardized mortality ratio [SMR] =123; 95% confidence interval [CI] =109–139), stomach cancer (SMR=131; 95% CI=105–161), and lung cancer (SMR=147; 95% CI=112–189) were

Table 3-1 Levels of Significant Exposure to Copper - Inhalation

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less Serious (mg/m3)	Serious (mg/m3)	
<b>ACUTE EXPOSURE</b>							
<b>Systemic</b>							
1	Mouse	3 hr	Resp	3.3			Drummond et al. 1986
2	Mouse	1-2 wk 5d/wk 3hr/d	Resp		0.12 (alveoli thickening)		Drummond et al. 1986
3	Hamster	3 hr	Resp	1.21	3.3 (decr cilia beating frequency)		Drummond et al. 1986
4	Hamster	1-2 wk 5d/wk 3hr/d	Resp	0.13			Drummond et al. 1986
<b>Immuno/ Lymphoret</b>							
5	Mouse	1-2 wk 5d/wk 3hr/d			0.12 (decr bactericidal activity)	0.13 (decr mean survival time)	Drummond et al. 1986
6	Mouse	3 hr			3.3 (decr bactericidal activity)	0.56 (decr mean survival time)	Drummond et al. 1986
<b>INTERMEDIATE EXPOSURE</b>							
<b>Systemic</b>							
7	Rabbit (NS)	1 mo 5d/wk 6hr/d	Resp	0.6 M			Johansson et al. 1983 copper chloride
8	Rabbit (NS)	4-6 wk 5d/wk 6hr/d	Resp	0.6 M			Johansson et al. 1984 copper chloride

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Table 3-1 Levels of Significant Exposure to Copper - Inhalation (continued)

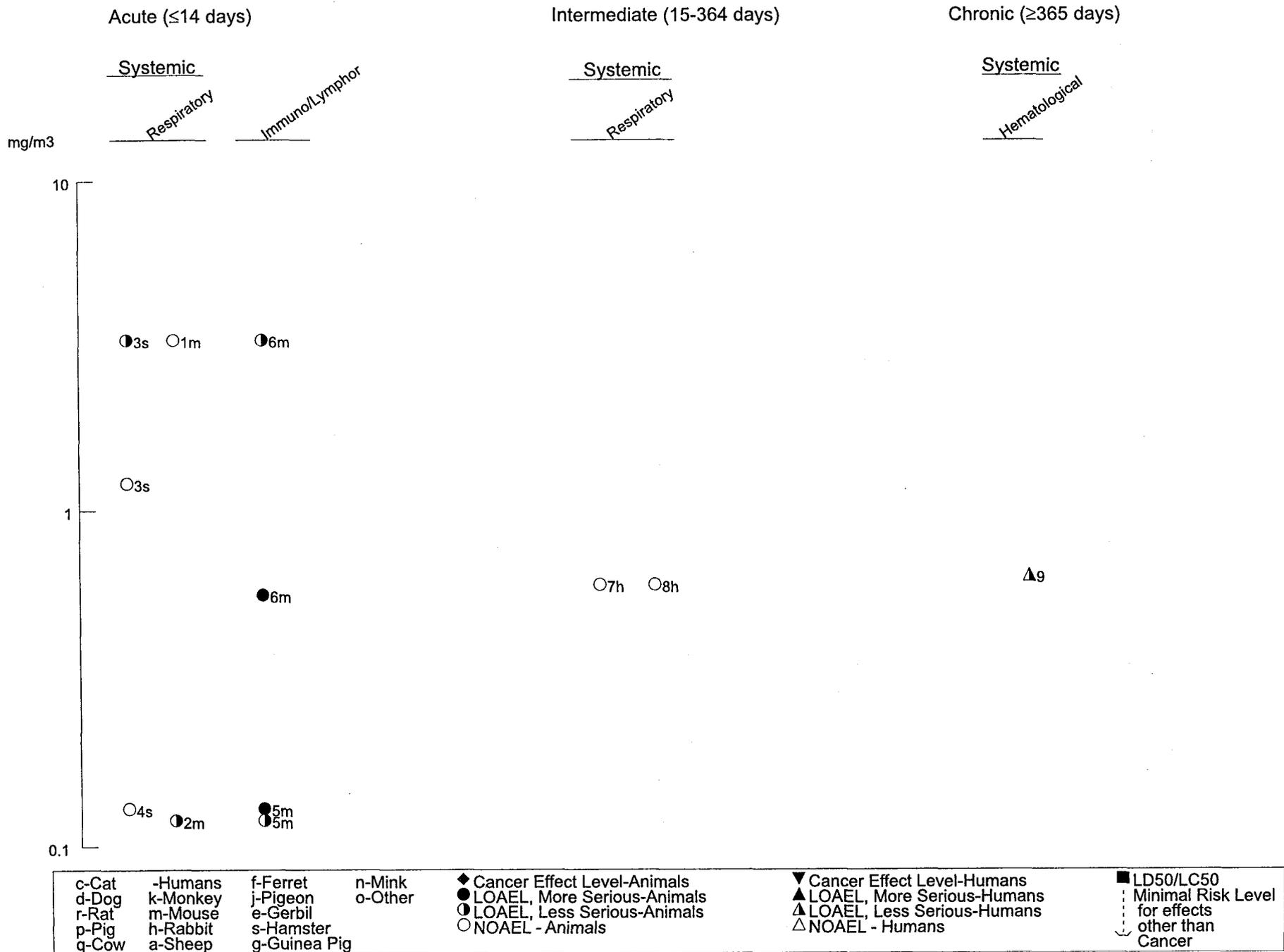
Key to figure <sup>a</sup>	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/m3)	Less Serious (mg/m3)	Serious (mg/m3)	
<b>CHRONIC EXPOSURE</b>							
<b>Systemic</b>							
9	Human	8 hr/d, 5 d/wk	Hemato		0.64 (decr hemoglobin and erythrocyte levels)		Finelli et al. 1981 NS

<sup>a</sup>The number corresponds to entries in Figure 3-1.

d = day(s); decr = decreased; hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; (NS) = not specified; Resp = respiratory; wk = week(s); yr = year(s)

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Figure 3-1 Levels of Significant Exposure to Copper - Inhalation



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### 3. HEALTH EFFECTS

observed (Chen et al. 1993). The cancer risk increased with increasing duration of employment and time since first exposure and was also higher in workers employed in the 1950s when there was a dramatic increase in production, dry drilling methods were used, and there was poor underground ventilation. The workers were divided into two groups underground miners and drilling miners, to assess the relative contribution of exposure to radon and radon daughters, radioactivity levels of  $1.29 \times 10^{-11}$  Ci/L measured between 1960 and 1990. Increases in lung cancer risk were observed in both groups, thus suggesting that exposure to radioactivity was not the primary source of increased cancer risk. Other exposures to silica, iron, titanium, sulfur, and arsenic that may have contributed to the overall cancer risk. A significant increase in the risk of silicosis was also observed in the miners. In a 7-year follow-up of this cohort (Chen et al. 1995), the risk of all sites of cancer (SMR=129; 95% CI=117–142), stomach cancer (SMR=141; 95% CI=116–169), and lung cancer (SMR=152; 95% CI=123–187) were still significantly elevated. This study also conducted a smoking survey and found that a higher percentage of the miners were smokers (71.7%) than in the control population of local residents (64.3%); this increased smoking rate, along with exposure to radioactivity, silica, iron, and arsenic may have contributed to the increased cancer risk.

#### 3.2.2 Oral Exposure

##### 3.2.2.1 Death

A number of deaths have been reported in individuals intentionally ingesting large doses of copper sulfate (Chuttani et al. 1965). Thirteen of 53 individuals died after ingesting 6–637 mg/kg copper; because the amount of copper sulfate was self-reported, the estimated doses may be inaccurate. The deaths were attributed to shock and hepatic and/or renal complications. Deaths, probably due to central nervous system depression and hepatic and renal failure, have also been reported in individuals ingesting “spiritual green water”, which contains 100 mg copper sulfate/L (Akintonwa et al. 1989).

Increased mortality was observed in rats fed a diet containing 4,000 ppm of copper (. 133 mg Cu/kg/day) for 1 week. Anorexia, possibly the result of taste aversion, contributed to the deaths (Boyden et al. 1938). Weanling rats exposed to 300 mg Cu/kg/day as Cu(II) in the diet (6,000 ppm) died after 2 weeks (Haywood 1985). The deaths were attributed to extensive centrilobular necrosis.

Lifetime exposure to 42.5 mg Cu/kg/day as copper gluconate in drinking water resulted in a 12.8% reduction of the maximal lifespan (from 986 to 874 days) in mice (Massie and Aiello 1984).

### 3. HEALTH EFFECTS

The doses associated with deaths in the Haywood (1985) and Massie and Aiello (1984) studies are recorded in Table 3-2 and plotted in Figure 3-2.

#### 3.2.2.2 Systemic Effects

No studies were located regarding endocrine, dermal, ocular, or metabolic effects in humans or animals following oral exposure to copper.

The highest NOAEL values and all reliable LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

**Respiratory Effects.** Data on the potential of copper to induce respiratory effects are limited to the NTP (1993) study that found no histological alterations in the lungs of rats exposed to 285 or 134 mg Cu/kg/day as copper sulfate in the diet for 14 or 90 days, respectively, or in mice exposed to 717 or 814 mg Cu/kg/day for 14 or 90 days.

**Cardiovascular Effects.** Several human studies have examined the possible relationship between increased serum copper levels and an increased risk of coronary heart disease. Although a number of studies have found increased risk of coronary heart disease deaths with increasing serum copper levels (Ford 2000), a number of studies have not found a relationship. However, whether copper directly affects atherosclerosis or is a marker of inflammation associated with atherosclerosis remains to be established.

There are limited data on the toxicity of copper to the cardiovascular system. A significant increase in systolic blood pressure was observed in rats exposed to 14 mg Cu/kg/day as copper carbonate in the diet for 15 weeks (Liu and Mederios 1986). Other studies have not examined effects on blood pressure. No histological alterations were observed in the hearts of rats or mice exposed to 285 or 717 mg Cu/kg/day, respectively, for 14 days or 134 or 814 mg Cu/kg/day for 90 days (NTP 1993).

Table 3-2 Levels of Significant Exposure to Copper - Oral

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat (Wistar)	2-15 wk (F)				550 M (increased mortality)	Haywood 1985 NS
2	Rat (Fischer- 344)	14 d (W)				31 F (100% mortality)	NTP 1993 copper sulfate
3	Mouse (B6C3F1)	14 d (W)				62 M (increased mortality)	NTP 1993 copper sulfate
<b>Systemic</b>							
4	Human	once (W)	Gastro	0.011	0.017	(nausea, vomiting, diarrhea, or abdominal pain)	Araya et al. 2001 copper sulfate
5	Human	once (W)	Gastro		0.03	(nausea and vomiting)	Gotteland et al. 2001 copper sulfate
6	Human	once (W)	Gastro		6	(vomiting)	Karlsson and Noren 1965 copper sulfate
7	Human	once (W)	Gastro		0.08 M	(vomiting, diarrhea)	Nicholas and Brist 1968 NS
8	Human	once (W)	Gastro	0.0057	0.011	(nausea)	Olivares et al. 2001 copper sulfate
9	Human	2 wks (W)	Gastro	0.0272 <sup>b</sup> F	0.0731 F	(abdominal pain, nausea, and/or vomiting)	Pizarro et al. 1999 copper sulfate

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Table 3-2 Levels of Significant Exposure to Copper - Oral

(continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Systemic</b>							
10	Human	1 wk (W)	Gastro		0.1 F (nausea, vomiting, and/or abdominal pain)		Pizarro et al. 2001 copper sulfate and copper oxide
11	Rat (NS)	1-2 wk (F)	Hepatic		300 M (parenchymal cell hypertrophy)		Haywood 1980 copper sulfate
			Renal	300 M			
12	Rat (NS)	1-2 wk (F)	Hepatic		300 M (increased alanine aminotransferase activity)		Haywood and Comerford 1980 copper sulfate
13	Rat (Wistar)	1-2 wk (F)	Hepatic		450 M (hepatocellular necrosis)		Haywood et al. 1985a NS
			Renal		450 M (copper-containing droplets and granules in proximal tubule cells)		
14	Rat (Wistar)	2 wk (F)	Renal		200 M (droplets in proximal tubule lumen)		Haywood et al. 1985b NS

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3. HEALTH EFFECTS

Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Systemic</b>							
15	Rat (Fischer- 344)	14 d (W)	Resp	29 M			NTP 1993 copper sulfate
			Cardio	29 M			
			Gastro	29 M			
			Hepatic	29 M			
			Renal		10 M (protein droplets in epithelial cells of proximal tubule)		
			Bd Wt	26 F			
16	Rat (Fischer- 344)	14 d (F)	Resp	285 F			NTP 1993 copper sulfate
			Cardio	285 F			
			Gastro	23 F	44 F (hyperplasia of forestomach mucosa)		
			Hemato	93 F	196 F (depletion of hematopoietic cells in bone marrow)		
			Hepatic	92 M	198 M (inflammation)		
			Renal	46 M	92 M (increased protein droplets in cortical tubules)		
			Bd Wt	93 F	196 F (18% decrease in body weight gain)		

Table 3-2 Levels of Significant Exposure to Copper - Oral

(continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Systemic</b>							
17	Mouse (B6C3F1)	14 d (W)	Resp	24 M			NTP 1993 copper sulfate
			Cardio	24 M			
			Gastro	24 M			
			Hepatic	24 M			
			Renal	24 M			
			Bd Wt	24 M			
18	Mouse (B6C3F1)	14 d (F)	Resp	717 M			NTP 1993 copper sulfate
			Cardio	717 M			
			Gastro	92 M	197 M (hyperplasia of forestomach mucosa)		
			Hepatic	717 M			
			Renal	717 M			
			Bd Wt	717 M			
<b>INTERMEDIATE EXPOSURE</b>							
<b>Systemic</b>							
19	Human	9 months (W)	Gastro	0.319			Olivares et al. 1998 copper sulfate
			Hepatic	0.319			
			Bd Wt	0.319			

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Table 3-2 Levels of Significant Exposure to Copper - Oral

(continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Systemic</b>							
20	Human	12 wks (C)	Gastro	0.14			Pratt et al. 1985 copper gluconate
			Hemato	0.14			
			Hepatic	0.14			
21	Rat (Sprague- Dawley)	30-58 d (F)	Hepatic	20 F			Cristofori et al. 1992 NS
			Renal	20 F			
22	Rat (Sprague- Dawley)	90 d (W)	Hepatic		8 M (increased aspartate aminotransferase activity)		Epstein et al. 1982 copper acetate
			Bd Wt	8 M			
23	Rat (Fischer- 344)	18 wks (F)	Hepatic		150 M (inflammation and increased serum enzyme activity in adult rats)		Fuentealba et al. 2000 copper sulfate
					120 M (inflammation, necrosis, and increases serum enzyme levels in young rats)		
24	Rat (NS)	3-15 wk (F)	Hepatic		180 M (necrosis)		Haywood 1980 copper sulfate
			Renal		180 M (cytoplasmic droplets and desquamation of epithelial cells in proximal tubules)		

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Table 3-2 Levels of Significant Exposure to Copper - Oral

(continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		Serious (mg/kg/day)
<b>Systemic</b>							
25	Rat (Wistar)	2-15 wk (F)	Hepatic		280 M (inflammation, necrosis)	550 M (chronic hepatitis)	Haywood 1985 NS
			Renal		280 M (degeneration of proximal tubule cells)		
			Bd Wt			550 M (weight loss) 280 M (50% decrease in body weight gain)	
26	Rat (NS)	3-15 wk (F)	Hepatic		180 M (increased alanine aminotransferase activity)		Haywood and Comerford 1980 copper sulfate
27	Rat (Wistar)	15 wk (F)	Hepatic		320 M (necrosis)	640 M (chronic hepatitis)	Haywood and Loughran 1985 copper sulfate
			Bd Wt			640 M (weight loss) 320 M (50% decrease in body weight gain)	
28	Rat (Wistar)	4-14 wks (F)	Hepatic		280 M (hepatocellular necrosis)		Haywood et al. 1985a NS
			Renal		280 M (tubular cell necrosis)		
29	Rat (Wistar)	4-15 wk (F)	Renal		200 M (reversible degeneration and necrosis of tubule cells)		Haywood et al. 1985b NS

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Table 3-2 Levels of Significant Exposure to Copper - Oral

(continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Systemic</b>							
30	Rat (NS)	30 d (G)	Hemato		100 M (decreased erythrocyte and hemoglobin levels)		Kumar and Sharma 1987 copper sulfate
			Hepatic		100 M (increased glucose, cholesterol, bilirubin, serum enzymes, and decreased total protein levels)		
			Renal		100 M (increased BUN levels)		
31	Rat (Wistar)	15 wks (F)	Cardio		14 M (increased blood pressure)		Liu and Medeiros 1986 copper carbonate
32	Rat (Holtzman)	21 wks (F)	Musc/skel	120 M			Llewellyn 1985 copper acetate
			Bd Wt		120 (23% decrease in body weight gain)		

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Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Systemic</b>							
33	Rat (Fischer- 344)	13 wk (F)	Resp	134 F			NTP 1993 copper sulfate
			Cardio	134 F			
			Gastro	16 M	33 M		
			Hemato	33 M	66 M		
			Hepatic	8 M	66 M (chronic active inflammation with focal necrosis)		
					16 M		
			Renal	9 F	17 F (increased BUN)	134 F (tubular degeneration)	
			Bd Wt	66 M	140 M (24% decrease in body weight gain)		
34	Rat (NS)	20 d (G)	Hemato		100 M (decreases in erythrocyte, hemoglobin, and hematocrit levels)		Rana and Kumar 1980 copper sulfate
			Hepatic		100 M (hepatocellular necrosis)		
			Renal		100 M (tubular cell necrosis)		

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Table 3-2 Levels of Significant Exposure to Copper - Oral

(continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Systemic</b>							
35	Mouse (B6C3F1)	13 wk (F)	Resp	814 M			NTP 1993 copper sulfate
			Cardio	814 M			
			Gastro	126 F	267 F (hyperplasia of forestomach mucosa)		
			Hepatic	814 M			
			Renal	814 M			
			Bd Wt	187 M	398 M (12% decrease in body weight gain)		
36	Pig (Hampshire)	54 d (F)	Hemato	11	24		Kline et al. 1971 copper sulfate
			Bd Wt	11	24 (decreased body weight gain)		
37	Pig (NS)	49 d (F)	Hemato		36 F (decreased hemoglobin levels)		Suttle and Mills 1966a copper carbonate
			Hepatic		36 F (increased aspartate aminotransferase activity)		
38	Pig (NS)	6 wks (F)	Hemato		35 F (decreased hemoglobin level)		Suttle and Mills 1966a copper carbonate
			Hepatic		35 F (increased aspartate aminotransferase activity)		
<b>Immuno/ Lymphoret</b>							
39	Mouse (C57BL/6N)	8 wks (W)			24 (impaired immune function)		Pocino et al. 1990 copper sulfate

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Table 3-2 Levels of Significant Exposure to Copper - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
		<b>Immuno/ Lymphoret</b>					
40	Mouse (C57BL/6N)	3-5 or 8-10 wks (W)			13	(altered cell-mediated and humoral immunity)	Pocino et al. 1991 copper sulfate
		<b>Neurological</b>					
41	Rat (Sprague-Dawley)	11 mo (W)			36 F	(decreased 3,4-dihydroxyphenylacetic acid levels in corpus striatum)	DeVries et al. 1986 copper sulfate
42	Rat (NS)	30 d (F)		23			Murthy et al. 1981 copper sulfate
		<b>Reproductive</b>					
43	Rat (Fischer- 344)	13 wk (F)		66 M 68 F			NTP 1993 copper sulfate
44	Mouse (B6C3F1)	13 wk (F)		398 M 536 F			NTP 1993 copper sulfate
45	Mink (dark mink)	153 or 367 d (F)		12			Aulerich et al. 1982 copper sulfate
		<b>Developmental</b>					
46	Rat (Wistar)	60-73 d (W)			130	(delayed growth and development)	Haddad et al. 1991 copper acetate
47	Mouse (C57BL/6N)	1 mo + gd 0-19 (F)		138 F	208	(decreased mean litter size and fetal body weights)	Lecyk et al. 1980 copper sulfate

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Table 3-2 Levels of Significant Exposure to Copper - Oral

(continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Developmental</b>							
48	Other (dark mink)	153 or 367 d (F)		13			Aulerich et al. 1982 copper sulfate
<b>CHRONIC EXPOSURE</b>							
<b>Death</b>							
49	Mouse (C57BL/6N)	850 d (W)				4.2 (14.7% decrease in lifespan)	Massie and Aiello 1984 copper gluconate
<b>Systemic</b>							
50	Mouse (C57BL/6N)	850 d (W)	Bd Wt	4.2 M			Massie and Aiello 1984 copper gluconate

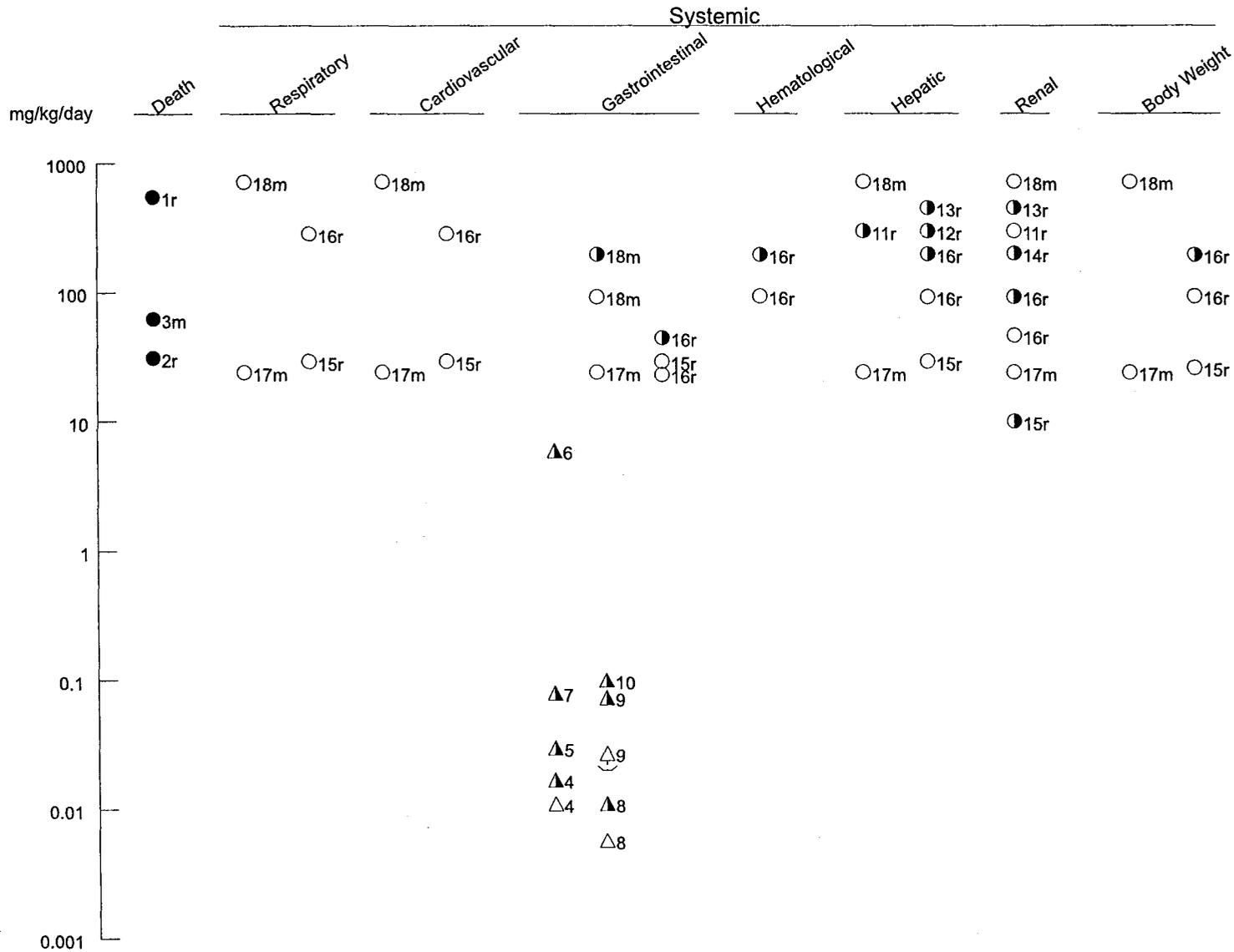
a The number corresponds to entries in Figure 3-2.

b Used to derive an acute-duration oral minimal risk level (MRL) of 0.02 mg Cu/kg/day. To estimate total copper exposure, the concentration of copper in the drinking water (0.0272 mg Cu/kg/day) was added to the reported average dietary copper intake (0.0266 mg Cu/kg/day). The total copper intake (0.0538 mg Cu/kg/day) was divided by an uncertainty factor of 3 to account for human variability.

The acute-duration oral MRL of 0.02 mg Cu/kg/day was also adopted for use as an intermediate-duration oral MRL.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; G = gavage; Gastro = gastrointestinal; gd = gestational day; Gn pig = guinea pig; hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; occup = occupational; NS = not specified; Resp = respiratory; (W) = drinking water; wk = week(s)

Figure 3-2 Levels of Significant Exposure to Copper - Oral  
Acute (≤14 days)

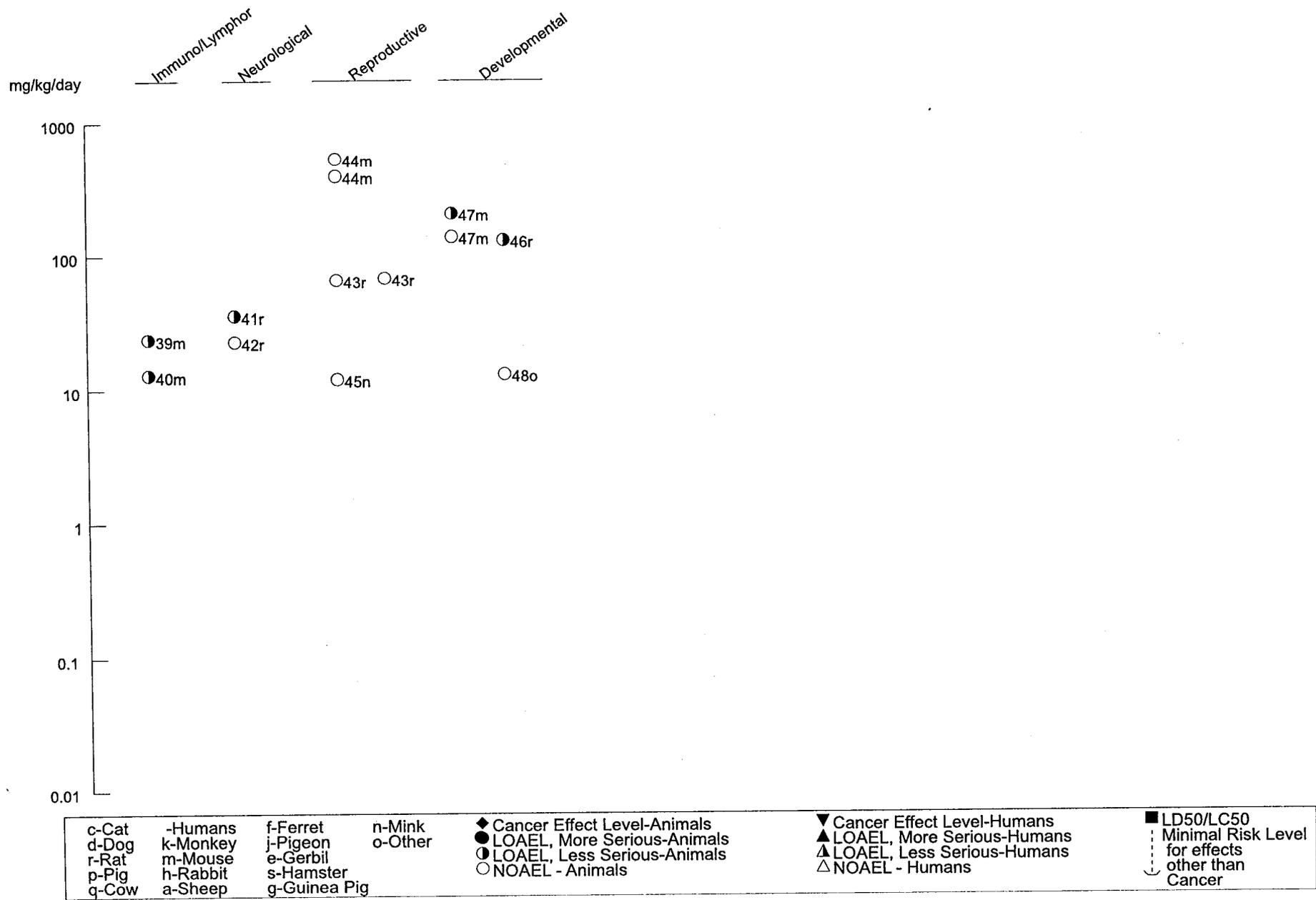


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c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	⋯ Minimal Risk Level
r-Rat	m-Mouse	e-Gerbil		○ LOAEL, Less Serious-Animals	△ LOAEL, Less Serious-Humans	⋯ for effects other than Cancer
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

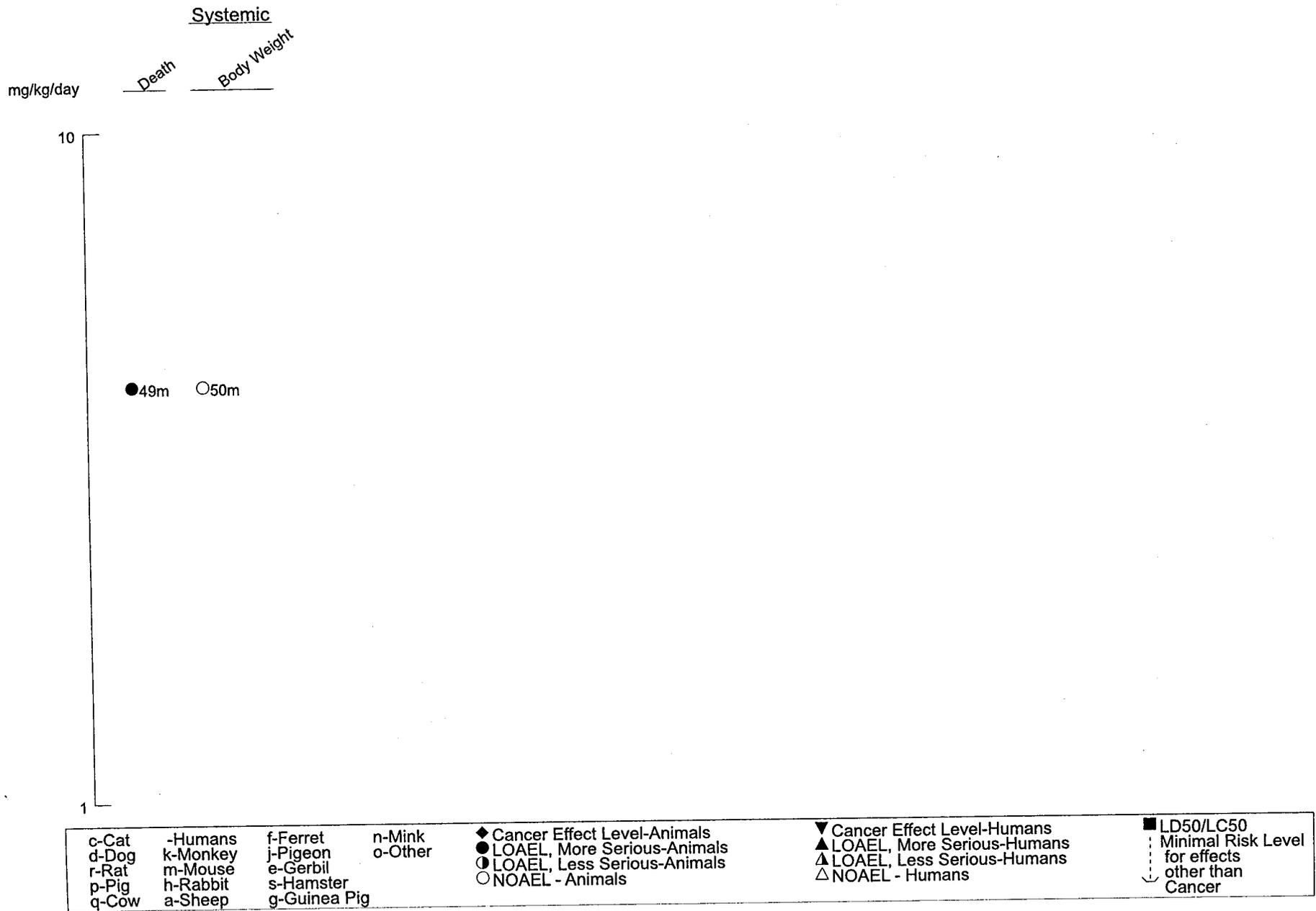


Figure 3-2 Levels of Significant Exposure to Copper - Oral (Continued)  
Intermediate (15-364 days)



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Figure 3-2 Levels of Significant Exposure to Copper - Oral (Continued)  
Chronic (≥365 days)



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## 3. HEALTH EFFECTS

**Gastrointestinal Effects.** There are numerous reports of acute gastrointestinal effects in humans after ingestion of large amounts of copper in drinking water or beverages. The most prevalent signs and symptoms are nausea, vomiting, abdominal pain, and diarrhea. With the exception of diarrhea, these effects usually occurred shortly after ingestion and were not persistent (Chuttani et al. 1965; Eife et al. 1999; Gill and Bhagat 1999; Gotteland et al. 2001; Holleran 1981; Jantsch et al. 1984, 1985; Karlsson and Noren 1965; Knobeloch et al. 1994, 1998; Nicholas and Brist 1968; Olivares et al. 2001; Pizarro et al. 1999, 2001; Semple et al. 1960; Spitalny et al. 1984; Walsh et al. 1977). Although most of the data on gastrointestinal effects in humans come from case reports with limited information on exposure levels, several recently conducted studies were designed to identify the threshold for gastrointestinal effects. In studies in which adults ingested a single dose of copper sulfate in water following an overnight fast, nausea was observed at copper concentrations of 4 ppm (0.01 mg Cu/kg) and higher (Gotteland et al. 2001; Olivares et al. 2001). A study by Araya et al. (2001) of 179 subjects ingesting a single dose of copper sulfate found a statistically significant increase in the occurrence of nausea only or nausea, vomiting, diarrhea, or abdominal pain at copper concentrations of 6 ppm; the NOAEL was 4 ppm. When the copper sulfate was administered in an orange-flavored drink, nausea was observed at 8 ppm (0.022 mg Cu/kg) and higher (Gotteland et al. 2001). Similar thresholds for nausea were observed in subjects exposed to copper-sulfate in drinking water for 1–2 weeks. Abdominal pain, nausea, and/or vomiting were reported at a water concentrations of 5 ppm (0.0731 mg Cu/kg/day); gastrointestinal effects were not reported at 3 ppm (0.0272 mg Cu/kg/day) (Pizarro et al. 1999, 2001). The study by Pizarro et al. (2001) did not find a difference in the occurrence of gastrointestinal effects (excluding diarrhea) when the subjects consumed water containing copper sulfate or copper oxide. Spitalny et al. (1984) described gastrointestinal effects in three of four family members. Recurrent, acute symptoms included nausea, vomiting, and abdominal pain after drinking juice, coffee, or water in the morning; the effects disappeared when the family switched to bottled water. An early morning water sample contained 7.8 ppm copper.

Gastrointestinal effects have also been reported in animal studies. Hyperplasia with hyperkeratosis of the squamous mucosa on the limiting ridge separating the forestomach from the glandular stomach was observed in rats and mice exposed to 44 and 197 mg Cu/kg/day, respectively, as copper sulfate in the diet for 14 days or 33 and 267 mg Cu/kg/day, respectively, as copper sulfate in the diet for 13 weeks (NTP 1990a). No gastrointestinal effects were observed in rats and mice exposed to 23 or 92 mg Cu/kg/day for 14 days or in rats and mice exposed to 16 or 126 mg Cu/kg/day 13 weeks. Additionally, no gastrointestinal effects were observed in rats and mice exposed to 29 or 24 mg Cu/kg/day as copper sulfate in drinking water (NTP 1990a).

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**Hematological Effects.** There are limited data on the effect of copper on the human hematological system. Acute hemolytic anemia was observed in an 18-month-old child 2 days after he drank a solution containing approximately 3 g of copper sulfate (Walsh et al. 1977). Acute intravascular hemolysis was also reported in 5 of 125 individuals intentionally ingesting a large dose of copper sulfate (Ahasan et al. 1994). No alterations in hematocrit level or mean corpuscular volume were observed in individuals ingesting 0.14 mg Cu/kg/day as copper gluconate in a capsule for 12 weeks (Pratt et al. 1985).

Information on the hematological effects in animals associated with exposure to high levels of copper is also limited to several studies that measured hemoglobin and hematocrit values. Decreased hemoglobin and hematocrit values were observed in rats exposed to \$66 mg Cu/kg/day (Kumar and Sharma 1987; NTP 1993; Rana and Kumar 1980) for 20–90 days and in pigs exposed to \$24 mg Cu/kg/day for 48–54 days (Kline et al. 1971; Suttle and Mills 1966a, 1966b). Depletion of hematopoietic cells in the bone marrow was observed in rats exposed to 196 mg Cu/kg/day as copper sulfate in the diet for 14 days (NTP 1993). Contrary to these findings, Liu and Medeiros (1986) observed an increase in hemoglobin levels and no change in hematocrit levels in rats fed a diet containing 14 mg Cu/kg/day as copper carbonate for 20 weeks.

**Musculoskeletal Effects.** No studies were located regarding musculoskeletal effects in humans following oral exposure to copper.

Equivocal results on the effects of copper on the musculoskeletal system have been found. Depressed skeletal growth has been observed in rats administered 100 mg Cu/kg/day via gavage; tail length was used to assess skeletal growth (Rana and Kumar 1980). Using radiographic data, no qualitative or quantitative differences were observed in bones of rats exposed to 120 mg Cu/kg/day as copper acetate in the diet for 21 weeks (Llewellyn et al. 1985). The different outcomes may reflect the different methods used to assess skeletal growth.

**Hepatic Effects.** With the exception of several defined syndromes—Wilson’s disease, Indian childhood cirrhosis, and iodopathic copper toxicosis—liver effects are rarely reported in humans, although this has not been extensively investigated. In a compilation of case reports of individuals intentionally ingesting copper sulfate, jaundice was reported in 11 of 53 individuals (Chuttani et al. 1965). Centrilobular necrosis, biliary stasis, elevated serum bilirubin level and aspartate aminotransferase activity, and elevated bile salts in the urine were found in five of the individuals with jaundice. Jaundice (Akintonwa et al. 1989), centrilobular congestion (Lamont and Duflou 1988), and acute hepatotoxicity

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(Ahasan et al. 1994) have also been reported in case reports of lethal ingestion of copper sulfate. O'Donohue et al. (1993) reported a case of an adult with jaundice and hepatomegaly following a 3-year exposure to copper supplements. For 2 years, the individual ingested 30 mg/day followed by 1 year of 60 mg/day. In a study of seven adults receiving capsules containing 0.14 mg Cu/kg/day as copper gluconate, no significant alterations in serum aspartate aminotransferase, alkaline phosphatase, serum gamma glutamyl transferase, or lactate dehydrogenase activities were found (Pratt et al. 1985). A no adverse effect level for liver effects was also identified in a study of infants (3 months of age at study initiation) exposed to 0.315 mg Cu/kg/day as copper sulfate in drinking water for 9 months (Olivares et al. 1998). No alterations in total bilirubin levels or serum alanine aminotransferase, aspartate aminotransferase, or gamma-glutamyl transferase activities were found. A higher percentage of copper-exposed infants (30.4%) were withdrawn from the study, as compared to the control group (11.1%). The reasons for being withdrawn from the study were blood sampling refusal (eight infants in the copper group and two infants in the control group), protocol transgression (four infants in the copper group and no infants in the control group), and change of address (five infants in the copper group and one infant in the control group).

There is strong evidence to suggest that Wilson's disease, Indian childhood cirrhosis, and possible idiopathic copper toxicosis are caused by an increased genetic susceptibility to copper toxicity.

***Wilson's Disease.*** Wilson's disease is an autosomal recessive genetic disorder with a worldwide occurrence of 1 in 30,000 (Scheinberg and Sternlieb 1996). It is characterized by high levels of copper in the liver and low levels of serum ceruloplasmin. One of the early manifestations of the disease, typically at 8–12 years of age, is liver damage. Three types of liver damage are seen—cirrhosis, chronic active hepatitis, and fulminant hepatic failure. It is unlikely that the manifestation of Wilson's disease is related to exposure to high levels of copper because reducing the dietary intake of copper cannot prevent the development of the disease (Scheinberg and Sternlieb 1996).

***Indian Childhood Cirrhosis (ICC).*** ICC is a type of cirrhosis typically seen in infants and young children (6 months to 5 years of age with a mean of 18 months) living in rural areas of the Indian subcontinent. Other features include high rates of parental consanguinity and up to 22% of siblings affected (Pandit and Bhawe 1996; Tanner 1998). Two of the most discriminatory features of ICC are coarse, dark brown orcein staining (representing copper) and intralobular pericellular fibrosis (Pandit and Bhawe 1996). Liver copper levels ranging from 790 to 6,654 µg/g dry weight (mean of 939 µg/g) were

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found in 53 children diagnosed with ICC, as compared to levels of 8–118 µg/g (mean 42–45 µg/g) in 12 controls aged 6 months to >1 year (Bhave et al. 1982).

In a study of 100 children with ICC and 100 age-, sex-, and caste-matched controls, it was determined that ICC was attributable to the early introduction of cow or buffalo milk feeds contaminated with copper from brass vessels, which were used to store and heat the milk (Bhave et al. 1987). Although a cause and effect relationship between high copper intake and ICC has not been firmly established, there is strong evidence to support an association. In a study in which the parents of 100 children with ICC were advised to use aluminum or stainless steel vessels for preparing infant milk feeds, only 1 of 86 younger siblings of the children with ICC developed ICC (this child was known to have received copper-contaminated milk) as compared to 30 of 125 older siblings (Tanner 1998).

***Idiopathic Copper Toxicosis (ICT).*** Although there are limited data on ICT, it is also believed to be caused by an autosomal-recessive inherited defect in copper metabolism and excess dietary copper (Müller et al. 1998). In the literature, ICT is also referred to as Indian childhood cirrhosis-like liver disease, copper-associated liver disease in childhood, and Tyrollean infantile cirrhosis. In the last 25 years, there have been <200 cases of ICT reported in a number of countries including Australia, Austria, Germany, Ireland, Italy, Kuwait, Mexico, United Kingdom, and United States. With the exception of a study of ICT in 138 children living in Tyrol Austria (Müller et al. 1996), most papers describe the clinical course of 1–4 children. Compiling the data from these studies, Müller et al. (1998) found a number of patterns: (1) the age of onset of clinical symptoms occurs before the age of 2 years (infantile onset) or before the age of 5 years (late onset), although onset as late as 10 years has also been observed; (2) rapid progression and death within 2 weeks to 11 months; (3) very high copper levels in the liver, 190–3,360 µg/g dry weight (normal is <50 µg/g); (4) abnormal biochemical markers of liver damage such as aminotransferases, alkaline phosphatase, bilirubin, albumin, and prothrombin time; and (5) marked panlobular and pericellular fibrosis associated with an usually mild inflammatory infiltrate, ballooning degeneration of hepatocytes, and an abundance of Mallory bodies. The high levels of copper in the liver, the identification of environmental copper exposure, and the similarity of the clinical presentation and histopathology with ICC suggest that copper is the causative agent. As with ICC, an increased genetic susceptibility to copper toxicity has been suggested. A genealogic investigation conducted by Müller et al. (1996) provided suggestive evidence that the disease is transmitted in an autosomal recessive mode.

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Hepatotoxicity of copper in animals has been described and investigated in numerous oral studies of acute and intermediate duration. Studies in rats provide information on the duration- and dose-response relationships. Significant increases in alanine aminotransferase activity were observed in rats fed a diet containing 300 mg Cu/kg/day for 1 week (Haywood and Comerford 1980). No histopathological alterations were observed after 1 week of exposure to 300 or 450 mg Cu/kg/day as copper sulfate in the diet (Haywood 1980; Haywood et al. 1985a). Two to 3 weeks of exposure to copper sulfate in the diet resulted in no effects at 92 mg Cu/kg/day (NTP 1993), necrosis at 100 mg Cu/kg/day (gavage administration) (Rana and Kumar 1980), inflammation at 180 mg Cu/kg/day (Haywood 1980) and 198 mg Cu/kg/day (NTP 1993), necrosis at 280 mg Cu/kg/day (Haywood 1985), parenchymal cell hypertrophy at 300 mg Cu/kg/day (Haywood 1980), and minimal hepatocellular necrosis at 450 mg Cu/kg/day (Haywood et al. 1985a). Several studies by Haywood and associates found that the severity of the necrosis peaked at 4–5 weeks of exposure to 280–320 mg Cu/kg/day (Haywood and Loughran 1985; Haywood et al. 1985a); at 100 mg Cu/kg/day as copper sulfate administered via gavage. Following 6 weeks of exposure, increases in alanine aminotransferase and aspartate aminotransferase activities were observed at 34 mg Cu/kg/day (Sugawara et al. 1995), necrosis and increased alanine aminotransferase activity at 180 mg Cu/kg/day (Haywood 1980; Haywood and Comerford 1980), regeneration of parenchymal tissue at 280 mg Cu/kg/day (Haywood 1985), and chronic hepatitis at 550 mg Cu/kg/day (Haywood 1985). No adverse effects were observed following a 30–60-day exposure to 17 or 20 mg Cu/kg/day (Cristofori et al. 1992; Sugawara et al. 1995). Exposure for 13–15 weeks resulted in no adverse effects (NTP 1993) or an increase in aspartate aminotransferase activity (Epstein et al. 1982) at 8 mg Cu/kg/day, increase in alanine aminotransferase activity at 16 mg Cu/kg/day (NTP 1993), chronic activity inflammation at 66 mg Cu/kg/day (NTP 1993), regeneration of parenchymal tissue at 280–530 mg Cu/kg/day (Haywood 1985; Haywood and Loughran 1985; Haywood et al. 1985a) and chronic hepatitis at 640 mg Cu/kg/day (Haywood and Loughran 1985).

These data, along with toxicokinetic data, suggest that there are three phases of copper toxicity in the rat. In the first phase, copper levels increase in the liver, with minimal to no damage to hepatic tissues. As the levels increase, inflammation and necrosis occurs. Thereafter, the copper levels in the liver begin to decrease and the parenchymal tissue begins to regenerate. At this point, the animal develops a tolerance to copper. After a 15-week exposure to 320 mg Cu/kg/day, a subsequent 3-week exposure to 640 mg Cu/kg/day did not result in adverse effects, which is in contrast to the severe hepatocellular necrosis that was observed in animals exposed to a control diet for 15 weeks followed by a 3-week exposure to 640 mg Cu/kg/day (Haywood and Loughran 1985). The time course of each period appears to be dose-related. At higher doses, the onset of the necrosis and regeneration occurred earlier as compared to lower doses.

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However, at exposures to 550 mg Cu/kg/day, regeneration of the parenchymal tissue was not observed and the animals developed chronic hepatitis (Haywood 1985; Haywood and Loughran 1985).

Pigs fed a diet providing 35–36 mg Cu/kg/day for 7 weeks had a significant increase in aspartate aminotransferase activities (Suttle and Mills 1966a, 1966b). It appears that rats and pigs are equally sensitive to high levels of copper in the diet or drinking water. In contrast, mice do not appear to be as sensitive to the hepatic toxicity of copper as rats. No hepatic effects were observed in mice exposed to 814 mg Cu/kg/day for 13 weeks as compared to rats, which exhibited an increase in alanine aminotransferase activity at 16 mg Cu/kg/day and chronic active inflammation at 66 mg Cu/kg/day (NTP 1993).

**Renal Effects.** There is limited information on the renal toxicity of copper in humans. Congestion of the glomeruli and denudation of tubular cells were observed in four individuals consuming a single lethal dose of copper sulfate (Chuttani et al. 1965). Acute renal failure was reported in 5 of 125 individuals intentionally ingesting large doses of copper sulfate (Ahasan et al. 1994). Hematuria, glycosuria, cylindruria, and proteinuria, indicative of renal tubular damage, were observed in a child who drank a solution containing approximately 3 g of copper sulfate (Walsh et al. 1977).

A number of animal studies confirm that the kidney is a target of copper toxicity. Renal toxicity as a result of copper loading follows a specific time course (Haywood 1980, 1985; Haywood et al. 1985a, 1985b). No treatment-related effects were observed in rats exposed to 300 mg Cu/kg/day as copper sulfate in the diet for 1–2 weeks (Haywood 1980). However, eosinophilic droplets were observed in the epithelial cell cytoplasm of the proximal convoluted tubules in rats exposed to 450 mg Cu/kg/day for 2 weeks (Haywood et al. 1985a). The number of eosinophilic droplets increased with increasing duration (Haywood 1980, 1985). Exposure to 100–280 mg Cu/kg/day for 3–5 weeks resulted in necrosis and degeneration of proximal tubule cells (Haywood 1985; Haywood et al. 1985a, 1985b; Rana and Kumar 1980). After 9 weeks, extensive desquamation of the epithelial cells of the proximal convoluted tubules was evident in rats exposed to 180 mg Cu/kg/day (Haywood 1980). Complete regeneration of the proximal tubules was observed after 15 weeks of copper treatment in rats exposed to 180–280 mg Cu/kg/day (Haywood 1980, 1985; Haywood et al. 1985a, 1985b). In contrast to the Haywood and associates studies, a 13-week study by NTP (1993) did not find evidence of regeneration of renal tissue. An increase in protein droplets in epithelial cell cytoplasm and the lumen of the proximal convoluted tubules was observed in rats exposed to 10 or 92 mg Cu/kg/day as copper sulfate in drinking water or diet, respectively, for 2 weeks or to 33 mg Cu/kg/day as copper sulfate in the diet for 13 weeks. At

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134 mg Cu/kg/day, karyomegaly and tubule cell degeneration were also observed. Additional renal effects observed in the intermediate-duration study included an increase in serum urea nitrogen levels in females exposed to 17 mg Cu/kg/day, increased urinary glucose output in males exposed to 66 mg Cu/kg/day, and increased urinary aspartate aminotransferase and N-acetyl- $\beta$ -glucosaminidase activities in male and female rats exposed to 140 or 134 mg Cu/kg/day, respectively. The NTP (1993) study identified a NOAEL of 9 mg Cu/kg/day. No effects were observed in mice fed a diet for 13 weeks which provided 814 mg Cu/kg/day as copper sulfate (NTP 1993).

**Body Weight Effects.** No studies were located regarding body weight effects in humans following oral exposure to copper.

Dietary exposure studies have reported 12–24% decreases in body weight gain in rats following exposure to 120–140 mg Cu/kg/day for 2–15 weeks (Llewellyn 1985; NTP 1993), in mice following exposure to 398 mg Cu/kg/day for 13 weeks (NTP 1993), or in pigs (magnitude of decreased weight gain not reported) following exposure to 24 mg Cu/kg/day for 54 days (Kline et al. 1971). No effect levels of 66 (NTP 1993), 187 (NTP 1993), and 11 mg Cu/kg/day (Kline et al. 1971) have been reported in rats, mice, and pigs, respectively; Epstein et al. (1982) also reported no adverse effects on body weight gain in rats exposed to 8 mg Cu/kg/day in drinking water. More severe decreases in body weight gain and weight loss have also been reported (Haywood 1985; Haywood and Loughran 1985); the weight loss was reported at lethal concentrations. Only one study examined the effect of copper on body weight gain following chronic-duration exposure, this study found no effect in mice exposed to 4.2 mg Cu/kg/day as copper gluconate in drinking water (Massie and Aiello 1984).

#### 3.2.2.3 Immunological and Lymphoreticular Effects

Information on the immunotoxicity of copper following oral exposure is limited to two drinking water studies in which mice were exposed to several concentrations of copper sulfate for 8 weeks (Pocino et al. 1990) or copper chloride for 3–5 or 8–10 weeks (Pocino et al. 1991). In these studies, groups of mice underwent several tests to assess immune function: *in vitro* lymphoproliferative responses to *Escherichia coli* lipopolysaccharide (LPS), and concanavalin A (Con A), induction and evaluation of antibody response to sheep red blood cells, evaluation of autoantibody production, and induction and elicitation of delayed-type hypersensitivity response (only tested in the Pocino et al. 1991 study). At the lowest dose tested (13 mg Cu/kg/day as copper chloride), impaired cellular (proliferative response to LPS) and humoral (autoantibody production) immunity were observed. Impaired performance on the remaining

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immune function tests were observed at \$26 mg Cu/kg/day as copper chloride (Pocino et al. 1991) or \$24 mg Cu/kg/day as copper sulfate (Pocino et al. 1990). The LOAEL values from these study are presented in Table 3-2 and Figure 3-2.

#### **3.2.2.4 Neurological Effects**

No studies were located regarding neurological effects in humans following oral exposure to copper.

No effects on spontaneous motor activity, learning ability, relearning capacity, or memory were observed in rats fed a diet containing 23 mg Cu/kg/day as copper sulfate (Murthy et al. 1981). This study found no alterations in dopamine or norepinephrine levels. De Vries et al. (1986) also did not find significant alterations in dopamine levels in rats exposed to 36 mg Cu/kg/day as copper sulfate in drinking water for 11 months. However, a 25% decrease in a dopamine metabolite, 3,4-dihydroxyphenylacetic acid, was found in the corpus striatum.

#### **3.2.2.5 Reproductive Effects**

No studies were located regarding reproductive effects in humans following oral exposure to copper.

Reproductive performance, as assessed by the length of gestation, number of kits whelped, and average kit weight, was not adversely affected in minks fed a diet containing 12 mg Cu/kg/day as copper sulfate (Aulerich et al. 1982). No other oral exposure studies examined reproductive function. The intermediate-duration study by NTP (1993) did not find any histological alterations or alterations in sperm morphology or vaginal cytology in male and female rats exposed to 66 and 68 mg Cu/kg/day, respectively, or in male and female mice exposed to 398 and 536 mg Cu/kg/day, respectively. The NOAEL values for reproductive effects are reported in Table 3-2 and plotted in Figure 3-2.

#### **3.2.2.6 Developmental Effects**

No studies were located regarding developmental effects of humans following oral exposure to copper.

There are limited data on the developmental toxicity of copper in experimental animals. Delayed growth and development were observed in the offspring of rats exposed to 130 mg Cu/kg/day as copper sulfate in the diet for 7 weeks prior to mating and during gestation (Haddad et al. 1991). In 11.5-day-old embryos,

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significant decreases in mean somite number, crown-rump length, and yolk sac diameter were observed. In 21.5-day-old fetuses and newborns, delayed ossification was observed in the cervical and cauda vertebrae, sternum, metacarpals, forelimb phalanges, metatarsals, and hindlimb phalanges. Exposure of mouse dams to a higher dose, 208 mg Cu/kg/day as copper sulfate in the diet, resulted in decreased mean litter size and decreased fetal body weights; statistical significance of these effects is not known (Lecyk 1980). No statistically significant alterations in newborn mortality or body weight were observed in the offspring of mink exposed to 13 mg Cu/kg/day as copper sulfate in the diet (Aulerich et al. 1982). There was a trend toward kit mortality between birth and 4 weeks of age in the offspring of mink exposed to 6 or 13 mg Cu/kg/day; incidences were 12, 9, 19, 38, and 32% in the 1, 6, 3, 6, and 13 mg Cu/kg/day groups, respectively. The NOAEL values and all reliable LOAEL values for developmental effects in each species are recorded in Table 3-2 and plotted in Figure 3-2.

#### **3.2.2.7 Cancer**

No studies were located regarding carcinogenic effects in humans following oral exposure to copper.

Several oral studies have examined the carcinogenicity of copper compounds in animals. These studies did not find increases in the occurrence of tumors in mice exposed to 86 mg Cu/kg/day as copper 8-hydroxyquinoline (BRL 1968), liver tumors in rats exposed to 130 mg Cu/kg/day as copper acetate (Kamamoto et al. 1973), or large intestine tumors in rats exposed to 9 mg Cu/kg/day as an unspecified copper compound (Greene et al. 1987). These studies are limited in scope and it can not be determined whether the maximum threshold dose (MTD) was achieved. An increased occurrence of hepatocellular carcinomas has been reported in Long-Evans Cinnamon rats (Sawaki et al. 1994), an animal model for Wilson's disease. However, liver cancer has not been reported in individuals with Wilson's disease; thus the significance of this finding is not known.

#### **3.2.3 Dermal Exposure**

##### **3.2.3.1 Death**

No studies were located regarding death in humans and animals following dermal exposure to copper.

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#### 3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, or body weight effects in humans or animals following dermal exposure to copper.

**Hematological Effects.** Hemolytic anemia was observed in a severely burned and debilitated child in whom copper sulfate crystals were being applied to granulation tissue. Increased serum and urine copper levels were observed (Holtzman et al. 1966). Because the skin was severely damaged, this study cannot be used to predict the dermal toxicity of copper following exposure to intact skin. No studies were located regarding hematological effects in animals following dermal exposure to copper.

**Ocular Effects.** Eye irritation has been reported by factory workers exposed to copper dust (Askergren and Mellgren 1975). No studies were located regarding ocular effects in animals following exposure to copper.

#### 3.2.3.3 Immunological and Lymphoreticular Effects

In some individuals, exposure to copper metal produces pruritic dermatitis. Saltzer and Wilson (1968) reported a case of a woman who had recurrent pruritus on her ring finger and wrist caused by copper metal in her ring and wristwatch. Allergic contact dermatitis has been observed in individuals following a patch test using a copper penny and/or a copper sulfate solution (Barranco 1972; Saltzer and Wilson 1968).

No studies were located regarding the following health effects in humans and/or animals after dermal exposure to copper:

#### 3.2.3.4 Neurological Effects

#### 3.2.3.5 Reproductive Effects

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**3.2.3.6 Developmental Effects****3.2.3.7 Cancer****3.2.4 Other Routes of Exposure**

**Cardiovascular Effects.** A dramatic decrease in pulse pressure and heart rate was observed in rabbits receiving a single intraperitoneal injection of 2.5 Cu mg/kg as copper sulfate (Rhee and Dunlap 1990). Systolic and diastolic pressure initially increased, then rapidly decreased.

**Reproductive Effects.** Intraperitoneal exposure to 0.95 or 1.4 mg Cu/kg/day for 26 days resulted in significant decreases in testes, seminal vesicle, and ventral prostate weights and in plasma testosterone levels in male rats (Chattopadhyay et al. 1999); decreases in testicular  $\Delta^5$ -3 $\beta$ -hydroxysteroid dehydrogenases and 17 $\beta$ -hydroxysteroid dehydrogenase activities were also observed at 1.4 mg Cu/kg/day. An *in vitro* study (Holland and White 1988) demonstrated that cupric ions and cuprous ions decrease human spermatozoa motility.

**Cancer.** Several studies have examined the carcinogenicity of copper compounds following parenteral administration. No significant alterations in tumor incidence were observed in rats receiving subcutaneous injections of 2 mg Cu/kg/day as copper acetate (Yamane et al. 1984) or intramuscular injections of 0.25 or 0.41 mg Cu/kg/day as finely ground copper (Furst 1971), 150 mg Cu/kg as copper oxide or copper sulfide (Gilman 1962), or 70 mg Cu/kg as copper sulfate (Gilman 1962). An increase in the occurrence of renal cell carcinoma was observed in male rats receiving 3–5 mg Cu/kg as cupric nitrilotriacetate 5 days/week for 12 weeks (Toyokuni et al. 1996); cupric nitrilotriacetate is a chelated compound of copper that is water soluble. A study by BRL (1968) did find a slight, but statistically significant, increase in the incidence of reticulum cell sarcomas in mice 18 months after receiving a single subcutaneous injection of copper 8-hydroxyquinoline; the significance of this finding is not known.

**3.3 GENOTOXICITY**

No studies were located regarding genotoxicity in humans after inhalation, oral, or dermal exposure to copper or its compounds. Several studies have assessed the genotoxicity of copper sulfate following oral or parenteral exposure; the results of these *in vivo* genotoxicity studies are summarized in Table 3-3. Significant increases in the occurrence of micronuclei and chromosomal aberrations have been observed in chick bone marrow cells and erythrocytes (Bhunya and Jena 1996) and mouse bone marrow cells

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(Agarwal et al. 1990; Bhunya and Pati 1987). A study by Tinswell and Ashby (1990) did not find increases in the number of micronuclei in mouse bone marrow cells. Increases in the occurrence of recessive lethals (Law 1938) and sperm abnormalities (Bhunya and Pati 1987) have also been observed in *Drosophila* and mice, respectively.

Several studies on the *in vitro* genotoxicity of copper sulfate and copper chloride did not find significant increases in the occurrence of reverse mutations in *Salmonella* (Marzin and Phi 1985; Tso and Fung 1981; Wong 1988) or *Saccharomyces* (Singh 1983). Demerec et al. (1951) found an increased occurrence of reverse mutations in *E. coli*, and Law (1938) found increases in the occurrence recessive lethals in *Drosophila*. The results of these studies and other *in vitro* genotoxicity studies are presented in Table 3-4. In contrast to the mixed results in gene mutation assays, the results of studies testing for DNA damage have found consistently positive results. Errors in DNA synthesis in viral DNA polymerase (Sirover and Loeb 1976), a reduction in DNA synthesis (Garrett and Lewtas 1983; Sirover and Loeb 1976), and an increase in the occurrence of DNA strand breaks (Sideris et al. 1988; Sina et al. 1983) have been observed. The increase in sister chromatid exchange in Chinese hamster cells (Sideris et al. 1988) is consistent with the clastogenic effects observed in *in vivo* assays.

#### 3.4 TOXICOKINETICS

The levels of copper in the body are held constant by alterations in the rate and amount of copper absorbed, its distribution, and rate and route of excretion.

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**Table 3-3. Genotoxicity of Copper *In Vivo***

Species (test system)	End point	Results	Reference	Compound
<i>Drosophila melanogaster</i> (injection into larvae)	Recessive lethals	+	Law 1938	Copper sulfate
White Leghorn chick bone marrow cells (intraperitoneal injection and oral exposure)	Chromosomal aberrations	+	Bhunya and Jena 1996	Copper sulfate
White Leghorn chick bone marrow cells (intraperitoneal injection and oral exposure)	Micronuclei	+	Bhunya and Jena 1996	Copper sulfate
White Leghorn chick erythrocytes (intraperitoneal injection and oral exposure)	Micronuclei	+	Bhunya and Jena 1996	Copper sulfate
Inbred Swiss mice bone marrow cells (intraperitoneal and/or subcutaneous injection)	Chromosomal aberrations	+	Bhunya and Pati 1987	Copper sulfate
Inbred Swiss mice bone marrow cells (intraperitoneal and/or subcutaneous injection)	Micronuclei	+	Bhunya and Pati 1987	Copper sulfate
Inbred Swiss mice (intraperitoneal injection)	Sperm abnormalities	+	Bhunya and Pati 1987	Copper sulfate
CBA mice bone marrow cells (intraperitoneal injection)	Micronuclei	-	Tinwell and Ashby 1990	Copper sulfate
Swiss mice (intraperitoneal injection)	Chromosomal aberrations	+	Agarwal et al. 1990	Copper sulfate

+ = positive results; - = negative results

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**Table 3-4. Genotoxicity of Copper *In Vitro***

Species (test system)	End point	Results		Reference	Compound
		With activation	Without activation		
Prokaryotic organisms:					
<i>Salmonella typhimurium</i> TA102	Reverse mutation	NT	–	Marzin and Phi 1985	Copper sulfate
<i>S. typhimurium</i> TA98, TA102, TA1535, TA1537	Reverse mutation	–	–	Wong 1988	Copper chloride
<i>S. typhimurium</i> TA100	Reverse mutation	NT	–	Tso and Fung 1981	Copper chloride
<i>Escherichia coli</i>	Reverse mutation	NT	+	Demerec et al. 1951	Copper sulfate
Avian myeloblastosis virus, DNA polymerase	Errors in DNA synthesis	NT	+	Sirover and Loeb 1976	Copper chloride
<i>Bacillus subtilis</i>	<i>rec</i> assay	NT	–	Nishioka 1975	Copper chloride
Eukaryotic organisms:					
Fungi:					
<i>Saccharomyces cerevisiae</i>	Reverse mutation	NT	–	Singh 1983	Copper sulfate
<i>S. cerevisiae</i>	Recombination	NT	–	Sora et al. 1986	
Insects:					
<i>Drosophila melanogaster</i>	Recessive lethals	NT	+	Law 1938	Copper sulfate
Mammalian cells:					
Chinese hamster ovary cells	DNA synthesis	NT	+	Garrett and Lewtas 1983	Copper chloride
Rat hepatocytes	DNA strand breaks	NT	+	Sina et al. 1983	Copper sulfate
Chinese hamster V79 cells	DNA strand breaks	NT	+	Sideris et al. 1988	Copper nitrate
Chinese hamster V79 cells	Sister chromatid exchange	NT	+	Sideris et al. 1988	Copper nitrate

– = negative result; + = positive result; DNA = deoxyribonucleic acid; NT = not tested

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**3.4.1 Absorption****3.4.1.1 Inhalation Exposure**

No studies were located regarding the rate and extent of absorption following inhalation exposure of humans to copper. There are limited data on copper absorption in animals. Copper oxide was observed in alveolar capillaries 3 hours after rats were exposed to a welding dust aerosol generated from pure copper wires (Batsura 1969). The half-time of copper sulfate in the lungs was estimated to be 7.5 hours after intratracheal instillation of 20 µg copper/rat (Hirano et al. 1990).

**3.4.1.2 Oral Exposure**

Copper is absorbed in the stomach and small intestine; there appears to be species differences in the site of maximal absorption. The site of maximal copper absorption is not known for humans, but it is assumed to be the stomach and upper intestine because of the rapid appearance of <sup>64</sup>Cu in the plasma after oral administration (Bearn and Kunkel 1955). Copper is absorbed from the stomach, but mainly from the duodenum in rats (Van Campen and Mitchell 1965) and from the lower small intestine in hamsters (Crampton et al. 1965).

Copper is absorbed from the gastrointestinal tract as ionic copper or bound to amino acids. Absorption of the latter apparently involves at least two kinetically distinguishable processes. The first mechanism transports copper from the mucosal side of the intestine to the serosal side. Only a small fraction of the ingested copper is transported via this mechanism (Crampton et al. 1965; Gitlan et al. 1960). The second mechanism of copper absorption involves the delivery of copper to the absorptive surface, mucosal uptake and binding to metallothionein or another intestinal binding protein (Evans and LeBlanc 1976). The copper bound to metallothionein can be slowly released to the blood (Marceau et al. 1970) or is excreted when the mucosal cell is sloughed off.

A number of human studies have examined the oral absorption of <sup>64</sup>Cu; the average absorption efficiencies ranged from 24 to 60% in presumably healthy adults (Jacob et al. 1987; Johnson et al. 1988b; Strickland et al. 1972; Turnlund et al. 1982, 1983, 1985, 1988a; 1988b; 1989; Weber et al. 1969).

Numerous factors may affect copper absorption. These factors include: the amount of copper in the diet (Farrer and Mistilis 1967; Strickland et al. 1972; Turnlund et al. 1989), competition with other metals,

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including zinc, iron, and cadmium (Davies and Campbell 1977; Hall et al. 1979; Haschke et al. 1986; Hoogenraad et al. 1979; Prasad et al. 1978; Turnland et al. 1988a) and age (Varada et al. 1993). The absorption of copper appears to be inversely related to the amount of copper in the gastrointestinal tract (Strickland et al. 1972; Turnland et al. 1989). In a study of 11 young men administered various copper doses, absorption efficiencies of 55–56, 36, and 12% were found at doses of 0.785, 1.68, and 7.53 mg/day, respectively (Turnland et al. 1989). In humans, the amount of stored copper does not appear to influence copper absorption (Strickland et al. 1972). In rats, the absorption of copper appears to be inversely related to the amount of cadmium in the diet (Davies and Campbell 1977). A significant decrease in copper absorption was observed when the copper:cadmium ratio was 1:4. The amount of copper retained in the intestinal mucosal cells was also inversely related to cadmium dietary concentration. Increased levels of zinc in the diet also results in a decrease in copper absorption in humans and rats (Hall et al. 1979; Hoogenraad et al. 1979; Prasad et al. 1978). Turnland et al. (1988a) found that diets low in zinc (below the dietary requirement) decreased copper absorption in humans; 48.1% of radiolabeled copper was absorbed when the diet contained 1.3 mg copper and 16.5 mg zinc (dietary requirement is 15 mg zinc), and 37.2–38.5% of radiolabelled copper was absorbed when the diet contained 1.3 mg copper and 5.5 mg zinc. A decrease in copper absorption has been observed in infants with high intakes of iron (Haschke et al. 1986). Apparently conflicting results have been reported on the effect of ascorbic acid on copper absorption in humans. Based on a decrease in serum ceruloplasmin levels, Finley and Cerklewski (1983) concluded that a diet high in ascorbic acid resulted in a decrease in copper status. In a study by Jacob et al. (1987), copper absorption was not affected by a high ascorbic acid intake. A decrease in serum ceruloplasmin activity was also found; however, the amount of ceruloplasmin protein was not affected.

Several studies of adults did not find differences in copper absorption between male and female adults aged 20–83 years (Johnson et al. 1992) or between elderly men (65–74 years) and young men (22–30 years) (Turnland et al. 1982, 1988b). However, a study in rats found significant age-related differences in copper absorption. In suckling (16 days of age) and weanling (21–22 days) rats, copper absorption was concentration-dependent (Varada et al. 1993). In contrast, copper absorption in adolescent rats (6 weeks of age) exhibited both saturable and nonsaturable components.

Human studies did not find that increased levels of fiber ( $\alpha$ -cellulose or phytate) (Turnland et al. 1985) or ascorbic acid (Turnland et al. 1987) significantly altered copper absorption. However, a study in rats found an increase in fecal excretion of copper (and a decrease in apparent absorption) in rats fed a high fiber (potato fiber or sugar beet pulp) diet (Gralak et al. 1996). The administration of copper in infant

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formula or in a solution high in fulvic acid did not appear to influence copper intake from the intestinal lumen to the intestinal mucosa of suckling rats, as compared to copper in drinking water (Lind and Glynn 1999). However, the absorption rate of copper into the circulatory system was decreased in the infant formula and fulvic acid solutions. Gender does not appear to influence copper absorption. Johnson et al. (1992) found that women aged 20–59 years absorbed more copper (66.1–74.1%) than similarly aged men (62.0–69.2%); however, when net copper absorption was normalized by body weight, no sex-related differences in absorption were found. No sex-related differences in net copper absorption was found in older (60–83 years) men and women.

#### 3.4.1.3 Dermal Exposure

The available *in vivo* data do not provide information on the rate and extent of absorption through intact skin following dermal exposure of humans or animals to copper. Following a copper azide explosion that yielded metallic copper and nitrogen fumes, a small increase in serum copper levels was found in the affected worker (Bentur et al. 1988). Similarly, animal studies demonstrate that copper can pass through dermal barriers when applied with an appropriate vehicle, (e.g., salicylic acid or phenylbutazone) (Beveridge et al. 1984; Walker et al. 1977). *In vitro* studies suggest that copper is poorly absorbed through intact skin. Less than 6% of copper deposited on *ex vivo* human skin samples was absorbed (Pirot et al. 1996a, 1996b); copper chloride was absorbed to a higher extent than copper sulfate (Pirot et al. 1996a).

#### 3.4.2 Distribution

##### 3.4.2.1 Inhalation Exposure

No studies were located regarding the rate and extent of distribution of copper following inhalation exposure of humans or animals.

##### 3.4.2.2 Oral Exposure

Following ingestion of copper, copper levels in the blood rapidly rise. The copper is predominantly bound to albumin. There is some evidence that albumin plays a passive role in copper transport, carrying a large portion of the exchangeable copper in the circulation and releasing this to other carriers for actual cell-specific uptake. There is also evidence that transcuprein is another plasma protein carrier (Weiss and

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Linder 1985). The dietary copper then enters the liver and kidney. Copper then reemerges into the plasma bound to the ceruloplasmin. Ceruloplasmin, which tightly binds six or seven copper atoms (Musci et al. 1993; Saenko et al. 1994), is the most abundant copper protein in the plasma; 60–95% of the plasma copper is bound to ceruloplasmin (Harris 1993). Copper is transported from the liver to other tissues via ceruloplasmin. Ceruloplasmin does not enter the cell (Percival and Harris 1990). Copper, probably as Cu(I) rather than Cu(II) (Dameron and Harris 1989; Percival and Harris 1989), enters the cell via a carrier-mediated process. Recent evidence suggests that the membrane-bound copper transporting adenosine triphosphatase (Cu-ATPase) is selective for copper ions involved in the transport into and out of cells (Harris et al. 1998). In most organs and tissues, copper turnover is biphasic (Levenson and Janghorbani (1994). In the plasma, the half-lives of the first and second components were 2.5 and 69 days, respectively. It is likely that the first order component is ceruloplasmin associated copper. The respective calculated copper half-lives for other tissues were 3.9 and 21 days for the liver, 5.4 and 35 days for the kidney, and 23 and 662 days for the heart; copper turnover in the brain was monophasic with a half-life of 457 days.

#### **3.4.2.3 Dermal Exposure**

No studies were located regarding the rate and extent of distribution of copper following dermal exposure of humans or animals to copper.

#### **3.4.3 Metabolism**

The metabolism of copper consists mainly of its transfer to and from various organic ligands, most notably sulfhydryl and imidazole groups on amino acids and proteins. Several specific binding proteins for copper have been identified that are important in the uptake, storage, and release of copper from tissues.

In the liver and other tissues, copper is stored bound to metallothionein and amino acids and in association with copper-dependent enzymes. Several studies have shown that copper exposure induces metallothionein synthesis (Mercer et al. 1981; Wake and Mercer 1985). Increased levels of metallothionein may be associated with resistance to copper toxicity in pigs (Mehra and Bremner 1984). Ceruloplasmin is synthesized in the liver. Copper is incorporated into the molecule, and it is released from the liver. Copper exposure has also been shown to induce ceruloplasmin biosynthesis (Evans et al. 1970b; Haywood and Comerford 1980).

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#### **3.4.4 Elimination and Excretion**

##### **3.4.4.1 Inhalation Exposure**

No studies were located regarding the rate and extent of excretion of copper following inhalation exposure of humans or animals.

##### **3.4.4.2 Oral Exposure**

Bile is the major pathway for the excretion of copper. After the oral administration of radioactive copper as copper acetate in healthy humans, 72% was excreted in the feces (Bush et al. 1955). A considerable fraction of fecal copper is of endogenous biliary origin. The remainder of the fecal copper is derived from unabsorbed copper and copper from desquamated mucosal cells. Copper in bile is associated with low molecular weight copper binding components as well as macromolecular binding species (Gollan and Dellar 1973). Reabsorption of biliary copper is negligible (Farrer and Mistilis 1967).

Normally, 0.5–3.0% of daily copper intake is excreted into the urine (Cartwright and Wintrobe 1964).

##### **3.4.4.3 Dermal Exposure**

No studies were located regarding the rate and extent of excretion of copper following dermal exposure of humans or animals to copper.

##### **3.4.4.4 Other Routes of Exposure**

Biliary excretion of copper following intravenous administration does not increase proportionally with dosage, suggesting that the hepatobiliary transport of copper is saturable (Gregus and Klaassen 1986). Thus, at high copper intakes, urinary copper excretion increases (Gitlan et al. 1960).

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**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 et al. 1987; Andersen and Krishnan 1994). 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 parametrization, (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) is adequately described, however, this simplification is desirable because data are often unavailable for

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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 3-3 shows a conceptualized representation of a PBPK model.

A PBPK model for copper has not been identified.

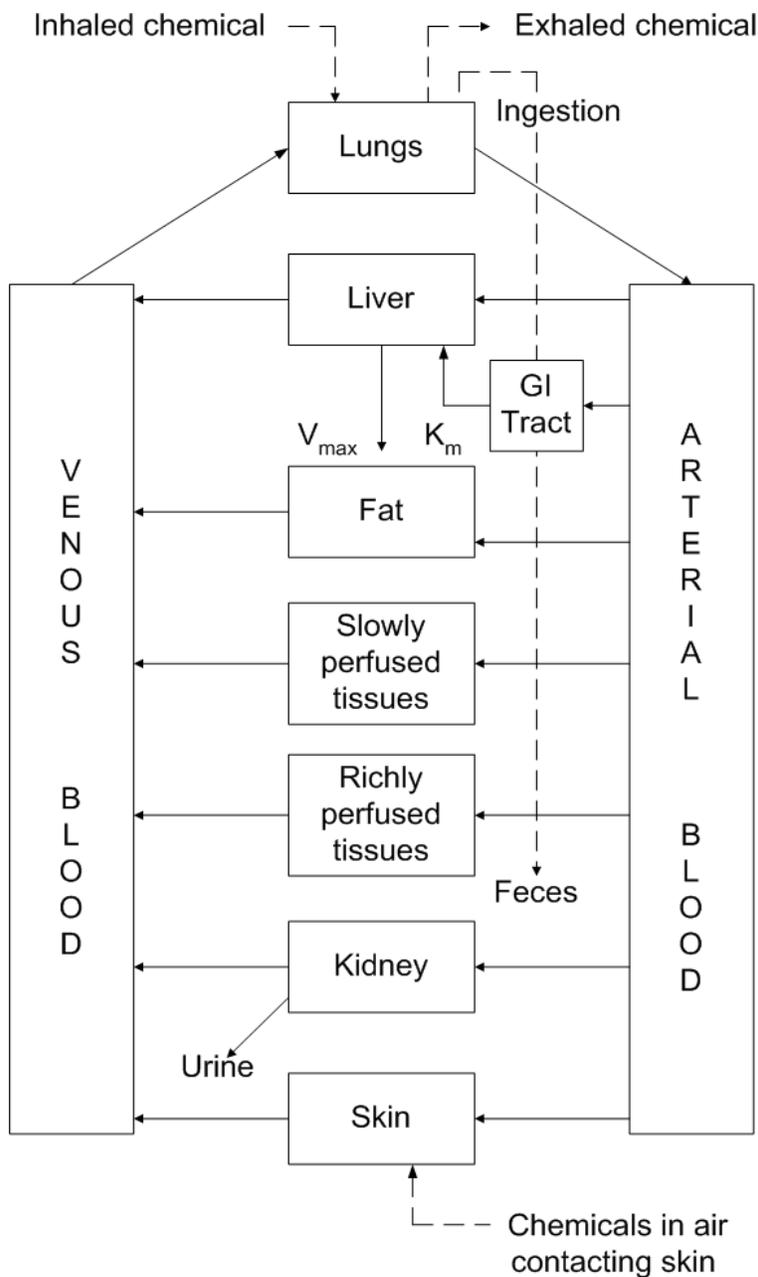
## 3.5 MECHANISMS OF ACTION

### 3.5.1 Pharmacokinetic Mechanisms

Copper is an essential element required for the normal functioning of at least 30 enzymes. The ability of copper to cycle between an oxidized state, Cu(II), and reduced state, Cu(I), is used by cuproenzymes involved in redox reactions. However, it is this property of copper that is also potentially toxic because the transitions between Cu(II) and Cu(I) can result in the generation of superoxide radicals and hydroxyl radicals (Camakaris et al. 1999). Under most circumstances, a number of homeostatic mechanisms maintain a physiologically essential concentration of copper. Copper homeostasis involves regulation of absorption, cellular uptake, intracellular transport, sequestration/storage, cellular efflux, and excretion from the body. Turnland et al. (1989) demonstrated that copper absorption from the gastrointestinal tract is dependent on dietary intake; as dietary copper increases, absorption efficiency decreases. At dietary

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



Source: adapted from

Krishnan et al. 1994

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.

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concentrations of 0.785, 1.68, and 7.53 mg/day (the recommended dietary allowance [RDA] for copper is 0.900 mg/day), 56, 36, and 12%, respectively, of the radiolabelled copper was absorbed. How the absorption of copper is regulated is not fully understood. *In vitro* studies provide evidence that copper uptake into intestinal cells is saturable (Arredondo et al. 2000). This study also provides suggestive evidence that copper uptake into the intestinal cell and efflux are influenced by intracellular copper concentrations. There is evidence that copper diffuses across the intestinal cell membrane; however, it is unlikely that this is the only absorption mechanism. It is possible that recently identified copper transporters (hCtr1 and hCtr2) may play a role in the regulation of copper uptake. The Menkes protein (MNK), a copper-translocating P-type ATPase, may be involved in the transport of copper across the basolateral membrane of intestinal cells (Pena et al. 1999). MNK protein is involved the delivery of copper to copper-dependent enzymes and the efflux of copper from the cell. The export of copper via the MNK protein appears to be regulated by intracellular copper concentration. Exposure to copper produces a conformational change in the MNK protein resulting in a copper cluster, which allows access to the phosphorylation site and the initiation of copper translocation (Dameron and Harrison 1998). Once copper is released from the intestinal cells, it is transported bound to albumin and histidine to the liver via portal circulation. Once in the hepatic cells, copper complexes with small cytoplasmic proteins known as copper chaperones. These copper chaperones are involved in intracellular distribution of copper ions. In the liver, another P-type ATPase, Wilson protein (WND), delivers copper to ceruloplasmin, which is then released to the blood for distribution to other tissues and organs. Under conditions of elevated copper, WND is involved in the release of copper at the canalicular membrane with ensuing biliary excretion of copper.

#### **3.5.2 Mechanisms of Toxicity**

Although a number of studies have investigated the mechanisms of copper hepatotoxicity in rats, it is not known whether rats would be a good model for human liver toxicity unrelated to a genetic defect in copper metabolism. Lysosomes serve an important role in hepatic copper metabolism. Excess copper is sequestered within hepatocyte lysosomes where it is complexed with metallothionein. However, this protective mechanism is saturable and liver lesions can develop. In copper loaded rats, lysosomes become enlarged and more fragile with decreased membrane fluidity (Myers et al. 1993). The results of the Haywood et al. (1985a) study do not suggest that the liver damage is due to rupturing of the lysosomes because the lysosomal instability precedes and is not synchronous with the liver damage. It is more likely that saturation of the lysosomes results in an accumulation of copper in the nucleus and subsequent nuclear damage (Fuentealba and Haywood 1988; Fuentealba et al. 1989; Haywood et al.

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1985a). The means by which copper accumulates in the nucleus and the mechanisms by which it provokes injury are not clear. It has been suggested that excess copper results in oxidative damage, including lipid peroxidation. Increases in the level of thiobarbituric acid reactive substance (TBARS), a measure of lipid peroxidation, have been found in copper-loaded rats (Myers et al. 1993; Sokol et al. 1993). However, a study by Aburto et al. (2001) did not find significant alterations in the levels of malondialdehyde, a lipid peroxidation by product, prompting the study authors to postulate that lipid peroxidation does not play a major role in copper toxicity although it may occur as a terminal event as a consequence of cell injury. Sokol et al. (1990, 1993) suggested that oxidant injury to hepatocyte mitochondria may be one of the initiating factors in hepatocellular damage. Numerous studies have shown that rats can develop tolerance to high levels of copper. After 3–5 weeks of copper loading, the copper levels in the liver begin to decline and the tissue begins to regenerate (Haywood and Loughran 1985). It is believed that the mechanism involved in tolerance development is the increased synthesis of metallothionein (Evering et al. 1991a, 1991b; Freedman and Peisach 1989).

Studies in monkeys, dogs, and ferrets provide strong evidence that copper-induced emesis results from stimulation of the vagus nerve. Abdominal vagotomy resulted in a dramatic decrease in the occurrence of emesis in dogs (Fukui et al. 1994) and ferrets (Makale and King 1992) orally exposed to copper sulfate and in monkeys receiving oral or intravenous injections of copper sulfate (Fukui et al. 1993). In monkeys, administration of compounds that block 5-HT<sub>3</sub> receptors also resulted in a decrease in emesis following oral or intravenous administration of copper sulfate (Fukui et al. 1993). In contrast, 5-HT<sub>3</sub> blockers did not affect the occurrence of emesis in dogs (Fukui et al. 1994) or ferrets (Bhandari and Andrew 1991) receiving an oral dose of copper sulfate, but compounds that block 5-HT<sub>4</sub> receptors did inhibit copper-induced vomiting. Fukui et al. (1994) suggested that copper sulfate caused gastrointestinal irritation, which resulted in the release of 5-HT and evoked emesis by activation of abdominal visceral afferents through 5-HT<sub>4</sub> receptors.

#### **3.5.3 Animal-to-Human Extrapolations**

The toxicity of copper has been assessed in a number of experimental animal species, and sensitivity to copper toxicity is highly species dependent. Ruminants are more susceptible than nonruminant species. NTP (1993) demonstrated that rats are much more sensitive than mice to the hepatotoxicity of copper. In rats, dietary exposure to 16 mg Cu/kg/day for 13 weeks resulted in an increase in alanine aminotransferase activity; chronic active liver inflammation was observed at 66 mg Cu/kg/day. In contrast, no evidence of liver damage was observed in mice exposed to 814 mg Cu/kg/day for 13 weeks.

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Although most of the available experimental data on the toxicity of copper are from studies in which rats were used, the relevance of this species to human toxicity is not known. The dietary requirement for copper in rats is 5 mg Cu/kg diet (NRC 1995); a commonly used diet for rats (AIN76, AIN 93G, AIN93M) has a cupric carbonate concentration of 300 mg/kg diet (160 mg Cu/kg diet). An intermediate-duration exposure to approximately 250 mg Cu/kg diet resulted in mild liver effects (increased serum alanine aminotransferase) (NTP 1993). With a few exceptions, it is unlikely that humans would tolerate exposure to a copper dose that is 50 times higher than the dietary requirement (0.65 mg Cu/kg/day); gastrointestinal disturbances were observed in women ingesting 0.0731 mg Cu/kg/day in drinking water (Pizarro et al. 1999). Thus, the applicability of these animal data to humans is not known.

The Long-Evans Cinnamon rat is often used as a model for Wilson's disease. This rat strain shares many characteristics with Wilson's disease: accumulation of liver copper, decreased serum copper and ceruloplasmin levels, and impaired biliary excretion of copper (Sugawara et al. 1991, 1992, 1994; Suzuki et al. 1995).

#### 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 Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (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), which in 1998 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 isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et

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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).

There is no evidence that copper interferes with the normal function of the neuroendocrine axis.

#### 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

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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).

Copper is an essential element required for normal growth and development and for a variety of metabolic functions including iron metabolism, cross-linking of connective tissue, and lipid metabolism. Signs of copper deficiency in infants and children include anemia that is unresponsive to iron supplementation, neutropenia, bone abnormalities, and hypopigmentation of the hair (Cordano 1998; Danks 1988).

Exposure to excess levels of copper has also been associated with adverse health effects in infants and children. There is an extensive body of literature on two syndromes that have been associated with exposure to high levels of copper. Indian childhood cirrhosis and idiopathic copper toxicosis are both characterized by severe liver damage in infants and children (<5 years of age). In the case of Indian childhood cirrhosis, excessive copper exposure has been traced to the use of brass or copper containers

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for storage and heating of milk. Doses as high as 0.930 mg/kg/day have been estimated; this dose is approximately 30 times higher than the dietary requirement for copper (Tanner 1998).

Idiopathic copper toxicosis has been linked to exposure to high levels of copper in drinking water and/or the use of copper utensils, although there have been some cases not associated with high copper exposure. A common finding in both syndromes is the early introduction of milk and/or formula. Genealogical investigations provide suggestive evidence that both syndromes are transmitted in an autosomal recessive mode. However, the mechanism of action has not been identified. It is possible that the genetic defect results in reduced copper efflux from the liver. Very high levels of copper have been detected in the livers of affected infants; copper levels ranging from 790 to 6,654  $\mu\text{g/g}$  dry weight (mean of 939  $\mu\text{g/g}$ ) have been reported in infants diagnosed with Indian childhood cirrhosis (levels in control infants ranged from 8–118  $\mu\text{g/g}$  (Bhave et al. 1982). Support for the genetic component comes from the finding that decreasing copper exposure levels dramatically decreases the occurrence of Indian childhood cirrhosis (Tanner 1998). Additionally, no alterations in serum biomarkers of liver damage (alanine aminotransferase activity, aspartate aminotransferase activity, gamma glutamyl transferase activity, and total bilirubin levels) were observed in infants ingesting water containing 2 mg/L copper (0.319 mg/kg/day) (Olivares et al. 1998). Together, these data suggest that high exposure to copper alone was not the causative agent for severe liver damage.

Another adverse health effect that has been reported in infants and children is gastrointestinal upset. This effect, which is one of the most commonly reported adverse health effect in adults, is manifested in nausea, vomiting, abdominal pain, and/or diarrhea. Symptoms usually occur shortly after ingesting a copper-contaminated beverage or drinking water containing a high level of copper. In most of the reports of gastrointestinal upset in children (Gill and Bhagat 1999; Karlsson and Noren 1965; Knobeloch et al. 1994; Spitalny et al. 1984; Walsh et al. 1977), no reliable information on copper concentration or dose was reported. In one report where school-age children ingested a beverage stored in an old urn, the concentration of copper in the beverage was estimated to be 300 mg/L (Gill and Bhagat 1999). Another study reported vomiting in infants ingesting a single dose of 7.5 mg/L copper sulfate (Karlsson and Noren 1965). Knobeloch et al. (1994) noted that children appear to be more sensitive to the gastrointestinal effects of copper than adults. This statement was based on two surveys of residents with elevated copper levels in the drinking water. In the first survey, it appears that children who were described as “unusually irritable” or had recurrent headaches were categorized as having gastrointestinal upset. In the second survey, mothers were asked to recall the frequency of gastrointestinal effects for all family members. A significantly higher percentage of children, as compared to adults, were reported to have gastrointestinal

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effects. It is difficult to determine what role recall bias had in the results and how well the mothers knew of symptoms of gastrointestinal upset in the adult members of the household. The available data are inconclusive to assess whether there is an age-related difference in the gastrointestinal toxicity of copper.

The potential age-related differences in the toxicity of copper has been assessed in rats exposed to 120 mg Cu/kg/day as copper sulfate in the diet for 12 weeks (Fuentelba et al. 2000). The observed liver effects were more severe in young rats (exposed *in utero*, during lactation, and for 12 weeks post weaning) as compared to the effects observed in adult rats. The copper levels in the liver were also higher in the young rats (1,553–1,635 versus 472–534 µg/g). The doses used in this study are very high, 1,000 times higher than the rat dietary requirement of 0.15–0.30 mg/kg/day (AIN 1977). It is not known if increased liver sensitivity would also occur at lower copper doses.

Several studies have investigated the potential developmental toxicity of copper sulfate in the diet; the results are suggestive that *in utero* exposure to copper will result in delays in growth and development in the offspring of rats exposed to 130 mg Cu/kg/day (Haddad et al. 1991) and mice exposed to 208 mg Cu/kg/day (Lecyk 1980). No developmental effects were observed in the offspring of mink exposed to 13 mg Cu/kg/day (Aulerich et al. 1982).

During the third trimester of pregnancy, the fetal liver accumulates high levels of copper; liver storage is efficient and copper efflux from the liver is low. This results in very high levels of copper in the liver. In full-term infants, the total amount of copper in the liver is 9 mg; total body copper is 15 mg (Widdowson et al. 1974). The magnitude of the amount of copper in the fetal liver is similar to levels observed in Wilson's disease. After birth, the copper levels in the liver steadily decrease from about 51 µg/g at birth to 5.7 µg/g at 6–14 months of age (Klein et al. 1991). How the fetal liver tolerates the high concentration of copper is not known. A study by Richards (1999) examined the levels of copper in maternal and fetal pig tissues. The level of copper in amniotic fluid reached its maximum level at gestation day 60; thereafter, the levels decreased. Maternal serum copper levels remained fairly steady throughout the gestational period, although a slight rise was observed at gestational day 70. Fetal serum copper levels gradually declined throughout the gestational period. Maternal serum ceruloplasmin activity levels were significantly higher than fetal levels and the trend in ceruloplasmin oxidase activity paralleled maternal and fetal copper concentrations. The concentration of copper in the fetal liver was significantly higher than in the maternal liver. In the fetus, the copper concentration reached a maximum level early in the second trimester and then declined toward term. The levels of copper in the fetal liver increased 5-fold during the second trimester and 2-fold during the third trimester. Most of the cytosolic copper in the liver

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was associated with metallothionein, which was similar to the findings in maternal livers. The copper content of the fetal kidney remained constant throughout gestation.

#### 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).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. 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 or 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 copper 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 copper 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

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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 Copper**

Copper levels can readily be measured in tissues, body fluids, and excreta. Following inhalation and oral exposure to copper, increased levels of serum, urine, hair, and hepatic copper have been reported in humans and animals. Increased whole blood and serum copper levels have been reported in humans following ingestion of 1–30 g of copper. Serum and whole blood levels ranging from 239 to 346 and from 383 to 684  $\mu\text{g}/100\text{ mL}$ , respectively, were observed. Serum and whole blood levels of 151.6 and 217  $\mu\text{g}/100\text{ mL}$ , respectively, were reported in controls (Chuttani et al. 1965). Plasma serum levels of  $>200\text{ }\mu\text{g}/100\text{ mL}$  were observed in 16% of the factory workers exposed to copper dust (111–464  $\text{mg Cu}/\text{m}^3$ ) (Suciu et al. 1981). Increased serum copper levels may only be reflective of recent exposure. Chuttani et al. (1965) observed that serum ionic copper rapidly diminishes to normal levels following an acute bolus dose.

Chuttani et al. (1965) attempted to correlate the levels of serum and whole blood copper with the severity of symptoms in adults after acute copper sulfate poisoning. It is unclear whether the authors statistically analyzed the correlations between symptoms (i.e., gastrointestinal effects, jaundice, renal manifestations) and blood copper levels. A significant correlation between whole blood copper and the severity of symptoms was found. Whole blood copper levels were 287 and 798  $\mu\text{g}/100\text{ mL}$  in individuals with gastrointestinal effects and in individuals with jaundice, renal manifestations, or shock, in addition to gastrointestinal symptoms, respectively.

Copper levels in hair and nails can also be used to assess copper exposure. In a study of preschool children, the levels of copper in hair and toenail samples were log-normally distributed (Wilhelm et al. 1991). The geometric mean concentrations of copper in hair and toenails were 10.6  $\mu\text{g}/\text{g}$  (range of 5.4–20.7  $\mu\text{g}/\text{g}$ ) and 7.5  $\mu\text{g}/\text{g}$  (range of 3.0–18.6  $\mu\text{g}/\text{g}$ ), respectively. Based on a hair growth rate of 10 mm per month, the copper levels in the first 2 cm proximal to the scalp would represent copper intake over 2 months (Hopps 1977). In contrast, toenail samples would represent copper intake over 12–18 months, based on a toenail growth rate of 1 mm/month (Fleckman 1985). Increased hair copper levels have been reported in workers exposed to 0.64–1.05  $\text{mg}/\text{m}^3$ ; the concentration of copper in the hair was 705.7  $\mu\text{g}/\text{g}$ , as compared to a 8.9  $\mu\text{g}/\text{g}$  concentration in non-exposed workers (Finelli et al. 1981), and

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increased hair and fingernail copper levels were observed in children with Indian childhood cirrhosis (Sharda and Bhandari 1984).

### 3.8.2 Biomarkers Used to Characterize Effects Caused by Copper

The harmful health effects of copper occur over a wide range of copper intakes from too little copper in the diet to excessive copper exposure.

***Low Intakes of Copper.*** The nutritional requirements of copper and the health effects associated with copper deficiency have been reviewed by numerous authors (Gallagher 1979; Mason 1979; O'Dell 1984). Copper deficiency is rarely observed in humans; the existence of covert copper deficiency among segments of the population is unknown. The limited data available on the human health effects of low copper intakes are derived mostly from case reports of severely malnourished children, patients maintained by total parenteral nutrition without copper, and children with Menkes' disease (a genetic disorder resulting in impaired copper absorption). Copper deficiency is characterized by hypochromic anemia, abnormalities of connective tissues, and central nervous system disorders. Sudden death associated with spontaneous rupture of a major blood vessel or the heart itself has been observed in some animal species.

The manifestations of copper deficiency are related to a decrease in several of the copper-containing metalloenzymes. The most severe biochemical alteration is a decrease in cytochrome oxidase activity; this is manifested as poor growth, anemia, and central nervous system effects. The decreased oxidative metabolism associated with decreased cytochrome oxidase results in poor growth in infants, weight loss, and emaciation. The hypochromic anemia observed during copper deficiency is not distinguishable from iron deficiency anemia; however, it is not responsive to iron administration. The exact mechanism involved in the development of the anemia is not known, but copper is thought to have a role in the transportation and utilization of iron (Underwood 1977). A decrease in protoheme synthesis, a result of decreased cytochrome oxidase, has also been observed. As with anemia, the central nervous system effects, primarily the result of hypomyelination, are associated with low activity levels of cytochrome oxidase. However, the decreased synthesis of phospholipids observed in copper deficiency may also contribute to the development of central nervous system effects. In addition to the decrease in cytochrome oxidase, a decrease in lysyl oxidase is also observed. Lysyl oxidase is involved in the formation of cross-links in collagen and elastin. Depending on the species, this impairment results in bone disorders, a defective cardiovascular system, or abnormal lung structure.

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***Exposure to Excess Levels of Copper.*** No copper-specific biomarkers of effects have been identified. The most notable sign of toxicity in humans ingesting a beverage or water containing copper is gastrointestinal distress. Symptoms (typically nausea, vomiting, and abdominal pain) usually occur shortly after ingesting the contaminated beverage. The liver is another sensitive target of copper toxicity. Alterations in a number of serum enzymes have been observed in humans and animals with copper-induced liver damage (Chuttani et al. 1965; Epstein et al. 1982; Haywood 1980; Haywood and Comerford 1980; Müller et al. 1998; NTP 1993; Sugawara et al. 1995). The affected serum enzymes include serum aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. Increases in serum bilirubin levels have also been observed in humans. Animal studies demonstrate that the rise in serum enzyme activities are the first evidence of liver damage. However, alterations in serum enzyme levels are not unique to copper-induced liver damage.

### 3.9 INTERACTIONS WITH OTHER CHEMICALS

Numerous studies have demonstrated the interaction between copper and several other metals. Dietary zinc strongly affects copper absorption. A diet high in zinc can result in copper deficiency. Reductions in erythrocyte superoxide dismutase, indicative of marginal copper deficiency, have been found in studies of women ingesting zinc supplements (50 mg zinc/day) for 10 weeks (Yadrick et al. 1989) and men ingesting 50 mg zinc/day for 6 weeks (Fisher et al. 1984). The exact mechanism of the zinc-copper interaction is not known. Increased dietary zinc results in induction of metallothionein synthesis in the intestine. Since metallothionein has a greater binding capacity for copper than for zinc, the dietary copper is sequestered in the intestinal mucosal cell and is eventually excreted in the feces when the mucosal cell is sloughed off (Hall et al. 1979; Whanger and Weswig 1971). Because exposure to excess dietary zinc results in decreased copper absorption, it is often used as a treatment for Wilson's disease (Brewer et al. 1993). An oral/intraperitoneal study in mice provides some evidence that zinc and copper may interact at sites other than the intestinal. In this study on the influence of zinc on mitigating the immunotoxicity of copper, mice were exposed to copper sulfate in the drinking water for 8 weeks and received an intraperitoneal injection of zinc sulfate once a week (Pocino et al. 1990). Decreases in the magnitude of the proliferative response to con A or LPS and the antibody response to sheep red blood cells were observed in the copper-exposed mice, but not the mice receiving copper and zinc. However, zinc did not modify the increased production of auto-antibodies reactive with bromelain-treated mouse red blood cells.

Several other divalent cations compete with copper for intestinal absorption. Exposure to dietary cadmium (Evans et al. 1970a), ferrous iron (Wapnir et al. 1993; Yu et al. 1994), and stannous tin

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(Pekelharing et al. 1994; Wapnir et al. 1993) can result in a decrease in copper absorption. In the case of cadmium, the decreased copper absorption is due to cadmium-induced induction of metallothionein and increased copper binding to metallothionein. Excessive dietary molybdenum can also result in decreases in copper utilization and toxicity. Tetrathiomolybdate is used for the treatment of Wilson's disease (Brewer 1995). Two mechanisms have been proposed: tetrathiomolybdate reacts with copper-metallothionein to form a soluble complex, which is then excreted (Ogra et al. 1996), and tetrathiomolybdate can complex with nonceruloplasmin plasma copper, which prevents its cellular absorption (Brewer 1995).

Because selenide is a strong reducing agent (Frost 1972), it has been postulated that selenium may play a role in detoxifying copper. Aburto et al. (2001a, 2001b) examined the possible interaction between copper and selenium. Selenium did not influence the hepatotoxicity of copper in rats fed diets with excess levels of copper and inadequate, adequate, or excess levels of selenium. Hepatic copper levels and histological alterations were not significantly different in rats receiving a high copper/high selenium diet as compared to rats receiving a high copper/adequate selenium diet.

#### **3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE**

A susceptible population will exhibit a different or enhanced response to copper than will most persons exposed to the same level of copper 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 copper, or compromised function of organs affected by copper. Populations who are at greater risk due to their unusually high exposure to copper are discussed in Section 6.7, Populations With Potentially High Exposures.

A number of populations of individuals unusually susceptible to copper toxicity have been identified. The increased susceptibility to copper toxicity is associated with genetic defects that impair copper homeostatic mechanisms. Wilson's disease, also referred to as hepatolenticular degeneration, is an autosomal recessive disorder with a worldwide incidence of 1 in 30,000 (Scheinberg and Sternlieb 1996). The primary genetic defect in Wilson's disease is in ATP7B, which encodes a P-type ATPase (Wilson protein), which delivers copper to ceruloplasmin. The genetic defect results in impaired biliary excretion of copper and an accumulation of copper in the liver. As described by Brewer and Yuzbasiyan-Gurkan (1992), the progression of the disease begins with an accumulation of copper in the liver, damage to the liver, and subclinical liver cirrhosis. Over time, the individual will develop hepatic, neurological, and

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psychiatric symptoms. The hepatic effects are characterized by jaundice, hypoalbuminemia, ascites, coagulation defects, hyperammonemia, hepatic encephalopathy, and/or liver failure; in the cases of massive liver failure, large amounts of copper are released from the liver resulting in hemolytic anemia. Neurological symptoms include tremors, speech abnormalities, and other evidence of movement disorders. Psychiatric and behavioral symptoms are often found in individuals also manifesting neurological symptoms; the psychiatric symptoms include reduced performance in school or work, inability to cope, depression, very labile moods ranging from mania to depression, sexual exhibitionism, and frank psychosis. Individuals with Wilson's disease have low serum ceruloplasmin levels, elevated urinary copper levels, and elevated liver copper levels; Kayser-Fleischer rings, which result from corneal copper deposits, are also detected in individuals with Wilson's disease.

Indian childhood cirrhosis (ICC) and idiopathic copper toxicosis (ICT) are two syndromes that result in severe, often fatal, liver cirrhosis in infants and young children. Although the causative agent has not been firmly established, the liver damage is believed to be due to an autosomal recessive inherited defect in copper metabolism and a high copper intake (Bhave et al. 1982, 1987; Müller et al. 1996, 1998). ICC occurs in infants and children living in rural areas of the Indian subcontinent who are introduced early to cow or buffalo milk that is stored or heated in brass or copper vessels. Copper is believed to be the causative agent because the milk has very high copper levels, very high copper levels are found in the liver, and replacing the brass or copper vessels with aluminum or stainless steel vessels eliminate the occurrence of ICC in siblings of ICC affected children (Bhave et al. 1982; Tanner 1998). A high degree of parental consanguinity, ICC occurring in children but not the parents, and 22% of siblings affected provide suggestive evidence that there is an autosomal recessive component to the disease (Pandit and Bhave 1996; Tanner 1998). For ICT, which includes Tyrolean infantile cirrhosis, sources of high copper exposure have been identified. For the 138 cases of ICT in children living in the Tyrolean region of Austria, the source of the copper was the use of a water/unpasteurized cow's milk mixture that was heated in a copper pot (Müller et al. 1996). For the other cases of ICT that have been identified in a number of countries, the source of the excess copper intake was drinking water (Müller et al. 1998). The similarity of ICT to ICC has prompted investigators to suggest that ICT may also be due to an autosomal recessive genetic defect in copper metabolism and excessive copper intake at a very young age. A geneological investigation by Müller et al. (1996) provides supportive evidence for a genetic basis to the disease.

It has been postulated that individuals with a deficiency in glucose-6-phosphate dehydrogenase enzyme would be susceptible to the toxic effects of oxidative stressors such as copper (Calabrese and Moore 1979; Chugh and Sakhuja 1979). This has not been supported by epidemiological or experimental data.

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In the blood, most of the copper is bound to ceruloplasmin. With the exception of ingestion of a very large dose of copper salts, the levels of nonceruloplasmin bound copper remain low following copper exposure. Thus, it is unlikely that this relatively small change in free copper would alter the survival of glucose-6-phosphate dehydrogenase deficient red cells.

#### **3.11 METHODS FOR REDUCING TOXIC EFFECTS**

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to copper. 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 copper. 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 copper:

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. *Medical toxicology: Diagnosis and treatment of human poisoning*. Second edition. Baltimore, MD: Williams & Wilkins, 1554-1556.

Goldfrank LR, Flomenbaum FE, Lewin NA, et al., eds. 1998. *Goldfrank's toxicologic emergencies*. Sixth edition. Stamford, CT: Appleton & Lange, 1339-1340.

Haddad LM, Shannon MW, Winchester JF, eds. 1998. *Clinical management of poisoning and drug overdose*. Third edition. Philadelphia, PA: WB Saunders, 165.

##### **3.11.1 Reducing Peak Absorption Following Exposure**

Following ingestion of copper or copper compounds, milk or water should be given immediately after ingestion and/or prior to vomiting. Because of the strong emetic properties of copper and copper compounds, vomiting usually occurs shortly after ingestion. Induction of vomiting and gastric lavage are contraindicated following ingestion of caustic copper salts, such as copper sulfate. Gastric lavage may be indicated after ingestion of noncorrosive copper compounds (HSDB 2002).

For individuals with Wilson's disease, the administration of a diet high in zinc is used as a maintenance treatment (Brewer et al. 1989). The zinc interferes with copper absorption by inducing intestinal metallothionein resulting in decreased copper absorption (Brewer et al. 1992).

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**3.11.2 Reducing Body Burden**

A number of methods have been reducing copper body burdens. These methods range from the use of chelating agents to increases in the dietary exposure of zinc and molybdenum. Gao et al. (1989) tested the *in vitro* effectiveness of five chelating agents in human serum albumin. The agents (in order of decreasing effectiveness) were ethylenediaminetetraacetate (EDTA), diethylene triaminopentaacetate, ethylene glycol-*bis*-(aminoethylether)-tetraacetate, nitrilotriacetate, and iminodiacetate. The *in vivo* effectiveness of these agents has not been established. D-penicillamine is often used to decrease the elevated levels of hepatic copper in individuals with Wilson's disease (Walshe 1996; Walshe and Yealland 1993) and idiopathic childhood cirrhosis (Rodeck et al. 1999). However, a number of potential side effects have been associated with penicillamine treatment (Brewer and Yuzbasiyan-Gurkan 1992). A variety of other chelating agents have been tested in copper loaded rats. Tetraethylenepentamine pentahydrochloride (TETREN) was more effective in increasing urinary excretion of copper than 1,4,7,11-tetraazaundecane tetrahydrochloride (TAUD) or penicillamine, which were equally effective (Domingo et al. 2000). TETREN did not result in a decrease in copper levels in the liver, although a significant decrease in kidney copper levels was observed. In contrast, TAUD and penicillamine reduced the levels of copper in the liver. None of the three chelating agents affected the amount of copper excreted into the feces.

The known interactions between copper and molybdenum and between copper and zinc have been used to treat individuals with Wilson's disease. The administration of tetrathiomolybdate to individuals with neurological or psychiatric symptoms associated with Wilson's disease has resulted in an improvement or reversal of symptoms (Brewer 1995). Absorbed tetrathiomolybdate complexes with nonceruloplasmin plasma copper, preventing its cellular absorption. Studies in Long-Evans Cinnamon rats, a model for Wilson's disease, and sheep have found that administration of tetrathiomolybdate results in a dramatic decrease in the levels of copper in the liver (Humphries et al. 1988; Kumaratilake and McC Howell 1989; Ogra et al. 1996) and decreased liver damage (Humphries et al. 1988). The tetrathiomolybdate reacts with copper bound to metallothionein resulting in a soluble copper-tetrathiomolybdate complex (Ogra et al. 1996). The addition of molybdenum to a high sulfur, low copper diet can result in a decrease in liver and plasma copper levels in copper loaded sheep (van Ryssen 1994). The administration of a low copper, high zinc diet did not have any effect on hepatic copper levels (van Ryssen 1994). Although a reduction in liver copper levels has been observed in dogs administered a high zinc diet (Brewer et al. 1992), it is believed that the reduction in copper levels was secondary to the induction of copper deficiency and the mobilization of copper from the liver (van Ryssen 1994).

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#### 3.11.3 Interfering with the Mechanism of Action for Toxic Effects

There are limited data on methods for interfering with the mechanisms of action of copper. An *in vitro* study provides suggestive evidence that lazaroids (21-aminosteroids) may have a protective effect against copper-induced erythrocyte lipid peroxidation (Fernandes et al. 1992). Oxidative damage to the erythrocyte membrane may be the cause of the hemolysis observed following exposure to very high doses of copper.

#### 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 copper 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 copper.

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 Copper

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to copper are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of copper. 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.

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Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

The toxicity of inhaled copper has been investigated in a couple of occupational exposure studies. These studies examined a limited number of systemic end points, and exposure is poorly characterized. There are numerous reports and studies on the toxicity of ingested copper in humans. A fair number of the reports and studies focused on the gastrointestinal effects following acute exposure to copper in drinking water or other beverages. Data on other health effects in humans comes from individuals with Wilson's disease, Indian childhood cirrhosis, and idiopathic copper toxicosis. These diseases/syndromes are the result of increased genetic susceptibility; the latter two syndromes are also associated with exposure to high levels of copper in drinking water or copper-contaminated milk (due to storage of milk in brass vessels). These studies provide information on potential targets of toxicity, primarily the liver.

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Figure 3-4. Existing Information on Health Effects of Copper

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation				•						•
Oral	•	•	•	•						
Dermal		•		•	•					

**Human**

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		•	•		•					
Oral	•	•	•	•	•		•	•	•	•
Dermal										

**Animal**

- Existing Studies

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Information on the dermal toxicity of copper is limited to reports of contact dermatitis in individuals and eye irritation in workers exposed to copper dust.

As with the human database, there are limited data on the toxicity of inhaled copper in animals. The available studies have primarily focused on potential respiratory effects. There is a more extensive database on the toxicity of ingested copper in animals. These studies have found a number of systemic effects, including gastrointestinal, hepatic, and renal effects following acute, intermediate, and chronic exposure. Immunological and developmental effects have also been reported in animal studies. Several studies have also examined potential neurological and reproductive targets, but have not found effects. Carcinogenic effects were not found in several animal studies; however, the studies are limited in scope and tested low doses. No animal studies examining the dermal toxicity of copper were identified.

#### 3.12.2 Identification of Data Needs

**Acute-Duration Exposure.** No data were located regarding health effects after acute inhalation exposure to copper in humans. Animal data are limited to information from studies in mice and hamsters conducted by Drummond et al. (1986). Respiratory tract irritation and impaired immune function were observed. This study was not selected as the basis of an acute-duration inhalation MRL because it only examined a limited number of end points, and the liver and kidney, which are targets following oral exposure, were not examined; in addition, the animals were only exposed for 3 hours/day. Additional inhalation studies are needed to identify the critical targets of toxicity and to establish concentration-response relationships for copper. The most commonly reported effect in humans acutely exposed to copper is gastrointestinal upset. The reported symptoms include nausea, vomiting, abdominal pain, and diarrhea (Chutanni et al. 1965; Gill and Bhagat 1999; Gotteland et al. 2001; Nicholas and Brist 1968; Olivares et al. 2001; Pizarro et al. 1999, 2001; Semple et al. 1960; Walsh et al. 1977). Hepatic and renal effects have also been seen in individuals ingesting lethal doses of copper sulfate (Chuttani et al. 1965). Animal studies support the identification of the gastrointestinal tract, liver, and kidneys as sensitive targets of copper toxicity. Hyperplasia of the forestomach has been observed in rats and mice exposed to copper sulfate in the diet for 14 days (NTP 1993). Hepatic effects ranging from increases in alanine aminotransferase activity to hepatocellular necrosis and renal effects (protein droplets in proximal tubules) have been observed in rats exposed to fairly high doses of copper sulfate in the diet (Haywood 1980; Haywood and Comerford 1980; Haywood et al. 1985b; NTP 1993). Decreases in body weight gain have also been observed in rats (NTP 1993). The acute-duration oral database was considered adequate for derivation of an MRL. The MRL was based on gastrointestinal upset in women ingesting drinking

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water containing copper sulfate for 2 weeks (Pizarro et al. 1999). There are limited data on the dermal toxicity of copper. Pruritic dermatitis and allergic contact dermatitis have been reported in humans exposed to copper. No animal studies were identified. These data provide suggestive evidence that copper may be irritative to the skin; additional studies are needed to determine whether copper exposure will also result in systemic effects.

**Intermediate-Duration Exposure.** No studies were located regarding health effects in humans after intermediate-duration inhalation. Only one animal inhalation exposure study was located. This study did not find any adverse histological alterations in the lungs or functional alterations in alveolar macrophages of rabbits exposed to copper chloride (Johansson et al. 1983, 1984). Because the lungs were the only tissues examined, these studies were not considered suitable for derivation of an intermediate-duration inhalation MRL for copper. Additional studies are needed to identify the critical targets of toxicity and establish concentration-response relationships for inhaled copper. Two human studies have examined the oral toxicity of copper. The primary focus of these studies were to examine the potential of low doses of copper to induce hepatic effects in adults (Pratt et al. 1985) or infants (Olivares et al. 1998); no adverse effects were found. A number of animal studies have reported adverse liver and kidney effects following intermediate-duration oral exposure to copper compounds (Epstein et al. 1982; Fuentealba et al. 2000; Haywood 1980, 1985; Haywood and Comerford 1980; Haywood and Loughran 1985; Haywood et al. 1985a, 1985b; Kumar and Sharma 1987; NTP 1993). The observed liver and kidney effects demonstrated dose- and duration-response relationships. The studies by Haywood and associates demonstrate that rats can develop a tolerance to copper following repeated oral exposure. Studies in other animal species are needed to determine if this phenomenon is unique to rats or is observed in other species as well. Other systemic effects that have been reported in animals include hyperplasia of the forestomach mucosa (NTP 1993), decreased erythrocyte and hemoglobin levels (Kumar and Sharma 1987; Rana and Kumar 1980; Suttle and Mills 1966a), and decreased body weight gain or weight loss (Haywood 1985; Haywood and Loughran 1985; Kline et al. 1971; Llewellyn 1985; NTP 1993). For the most part, these studies involved dietary exposure of rats to copper sulfate; additional studies in other species would be useful for identifying a model for human toxicity. The oral toxicity database was considered inadequate for derivation of an intermediate-duration oral MRL for copper. The acute-duration oral MRL was adopted as the intermediate-duration MRL. Additional oral studies are needed to derive an MRL that is based on intermediate-duration exposure data. No data on the dermal toxicity of copper following intermediate-duration exposure were identified. Studies are needed to identify the critical targets of copper toxicity following dermal exposure.

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**Chronic-Duration Exposure and Cancer.** Systemic effects such as nausea (Suciu et al. 1981), hepatomegaly (Suciu et al. 1981), decreased hemoglobin and erythrocyte levels (Finelli et al. 1981), and respiratory irritation (Askergren and Mellgren 1975; Suciu et al. 1981) have been observed in workers exposed to copper dust. The mild gastrointestinal effects were attributed to swallowing airborne copper dust were observed in some workers (Suciu et al. 1981). The poor exposure characterization and/or the lack of controls precludes deriving a chronic-duration inhalation MRL based on the occupational exposure studies. Additional studies are needed to identify the critical targets of toxicity of inhaled copper. There are numerous reports of severe health effects in infants and children ingesting copper-contaminated milk or water with high levels of copper (Müller et al. 1996, 1998; Pandit and Bhave 1996; Tanner 1998). Indian childhood cirrhosis and idiopathic copper toxicosis are characterized by severe liver cirrhosis occurring before the age of 5 years. There is strong suggestive evidence that both of these syndromes are related to increased dietary intake of copper and an increased genetic susceptibility. Nausea, vomiting, and abdominal pain were reported by members of a family with very high levels of copper in the drinking water (Spitalny et al. 1984). The animal database on the oral toxicity of copper following chronic-duration exposure is limited to one study (Massie and Aiello 1984) that found a decrease in lifespan and no effect on body weight gain in mice exposed to copper gluconate for 850 days. No other end points of toxicity were examined in this study. The database was considered inadequate for derivation of a chronic-duration oral MRL. Additionally, studies that examine a variety of end points are needed to identify the critical targets of toxicity and establish dose-response relationships. Information on the dermal toxicity of copper is limited to a report of ocular irritation in workers exposed to copper dust (Askergren and Mellgren 1975). Additional dermal toxicity studies are needed to identify the critical targets of toxicity following dermal exposure.

Data on the carcinogenicity of copper in humans are limited to a study of copper miners (Chen et al. 1993) and a follow-up to this study (Chen et al. 1995). Increased risk of cancer, stomach cancer, and lung cancer were observed. Because the workers were also exposed to radon and radon daughters, silica, iron, titanium, sulfur, and arsenic, a causal relationship between copper and increased cancer risk can not be established. No studies examining the association between copper ingestion and cancer risk in humans were identified. Several animal studies have examined the carcinogenic potential of ingested copper (BRL 1968; Greene et al. 1987; Kamamoto et al. 1973). These studies are limited in scope, the studies by Green et al. (1987) and Kamamoto et al. (1973) only examined one potential target, and tested fairly low doses of copper. No dermal carcinogenicity studies in humans or animals were identified. Additional studies by the inhalation, oral, and dermal routes are needed to assess the carcinogenic potential of copper in humans.

## 3. HEALTH EFFECTS

**Genotoxicity.** No data on the genotoxicity of copper in humans were located; studies in workers or individuals accidentally exposed to high levels of copper would provide value information on genotoxic potential in humans. The available genotoxicity data suggest that copper is a clastogenic agent (Agarwal et al. 1990; Bhunya and Jena 1996; Bhunya and Pati 1987; Sideris et al. 1988). However, mixed results have been found in point mutation assays (Demerec et al. 1951; Marzin and Phi 1985; Singh 1983; Tso and Fung 1981; Wong 1988). Additional studies are need to assess copper's potential to induce point mutations. Several studies have also shown that exposure to copper can result in DNA damage (Garrett and Lewtas 1983; Sideris et al. 1988; Sina et al. 1983).

**Reproductive Toxicity.** There are no human studies and two animal studies that examined the potential of copper to induce reproductive effects. These studies did not find any adverse alterations in reproductive performance in mink (Aulerich et al. 1982), sperm morphology in rats and mice (NTP 1993), or vaginal cytology in rats or mice (NTP 1993). The NTP (1993) study also did not find histological alterations in reproductive tissues. Multigeneration or continuous breeding studies would provide information on the reproductive effects of copper in animals, which may be used to assess possible reproductive effects in humans exposed to high levels of copper.

**Developmental Toxicity.** Developmental studies by the oral route in rats (Haddad et al. 1991) and mice (Lecyk 1980) have shown that high copper intakes can result in impaired growth. The developmental toxicity of copper in humans has not been adequately investigated. No data were located regarding developmental effects of copper after inhalation or dermal exposures in humans or animals. Further developmental studies in other animals would provide valuable information on possible developmental toxicity of copper. Such information might be relevant to humans.

**Immunotoxicity.** There are limited data on the immunotoxic potential of copper and its compounds. Reports on individuals developing dermatitis after dermal exposure to copper (Barranco 1972; Saltzer and Wilson 1968) suggest that copper is an allergen. This is supported by a report of a woman developing dermatitis after insertion of a copper IUD (Barranco 1972). Immunological effects have been observed in mice (Drummond et al. 1986) following acute inhalation exposure to copper sulfate. Impaired immune function has also been observed in mice exposed to copper chloride (Pocino et al. 1991) or copper sulfate (Pocino et al. 1990) in drinking water. Intermediate-duration studies concentrating on immunologic effects in different species would be useful for establishing dose-response relationships and assessing whether there are species differences. More studies that examine the immune response and the mechanisms involved in animals and humans following exposure to copper would also be useful.

### 3. HEALTH EFFECTS

**Neurotoxicity.** Neurological impairment has been observed in factory workers exposed to copper dust. No effects on neurobehavioral performance were observed in rats exposed to copper in the diet (Murthy et al. 1981). This study did find alterations in the levels of a dopamine metabolite, suggesting that copper may adversely affect the nervous system. Additional studies are needed to further investigate the neurotoxic potential of copper; these studies should also assess sensitive measures of dopaminergic pathways and related functions.

**Epidemiological and Human Dosimetry Studies.** Several studies have examined the toxicity of inhaled copper in workers (Askergren and Mellgren 1975; Finelli et al. 1981; Suciú et al. 1981). These studies have primarily focused on the respiratory tract, although health examinations revealed other adverse effects (e.g., hepatomegaly). Chen et al. (1993, 1995) examined the carcinogenic potential of inhaled copper. In general, these studies are limited by poor exposure characterization, co-exposure to several toxic and/or carcinogenic compounds (e.g., arsenic, cadmium, radon, lead), and limited number of end points examined. Occupational exposure studies examining populations of workers exposed to copper and with minimal exposure to other metals would be useful in assessing the toxicity of inhaled copper. These studies should examine a wide variety of end points, particularly the gastrointestinal tract, liver, and kidneys, which are targets of toxicity following oral exposure.

There are numerous reports of accidental or intentional ingestion of copper. The most commonly reported effect in these studies is gastrointestinal upset. There have also been several experimental studies designed to identify a no effect level for gastrointestinal upset following short-term (2 weeks or less) exposure to copper in drinking water (Olivares et al. 2001; Pizarro et al. 1999, 2001). There are several subpopulations of individuals exposed to higher than normal levels of copper; these groups include communities with higher than normal levels of copper in drinking water and individuals ingesting higher than normal levels of copper in the form of supplements. Studies of these groups that involved examination for a variety of potential effects (including gastrointestinal, hepatic, and renal effects which are shown to be sensitive end points in animal studies) could provide useful information on the toxicity of copper in healthy humans. In addition, if the study group included both children and adults, these data would address the issue of age-related differences in toxicity.

#### **Biomarkers of Exposure and Effect.**

**Exposure.** Copper levels can be measured in tissues, body fluids, and excreta. Whole blood, serum, and urine copper levels have been established in healthy individuals. It has been demonstrated that copper

### 3. HEALTH EFFECTS

levels in the body increase with increased exposure after acute poisoning. Similarly, increased copper levels were observed in workers after occupational exposure.

*Effect.* There are no specific biomarkers for copper toxicity. Individuals with Wilson's disease are usually diagnosed by examining serum and urine copper levels, plasma ceruloplasmin levels, and clinical manifestations. However, the relationship between serum and urine levels of copper and health effects are not known. An attempt to correlate levels of serum and whole blood copper with the severity of symptoms in adults after acute copper sulfate poisoning failed to establish a relationship. Further attempts to correlate blood levels or excreta levels of copper with effects would facilitate medical surveillance leading to early detection and possible treatment.

**Absorption, Distribution, Metabolism, and Excretion.** The absorption, distribution, metabolism, and excretion of copper administered orally have been studied in animals and, to some extent, in humans. Furthermore, alterations in copper absorption, distribution, and excretion have been studied in deficiency and toxicity states. Despite the information on copper absorption, there is very little information on differences between absorption rates of the various Cu(II) compounds and differences between the bioavailability of copper from food and water.

Several studies have shown that ingested or implanted metallic copper results in increased serum copper levels and liver toxicity (Keller and Kaminski 1984; Yelin et al. 1987). Studies on the release of copper ions from metallic copper would be useful.

There is very limited information on copper absorption following inhalation exposure, and data on the absorption of copper through the skin are limited. Further studies in animals on the rate and extent of copper absorption following exposure by inhalation or dermal routes would fully characterize the pharmacokinetics of copper in humans and animals.

There is evidence that animals develop a tolerance to continued high doses of copper; more information on the mechanism involved and studies to determine if humans also develop a tolerance to copper may provide insight into the treatment of copper toxicity.

### 3. HEALTH EFFECTS

**Comparative Toxicokinetics.** The metabolism of copper has been studied in rats, pigs, hamsters, and humans. However, there are no comparative studies on the effects of high copper intakes on the distribution of copper in the body or the development of tolerance to continued high intakes of copper. Furthermore, the animal species that serves as the best model for extrapolating results to humans is not known.

**Methods for Reducing Toxic Effects.** Methods for reducing the toxic effects of copper have primarily focused on reducing body burdens. Many of these methods have been designed for individuals with Wilson's disease; however, it is likely that these would also be effective in other instances. D-penicillamine (Rodeck et al. 1999; Walshe 1996; Walshe and Yealland 1993) is the most commonly used agent; however, it has a number of potential side effects. Studies in animals suggest that TETREN and TAUD may also be effective chelating agents (Domingo et al. 2000). Other treatment methods include administration of tetrathiomolybdate (Humphries et al. 1988; Kumaratilake and McC Howell 1989; Ogra et al. 1996), diets high in molybdenum and sulfur (van Ryssen 1994), and diets high in zinc (Brewer et al. 1992; van Ryssen 1994). Further studies are needed to identify treatments that would interfere with copper's mechanism of action and reduce the body burden with minimal side effects.

**Children's Susceptibility.** There are some human data on the toxicity of copper in children. Severe liver damage has been reported in infants and children. These effects are typically clustered in geographically regions and have been grouped into two syndromes: Indian childhood cirrhosis and idiopathic copper toxicosis. Both of these syndromes are associated with elevated copper intakes, and early introduction of milk and/or formula, and are believed to have a genetic component. Very high levels of copper are found in the livers of affected children, suggesting that the mechanism of action is related to impaired copper efflux. Additional studies are needed to determine the mechanism of toxicity and to determine copper's role in the observed effects. Information that would provide a better understanding of copper absorption and excretion in early infancy and homeostatic mechanisms in infants would also provide valuable information on these syndromes and their relationship to copper.

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

## 3. HEALTH EFFECTS

**3.12.3 Ongoing Studies**

Ongoing studies pertaining to copper have been identified and are shown in Table 3-5.

## 3. HEALTH EFFECTS

**Table 3-5. Ongoing Studies on Copper**

Investigator	Affiliation	Research description	Sponsor
Turnland JR	Agricultural Research Service, Davis California	Influence of high copper intake on copper homeostasis and mineral metabolism	USDA
Kelvay LM	Agricultural Research Service, Grand Forks North Dakota	Determination of a no effect level for copper	USDA
Reeves PG	Agricultural Research Service, Grand Forks North Dakota	Correlation between sperm motility and copper status in humans and animals	USDA
Harris ED	Texas A & M University	Copper metabolism and homeostasis in humans and animals	CSREES TEX
Thiele DJ	University of Michigan at Ann Arbor	Copper homeostasis	NIGMS
Culotta VC	Johns Hopkins University	Intracellular pathways of copper trafficking	NIEHS
Gitlin JD	Washington University	Copper chaperones	NIDDKD

CSREES TEX = Cooperative State Research Education and Extension Service, Texas; NIDDKD = National Institute of Diabetes and Digestive and Kidney Disease; NIEHS = National Institute of Environmental Health and Science; NIGMS = National Institute of General Medical Sciences; USDA = U.S. Department of Agriculture



## 4. CHEMICAL AND PHYSICAL INFORMATION

### 4.1 CHEMICAL IDENTITY

Copper is the first element of Group IB of the periodic table and displays four oxidation states: Cu(O), Cu(I), Cu(II), and Cu(III). Along with silver and gold, it is classified as a noble metal and, like them, can be found in nature in the elemental form. Copper's unique chemical and physical properties have made it one of the most important metals. These properties include high thermal conductivity, high electrical conductivity, malleability, low corrosion, alloying ability, and appearance. Properties of metallic copper such as electrical conductivity and fabricability vary markedly with purity. Standard classifications have been defined according to processing method. For example, ASTM B5-74 is >99.90% pure and is the accepted basic standard for electrolyte copper wire bars, etc. (Tuddenham and Dougall 1978). Data on the chemical identity of copper are shown in Table 4-1. Data on the chemical identity of copper sulfate, the most important commercial compound of copper, are shown in Table 4-2.

### 4.2 PHYSICAL AND CHEMICAL PROPERTIES

Copper is positioned below hydrogen in the electromotive-force series, so it will not displace hydrogen ions from dilute acid. Accordingly, copper will not dissolve in acid unless an oxidizing agent is present. Therefore, while it readily dissolves in nitric and hot concentrated sulfuric acid, it only dissolves slowly in hydrochloric and dilute sulfuric acid, and then only when exposed to the atmosphere (Hawley 1981). It is also attacked by acetic acid and other organic acids. When exposed to moist air, a characteristic green layer of the basic copper carbonate slowly forms (Windholz 1983). This tightly adherent coating protects the underlying metal from further attack and is also prized for its appearance. Copper dissolves in ammonia in the presence of air, forming the cupric ammonium complex ion  $\text{Cu}(\text{NH}_3)_4^{2+}$  (Cotton and Wilkinson 1980).

Cu(I) or the cuprous ion disproportionates rapidly (<1 second) in aqueous solution to form Cu(II) and Cu(0) (Cotton and Wilkinson 1980). The only Cu(I) compounds that are stable in water are extremely insoluble ones such as CuCl. It has been shown that Cu(I) complexes may be formed in seawater by photochemical processes and may persist for several hours (Moffett and Zika 1987). Cuprous compounds are generally colorless.

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Copper**

Characteristic	Information	Reference
Chemical name	Copper	
Synonym(s)	Not reported	
Registered trade name(s)	Not reported	
Chemical formula	Cu	HSDB 2002
Chemical structure	Face-centered cubic	Budavari 2001
Identification numbers:		
CAS Registry	7440-50-8	HSDB 2002
NIOSH RTECS	GL5324000	HSDB 2002
EPA Hazardous Waste OHM/TADS	Not reported	
DOT/UN/NA/IMCO shipping	Not reported	
HSDB	1622	HSDB 2002
NCI	Not reported	

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = 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

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Chemical Identity of Copper Sulfate**

Characteristic	Information	Reference
Chemical name	Cupric sulfate	
Synonym(s)	Copper sulfate; blue stone; blue vitriol; cupric sulphate; Roman vitriol; Salzburg vitriol; blue copperas; copper(II) sulfate	HSDB 2002 Budavari 2001 Hawley 1997
Registered trade name(s)	Not reported	
Chemical formula	CuO <sub>4</sub> S	Budavari 2001
Chemical structure	CuSO <sub>4</sub>	Budavari 2001
Identification numbers:		
CAS Registry	7758-98-7	HSDB 2002
NIOSH RTECS	GL8800000	HSDB 2002
EPA Hazardous Waste	Not reported	
OHM/TADS	Not reported	
DOT/UN/NA/IMCO shipping	Not reported	
HSDB	916	HSDB 2002
NCI	Not reported	

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = 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

## 4. CHEMICAL AND PHYSICAL INFORMATION

Cu(II) or the cupric ion is the most important oxidation state of copper. Cu(II) is the oxidation state of copper generally encountered in water (Cotton and Wilkinson 1980). Cupric ions are coordinated with six water molecules in solution; the arrangement of the water molecules is distorted in that four molecules closely bound to the copper in a planar array and the other two more loosely bound in polar position (Cotton and Wilkinson 1980). Addition of ligands such as  $\text{NH}_3$  to the solution will successively displace only the four planar water molecules. Most cupric compounds and complexes are blue or green in color. They are frequently soluble in water.

When Cu(II) is introduced into the environment, the cupric ion typically binds to inorganic and organic materials contained within water, soil, and sediments. In water, Cu(II) binds to dissolved organics (e.g., humic or fulvic acids). The Cu(II) ion forms stable complexes with  $-\text{NH}_2$ ,  $-\text{SH}$ , and, to a lesser extent,  $-\text{OH}$  groups in these organic acids. Cu(II) will also bind to inorganic and organic components in sediments and soils with varying affinities. For example, Cu(II) binds strongly to hydrous manganese and iron oxides in clay and to humic acids in organic matter, but much less strongly to aluminosilicates in sand. As in water, the binding affinities of Cu(II) with inorganic and organic matter in sediments and soils is dependent on pH, the oxidation-reduction potential in the local environment, and the presence of competing metal ions and inorganic anions.

Cu(III) is strongly oxidizing and only occurs in a few compounds (Kust 1978). At this time, none of these compounds are industrially important or environmentally significant.

Data on the physical and chemical properties of copper and copper sulfate are shown in Table 4-3.

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-3. Physical and Chemical Properties of Copper and Copper Sulfate**

Property	Copper	Copper Sulfate
Molecular weight	63.546 <sup>a</sup>	159.61 <sup>a</sup>
Color	Reddish <sup>b</sup>	Blue crystals, white dehydrated <sup>b</sup>
Physical state	Solid <sup>b</sup>	Solid <sup>b</sup>
Melting point	1,083 <sup>c</sup>	Decomposes at 560 <sup>a</sup>
Boiling point	2,595 <sup>c</sup>	No data
Specific gravity (20/4 EC)	8.94 <sup>c</sup>	3.60 <sup>a</sup> 2.286 (pentahydrate) <sup>a</sup>
Odor	No data	None <sup>d</sup>
Odor threshold:		
Air	No data	No data
Water	No data	No data
Taste	No data	No data
Taste threshold	No data	No data
pK <sub>a</sub>		
Solubility:		32.0 g/100g (20 EC) <sup>f</sup>
Water	Insoluble <sup>e</sup>	Soluble in methanol, slightly
Organic solvent(s)		Soluble in ethanol <sup>b</sup>
Partition coefficients:		
Log K <sub>ow</sub>	No data	No data
Log K <sub>oc</sub>	No data	No data
Vapor pressure:	1 (1,628 EC) <sup>g</sup>	No data
Henry's law constant at 25 EC	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors at 25 EC ppm to mg/m <sup>3</sup>	h	h
Explosive limits	No data	No data

<sup>a</sup>Lide 2000<sup>b</sup>Lewis 1997<sup>c</sup>Budavari et al. 2001<sup>d</sup>Meister et al. 2001<sup>e</sup>Stewart and Lassiter 2001<sup>f</sup>Dean 1985<sup>g</sup>Lewis 2000<sup>h</sup>Since these substances exist in the atmosphere in the particulate state, the concentration is expressed as mg/m<sup>3</sup>.pK<sub>a</sub> = The dissociation constant of the conjugate acid



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

### 5.1 PRODUCTION

Copper occurs naturally in many minerals, such as cuprite ( $\text{Cu}_2\text{O}$ ), malachite ( $\text{CuCO}_3 \cdot \text{Cu}(\text{OH})_2$ ), azurite ( $2\text{CuCO}_3 \cdot \text{Cu}(\text{OH})_2$ ), chalcopyrite ( $\text{CuFeS}_2$ ), chalcocite ( $\text{Cu}_2\text{S}$ ), and bornite ( $\text{Cu}_5\text{FeS}_4$ ). It also occurs uncombined as metal (Tuddenham and Dougall 1979; Weast 1980). The copper content of ore deposits ranges from 0.5 to 5% by weight, whereas igneous rock contains 0.010% (Duby 1980) and crystalline rock contains 0.0055% by weight (55 ppm) (Weant 1985). The three most important sources of copper are chalcocite, chalcopyrite, and malachite (Weant 1985). The major U.S. deposits are porphyry, indicating that they are of hydrothermal origin and are uniformly distributed in fractures or veins.

The United States is the world's second leading copper producer. The country produced 202 million metric tons of ore in 2000, with an average copper content of 0.44% (USGS 2000). Mine production of recoverable copper in the United States totaled 1,440,000 metric tons in 2000, an estimated 11% of world production behind Chile, which accounted for 35%. Copper was mined in seven states in 2000, with Arizona accounting for 66% of U.S. copper production, followed by Utah (18%), New Mexico (11%), and Montana (3%). There were 27 copper-producing mines in 2000. Fourteen of these were copper mines; the remaining mines yielded copper as a by-product of gold, lead, silver, or zinc mining. Of the 14 largest mines, 10 were in Arizona, 2 were in New Mexico, 1 was in Utah, and 1 was in Montana. Production, processing and use of copper and compounds in the United States, listed by state, are given in Tables 5-1 and 5-2, respectively.

After mining, most of the ore is crushed and concentrated to a material containing 15–35% copper using flotation. The remaining copper is obtained by first leaching the ore or tailings and then concentrating the leachate by applying solvent extraction or ion exchange (Butterman 1982).

Most primary copper is produced from its sulfide ore by matte smelting, an operation yielding a molten sulfide of copper and iron, called matte, which is further oxidized in a conversion step to yield metallic copper. The conversion operation takes place in two stages. In the first, slag-forming stage,  $\text{FeS}$  is oxidized to iron oxides, which combine with a silica flux to form a slag. In the second, copper-producing stage,  $\text{CuS}_2$  is oxidized to form sulfur dioxide and metallic copper. The product of the conversion operation is blister copper, which is 98.5–99.5% copper. Concentrated leachate from low-grade ore is

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

**Table 5-1. Facilities that Produce, Process, or Use Copper**

State <sup>a</sup>	Number of facilities	Minimum amount on site in pounds <sup>b</sup>	Maximum amount on site in pounds <sup>b</sup>	Activities and uses <sup>c</sup>
AL	45	100	49,999,999	1, 2, 3, 5, 7, 8, 9, 11, 12, 13
AR	44	100	9,999,999	1, 4, 7, 8, 9, 11, 12, 13, 14
AZ	27	100	999,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	153	0	49,999,999	14
CO	15	1,000	9,999,999	2, 3, 4, 7, 8, 11, 12, 14
CT	50	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
DE	1	10,000	99,999	8
FL	20	1,000	9,999,999	7, 8, 10, 11
GA	48	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
IA	32	100	99,999,999	1, 2, 3, 4, 5, 7, 8, 9, 12
ID	4	10,000	999,999	1, 5, 8, 9, 12
IL	151	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
IN	158	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
KS	26	100	9,999,999	1, 2, 3, 4, 6, 7, 8, 11, 12, 14
KY	69	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
LA	7	100	9,999,999	6, 7, 8, 10
MA	63	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
MD	7	1,000	999,999	1, 2, 4, 5, 7, 8, 9, 13
ME	9	10,000	9,999,999	2, 3, 8
MI	130	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
MN	49	100	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 14
MO	77	1,000	99,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13
MS	29	1,000	49,999,999	2, 3, 4, 7, 8, 9, 12
MT	2	1,000	99,999	1, 5, 6, 11
NC	67	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12
ND	2	10,000	99,999	8
NE	19	1,000	9,999,999	1, 2, 3, 4, 7, 8, 9, 11, 12, 13
NH	20	1,000	49,999,999	2, 3, 4, 8, 9
NJ	40	1,000	49,999,999	1, 2, 3, 4, 6, 7, 8, 9, 11, 12
NM	6	1,000	9,999,999	2, 3, 8, 12
NV	5	1,000	99,999	8, 11, 12
NY	91	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
OH	223	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OK	46	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13
OR	18	0	999,999	2, 3, 4, 7, 8, 9, 10, 12
PA	215	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
PR	22	10,000	9,999,999	2, 3, 6, 7, 8, 11
RI	29	1,000	9,999,999	2, 3, 4, 6, 7, 8, 9, 10, 11, 12
SC	51	100	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12

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

**Table 5-1. Facilities that Produce, Process, or Use Copper (continued)**

State <sup>a</sup>	Number of facilities	Minimum amount on site in pounds <sup>b</sup>	Maximum amount on site in pounds <sup>b</sup>	Activities and uses <sup>c</sup>
SD	8	1,000	999,999	1, 5, 7, 8 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TN	87	0	499,999,999	14
TX	95	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
UT	10	1,000	9,999,999	1, 3, 4, 5, 6, 7, 8, 11, 12 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
VA	44	100	9,999,999	14
VT	3	1,000	999,999	2, 3, 4, 6, 8, 9
WA	28	0	9,999,999	1, 2, 5, 6, 7, 8, 9, 10, 11, 12, 14
WI	126	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
WV	14	0	9,999,999	2, 3, 6, 7, 8, 12
WY	3	10,000	999,999	1, 4, 9, 10, 12

Source: TRI00 2002

<sup>a</sup>Post office state abbreviations used<sup>b</sup>Amounts on site reported by facilities in each state<sup>c</sup>Activities/Uses:

- |                      |                             |                          |
|----------------------|-----------------------------|--------------------------|
| 1. Produce           | 6. Reactant                 | 11. Manufacture Aid      |
| 2. Imported          | 7. Formulation Component    | 12. Ancillary/Other Uses |
| 3. Used Processed    | 8. Article Component        | 13. Manufacture Impurity |
| 4. Sale Distribution | 9. Repackaging              | 14. Process Impurity     |
| 5. Byproduct         | 10. Chemical Processing Aid |                          |

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

**Table 5-2. Facilities that Produce, Process, or Use Copper Compounds**

State <sup>a</sup>	Number of facilities	Minimum amount on site in pounds <sup>b</sup>	Maximum amount on site in pounds <sup>b</sup>	Activities and uses <sup>c</sup>
AK	4	100,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 10, 12, 14
AL	39	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
AR	25	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
AZ	28	1,000	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
CA	79	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	8	100	99,999	1, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14
CT	22	100	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
DC	2	1,000	99,999	12
DE	4	100	99,999	1, 5, 9, 12, 13
FL	34	0	999,999	1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
GA	27	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
IA	25	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
ID	7	10,000	9,999,999	1, 3, 4, 5, 6, 7, 8, 9
IL	94	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	72	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	9	0	999,999	1, 5, 7, 8, 9, 10, 11, 12, 13
KY	40	1,000	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
LA	21	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13
MA	24	1,000	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
MD	8	100	9,999,999	1, 2, 3, 5, 6, 7, 8, 12, 13
ME	5	100	999,999	1, 3, 5, 7, 8, 11, 13
MI	55	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MN	28	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	35	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	12	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
MT	9	100	10,000,000,000	1, 2, 3, 4, 5, 6, 8, 11, 12, 13, 14
NC	50	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	7	100	99,999	1, 5, 7, 9, 12, 13, 14
NE	9	10,000	499,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
NH	10	1,000	9,999,999	1, 5, 6, 7, 8, 11, 12
NJ	27	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
NM	6	1,000	499,999,999	1, 3, 4, 5, 6, 8, 9, 12, 13
NV	18	1,000	99,999,999	1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NY	31	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

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

**Table 5-2. Facilities that Produce, Process, or Use Copper Compounds  
(continued)**

State <sup>a</sup>	Number of facilities	Minimum amount on site in pounds <sup>b</sup>	Maximum amount on site in pounds <sup>b</sup>	Activities and uses <sup>c</sup>
OH	82	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	16	100	9,999,999	1, 2, 3, 4, 5, 6, 8, 9, 10, 12, 13, 14
OR	14	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
PA	92	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	3	10,000	99,999	7, 10
RI	10	100	9,999,999	1, 4, 5, 6, 7, 8, 12
SC	36	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
SD	2	1,000	99,999	1, 3, 5, 6, 9, 10, 12, 13
TN	46	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
TX	93	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	14	1,000	10,000,000,000	1, 3, 4, 5, 6, 7, 8, 9, 12, 13
VA	38	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WA	18	1,000	999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
WI	43	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	17	1,000	999,999	1, 3, 4, 5, 7, 8, 9, 12, 13, 14
WY	4	100	99,999	1, 4, 5, 9, 12, 13

Source: TRI00 2002

<sup>a</sup>Post office state abbreviations used<sup>b</sup>Amounts on site reported by facilities in each state<sup>c</sup>Activities/Uses:

- |                      |                             |                          |
|----------------------|-----------------------------|--------------------------|
| 1. Produce           | 6. Reactant                 | 11. Manufacture Aid      |
| 2. Imported          | 7. Formulation Component    | 12. Ancillary/Other Uses |
| 3. Used Processed    | 8. Article Component        | 13. Manufacture Impurity |
| 4. Sale Distribution | 9. Repackaging              | 14. Process Impurity     |
| 5. Byproduct         | 10. Chemical Processing Aid |                          |

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

subject to electrowinning, which electrolyzes aqueous sulfate solutions, or to cementation, which displaces copper from solution by a more active metal such as iron (Duby 1980). Further purification is obtained by electrolytic refining. For more details on copper mining, ore processing, smelting, and refining, see Duby (1980) and EPA (1980b).

Production of copper in the United States includes not only the processing of both domestic and foreign ores, but also the recovery of scrap. Scrap is a significant part of the U.S. copper supply. Scrap refers to both 'old scrap' (metal that has been used) and 'new scrap' (generated during fabrication). In 1999, smelting was performed in the United States by four primary smelters and two secondary smelters with a combined capacity of 1,750,000 metric tons per year (USGS 2000). Together, they produced 1,600,000 metric tons of copper from both domestic and foreign ores in 1999, 9% of the world's supply. Additionally, 205,000 metric tons of copper were recovered from old and new scrap. During 1999, 23 refineries operated, producing 1,890,000 metric tons of copper from domestic and foreign ores. An additional 230,000 metric tons of copper was produced from new and old scrap. Apparent consumption for 1999 was 3,130,000 metric tons (USGS 2000). This includes domestic refined copper production, net imports of refined copper, copper recovered from old scrap, and stock adjustments. In 2000, smelting was performed in the United States by four primary smelters and one secondary smelters with a combined capacity of 1,180,000 metric tons per year. During 2000, 23 refineries operated with a combined capacity of 2,400,000 metric tons per year. However, no data had yet been provided for the production of copper from U.S. smelters or refineries. Apparent consumption for 2000 was 3,110,000 metric tons (USGS 2000). Production of secondary copper and copper-alloys amounted to 1,490,000 metric tons in both 1999 and 2000 (USGS 2000). These alloys, primarily brass and bronze, contain approximately 60–90% copper.

Most industrially important copper compounds are made starting with copper metal. Copper sulfate, the most commercially important copper compound, was produced by at least six companies in plants in Casa Grande, Arizona; Sewaren and Oak Bridge, New Jersey; El Paso and Garland, Texas; Sante Fe Springs, California; Union, Illinois; Copperhill, Tennessee; and Sumter, South Carolina (Jolly and Edelstein 1987).

Copper sulfate is also produced as a by-product of copper production by ore-leaching with sulfuric acid. Production of copper sulfate has increased by 29% from 1996 to 2000, standing at 55,500 metric tons in 2000 (USGS 2000). Recent production figures for other copper compounds were not located.

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

**5.2 IMPORT/EXPORT**

In 2000, 1,270,000 million tons of unmanufactured copper were imported, of which 83% was refined copper. Peru, Canada, and Chile were the principal sources of imported refined copper. The quantity of imported unmanufactured copper increased by 88% since 1994; the increase was almost entirely in the importation of refined powder, as opposed to ore concentrate, blister copper, or scrap (USGS 1994, 2000). Imports of copper sulfate amounted to 9,910 metric tons and were primarily obtained from Australia and Mexico (USGS 2000).

In 2000, 483,000 metric tons of copper were exported, of which 19% was refined copper (USGS 2000).

**5.3 USE**

Copper is one of the most important metals because of its durability, ductility, malleability, and electrical and thermal conductivity. It is used primarily as the metal or in alloys. Its alloys, including brass, bronze, gun metal, and Monel metal, are important commodities. All current American coins are copper alloys. A small percentage of copper production goes into the manufacture of copper compounds, primarily copper sulfate.

The Copper Development Association's 2000 estimates of the end-use distribution of copper and copper-alloy products by the industrial sector were: construction, 39%; electrical and electrical products, 28%; transportation equipment, 11%; industrial machinery and equipment, 11%; and consumer and general products, 11% (USGS 2002). The top 10 markets for copper and copper-alloy during 1986 were, in order of importance: plumbing, building wire, telecommunications, power utilities, in-plant equipment, air conditioning, automotive electrical, automotive nonelectrical, business electronics, and industrial valves and fittings (Jolly and Edelstein 1987).

Copper sulfate was the only copper compound for which end-use distribution data were available; these data addressed only domestic producers. Sixty-five percent of production went into agricultural use, 28% for industrial uses such as metal finishing, mineral froth flotation, and wood preservatives, and 7% for water treatment.

In agriculture, copper compounds are used as fungicides and to prepare copper fungicidal products, algicides in reservoirs and streams, and nutritional supplements in animal feed and fertilizers. Industrial

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

applications of copper sulfate include use as an activator in froth flotation of sulfide ores, production of chromated copper arsenate wood preservatives, electroplating, azo dye manufacture, mordant for textile dyes, petroleum refining, and in the manufacture of other copper compounds such as copper hydroxide and copper carbonate (Mannsville Chemical Products 1984).

Copper compounds are applied as fungicides to foliage, seed, wood, fabric, and leather to protect against blight, downy mildew, and rust. The 1982 consumption of copper-containing fungicides was 2.8 million pounds (Mannsville Chemical Products 1984). The major copper compound used for this purpose was the basic copper sulfate (1.8 million pounds). Other important fungicidal compounds were copper hydroxide, copper ammonium carbonate, copper oxychloride, and copper oxychloride sulfate. The major target crops of copper-containing fungicides are citrus fruits, peanuts, deciduous fruits (other than apples), potatoes, vegetables, and other field crops. Copper compounds are also used as algicides, insecticides, and repellents. Products containing copper compounds are frequently combined with other chemicals and may be sold under various trade names. Formulation may be in wettable powders or aqueous solutions.

#### 5.4 DISPOSAL

It is estimated that 60% of copper in scrap is recycled (Tuddenham and Dougall 1978). In 1986, ~40% of the copper produced came from this source (Jolly and Edelstein 1987). Copper-containing wastes can be concentrated using ion exchange, reverse osmosis, or evaporation, and then reclaimed by electrolysis (HSDB 2002). Copper and copper compounds not recycled are disposed of in landfills or released into waste water. Methods of copper containing sludge disposal from waste water treatment facilities include landfilling, landspreading, incineration, or ocean disposal.

In case of a solid copper sulfate spill on land, the solids should be protected from rain and fire-fighting water by covering the material with plastic sheeting (HSDB 2002). In the event of a water spill, the copper sulfate should be neutralized with crushed limestone, slaked lime, or sodium bicarbonate, and the solidified masses should be removed.

## 6. POTENTIAL FOR HUMAN EXPOSURE

### 6.1 OVERVIEW

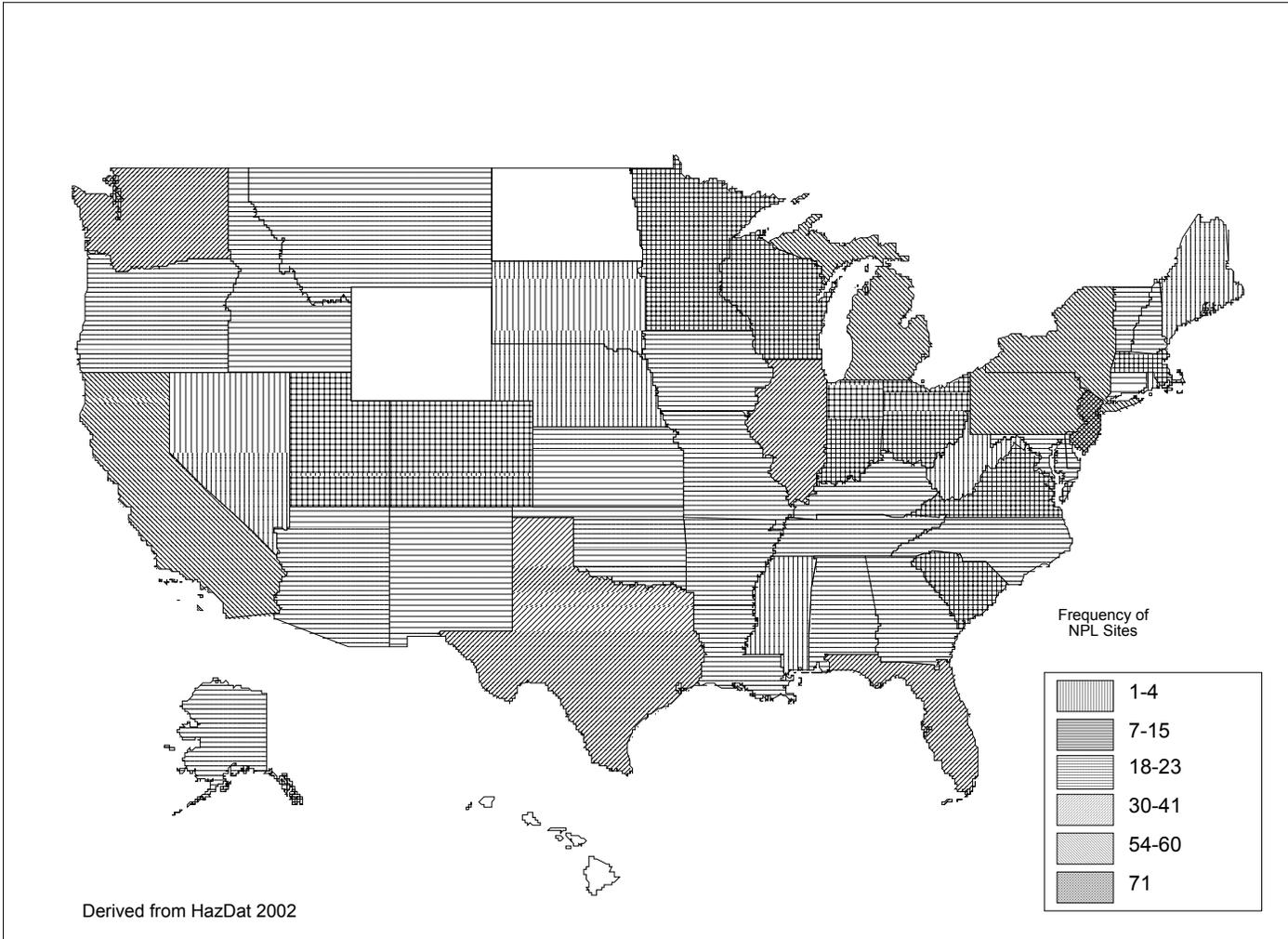
Copper has been identified in at least 884 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2002). However, the number of sites evaluated for copper is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 873 are located within the United States, 8 are located in the Commonwealth of Puerto Rico, 1 is located in the Virgin Islands, and 2 are located in the Territory of Guam (the Commonwealth of Puerto Rico, the Virgin Islands, and the Territory of Guam are not shown in Figure 6-1).

Copper and its compounds are naturally present in the earth's crust. Natural discharges to air and water, such as windblown dust, volcanic eruptions, etc., may be significant. Therefore, it is important to consider the background levels that are commonly found in order to distinguish these from levels that can be attributed to anthropogenic activity.

The median concentration of copper in natural water is 4–10 ppb. It is predominantly in the Cu(II) state. Most of it is complexed or tightly bound to organic matter; little is present in the free (hydrated) or readily exchangeable form. The combined processes of complexation, adsorption, and precipitation control the level of free Cu(II). The chemical conditions in most natural water are such that, even at relatively high copper concentrations, these processes will reduce the free Cu(II) concentration to extremely low values. Sediment is an important sink and reservoir for copper. In relatively clean sediment, the copper concentration is <50 ppm; polluted sediment may contain several thousand ppm of copper. The form of copper in the sediment will also be site-specific. Organics (humic substances) and iron oxides are the most important contributor to binding of copper by aerobic sediments. However, in some cases, copper is predominantly associated with carbonates. In anaerobic sediment, Cu(II) will be reduced to Cu(I) and insoluble cuprous salts will be formed.

The largest release of copper by far will be to land, and the major sources of release are mining operations, agriculture, solid waste, and sludge from publicly-owned treatment works (POTWs). Mining and milling contribute the most waste.

Figure 6-1. Frequency of NPL Sites with Copper Contamination



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## 6. POTENTIAL FOR HUMAN EXPOSURE

Copper is released to water as a result of natural weathering of soil and discharges from industries and sewage treatment plants. Most of this copper is attached to particulate matter. Copper compounds may also be intentionally applied to water to kill algae. Of special concern is copper that gets into drinking water from the water distribution system. When the system has not been flushed after a period of disuse, the concentration of copper in tap water may exceed 1.3 ppm, the EPA drinking water limit.

Copper is emitted into the air naturally from windblown dust, volcanoes, and anthropogenic sources, the largest of which are being primary copper smelters and ore processing facilities. It is associated with particulate matter. The mean concentration of copper in the atmosphere is 5–200 ng/m<sup>3</sup>. In comparison, the concentration of copper in emissions from copper smelters have been found to range between 7 and 137.8 ng/m<sup>3</sup> (Hutchinson 1979; Romo-Kröger et al. 1994).

The general population may be exposed to high concentrations of copper from drinking water that has picked up copper from the distribution system (both from the water treatment plant and in the home). Contact with available copper may also result from using copper fungicides and algicides. Many workers are exposed to copper in agriculture, industries connected with copper production, metal plating, and other industries. Little information is available concerning the forms of copper to which workers are exposed. At this time, copper has been identified at 873 out of 1,613 NPL hazardous waste sites in the United States (HazDat 2002). The frequency of these sites within the United States can be seen in Figure 6-1. While experiments show that copper does not leach significantly from soil, levels of copper as high as 2.8 ppm have been found in some groundwater (Page 1981).

## 6.2 RELEASES TO THE ENVIRONMENT

Industrial manufacturers, processors, and users of copper and copper compounds are required to report the quantities of this substance released to environmental media annually (EPA 1988d). The data compiled in the Toxics Release Inventory (TRI00 2002), are for releases in 2000 to air, water, soil, and transfers for offsite disposal. These data are summarized in Tables 6-1 (copper) and 6-2 (copper compounds). Total releases (rounded to three-place accuracy) of copper into the environment in 2000 were approximately 9,210,000 pounds (approximately 4,180 metric tons) (TRI00 2002), of which approximately 1,180,000 pounds (536 metric tons), or 12.8% of the total, were released to air. Another 40,000 pounds (18 metric tons) or approximately 0.4% of the total, were released into water, 0.8% (70,600 pounds, 32 metric tons) was injected underground, and 86.0% (7,920,000 pounds, 3,600 metric

**Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Copper**

State <sup>b</sup>	Number of facilities	Reported amounts released in pounds per year <sup>a</sup>						Total on and off-site release
		Air <sup>c</sup>	Water	Underground injection	Land	Total on-site release <sup>d</sup>	Total off-site release <sup>e</sup>	
AL	45	15,983	1,820	No data	454	18,257	348,725	366,982
AR	44	5,932	1,727	No data	186,925	194,584	333,088	527,672
AZ	27	1,812	537	No data	81,842	84,191	41,647	125,838
CA	153	35,838	1,320	No data	309,783	346,941	57,669	404,611
CO	15	1,097	21	No data	55,556	56,674	25,937	82,611
CT	50	12,357	1,646	No data	1,503	15,506	106,385	121,891
DE	1	No data	No data	No data	No data	No data	No data	0
FL	20	2,381	1,455	67,858	631	72,325	56,440	128,765
GA	48	3,498	807	No data	31,670	35,975	389,388	425,363
IA	32	3,623	261	No data	4,603	8,487	127,744	136,231
ID	4	297	No data	No data	544,000	544,297	5,780	550,077
IL	151	63,734	5,537	No data	1,645,215	1,714,486	845,173	2,559,659
IN	158	51,990	1,417	No data	147,739	201,146	2,421,974	2,623,120
KS	26	5,890	251	No data	63,005	69,146	61,547	130,693
KY	69	25,029	485	No data	62,455	87,969	245,453	333,422
LA	7	22	738	2,100	205	3,065	15,927	18,992
MA	63	5,338	68	No data	No data	5,406	78,600	84,006
MD	7	253	10	No data	250	513	85,596	86,109
ME	9	114	31	No data	5	150	9,139	9,289
MI	130	115,647	670	17	167	116,501	616,441	732,942
MN	49	20,778	8	No data	5	20,791	939,660	960,451
MO	77	22,823	612	No data	9,826	33,261	178,639	211,900
MS	29	2,685	129	No data	505	3,319	66,681	70,000
MT	2	417	No data	No data	2,940,000	2,940,417	No data	2,940,417
NC	67	8,575	1,563	0	272	10,410	1,471,083	1,481,493

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Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Copper (continued)

State <sup>b</sup>	Number of facilities	Reported amounts released in pounds per year <sup>a</sup>						Total on and off-site release
		Air <sup>c</sup>	Water	Underground injection	Land	Total on-site release <sup>d</sup>	Total off-site release <sup>e</sup>	
ND	2	18	15	No data	No data	33	707	740
NE	19	4,185	31	No data	36,000	40,216	14,260	54,476
NH	20	1,057	25	No data	0	1,082	141,099	142,181
NJ	40	19,383	171	1	No data	19,555	11,202	30,757
NM	6	500	No data	No data	48,117	48,617	27,837	76,454
NV	5	502	No data	No data	21,000	21,502	93	21,595
NY	91	15,456	3,752	No data	63	19,271	643,566	662,837
OH	223	49,464	6,083	0	1,180,213	1,235,760	635,915	1,871,675
OK	46	15,142	307	No data	52,882	68,331	69,013	137,344
OR	18	784	6	No data	14,754	15,544	1,765	17,309
PA	215	107,564	2,668	No data	45,649	155,881	2,504,799	2,660,680
PR	22	15,251	35	No data	5	15,291	1,155	16,446
RI	29	6,569	5	No data	0	6,574	39,076	45,650
SC	51	13,643	685	No data	4,425	18,753	185,338	204,091
SD	8	19	No data	No data	No data	19	10,818	10,837
TN	87	421,476	868	No data	461	422,805	316,473	739,278
TX	95	18,694	1,187	596	155,144	175,621	251,209	426,830
UT	10	192	17	No data	10,767	10,976	40,103	51,079
VA	44	39,599	1,095	No data	160,092	200,786	157,407	358,193
VT	3	No data	No data	No data	250	250	760	1,010
WA	28	1,987	695	No data	12,463	15,145	87,031	102,176
WI	126	39,480	873	No data	2,058	42,411	427,058	469,469

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**Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Copper (continued)**

State <sup>b</sup>	Number of facilities	Reported amounts released in pounds per year <sup>a</sup>						Total on and off-site release
		Air <sup>c</sup>	Water	Underground injection	Land	Total on-site release <sup>d</sup>	Total off-site release <sup>e</sup>	
WV	14	1,951	27	5	30,158	32,141	35,481	67,622
WY	3	392	1	No data	57,046	57,439	93	57,532
Total	2,487	1,179,421	39,659	70,577	7,918,163	9,207,819	14,130,974	23,338,793

Source: TRI00 2002

<sup>a</sup>Data in TRI are maximum amounts released by each facility.

<sup>b</sup>Post office state abbreviations are used.

<sup>c</sup>The sum of fugitive and stack releases are included in releases to air by a given facility.

<sup>d</sup>The sum of all releases of the chemical to air, land, water, and underground injection wells.

<sup>e</sup>Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

**Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Copper Compounds**

State <sup>b</sup>	Number of facilities	Reported amounts released in pounds per year <sup>a</sup>						Total on and off-site release
		Air <sup>c</sup>	Water	Underground injection	Land	Total on-site release <sup>d</sup>	Total off-site release <sup>e</sup>	
AK	4	470	38	1,300,000	4,856,411	6,156,919	750	6,157,669
AL	39	25,437	21,433	No data	12,406,258	12,453,128	183,324	12,636,452
AR	25	16,170	4,726	No data	110,712	131,608	481,062	612,670
AZ	28	183,722	1,796	No data	579,148,733	579,334,251	330,839	579,665,090
CA	79	6,130	734	No data	1,166,647	1,173,511	482,758	1,656,269
CO	8	752	11,808	No data	106,817	119,377	77,684	197,061
CT	22	2,626	797	No data	0	3,423	195,677	199,100
DC	2	No data	3	No data	3,017	3,020	No data	3,020
DE	4	2,113	9,700	No data	25,546	37,359	27,738	65,097
FL	34	83,333	21,193	42	1,024,922	1,129,490	151,922	1,281,412
GA	27	20,006	51,039	No data	839,269	910,314	1,716,060	2,626,374
IA	25	24,248	2,922	No data	170,605	197,775	115,212	312,987
ID	7	1,288	230	No data	706,894	708,412	20,616	729,028
IL	94	46,302	4,294	No data	541,813	592,409	986,870	1,579,279
IN	72	88,214	17,573	1,300	1,102,587	1,209,674	1,248,657	2,458,331
KS	9	4,026	255	No data	166,107	170,388	69,525	239,913
KY	40	34,176	30,153	No data	853,002	917,331	440,093	1,357,424
LA	21	6,380	18,145	No data	163,296	187,821	264,589	452,410
MA	24	872	30	No data	1,400	2,302	91,024	93,326
MD	8	1,232	7,056	No data	16,700	24,988	14,057	39,045
ME	5	2,200	0	No data	0	2,200	43,484	45,684
MI	55	95,317	10,004	No data	551,990	657,311	561,607	1,218,918
MN	28	9,668	971	No data	327,020	337,659	1,600,338	1,937,997
MO	35	38,164	3,229	No data	4,909,325	4,950,718	358,332	5,309,050

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**Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Copper Compounds  
(continued)**

State <sup>b</sup>	Number of facilities	Reported amounts released in pounds per year <sup>a</sup>						Total on and off-site release
		Air <sup>c</sup>	Water	Underground injection	Land	Total on-site release <sup>d</sup>	Total off-site release <sup>e</sup>	
MS	12	34,588	1,044	21,000	64,900	121,532	156,630	278,162
MT	9	12,936	9	No data	15,557,393	15,570,338	135,358	15,705,696
NC	50	26,734	43,507	No data	747,663	817,904	133,282	951,186
ND	7	654	10,862	No data	126,430	137,946	168,818	306,764
NE	9	6,482	339	No data	279,658	286,479	404,286	690,765
NH	10	775	21	No data	500	1,296	36,763	38,059
NJ	27	2,148	10,065	No data	26,186	38,399	407,668	446,067
NM	6	16,449	5,305	No data	83,263,458	83,285,212	178,260	83,463,472
NV	18	325,559	310	11	32,068,686	32,394,566	173,849	32,568,415
NY	31	14,128	11,379	No data	1,005,441	1,030,948	614,160	1,645,108
OH	82	18,867	31,896	190,000	1,305,202	1,545,965	1,281,479	2,827,444
OK	16	2,918	6,838	675	356,902	367,333	85,090	452,423
OR	14	2,737	1,339	No data	156,061	160,137	126,215	286,352
PA	92	145,905	4,798	0	459,070	609,773	3,625,910	4,235,683
PR	3	300	550	0	0	850	23,760	24,610
RI	10	15	61	No data	No data	76	15,244	15,320
SC	36	42,578	6,926	No data	261,695	311,199	599,382	910,581
SD	2	412	No data	No data	22,000	22,412	951	23,363
TN	46	20,870	24,684	0	1,682,648	1,728,202	252,578	1,980,780
TX	93	87,395	12,737	224,223	1,499,493	1,823,848	1,696,719	3,520,567
UT	14	127,695	1,010	No data	596,061,674	596,190,379	193,222	596,383,601
VA	38	44,688	9,886	No data	383,479	438,053	242,073	680,126
WA	18	13,972	1,075	No data	203,260	218,307	97,606	315,913
WI	43	7,755	11,422	No data	19,654	38,831	260,785	299,616

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**Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Copper Compounds  
(continued)**

State <sup>b</sup>	Number of facilities	Reported amounts released in pounds per year <sup>a</sup>						Total on and off-site release
		Air <sup>c</sup>	Water	Underground injection	Land	Total on-site release <sup>d</sup>	Total off-site release <sup>e</sup>	
WV	17	4,990	12,140	0	1,045,151	1,062,281	159,356	1,221,637
WY	4	1,710	87	No data	266,170	267,967	43,000	310,967
Total	1,402	1,656,106	426,419	1,737,251	1,346,061,845	1,349,881,621	20,574,661	1,370,456,283

Source: TRI00 2002

<sup>a</sup>Data in TRI are maximum amounts released by each facility.

<sup>b</sup>Post office state abbreviations are used.

<sup>c</sup>The sum of fugitive and stack releases are included in releases to air by a given facility.

<sup>d</sup>The sum of all releases of the chemical to air, land, water, and underground injection wells.

<sup>e</sup>Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

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tons) was released to land. Total releases (rounded to three-place accuracy) of copper compounds to the environment in 2000 were approximately 1,350,000,000 pounds (approximately 613,000 metric tons) (TRI00 2002), of which approximately 1,660,000 pounds (752 metric tons), or 0.1% of the total, were released to air. Another 426,000 pounds (194 metric tons) or approximately 0.03% of the total, were released into water, 0.1% (1,740,000 pounds, 789 metric tons) was injected underground, and 99.7% (1,350,000,000 pounds, 611,000 metric tons) was released to land. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Industrial releases are only a fraction of the total environmental releases of copper and copper compounds. Other sources of copper release into the environment originate from domestic waste water, combustion processes, wood production, phosphate fertilizer production, and natural sources (e.g., wind blown dust, volcanoes, decaying vegetation, forest fires, and sea spray) (Georgopoulos et al. 2001). Quantitative information on release of copper to specific environmental media are discussed below; a summary of copper concentrations in environmental media is provided in Table 6-3.

### 6.2.1 Air

Copper is emitted into the air from both natural and anthropogenic sources. Since copper is a component of the earth's crust, the primary natural source of copper is windblown dust with an estimated mean worldwide emission of  $0.9\text{--}15 \times 10^6$  kg/year (WHO 1998). Other natural sources of copper emitted into air, including estimated mean worldwide emissions, are forest fires ( $0.1\text{--}7.5 \times 10^6$  kg/year), volcanoes ( $0.9\text{--}18 \times 10^6$  kg/year), biogenic processes ( $0.1\text{--}6.4 \times 10^6$  kg/year), and sea spray ( $0.2\text{--}6.9 \times 10^6$  kg/year) (WHO 1998). Anthropogenic emission sources include nonferrous metal production, wood production, iron and steel production, waste incineration, industrial applications, coal combustion, nonferrous metal mining, oil and gasoline combustion, and phosphate fertilizer manufacture. It is estimated that only 0.04% of copper released to the environment is to air (Perwak et al. 1980). Global atmospheric anthropogenic and natural emission of copper have been estimated to be  $35 \times 10^6$  and  $28 \times 10^6$  kg/year, respectively (Guisti et al. 1993).

The EPA conducted a detailed study of copper emissions into the atmosphere to estimate exposure (Weant 1985). The sources of emissions and the estimated quantities of copper emitted in  $10^3$  kg/year are: primary copper smelters, 43–6,000; copper and iron ore processing, 480–660; iron and steel production, 112–240; combustion sources, 45–360; municipal incinerators, 3.3–270; secondary copper

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**Table 6-3. Summary of Copper Concentrations in Environmental Media<sup>a</sup>**

Environmental media		Concentration	Units
Atmosphere			
Aerosol		0.1–382	ppt
Hydrosphere—water			
Coastal	Dissolved	0.06–4.3	ppb
	Total	0.5–13.8	ppb
	Suspended solids	0.6–370,000	ppm
Estuarine	Dissolved	0.02–4.7	ppb
	Total	1.2–71.6	ppb
	Suspended solids	0.38–72	ppm
Ocean	Dissolved	Not detected–10	ppb
	Total	0.04–10	ppb
	Suspended solids	0.01–2.8	ppm
Lake	Dissolved	0.1–15.6	ppb
	Total	0.1–15.6	ppb
River	Dissolved	0.18–3,000	ppb
	Total	0.5–5,800	ppb
Groundwater	Dissolved	0.003–70	ppb
	Total	1–1,160	ppb
Drinking water	Total	0.3–1,352	ppb
Hydrosphere—sediments			
Coastal	Particulate	0.03–3,789	ppm
	Interstitial water	25.5–32.7	ppb
Estuarine	Particulate	0.3–2,985	ppm
	Interstitial water	0.3–100	ppb
Ocean	Particulate	3.1–648	ppb
	Interstitial water	22–45	ppm
Lake	Particulate	0.4–796	ppm
	Interstitial water	45.6–52	ppb
River	Particulate	5.3–4,570	ppm
Pedosphere			
Soil	Total	0.01–3,138	ppm
	Organic	293–7,634	ppm
Dust	Total	2.9–76	ppm

<sup>a</sup>As reported in the Copper Sourcebook 1998 (Harrison 1998), covering years 1993–1996.

Source: Georgopoulos et al. (2001)

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smelters, 160; copper sulfate production, 45; gray iron foundries, 7.9; primary lead smelting, 5.5–65; primary zinc smelting, 24–340; ferroalloy production, 1.9–3.2; brass and bronze production, 1.8–36; and carbon black production, 13. Using the most probable emission value for primary copper smelters and the range for other sources, estimated U.S. copper emissions are 2,959,000–4,300,000 kg annually. Daily stack emission rates have been reported for three coal-burning power plants on a kg/day/1,000 megawatt basis (Quee Hee et al. 1982); they are 0.3–0.7 and 2.00 kg/day/1,000 megawatt for those using low-sulfur western coal and high-sulfur eastern coal, respectively. In another report, emission of copper into air from a 650 megawatt electrical power plant, burning bituminous coal, was estimated at 213 kg/year, based on a summary of reportable TRI releases (Rubin 1999).

Emission factors in grams of copper released to the atmosphere per ton of product have been estimated for various industries (Nriagu and Pacyna 1988). These factors would enable estimation of an industry's copper emissions from its production volume. Missing from these emission estimates is fugitive dust arising from drilling, blasting, loading, and transporting operations associated with copper mining. The only control of fugitive dust is the manual use of water sprays (EPA 1980b). The highest concentrations of copper in particulate matter were obtained from mining activities, primary and secondary production, and industrial manufacturing (Table 6-4).

Romo-Kröger et al. (1994) were able to show, through the use of radioactive tracers and cluster analysis of interelemental correlations, that Cu, S, Zn, and As measured near a copper smelter in Chile were derived from the plant and not from the surrounding soil. The concentration of copper in air near the plant decreased from 66 ng/m<sup>3</sup> (fine particles) and 131 ng/m<sup>3</sup> (coarse particles) to 22 ng/m<sup>3</sup> (fine particles) and 50 ng/m<sup>3</sup> (coarse particles) during a period of inactivity at the plant, clearly demonstrating the contribution of plant emissions to copper levels in the surrounding area.

The amount of copper and other pollutants originating from copper production sites, such as fugitive dust from smelter bag houses, or waste sites in windblown dust is of some concern. In one study, the amount of airborne copper and other heavy metals deposited near a large refuse dump that received municipal and industrial waste and sewage sludge was determined by first measuring the amount of the metal accumulated in moss bags. The deposition rate was then determined and compared with that for an agricultural control area. The mean copper deposition rates in the two areas were about the same; the maximum deposition rate was twice as much near the dump as in the control area (Lodenius and Braunschweiler 1986).

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**Table 6-4. Concentrations of Copper in Particulate Matter (<10 µm) Generated from Various Sources<sup>a</sup>**

Source	Copper concentration (percent, w/w)
Metal mining	6.17 <sup>b</sup>
Secondary metal production	4.6 <sup>b</sup>
Primary metal production	3.50 <sup>b</sup>
Industrial manufacturing	2.16 <sup>b</sup>
Steel production	0.55 <sup>b</sup>
Gray iron foundries	0.19 <sup>b</sup>
Steel foundry, general	0.17 <sup>b</sup>
Solid waste	0.09 <sup>b</sup>
Food and agriculture	0.05 <sup>b</sup>
Chemical manufacturing	0.03 <sup>b</sup>
Petroleum industry	0.03 <sup>b</sup>
Gasoline vehicle exhaust	0.05 <sup>c</sup>
Paved road dust	0.0162 <sup>c</sup>
Construction dust	0.0102 <sup>c</sup>
Landfill dust	0.0102 <sup>c</sup>
Unpaved road dust	0.0087 <sup>c</sup>
Agricultural lands, dust	0.0067 <sup>c</sup>
Diesel vehicle exhaust	0.003 <sup>c</sup>

<sup>a</sup>Values obtained from CEIDARS 2000

<sup>b</sup>Data obtained from USEPA Speciate 3.0; Shareef, G.S; Radian, September, 1987

<sup>c</sup>Data obtained from KVB Literature Search

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Automobile exhaust has been shown to make small local contributions to copper in air. The amount of copper emitted in the exhaust from gasoline powered automobiles has been measured to be 0.001–0.003 mg/mile driven; 0.005–0.039 mg/mile driven for diesel powered vehicles (Cadle et al. 1999)

Only in a few cases has the form of copper released into the air been determined. In general, metals released into the atmosphere will be in particulate matter in the form of an oxide, sulfate, or carbonate. Because copper smelters co-emit SO<sub>x</sub> gases, copper is expected to be released largely as the sulfate in particulate matter from these facilities. Combustion processes are reported to release copper into the atmosphere as the oxide, elemental copper, and adsorbed copper. Cupric oxide has been identified in emissions from steel manufacturing and in fly ash from oilfired power plants and open-hearth steel mills (Graedel 1978; Perwak et al. 1980). Copper associated with fine particles (<1 µm) tends to result from combustion and other high-temperature sources, while that associated with large particles (>10 µm) is likely to originate from wind blown soil and dust (Schroeder et al. 1987).

Copper has been identified in air samples collected from 38 of the 884 NPL hazardous waste sites where copper has been detected in environmental media. Copper was detected in offsite air samples at concentrations ranging from 0.02–10 µg/m<sup>3</sup> (median concentration of 0.38 µg/m<sup>3</sup>) (HazDat 2002).

### 6.2.2 Water

Much of the copper that enters environmental waters will be associated with particulate matter. Copper is a natural constituent of soil and will be transported into streams and waterways in runoff either due to natural weathering or disturbed soil. Sixty-eight percent of releases to water is estimated from this source. Copper sulfate use represents 13% of releases to water, and urban runoff contributes 2% (Perwak et al. 1980). In the absence of specific industrial sources, runoff is the major factor contributing to elevated copper levels in river water (Nolte 1988). In the EPA-sponsored National Urban Runoff Program, in which 86 samples of runoff from 19 cities throughout the United States were analyzed, copper was found in 96% of samples, at concentrations of 1–100 µg/L (ppb) (Cole et al. 1984). Of the 71 priority pollutants analyzed for, copper, along with lead and zinc, was the most frequently detected. The geometric mean copper concentration in runoff water was 18.7 µg/L.

Yang et al. (1993) provided estimates of global anthropogenic and natural copper inputs into oceans that are derived from two sources, atmospheric deposition and riverine input. Atmospheric input has been estimated at 14–45x10<sup>6</sup> kg/year for copper in a dissolved form and 2–7x10<sup>6</sup> kg/year for copper in a

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particulate form. Riverine input is estimated to be  $10 \times 10^6$  kg/year as dissolved copper and  $1,500 \times 10^6$  kg/year as copper bound to particulates.

Domestic waste water is the major anthropogenic source of copper in waterways (Isaac et al. 1997; Nriagu and Pacyna 1988). Studies in Cincinnati and St. Louis showed discharges of copper into sewer systems from residential areas to be significant, with an average loading of 42 mg/day/person (Perwak et al. 1980). In a more comprehensive review, Jenkins and Russell (1994) reported a range of average copper loadings derived from residential and some small industrial contributions of 2.8–83 mg/capita/day. Concentrations of copper in influents to 239 waste water treatment plants (12,351 observations) were 0.0001–36.5 ppb, and the median value was ~0.4 ppb (Minear et al. 1981). Copper is not entirely removed in POTWs, and releases from these facilities contribute ~8% of all copper released to water (Perwak et al. 1980). Inputs into the Narraganset Bay, Rhode Island, in decreasing order of importance, are sewage effluent, rivers, urban runoff, and atmospheric fallout (Mills and Quinn 1984; Santschi et al. 1984). Ninety percent of both dissolved and particulate copper was from effluent of sewage treatment plants that discharged into the Providence River.

While copper is removed from the waste stream by sewage treatment facilities, considerable copper remains in the effluent and is released into receiving waters (EPA 1981; Perwak et al. 1980). Because removal efficiencies for copper from waste streams tend to remain constant, increases in copper concentrations in POTW influent streams will also result in increased copper concentrations in the effluent streams (Isaac et al. 1997). The range of removal efficiencies reported for pilot and full scale plants suggests that removal depends strongly on plant operation or influent characteristics. The median copper concentrations in domestic waste water have been found to make up a substantial fraction of the median concentration found in POTW influent in the waste water systems of four Massachusetts municipalities, with ratios ranging from 0.36 to 1.25 (Isaac et al. 1997).

A source of copper released to waterways is urban storm water runoff. Copper in storm water runoff originates from the sidings and roofs of buildings, various emissions from automobiles, and wet and dry depositional processes (Davis et al. 2001). Concentrations of between 1 and 100  $\mu\text{g/L}$  of copper in storm water runoff have been measured (Georgopoulos et al. 2001). Storm water runoff normally contributes approximately 2% to the total copper released to waterways. In contrast, copper in runoff that is obtained from the natural weathering of soil or is release from disturbed soils contributes 68% of the copper released to waterways (Georgopoulos et al. 2001).

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The best data on typical POTWs using secondary treatment are that 55–90% of copper is removed in these plants with a median and mean removal of 82% (Perwak et al. 1980). By contrast, those plants using only primary treatment had a 37% median removal efficiency. A more recent study focused on heavy metal removal in three POTWs that received primarily municipal sewage and used activated sludge as a secondary treatment. The study looked at removals in both the primary and secondary treatment stage. The average removals of soluble copper and total copper after secondary treatment were 49–82 and 83–90%, respectively. The average copper concentration in the final effluent was 17–102 ppb (Aulenbach et al. 1987; Stephenson and Lester 1987).

Combined sewer outflows are the primary sources of direct and indirect copper pollutants entering estuaries and other coastal areas of the United States (Crawford et al. 1995; Georgopoulos et al. 2001; Huh 1996; Iannuzzi et al. 1997). For example, Crawford et al. (1995) compiled a summary of the sources of various metals and other contaminants into the Newark Bay estuary. The mass loadings of copper into the estuary as a function of source are (in kg/day): municipal treatment systems, 103.4; industry direct discharge, 8.82; combined sewer overflows, 48.0; storm-water runoff, 62.2; tributary flow, 39.1 and indirect charges from the Passaic Valley Commission and Middlesex County Sewerage Authority, 126.5.

Discharges to water from active mining and milling are small, and most of the western operations do not release any water; water is a scarce resource and is recycled (Perwak et al. 1980). Discharges from electroplating operations are either directly to water or indirectly via POTWs. Runoff from abandoned mines is estimated to contribute 314 metric tons annually (Perwak et al. 1980). These discharges are primarily insoluble silicates and sulfides and readily settle out. Releases from copper-containing products may be substantial, but are difficult to predict. Corrosion of copper in plumbing or construction may result in direct discharges or runoff into waterways. Copper and brass production releases relatively little copper to water.

Waste water generated from mining operations comes from seepage, runoff from tailing piles, or utility water used for mine operation. The amount of waste water generated ranges from 0–300 L water/metric ton of ore mined for open pit copper mines and 8–4,000 L water/metric ton of ore mined underground (EPA 1980b). Copper concentrations in waste water from a selected open pit and underground copper mine were 1.05 and 0.87 ppm, respectively. Data regarding copper concentrations in waste water associated with selected concentrating, smelting, and refining operations can be found in EPA (1980b). Drainage from mining operations and abandoned mines has been shown to have an effect on copper

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content in local surface waters (see Table 6-7) with concentrations as high as 69,000 ppb being measured (Rösner 1998).

Results of an EPA industrial effluent survey show that mean and maximum levels of copper in treated waste water from six industries exceeded 1 and 10 ppm, respectively (EPA 1981). These industries and their mean and maximum discharges in ppm are: inorganic chemicals manufacturing (<1.6, 18); aluminum forming (<160, 2,200); porcelain enameling (1.3, 8.8); gum and wood chemicals (1.4, 3.0); nonferrous metals manufacturing (1.4, 27.0); and paint and ink formulation (<1.0, 60.0). Emission factors in nanograms of copper released per L of water outflow have been estimated for various industries. These factors would enable estimation of an industry's copper releases if the discharge volume were known (Nriagu and Pacyna 1988).

Effluents from power plants that use copper alloys in the heat exchangers of their cooling systems discharge copper into the receiving waters (Harrison 1984). The largest discharges occur after start-up and decrease rapidly thereafter. At the Diablo Canyon Nuclear Power Station, a very high start-up discharge containing 7,700 ppb of copper fell to 67 ppb after 24 hours (Harrison 1984). During normal operation at two nuclear power stations, copper levels ranged between 0.6 and 3.3 ppb. Except for after start-up of the cooling system, most of the soluble copper (that which passes through a 0.45  $\mu\text{m}$  filter) discharged was in bound forms (Harrison et al. 1980). During normal operation, <20% of the copper released was in the <1,000 molecular weight fraction, which contains the more available copper species.

Copper sulfate is directly added to lakes, reservoirs, and ponds for controlling algae. However, the copper concentration in the water column generally returns to pretreatment levels within a few days (Effler et al. 1980; Perwak et al. 1980).

One potential source of copper release into waterways is leachate from municipal landfills. However, copper concentrations in leachate obtained from these waste sites have been found to vary widely. For example, copper concentrations in leachate from municipal landfills have been found to range from 0.005 to 1,110 ppm (Christensen et al. 1994; Perwak et al. 1980; Roy 1994). Although copper was measured in these leachates, its origin may not be from copper contained within the waste site, but from the surrounding soils. Cyr et al. (1987) reported that leachate from three municipal landfills in New Brunswick, Canada, did not contain copper concentrations significantly above those in control samples representing the surrounding soil types. Therefore, the emissions of copper from landfills into leachates

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should be made relative to the contribution of copper from surrounding soils, as determined from appropriately selected control samples.

Copper can enter surface waters as a result of agricultural runoff. For example, estimated loading rates of copper into surface water from irrigation water runoff near the Stillwater National Wildlife Refuge ranged from 0.307 to 8.34 mg/hour, depending on what period of the irrigation season samples were taken (Kilbride et al. 1998). The highest concentrations were obtained during the middle period (August through mid-September) of the irrigation season.

Copper has been identified in groundwater samples collected from 788 groundwater samples and 306 surface water samples of the 884 NPL hazardous waste sites where copper has been detected in environmental media. Copper was detected at concentrations ranging from 0.006 to 5.6 ppm (median concentration of 0.103 ppm) in offsite groundwater and 0.00025–590 ppm (median concentration of 0.0282 ppm) in offsite surface water (HazDat 2002).

### 6.2.3 Soil

An estimated 97% of copper released into the environment is to land (Perwak et al. 1980). These are primarily tailings and overburdens from copper mines and tailings from mills. The copper in the tailings represents the portion of copper that could not be recovered from the ore and is generally in the form of insoluble sulfides or silicates (Perwak et al. 1980). These wastes are disposed in mining states. Other releases to land include sludge from POTWs, municipal refuse, and waste from electroplating, iron and steel producers, and discarded copper products (e.g., plumbing, wiring) that are not recycled. The copper content of municipal solid waste is 0.16%; much of this will be landfilled directly or as residues from incineration. Emission factors in milligrams of copper released per gram of solid waste have been estimated for various industries. These factors would enable the estimation of an industry's copper releases in terms of quantity of solid waste discharged. Sludge from sewage treatment plants is a major source of copper released to land (Nriagu and Pacyna 1988). Agricultural products are believed to constitute 2% of the copper released to soil (Perwak et al. 1980). However, even though the largest releases of copper are to land, exposures to human populations to copper in soil are expected to be minimal in comparison to the primary route of exposure through drinking water (see Section 6.5).

Copper has been identified in soil samples collected from 742 soil samples and 361 sediment samples of the 884 NPL hazardous waste sites where copper has been detected in environmental media. Copper was

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detected at concentrations ranging from 0.01 to 182,000 ppm (median concentration of 0.103 ppm) in offsite soils and 0.022–14,000 ppm (median concentration of 43 ppm) in offsite sediments (HazDat 2002).

### 6.3 ENVIRONMENTAL FATE

It is not always possible to separate the environmental fate processes related to transport and partitioning from those related to transformation and degradation for a metal, its various compounds and complexes. Part of this problem is that the form of copper is rarely identified. It is also difficult to determine when a process such as adsorption should be treated as partitioning or transformation, since the formation of strong bonds to an adsorbent may be construed as a transformation to new molecular species. Separating weak and strong adsorption is awkward and not always possible. Deposition and general adsorption of copper are discussed in Section 6.3.1. Speciation, compound formation, and oxidation-reduction are examined in Section 6.3.2.

#### 6.3.1 Transport and Partitioning

##### 6.3.1.1 Ambient Air

Copper is released to the atmosphere in the form of particulate matter or adsorbed to particulate matter. It is removed by gravitational settling (bulk deposition), dry deposition (inertial impaction characterized by a deposition velocity), washout by rain (attachment to droplets within clouds), and rainout (scrubbing action below clouds) (Schroeder et al. 1987). The removal rate and distance traveled from the source will depend on source characteristics, particle size, and wind velocity.

Gravitational settling governs the removal of large particles ( $>5 \mu\text{m}$ ), whereas smaller particles are removed by the other forms of dry and wet deposition. The importance of wet to dry deposition generally increases with decreasing particle size. The scavenging ratio (ratio of the copper concentration in precipitation [ppm] to its air concentration [ $\mu\text{g}/\text{m}^3$ ]) for large particles displays a seasonal dependence that reflects their more effective scavenging by snow than by rain (Chan et al. 1986). Copper from combustion sources is associated with sub-micron particles. These particles remain in the troposphere for an estimated 7–30 days. In that time, some copper may be carried far from its source (Perwak et al. 1980).

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Metal deposition is characterized by large temporal and spatial variability. Estimated copper deposition rates in urban areas are 0.119 and 0.164 kg/ha/year for dry and wet deposition, respectively (Schroeder et al. 1987). Bulk deposition reportedly ranges from 0.002–3.01 kg/ha/year. For rural areas, bulk deposition reportedly ranges from 0.018 to 0.5 kg/ha/year, and wet deposition is 0.033 kg/ha/year. The washout ratio is 114,000–612,000 ( $\mu\text{g}/\text{m}^3$  rain)/( $\mu\text{g}/\text{m}^3$  air) or, expressed on a mass basis, 140–751 ( $\mu\text{g}/\text{kg}$  rain)/( $\mu\text{g}/\text{kg}$  air). In southern Ontario, Canada, where the average concentration of copper in rain was 1.57 ppb during 1982, 1.36 mg of copper was deposited annually per square meter as a result of wet deposition (Chan et al. 1986). For central and northern Ontario, the mean concentrations of copper in rain were 1.36 and 1.58 ppb, respectively, and the annual wet depositions averaged in both instances 1.13 mg/m<sup>2</sup>.

For the majority of the time, the concentration of toxic trace compounds, like copper, approach regional background levels with only episodic increases, depending on wind speed and direction and location relative to local point sources; smelters are primary source of copper in this study (East St. Louis) (Sweet et al. 1993). Copper depositional fluxes follow an exponential decay curve as one transitions from urban to rural settings. Soil is not the major source of copper in cities or nearby rural soils, but is the predominant source for copper in the atmosphere over more remote areas (Fergusson and Stewart 1992). Sources of copper in urban areas include coal, soil, tire wear, and automobile emissions (Kim and Fergusson 1994). Copper emission from combustion processes is typically associated with fine particles; however, there can be instances where the highest concentrations of copper are measured in coarse particles, thus giving the impression that the copper is derived from crustal sources (Paode et al. 1998).

Depositional fluxes of copper over Chicago have been observed to average between 0.06 mg/m/day, 0.01 mg/m/day over Lake Michigan, and 0.007 mg/m/day over South Haven, Michigan (Paode et al. 1998). Estimated depositional velocities for fine particles (<2.5  $\mu\text{m}$ ) and coarse particles (2.5–10  $\mu\text{m}$ ) in urban (Chicago) and rural (Kankalee, Illinois) areas have been made (Pirrone and Keeler 1993). These are: urban, 0.25–0.46 cm/second and rural, 0.18–0.25 in (rural) Kankalee, Illinois for fine particles; and urban, 1.47–2.93 cm/second and rural, 0.87–1.71 cm/second. The differences in velocities are due to higher surface roughness and wind velocities in Chicago. Combined (dry+wet) deposition of copper has been determined for Massachusetts Bay, with a value of 3,500  $\mu\text{g}/\text{m}^2/\text{year}$  (Golomb et al. 1997). Landing et al. (1995) have reported combined (dry+wet) deposition ranging from 430 to 1,840  $\mu\text{g}/\text{m}^2/\text{year}$  in Florida, whereas Scudlark et al. (1994) have reported a wet copper flux in Chesapeake Bay of 260  $\mu\text{g}/\text{m}^2/\text{year}$ .

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Copper concentrations in particulates formed from the combustion of waste oil are (in  $\mu\text{g/g}$ ):

$687 \pm 11$  ( $10 \mu\text{m}$ ),  $575 \pm 8$  ( $50 \mu\text{m}$ ),  $552 \pm 12$  ( $100 \mu\text{m}$ ),  $568 \pm 9$  ( $300 \mu\text{m}$ ), and  $489 \pm 8$  ( $500 \mu\text{m}$ ).

Approximately 25% of copper is in the  $10 \mu\text{m}$  fraction and 18% is in each of the larger fractions (Nerín et al. 1999).

### 6.3.1.2 Ambient Waters

The average concentrations of copper in Lakes Superior, Erie, and Ontario are 760, 870, and 830 ng/L, respectively (Georgopoulos et al. 2001; Nriagu et al. 1996). The atmospheric input of copper into the Great Lakes is substantial, 330–1,470 ng/m<sup>2</sup>/year, and accounts for 60–80% of the anthropogenic input into Lake Superior and 20–70% into Lakes Erie and Ontario. The mean residency times of copper in sediments are estimated to be 15 years in Lake Erie and 101 years in Lake Superior.

Much of the copper discharged into waterways is in particulate matter and settles out, precipitates out, or adsorbs to organic matter, hydrous iron and manganese oxides, and clay in sediment or in the water column. A significant fraction of the copper is adsorbed within the first hour, and in most cases, equilibrium is obtained within 24 hours (Harrison and Bishop 1984). In fact, most of the copper in POTW effluent and surface runoff is already complexed (Sedlak et al. 1997). Copper in waste water discharged into a river leading into Chesapeake Bay, Maryland, contained 53 ppb of copper, of which 36 ppb was in the form of settleable solids (Helz et al. 1975). The concentration of copper rapidly decreased downstream of the outfall; 2–3 km from the outfall, the copper concentration had fallen to 7 ppb. The concentration of copper in sediment downstream from the outfall was about a factor of 10 higher than in uncontaminated areas.

Copper binds primarily to organic matter in estuarine sediment, unless the sediment is organically poor. A study evaluated the importance of different nonlithogenic components of aerobic estuarine sediment to copper by determining copper's adsorptivity to model sedimentary phases from artificial seawater (Davies-Colley et al. 1984). These phases included hydrous iron and manganese oxides, clay, aluminosilicates, and organic matter. The binding affinities varied by over a factor of 10,000 and were in the following order: hydrous manganese oxide > organic matter > hydrous iron oxide > aluminosilicates > clay (montmorillonite). The partition coefficients at pH 7 for the more strongly bound phases (manganese oxide, iron oxide, and estuarine humic material), were 6,300, 1,300, and 2,500, respectively. The affinity increased somewhat with pH, but did not vary appreciably when salinity was reduced. Considering the compositional characteristics of estuarine sediment, the results indicate that copper binds predominantly

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to organic matter (humic material) and iron oxides. Manganese oxide contributes only 1% to the binding because of its low concentration in sediment; the other phases are generally unimportant. These findings concur with results of selective extraction experiments (Badri and Aston 1983) and the association of copper with humic material (Raspor et al. 1984).

**6.3.1.3 Ambient Soils**

Most copper deposited in soil from the atmosphere, agricultural use, and solid waste and sludge disposal will be strongly adsorbed and remain in the upper few centimeters of soil, except in sandy soils where the lability of bound copper is greater. Copper's movement in soil is determined by a host of physical and chemical interactions of copper with the soil components. In general, copper will adsorb to organic matter, carbonate minerals, clay minerals, or hydrous iron and manganese oxides (EPA 1979; Fuhrer 1986; Janssen et al. 1997; Petruzzelli 1997; Tyler and McBride 1982). Sandy soils with low pH have the greatest potential for leaching. Luncan-Bouché et al. (1997) have shown that between 55 and 85% of copper bound to sand is remobilized upon reduction of the pH from 9 to 4. In most temperate soils, the pH, organic matter, concentrations of metal oxyhydroxides, and ionic strength of the soil solutions are the key factors affecting adsorption (Elliot et al 1986; Fuhrer 1986; Gerritse and Van Driel 1984; Janssen et al. 1997; Rieuwerts et al. 1998; Tyler and McBride 1982). The ionic strength and pH of the soil solution affect the surface charge of soils and thereby influence ionic interaction (Rieuwerts et al. 1998). When the amount of organic matter is low, the mineral content of Fe, Mn, and Al oxides become important in determining the adsorption of copper. Fuhrer (1986) reported that, in oxidized estuarine sediment, adsorption of copper is dominated both by amorphous iron oxide and estuarine humic material.

Copper binds to soil much more strongly than other divalent cations, and the distribution of copper in the soil solution is less affected by changes in pH (within the range of pHs normally encountered in the environment) than other metals are (Gerritse and Van Driel 1984). In a study of competitive adsorption and leaching of metals in soil columns of widely different characteristics, copper eluted much more slowly and in much lower quantities than Zn, Cd, and Ni from two mineral soils and not at all from peat soil, which contained the greatest amount of organic matter (Tyler and McBride 1982). Elliot et al. (1986) looked at pH-dependent adsorption of the bivalent transition metal cations (Cd, Cu, Pb, and Zn) in two mineral soils and two soils containing considerable organic matter. Adsorption increased with pH, and Cu and Pb were much more strongly retained than Cd and Zn. Reduction in absorptivity after removal of the organic matter demonstrated the importance of organic matter in binding copper. However, in a study of clay soils, Wu et al. (1999) observed that although there was a preference for

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copper binding to organic matter in the overall clay soil, higher copper retentions were obtained in the fine ( $<0.2 \mu\text{m}$ ) clay fractions once the organic matter had been removed.

To determine the factors affecting copper solubility in soil, Hermann and Neumann-Mahlkau (1985) performed a study in the industrial Ruhr district of West Germany, which has a high groundwater table (10–80 cm from the surface) and a history of heavy metal pollution. Groundwater samples were taken from six locations and two horizons of soil, an upper oxidizing loam, and a lower reducing loam. Total copper concentrations were high in the upper soil horizons and low in the lower horizons. Copper showed a pronounced solubility only in the oxidizing environment; in the reducing environment, solubility was low, possibly due to the formation of sulfides.

The form of copper at polluted and unpolluted sites may affect its leachability, particularly by acid rain. The leaching of heavy metals by simulated acid rain (pH 2.8–4.2) was measured by applying rainwater to columns containing humus layers from sites in a Swedish spruce forest both near to and far from a brass mill (Strain et al. 1984). Leaching of copper increased considerably when water with a pH  $<3.4$  was applied to soil from polluted sites. Acid rain produced from  $\text{SO}_x$  emitted from smelters may increase the leachability of copper in areas affected by smelter stack emissions. Mobility of copper from soils was also found to increase upon introduction of deicing salts into soil, due to the increased mobilization of organic matter in soils, especially in soils with high exchangeable Na and low electrolyte concentrations (Amrhein et al. 1992).

Since 25–75% of copper entering POTWs is removed in sludge, much of which is disposed of by spreading on land, it is important to ascertain whether copper in sludge is apt to leach into soil. This does not appear to be the case; leachate collected from sludge-amended soil contained  $<12$  ppb of copper (Perwak et al. 1980). In laboratory experiments, three sludges containing 51, 66, and 951 ppm (dry weight) of copper were applied to soil columns containing four coastal plain soils. The columns were subsequently leached with distilled water at a rate of 2.5 cm/day for a total column application of 25.4 cm of water. Only small amounts ( $<0.01$ – $0.87$  ppm) of copper were found in the leachate (Ritter and Eastburn 1978). This indicates that hazardous amounts of copper should not leach into groundwater from sludge, even from sandy soils. In another study, soil cores taken after sewage sludge was applied to grassland for 4 years showed that 74 and 80% of copper remained in the top 5 cm of a sandy loam and calcareous loam soil (Davis et al. 1988). Similar studies have also shown that copper is typically confined to the upper 5–10 cm of sludge-amended agricultural soils (Breslin 1999; Giusquiani et al. 1992). In soils receiving long-term, heavy applications of sludge, high copper concentrations (471 mg/kg

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in comparison to 19.1 mg/kg in unamended control soils) were reported to depths of up to 25 cm (Richards et al. 1998). The mobility of copper into soil from sludge was found to be determined mainly by the amount of soil organic carbon and soil surface area (Domergue and Védy 1992; Gao et al. 1997). In addition, soils amended by sludge with low metal content were found to have increased sorption for copper due to the increased binding capacity provided by the “low metal” organics in the sludge (Petruzzelli et al. 1994).

Similarly, copper remains in the surface layer when it is applied to soil as a liquid. Secondary sewage effluent spiked with 0.83 ppm of copper was applied weekly to four different soils. After 1 year of treatment, the concentration of copper in the surface horizons increased greatly; 50–76% of applied copper was found in the upper 2.5 cm and 91–138% was found in the upper 12.7 cm (Brown et al. 1983). In a study of accumulation and movement of metal in sludge-amended soils, field plots received massive amounts of sewage over a period of 6 years. Two sludges (one containing industrial waste), with average copper contents of 0.29 and 23 ppm were incorporated into the top 20 cm of soil in the spring; barley was grown, and after harvest, core samples of soil taken down to 1 m. Some movement of copper into the 22.5–25 cm layer of soil was observed, but little, if any, below this zone. However, at this depth, the copper is still within the root zone of many important food crops and is therefore available for uptake into these plants. Also, the availability of the copper in soil, as determined by its extractability with diethylenetriamine pentaacetic acid (DTPA) and nitrate, remained constant over a 4-year period at all depths. From the results of other work, it is expected that the major portion of the copper (40–74%) is associated with the organic, Fe-Mn-oxide and carbonate fractions of most soils (Ma and Rao 1997).

#### 6.3.1.4 Bioconcentration and Biomagnification

The bioconcentration factor (BCF) of copper in fish obtained in field studies is 10–100, indicating a low potential for bioconcentration. The BCF is higher in molluscs, especially oysters, where it may reach 30,000 (Perwak et al. 1980). This may be due to the fact that they are filter feeders, and copper concentrations are higher in particulates than in water. However, there is abundant evidence that there is no biomagnification of copper in the food chain (Perwak et al. 1980). A study was conducted with white suckers and bullheads, both bottom-feeding fish, in two acidic Adirondack, New York, lakes (Heit and Klusek 1985). These lakes were known to have received elevated loadings of copper, but the suckers and bullhead had average copper levels of only 0.85 and 1.2 ppm (dry weight) in their muscle tissue. The biomagnification ratio (the concentration of copper in the fish to that in potential food) was <1, indicating no biomagnification in the food chain. Similarly, the copper content of muscle tissue of fish from copper-

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contaminated lakes near Sudbury, Ontario, did not differ significantly from that of fish in lakes far from this source (Bradley and Morris 1986).

Diks and Allen (1983) added copper to four sediment/water systems and studied the distribution of copper among five geochemical phases. The investigators then attempted to correlate the concentration in each phase with the copper uptake by tubificid worms. Only copper extracted from the manganese oxide/easily-reducible phase correlated with the copper content of worms at the 95% confidence level.

No evidence of bioaccumulation was obtained from a study of pollutant concentrations in the muscle and livers of 10 mammal species in Donana National Park in Spain (Hernandez et al. 1985). The animals were classified into three categories (herbivorous, omnivorous, and carnivorous) to ascertain if the pollutants were showing biomagnification in higher trophic levels of animals. No evidence of copper biomagnification in the food chain was observed. A study of heavy metals in cottontail rabbits on mined land treated with sewage sludge showed that, while the concentration of copper in surface soil was 130% higher than in a control area, the elevation was relatively little in foliar samples. No significant increase in copper was observed in rabbit muscle, femur, kidney, or liver, indicating that copper was not bioaccumulating in the food chain (Dressler et al. 1986). Even at the lowest levels of the food chain, there is little evidence of copper bioaccumulation. In a study of earthworms and soil from 20 diverse sites in Maryland, Pennsylvania, and Virginia, copper concentrations in earthworms poorly correlated with that in soil (Beyer and Cromartie 1987).

### 6.3.2 Transformation and Degradation

#### 6.3.2.1 Air

Few data are available regarding the chemical forms of copper in the atmosphere and their transformations. In the absence of specific information, it is generally assumed that metals of anthropogenic origin, especially those from combustion sources, exist as oxides. Metallic species are attacked by atmospheric oxidants in the atmosphere, resulting in the formation of oxides. As these oxides age, sulfatization may occur, but only when SO<sub>x</sub> gases are co-emitted. For example, in Arizona, atmospheric copper originating from smelters was strongly correlated with sulfur (Schroeder et al. 1987).

In fogwater, Cu(II) is reduced to Cu(I) by sulfite and is enhanced by the fact that sulfite is also a ligand for Cu(I) (Xue et al. 1991). Concentrations of Cu(I) in fogwater ranged between 0.1 and 1 μM, which

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amounted to 4 and >90% of copper in the Cu(I) state. The reduction of Cu(II) to Cu(I) is pH dependent and occurs rapidly at pHs>6 (Xue et al. 1991)

**6.3.2.2 Water**

The Cu(I) ion is unstable in aqueous solution, tending to disproportionate to Cu(II) and copper metal unless a stabilizing ligand is present (EPA 1979; Kust 1978). The only cuprous compounds stable in water are insoluble ones such as Cu<sub>2</sub>S, CuCN, and CuF. In its Cu(II) state, copper forms coordination compounds or complexes with both inorganic and organic ligands. Ammonia and chloride ions are examples of species that form stable ligands with copper. Copper also forms stable complexes with organic ligands such as humic acids, binding to -NH<sub>2</sub> and -SH groups and, to a lesser extent, with -OH groups. Natural waters contain varying amounts of inorganic and organic species; this affects the complexing and binding capacity of the water and the types of complexes formed. In seawater, organic matter is generally the most important complexing agent (Coale and Bruland 1988). The formation of ligands may affect other physicochemical processes such as adsorption, precipitation, and oxidation-reduction in water (EPA 1979).

The major species of soluble copper found in freshwater, seawater, and a combination of the two over a range of pHs is Cu<sup>2+</sup>, Cu(HCO<sub>3</sub>)<sup>+</sup>, and Cu(OH)<sub>2</sub> (Long and Angino 1977). At the pH values and carbonate concentrations characteristic of natural waters, most dissolved Cu(II) exists as carbonate complexes rather than as free (hydrated) cupric ions (Stiff 1971).

The concentration of dissolved copper depends on factors such as pH, the oxidation-reduction potential of the water, and the presence of competing cations (Ca<sup>2+</sup>, Fe<sup>2+</sup>, Mg<sup>2+</sup>, etc.), salts (OH<sup>-</sup>, S<sup>2-</sup>, PO<sub>4</sub><sup>3-</sup>, CO<sub>3</sub><sup>2-</sup>), and anions of insoluble cupric and organic and inorganic complexing agents. If the concentration of a particular anion is high enough to exceed the solubility of a copper salt, precipitation of that salt will occur. The most significant precipitate formed in natural waters is malachite (Cu<sub>2</sub>[OH]<sub>2</sub>CO<sub>3</sub>); other important precipitates are Cu(OH)<sub>2</sub> (and ultimately CuO) and azurite (Cu<sub>3</sub>[OH]<sub>2</sub>[CO<sub>3</sub>]<sub>2</sub>) (Sylva 1976). In anaerobic waters, Cu<sub>2</sub>S, Cu<sub>2</sub>O, and metallic copper forms and settles out (EPA 1979). The combined processes of complexation, adsorption, and precipitation control the level of free Cu(II). The chemical conditions in most natural water are such that, even at relatively large copper concentrations, these processes will reduce the free Cu(II) concentration to extremely low values.

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As a result of all of the aforementioned physico-chemical processes, copper in water may be dissolved or associated with colloidal or particulate matter. Copper in particulate form includes precipitates, insoluble organic complexes, and copper adsorbed to clay and other mineral solids. In a survey of nine rivers in the United Kingdom, 43–88% of the copper was in the particulate fraction (Stiff 1971). A study using suspended solids from the Flint River in Michigan found that the fraction of adsorbed copper increased sharply with pH, reaching a maximum at a pH of 5.5–7.5 (McIlroy et al. 1986).

The colloidal fraction may include hydroxides and complexes with amino acids. The soluble fraction is usually defined as that which will pass through a 0.45  $\mu\text{m}$  filter; it includes free copper and soluble complexes as well as fine particulates and colloids. The soluble fraction may be divided according to the lability of the copper forms in the water. Categories range from the very labile (e.g., free metal ion) to nonlabile (e.g., colloidally bound) metal (Tan et al. 1988). Various techniques may be used to classify the lability of different fractions of soluble copper; these techniques include solvent extraction, ion-specific electrodes, ion exchange, ultrafiltration, electrochemical methods such as anodic stripping voltammetry, and gel filtration chromatography (Harrison and Bishop 1984). The resulting classification depends on the specific procedure employed; therefore, it is not possible to compare the results of different researchers, except in general terms. In a typical study, 18–70% of dissolved copper in river water was moderately labile and 13–30% was slowly labile (Tan et al. 1988).

The nature of copper's association with inorganic and organic ligands will vary depending on the pH, copper concentration, concentration of competing ligands in the body of water, binding capacity of the ligands, and hardness or salinity of the water (Breault et al. 1996; Cao et al. 1995; Gardner and Ravenscroft 1991; Giusti et al. 1993; Lores and Pennock 1998; Town and Filella 2000). In river water from the northwestern United States that had a relatively high pH (7.0–8.5) and alkalinity (24–219 ppm as  $\text{CaCO}_3$ ), inorganic species like  $\text{CO}_3^{2-}$  and  $\text{OH}^-$  were the most important ligands at high copper concentrations. However, other species were important at low copper concentrations. On the other hand, samples from lakes and rivers in southern Maine with a relatively low pH (4.6–6.3) and alkalinity (1–30 ppm as  $\text{CaCO}_3$ ) were largely associated with organic matter. The binding of copper to dissolved organics was found to be dependent on the specific chemical species (e.g., fulvic acid and EDTA) and their concentrations in the surface water, the number of binding sites per fulvic acid carbon, and the hardness of the water (Breault et al. 1996). Increasing water hardness results in decreased fulvic acid binding sites; this effect is due more to the suppression of high molecular weight fulvic acid solubility in the presence of Ca and Mg ions than to competition of these ions with copper for the fulvic acid binding

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sites. Increasing pH from 8 to 6 resulted in a 7-fold increase in the conditional binding constant for Cu(II) with humic acid (Cao et al. 1995).

The extent to which copper binds to inorganic and organic ligands can be altered by materials carried in runoff. For example, after a period of rain in southeastern New Hampshire, inorganic constituents contributed more to the copper binding in lakes and rivers than did dissolved organic matter (Truitt and Weber 1981). Runoff induced by the rain had added to the inorganic load of the rivers and lakes, as was evidenced by their pH (5.7–7.4) and alkalinity (1.7–43.4 ppm as CaCO<sub>3</sub>). A green precipitate, confirmed to be malachite (Cu<sub>2</sub>[OH]<sub>2</sub>CO<sub>3</sub>) was formed in river water in Exeter; this water had the highest pH and alkalinity. A computer simulation of the copper species in pond water and artesian well water that fed the pond predicted that 98% of the copper in the artesian well water would be bound to organic matter, whereas 88 and 63% of the copper in pond water would be bound to organics in the spring and fall, respectively (Giesy et al. 1983).

Seawater samples obtained in a transect of the uppermost Narragansett Bay in August 1980 were analyzed for dissolved, particulate, and organically bound copper to investigate the geochemistry of copper-organic complexes (Mills and Quinn 1984). Narragansett Bay is a partly mixed estuary in Massachusetts and Rhode Island that receives organic matter and metals from rivers, municipal and industrial effluents, and runoff. Dissolved copper represented 60% of the total copper and ranged from 16.4 µg/kg in the Providence River to 0.23 µg/kg in Rhode Island Sound. Analysis of the data indicated that . 75% of this copper is removed within the Providence River. Particulate copper concentrations ranged from 2.42 to 0.06 µg/kg and generally comprised 40% of the total copper. Fourteen to 70% (0.12–2.30 µg/kg) of the dissolved copper was complexed with organic matter.

Organic ligands may contain a variety of binding sites, and the strength of the resulting copper complexes will vary accordingly. Over 99.7% of the total dissolved copper in surface ocean water from the northeast Pacific was associated with organic ligands (Coale and Bruland 1988). The dominant organic complex, limited to surface water, was a strong ligand of biogenic origin. A second, weaker class of organic ligand was of geologic origin. An independent study showed the copper binds to humic material at a number of sites; the binding strength of the sites varied by two orders of magnitude (Giesy et al. 1986). The humic material in the study was derived from nine surface waters in the southeastern United States. Soluble copper in water discharged from a nuclear power station was primarily complexed with organic matter in the 1,000–100,000 molecular weight range (Harrison et al. 1980). Ten to 75% of the discharged copper was in particulate form.

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The bioavailability of Cu(I) has been largely ignored since soluble or complexed forms of copper in this oxidation state have not been thought to occur in significant amounts in aerobic environments.

Investigators have speculated on the possibility that Cu(II) can be directly or indirectly reduced to Cu(I) by photochemical processes (Moffett and Zika 1987). If this should occur, it would be more likely to occur in seawater, where chloride ions might stabilize the Cu(I) through complex formation. Cu(II)-organic complexes absorb radiation  $>290$  nm and can undergo charge transfer reactions where the Cu(II) is reduced and the ligand is oxidized. Photochemically-generated reducing agents such as  $O_2^-$  and  $H_2O_2$  could also reduce Cu(II) to Cu(I).

Experiments performed in synthetic seawater and water from Biscayne Bay, Florida, showed that in the reduction of Cu(II) to Cu(I), the rate was first-order in  $Cl^-$  and second-order in  $H_2O_2$ . The chloride ion is thought to be required for forming stable  $CuClOH^-$ . Experiments showed that as much as 15% of copper in seawater was as Cu(I). Additionally, sunlight increases the percentage of free Cu(II). The photochemical reduction mechanism is supported by the observation that the Cu(I) concentration is highest in the surface layer of seawater and that the hydrogen peroxide concentration increases in parallel to that of Cu(I) (Moffett and Zika 1987). In addition, the percentage of free Cu(II) is highest on the surface.

Once Cu(I) is formed, its lifetime is determined by its rate of oxidation to Cu(II). After Biscayne Bay water was exposed to sunlight for 5 hours, the Cu(I) formed was oxidized to Cu(II); the half-life of the Cu(I) was 12 hours. Dissolved oxygen is primarily responsible for this reaction. Since the oxidation of Cu(I) by  $O_2$  in distilled water occurs in  $<6$  minutes, the Cu(I) apparently is stabilized in seawater by the formation of complexes. In the presence of humic acids, the oxidation of Cu(I) occurs very rapidly. In coastal water off the Everglades in Florida, no Cu(I) was detected, due to the tying up of Cu(II) in organic complexes and the high concentration of radical oxidants in the water. Sharma and Millero (1988) measured the rate of Cu(I) oxidation in seawater as a function of pH, temperature, and salinity. The rate of reaction increased with pH and temperature, and decreased with increasing ionic strength (or salinity). The results suggested that the rates are controlled by  $Mg^{2+}$ ,  $Ca^{2+}$ ,  $Cl^-$ , and  $HCO_3^-$  through their involvement in complex formation and ligand exchange.

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**6.3.2.3 Sediment and Soil**

The adsorption of copper to soil and sediment has been discussed in Section 6.3.1 under transport and partitioning, even though adsorption may really be complexation and transformation. Between pH 5 and 6, adsorption is the principal process for removing copper from water; above pH 6, precipitation becomes more dominant (Perwak et al. 1980). Copper binding in soil may be correlated with pH, cation exchange capacity, the organic content of the soil, the presence of manganese and iron oxides, and even the presence of inorganic carbon such as carbonates (Petruzzelli 1997; Rieuwerts et al. 1998). However, broad generalizations about the lability of copper in soils are not possible since the situation will differ among different soil types and environmental conditions.

The form of copper in soil is determined by measuring the extractability of the copper with different solvents. This extractability is determined by the nature of the soil and the form of copper deposited in the soil. If a relatively labile form of copper is applied, binding to inorganic and organic ligands may occur, as well as other transformations. On the other hand, if a mineral form is deposited, it would be unavailable for binding. The capacity of soil to remove copper and the nature of the bound copper were evaluated by incubating 70 ppm of copper with 5 g samples of soil for 6 days (King 1988). Twenty-one samples of soils (10 mineral and 3 organic) from the southeastern United States were included in the study. Some soil samples were taken from the subsoil as well as the surface. The amount of adsorbed copper ranged from 36 to 100%, of which 13–100% was nonexchangeable when extracted with KCl. Removal of copper from solution was much higher with surface soils than with subsurface sandy soils; 95–100% of the copper was removed by five mineral surface soils and all three organic soils. The percentage of copper that was nonexchangeable was relatively high in all but some of the acid subsoils. While the fraction of exchangeable copper was not dependent on pH in surface soils, 96% of the variation in exchangeability was correlated with pH in subsoils. The soil/water partition coefficient for copper was  $>64$  for mineral soils and  $>273$  for organic soils. Of the eight heavy metals in the study, only Pb and Sb had higher partition coefficients than copper. Most of the copper in Columbia River estuary sediment and soil was correlated with inorganic carbon (e.g., carbonate), but not with the amount of extractable Fe or the organic carbon content of the sediment (Fuhrer 1986).

The amount of ammonium acetate- and DTPA-extractable copper in wetland soil/sediment resulting from atmospheric deposition from smelters in Sudbury, Ontario, showed the same pattern as total copper, despite random variations in soil pH, redox potential, and organic carbon (Taylor and Crowder 1983). Therefore, in this case, soil characteristics were not the dominant factors determining extractability and

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availability, but rather the form of copper that was deposited. The median concentrations of total copper, ammonium acetate-extractable copper, and DTPA-extractable copper at 25 sample sites were 371, 49, and 98 ppm, respectively.

In another study, copper fractionation in nine different contaminated soils, sequential extractions were used to operationally define six soil fractions in decreasing order of copper availability; water soluble > exchangeable > carbonate > Fe-Mn oxide > organic > residual (Ma and Rao 1997). The results of this study showed that distribution of copper in these six soil fractions differed depending on the total copper concentration in the soil. As the copper concentration increased above 240 mg/kg, between 69 and 74.4% of the total copper was found in the water soluble, carbonate, Fe-Mn oxide, and organic fractions. In relatively uncontaminated soils (<240 mg/kg copper), between 97.6 and 99.6% of the copper was found to be associated with the residual fraction.

Within the estuarine environment, anaerobic sediments are known to be the main reservoir of trace metals. Under anaerobic conditions, cupric salts will reduce to cuprous salts. The precipitation of cuprous sulfide and the formation of copper bisulfide and/or polysulfide complexes determine copper's behavior in these sediments (Davies-Colley et al. 1985). In the more common case where the free sulfide concentration is low due to the controlling coexistence of iron oxide and sulfide, anaerobic sediment acts as a sink for copper. However, in the unusual situation where the free sulfide concentration is high, soluble cuprous sulfide complexes may form, and the copper concentration in sediment pore water may then be high.

In sediment, copper is generally associated with mineral matter or tightly bound to organic material (Kennish 1998). As is common when a metal is associated with organic matter, copper is generally associated with fine, as opposed to coarse, sediment. Badri and Aston (1984) studied the association of heavy metals in three estuarine sediments with different geochemical phases. The phases were identified by their extractability with different chemicals and termed easily or freely leachable and exchangeable; oxidizable-organic (bound to organic matter); acid-reducible (Mn and Fe oxides and possibly carbonates); and resistant (lithogenic). In the three sediments, the nonlithogenic fraction accounted for 14–18% of the total copper, and the easily exchangeable component was 5% of the total copper. Sediment samples taken from western Lake Ontario were similarly analyzed in regard to the compositional associations of copper by a series of sequential extractions (Poulton et al. 1988). The mean and standard deviation percentages of copper in the various fractions were: exchangeable, 0 (0); carbonate, 0.1 (0.3); iron or manganese oxide-bound, 0.2 (0.3); organic-bound, 40 (11); and residual, 60 (8). Another study found

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that 10–20% of the copper in Lake Ontario sediment samples was bound to humic acids, and virtually all of the copper was bound to organic matter (Nriagu and Coker 1980). The concentration of copper associated with humic acids was 21–40 times greater than in the sediment as a whole.

### 6.3.2.4 Other Media

Copper is an essential nutrient in plant metabolism. Therefore, uptake of copper from soil in plants through the roots is a natural and necessary process, a process that is actively regulated by the plant (Clemens 2001). The uptake of copper into plants is dependent on the concentration and bioavailability of copper in soils. The bioavailability of copper is determined largely by the equilibrium between copper bound to soil components and copper in soil solution. As noted in the discussion of copper binding in soils (Section 6.3.1.3), this is determined by copper concentrations in soil, soil type, soil components, pH, oxidation-reduction potential in the soil, and concentrations of other cations and anions in the soil, etc. (Rieuwerts et al. 1998). Other factors include root surface area, plant genotype, stage of plant growth, weather conditions, interaction with other nutrients in the soil, and water table (Gupta 1979). Liming is another factor that affects copper uptake. For example, liming acidic soils has been shown to increase copper uptake in hay, but to decrease copper uptake in wheat (Gupta 1979). However, the effect that liming has on increasing soil pH does not appear to be the overriding mechanism behind the changes in copper uptake in plants, even though there is evidence that the addition of lime to soil to increase the pH to 7 or 8 reduces copper availability to plants (Perwak 1980). This is evidenced by the fact that changes in pH (5.4–8.0) have been found to have little effect on copper concentrations in plant tissues (Gupta 1979).

## 6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

### 6.4.1 Air

The concentrations of copper in air depend on the proximity of the site to major sources such as smelters, power plants, and incinerators. The results of several studies in which concentrations of copper in air were reported appear in Table 6-5.

According to the EPA's National Air Surveillance Network report for the years 1977, 1978, and 1979, median copper concentrations were 133, 138, and 96 ng/m<sup>3</sup>, respectively, for urban samples and 120, 179, and 76 ng/m<sup>3</sup> for nonurban samples, respectively (Evans et al. 1984). In this study, 10,769 urban and

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1,402 nonurban air samples collected for 24 hours were analyzed. For 1977, 1978, and 1979, 1% of urban samples exceeded 1,156, 975, and 843 ng/m<sup>3</sup>, respectively, and 1% of nonurban samples exceeded 1,065, 1,396, and 645 ng/m<sup>3</sup>, respectively. The maximum urban and nonurban copper concentrations reported were 4,625 and 4,003 ng/m<sup>3</sup>, respectively. Davies and Bennett (1985) reported average atmospheric copper concentrations of 5–50 ng/m<sup>3</sup> in rural areas and 20–200 ng/m<sup>3</sup> in urban locations. The concentrations in rural areas are considerably lower than those reported in the EPA survey. Data from many urban locations in the United States show concentrations of copper associated with particulate matter ranging from 3 to 5,140 ng/m<sup>3</sup> (Schroeder et al. 1987). Remote and rural areas have concentrations of 0.029–12 and 3–280 ng/m<sup>3</sup>, respectively. The levels reported by Schroeder et al. (1987) are consistent with those obtained in a study of airborne trace elements in national parks (Davidson et al. 1985). In the Smokey Mountain National Park, the copper concentration in air was 1.6 ng/m<sup>3</sup>, while in the Olympic National Park, where several locations were monitored, 3.3–6.7 ng/m<sup>3</sup> of copper was measured in the atmosphere. The lower copper concentrations found in Smokey Mountain Park compared with those in the Olympic National Park have been attributed to greater vegetative cover and higher moisture in the former and larger amounts of exposed rock and soil in the latter. Average

**Table 6-5. Concentrations of Copper in Air**

Date/sample	Location	Concentration <sup>a</sup> (ng/m <sup>3</sup> ) (mean) [median]	Comments	Reference
1977, urban	United States	[133], 433 <sub>90</sub> , 1,156 <sub>99</sub> (207.5), 3,296 <sub>max</sub>	4,648 samples, National Survey	Evans 1984
1978, urban	United States	[138], 430 <sub>90</sub> , 975 <sub>99</sub> (200.8), 4,625 <sub>max</sub>	3,615 samples, National Survey	Evans 1984
1979, urban	United States	[96], 363 <sub>90</sub> , 519 <sub>99</sub> (259.3), 1,627 <sub>max</sub>	2,507 samples, National Survey	Evans 1984
1977, nonurban	United States	[120], 450 <sub>90</sub> , 1,065 <sub>99</sub> (193.2), 16,706 <sub>max</sub>	709 samples, National Survey	Evans 1984
1978, nonurban	United States	[179], 607 <sub>90</sub> , 1,396 <sub>99</sub> (265.7), 1,396 <sub>max</sub>	458 samples, National Survey	Evans 1984
1977, nonurban	United States	[76], 322 <sub>90</sub> , 645 <sub>99</sub> (141.7), 4,003 <sub>max</sub>	235 samples, National Survey	Evans 1984
Urban		20–200, [50]	Representative values	Davies and Bennett 1985
Rural		5–50, [20]		
Remote		0.29–12	Values from literature survey	Schroeder et al. 1987
Rural		3–280		
Urban	Canada	17–500		
Urban	United States	3–5,140		
Urban	Europe	13–2,760		
Urban	Other	2.0–6,810		
1979, remote	Smokey Mountain National Park	(1.6)	Above canopy, crustal enrichment factor 31	Davidson et al. 1985

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**Table 6-5. Concentrations of Copper in Air (continued)**

Date/sample	Location	Concentration <sup>a</sup> (ng/m <sup>3</sup> ) (mean) [median]	Comments	Reference
1980, remote	Olympic National Park	3.3–6.7, (5.6)	Crustal enrichment factor 76	Davidson et al. 1985
1981, 1982, summer	Camden, New Jersey	16.0–18.0 <sup>b</sup> , 100.0 <sub>max</sub>	Seasonal variations noted; three urban areas and one rural area.	Liroy et al. 1987
	Elizabeth, New Jersey	21.0–29.0, 120.0 <sub>max</sub>		
	Newark, New Jersey	25.0–33.0, 131.0 <sub>max</sub>		
	Ringwood, New Jersey	13.0–63.0, 77.0 <sub>max</sub>		
1982, 1983, winter	Camden, New Jersey	17.0–21.0, 231.0 <sub>max</sub>		
	Elizabeth, New Jersey	28.0–36.0, 493.0 <sub>max</sub>		
	Newark, New Jersey	21.0–27.0, 380.0 <sub>max</sub>		
	Ringwood, New Jersey	6.0–18.0, 29.0 <sub>max</sub>		

<sup>a</sup>Percentile level and maximum indicated as subscripts.

<sup>b</sup>Concentrations in Liroy et al. (1987) are geometric means, unless otherwise noted.

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copper crustal enrichment factors (the concentration of copper in air compared with the average concentration in the earth's crust) were 31 and 76, respectively.

As part of the Airborne Toxic Element and Organic Substances (ATEOS) project for determining patterns of toxic elements in different settings, three urban areas (Camden, Elizabeth, and Newark) and one rural site (Ringwood) in New Jersey were studied during two summers and winters between 1981 and 1983 (Lioy et al. 1987). Each site was sampled every 24 hours for 39 consecutive days. The geometric mean copper concentrations were 16.0–21.0, 21.0–36.0, 21.0–33.0, and 6.0–63.0 ng/m<sup>3</sup> for Camden, Elizabeth, Newark, and Ringwood, respectively. The levels of copper measured in these industrial urban areas are considerably lower than the mean values reported in the National Air Surveillance survey (201–259 mg/m<sup>3</sup> for 1977–1979 [Evans et al. 1984]). Summer and winter maxima in the three urban areas were 100.0–131.0 and 231.0–493.0 ng/m<sup>3</sup>, respectively, and 77.0 and 29.0 ng/m<sup>3</sup>, respectively, for Ringwood. Copper follows the same pattern as other heavy metals, in that increased copper levels are present in winter in urban areas and in summer in rural areas. No explanation for this pattern has been offered.

Airborne concentrations of copper in the indoor atmosphere average between 8 and 12 ng/m<sup>3</sup> (Koutrakis et al. 1992). The concentration was significantly affected by the use kerosene heaters, which were found to emit copper into the indoor air at a rate of 15,630 ng/hour (Koutrakis et al. 1992).

Anderson et al. (1988) performed a study of the atmospheric aerosols collected at a site in Chandler, Arizona, over a 12-day period in February and March 1982. Several major copper smelters are located 120 km to the southeast. Particles containing >0.5% Cu were termed 'Cu-bearing' particles; 5.6% of the fine (0.4 to 2 μm) particles collected were in this category. The most abundant type of Cu-bearing particle, representing 74% of the total, was associated with sulfur; however, the analysis was not able to specify the form of sulfur present. These particles were often associated with Zn, Fe, Pb, As, and Ca. Sixteen percent of the Cu-bearing particles were associated with silicon and 4% were associated with chloride. The concentration of Cu-S particles was highest when the surface and upperlevel winds were from the southeast to the east, and reached a maximum 1–2 days after the winds began to blow from the southeast; the smelters to the southeast were the probable source. The particles associated with silicon and chlorine did not show any apparent correlation with wind and were either from a diffuse regional source or a local source.

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Mine waste dump sites are a source of airborne copper carried in dust (Table 6-6). Particle size distribution and the concentration of copper in particle size ranges differ depending on the mine waste site (Mullins and Norman 1994). For example, the mean concentrations (ppm, w/w) of copper in dust (<10  $\mu\text{m}$  particle size range) collected at four mine waste dump sites in Butte, Montana, were 3,370 (Gray Rock), 1,950 (Corra), 1,960 (Late Acquisition), and 2,570 (Railroad Bed).

Mean concentrations of copper in remote and rural precipitation ranges were 0.013–1.83 and 0.68–1.5 ppb, respectively, on a volume-weighted basis (Barrie et al. 1987). Although an earlier survey referred to by these investigators yielded much higher values, 0.060 and 5.4 ppb, these were ascribed to sample contamination. The mean concentration of copper in rain reported in an extensive study in southern Ontario, Canada, was 1.57 (0.36 standard deviation) ppb during 1982 (Chan et al. 1986). These concentrations showed little spatial variability and agree with those reported by Barrie et al. (1987). Concentration of copper in cloud water over Olympic Peninsula in Washington State has been measured at  $1.7 \pm 1.6$   $\mu\text{g/L}$  (air-equivalent mean concentration of  $0.5$   $\text{ng/m}^3$ ) (Vong et al. 1997).

Elevated levels of copper in fog water have been observed 3 km downwind from a refuse incinerator in Switzerland (Johnson et al. 1987). High concentrations of copper were associated with low pH. The maximum concentration, 673 ppb, occurred at pH 1.94; levels >127 ppb were associated with pH values <3.6. Copper(II) concentrations in fog water from the central valley of California were 1.7–388 ppb (Miller et al. 1987). The source of the copper was not investigated. High values were recorded just as the fog was dissipating.

The concentration of copper in rain in proximity to a municipal waste incinerator has been found to range from 0.11 to 2.12  $\mu\text{g/L}$  with a mean concentration of 0.87  $\mu\text{g/L}$ . The total mean deposition rate of airborne copper from rain was measured at 4.0  $\mu\text{g/m}^2/\text{day}$  (Feng et al. 2000). However, copper deposition from automobile emissions, as measured by the concentration of copper in snow, did not vary significantly as a function of distance from a roadway (15–150 meters). Mean concentrations of copper in snow (expressed as mg/L [and standard deviations] were measured as; 0.051 (0.073); 0.065 (0.127); 0.034 (0.027); and 0.044 (0.051) at 15, 20, 15, and 150 meters, respectively (Lorganger et al. 1996).

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**Table 6-6. Particle Size Distributions and Total Copper Concentrations in Dust Collected at Four Mine Waste Pump Sites in Butte, Montana<sup>a</sup>**

Site	Particle size ( $\mu\text{m}$ )	Percent in total dust collected	Concentration of copper (ppm, w/w)
Corra	4.7–10	76.6 $\pm$ 4.8	1,550
	1.1–4.7	20.9 $\pm$ 0.63	3,110
	<1.1	1.9 $\pm$ 0.14	4,900
Gray Rock	4.7–10	84.5 $\pm$ 0.93	3,240
	1.1–4.7	13.6 $\pm$ 0.82	4,120
	<1.1	1.9 $\pm$ 0.14	4,370
Railroad Bed	4.7–10	61.5 $\pm$ 1.06	2,580
	1.1–4.7	31.3 $\pm$ 0.96	2,850
	<1.1	7.2 $\pm$ 0.26	1,400
Late Acquisition	4.7–10	70.3 $\pm$ 1.36	1,560
	1.1–4.7	25.0 $\pm$ 1.18	2,730
	<1.1	4.7 $\pm$ 0.44	3,330

<sup>a</sup>Data obtained from Mullins and Norman 1994

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**6.4.2 Water**

Copper is widely distributed in water since it is a naturally occurring element. Copper levels in surface water range from 0.5–1,000 ppb, with a median of 10 ppb; seawater contains <1–5 ppb (Davies and Bennett 1985; Mart and Nurnberg 1984; Page 1981; Perwak et al. 1980; Yeats 1988). The results of several studies in which copper was detected in drinking water, surface water, and groundwater are presented in Table 6-7. The information in Table 6-7 demonstrates that copper concentrations in drinking water can vary widely (#5–10,200 ppb) and can exceed the action limits of 1,300 ppb that have been set for copper in drinking water (EPA 1991). The table also emphasizes the importance of running tap water before using it and the need to control corrosion of piping in water distribution systems.

Copper concentrations in drinking water vary widely as a result of variations in pH, hardness of the water supply, and copper picked up in the water distribution system (Davies and Bennett 1985; Yannoni and Piorkowski 1995). Copper concentrations in drinking water range from a few ppb to 10 ppm. A Canadian national survey of copper and other metals in drinking water was conducted from November 1976 to January 1977 (Meranger et al. 1979). Supplies from 70 municipalities representing 38% of the Canadian population were included in the survey, including 50 derived from river or lake water and 20 derived from groundwater. Unfiltered raw, treated, and distributed drinking waters were analyzed. Whether the water was derived from river, lake, or well water did not significantly affect the copper concentration in the raw water. Only in a few supplies did copper levels in raw water exceed 20 ppb, and only one of these was derived from groundwater. The results in groundwater contrast with those of Page (1981) in New Jersey, in which over 100 wells contained copper levels in excess of 64 ppb. However, that study included groundwater that was a source of drinking water and as well as groundwater that was not. The copper concentration in Canadian treated water was generally . 10 ppb (Meranger et al. 1979). In 20% of the samples, the copper level in distributed water was significantly higher than the treated water; the increase was greater in areas where the water was soft and corrosive, thus enhancing leaching of copper from the distribution system.

Elevated concentrations of copper in drinking water can result as a consequence of leaching processes that occur in water distribution systems. A study of 1,000 water samples from random households in Ohio found that ! 30% contained copper levels >1 ppm (Strain et al. 1984). The highest copper level in the study was 18 ppm. In a study of private water wells in four communities in Nova Scotia, Maessen et al. (1985) found that the concentrations of copper increased in water that remained in the distribution

Table 6-7. Concentrations of Copper in Water

Sample type/ source	Location	Concentration (ppb) Range (mean) [median]	Comments	Reference
Drinking water				
Private wells	Nova Scotia four communities	40–200 130–2,450, 53% of samples >1,000 ppm	at tap, running water at tap, standing water	Maessen et al. 1985
Private wells	New Bedford, Massachusetts	(330)	at tap, running water	Yannoni and Piorkowski 1995
Not specified	Seattle, Washington	(160) (450), 24% of samples >1,000 ppm	running water standing water	Maessen et al. 1985
River water	Canada (National Survey)	#5–530 [#5] #5–100 [#5] #5–220 [20]	raw water treated water distributed water	Meranger et al. 1979
Lake water	Canada (National Survey)	#5–80 [#5] #5–100 [#5] #5–560 [40]	raw water treated water distributed water	Meranger et al. 1979
Well water	Canada (National Survey)	#5–110 [#5] #5–70 [#5] 10–260 [75]	raw water treated water distributed water	Meranger et al. 1979
School drinking water	New Jersey	BD–10,200 <sup>a</sup> BD–7,800 BD–8,500	first draw 10-minute flush mid-day, first draw	Murphy 1993
Groundwater				
Representative sample	New Jersey	[5.0]	1,063 samples, 90 <sup>th</sup> percentile 64.0 ppb, maximum 2,783 ppb, groundwater may or may not be used for drinking water	Page 1981

**Table 6-7. Concentrations of Copper in Water (continued)**

Sample type/ source	Location	Concentration (ppb) Range (mean) [median]	Comments	Reference
Shallow monitoring well	Denver, Colorado	<1–14 [2]	30 monitoring wells, 22 with PVC casings and 8 with metal casings; samples obtained after purging well from 20 minute	Bruce and McMahon 1996
Surface water				
U.S. Geological Survey stations	United States	(4.2) [4.0]	53,862 occurrences	Eckel and Jacob 1988
Representative sample	New Jersey	[3.0]	590 samples, 90 <sup>th</sup> percentile 9.0 ppb, maximum 261 ppb	Page 1981
Surface, marine	East Arctic Ocean	(0.126)	26 locations 0.5–1 m depth	Mart and Nurnberg 1984
Surface, marine	Atlantic Ocean	0.0572–0.0210	20 sites, 2 cruises, 0–1 m depth	Yeats 1988
Pond	Massachusetts	<10–105	Low in summer, high in winter	Kimball 1973
Lakes	Canada	1–8 (2)	Acid sensitive lakes	Reed and Henningson 1984
Lakes	Great Lakes	629–834 (756) 703–1,061 (870) 540–1,098 (830)	Lake Superior Lake Erie Lake Ontario	Nriagu et al. 1996
	Representative samples, nearby to acidic mine drainage	32-1,200 (736)	12 samples taken from streams and ponds near abandoned coal mines in Indiana	Allen et al. 1996
	Representative samples from copper mining areas in Arizona	100–69,000 [1,200]	Samples obtained from the Cerbat Mountains mining area; 15 surface water sites with 14 sites downstream from old tailings and adits	Rösner 1998

<sup>a</sup>BD = below detection limit

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system overnight, indicating that copper was mobilized from the distribution system. Whereas the level of copper in running water was generally very low, that in the standing water was variable and exceeded 1.0 ppm in 53% of the homes. Correlation with pH and nitrate, chloride, and manganese concentrations accounted for >99% of the copper picked up from the distribution system. Similar results were reported for U.S. cities (Maessen et al. 1985; Schock and Neff 1988; Strain et al. 1984). In a study in Seattle, Washington, the mean copper concentrations in running and standing water were 0.16 and 0.45 ppm, respectively, and 24% of the standing water samples exceeded 1.0 ppm (Maessen et al. 1985). The difference in copper level between standing and flushed systems became evident at pH 7 and increased with decreasing pH (Strain et al. 1984). Copper levels in school drinking water were found to differ by 3-fold between first draw and 10-minute flush water samples, irrespective of the corrosiveness of the water (Murphy 1993). However, the concentration of copper in both first draw and 10-minute flush samples decreased by approximately 10-fold as the corrosiveness of the water decreased. Increasing pH in water distribution lines has been found to result in an overall decrease in metal concentrations. For example, increasing the pH of water from 7.5 to 8.5 in distribution lines decreased copper concentration by 50% (Yannoni and Piorkowski 1995).

The geometric mean (standard deviation) and median concentration of dissolved copper in surface water based on 53,862 occurrences in EPA's STORET database are 4.2 (2.71) and 4.0 ppb, respectively (Eckel and Jacob 1988). Higher concentrations tend to be found in New England, the western Gulf, and the lower Colorado River (Perwak et al. 1980). An analysis of high concentrations of copper in minor river basins reported in EPA's STORET database in 1978 revealed that sources of copper in the Gila, Coeur D'Alene, and Sacramento River Basins appear to be primarily mining activities, especially abandoned sites (Perwak et al. 1980). The high concentrations were generally observed at localized stations. The low pH of the surface water in these areas was reported to exacerbate the situation. However, in another study concerning lakes sensitive to acid rain, copper values were relatively low (1–8 ppb range, 2 ppb mean) regardless of pH or alkalinity (Reed and Henningson 1984).

Copper concentrations were measured in surface water obtained from sampling sites in the Spearfish Creek, Whitewood Creek, and Bear Butte Creek watersheds. These watersheds are affected by water leaching processes tailings and acid-mine drainage from gold mining operations in the Black Hills of South Dakota. Concentrations of <0.24–28 µg/L were measured in surface water, whereas concentrations in sediments were much higher, ranging from 7.8 to 159 µg/g (May et al. 2001).

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In a survey of sources of copper in storm water, measurements of copper concentrations in storm water samples were taken from various urban locations in Birmingham, Alabama. Copper concentrations were generally low in filtered samples (dissolved copper), ranging between 1.4 and 20 µg/L, but were much higher in unfiltered samples (copper bound to particulate matter) with mean values (in µg/L) of 110 (roof areas), 116 (parking areas), 280 (street runoff), 135 (vehicle service areas), 81 (landscaped areas), 50 (urban creeks), and 43 (detention ponds) (Pitt et al. 1995).

As a result of improvements in controlling discharges from municipal and industrial waste water treatment plants mandated in the Clean Water Act, copper concentrations have been declining in surface waters. For example, median copper concentrations in the Hudson River estuary have fallen 36–56% between the mid-1970s and the mid-1990s (Sañudo-Wilhelmy and Gill 1999).

In a study of representative groundwaters and surface waters throughout New Jersey in which >1,000 wells and 600 surface sites were sampled, the median copper levels in groundwater and surface water were 5.0 and 3.0 ppb, respectively (Page 1981). The respective 90<sup>th</sup> percentile and maximum levels were 64.0 and 2,783.0 ppb for groundwater and 9.0 and 261.0 ppb for surface water. The pattern of contamination in surface water correlates with light hydrocarbons, while that in groundwater correlates with heavy metals. This indicates that the sources of contamination of surface water and groundwater are probably different. The nature of the sites with elevated levels of copper was not indicated. Experimental data demonstrate that leaching of copper is minimal.

The copper concentration in some bodies of water evidently varies with season. In one small pond in Massachusetts, the concentration varied from <10 to 105 ppb (Kimball 1973); copper levels were low from summer to late fall and rose to maximum levels in midwinter. Similar seasonal variations are also noted in the epilimnion of the offshore waters of the Great Lakes (Nriagu et al. 1996). This cycling in copper concentrations is thought to be a response to biological need and uptake of copper during the growing season and its subsequent release from decay of biota.

Copper concentrations in seawater are usually in the 1–5 ppb range (Perwak et al. 1980). Copper levels are lower in the Pacific Ocean than in the Atlantic Ocean and higher near the continental shelf than in the open ocean. Copper concentrations in surface water transected on a cruise from Nova Scotia to the Sargasso sea ranged from 57.2 to 210 parts per trillion (ppt) (Yeats 1988). The mean value in surface water of the eastern Arctic Ocean was 93 ppt (Mart and Nurnberg 1984). In a review by Kennish (1998), concentrations of copper were 0.3–3.8 ppb in estuarine waters and in 0.1–2.5 ppb in coastal waters.

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**6.4.3 Soil and Sediment**

Copper occurs naturally at levels of ~ 50 ppm in the earth's crust, which includes soil and parent rock (Perwak et al. 1980). In the United States, copper concentrations in differing soil types can vary over a large range (1–300 mg/kg, dry weight), but the mean values are relatively similar (14–41 mg/kg, dry weight) as a function of soil type (Table 6-8) and land resource region (Table 6-9). In agriculturally productive soils, copper ranges from 1 to 50 ppm, while in soil derived from mineralized material copper, levels may be much higher (NRC 1977; Perwak et al. 1980). Copper concentrations in soil samples collected throughout the United States yielded a geometric mean of 17–18 ppm (Chen et al. 1999; Fuhrer 1986). Samples were taken at a depth of 8 inches to avoid anthropogenic contamination; 2/3 of the samples contained copper concentrations between 8 and 40 ppm. These copper levels are supported by a review of soil copper concentrations that reported a median concentration of 30 ppm (dry weight) and a range of 2–250 ppm (Davies and Bennett 1985). Copper concentrations in soil may be much higher in the vicinity of a source. Concentrations in the top 5 cm of soil near the boundary of a secondary copper smelter were  $2,480 \pm 585$  ppm (Davies and Bennett 1985). Maximum wetland soil/sediment copper concentrations were 6,912 ppm in the immediate vicinity of a Sudbury, Ontario smelter, but the concentration decreased logarithmically with increasing distance from the smelter (Taylor and Crowder 1983). Results suggest that copper in the soil from the study area was primarily from particulate emissions from the smelter.

In a study in which the copper concentrations of 340 soil samples were presented in terms of land-use types, the average copper concentrations reported were 25 ppm in agricultural land, 50 ppm in suburban/residential land, 100 ppm in mixed industrial/residential land, and 175 ppm in industrial/inner urban areas (Haines 1984). From an analysis of the spatial distribution of the copper, it was concluded that most of the contamination was a result of airborne deposition from industrial sources. Soils from Lemhi, Twin Falls, and the Idaho National Engineering Laboratory in southern Idaho had geometric mean copper concentrations of 13.4–20.4 ppm dry weight (Rope et al. 1988).

The concentration of copper in soils and sediments was assessed as part of the National Water-Quality Assessment Program (Rice 1999). The median concentrations of copper at 541 sites throughout the

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**Table 6-8. Concentration of Copper in Surface Soils of the United States  
(in ppm-Dry Weight [dw], Equivalent to mg/kg-dw)<sup>a</sup>**

Soil	Range	Mean
Sandy soils and lithosols on sandstones	1–70	14
Light loamy soils	3–70	25
Loess and soils on silt deposits	7–100	25
Clay and clay loamy soils	7–70	29
Alluvial soils	5–50	27
Soils over granites and gneisses	7–70	24
Soils over volcanic rocks	10–150	41
Soils over limestones and calcareous rocks	7–70	21
Soils on glacial till and drift	15–50	21
Light desert soils	5–100	24
Silty prairie soils	10–50	20
Chernozems and dark prairie soils	10–70	27
Organic light soils	1–100	15
Forest soils	7–150	17
Various soils	3–300	26

<sup>a</sup>From Breckenridge and Crockett 1995

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**Table 6-9. Geometric Means of Selected Soil Elements and Associated Soil Parameters in U.S. Surface Soils by Land Resource Regions<sup>a</sup>**

Land resource region	mg/kg dry soil
Mineral soils	
Northwestern specialty	34.3
Northwestern wheat	23.2
California subtropical	43.4
Western range and irrigated	26.8
Rocky Mountain	19.1
Northern Great Plains	20.2
Western Great Plains	16.3
Central Great Plains	12.6
Southwest Plateau	10.0
Southwest Prairie	4.9
Northern lake states	15.4
Lake states	18.2
Central feed grains	19.7
East and central farming	8.0
Mississippi Delta	21.1
South Atlantic and Gulf slope	6.3
Northeastern forage	34.0
Northern Atlantic slope	13.5
Atlantic and Gulf coast	7.6
Florida subtropical	31.9
All mineral soils	15.6
Histosols	
Northern lake states	59.6
Lake states	84.7
Northeastern forage	149.0
Florida subtropical	94.3
All histosols	86.9

<sup>a</sup>Source: Holmgren et al. (1993)

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conterminous United States ranged from 5 to 70  $\mu\text{g/g}$  (dry weight). At nonurban indicator sites, the median concentrations ranged from 13 to 47  $\mu\text{g/g}$ . The same study derived an average crustal abundance of copper of 60  $\mu\text{g/g}$ . In the work of Ma et al. (1997), the typical concentration of copper in soils of the United States was determined to be 30 mg/kg, whereas the copper concentration in agricultural surface soils was found to be 18 mg/kg. In Florida surface soils, the geometric mean of copper concentration in all soils was 4.10 mg/kg, with a range of 1.89–10.7 mg/kg with highest levels in ultisol soils (Ma et al. 1997). Chen et al. (1999) reported copper concentrations in Florida soils ranging from 0.1 to 318 mg/kg with a geometric mean of  $2.21 \pm 3.15$  mg/kg (arithmetic mean of  $6.10 \pm 22.1$  mg/kg). These investigators also reported geometric means of 24.0 mg/kg in California soils and 17 mg/kg in U.S. soils.

Sediment is an important sink and reservoir for copper. In pristine areas, sediment generally contains <50 ppm copper; the level can reach several thousand ppm in polluted areas (Harrison and Bishop 1984). The mean copper level in surficial sediment of Penobscot Bay, Maine, was 14.1 ppm (dry weight), while that in estuaries or bays in other New England locations ranged from 4.4 to 57.7 ppm (Larsen et al. 1983b). Levels reflect anthropogenic input as well as the mineral content of the regional bedrock. Copper levels in sediment from 24 sites along the New Jersey coast ranged from <1.0 to 202 ppm, with a mean value of 66 ppm (Renwick and Edenborn 1983). The texture of the sediment varied from 94% clay to 100% sand, and the copper level was correlated negatively with the percentage of sand in the sediment.

Surficial sediment in lakes in the Sudbury region of northeastern Ontario, where several smelters operate, decreased rapidly with increasing distance from the smelters (Bradley and Morris 1986). Three lakes, 10 km from the Sudbury smelters, contained copper concentrations in sediment approaching 2,000 ppm dry weight, over 100 times the concentration in a baseline lake 180 km away.

An analysis of the Coastal Sediment Database (COSED) showed that 75% of coastal waterways had copper concentrations below 42  $\mu\text{g/g}$ ; 2% were above 210  $\mu\text{g/g}$ . These higher concentrations are associated with locations of high ship traffic, industrial activity, and relatively poor water flushing (Daskalakis and O'Connor 1995). In coastal areas receiving persistently high influxes of contaminants, high concentrations of copper have been measured to sediments to depths of 54 cm. Combined sewer outflows can also contribute significantly to the copper content in sediments. For example, mean (arithmetic) copper concentrations of 180, 208, 280, and 284 mg/kg were measured in sediment samples obtained near four sewer outflows in the lower Passaic River, New Jersey (Iannuzzi et al. 1997). In Jamaica Bay, New York, copper concentrations in sediments were 151–406 ppm, with a concentration of 151 ppm in sediment core samples obtained at a depth of 52–54 cm (Bopp et al. 1993). The highest

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concentrations were found in the middle depths (16–44 cm) ranging from 280 to 406 ppm, whereas copper concentrations in surface sediments (0–2 cm) were measured at 208 ppm. The decrease in copper concentration in the surface sediments suggests that efforts to reduce metal contaminants from sewage outflows has been making an impact on the copper concentrations in receiving waters and their sediments.

Copper and its compounds were found at 884 of 1,613 hazardous waste sites on the NPL of highest priority sites for possible remedial action (HazDat 2002). Since copper is found in soil, it should occur at all sites. In past work, data analysis of metal concentrations in soil at hazardous waste sites taken from the 1980–1983 Contract Laboratory Program (CLP) Analytical Results Data Base (CARD) was conducted to ascertain whether elemental concentrations at hazardous waste sites were elevated above that which would normally be expected in soil. Of the 1,307 samples in CARD, 10.5 and 7.3% had copper concentrations exceeding the number normally expected in soil at the 95 and 99% confidence intervals, respectively (Eckel and Langley 1988).

#### **6.4.4 Other Environmental Media**

More recent measurements of copper concentrations in 265 foods measured from 1991 to 1996 and from 1991 to 1999 have been obtained from the FDA Total Diet Study (Capar and Cunningham 2000; FDA 2000). The copper contents of selected foods provided in the most recent FDA Total Diet Study (FDA 2000) are similar to those obtained from the 1982–1984 FDA study; therefore, the daily dietary copper intakes determined in the work of Pennington et al. (1986) are expected to be reliable for estimating current dietary copper intakes. The contribution of food groups to copper intake varies depending on the age group (Pennington and Schoen 1996). For example, animal flesh only contributes to 18% of the copper intake for a 2-year-old child, but contributes to 38% of the copper intake for a 60–65-year-old male. The results of a 1994–1996 Continuing Survey of Food Intakes (CSFII) found that the daily intakes of copper for men and women ages 60 years old are 1.3 and 1.0 mg/day, respectively (Ma and Betts 2000). In a separate study by Ellis et al. (1997), copper intake for male and female African-Americans ages 21–65 years old was determined to be 1.0 mg/day for both sexes.

Daily intakes of copper and other essential minerals were estimated for eight age-sex groups of the United States population as part of the FDA's Total Diet Study (Pennington et al. 1986). By analyzing the mineral content of composite samples of 234 foods obtained in 24 cities from mid-1982 to mid-1984 and by using previously determined daily intakes of each food, the daily mineral intake for the age-sex groups

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was determined. The copper intakes in mg/day of the eight age-sex groups were: 6–11-month-old infant, 0.47; 2-year-old child, 0.58; 14–16-year-old girl, 0.77; 14–16-year-old boy, 1.18; 25–30-year-old woman, 0.93; 25–30-year-old man, 1.24; 60–65-year-old woman, 0.86; and 60–65-year-old man, 1.17. All values were low in terms of the estimated safe and adequate daily dietary intake of this nutrient. The food item with the highest copper level was beef/calf liver (61 ppm).

A baseline value for the copper content of mother's milk was determined by screening literature values. The 28 samples selected had copper concentrations ranging from 197 to 751 ppb and a median of 290 ppb (Iyengar and Woittiez 1988). In a separate study, it was found that the variability was primarily subject-related, but for individuals, the copper concentration in milk declined moderately with the duration of lactation (Vaughan et al. 1979). In a study of 82 healthy, lactating women, the copper concentration in breast milk ranged between 0.8 and 1.1 ppm and remained relatively constant in individual women over the first 7 days postpartum (Arnaud and Favier 1995).

As a part of the National Contaminant Biomonitoring Program of the U.S. Fish and Wildlife Service, eight species of freshwater fish were collected at 112 stations in the United States in 1978–1979 and 1980–1981 (Lowe et al. 1985). The geometric mean concentrations of copper in ppm (wet weight, whole fish) for these two periods were 0.86 and 0.68, respectively; the 85th percentiles were 1.14 and 0.90, respectively, and the ranges were 0.29–38.75 and 0.25–24.10, respectively. The highest concentration, 38.75 and 24.10 ppm, during both collecting periods was in white perch from the Susquehanna River and the second highest concentration, 19.3 ppm, was found in white perch from the Delaware River near Trenton, New Jersey. However, copper concentrations in common carp and white catfish collected from the same station at the same time were 0.76 and 1.35 ppm, respectively.

In bluefin tuna caught in the northwest Atlantic off Newfoundland, the mean copper concentration in muscle tissue has been measured at 1.0 ppm (dry weight) (Hellou et al. 1992a). In cod caught off the coast of Newfoundland, mean copper concentrations of <1.2–1.5 µg/g (dry weight) in muscle and 5–10 ppm (dry weight) in liver have been determined (Hellou et al. 1992b).

Copper residues in muscle of 268 fish specimens were analyzed over a 5-year period in several surface water systems in eastern Tennessee (Blevins and Pancorbo 1986). The mean residue levels in the muscle of different species of fish from nine stations ranged from 0.12–0.86 ppm (wet weight). Maximum levels ranged from 0.14 to 2.2 ppm.

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Concentrations of copper in three species of fish living in storm treatment ponds have been compared to copper concentrations in controls collected from surrounding surface waters near Orlando, Florida (Campbell 1994). In bluegill sunfish collected from storm water ponds, the mean whole body copper concentrations were 6.37 and 2.08 mg/kg wet weight, respectively, and were significantly higher than the mean concentrations of copper in controls, 0.879 and 1.07 mg/kg wet weight, respectively. However, in largemouth bass, the mean copper concentrations in fish collected from storm water ponds and controls did not significantly differ, with values of 3.81 and 4.71 mg/kg wet weight, respectively.

Respective mean and median copper concentrations of 127 samples of fish from Chesapeake Bay and its tributaries were 1.66 and 0.36 ppm in 1978, and 1.85 and 0.61 ppm in 1979 (Eisenberg and Topping 1986). Copper levels were increased in the livers and to a lesser degree, the gonads, compared with the flesh. The copper content of muscle tissue of several species of fish collected from metal-contaminated lakes near Sudbury, Ontario, ranged from 0.5 to 1.4 ppm (dry weight). No major pattern in variation was evident among species or among the study lakes (Bradley and Morris 1986). The copper concentration in the livers, however, ranged from 5 to 185 ppm (dry weight) and differed significantly among species and among lakes. Unlike muscle tissue, liver tissue is a good indicator of copper availability, although the data indicate that there are other factor(s) that influence the availability and bioaccumulation of copper in these fish.

The copper concentrations in the liver of lake trout and grayling taken from Arctic fresh water lakes did not correlate well with the concentrations of copper in the sediments of these lakes (Allen-Gil et al. 1997). Lake trout were found to have higher burdens of copper than grayling, and the concentrations of copper in trout varied considerably depending on the lake from which they were collected. The species and site differences in copper concentrations have been attributed to differences in dietary patterns, (grayling consume mainly insects, whereas trout consume a mix of snails, insects, and small fish) and time spent at various depths of the water column.

The concentrations of copper in the soft tissue in mussels and oysters collected as part of the U.S. Mussel Watch Program in 1976–1978 were 4–10 ppm (dry weight) for mussels and 25–600 ppm for oysters (Goldberg 1986). Copper concentrations in mussels collected from 11 sites near Monterey Bay, California, were 4.63–8.93 ppm (dry weight) (Martin and Castle 1984). Perwak et al. (1980) reported similar results for mussels (3.9–8.5 ppm) and clams (8.4–171 ppm). Recent measurements of copper concentrations in zebra and quagga mussels taken from Lakes Erie and Ontario in 1997 ranged from between 21 to 41 ppm (dry weight) (Rutzke et al. 2000). In the National Oceanic and Atmospheric

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Administration (NOAA) Mussel Watch Project, copper concentrations were quantified in mollusks from 113 sites around the United States in 1993 and compared to copper concentrations measured in mollusks taken from the same site in the EPA2 Mussel Watch Program, 1976–1978 (Lauenstein and Daskalakis 1998). The results of the comparison indicate that the decreasing and increasing trends in copper concentrations in mollusks were approximately equal among the sites except in California, where increasing trends were noted at five sites.

Although the concentrations of copper in plants vary widely, they usually range from 1 to 50 ppm (dry weight) (Davies and Bennett 1985; Perwak et al. 1980). Concentration ratios of copper in plants relative to soil (concentration factors or CF) demonstrate that copper uptake and demand differs significantly between plants. For example, CF values have been found to vary from 0.02 (onion), 0.13 (celery), 0.21 (lettuce), and 0.30 (potato) to 2 (grapes), 4.5 (alfalfa), and 6.8 (grass) (Pinochet et al. 1999). Concentration factors in rice were found to vary among soil types (0.59–3.58) with copper concentrations in rice ranging from 1.7 to 5.1  $\mu\text{g/g}$  (Herawati et al. 2000). Copper concentrations in the rice grain have been found to increase significantly from 1.4 to 15.5  $\mu\text{g/g}$  when copper concentrations in waste water irrigated soils increased from 17.0 mg/kg (wet weight) to 101.2 mg/kg (wet weight) (Cao and Hu 2000).

The FDA Total Diet Survey has provided copper concentration in various foods, example of which are given in Table 6-10 (FDA 2001). For copper concentrations measured in the edible tissues of livestock and poultry, the highest mean concentrations (ppm) were found in liver (cow 43.7; lamb 89.8; chicken 4.60; turkey 7.14), followed by kidney (cow 8.15; lamb 5.39; chicken 3.07; turkey 3.68), and muscle (cow 1.41; lamb 1.47; chicken 0.67; turkey 0.83) (Coleman et al. 1992).

Studies of copper in human tissues suggest that copper content in a 70 kg adult range from 50–70 mg (Davies and Bennett 1985). Wise and Zeisler (1984) reported an average copper concentration of 10 ppm in the human liver in 36 samples. Despite the wide variation in copper concentrations in the

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**Table 6-10. Copper Content of Selected Foods (mg/kg)<sup>a</sup>**

Food description	Mean	S.D.	Food description	Mean	S.D.
<b>Breads</b>			green pepper, raw	0.7	0.3
bagel, plain	1.3	0.2	iceberg lettuce, raw	0.2	0.2
cracked wheat bread	1.8	0.2	lima beans, immature, frozen,	1.5	0.2
English muffin, plain, toasted	1.3	0.1	mixed vegetables, frozen,	0.6	0.2
graham crackers	1.5	0.3	mushrooms, raw	2.4	0.6
rye bread	1.5	0.2	okra, fresh/frozen, boiled	0.8	0.3
saltine crackers	1.4	0.1	onion, mature, raw	0.4	0.1
white bread	1.1	0.2	peas, mature, dry, boiled	2.3	0.3
white roll	1.3	0.2	spinach, fresh/frozen, boiled	0.8	0.3
whole wheat bread	2.3	0.3	summer squash, fresh/frozen,	0.5	0.1
<b>Cereal, rice, and pasta</b>			sweet potato, fresh, baked	1.4	0.4
corn flakes	0.5	0.1	tomato, red, raw	0.5	0.2
crisped rice cereal	2.0	0.2	tomato sauce, plain, bottled	1.2	0.4
egg noodles, boiled	1.0	0.2	tomato, stewed, canned	0.7	0.2
granola cereal	3.0	0.4	turnip, fresh/frozen, boiled	0	0.1
macaroni, boiled	0.9	0.1	white potato, baked with skin	1.0	0.4
oatmeal, quick (1–3 minutes),	0.7	0.1	white potato, boiled without	0.6	0.2
oatring cereal	3.3	0.4	winter squash, fresh/frozen,	0.6	0.2
raisin bran cereal	4.4	0.4	<b>Fruits</b>		
shredded wheat cereal	3.7	0.5	apple, red, raw	0.2	0.2
wheat cereal, farina, quick	0.3	0.3	applesauce, bottled	0.2	0.1
white rice, cooked	0.7	0.1	apricot, raw	0.8	0.3
<b>Vegetables</b>			avocado, raw	2.2	0.6
asparagus, fresh/frozen,	1.0	0.2	banana, raw	1.1	0.2
beets, fresh/frozen, boiled	0.7	0.2	cantaloupe, raw	0.3	0.1
black olives	1.4	0.4	fruit cocktail, canned in heavy	0.5	0.1
broccoli, fresh/frozen, boiled	0.2	0.1	grapefruit, raw	0.3	0.1
Brussels sprouts, fresh/frozen,	0.4	0.1	grapes, red/green, seedless,	1.1	0.6
cabbage, fresh, boiled	0	0	orange, raw	0.4	0.1
carrot, fresh, boiled	0.3	0.2	peach, canned in light/medium	0.3	0.2
cauliflower, fresh/frozen,	0	0	peach, raw	0.7	0.2
celery	0	0.1	pear, canned in light syrup	0.4	0.1
collards, fresh/frozen, boiled	0.5	0.4	pear, raw	0.8	0.1
corn, fresh/frozen, boiled	0.3	0.2	pineapple, canned in juice	0.5	0.1
cream style corn, canned	0.1	0.2	plums, raw	0.6	0.1
cucumber, raw	0.2	0.2	prunes, dried	2.9	0.3
eggplant, fresh, boiled	0.5	0.2	raisins, dried	3.3	0.4
green beans, fresh/frozen,	0.5	0.3	strawberries, raw	0.5	0.3
green peas, fresh/frozen,	1.0	0.2	watermelon, raw	00.4	0.1

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**Table 6-10. Copper Content of Selected Foods (mg/kg)<sup>a</sup> (continued)**

Food description	Mean	S.D.	Food description	Mean	S.D.
<b>Fruit juices</b>			pork roast, baked	0.8	0.1
apple juice, bottled	0	0.1	pork sausage, pan-cooked	0.8	0.1
grape juice, bottled	0	0.1	quarter-pound hamburger on	0.9	0.1
grapefruit juice, from frozen	0.3	0.1	salami, sliced	1.0	0.2
orange juice, from frozen	0.3	0.1	salmon, steaks or filets, fresh	0.5	0.1
pineapple juice from frozen	0.4	0.1	shrimp, boiled	2.3	0.6
prune juice	0.1	0.1	tuna, canned in oil	0.5	0.1
tomato juice, bottle	0.6	0.1	turkey breast, roasted	0.4	0.1
			veal cutlet, pan-cooked	1.0	0.3
<b>Dairy products</b>			<b>Legumes, nuts, and nut products</b>		
American, processed cheese	0.1	0.2	kidney beans, dry, boiled	2.7	0.5
chedder cheese	0.3	0.2	mixed nuts, no peanuts, dry	15.5	2.6
chocolate milk, fluid	0.3	0.2	peanut butter, smooth	5.2	0.6
cottage cheese, 4% milkfat	0	0	peanuts, dry roasted	5.8	0.6
cream cheese	0	0	pinto beans, dry, boiled	2.4	0.2
eggs, boiled/fried	0.6	0.1	pork and beans, canned	1.8	0.2
eggs, scrambled	0.5	0.1	<b>Fats, oils, condiments, snacks, and sweets</b>		
half & half	0	0	butter, regular (salted)	0	0
lowfat (2%) milk, fluid	0	0	corn chips	1.0	0.2
skim milk	0	0	fruit flavor sherbert	0	0.1
sour cream	0	0	gelatin dessert, any flavor	0	0
Swiss cheese	0.4	0.4	honey	0	0
whole milk	0	0	jelly, any flavor	0	0.1
<b>Meat, poultry, and seafood</b>			margarine, stick, regular	0	0
beef chuck roast, baked	1.0	0.1	mayonaise, regular, bottled	0	0
beef steak, loin, pan-cooked	1.0	0.2	olive/safflower oil	0	0
bologna, sliced	0.4	0.2	popcorn, popped in oil	1.7	0.4
chicken breast, roasted	0.3	0.1	potato chips	2.8	0.8
chicken, fried (breast, leg, and	0.7	0.1	pretzels, hard, salted, any	1.6	0.2
frankfurters, beef, boiled	0.4	0.1	vanilla ice cream	0.06	0.24
ground beef, pan-cooked	0.8	0.1	white sugar, granulated	0	0
haddock, pan-cooked	0.06	0.13	<b>Beverages</b>		
ham, baked	0.6	0.2	coffee, from ground	0	0
ham luncheon meat, sliced	0.5	0.1	cola carbonated beverage	0	0
lamb chop, pan-cooked	1.4	0.2	tea, from tea bag	0	0
liver, beef, fried	123	57			
pork bacon, pan-cooked	1.2	0.4			
pork chop, pan-cooked	0.8	0.2			

<sup>a</sup>Data excerpted from the U.S. FDA Total Diet Study (2001).  
S.D. = Standard Deviation

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environment, the copper concentration in the liver only varied by a factor of 2–3.5. Copper concentrations in human tissues are given in Table 6-11 (Georgopoulos et al. 2001). The concentration of copper in blood is not expected to be predictive of the total body burden of copper; Saltzman et al. (1990) have found that the correlation between copper concentrations measured in blood and total body burden was poor ( $r=0.54$ ).

The mean copper content of cigarette tobacco was 24.7 ppm, with a standard deviation of 10.8 ppm (Mussalo-Rauhamaa et al. 1986). However, only 0.2% of this copper passes into mainstream smoke. This translates to a daily exposure of approximately 1 µg of copper in a pack of 20 cigarettes.

In an EPA-sponsored study conducted to determine the metal concentration in sewage sludge (Feiler et al. 1980), copper concentrations in primary sludge at seven POTWs were reported to be 3.0–77.4 ppm, with a median concentration of 20.5 ppm. The plant with the highest copper concentrations received wastes from plating industries, foundries, and coking plants. In a comprehensive survey of heavy metals in sewage sludge, 30 sludges from 23 American cities were analyzed (Mumma et al. 1984). The copper concentration in the sludges ranged from 126 to 7,729 ppm (dry weight), with a median value of 991 ppm. In the EPA National Sewage Sludge Survey, the mean concentration of copper in sewage sludge was 741 mg/kg (dry weight) (He et al. 1995). Gutenmann et al. (1994) report similar concentrations (217–793 ppm, dry weight) in sewage sludge obtained from 16 major cities in the United States. The proposed limit for copper in sludge spread on agricultural land is 1,000 ppm (Mumma et al. 1984). For comparison, the concentration of copper in cow's manure is . 5 ppm (Mumma et al. 1984).

In municipal solid waste compost obtained from nine sites in the United States, a mean copper concentration of 281 mg/kg (dry weight) was obtained with range of 36.4–424 mg/kg (He et al. 1995). Lisk et al. (1992) reported copper concentrations in composts formed from yard waste, ranging from 22.7 to 327 ppm, from sewage sludge ranging from 432 to 1,019 ppm, and from municipal solid waste ranging from 191 to 1,143 ppm.

Copper concentrations in waste from the combustion of municipal solid waste and other combustion processes have been reported. Copper in incinerator bottom ash and fly ash has been measured at mean concentrations of 1,700 and 1,000 mg/kg, respectively (Goldin et al. 1992). Buchholz and Landberger (1995) report concentrations of copper of 390–530 µg/g in fly ash, 1,560–2,110 µg/g in bottom ash, and

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**Table 6-11. Copper Content of Human Tissues and Body Fluids**

Tissue	Mean content ( $\mu\text{g/g}$ dry weight)	
	Normal	Wilson's disease
Adrenal	7.4	17.6
Aorta	6.7	—
Bone	4.2	—
Brain	—	—
Caudate nucleus	—	212
Cerebellum	—	261
Frontal lobe cortex	—	118
Globus pallidus	—	255
Putamen	—	314
Cornea	—	92.9
Erythrocytes (per 100 ml packed red blood cells)	23.1	—
Hair	89.1	—
Heart	16.5	12.7
Kidney	14.9	96.2
Leukocytes (per 10 <sup>9</sup> cells)	0.9	—
Liver	25.5	584
Lung	9.5	15.5
Muscle	5.4	25.9
Nail	18.1	—
Ovary	8.1	5.2
Pancreas	7.4	4.2
Placenta	13.5	—
Prostate	6.5	—
Skin	2	5.2
Spleen	6.8	5.6
Stomach and intestines	12.6	22.9
Thymus	6.7	—

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**Table 6-11. Copper Content of Human Tissues and Body Fluids (continued)**

Tissue	Mean content ( $\mu\text{g/g}$ dry weight)	
	Normal	Wilson's disease
Thyroid	6.1	—
Uterus	8.4	—
Aqueous humor	12.4	—
Bile (common duct)	1,050	173
Cerebrospinal fluid	27.8	—
Gastric juice	28.1	—
Pancreatic juice	28.4	—
Plasma, Wilson's disease		—
Saliva	50	—
Serum		
Female	120	—
Male	109	—
Newborn	36	—
Sweat		
Female	148	—
Male	55	—
Tissue		
Synovial fluid	21	—
Urine (24-hour)	18	—

Source: Georgopoulos et al. (2001); Scheinberg (1979); Sternlieb and Scheinberg (1977)

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1,140–1,540 µg/g in combined ash. In sewage sludge incineration process steams, copper concentrations were 4,561 mg/kg in sludge cake, 3,465 mg/kg in bottom ash, 3,707 mg/kg in cyclone ash, 3,684 mg/kg in scrubber particulate matter, and 6,666 mg/kg in stach particulate matter (Balogh 1996). In fossil fuel wastes, copper concentrations of 33–2,200 mg/kg in fly ash, 4–930 mg/kg in bottom ash, 6–340 mg/kg in flue gas desulfurization sludge, 10–130,000 mg/kg oil ash, and 2–190 mg/kg in coal have been obtained (Eary et al. 1990).

Agricultural sources of copper contamination in soils has been summarized by EPA (1995) and are shown in Table 6-12. Concentrations of copper in fertilizers, soil amendments, and other agricultural materials have been measured by Raven and Loeppert (1997). The materials and mean concentrations: urea (<0.6 µg/g), ammonium nitrate (<0.6 µg/g), ammonium sulfate (<0.6 µg/g), ammonium phosphate (<2–41.8 µg/g), potassium chloride (<2–3.5 µg/g), potassium-magnesium-sulfate (1.4–5 µg/g), North Carolina rock phosphate (9.6 µg/g), calcite (2.3 µg/g), corn leaves (9.4 µg/g), manure (17.5 µg/g), and austinite (300 µg/g).

### 6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Due to the ubiquitousness of copper in the environment and the general occurrence of copper in airborne particulates, exposure to copper through inhalation is commonplace. Estimates of atmospheric copper concentrations from representative source categories yielded a maximum annual concentration of 30 µg/m<sup>3</sup> (EPA 1987a). If a person is assumed to inhale 20 m<sup>3</sup> of air/day, this would amount to an average daily intake of 600 µg of copper. For the reported range of annual atmospheric copper concentrations, 5–200 ng/m<sup>3</sup> (EPA 1987a), the average daily intake by inhalation, would range from 0.1–4.0 µg. At the maximum reported ambient air concentration, 100 µg/m<sup>3</sup> for a 24-hour period at a location within one-half mile of a major source (EPA 1987a), the average daily intake would rise to 2,000 µg. These estimates assume that all of the copper is attached to particles of inhalable size, which is usually not the case. The average daily dietary intake of copper from food is <2 mg/day. Assuming a median copper concentration in drinking water of 75 µg/L, the average daily copper exposure from consumption of 2 L of water per day is 0.15 mg; however, many people may have high levels of copper in their tap water from the water distribution system. If the system is not permitted to flush out, average intakes from water may be >2 mg/day. It is less likely that high dermal exposures will result from bathing in this tap water because the distribution system will flush itself out as the water is drawn. The

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**Table 6-12. Agricultural Sources of Copper Contamination in Soils<sup>a</sup>**

Source	Concentration (ppm dry weight) <sup>b</sup>
Sewage sludges	50–3,300
Phosphate fertilizers	1–300
Limestones	2–125
Nitrogen fertilizers	<1–15
Manure	2–60
Pesticides (percent)	12–50

<sup>a</sup>From EPA 1995<sup>b</sup>Equivalent to mg/kg-dry weight

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total exposure of copper for the average person from all sources (e.g., air, drinking water, and food) is estimated to be 2.75 mg/day.

A National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that potentially 505,982 workers, including 42,557 women, were occupationally exposed to copper in the United States (NIOSH 1988). The NOES estimate is provisional because all of the data for trade name products that may contain copper have not been analyzed. Of the potential exposures, 1,073 are to pure copper, while in the other cases, the molecular form of copper was unspecified. Additionally, according to the NOES, 125,045 workers, including 38,075 women, were potentially exposed to copper sulfate (NIOSH 1988). The NOES was based on field surveys of 4,490 facilities and was designed as a nationwide survey based on a statistical sample of virtually all workplace environments in the United States where eight or more persons are employed in all standard industrial codes (SIC) except mining and agriculture. The exclusion of mining and agriculture is significant for estimating exposure to copper since there is a high potential for exposure in these industries. Current occupational exposure limits for copper fume are 0.2 and 1 mg/m<sup>3</sup> for dust and mists (Frazier and Hage 1998).

## 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 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).

Exposures of children to copper are not expected to be very different from those in the general population with respect to inhalation. However, exposure of copper through oral routes may differ, due to differences in the consumption of various food groups between children and adults and ingestion of dust and soils. The dietary copper intake for infants who receive the major portion of their nutritional

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requirements from breast milk is likely to be different from infants whose nutritional needs are either supplemented or entirely received through the consumption of formula. From the work of Pennington et al. (1986), the copper intake for a 6- to 11-month-old infant and a 2-year-old child are estimated to be 0.47 and 0.58 mg/day, values which are lower than the adult intake of 1 mg/day. However, little information is available on estimates of copper intake from inhalation and other oral routes for children in the United States. However, one study has provided estimated inhalation and ingestion exposures of copper for children in India (Raghunath et al. 1997). In this work, concentrations of copper in particulates in air were measured at 0.01–0.26  $\mu\text{g}/\text{m}^3$ . Based on these measurements, estimated inhalation exposures of children to copper were calculated to be 0.1–3.2  $\mu\text{g}/\text{day}$ . In this same work, exposures to copper through ingestion were estimated to be between 684–1,732  $\mu\text{g}/\text{day}$ .

Exposures of children to copper are likely to increase in areas where copper concentrations in air are expected to be high, such as mining sites, waste dump sites, smelters, and foundries. For example, copper burdens in children living near a lead smelter, as measured by copper concentration in teeth, increased with decreasing distance from the smelter (Blanuša et al. 1990). Children are also at risk for increased copper intake through consumption of drinking water where leaching of copper from the distribution system has occurred (Murphy 1993; Yannoni and Piorkowski 1995). This route of copper exposure can be minimized through the flushing of drinking water supply lines or increasing the pH of the water in the distribution system.

### 6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In discussing exposure to copper, the important question is whether individuals are exposed to readily available copper, which in general, means free (hydrated) Cu(II), and perhaps some weakly complexed or adsorbed forms of copper. The available data indicate that copper in natural water, sediment, and soil is in a bound form. Even so, the free form of copper can be readily obtained from ingested materials, for example a child's sampling of soil, after exposure to the low pHs encountered in the stomach. Potential for high exposure of the general population to copper may exist where people consume large amounts of tap water that has picked up copper from the distribution system, or already has a high copper background due to natural or anthropogenic activities (e.g., close proximity to mining activities or mine drainage). Leaching of copper from water distribution systems is likely to occur where the water is soft and is not allowed to run and flush out the system. In such cases, the concentration of copper frequently exceeds 1 ppm and a large fraction of the copper may be free cupric ion, and exposure will result by ingestion and dermal contact. A less likely situation where exposure to high levels of free Cu(II) may occur is from

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swimming in water that has been recently treated with a copper-containing algicide. Soluble cupric salts are used extensively in agriculture and in water treatment. Workers engaged in the formulation and application of these chemicals and industrial workers, such as those in the plating industry, may come into dermal contact with these copper-containing chemicals.

Based on the available data, people living close to NPL sites may be at greater risk for exposure to copper than the general population. This exposure can occur through particulates that have been blown offsite from NPL sites, ingestion of water from private wells which are in close proximity to NPL sites, ingestion of contaminated soil, or uptake of copper into fruits and vegetables raised in gardens of residents living near NPL sites.

People living near copper smelters and refineries and workers in these and other industries may be exposed to high levels of copper in dust by inhalation and ingestion. In some industries, workers may be exposed to fumes or very fine dust that may be more hazardous than general dust.

### **6.8 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 copper 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 copper.

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.

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**6.8.1 Identification of Data Needs**

**Physical and Chemical Properties.** The available data on the physical and chemical properties of copper and copper sulfate are generally sufficient for estimating their environmental fate. That no numerical value is listed for the water solubility of copper in Table 4-3 is of no special significance. For inorganic salts, the solubility product coupled with stability constants for the ionic species in solution are the factors determining how much of a compound goes into solution; the solubility in terms of the number of milligrams of the parent compound in solution, as used for organic compounds, is not meaningful. The important solubility products and stability constants for copper that are required for determining the copper species in natural water and their concentrations are known (Schnoor et al. 1987; Town and Filella 2000). Although no  $K_{oc}$  values are listed, copper binds very strongly to organic matter, and values for the binding constants and solubility products to humic acids are available (Schnoor et al. 1987). Similarly, there are binding constants and solubility products for other species that bind or coprecipitate with copper, such as clay minerals and iron and manganese oxides (Schnoor et al. 1987). Binding constants for copper in specific natural waters are also available (Town and Filella 2000). Other physical and chemical properties in Table 4-3 for which there is no data are generally negligible (e.g., Henry's law constant, vapor pressure) or not well defined for copper.

In general, experimental confirmation is required for predicting copper's fate in the environment. The factors which determine the copper species present or the material to which copper may be bound and the strength of the binding are site specific. If the level of detail requires knowledge of, for example, the percentage of copper associated with iron oxides or that which is easily exchangeable, the experimental confirmation is necessary.

**Production, Import/Export, Use, Release, and Disposal.** In the absence of information on the number of, information on the production, use, release, and disposal of copper is used for evaluating the potential for exposure of people to copper who live or work near waste sites and other sources. Copper exposure is widespread, but much of this exposure is to generally benign forms, such as metallic copper. The information available often does not distinguish between these forms and those of greater toxicological significance.

Information on the production, use, release, and disposal of copper and copper sulfate is generally available. The two chemicals account for most of the copper used. This information is tabulated by the U.S. Geological Survey every year in the Minerals Yearbook, and future trends in production and use are

## 6. POTENTIAL FOR HUMAN EXPOSURE

available. Such information is not available for other copper compounds. We also know the major uses of copper and whether these uses occur in the home, workplace, or environment.

According to the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The TRI contains release information for copper and copper compounds and is updated yearly.

For disposal, industrial waste copper is generally either recycled or landfilled. Data on secondary copper production (i.e., copper produced from scrap) is compiled by the U.S. Geological Survey. Effluent and disposal regulations for copper and its compounds are listed in the Clean Water Act and the Resource Conservation and Recovery Act (RCRA).

**Environmental Fate.** Information on how copper and its compounds partition in the environment (i.e., to soil and sediment), and the type of transformations that occur in different media, is available. We also have data concerning its transport in the environment. Although information on the fate of copper in air, water, and soil is available, the fate of copper is both species- and site- specific. Information concerning the forms of copper (i.e., specific compound, to what it is bound or complexed, or, in the case of air, the particle size) or the lability of the copper in particular media is available from only a few studies. These are sufficient to understand many contributors to the fate of copper and its compounds, but are not as comprehensive as one might like. In addition, studies of how fate data are directly relevant to human exposures, especially in regards to projecting copper toxicity in children is inadequate.

**Bioavailability from Environmental Media.** Copper is found in food, water, ambient air, and soil. The bioavailability of copper from food and water has been investigated in animals and humans. No information on the availability of copper from air was located. Copper in air originating from smelter sites is predominantly associated with sulfur, presumably as the sulfate. Copper dust from soil or around mining and smelter sites may be in a mineral form or as silicates. No information was located on the availability of copper in air. Copper in the soil is often bound to organic molecules; therefore, the bioavailability of the copper from soil cannot be assessed based on bioavailability information from drinking water or food studies. Studies on the bioavailability of copper from soil and ambient air would be useful in assessing potential toxicity to people living near a hazardous waste site.

The form and lability of copper in the environment is known in only a few site-specific cases. None of these cases include hazardous waste sites. More information on the forms of copper found at industrial

## 6. POTENTIAL FOR HUMAN EXPOSURE

sites and hazardous waste sites would be useful, especially since data from the Hazardous Substances Database Bank (HSDB) indicate that concentrations of copper as high as 182,000 ppm in soil and 14,000 ppm in sediments have been measured offsite of listed NPL sites (HazDat 2002). Monitoring groundwater near industries that use highly acid, copper-containing solutions, such as electroplating, electrowinning, and ore leaching industries, is important with respect to presenting highly mobile and highly bioavailable copper to human risk populations.

**Food Chain Bioaccumulation.** Because copper occurs in different forms in soil and water, the bioaccumulation of copper is expected to vary according to site and species. Data are generally available on the bioconcentration of copper in aquatic organisms, plants, and animals, as well as biomagnification in the food chain. This information is useful in assessing the potential for exposure from ingesting food originating from contaminated areas.

**Exposure Levels in Environmental Media.** Data are generally available regarding the concentrations of copper in environmental media, including the concentration of copper in soil at some hazardous waste sites. Since copper is naturally present in soil, statistical techniques can be used to determine whether the copper found at these sites is elevated above normal levels. Monitoring data are reasonably current. Human intake of copper from food, water, and air can be estimated.

**Exposure Levels in Humans.** Reasonably current data report levels of copper in human tissue and human milk. Although there is an increasing battery of information becoming available that describes copper concentrations in individuals exposed within specific work settings (for example, Gerhardsson et al. 1993; Saltzman et al. 1990), none of these studies address specific U.S. populations living around hazardous waste sites. There are quantitative data relating occupation, level and route of exposure, or the form of copper to which people are exposed. There is some limited information correlating the copper concentration and form to levels in the body in general populations; however, information is needed for occupational and at-risk populations.

**Exposures of Children.** Reasonably current data report levels of copper intake in infants and children. Information on copper intake for infants from human milk is also available. Exposure of children to copper in drinking water has been assessed and methods to decrease this exposure have been identified. However, only limited information on inhalation and other oral routes is available. Some information on exposure of children to copper near mining, smelting, refining, manufacture facilities, waste sites, and other hazardous sites is available, but not for U.S. populations. This information is

## 6. POTENTIAL FOR HUMAN EXPOSURE

needed to better estimate exposures of children in U.S. populations living near these facilities and sites. The use of copper concentrations in toenails and hair has been investigated as a surrogate measure of copper exposure in children and adults, and more research into testing the use of these surrogates is underway.

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

**Exposure Registries.** No exposure registries for copper and its compounds were located. No subregistry has currently been established for these chemicals. They will be considered in the future when chemical selection is made for subregistries 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 the exposure to these chemicals.

### 6.8.2 Ongoing Studies

Ongoing studies of copper in soils, sediments, and aquifers have been identified and are listed in Table 6-13. Also included in Table 6-13 are ongoing investigations of human exposures to copper.

## 6. POTENTIAL FOR HUMAN EXPOSURE

**Table 6-13. Ongoing Studies on Environmental Fate and the Potential for Human Exposure to Copper<sup>a</sup>**

Investigator	Affiliation	Research Description	Sponsor
Barnhisel, RI; Karathanasis, AD; Smith, BR	University of Kentucky; Clemson University	Evaluate the capacity of colloid dispersion models to predict water-dispersible colloid content based on quantifiable mineralogical properties of southern regional soils. Determine the nature of contaminant (e.g., copper)-mineral associations in selected soils as influenced by mineralogy and pedogenic properties and processes.	Hatch
Bleam, WF; Helme, PA	University of Wisconsin at Madison	Investigation of how humic substances in soil bind trace metals. Specific objectives include determining whether nitrogen amine ligands dominate $\text{Co}^{+2}$ , $\text{Ni}^{+2}$ , and $\text{Cu}^{+2}$ complexes at metal:N ratios in the range of 0.2–5.0.	NRI comp. grant
Chaney, RL	Beltsville ARC, Beltsville, Maryland	Comparison of the phytoavailability of Cd, Zn, and Cu in unamended soils versus long-term biosolids amended at equivalent pH to characterize changes in the adsorption equilibria of the paired soils. Evaluation of how changes in Fe and Mn oxides or humics content affect metal uptake.	USDA In-house
Chaney, RL; Daniels, WL	Virginia Polytechnic Institute	Comparison of the phytoavailability of Cd, Zn, and Cu in unamended soils versus long-term biosolids amended at equivalent pH to characterize changes in the adsorption equilibria of the paired soils as a function of the properties of the biosolids and soils. Evaluation of how changes in Fe and Mn oxides or humics content affect metal uptake.	USDA
Eick, MJ	Virginia Polytechnic Institute	Determine the kinetics and mechanisms of orthophosphate and trace elements (Cu, Pd, Cd, and Co) adsorption/desorption reactions on mineral and organic surfaces using a pressure jump relaxation spectrometer.	Hatch
Guo, MG; Tyzbir, R	University of Vermont	The objective is to determine the effective solubility of inorganic versus organic salts of Zn, Fe, and Cu in infant formula and how antioxidants influence the solubility of minerals in formula.	Hatch
Hesterberg, DL	North Carolina State University	Ascertain the nature of heavy metal binding to clay-organic systems and determine the significance of metal sulfides and other stable chemical species for reducing the mobility and bioavailability of metals in soils.	Hatch

## 6. POTENTIAL FOR HUMAN EXPOSURE

**Table 6-13. Ongoing Studies on Environmental Fate and the Potential for Human Exposure to Copper<sup>a</sup> (continued)**

Investigator	Affiliation	Research Description	Sponsor
Louma, SN	Water Resources Division, USGS	Investigate the partitioning of trace metals in sediments and how the partitioning is controlled. Geochemical partitioning, metal uptake into aquatic organisms, and the effects of the metals on these organisms will be examined.	USGS In-house
Morgan, DL	NIEHS	Investigate the absorption, distribution, and pulmonary toxicity of copper-indium diselenide and other novel chemicals used in the semiconductor and photovoltaic industries.	NIEHS Intra-mural
Parker, DR	University of California at Riverside	Objectives are to reexamine the Free Ion Activity Model (FIAM), which describes trace-metal toxicities in crop plants based on the chemical activity of the free metal ion in soil solution.	NRI comp. grant
Simon, NS	Water Resources Division, USGS	Determine the speciation of dissolved, free, inorganic, and organic complexed metals and how inorganic-organic reactions by which metals are retained in, or mobilized from, influence the distribution and partitioning of metals between solution and solid phases in sediments.	USGS
Sparks, DL; Ford, RG	University of Delaware	Determine the sorption-desorption kinetics of Ni, Cu, and Zn in model soils and examine the effect of Al-bearing clay minerals, iron oxides, and organic matter on the formation of mixed metal-Al precipitates.	NRI comp. grant
Strawn, DG	University of Idaho	Investigate Cu and Pd sorption mechanisms on distinct clay mineral surfaces under various equilibrium conditions.	Hatch
Thompson, ML	Iowa State University	Ascertain the binding nature and capacity of copper and Pb with humic components in aquifers and predict transport of these metals in aquifers using nonequilibrium models.	NRI comp. grant
Thompson, ML et al.	Iowa State University	Determine the mineralogical and microenvironmental contexts of Pd, Ni, Cu, and Zn in the solid and liquid phases of metal-contaminated soils.	Hatch

## 6. POTENTIAL FOR HUMAN EXPOSURE

**Table 6-13. Ongoing Studies on Environmental Fate and the Potential for Human Exposure to Copper<sup>a</sup> (continued)**

Investigator	Affiliation	Research Description	Sponsor
Zelazny, LW	Virginia Polytechnic Institute	Determine the quantity and chemical forms of P, Cu, and Zn in manure before and after application to soil and ascertain the bioavailability of these metals to plants.	Hatch

<sup>a</sup>CRIS 2002; FEDRIP 2002

ARC = Agricultural Research Center; NIEHS = National Institute of Environmental Health Sciences; NRI = National Research Institute; USDA = U.S. Department of Agriculture; USGS = U.S. Geological Survey

## 7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring copper and copper compounds, its metabolites, and other biomarkers of exposure and effect to copper and copper compounds. 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

Analytical methods and detection limits for copper in biological materials are given in Table 7-1. Copper in other biological materials such as hair and nails can be determined by using suitable procedures for dissolving the sample matrix and employing the same analytical techniques as with blood and tissue. These methods determine the total amount of copper in the sample. The methodology for analyzing biological material is similar to that used for environmental samples. The most commonly employed methods use atomic adsorption spectroscopy (AAS) or inductively coupled plasma-atomic emission spectroscopy (ICP-AES) (Araki et al. 1990; Lo and Araki 1989; Lopez-Artiguez et al. 1993). Differential-pulse anodic stripping voltammetry techniques have also been used to quantify copper in urine, yielding detection limits of 0.041 µg/L and an accuracy of 97% (Horng 1996).

### 7.2 ENVIRONMENTAL SAMPLES

Analytical methods and detection limits for copper in environmental media are given in Table 7-2. Analytical methods determine the total copper content of the samples; determining specific copper compounds and complexes in samples is difficult. The most common methods used for environmental samples are AAS, either flame or graphite furnace, ICP-AES, and inductively coupled plasma-mass spectrometry (ICP-MS). Water and waste water samples can be analyzed for copper by EPA Test Method 200.1 (flame atomic absorption), 200.7 ICP-AES, or EPA Test Method 200.9 (temperature

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**Table 7-1. Analytical Methods for Determining Copper in Biological Materials**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood or tissue	Acid digestion	Method 8005 <sup>a</sup> ; ICP-AES	1 µg/100 mL blood; 0.2 µg/g tissue	Not available	NIOSH 1987
Urine	Filter and polydithiocarbamate resin collection followed by low temperature plasma ashing or acid digestion	Method 8310 <sup>a</sup> ; ICP-AES	0.1 µg	Not available	NIOSH 1987
Tissue	HNO <sub>3</sub> digestion	AAS/graphite furnace	0.25 µg/g wet weight	103.1±7.7% mean recovery; 8.2±6.9% mean difference in duplicates <sup>b</sup> ; 0.01% accuracy	Lowe et al. 1985
Toenails	HNO <sub>3</sub> digestion	AAS/graphite furnace	0.6 µg/g	<5% within run precision; 3.5% day-to-day precision	Wilhelm et al. 1991

<sup>a</sup>Simultaneous, multielemental analysis, not compound specific.

<sup>b</sup>Mean±1 standard deviation

AAS = atomic absorption spectrometry; ICP-AES = inductively coupled plasma-atomic emission spectroscopy

## 7. ANALYTICAL METHODS

**Table 7-2. Analytical Methods for Determining Copper in Environmental Samples**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Filter collection on 0.8 µm membrane filter and acid digestion	Method 730, ICP-AES	1 µg	No bias identified	NIOSH 1987
Air	Filter collection on 0.8 µm membrane filter and acid digestion	Method 7029, AAS	0.05 µg	No significant bias	NIOSH 1987
Water, waste water	Acidify with 1:1 HNO <sub>3</sub> to a pH<2	Method 220.1, AAS/direct aspiration	20 µg/L	0.9–29.7% bias between 7.5 and 332 µg/L	EPA 1983
Water, waste water	Sample solutions should contain 0.5% HNO <sub>3</sub>	Method 220.2, AAS/furnace technique	1 µg/L	Not available	EPA 1983
Water, waste water	Filter and acidify sample	Method 200.7 CLP-M ICP-AES	6 µg/L	Not available	EMMI 1997
Water, waste water	Digestion with H <sub>2</sub> SO <sub>4</sub> and HNO <sub>3</sub>	Neocuproine, spectrometric	120 µg/L in 1 cm cell	Not available	Greenberg et al. 1985
Waste water	Adjust pH to 1.65–1.85, mix, filter	Method 200.1, flame atomic absorption	4 mg/L	Not available	EMMI 1997
Water, waste water	Filter and acidify	Method 200.7_M, ICP-AES	25 µg/L	Not available	EMMI 1997
Groundwater, surface water, and drinking water	Filter and acidify	Method 200.8, ICP-MS	20 µg/L	Not available	EMMI 1997
Marine waters	Digest in HNO <sub>3</sub> , concentrate on iminodiacetate chelating resin, elute with 1.25 M HNO <sub>3</sub>	Method 200.10, ICP-MS	7 µg/L	Not available	EMMI 1997

## 7. ANALYTICAL METHODS

**Table 7-2. Analytical Methods for Determining Copper in Environmental Samples (continued)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Marine waters, estuarine waters, seawaters, and brines	Digest in HNO <sub>3</sub> , concentrate on iminodiacetate chelating resin, elute with 1.25 M HNO <sub>3</sub>	Method 200.13, GFAA	5 µg/L	Not available	EMMI 1997
Soil, sediment, sludge, and solid waste	Digestion with HNO <sub>3</sub> and H <sub>2</sub> O <sub>2</sub> , reflux with dilute HCl	Method 7210, AAS	20 µg/L	As in Method 220.1	EPA 1986
Food	Closed-system digestion	AAS or ASV	0.32 µg/g (ASV), not reported (AAS)	94–100	Holak 1983
Biological tissues	HNO <sub>3</sub> digestion, reaction with H <sub>2</sub> O <sub>2</sub>	Method 200.3, ICP-MS	18 µg/L	Not available	EMMI 1997
Fish tissue (fresh edible tissue)	Dissociate tissue in tetraammonium hydroxide, acidify with HNO <sub>3</sub>	Method 200.11, ICP-AES	18 µg/L	Not available	EMMI 1997

AAS = atomic absorption spectrometry; ASV = anodic stripping voltammetry; GFAA = graphite furnace atomic absorption; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; ICP-MS = inductively coupled plasma-mass spectrometry

## 7. ANALYTICAL METHODS

stabilized graphite furnace atomic absorption) (EMMI 1997). These methods are suitable for groundwater and surface water as well as domestic and industrial effluents. EPA Test Method 200.8 ICP-MS or EPA Test Method 200.15 ICP-AES are suitable for analysis of groundwater, surface water, and drinking water. EPA Test Method 200.8, EPA Test Method 200.10 (on-line chelation and ICP-MS), or EPA Test Method 200.13 (chelation and graphite furnace atomic absorption) are suitable for marine, estuary, and brine waters. If the determination of dissolved and suspended copper is required, samples should be filtered using a 0.45 µm membrane filter. Suspended solids, as well as sludge and sediment, may be analyzed by EPA Methods 200.1 and 200.13 after an initial acid digestion with HNO<sub>3</sub>. Interference by other elements is not a problem in the analysis; however, background correction may be required in using atomic absorption to correct for nonspecific absorption and scattering, which may be significant at the analytical wavelength, 324.7 nm (EPA 1986). In the determination of trace metals, major concerns are contamination and loss. Contamination can be introduced from impurities in reagents and containers as well as from laboratory dust. Losses may also occur due to adsorption onto containers.

Other analytical methods used for copper analysis include x-ray fluorescence, anodic stripping voltammetry, neutron activation analysis, photon-induced x-ray emission, as well as chemical derivation, followed by gas chromatographic or liquid chromatographic analysis. Discussion of these methods are beyond the scope of this profile; however, methodology for the determination of copper has been reviewed by Gross et al. (1987) in food, Fox (1987) in air, MacCarthy and Klusman (1987) in water, and Lichte et al. (1987) in geological materials.

### 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 copper and copper compounds 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 copper and copper compounds.

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

## 7. ANALYTICAL METHODS

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.* Methods for determining background and elevated levels of copper in biological materials are well developed, sensitive, specific, and reliable. Standardized methods are available from NIOSH and other sources. The use of copper concentrations in toenails and hair has been investigated as surrogate markers of copper exposure, with validation studies currently underway.

*Effect.* No specific biomarkers of copper toxicity have been determined. Until these biomarkers are determined, the methodology needed to identify them cannot be established.

#### **Methods for Determining Parent Compounds and Degradation Products in Environmental**

**Media.** Methods for determining background and elevated levels of copper in environmental media are well-developed, sensitive, and selective. Water is the medium of most concern, since the form of copper generally associated with health effects is soluble copper(II). Standardized methods of analysis for copper in air, water, soil, and food are available from EPA, NIOSH, and other sources. Analytical methods measure total copper; consequently, the methods of analyzing for a parent compound and a degradation product are identical.

### 7.3.2 Ongoing Studies

Ongoing studies regarding new analytical methods for measuring copper in biological materials or environmental media were located in the literature. Dr. M. Longnecker at the National Institute of Environmental Health Sciences is working to validate toenail copper concentrations as a surrogate measure of exposure to copper. Development of high-performance liquid chromatography (HPLC) and derivatization techniques to identifying natural copper chelators in marine water is being conducted at Cornell University under the guidance of Drs. B.A. Ahner and J.W. Moffett. Dr. D.L. Sparks at the University of Delaware is developing x-ray absorption fine structure (XAFS) and atomic force microscopy (AFS) techniques for the study of metal/metalloid reactions in soil. Dr. J.F. Tyson and

## 7. ANALYTICAL METHODS

colleagues at the University of Massachusetts at Amherst are developing liquid-liquid extraction pretreatment techniques that can be interfaced with HPLC-ICP-MS instrumentation.



## 8. REGULATIONS AND ADVISORIES

An acute-duration oral MRL of 0.02 mg copper/kg/day was derived for copper. This MRL is based on the occurrence of gastrointestinal disturbances in women ingesting 0.0731 mg Cu/kg/day in drinking water for 2 weeks; no adverse effects were observed at a drinking water dose of 0.0272 mg Cu/kg/day (Pizarro et al. 1999). To calculate an MRL, the copper dose provided in the drinking water was added to the average dietary intake (0.0266 mg Cu/kg/day). The total copper intake of 0.0538 mg Cu/kg/day was divided by an uncertainty factor of 3 to account for human variability.

The acute-duration oral MRL of 0.02 mg Cu/kg/day was adopted for use as the intermediate-duration oral MRL for copper.

IARC (1993) has classified copper 8-hydroxyquinoline in Group 3, unclassifiable as to carcinogenicity in humans. EPA (IRIS 2002) has classified copper in Group D, not classifiable as to human carcinogenicity.

International, national, and state regulations and guidelines regarding human exposure to copper are summarized in Table 8-1.

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Copper**

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenicity classification Copper 8-hydroxyquinoline	Group 3 <sup>a</sup>	IARC 2002
<u>NATIONAL</u>			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA ) Fume (Cu) Dusts and mists (as Cu)	0.2 mg/m <sup>3</sup> 1.0 mg/m <sup>3</sup>	ACGIH 2001
EPA	Serious health effects from ambient air exposure (Cu)		EPA 2002b 40CFR61.01(b)
NIOSH	REL (10-hour TWA) Fume (as Cu) Dusts and mists (as Cu) IDLH Fume, dusts, and mists (as CU)	0.1 mg/m <sup>3</sup> 1.0 mg/m <sup>3</sup> 100 mg/m <sup>3</sup>	NIOSH 2002
OSHA	PEL (8-hour TWA) for general industry Fume (as Cu) Dusts and mists (as Cu)	0.1 mg/m <sup>3</sup> 1.0 mg/m <sup>3</sup>	OSHA 2002c 29CFR1910.1000
	PEL (8-hour TWA) for construction industry Fume (as Cu) Dusts and mists (as Cu)	0.1 mg/m <sup>3</sup> 1.0 mg/m <sup>3</sup>	OSHA 2002b 29CFR1926.55
	PEL (8-hour TWA) for shipyard industry Fume (as Cu) Dusts and mists (as Cu)	0.1 mg/m <sup>3</sup> 1.0 mg/m <sup>3</sup>	OSHA 2002a 29CFR1915.1000
b. Water			
DOT	Marine pollutant (Cu metal powder and cupric sulfate)		DOT 2002 49CFR172.101, Appendix B
EPA	Drinking water standard Action level (Cu)	1.3 mg/L	EPA 2002c
	MCLG (Cu)	1.3 mg/L	EPA 2002d 40CFR141.51(b)

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Copper (continued)**

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
EPA	Groundwater monitoring (Cu)		EPA 2002g
	Suggested method	<u>PQL</u>	40CFR264,
	6010	60 µg/L	Appendix IX
	7210	200 µg/L	
	Hazardous substance in accordance with Section 311 (b)(2)(A) of the Clean Water Act (cupric sulfate and cupric sulfate, ammoniated)		EPA 2002j 40CFR116.4
	Reportable quantity of hazardous substance designated pursuant to Section 311 of the Clean Water Act		EPA 2002k 40CFR117.3
	Cupric sulfate	10 pounds	
	Cupric sulfate, ammoniated	100 pounds	
	Secondary MCL for public water systems (Cu)	1.0 mg/L	EPA 2002e 40CFR143.3
	Toxic pollutant designated pursuant to Section 307(a)(1) of the Federal Water Pollution Control Act and is subject to effluent limitations (Cu and compounds)		EPA 2002a 40CFR401.15
Water quality criteria (Cu)	Freshwater		EPA 1999
	CMC	13.0 µg/L	
	CCC	9.0 µg/L	
	Saltwater		
	CMC	4.8 µg/L	
	CCC	3.1 µg/L	
	Human health for consumption of water and organism	1,300 µg/L	
	Organoleptic effect criteria	1,000 µg/L	
c. Food and Drugs			
EPA	Exemption from requirement of a tolerance in meat, milk, poultry, eggs, fish, shellfish, and irrigated crops when it results from the use as an algicide, herbicide, and fungicide when used in accordance with good agricultural practices (Cu)		EPA 2002f 40CFR180.1021

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Copper (continued)**

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
FDA	Bottled water; allowable level (Cu)	1.0 mg/L	FDA 2001a 21CFR165.110
	Clinical chemistry test system; copper test system measures copper levels in plasma, serum, and urine	Exempt from premarket notification procedures in Subpart E of Part 807	FDA 2001b 21CFR862.1190
	Color additives exempt from certification—copper powder for use in externally applied drugs	Cu not less than 95%	FDA 2001e 21CFR73.1647
	Color additives exempt from certification—copper powder for use in cosmetics		FDA 2001f 21CFR73.2647
	Direct food substance affirmed as generally recognized as safe when used as a nutrient supplement or as a processing aid (cupric sulfate)		FDA 2001c 21CFR184.1261
	Drug products containing certain active ingredients offered over-the-counter; inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses (Cu)	Weight control drug product	FDA 2001g 21CFR310.545 (a)(20)
	Trace minerals added to animal feeds as nutritional dietary supplements are generally recognized as safe when added at levels consistent with good feeding practices (Cu compounds)		FDA 2001i 21CFR582.80
IOM	Recommended dietary allowance (RDA)	0.9 mg/day	IOM 2001
d. Other			
EPA	Carcinogenicity classification (Cu) RfC RfD	Group D <sup>b</sup> No data No data	IRIS 2002

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Copper (continued)**

Agency	Description	Information	Reference
<u>NATIONAL</u> (cont.)			
EPA	Reportable quantity designated as a CERCLA hazardous substance under Section 307(a) of the Clean Water Act (Cu)	5,000 pounds	EPA 2002h 40CFR302.4
	Reportable quantity designated as a CERCLA hazardous substance under Section 311(b) (4) of the Clean Water Act (cupric sulfate)	10 pounds	EPA 2002h 40CFR302.4
	Toxic chemical release reporting; community right-to-know; effective date of reporting (Cu)	01/01/87	EPA 2002i 40CFR372.65(a)
<u>STATE</u> Regulations and Guidelines:			
a. Air			
Illinois	Toxic air contaminant (Cu)		BNA 2001
Louisiana	Toxic air pollutant <sup>c</sup> Minimum emission rate (Cu and compounds)	25 pounds/year	BNA 2001
New Mexico	Toxic air pollutant Fume (Cu) OEL Emissions Dusts and mists (as Cu) OEL Emissions	0.2 mg/m <sup>3</sup> 0.0133 pounds/hour	BNA 2001
Vermont	Cu compounds Hazardous ambient air standard Averaging time Action level	100 µg/m <sup>3</sup> 8 hours 4 pounds/hour	BNA 2001
b. Water			
Arizona	Drinking water guideline (Cu)	1,300 µg/L	HSDB 2002
North Carolina	Groundwater quality standard (Cu)	1.0 mg/L	BNA 2001
c. Food	No data		

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Copper (continued)**

Agency	Description	Information	Reference
<u>STATE</u> (cont.)			
d. Other			
Arizona	Soil remediation levels (Cu and compounds)		BNA 2001
	Residential	2,800 mg/kg	
	Non-residential	63,000 mg/kg	
Florida	Toxic substance in the workplace (Cu fume, dust, and mist)		BNA 2001

<sup>a</sup>Group 3: unclassifiable as to carcinogenicity to humans

<sup>b</sup>Group D: not classifiable as to human carcinogenicity

<sup>c</sup>Class II: suspected human carcinogen and known or suspected human reproductive toxin

ACGIH = American Conference of Governmental Industrial Hygienists; BNA = Bureau of National Affairs; CERCLA = Comprehensive Environmental Response Compensation and Liability Act; CFR = Code of Federal Regulations; CCC = criterion continuous concentration; CMC = criteria maximum concentration; Cu = copper; DOT = Department of Transportation; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IOM = Institute of Occupational Medicine; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limits; PQL = practical quantitation limits; RDA = recommended dietary allowance; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit value; TWA = time-weighted average

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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 ( $K_d$ )**—The amount of a chemical adsorbed by a 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 which 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.

## 10. GLOSSARY

**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 which 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.

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**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.

**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.

**In Vitro**—Isolated from the living organism and artificially maintained, as in a test tube.

**In Vivo**—Occurring within the living organism.

**Lethal Concentration<sub>(LO)</sub> (LC<sub>LO</sub>)**—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)**—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<sub>(LO)</sub> (LD<sub>LO</sub>)**—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<sub>(50)</sub> (LD<sub>50</sub>)**—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>(50)</sub> (LT<sub>50</sub>)**—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.

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**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) which 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 odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

**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 science of quantitatively predicting 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 whereby 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 which 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.

## 10. GLOSSARY

**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  $\mu\text{g/L}$  for water,  $\text{mg/kg/day}$  for food, and  $\mu\text{g/m}^3$  for air).

**Recommended Exposure Limit (REL)**—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations 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  $\text{mg/m}^3$  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.

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**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.

**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 min continually. No more than four excursions are allowed per day, and there must be at least 60 min 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<sub>(50)</sub> (TD<sub>50</sub>)**—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 study of 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 one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

**Xenobiotic**—Any chemical that is foreign to the biological system.

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## APPENDIX A

### ATSDR MINIMAL RISK LEVEL 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.

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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 a hundredfold 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, expert panel peer reviews, and agencywide 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, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Copper and Compounds  
CAS Number:  
Date: July 3, 2002  
Profile Status: Third Draft  
Route: [ ] Inhalation [X] Oral  
Duration: [ X ] Acute [ ] Intermediate [ ] Chronic  
Key to Figure: 9  
Species: Humans

Minimal Risk Level: 0.02 [X] mg copper/kg/day [ ] ppm

Reference: Pizarro F, Olivares M, Uauy R, et al. 1999. Acute gastrointestinal effects of graded levels of copper in drinking water. Environ Health Perspect 107:117-121.

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

A group of 60 healthy women (mean ages of 32.9–36.3 years) were divided into four groups. Each group consumed water containing 0, 1, 3, or 5 mg ionic copper as copper sulfate (0, 0.0272, 0.0731, and 0.124 mg Cu/kg/day) for a 2-week period with a 1-week rest between copper exposures. Every week the subjects received a bottle containing copper sulfate solution and were asked to mix this solution bottle with 3 L water; this water was then used for drinking and cooking. The subjects recorded daily water consumption and any symptoms. Blood samples were collected 1 week before the study, at the end of the first 2-week exposure period, and at the end of the study; the blood was analyzed for serum copper, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase activities, and hemoglobin levels. The average copper dietary intake, based on a 24-hour dietary recall, was 1.7 mg Cu/day (0.0266 mg Cu/kg/day using an average body weight of 64 kg).

Effects noted in study and corresponding doses:

No significant alterations in serum copper, ceruloplasmin, hemoglobin, or liver enzymes were observed. Twenty-one subjects reported gastrointestinal symptoms, predominantly nausea. Nine subjects reported diarrhea with or without abdominal pain, no association between copper level and diarrhea was found. Six of these episodes of diarrhea occurred during the first week of the study independent of copper concentration. Twelve subjects reported abdominal pain, nausea, or vomiting; the incidences were 3/60, 1/60, 10/60, and 9/60 in the control, 0.0272, 0.0731, and 0.124 mg/kg/day groups, respectively. There was a significant difference between in the incidences at concentrations of #1 mg/L (0.0272 mg/kg/day) versus \$3 mg/L (0.0731 mg/kg/day). No other differences between groups were found.

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Dose and end point used for MRL derivation:

The MRL is based on the NOAEL of 0.0272 mg Cu/kg/day for gastrointestinal effects in women ingesting copper sulfate in drinking water (Pizarro et al. 1999). To estimate total copper exposure, the concentration of copper in the drinking water (0.0272 mg Cu/kg/day) was added to average dietary copper intake (0.0266 mg Cu/kg/day). The total copper exposure level of 0.0538 mg Cu/kg/day was considered a no-observed-adverse-effect-level (NOAEL) for gastrointestinal effects.

NOAEL  LOAEL

Uncertainty Factors used in MRL derivation:

10 for use of a extrapolation from animals to humans  
 3 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

Yes. Daily doses were calculated using reported daily copper intakes (0.04, 1.74, 4.68, and 7.94 mg) and the average of the mean reported body weights (64 kg).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Was a conversion used from intermittent to continuous exposure?

No

Other additional studies or pertinent information that lend support to this MRL:

Several other studies conducted by this group and by other investigators support the identification of the gastrointestinal tract as a sensitive target of copper toxicity. Nausea and/or vomiting was reported by adults ingesting a single dose of 0.011 to 0.08 mg Cu/kg/day as copper sulfate (Araya et al. 2001; Gotteland et al. 2001; Nicholas and Brist 1968; Olivares et al. 2001); no gastrointestinal effects were reported after ingesting 0.0057 mg Cu/kg/day as copper sulfate (Olivares et al. 2001). Daily exposure to 0.1 mg Cu/kg/day for 1 week also resulted in an increased occurrence of nausea, vomiting, and/or abdominal pain (Pizarro et al. 2001). An intermediate-duration study in infants receiving 2 mg/L copper sulfate (0.3 mg Cu/kg/day) in drinking water for 9 months (starting at 3 months of age) did not find an increased occurrence of gastrointestinal effects or alterations in biomarkers of liver toxicity (Olivares et al. 1998). Although the LOAEL identified in the Olivares et al. (2001) study is lower than the NOAEL identified in the Pizarro et al. (1999) study, the Pizarro et al. (1999) study was selected as the critical study because it is a longer-duration study and it more closely mimics an exposure scenario of a population drinking copper-contaminated drinking water. Animal studies support the identification of the gastrointestinal tract as the most sensitive target of toxicity. Hyperplasia of the forestomach mucosa was observed in rats exposed to 44 mg Cu/kg/day as copper sulfate in the diet (NTP 1993) and in mice exposed to 197 mg Cu/kg/day as copper sulfate in the diet (NTP 1993). At higher doses, liver and kidney damage have been observed (Haywood 1980; Haywood and Comerford 1980; Haywood et al. 1985b; NTP 1993).

Agency Contact (Chemical Manager): Alfred Dorsey

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## 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 they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, 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. If data are located in the scientific literature, a table of genotoxicity information is included.

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.

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**Interpretation of Minimal Risk Levels**

Where sufficient toxicologic information is available, we have derived minimal risk levels (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. They 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 the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

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 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 LSE Tables.

**Chapter 3****Health Effects****Tables and Figures for Levels of Significant Exposure (LSE)**

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) 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, minimal risk levels (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 No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

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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 LSE Table 3-1**

- (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. When sufficient data exists, 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 Table 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 2 "18r" data points in 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 regimen 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 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 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, 1 systemic effect (respiratory) was investigated.

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- (8) NOAEL A No-Observed-Adverse-Effect Level (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 Lowest-Observed-Adverse-Effect Level (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 Cancer Effect Level (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 the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND****See Figure 3-1**

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 intermediate and chronic 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<sup>3</sup> 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 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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- (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 6

**Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
<b>INTERMEDIATE EXPOSURE</b>							
2 6	5	6	7	8	9		10
3 6	Systemic	9	9	9	9		9
4 6	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 <sup>b</sup>	10 (hyperplasia)	Nitschke et al. 1981
<b>CHRONIC EXPOSURE</b>							
						11	
	Cancer					9	
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

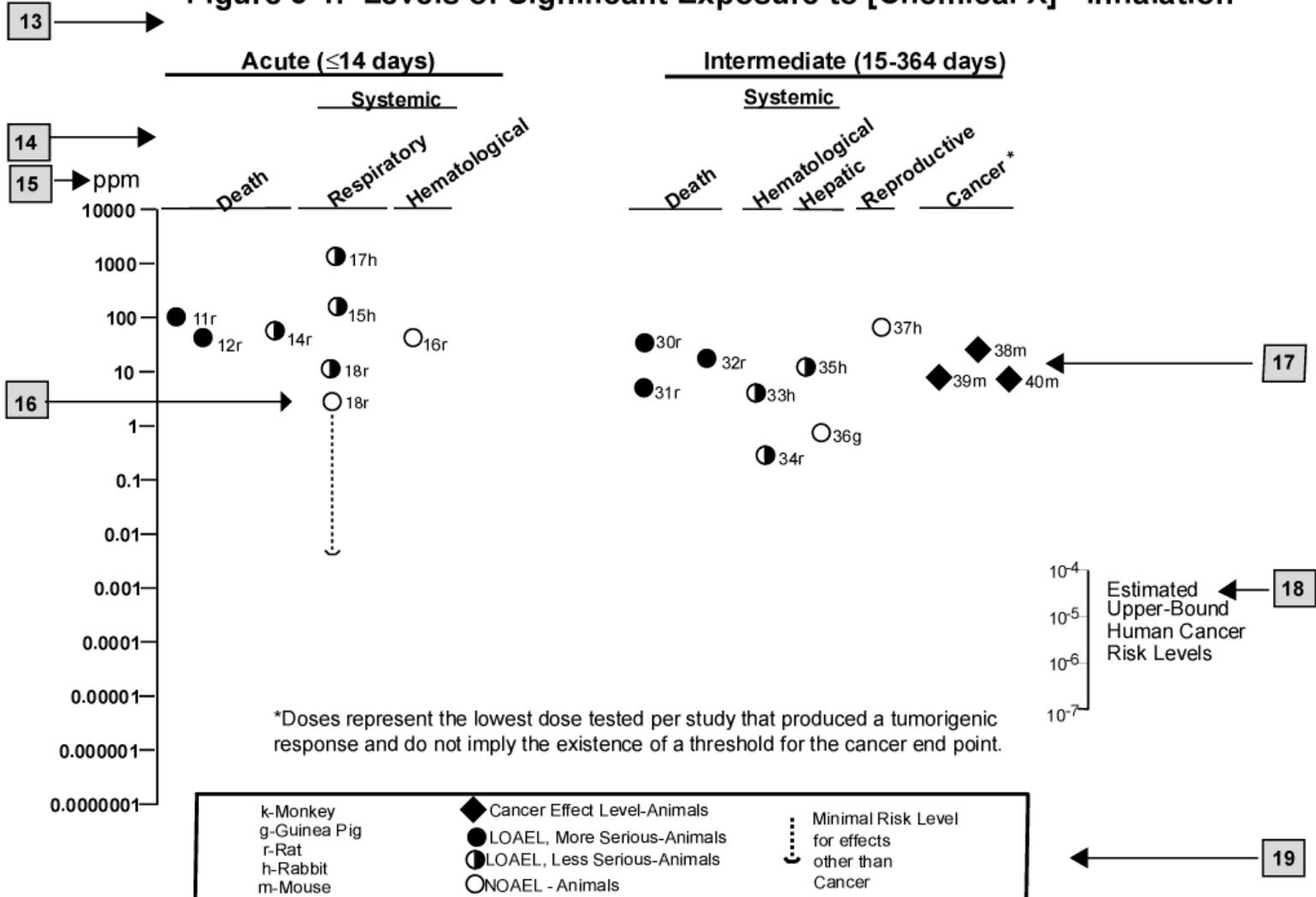
<sup>a</sup> The number corresponds to entries in Figure 3-1.

12 6

<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of  $5 \times 10^{-3}$  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

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
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
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
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

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DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International 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 <sub>1</sub>	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	<i>Federal Register</i>
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
K <sub>d</sub>	adsorption ratio
kg	kilogram
K <sub>oc</sub>	organic carbon partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC <sub>Lo</sub>	lethal concentration, low
LC <sub>50</sub>	lethal concentration, 50% kill
LD <sub>Lo</sub>	lethal dose, low
LD <sub>50</sub>	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	lutinizing hormone
LT <sub>50</sub>	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal

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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
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
NHANES	National Health and Nutrition Examination Survey
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
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic

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PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
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
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
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 <sub>50</sub>	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

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#	less than or equal to
%	percent
$\alpha$	alpha
$\beta$	beta
$\gamma$	gamma
$\delta$	delta
$\mu\text{m}$	micrometer
$\mu\text{g}$	microgram
$q_1^*$	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result



## APPENDIX D

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